The Generation and Reactivity of Organozinc Carbenoids

A Thesis Presented by

Caroline Joy Nutley

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Christopher Ingold Laboratories
Department of Chemistry
University College London
London WC1H 0AJ

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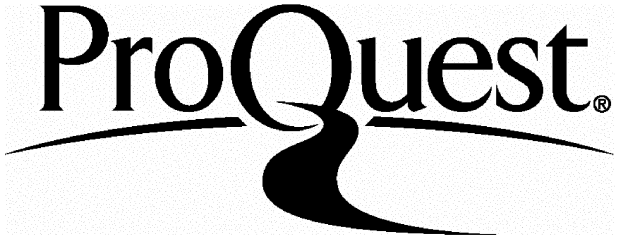

Through doubting we come to questioning and through questioning we come to the truth.

Peter Abelard, Paris, 1122

Abstract

This thesis concerns an investigation into the generation and reactivity of organozinc carbenoids, from both a practical and mechanistic standpoint, using the reductive deoxygenation of carbonyl compounds with zinc and a silicon electrophile.

The first introductory chapter is a review of organozinc carbenoids in synthesis.

The second chapter opens with an overview of the development of the reductive deoxygenation of carbonyl compounds with zinc and a silicon electrophile since its inception in 1973. The factors influencing the generation of the zinc carbenoid are then investigated using a control reaction, and discussed. The results from a study to determine whether the carbenoid is homogeneous or heterogeneous are given, and the implications of the results considered. The influence of the electronic nature of the alkene on cyclopropanations is then examined using firstly a series of variously *para*-substituted alkenes, and then a series of electronically 'extreme' alkenes. In spite of the complexity of this heterogeneous system, a mechanistic rationale is presented to account for all the results.

More preparative applications of the reactivity of the carbenoid are then presented. The first report of the cyclopropanation of cyclic enol ethers using the reaction system developed is made. The synthetic scope of a novel intermolecular C-H insertion reaction found in this system is also probed.

The implications of preliminary results from a complex intramolecular system are discussed. Attempts to provide a mechanistic appraisal of the results using a specifically labelled system are then presented.

Finally, attempts to carry out ylide-rearrangement reactions, and particularly a biomimetic [2,3]-sigmatropic rearrangement of an S-prenyl ylide, derived by trapping the carbenoid formed from prenal onto 3-methyl-1-thiophenyl-but-2-ene, are discussed.

These results, and their implications, are drawn together in a concluding chapter, and full experimental details (together with complete spectral data for all compounds synthesised) are appended.

Contents

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Abbreviations

Ac	Acetyl
Ar	Unspecified aromatic group
Bn	Benzyl
b.pt.	Boiling point
br.	Broad
Bu^n	*n*-Butyl
cat.	Catalytic
CI	Chemical ionisation
Δ	Heat
d	Doublet / Day(s) as appropriate
DCM	Dichloromethane
de	Diastereomeric excess
DET	Diethyl tartrate
DIPT	Diisopropyltartrate
DMAP	4-(Dimethylamino)pyridine
DME	1,2-Dimethoxyethane
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
E	Unspecified electrophile
ee	Enantiomeric excess
EI	Electron impact
eq.	Equivalent
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
FTIR	Fourier transform infra red
g	Gram(s)
GC	Gas chromatography
GCMS	Gas chromatography coupled mass spectrometry
h	Hour(s)

HPLC	High performance liquid chromatography
IR	Infra red
L	Unspecified ligand
lit.	Literature value
m	Meta
m	Mutliplet
M	Unspecified metal
Me	Methyl
mg	Milligram(s)
min.	Minutes
ml	Millilitre(s)
mmHg	Millimetres of mercury
MOM	Methoxymethyl
m.pt.	Melting point
NMR	Nuclear magnetic resonance
Nu	Unspecified nucleophile
o	Ortho
p	Para
	Polymer
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Ph	Phenyl
ppm	Parts per million
^{i}Pr	Isopropyl
PVP	poly-4-Vinylpyridine
py	Pyridine
q	Quartet
quin	Quintet
R	Unspecified carbon substituent
r.t.	Room temperature
s	Singlet
sec	Second(s)
t	Triplet

t	Tertiary
$t_{1/2}$	Half-life
t_R	Retention time
TBDPS	^{t}Butyldiphenylsilyl
THF	Tetrahydrofuran
THP	Tetrahydropyran
tlc	Thin layer chromatography
TMEDA	*N,N,N,N*-Tetramethylethylenediamine
TMS	Trimethylsilyl
TMTA	*N,N,N',N'*-Tetramethyltartaramide
Ts	*p*-Toluenesulfonyl
UV	Ultra violet
X	Unspecified heteroatom
Y, Z	Unspecified substituent

Chapter 1. The Role of Zinc Carbenoids in Organic Synthesis[1]

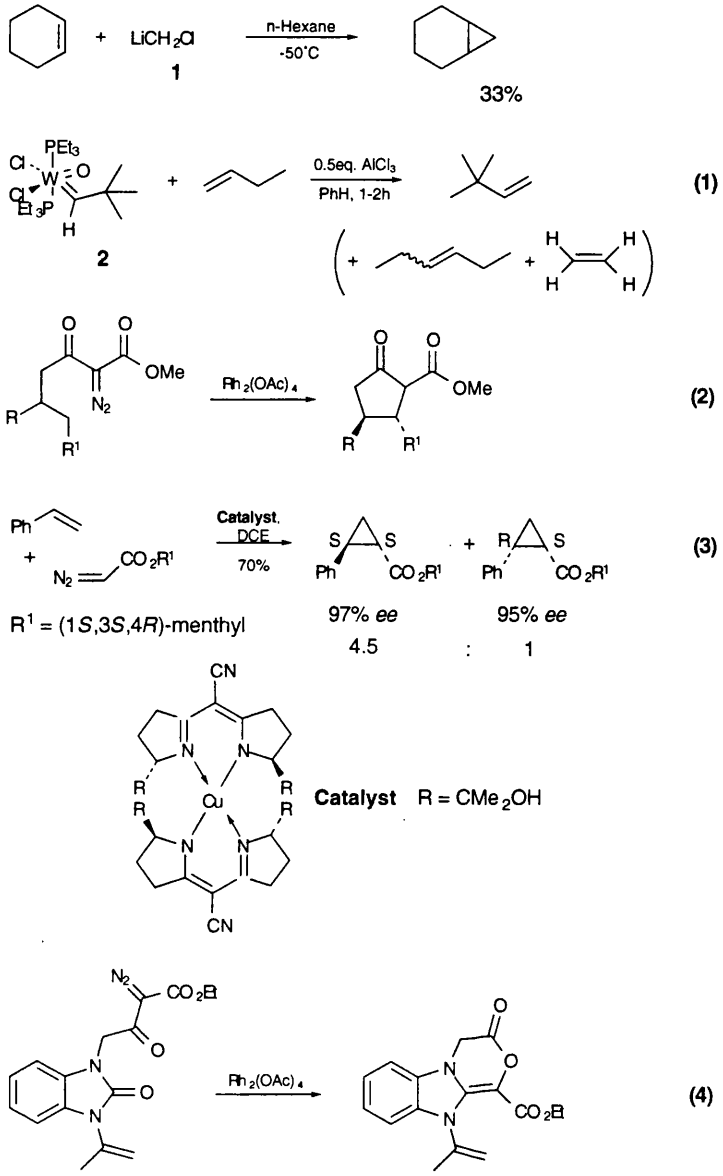
1.1 Introduction

1.1.1 Carbenes and Carbenoids

The unique electronic structure of the free divalent carbene intermediate,[2] either in its singlet state or in its biradical like triplet state, has proven over many years, to be a fascinating area of study for the synthetic organic chemist. Thus the singlet carbene may be viewed simultaneously either as an electron deficient species, comparable to the carbonium ion, or as a carbanion delivering a pair of non-bonding electrons. The overall reactivity in terms of nucleophilic or electrophilic character is strongly dependent on the electron withdrawing or donating ability of the two groups which are attached to the carbene carbon atom. However, to those synthetic organic chemists interested in the selective manipulation of sensitive polyfunctional molecules, such intermediates have often been rejected as being rather indiscriminate and hyperactive in their behaviour.

Fortunately, within the last thirty years, these schizophrenic and over-aggressive tendencies of the less electron rich free carbenes have been 'domesticated' through the introduction of an ever increasing range of carbenoids which can generally be considered as derived by complexation of the free carbene with a metal.[3] The influence of the metal both in terms of structure, and as a control element in terms of reactivity, is of paramount importance. Furthermore, the nature of the ancillary ligands around the transition metal, and the selection of a cationic or a neutral complex, can also be used to great advantage as additional methods of attenuating reactivity.

Many of these facets are encapsulated by the selected examples shown in **Scheme 1**. Thus structures may vary from the tetrahedral lithium chlorocarbenoids (**1**),[4] to those which possess a formal metal-carbon double bond (**2**). In terms of reactivity, there is an evident bifurcation between the behaviour of the early transition metal carbenoids or alkylidenes which undergo olefin metathesis (Equation **(1)**),[5] and those which effectively mirror their free carbene counterparts in terms of insertion (Equation **(2)**),[6] cyclopropanation (Equation **(3)**),[7] and ylide formation and rearrangement reactions (Equation **(4)**).[8] A substantial number of extensive reviews dealing with the carbenoid behaviour of individual metals are currently available.[9-12] In recent years, however, it has become apparent that the use of stoichiometric metal carbenoids is less attractive than the development of catalytic cycles, especially when the latter involve chiral ligands. In this respect, the use of rhodium and copper carbenoids, invariably generated *in situ* from α-diazo carbonyl precursors, is proving to be the most popular choice at the present time.



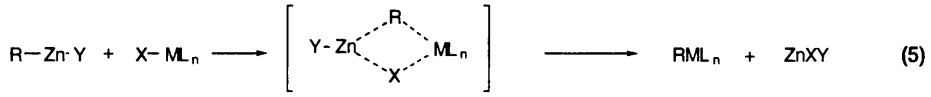
Scheme 1

1.1.2 Organozinc Reagents and their Carbenoid Connection

The purpose of the present review is to highlight the current status of organozinc carbenoids within the above framework, both from the practical standpoint of their generation and synthetic utility, and also in terms of current mechanistic understanding.

In the wider context, it is interesting to reflect on the sinusoidal popularity of organozinc reagents for synthesis. Thus, although the reactivity of dialkylzinc reagents was studied for some thirty years after the first preparation of diethylzinc by Frankland in 1849,[13,14] by the turn of the century attention had turned to the more reactive Grignard reagents. The highly covalent character of the carbon-zinc bond which is responsible for the relative lack of reactivity of these organometallics is, however, the very reason for their current renaissance. With zinc possessing low-lying p orbitals, transmetallation with metallic salts

is a facile process, as long as it is thermodynamically favoured. In this way, zinc can be used to convert a highly functionalised organic substrate into a stable organometallic, which can then be transmetallated to a more reactive organometallic (M = Cu, Pd, Ti etc.), capable of reacting with an electrophile (Equation **(5)**).



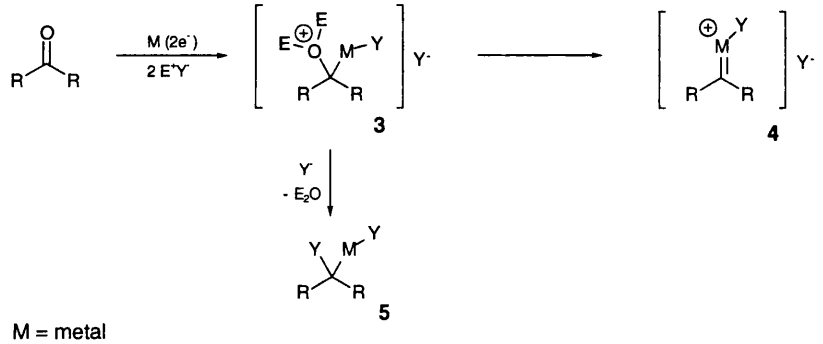
Y = R, halide, ...
M = Ti, Mo, Ta, Nb, V,
Pd, Ni, Pt, Cu, ...

Unfortunately, the intermediate species RZnY has frequently been referred to as an organozinc carbenoid, even when the carbenoid carbon is not geminally substituted with zinc and a leaving group. The reactivity of these very versatile, but non-carbenoid, organozinc compounds, whose use in synthesis has increased dramatically in the past 15 years, is the subject of a recent very comprehensive review.[15]

These fundamental properties of the carbon-zinc bond are also of course germane to the generation and behaviour of organozinc carbenoids. To the vast majority of synthetic organic chemists, such reagents are still commonly encountered in the Simmons-Smith cyclopropanation reaction[16] and its variants, and recent developments in this area are highlighted in chapter 1.3. The idea that a readily available carbonyl compound, rather than a *gem* dihalide may be used as a direct precursor of an organozinc carbenoid, may still be somewhat foreign. The major portion of this review is accordingly devoted to this less frequently encountered area of organozinc carbenoid reactivity.

1.2 Zinc Carbenoids From Carbonyl Compounds

From the most simplistic viewpoint of electronic stocktaking, the conversion of a carbonyl compound to an organometallic carbenoid requires only the delivery of two electrons from a metal or metal complex M and the addition of two equivalents of an electrophilic reagent (E^+Y^-) in order to generate the classical reactivity pattern of a geminally substituted carbon atom possessing both the carbon-metal bond and a leaving group shown in **3** (**Scheme 2**). The further evolution of this intermediate to other metallocarbenoid structures such as **4** and **5** is then a function of the leaving group ability of E_2O, the nucleophilicity of Y^-, and the nature of the metal M in terms of wishing to sustain a carbon-metal double bond, or otherwise.



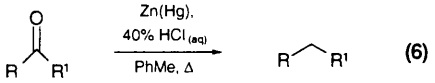
M = metal
E-Y = electrophilic reagent

Scheme 2

The substitution of zinc as the metal and the proton as the ultimate electrophile in **Scheme 2** immediately leads to the recognition of the Clemmensen reduction, and to the notion that some form of organozinc carbenoid should be involved in such reactions, even though further reduction steps are still required. However, as is clearly illustrated in the following sections, considerable problems arise as soon as the timing of various electronic events is subject to scrutiny. It is therefore highly instructive in this section to discuss the behaviour and mechanisms involved in the Clemmensen reduction of various carbonyl substrates, since this provides valuable insight for the exploitation of other conceptually similar, but more controlled, methods of generating the same organozinc carbenoids.

1.2.1 The Clemmensen Reduction

The Clemmensen reduction of a carbonyl group to give, in the simplest cases, a methylene unit, is perhaps one of the most familiar reactions in organic chemistry (Equation **(6)**). Since its discovery by Clemmensen[17-19] over 80 years ago, the original procedure employing amalgamated zinc and 40% aqueous hydrochloric acid, with an immiscible co-solvent, has undergone considerable modification. Commonly used procedures today are more suitable for use with compounds that were very labile under the original harsh conditions of Clemmensen's reaction. The reaction has been extensively reviewed.[20-22]

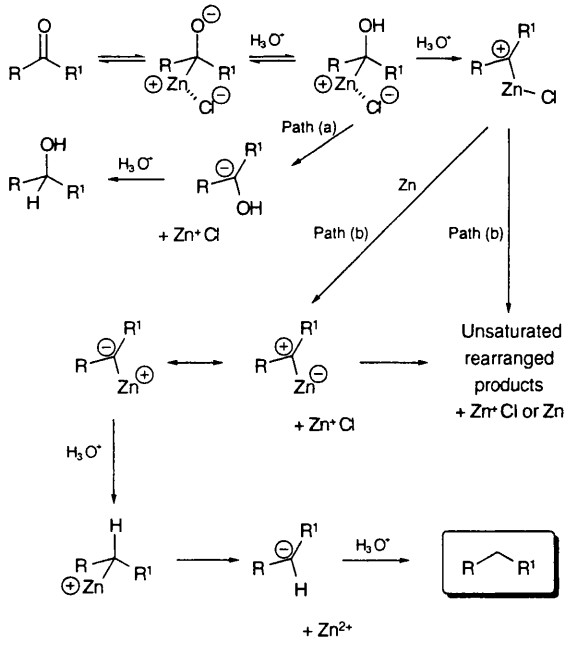


(6)

1.2.1.1 Mechanistic Studies

It is intriguing, however, that so long after its discovery, the mechanism of such an apparently simple transformation is still far from clear. Although free alcohols have been ruled out as intermediates, a unifying mechanism that explains the various reactivities of substrates such as diketones and α,β-unsaturated ketones under Clemmensen conditions, has yet to be found.

Some of the earliest detailed work was carried out by Brewster and co-workers.[23-25] In the first paper in this series, Brewster presented evidence that the mechanism involved direct metal intervention - i.e. formation of some metal bound intermediate. He termed this process 'chemisorption' of the ketone on the metal surface (bonding via carbon or oxygen of the carbonyl group). Following on from this chemisorption theme, Brewster suggested that the zinc in the reduction acts essentially as an electron pump, and hence the mechanism demands the formation of partially reduced intermediates. Nakabayashi's[26-28] work also concluded that the mechanism was a stepwise process involving organozinc intermediates. As alcohols are not generally reduced under Clemmensen conditions, Brewster ruled free alcohols out as intermediates in the reduction. In Nakabayashi's studies, stopping the reduction of acetophenone or *t*-butyl phenyl ketone after 5 minutes, a complex product mixture was found, including saturated, unsaturated and rearranged hydrocarbons, alcohols, and pinacol coupling-derived products. The hydrocarbon products were shown not to have arisen via alcohol intermediates - indeed when the alcohols isolated were separately subjected to the reaction conditions, no reduction was observed. He suggested that the major products of the reduction were derived from a carbocationic intermediate [Path (b)], and that there was a minor side reaction leading to the formation of the observed alcohol(s) [Path (a)] (**Scheme 3**). Furthermore, it was claimed that the pinacol coupling, which may occur at the one-electron reduction stage of a carbonyl compound, came about via a mechanism (termed as electrochemical) that shared no common intermediates with the Clemmensen reduction.



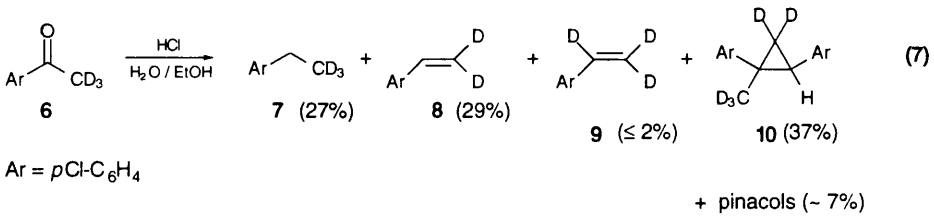
Scheme 3

Nakabayashi found in kinetic studies that the chloride ion concentration had a considerable influence on the reaction, and rationalised this as due to chloride ions being involved in the rate determining step. As the zinc concentration in the amalgam is also important, and the yields of Clemmensen-type products fall with the concentration of zinc in the amalgam, it was concluded that the rate determining step involved attack of zinc and chloride ion on the

carbonyl group (the first step in the mechanism shown in **Scheme 3**). However, as an added complication, at very low zinc concentrations in the amalgam, Nakabayashi found that the one electron pinacol processes dominated, with an absence of Clemmensen-type products. It was on the basis of this result that he concluded that the mechanisms of the pinacol process and the Clemmensen reduction were quite different.

Indication that the mechanism of the Clemmensen reduction involved a carbenoid intermediate was, in fact, present in Clemmensen's original work on the reaction. He noted that on the reduction of acetophenone at low acid concentration, styrene rather than ethylbenzene was obtained. With this result strongly suggesting a C-H insertion reaction of an intermediate carbenoid, this aspect of the reaction became the subject of further investigations by other workers.[29] The effect of acid concentration on the reduction of 11 different carbonyl compounds was examined, and the ratio of alkane to alkene found. Generalising the results, the formation of alkenes is favoured over alkanes as the acid concentration falls. It was interesting to note that under all reaction conditions, cyclohexanone gave exclusively cyclohexene, but that *p*-ethoxy and *p*-methoxyacetophenone gave exclusively the corresponding alkane, presumably due to electronic influences which facilitate further reduction of the carbenoid. When the derived alcohol corresponding to several of the ketones was subjected to the reaction conditions, different product distributions were obtained to those from the parent compound, strongly suggesting yet again that alcohols are not free intermediates in the reduction.

In 1986, an elegant study by Burdon[30] provided results further indicative of a carbenoid mechanism. Under the reduction conditions studied - zinc in 50% aqueous ethanol at 20°C - the chosen substrates, acetophenone, substituted acetophenones and propiophenone, were found to give classic Clemmensen reduction products, and products formed via 'carbenoid chemistry'. Cyclopropanes were formed, in the first instance by the trapping of alkenes formed in the reaction, and later by trapping alkenes added to the reaction mixture. The alkenes formed during the reaction are proposed to have been formed by a C-H insertion process, another classic carbene reaction. Deuterium labelling studies provided further backing for the intervention of a zinc carbenoid in the reduction. The product distribution from the reduction of **6** is shown in Equation **(7)**.



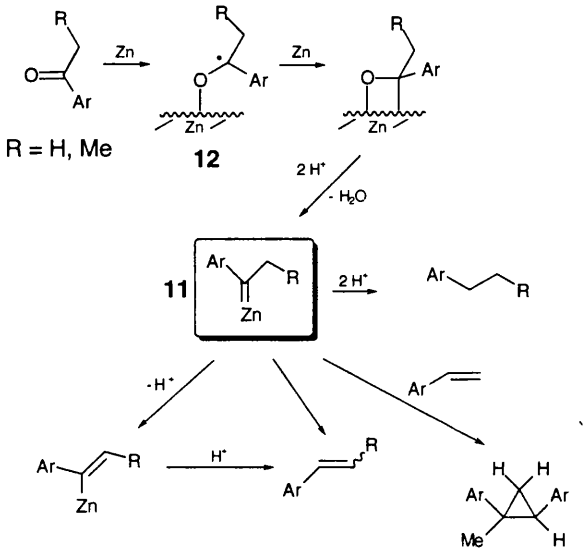
6 **7** (27%) **8** (29%) **9** (≤ 2%) **10** (37%) **(7)**

Ar = *p*Cl-C$_6$H$_4$

+ pinacols (~ 7%)

Thus, **7**, the alkane product, occurs via the transfer of two electrons and two protons to the carbenoid. Compound **8** results from the loss of D^+ from the carbenoid to give a vinyl zinc species, and hence for this substrate this is almost exclusively the route to the unsaturated

products. Compound **9**, the other olefinic product, results from a C-D insertion of the carbenoid (i.e. a 1,2-shift). The cyclopropane **10** results from the cyclopropanation of styrene formed during the reaction by further carbenoids. The high percentage yield of this species suggests that cyclopropanation by the carbenoid is a very facile process. These results allowed Burdon to propose the mechanism shown in **Scheme 4**. The route shown for the formation of the carbenoid **11** was only tentatively proposed by Burdon, although he did suggest that radical intermediate **12** could explain the pinacol type products obtained in the reaction (in direct opposition to Nakabayashi's earlier conclusions on the mechanism of these two processes).[28]



Scheme 4

A recent series of papers by Rosnati and co-workers,[31-35] has also examined the particular cases of mono- and diarylcarbonyl compounds, in which sequential halide anion displacement may, not surprisingly, also intervene.

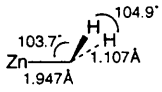
From these studies it is clear that the tortuous path to the carbenoid is highly substrate and concentration dependent, and that competing pathways such as pinacolic coupling may well intervene when intermediates generated at the one electron reduction level are particularly stable.

1.2.1.1.1 Spectral Studies on Prototypical Zinc Carbenoids

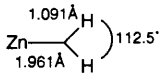
The carbenoid mechanism that Burdon[30] invoked for the Clemmensen reduction prompted the publication of a study on the isolation and characterisation of the parent methylene zinc carbenoid, $ZnCH_2$.[36] A 1:1 adduct was produced by codeposition of zinc atoms with diazomethane and argon onto a rhodium plated copper mirror at 12K. Under photolysis conditions ($\lambda > 400$nm), the adduct was converted to $ZnCH_2$, whose structure was examined by Fourier transform I.R.. The frequencies measured for the adduct, as well as for isotopically

labelled species, agreed well with those calculated by a normal co-ordinate analysis. Later, *ab initio* quantum mechanical calculations[37] showed that the species Billups and co-workers had isolated[36] was a triplet carbene, and predicted that the singlet state species would lie only 49.6kJmol^{-1} higher in energy.

Considering the equilibrium geometries of the singlet and triplet carbenes, it was calculated that both the singlet **13** and triplet states **14** would have a pyramidal structure about carbon. The structure of the singlet state would be that preferred by the interaction of zinc with the empty p orbitals of carbenes with singlet ground states. Experimental data suggests a zinc-carbon bond distance of 1.93-1.96Å in the zinc carbenoid, which probably corresponds to a single bond (when compared to zinc-carbon bond distances measured for zinc carbynes), although the accuracy of calculations performed to date has not permitted confirmation of this. The estimated Mullikan charges for the zinc carbene of +0.43 on Zn and -0.66 on C indicate that the species has some ionic character.



$^1A'$



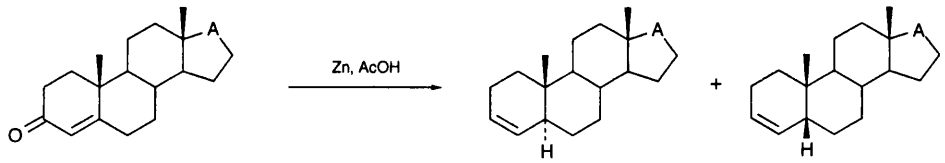
$^3B_1$

13 **14**

1.2.1.2 α,β-Unsaturated Ketones in the Clemmensen Reduction

Whilst strong presumptive evidence for the intermediacy of an organozinc carbenoid may be found in the reactions of simple carbonyl compounds, the reduction of α,β-unsaturated compounds under Clemmensen conditions presents a very different picture. Typical products include the saturated ketone and derived hydrocarbons, hydrocarbon dimers from radical couplings at the β-terminus induced at the one electron reduction stage, similarly derived pinacol coupling products, and, perhaps most noticeably in a more general context, rearrangement products derived from cyclopropanol derivatives. Some of these reactions are illustrated below.

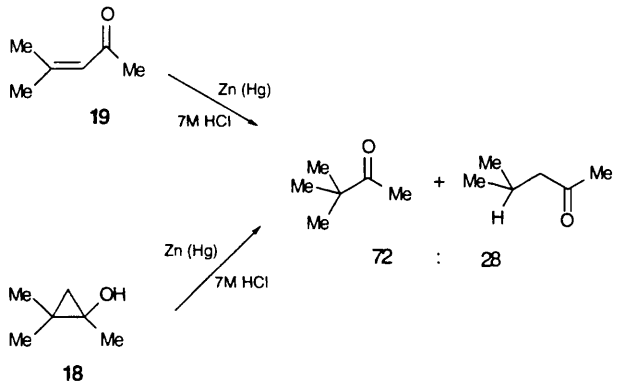
Steroidal enones have proved interesting substrates in many studies.[22] An example of such work is that of McKenna and co-workers.[38] They examined the reduction of many different steroidal enones, amongst which were cholest-4-en-3-one **15**, testosterone acetate **16** and androst-4-ene-3,17-dione **17**. It is interesting to note that the reduction of the carbonyl group in the enone proceeds with shift of the alkene towards what was the carbonyl carbon. The isolated 17- ketone in androst-4-ene-3,17-dione remains untouched under the conditions employed (**Scheme 5**).



15 A = $CH.C_8H_{17}$ **15'** exclusive
16 A = CH.OAc **16'** ~ 1 : 1
17 A = CO **17'** exclusive

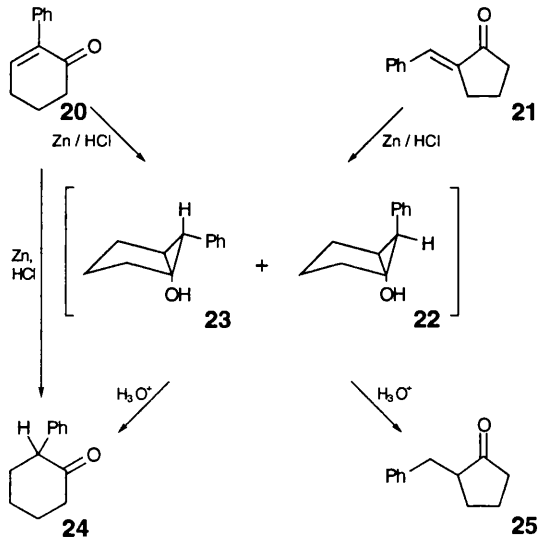
Scheme 5

In terms of the more often observed rearrangement process, Davis and Woodgate had proposed[39] that the reduction of α,β-unsaturated ketones under Clemmensen conditions proceeded via a cyclopropanol, which, depending upon its mode of ring-opening, could give two structurally isomeric saturated ketones. In their study, the authors independently synthesised the cyclopropanol **18** they believed to be an intermediate in the reduction 4-methylpent-3-en-2-one **19** (**Scheme 6**). On acid catalysed cleavage of this cyclopropanol, they formed the two isomeric ketones isolated from the reduction of the α,β-unsaturated ketone, in the same ratio.



Scheme 6

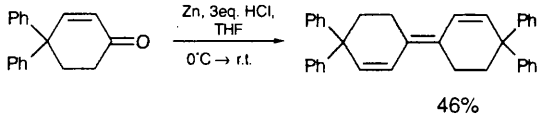
In a very beautifully conceived study, Elphimoff-Felkin and Sarda examined the reductive behaviour of the two α,β-unsaturated ketones (**20** and **21**) which could be expected to undergo reduction via rearrangement of the same cyclopropanol intermediates (*endo* **22** and *exo* **23**).[40] The latter were not only isolated from the reactions as their acetates by carrying out the reactions in acetic anhydride, but also subjected to solvolytic proton catalysed rearrangement to give the final product ketones (**24** and **25**). On the basis of the differing ratios of ketonic products formed from **20**, **21**, **22** and **23**, it was concluded that direct reductive routes with skeletal preservation also exist in competition with the bicyclic cyclopropanol pathway (**Scheme 7**).



Scheme 7

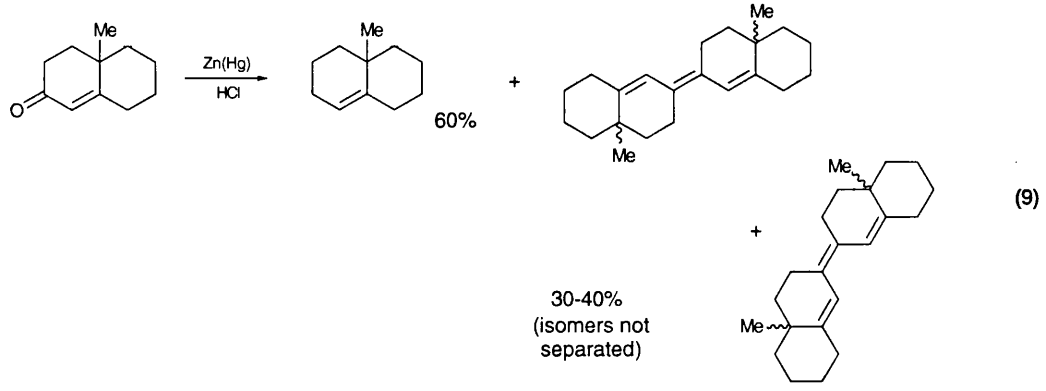
In a very comprehensive study, a wide range of enones were subjected to the Clemmensen reduction, in anhydrous conditions (Zn(Hg), Et_2O - HCl, Ac_2O).[41] For each enone, the product ratios were determined, but in all cases a cyclopropanol acetate was isolated, adding further weight to the evidence suggesting that such species are intermediates in the reduction. The results also reinforced the idea that the configuration of the starting enone dictated the stereochemical outcome of the cyclopropanol formed and hence the regiochemical outcome of the reaction, and that an allylic anion was the key intermediate. This postulate arose partly due to the dismissal of radical intermediates, as the addition of a radical quench had no influence on the reaction.

From the above examples, it might well be concluded that such competing pathways preclude access to α,β-unsaturated organozinc carbenoids. By way of contrast, however, two isolated reports of 'carbene dimers' have been described, Equations **(8)** and **(9)**.[22,42]



(8)

46%



(9)

30-40%
(isomers not
separated)

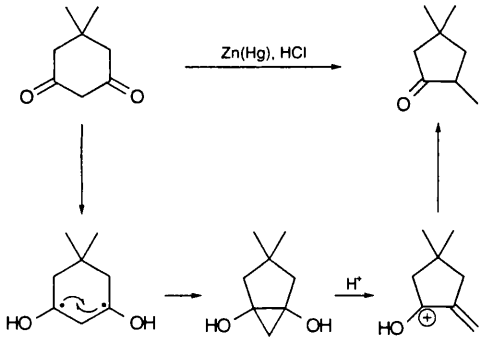
In both of these cases, neither double bond reduction nor skeletal rearrangement were observed, and, on the basis of later studies of dicarbonyl coupling using zinc and chlorotrimethylsilane (*vide infra* chapter 1.2.2), it is highly probable that the carbenoid is in fact involved.

Nevertheless, in general terms it would appear that the influence of the substrate structure is the determining factor in deciding which electronic pathway is to be followed under Clemmensen conditions for α,β-unsaturated carbonyl compounds.

1.2.1.3 Diketones in the Clemmensen Reduction

Diketones, particularly 1,3- and 1,4-diketones, are rarely found to give useful yields of the normal products expected from the Clemmensen reduction. Instead, they are frequently found to undergo intramolecular pinacol couplings at the one-electron reduction stage, with the products observed deriving from this pathway. This type of reaction has been reviewed,[43] and numerous examples are available to show the generality of the reaction.[44-48]

The mechanism for dimedone, the first example studied in 1935 by Dey and Linstead,[49] **Scheme 8**, is illustrative, and carbenoid chemistry has not been observed in these cases.



Scheme 8

1.2.1.4 Practical Advances in the Clemmensen Reduction

With the Clemmensen reduction classically being carried out using amalgamated zinc and 40% aqueous hydrochloric acid, with an immiscible co-solvent, typically toluene, the conditions are simply too harsh for many highly functionalised substrates to tolerate. Although the process was modified relatively early on to use organic solvents such as alcohols and acetic acid,[21] such a homogeneous system was found to favour the formation of pinacols. Perhaps the most significant advance was made by Yamamura and co-workers.[50] They showed that by employing a large excess of activated zinc dust in diethyl ether saturated with hydrogen chloride at 0 °C, optimum results could be obtained in the reduction, with reactions typically complete in 1 hour.

Surprisingly, little study seems to have been made of the effect of sonication on the reaction. Reeves and co-workers have published results on the reduction of ketones to the corresponding methylene compound using zinc amalgam and hydroiodic acid in methanol, with sonication (5 hours).[51] For the ketones selected, yields were high in most cases, with aromatic ketones generally giving better results than their aliphatic counterparts. It was found that amalgamation of the zinc was crucial to the reaction; without amalgamation, yields were found to be significantly lower.

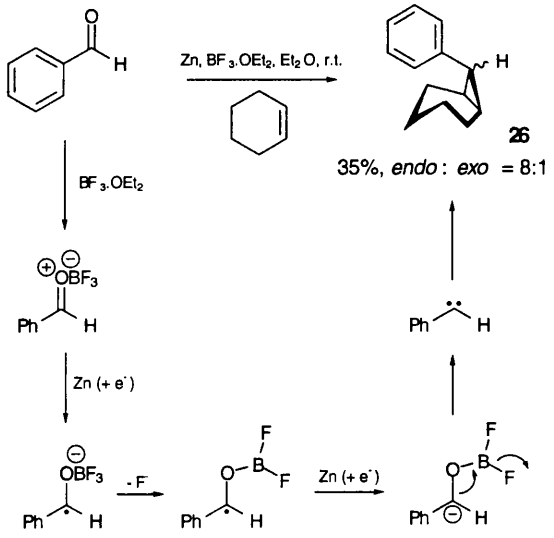
Finally, report of an electrochemical reduction of a diketone has been made that permitted the isolation of the labile cyclopropanediol as its diacetate.[52] Triangular wave cyclic voltammetry was used on a hanging drop mercury electrode. With such electrochemical reductions being a powerful yet simple technique in organic synthesis, it is indeed surprising that these methods have not been exploited more, particularly using a zinc anode.

1.2.2 Controlled Reductive Deoxygenation of Carbonyl Compounds

1.2.2.1 The Demise of the Proton

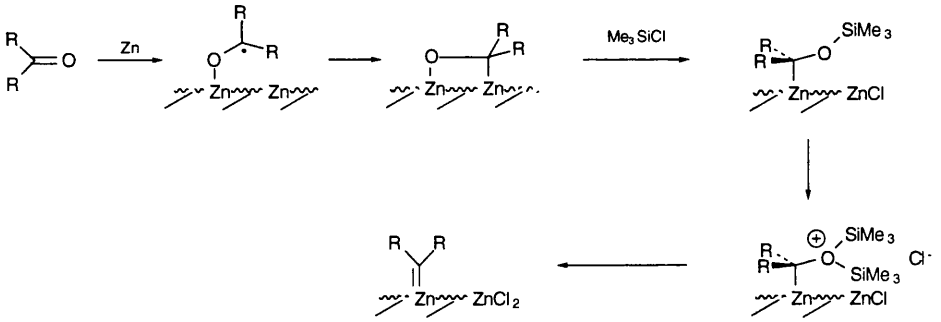
Although convincing evidence has accumulated over the years for the intermediacy of a zinc carbenoid in the Clemmensen reduction, classic carbenoid reactivity is not routinely observed since the vigorous reaction conditions employed are also ideal for further protonations and two electron reduction to the methylene group. In order to exploit the carbenoid's reactivity, reaction conditions are therefore required in which these later steps are effectively precluded.

Two conceptually similar solutions, both involving replacement of the proton, have evolved. In the first of these, reported by Elphimoff-Felkin in 1969,[53] the use of boron trifluoride etherate as a Lewis acid under Clemmensen-type reductive conditions allowed the carbenoid from benzaldehyde to be trapped by an alkene, to give cyclopropanes (**Scheme 9**). The yield of 7-phenylnorcarane **26** obtained was almost doubled (60%) by the use of the alkene as the reaction solvent. In the few examples studied, whilst yields were only moderate, a notable feature was that cyclic alkenes gave the more hindered *endo* isomer preferentially (*vide infra* Section 1.2.2.4)



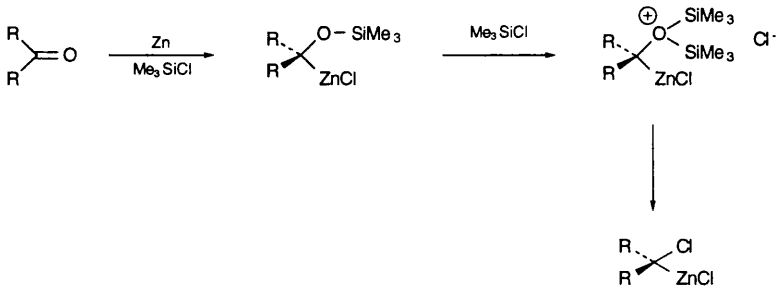
Scheme 9

In 1973 Motherwell[54] also published results in this area, concerning a study of the behaviour of alicyclic ketones using chlorotrimethylsilane as a replacement for hydrogen chloride. This selection was made since the silicon electrophile is also capable of forming a very strong bond to oxygen. When viewed in this way, a mechanistic pathway for the formation of a heterogeneous organozinc carbenoid analogous to that proposed by Burdon[30] (Section 1.2.1.1) for the Clemmensen reduction may be proposed (**Scheme 10**).



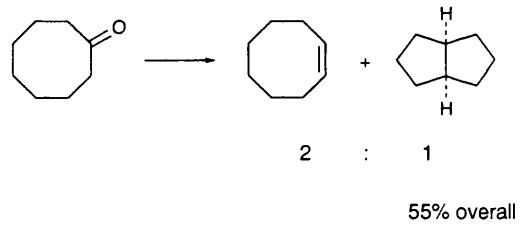
Scheme 10

Alternatively, by analogy with the Simmons-Smith reaction, the carbenoid may be viewed as a tetrahedral chloro congener, arising from the series of electron transfer steps indicated in **Scheme 11**.



Scheme 11

In this particular reductive system (i.e. zinc and chlorotrimethylsilane), further reduction of the organozinc carbenoid in the presence of silicon reagent to give a geminal disilane was not observed. This was presumably as a result of prohibitive steric interactions, with 'carbenoid reactivity' being observed as a result. The fate of the organozinc carbenoid in these cases was to undergo C-H insertion reactions (*vide infra* Section 1.2.2.2), and the case of cyclooctanone, which furnished not only *cis* cyclooctene, but also bicyclo[3,3,0]octane as a result of transannular interaction (**Scheme 12**), was particularly indicative of carbenoid intermediacy. The ratio of olefin to bicyclic hydrocarbon was different from that observed in the Bamford-Stevens reaction via the free carbene, although this was not surprising since the metal might well be expected to have a considerable moderating influence.



2 : 1

55% overall

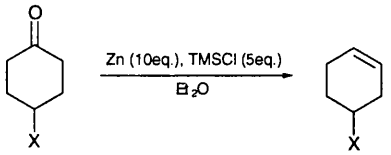
Scheme 12

Following on from these original observations, a variety of useful reactions have been developed, based on the above methods and variants thereof. In the following sections, these have been conveniently grouped from a synthetic standpoint according to the fate of the carbenoid involved.

1.2.2.2 Direct Deoxygenation of Carbonyl Compounds to Give Alkenes

The reaction of a variety of cyclic ketones with zinc and chlorotrimethylsilane offers a very simple 'one-pot' method for the conversion of this functional group to an alkene, without any need for prior formation of derivatives such as enol phosphonates, enamines, or tosylhydrazones.[54] Trimethylsilylenol ethers are not intermediates in this reaction, and can in fact be recovered unchanged after exposure to zinc and chlorotrimethylsilane. As in the case of the Clemmensen reduction performed at very low acid concentrations, alkene formation most probably arises by insertion of the organozinc carbenoid into the neighbouring C-H bond.

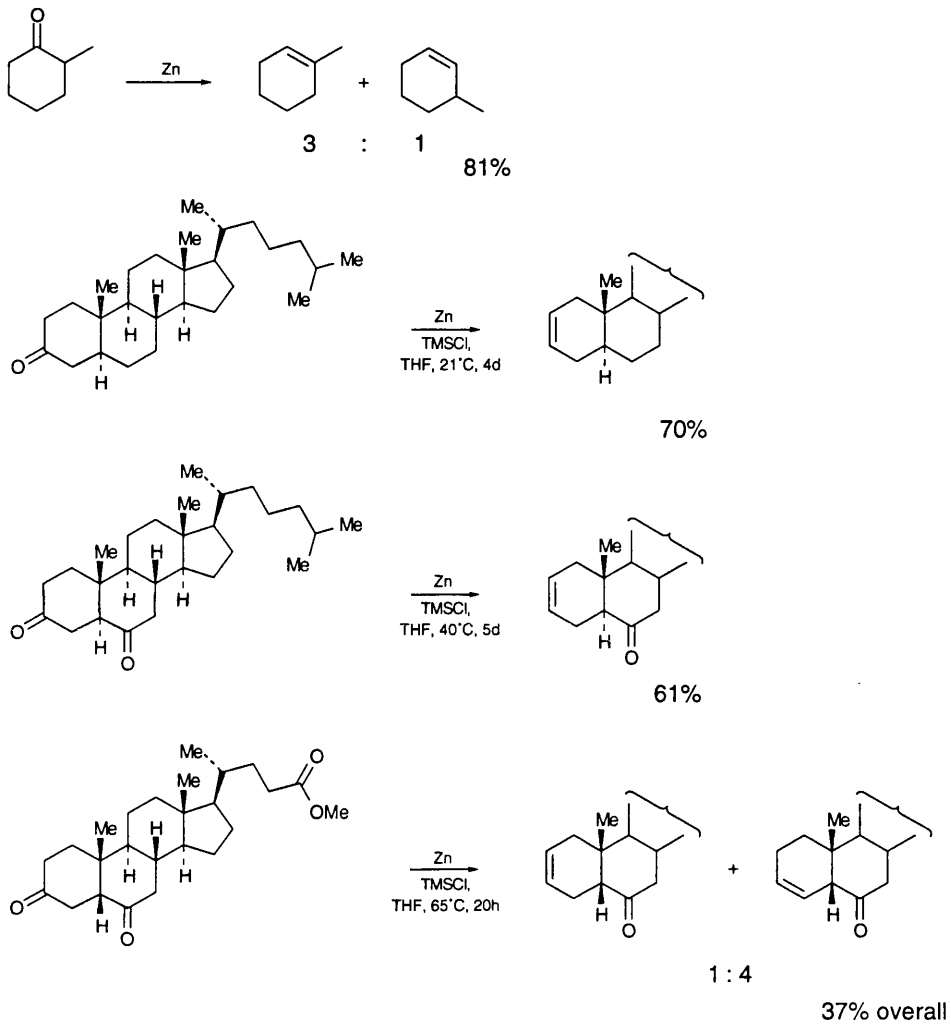
In chemoselective terms, the reaction conditions are very mild, and remote ester functionality and even alkyl bromides are tolerated, as shown by the examples in **Scheme 13**.



X = H 72%
X = Br 48%
X = OAc 60%

Scheme 13

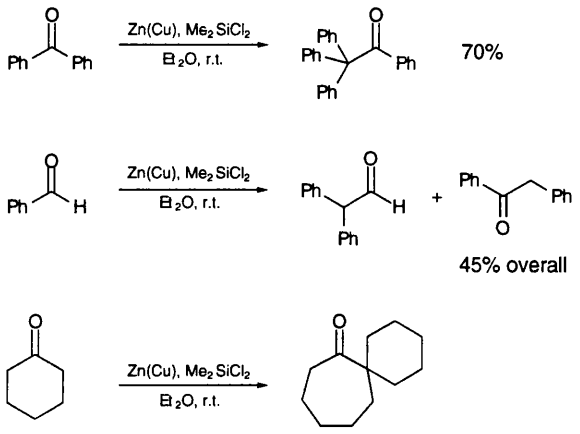
The behaviour of unsymmetrical ketones also reveals some features of interest. Thus, for 2-methylcyclohexanone,[54] although a relative series of migratory aptitudes for alkyl, hydrogen and aryl substituents remains to be established, there is a preference for formation of the more substituted alkene. A useful study by Hodge and Khan[55] in the steroidal series revealed that, as in the Clemmensen reduction, an unhindered 3-oxo steroid can react while carbonyl functionality in 6, 7, 12, 17 and 20-oxo steroids remain intact. The regioselectivity in the reactions is also noteworthy, with a preference for formation of the less strained Δ^2-alkene from the *trans* fused decalin moiety in 5α-cholestone derivatives, presumably as a result of a relatively late transition state for the C-H insertion reaction. This notion is supported by the isolation of a mixture of Δ^2- and Δ^3-alkenes from the *cis* fused methyl 3-oxo-5β-cholanate derivative (**Scheme 14**).



Scheme 14

1.2.2.3 Dicarbonyl Coupling Reactions

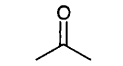
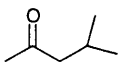
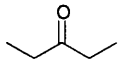
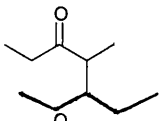
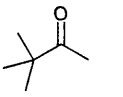
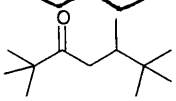
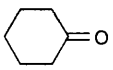
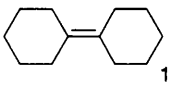
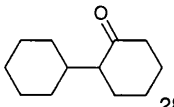
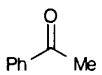
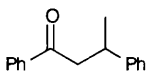
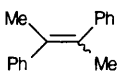
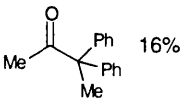
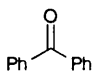
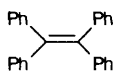
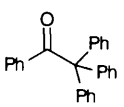
The first report of a dicarbonyl coupling reaction appeared in 1980, using a zinc copper couple and dichlorodimethylsilane as the silicon electrophile.[56] The vast majority of the products from benzophenone, benzaldehyde, and cyclohexanone, shown in **Scheme 15**, were most readily rationalised by invoking pinacolic coupling followed by rearrangement. However, the isolation of 2-phenylacetophenone was indicative of the intermediacy of stilbene epoxide, and led the authors to propose that oxiranes could be formed by reaction of a derived organozinc carbenoid with the carbonyl partner. Support for the presence of such an intermediate was adduced from a trapping experiment using cyclohexene and benzaldehyde to give 7-phenylnorcarane in 15% yield. Clearly, however, the major products need not necessarily have involved this pathway.



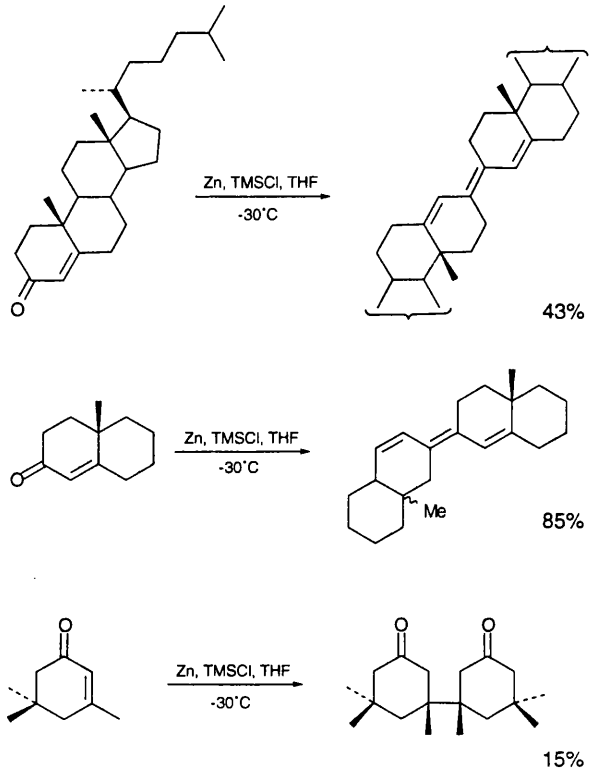
Scheme 15

Curiously, in the same year, Ando and Ikeno[57] found that it was only possible to achieve the reduction of ketones using zinc and diiododimethylsilane in dichloromethane. These authors stated that 'dichlorodimethylsilane did not show any reaction with ketones'. Their results (**Table 1**) were also at variance with those of Smith and co-workers[56] for the product(s) derived from cyclohexanone. With the exception of aromatic carbonyl compounds, the major products reported by Ando and Ikeno are most readily explicable in terms of an aldol condensation followed by dehydration and subsequent zinc reduction of the α,β-unsaturated carbonyl compound (**Table 1**).

Table 1. Products Derived From Ketone Reduction Using Zinc and Diiododimethylsilane in Dichloromethane[57]

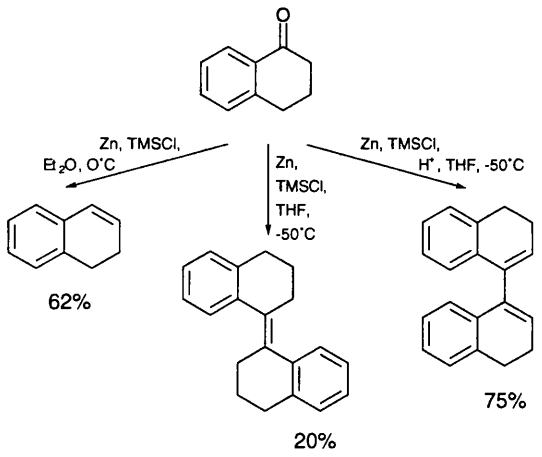
Ketone	Product	
		25%
		70%
		86%
		12%
		28%
		40%
		10%
		16%
		4%
		70%

Motherwell[58] later published results in this area in collaboration with the group of Banerjee, who had discovered that certain aryl and α,β-unsaturated carbonyl compounds could be induced to undergo a McMurry-like dicarbonyl coupling under Clemmensen conditions (chapter 1.2.1.2, Equation (9)).[42] Although several coupling reactions could be achieved in a very high yield using the basic chlorotrimethylsilane - zinc system (**Scheme 16**), other substrates such as isophorone yielded complex mixtures which included one electron induced dimerisation at the softer β-carbon atom.



Scheme 16

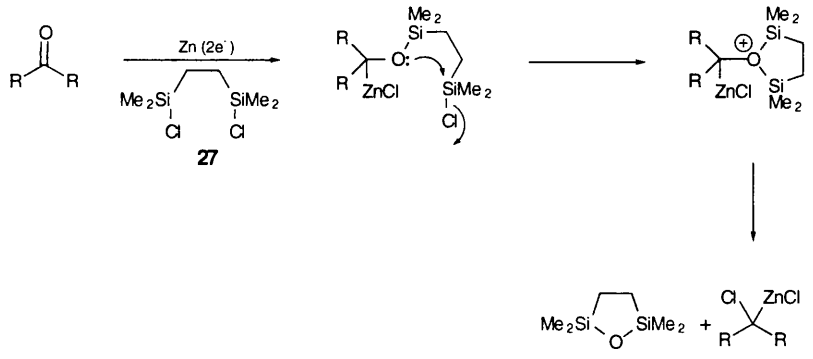
Their results strongly indicated that these reactions were not only highly substrate dependent, but also crucially influenced by the relative concentrations of substrate, reagents, and the presence or absence of small amounts of hydrogen chloride. The case of α-tetralone (**Scheme 17**), where the reaction could be channelled to unimolecular C-H insertion, to pinacolic coupling followed by dehydration, or to dicarbonyl coupling, is illustrative.



Scheme 17

A series of control experiments in the case of the formation of stilbene from benzaldehyde indicated that neither benzpinacol nor its silylated derivative was a precursor of the alkene. As in the work of Smith,[56] however, when *trans* stilbene oxide was subjected to the reaction conditions, alkene formation was observed, together with diphenylacetaldehyde, thereby implying that the epoxide was a viable intermediate. Interestingly, a sonochemical study of the coupling of aromatic and α,β-unsaturated carbonyl compounds in the presence of zinc and chlorotrimethylsilane,[59] which was published shortly afterwards, indicated that pinacolic coupling was a dominant pathway under these conditions.

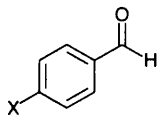
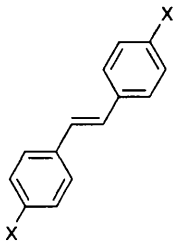
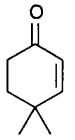
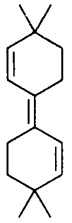
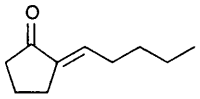
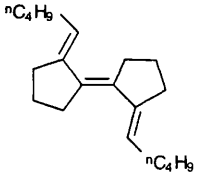
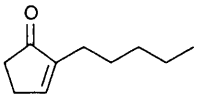
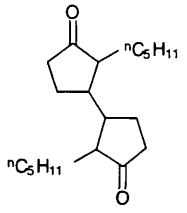
Thus, the major problem with these dicarbonyl coupling reactions was that there were competing intermolecular reactions at the one electron reduction level which reduced yields of the desired products. To overcome this problem, it was necessary to reduce the 'longevity' of the radical intermediates, thereby enhancing the efficiency of carbenoid generation. Consideration of the overall stoichiometry of the reaction, which requires two silicon electrophiles to produce hexamethyldisiloxane as a leaving group, allowed Motherwell to suggest the elegant solution shown in **Scheme 18**.[60] Quite simply, selection of 1,2-*bis*(chlorodimethylsilyl)ethane **27** as a bis electrophile would permit *intramolecular* delivery of the second necessary silicon atom.



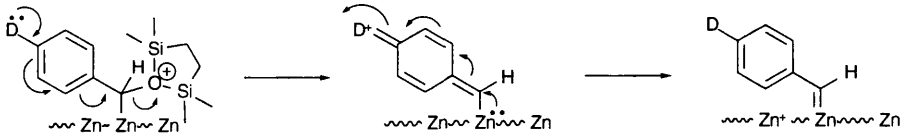
Scheme 18

The use of this reagent in the symmetrical dicarbonyl coupling reaction with aryl and α,β-unsaturated carbonyl compounds led to a significant improvement in yield.[60] Some examples are shown in **Table 2**, and reveal several aspects worthy of comment.

Table 2. Reaction of Aromatic Aldehydes and α,β-Unsaturated Carbonyl Compounds With 1,2-*bis*(chlorodimethylsilyl)ethane and Zinc

Substrate	Product	X	Yield
		OMe	79%
		Me	86%
		H	69%
		Cl	26%
			76%
			72%
			18%

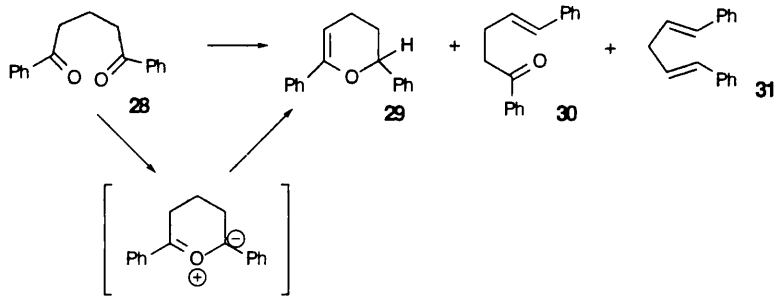
The best yields of stilbene derivatives are obtained from aromatic aldehydes possessing electron-releasing groups. This trend is also mirrored in the Clemmensen reduction of some substrates, and may well be a consequence of anchimeric assistance towards the departure of the cyclic siloxane (or water) as a leaving group, as implied in **Scheme 19**.



Scheme 19

Examination of the enone substrates reveals that the construction of oxygen sensitive s-*trans*-trienes which contain a highly hindered tetrasubstituted central double bond is possible. As with cyclopropanation studies, however (Section 1.2.2.4), the generation of an α,β-unsaturated organozinc carbenoid is very substrate dependent. This is emphasised by the two cyclopentenone derivatives, of presumably similar redox potential, which behave in a very different fashion.

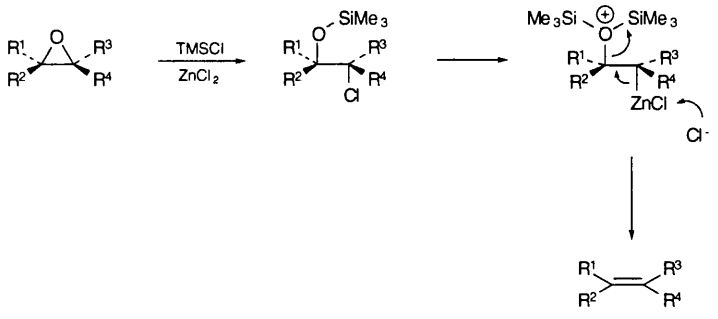
In mechanistic terms, a very significant result came from attempted intramolecular dicarbonyl coupling of **28** to give three products **29** (31%), **30** (14%), and **31** (21%) (**Scheme 20**), without any indication for formation of a cyclopentenoid.



Scheme 20

The isolation of the dihydropyran **29** is most readily understood in terms of the carbonyl ylide shown, whose ring closure to the epoxide, necessary for deoxygenation to an alkene, is retarded by a combination of electronic effects and ring strain.

At the present time, the convoluted mechanistic pathway from carbonyl to organozinc carbenoid, and then via carbonyl oxide to epoxide followed by deoxygenation, has been restricted to symmetrical coupling and to aryl and α,β-unsaturated carbonyl substrates. A separate study of the epoxide deoxygenation step using chlorotrimethylsilane and zinc has also been carried out,[61] and reveals that one of the pathways for this transformation involves ring-opening to a siloxychlorohydrin followed by zinc induced elimination of hexamethyldisiloxane, as shown in **Scheme 21**.



Scheme 21

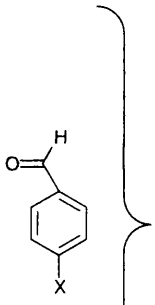
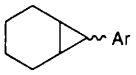
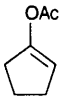
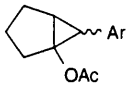
A limiting factor is that the chloride formed must be at least tertiary in order for further zinc induced elimination to occur. Benzylic and allylic substrates which are formed in the observed dicarbonyl coupling are therefore particularly favoured. While a range of unsymmetrical couplings may be possible, it is nevertheless unlikely that this approach will replace the inherently more flexible and mechanistically simpler McMurry reaction.[62]

1.2.2.4 Cyclopropanation Reactions

The formation of cyclopropanes from alkenes and carbenes or metallocarbenoids is certainly a very useful synthetic operation. On a large scale, however, the necessity for preparing or handling all but the simplest of the most often used *gem* dihalo or diazo precursors, is not an attractive proposition.

As earlier shown (Section 1.2.2.1), the first observations of useful trapping of an organozinc carbenoid by an alkene were made by Elphimoff-Felkin and Sarda.[53] At a later stage the same authors published a series of cyclopropanation reactions for a range of olefins with benzaldehyde, and for the same olefin, various *para*-substituted benzaldehydes.[63] Motherwell has also examined the cyclopropanation of alkenes with aromatic aldehydes using the zinc - 1,2-*bis*(chlorodimethylsilyl)ethane system,[64] and a selection of the results from both groups are displayed in **Table 3**. Not surprisingly, both reagent systems exhibit similar trends.

Table 3. Cyclopropanes Derived From Aromatic Aldehydes

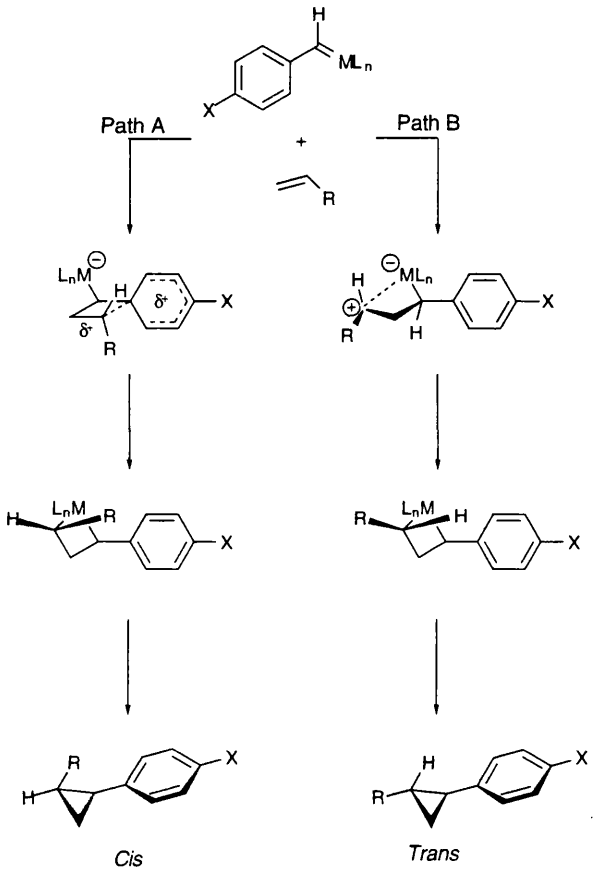
Substrate	X	Method	Alkene	Product	Yield, Ratio (*endo*: *exo*)
	OMe	A			60%, 19:1
	OMe	B			96%, 15:1
	Me	A			63%, 7.5:1
	Me	B			75%, 8:1
	H	A			43%, 5:1
	H	B			68%, 4:1
	Cl	A			43%, 4.5:1
	Cl	B			46%, 3:1
	H	A			20%, 1:1
	OMe	B			53%, 1:1

Method A: Zn, BF_3OEt_2
Method B: Zn, $(CH_2SiMe_2Cl)_2$

Once again, as in the dicarbonyl coupling reaction, yields are best for electron rich substrates, thereby lending additional credence to the idea that these participate most efficiently in

carbenoid generation. The virtual quantitative yield in the trapping of the carbenoid from *p*-anisaldehyde in the presence of only two equivalents of cyclohexene, using the zinc and silicon electrophile system is particularly noteworthy. Reactions with *cis* and *trans* but-2-ene lead to retention of the original alkene geometry, and there is a highly stereoselective tendency for formation of the more hindered isomer, which is particularly marked in the case of *p*-anisaldehyde, but apparently falls off as a function of decreasing electron release from the aromatic ring.

An elegant rationalisation of these trends has been published by Casey[65] in a study of cyclopropanation by stoichiometric tungsten alkylidenes (**Scheme 22**), and would also seem to be applicable in the case of zinc carbenoids.



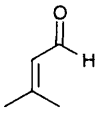
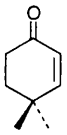
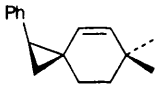
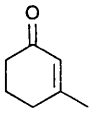
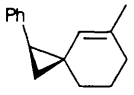
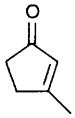
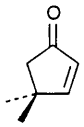
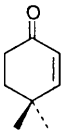
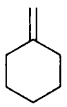
Scheme 22

Thus, approach of the alkene to the metal carbenoid always occurs in such a way as to place any substituents on the alkene *trans* to, or away from, the metal. As the bulk of the substituent increases, this tendency increases, and path B, resulting in formation of the *trans* isomer, is favoured. However, in less sterically demanding cases, opportunities exist for additional electronic stabilisation of the developing positive charge on the alkene, through electron donation via the *ipso* carbon of the aromatic ring, and path A, leading to the more hindered *cis* substituted cyclopropane, is then followed. This model also rationalises the general observation that yields in the metallocarbenoid cyclopropanation of *trans*

disubstituted alkenes always tend to be lower than in the case of their *cis* counterparts, as a result of increased demands in steric approach control.

Motherwell has also examined the behaviour of non-aromatic α,β-unsaturated organozinc carbenoids in cyclopropanation reactions.[64] This was a particularly interesting study as conventional wisdom relating both to the isolation of cyclopropanol acetates by Elphimoff-Felkin,[66] and to the reductive ring contractions observed under Clemmensen conditions (Section12.1.3) would argue that carbenoid reactivity should not be observable. The results obtained, however, as shown in **Table 4**, indicate that a useful range of carbenoids from both cyclic and acyclic enones and enals may be trapped.

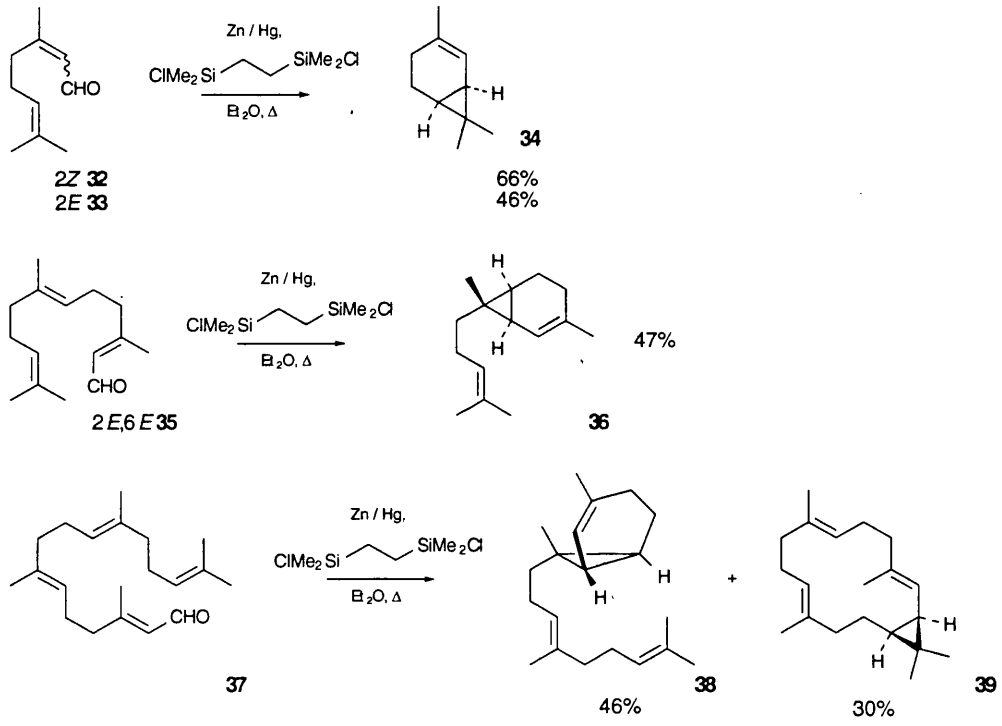
Table 4. Cyclopropanes Derived From Alicyclic Ketones and Acyclic Aldehydes

Carbonyl Compound	Alkene	Product	Yield, Ratio (*cis*:*trans*)
			53%, all *cis*
			55%, 20:1
			59%, 11:1
			44%, 1:1
			19%, 1:1
			34%

A curious prerequisite for successful generation and trapping of these vinylidene organozinc carbenoids is the presence of some degree of steric crowding around the β-olefinic terminus of the enone or enal. Thus, attempted cyclopropanation reactions using 'parent' systems such as cyclohexenone, cyclopentenone and cyclopenten-1-carboxaldehyde, were without success. From the stereochemical standpoint, the *cis* selective preference observed in the case of aromatic aldehydes also seems to be maintained in the cases of the isoprenoid enal and cyclohexenone substrates. It is, however, absent in the more planar cyclopentenones,

suggesting perhaps again that the three-dimensional shape around the β-terminus has a profound role in governing reactivity.

More recently, Motherwell has extended this work to intramolecular cyclopropanation reactions of carbenoids derived from terpenoid enals.[67] Using high dilution conditions (achieved by the slow addition of a solution of the terpenoid enal to the other reagents), neral **32** or geranial **33** could be cyclised to Δ^2-carene **34**, farnesal **35** (both the 2*Z*,6*E* isomer *and* the 2*E*,6*E* isomer) cyclised to sesquicarene **36**, and, perhaps most dramatically, geranylgeranial **37** cyclised to the macrocycle casbene **39** (30%), although the prenyl homologue of sesquicarene **38** was the major product (46%) (**Scheme 23**).



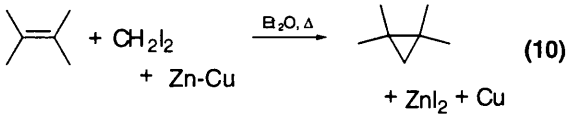
Scheme 23

The loss of geometrical integrity around the initial enal unit was explained by the authors in terms of a vinyl zinc carbenoid, with considerable dipolar or ionic character, that had as a consequence a very low energy barrier for *Z*,*E* isomer interconversion (**Scheme 24**).

Scheme 24

1.3 The Simmons-Smith Reaction and Furukawa Modification

The Simmons-Smith reaction, first reported in 1958,[16] involves the cyclopropanation of an alkene with a reagent prepared *in situ* from a zinc-copper couple and diiodomethane (Equation **(10)**). The reaction is stereospecific with respect to the geometry of the alkene, and unlike reactions involving free carbenes, is generally free from side reactions.



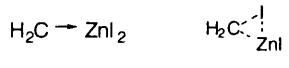
(10)

Since that time, it has become the most frequently used method for the preparation of simple cyclopropanes. The reaction has been reviewed very comprehensively,[68] and hence for the purposes of this review an overview of the more recent key synthetic modifications and applications of the reaction, as well as the methodological advances, will be presented. Of these, the most significant variation lies in the use of diethyl zinc and diiodomethane in place of a zinc couple and diiodomethane (or substituted diiodides). First reported by Furukawa,[69] this adaptation will be considered in this section, as it is frequently used to provide a comparison with the Simmons-Smith reagent system. The other reagent system of importance involves the reaction of diazomethane with zinc iodide to give a cyclopropanating agent, and will be discussed in Section 1.4.

1.3.1 The Simmons-Smith Reaction

In their first report of the reaction,[16] the authors obtained cyclopropanes in yields ranging from 10-70%, depending on the type of couple employed. They considered that the reactive intermediate, i.e. the cyclopropanating agent, was iodomethylzinc iodide, and that it would be displaced by the π-bond of an olefin to give a cyclopropane and zinc iodide. A full paper was later published on the reaction,[70] and was followed by two papers which sought to define the nature of the intermediate, and the optimum conditions for synthesis.[71,72]

Studies indicated that diiodomethane formed a 1:1 complex with zinc (from a zinc-copper couple), which existed as a colourless homogeneous solution, capable of forming cyclopropanes with alkenes.[70] It was proposed that this complex may best be represented as **40** or **41**, and was also shown in the same study that the copper simply acted via activation of the zinc surface, and had no other role.



40 **41**

Mechanistically, it was suggested that the reaction proceeded by a one-step methylene transfer , where the quasi-trigonal methylene group of the active cyclopropanating agent **41** adds to the alkene, with essentially simultaneous formation of two bonds. This interpretation fitted well with the following experimental observations: (i) few side reactions are found, suggesting that free methylene is not an intermediate; and (ii) the reaction follows second-order kinetics, in accordance with a bimolecular process; and, cyclopropane formation is stereospecific. It was also shown that the iodomethylzinc iodide behaves as a weak electrophile, since alkene reactivity increased with alkyl substitution (although, of course, at the price of a balanced steric payoff).

1.3.2 The Furukawa Modification

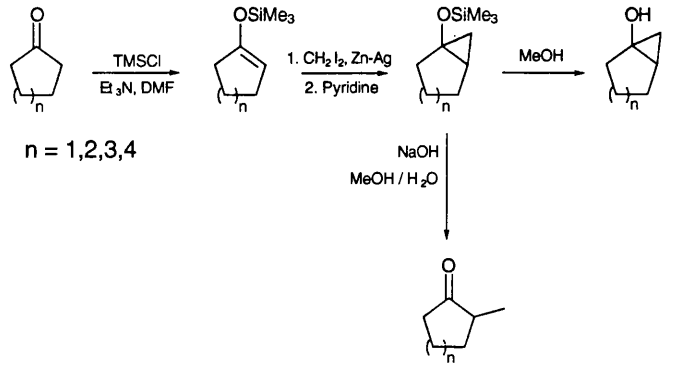
In many ways, the reagent generated by Furukawa's method,[69] is very similar to the Simmons-Smith reagent. The major advantages of Furukawa's system are the following: (i) the reaction is homogeneous; (ii) reagent formation is rapid under mild conditions; (iii) it is suitable for the cyclopropanation of vinyl ethers and similar substrates that are prone to undergo polymerisation under Simmons-Smith conditions;[73] and (iv) the reaction is not restricted to methylene transfer, but may also be used with alkyl and phenyl carbenoids.[74] As with the Simmons-Smith reaction, cyclopropanes were found to form stereospecifically. The observed *syn*-selectivity was augmented with increased electron donating ability of the substituents on the carbenoid.[75,76] It was also found that electron-donating substituents on the olefin increase both the yield and rate of reaction, strongly indicating that the cyclopropanating agent is electrophilic (and hence analogous to the Simmons-Smith reagent).[77] Reactions were found to give the highest yields when a hydrocarbon solvent was employed. Polar solvents, such as ethers, gave far lower yields.[73]

Denmark has made an extensive study of the nature of the reagent generated by the Furukawa procedure.[78,79] The research demonstrated that the highly reactive *bis*(halomethyl)zinc reagents generated are stabilised by coordination to ethers or acetone. The first X-ray crystallographic analysis of an (iodomethyl)zinc complex was also undertaken, and gave a strong indication as to the structural parameters of reagent stabilisation by proximal oxygenated functionality.

1.3.3 A Synthetic Overview

The Simmons-Smith reaction provides a route for the introduction of a methyl group to a molecule bearing an alkene unit suitable for cyclopropanation. Cleavage of such an introduced cyclopropane furnishes an angular methyl group. Conia and co-workers published some very elegant work on this theme.[80-83] In essence, by a three step sequence, it was possible to introduce an α-methyl group to a ketone. A silyl enol ether was generated from the desired ketone, and this cyclopropanated with zinc-silver couple and diiodomethane, using a pyridine work-up. The cyclopropane thus generated could then undergo either a

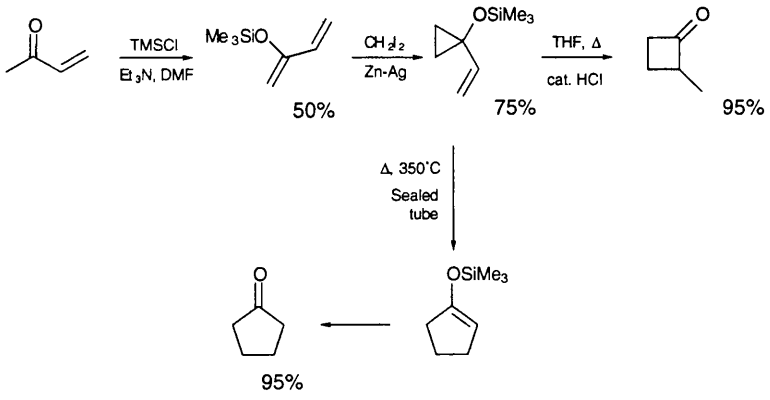
standard deprotection sequence to yield the cyclopropanol, or hydrolysis to yield the α-monomethylated ketones (**Scheme 25**). The reaction sequence was found to work for cyclopentanones, cyclohexanones, cycloheptanones and cyclooctanones, as well as aldehydes.[80] In the case of unsymmetrical ketones, it was possible, through selection of the appropriate silyl enol ether, to orientate methylation to the α or α' position. In all cases, the yields were good.



Scheme 25

When 2-trimethylsiloxycycloalka-1,3-dienes were examined,[81] it was found that monocyclopropanation occurred almost exclusively on the double bond bearing the trimethylsiloxy group (using 1.1 equivalents of diiodomethane). The 2-trimethylsiloxycycloalka-1,3-dienes were prepared from the corresponding α,β-unsaturated ketones. In the presence of 3 equivalents of diiodomethane, cyclopropanation of both double bonds occurred in 80-90% yields.[83] The relative stereochemistry of the two cyclopropane rings was believed to be *anti*, since the second cyclopropanation reaction of the 3,4-alkene would be directed to occur on the same face as the siloxy group.

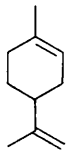
Using the same methodology, Conia accessed cyclobutanones and cyclopentanones via the rearrangement (either acid catalysed or thermal) of 1-siloxy-1-vinyl cyclopropanes, formed via the cyclopropanation of silyl enol ethers of cisoid or labile α-ethylenic ketones (**Scheme 26**).[82]



Scheme 26

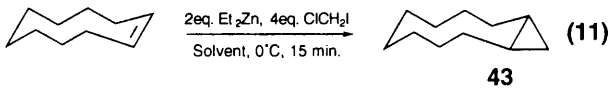
Since the initial studies made on the Simmons-Smith reagent, there have been several studies on the influences which affect its reactivity. Recently, work was published comparing the regioselectivities of the mono-cyclopropanation of such substrates as limonene **42** and 4-vinylcyclohexene with the classic Simmons-Smith reagent (diiodomethane, zinc and copper (I) chloride in diethyl ether), the modified Furukawa conditions (diiodomethane with diethyl zinc in toluene) and the Yamamoto conditions[84] (diiodomethane and triethylaluminium in toluene-dichloromethane).[85] The relative reactivity of dibromomethane, zinc and copper (I) chloride in diethyl ether was also examined. Earlier results had suggested that CH_2I_2 - Zn-Cu gave rise to an electrophilic cyclopropanating agent, which was sterically hindered,[71] whilst the Furukawa system was known to provide a less sterically hindered reagent, especially in non-coordinating solvents. The final triethylaluminium based system[84] had been found to cyclopropanate exclusively at an alkene distant from a hydroxyl group, the opposite of the other two systems, although this facet of the system's reactivity was not relevant in this particular study.

Thus it was found that in the case of limonene **42**, the Et_2Zn - CH_2I_2 system exhibited the lowest regioselectivity for mono-cyclopropanation, and was hence determined to have the lowest steric requirements of all the systems examined. CH_2I_2 or CH_2Br_2 - Zn-Cu both gave similar regioselectivities, with an average of 3:1 preference for the exocyclic disubstituted alkene. The regioselectivity of the Et_3Al system was found to lie between the other two systems. These findings were confirmed with 4-vinylcyclohexene.



42

Denmark and co-workers made a comparison of (chloromethyl)- and (iodomethyl)zinc as cyclopropanation reagents in the modified Furukawa process,[86] using the reaction shown in Equation **(11)**. Initially, the influence of the solvent was examined. Dichloroethane was found to be the superior solvent for the reaction, giving **43** in a yield of 94%, while other solvents assessed included diethyl ether (<1%), toluene (75%), benzene (83%) and hexane (7%).



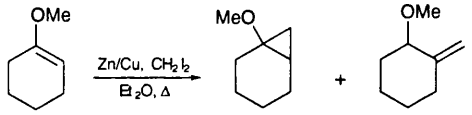
(11)

43

In the cyclopropanation of a variety of alkenes using diethyl zinc and either $ClCH_2I$ or CH_2I_2, $ClCH_2I$ was found to give far superior reaction rates. NMR spectra of the solution state species formed indicated that each gave rise to a different organometallic species. As is generally expected, the presence of an allylic oxygen led to a large rate enhancement, and

more remote neighbouring oxygen atoms were also found to direct the stereochemical course of the reaction. The evident superiority of the chloromethylzinc reagent examined here over the more normal iodomethylzinc would suggest that this should become the reagent of choice for Furukawa modified Simmons-Smith cyclopropanations.

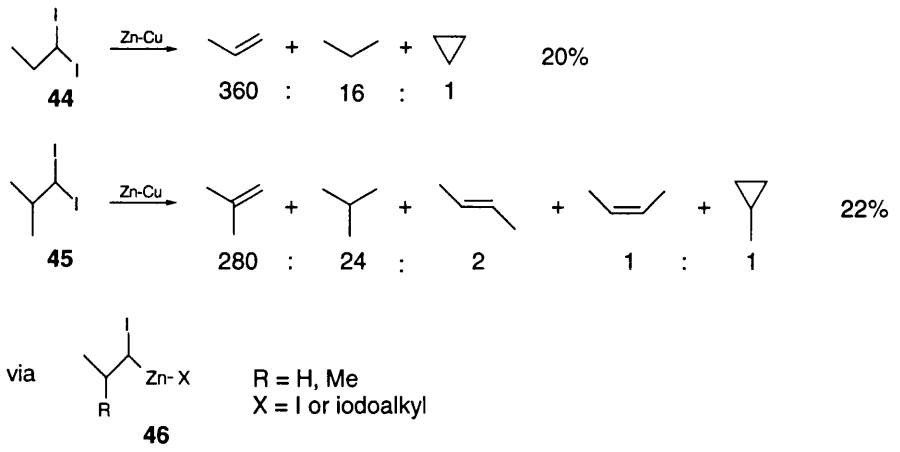
The Simmons-Smith cyclopropanation of enol ethers has been found to give different results depending on the concentration of the reaction mixture.[87] Under dilute conditions (~0.5M with respect to the substrate), it was found that cyclopropanation occurred exclusively, whereas under much higher concentrations, allylic ethers were generally found to be the exclusive product (**Scheme 27**). The allylic ether products were assumed to have formed via zinc iodide catalysed rearrangement of the initially formed cyclopropane. The isomerisation step was also examined, although less successfully, using diiodomethane and diethylzinc. It was found that although the isomerisation of the cyclopropane occurred, the resulting allyl ether then underwent rapid cyclopropanation itself. In general, the isomerisation reaction proceeds more smoothly in less coordinating solvents.



Concentration	Product Ratio	Total Yield (%)
~0.5M	98 : 2	72
~1.25M	83 : 17	59
~2.0M	2 : 98	66

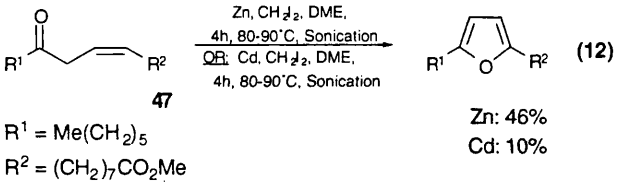
Scheme 27

In an early study, the carbenoid nature of the Simmons-Smith cyclopropanation reagent was shown by the ability of a modified reagent to undergo intramolecular C-H insertion reactions.[88] The reagents concerned were prepared from the reaction of 1,1-diiodopropane **44** or 1,1-diiodo-2-methylpropane **45** with a zinc-copper couple. After a short induction period, volatile products were found to form (**Scheme 28**), and were proposed to have arisen via the intermediacy of **46**.



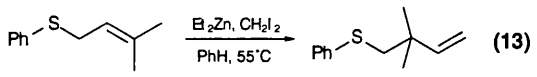
Scheme 28

The heterogeneity of the Simmons-Smith reaction would suggest that reactivity would be increased enormously by sonication. Repic and Vogt undertook such a study,[89] and found that whereas the Simmons-Smith reaction normally requires prior activation of the zinc, i.e. formation of a couple (a capricious process), by sonicating the reaction, ordinary unactivated zinc is sufficiently reactive. They also found that it was possible to cyclopropanate alkenes with consistently higher yields than in the literature. It is surprising in view of these results that sonication of such reactions has not met with wider use. Lie Ken Jie and Lam later published on the influence of sonication in the cyclopropanation of unsaturated long chain keto esters, and the effect of changing the metal employed (zinc versus cadmium versus copper).[90] It was found that under sonication at 80-90°C in DME, copper metal and diiodomethane were able to effect alkene cyclopropanation. Interestingly, when **47** was sonicated in the presence of either cadmium or zinc and diiodomethane, furan formation was observed (Equation **(12)**).



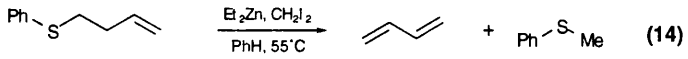
Sibille and co-workers examined what may be considered an electrochemical version of the Simmons-Smith reaction.[91] The optimised reaction conditions were found to be a 9:1 dichloromethane : dimethylformamide solvent mixture, using a carbon fibre cathode and zinc anode. Zinc bromide was then generated *in situ* by the electrolysis of 1,2-dibromoethane, in the presence of the alkene, and then dibromoethane added to facilitate cyclopropanation. In this manner cyclopropanes were obtained in yields ranging from 8-75%, with the best yields for allylic or unfunctionalised alkenes. *Syn* addition was observed in all cases. The authors suggested that the cyclopropanating agent formed in this process is a zinc carbenoid 'as proposed for the classical chemical reaction', on the basis of similarities in reactivity observed.

The use of allyl thioethers[92] and α-oxoketene dithioacetals[93,94] as substrates in the Simmons-Smith reaction has led to some interesting reactions. It was found that the cyclopropanation of cyclohexene was completely suppressed in the presence of an allyl or alkyl thioether using diiodomethane and either a zinc-copper couple, zinc-silver couple or copper powder.[92] However, taking 3-methyl-1-phenylthio-2-butene, diethyl zinc and diiodomethane, a methylene homologation reaction is observed, which presumably proceeds via the formation of a sulfur ylide and a [2,3]-sigmatropic rearrangement (Equation **(13)**). If a homoallylic sulfide is used, it can form an ylide capable of elimination to form dienes (Equation **(14)**).



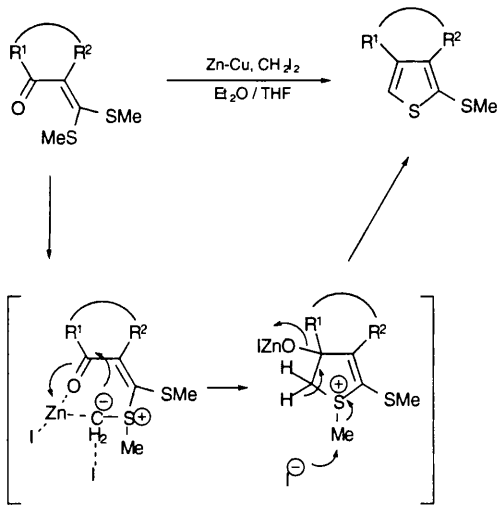
(13)

80%



(14)

The attempted cyclopropanation of α-oxoketene dithioacetals gave rise to a new route to 3,4-substituted and annelated thiophenes.[93,94] In essence, under normal Simmons-Smith conditions, the carbenoid intermediate forms a sulfur ylide with the α-oxoketene dithioacetal, which then reacts intramolecularly to yield a thiophene (**Scheme 29**). The reaction was found to be unaffected by the presence of additional alkene units, and in the examples examined, yields of the thiophenes ranged from 53-65%. In some cases, dethiomethylation of the resulting thiophene was possible using Raney nickel in methanol.



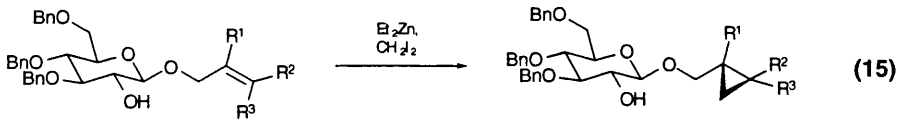
Scheme 29

It is thus possible that a whole range of ylide chemistry could be accessed via the zinc carbenoid formed in the Simmons-Smith reaction. One interesting aspect of this is that in the Simmons-Smith reaction a neighbouring oxygen (alcohol) serves to promote the rate of cyclopropanation, an effect considered to be due to coordination of the zinc via the oxygen.

There have apparently been no similar examples of oxonium ylide chemistry, which reflects on the relative availability of the lone pairs of electrons in divalent sulfur and oxygen, and the rate of cyclopropanation versus ylide formation.

The goal of many of the more recent studies on the Simmons-Smith reaction has been to achieve an enantioselective cyclopropanation reaction. Nearly all strategies to date have involved the use of a chiral auxiliary, and in the majority of cases the auxiliary contains oxygenated functionality capable of coordinating to the incoming zinc carbenoid. Thus, a continuing theme in this section will be the directing effect of oxygenated substituents in the Simmons-Smith reaction.

Charette has published some particularly elegant work recently, employing carbohydrates as a chiral auxiliary to achieve a highly stereoselective cyclopropanation of allylic alcohols.[95,96] This methodology capitalises on the fact that one of the oxygen atoms in the auxiliary (the free hydroxyl at the 2-position) proximal to the alkene undergoes direct attack by the reagent to facilitate prior coordination of the zinc. This anchoring of the reagent was found to give good diastereoselection and high yields of the cyclopropane (Equation **(15)**). A large excess of reagents is required, and the exact reagent ratios were found to be important.

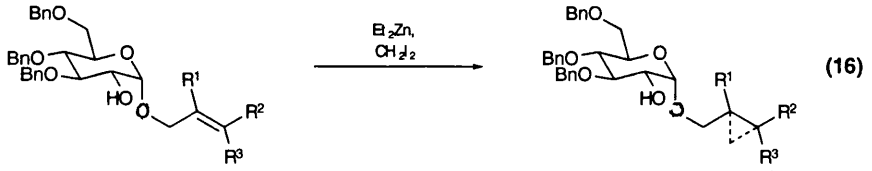


(15)

Yields > 97%
Diastereoselectivities > 50:1

Cleavage to the cyclopropylmethanol was achieved via the conversion of the product into the corresponding triflate, and then heating in DMF-water at 160°C, yielding the free cyclopropane (90%) via a novel fragmentation of the 2-hydroxyglucopyranoside. The other enantiomer of the cyclopropane was also available by using a pseudo mirror image of *D*-glucose - 6-deoxy-*L*-glucose, with the drawback that this was only available via a relatively long synthesis, starting from expensive *L*-rhamnose.

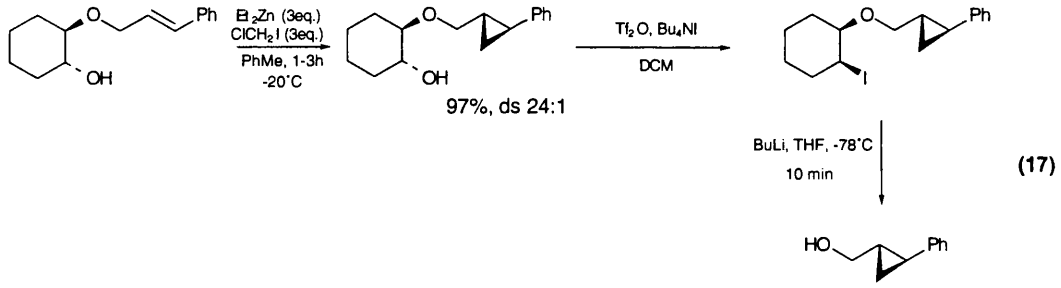
However, using the auxiliary with the opposite anomeric configuration also afforded the cyclopropane of opposite relative configuration, and preliminary results indicated that this reaction proceeded with a good level of asymmetric induction (diastereoselectivity >12:1, yield >97%). Charette pursued these early results,[97] and after 'optimisation', carrying out the cyclopropanation using diethyl zinc and diiodomethane in *t*-butylmethylether at 0 °C gave consistently high yields (>83%) and diastereoselectivities (>11:1) for the substrates examined (Equation **(16)**).



(16)

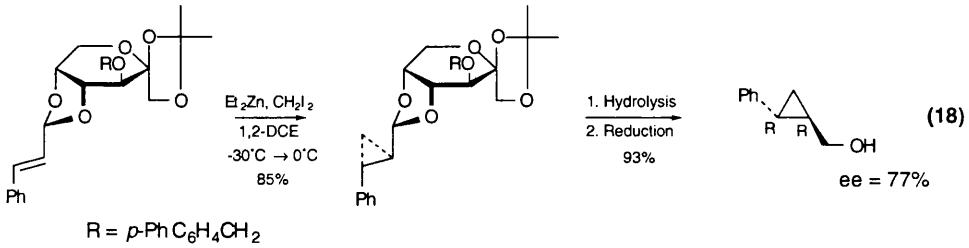
Yields > 83%
Diastereoselectivities > 11:1

Developing and simplifying this carbohydrate strategy, Charette later published results on the use of 1,2-*trans*-cyclohexanediol as the chiral auxiliary for the asymmetric cyclopropanation of allylic ethers.[98] After optimisation studies the auxiliary was found to give a high level of stereochemical induction (>20:1) if *bis*(chloromethyl)zinc was used instead of *bis*(iodomethyl)zinc. In this instance, in contrast to the sugar-based auxiliaries, only 3 equivalents of the reagent in toluene were necessary to maximise yields and diastereoselection. Furthermore, protection of the secondary alcohol was found to be detrimental to the diastereoselectivities, indicating the pivotal importance of zinc coordination to the free hydroxyl group on the stereochemical outcome. A typical reaction, and the sequence for removal of the auxiliary, is shown in Equation **(17)**.



(17)

More recently, a Korean group also examined the potential of an asymmetric cyclopropanation reaction of α,β-unsaturated carbonyl compounds using a carbohydrate derived from D-fructose as the chiral auxiliary.[99] The best results in terms of enantioselectivity and chemical yields were obtained with the *endo* acetals of 1,2-*O*-isopropylidene-3-*O*-(*p*-phenylbenzyl)-β-D-fructopyranose, although the diastereoselectivity was not good in all cases, possibly caused by *endo* to *exo* isomerisation during the cyclopropanation. The reaction sequence and auxiliary removal are shown in Equation **(18)**. Overall, the length of the synthetic sequence necessary to access the auxiliaries, and the problems encountered with diastereoselectivity, make it unlikely that this method will be adopted widely.

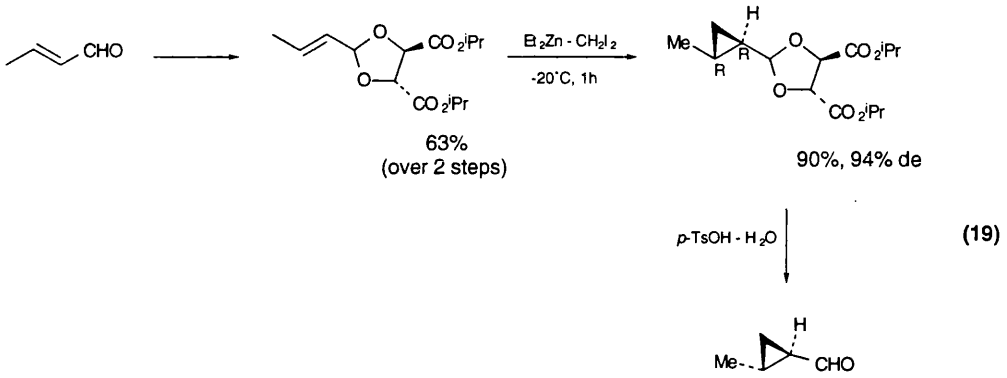


(18)

ee = 77%

R = *p*-Ph $C_6H_4CH_2$

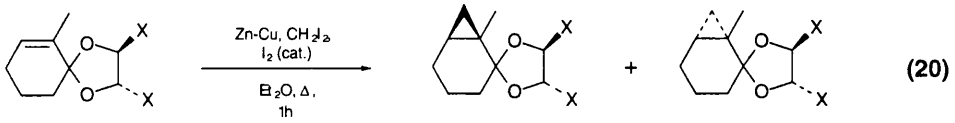
A considerable body of work has been published using homochiral ketals as auxiliaries in the cyclopropanation reaction. The first results in this area were published simultaneously by Yamamoto[100] and Mash.[101] Yamamoto had employed an acetal of an α,β-unsaturated aldehyde, derived from diisopropyl tartrate, as the chiral auxiliary (since this substrate was found to give slightly higher enantiomeric excesses than that derived from diethyl tartrate). Cyclopropanation was then carried out using diethyl zinc and diiodomethane. Yields were high, as were the diastereomeric excesses (Equation **(19)**). The acetal could be transformed to the aldehyde (*p*-TsOH-H_2O) or to the ester (ozonolysis). The ready availability of both the (*R,R*)- and (*S,S*)-tartaric acid esters allows the synthesis of both enantiomers of cyclopropanes from α,β-unsaturated aldehydes.



(19)

Yamamoto then used this methodology in the synthesis of (5*R*,6*R*)-5,6-methanoleukotriene A_4.[102] In the same paper results were also presented on the use of acetals derived from (2*R*,4*R*)-2,4-pentanediol, which gave the corresponding (*R,R*)-cyclopropane in good to high yield (69-95%) and moderate diastereomeric excess (29-75%). The mechanism for the action of these auxiliaries was suggested to be via the coordination of the incoming cyclopropanating agent to the more exposed acetal oxygen on the auxiliary.

Mash employed homochiral cycloalkenone ketals, prepared by the direct ketalisation of the corresponding α,β-unsaturated ketones and aldehydes using 1,4-di-*O*-benzyl-*L*-threitol as the diol component.[101] These ketals were then cyclopropanated using zinc-copper couple, diiodomethane and a crystal of iodine in refluxing diethyl ether. After a short reaction time (~1 hour), yields were found to be in the range 90-98%, with, in the case of the cycloalkenone ketals, a good diastereomeric excess (Equation **(20)**). However, acyclic ketals derived from α,β-unsaturated aldehydes were found to give very poor diastereoselection.



(20)

X = CH_2OCH_2Ph 99% 20:1 dr

In a later paper the methodology was expanded successfully to synthesise tricyclo[m.n.1.0]-alkanones as well as bicyclo[m.1.0]-alkanones of the sort shown in Equation **(20)**.[103] As with Yamamoto's method, both cyclopropane enantiomers could be accessed by using either the *L*- or *D*- forms of 1,4-di-*O*-benzyl-threitol, available from natural and unnatural tartaric acids. The ketal was readily hydrolysed in acidic methanol, and the auxiliary easily recovered. The stereochemistries of the cyclopropanes thus synthesised suggested that a common mode of reagent delivery is operative (Figure **1**). The major drawback, however, with this method, was found to be that the diastereomers produced were neither crystalline nor chromatographically separable, and so it was not possible to obtain enantiomerically pure cyclopropyl ketones by this route.

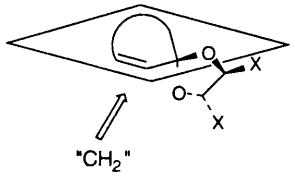
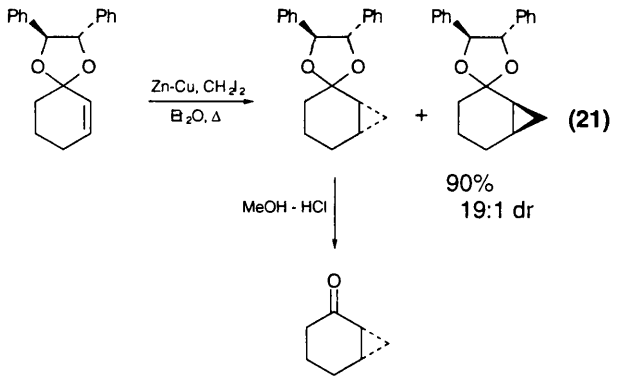


Figure 1

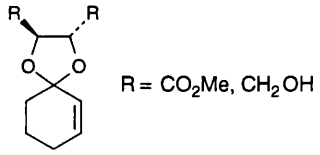
This work was later applied by Mash in the total synthesis of (+)-modhephene, using a slightly modified auxiliary. The first steps in the synthesis involved an enantioselective cyclopropanation, which, on ring opening of the cyclopropane, eventually furnished an angular methyl group.[104]

Mash went on to examine other diols, which allowed more successful separation of the diastereomers produced, and all recent work has employed the diol (*S,S*)-(-)-hydrobenzoin, giving the corresponding 2-cycloalken-1-one (*S,S*)-(-)-hydrobenzoin ketals. These were found to give good yields of the cyclopropane, and high diastereomeric ratios (Equation **(21)**).[105]



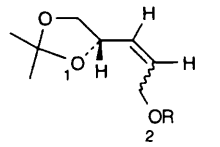
An interesting study was also made on the influence on the diastereoselectivities of having strongly Lewis basic oxygenated appendages on the ketals **48**.[106] These were found to both lower yields and diastereoselectivity, and the results were in contrast to those of Yamamoto, shown in Equation **(19)**.[100] Yamamoto had reported similar yields and diastereomeric

excesses to Mash, who was employing either ether or alkyl appendages on the ketal, using diisopropyl tartrate as the chiral auxiliary, i.e. R = $CO_2{}^iPr$ in **48**. Mash discusses the mechanistic implications of the observed effects. Studies were also carried out on the effect of ring conformation on diastereoselectivity.[107]

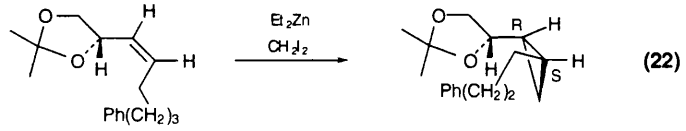


48

Taguchi's group recently published work on the cyclopropanation of allyl alcohols derived from (*R*)-2,3-*O*-isopropylideneglyceraldehyde **49**.[108] Using diethyl zinc and diiodomethane, they found that for both the *Z* and *E* isomers, diastereoselectivity for the protecting groups R increased in the order Bn < MOM < TBDPS, and that the *Z* isomers gave consistently higher diastereoselectivities. Interestingly, when the allylic alcohol group was replaced by a bulky alkyl group, the diastereoselectivity increased to >98%, indicating that the incoming carbenoid reagent was not coordinating to O-2, only O-1 (Equation **22**). This method again suffers from the drawback of so many of these chiral auxiliary strategies in that a three step deprotection protocol is required to afford the cyclopropylmethanol unit.

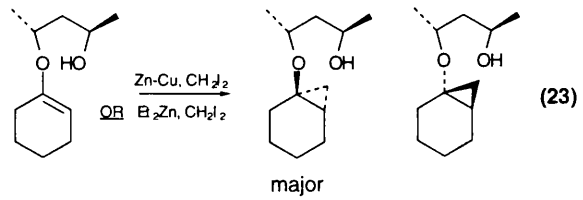


49



(22)

Tai and co-workers examined the use of 2,4-pentanediol or 2,6-dimethyl-3,5-heptanediol as an auxiliary. Early work employing 2,4-pentanediol gave moderate yields (~55%) and high diastereomeric excesses (>95%) (Equation **(23)**).[109] The use of both the classic Simmons-Smith reagent, and the Furukawa modified procedure was examined. The chiral auxiliary was removed by PCC oxidation followed by treatment with potassium carbonate in methanol.

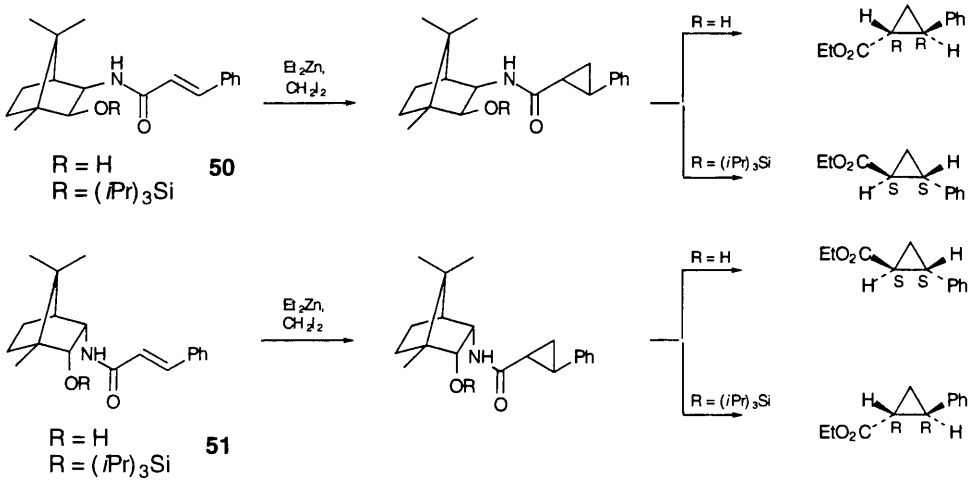


(23)

major

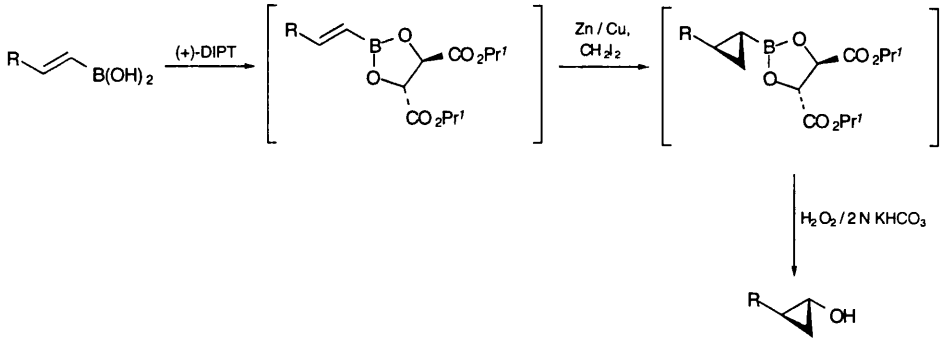
Using the more sterically congested chiral auxiliary 2,6-dimethyl-3,5-heptanediol, and cyclopropanating using diethylzinc and diiodomethane in diethyl ether at 20°C, yields were elevated up to 86%, with excellent diastereomeric excesses (>99.5%).[110] The major drawback to this auxiliary appears to be that, as with the 2,4-pentanediol derivative, a two step deprotection protocol is necessary.

In a departure from the strategies adopted by most groups working in this area, Tanaka has found it possible to diastereoselectively cyclopropanate α,β–unsaturated carboxamides using *exo*- and *endo*-3-amino-2-hydroxybornanes as chiral auxiliaries (**50** and **51** respectively).[111] However, even with solvent variation, yields were modest in most cases, with very variable diastereoselectivities. Using diethyl tartrate as an additive elevated the diastereomeric excess to 98%, although it seems likely that such results could be achieved using diethyl tartrate in the absence of the chiral auxiliary![112] Interestingly, by using the *O*-tri-isopropyl derivatives of the amides, a complete reversal of diastereoselectivity was observed (**Scheme 30**).



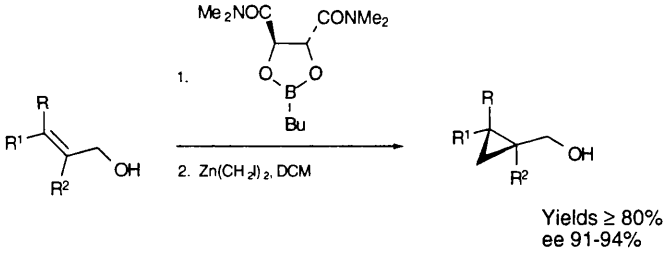
Scheme 30

Imai and co-workers have reported the asymmetric cyclopropanation of alkenyl boronic esters.[113] The strategy they employed was very simple: an alkenylboronic acid was reacted with an inexpensive 'chiral modifer' such as (+)-diethyl tartrate (DET), (+)-di-isopropyltartrate (DIPT) or (+)-*N,N,N',N'*-tetramethyltartaramide (TMTA), and the resulting ester then reacted with di-iodomethane and a zinc - copper couple in refluxing diethyl ether. The crude product mixture would then be treated with 30% hydrogen peroxide and 2 N aqueous potassium bicarbonate to afford the cyclopropanol. Although yields were modest (41-67%, over the complete sequence), the enantiomeric excesses were good (73-94%) (**Scheme 31**).



Scheme 31

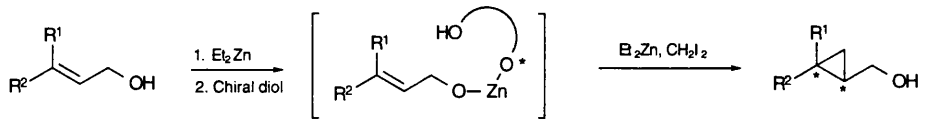
Charette later took this idea one stage further, and used a dioxalborolane (prepared from (*R,R*)-(+)-*N,N,N',N'*-tetramethyltartaric acid diamide and butylboronic acid) as a chiral ligand in the cyclopropanation of allylic alcohols using a preformed solution of *bis*(iodomethyl)zinc.[114] The results were very encouraging, and the scope of the reaction found to be very broad, giving high enantioselectivities and yields with *trans-*, *cis-*, and trisubstituted double bonds (**Scheme 32**). Several important points were noted: (i) the alcohol group in the allylic alcohol must not be protected, as it appears that the first stage in the reaction is the conversion of the alcohol into an (iodomethyl)zinc alkoxide; (ii) the presence of basic groups on the ligand is crucial for obtaining high enantioselectivities - using the dioxaborolane derived from (*S,S*)-(-)-1,2-diphenyl-1,2-ethanediol led to racemic material in the cyclopropanation. However, in a later report[115] it was noted that the exotherm was such on the addition of the preformed *bis*(iodomethyl)zinc to the other reagents, that on an 8 mmol scale a violent explosion resulted. Using instead a homogeneous solution of $Zn(CH_2I)_2 \cdot DME$ complex in dichloromethane, and adding it to the other reagents at a rate which permitted the internal temperature to be maintained at -10 °C, it was possible to achieve results which were directly comparable to the initially reported method.



Scheme 32

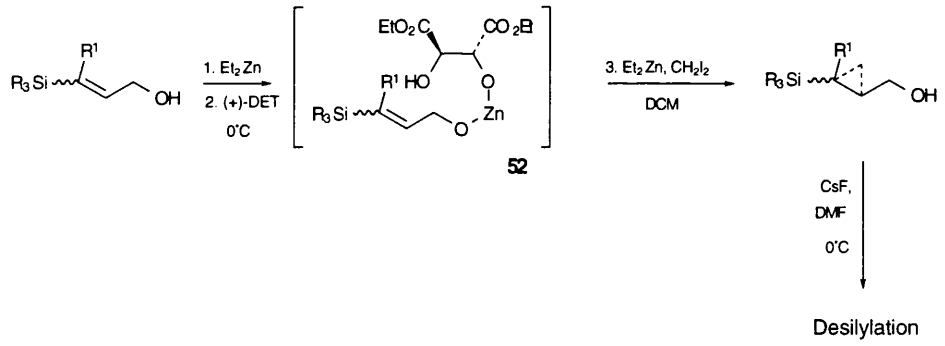
In an interesting variant on the chiral auxiliary theme Fujisawa and co-workers found that they were able to take an allylic alcohol, form *in situ* a complex with diethyl zinc and (+)-diethyl tartrate (other esters of *R,R*-tartaric acid were also examined), such that the tartrate moiety still had one free pendant hydroxyl group. On the addition of the second equivalent of diethyl zinc and diiodomethane, the cyclopropanating agent formed carried out a stereospecific methylene delivery by virtue of the transient auxiliary-substrate complex formed (**Scheme 33**).[112] Although the results reported were variable, this

approach to the enantioselective synthesis of cyclopropanes from allylic alcohols seems promising.



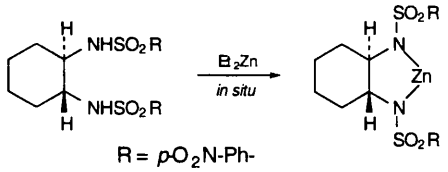
Scheme 33

Fujisawa's preliminary results in this area were extended by Ukaji and co-workers.[116] Optically active silicon substituted cyclopropylmethyl alcohols were prepared by the reaction of γ-trimethylsilyl substituted allylic alcohols with diethyl zinc, diiodomethane and (+)-DET (**Scheme 34**). The products were formed with a high diastereoselectivity (up to 92% ee), and in most cases in high yield. It was found that using dichloroethane as the reaction solvent lowered the selectivity compared with dichloromethane, and that lowering the reaction temperature enhanced selectivity. It was assumed as before that the addition of the first equivalent of the diethyl zinc and (+)-DET led to the formation of the zinc bridging intermediate **52**.



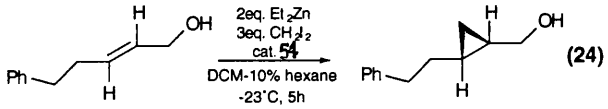
Scheme 34

In a very exciting development, allylic alcohols have also been enantioselectively cyclopropanated in a catalytic fashion via the use of a C_2-symmetric disulfonamide as a chiral ligand.[117] Thus, a catalytic quantity of the disulfonamide **53** is reacted with diethyl zinc to generate what is assumed to be species **54**. When diiodomethane is added, a chiral cyclopropanating agent is formed, giving excellent chemical yields, and good enantiomeric excesses (Equation **(24)**). The free hydroxyl group of the allylic alcohol was found to be very important, and when ether derivatives were subjected to these reaction conditions, racemic mixtures of cyclopropanes resulted.



R = *p*-O_2N-Ph-

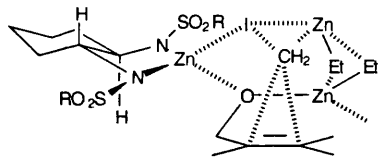
53 **54**



(24)

Quantitative yield
ee 82%

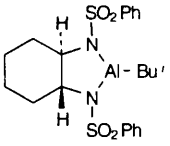
The authors suggested, in view of the experimental results, that the chiral Lewis acid zinc complex **54**, formed a chiral complex of type **55** in the transition state, which must of course react even faster than the normal achiral reagent. Thus the oxygen atom of a zinc alkoxide and an iodine atom of iodomethylzinc coordinate to the zinc atom in **55**, giving rise to a trinuclear complex. The enhanced reactivity observed by the authors could thus be attributed to the coordination of the zinc atom of **54** with an iodine atom of iodomethylzinc.



R = *p*-O_2N-Ph-

55

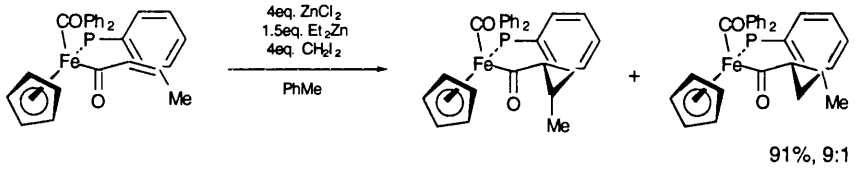
The same group later reported that a chiral disulfonamide-alkylaluminium complex also catalyses the cyclopropanation of allylic alcohols with diethyl zinc and di-iodomethane.[118] The best results were achieved using the complex **56** formed from (1*R*,2*R*)-*N*,*N*'-*bis*(phenylsulfonyl)-1,2-cyclohexanediamine and di-isobutylaluminium hydride, which gave enantioselectivities and yields very similar to those found with the chiral zinc catalyst. The advantage of this system over the zinc system is that at higher concentrations there was no decrease in enantioselectivity.



56

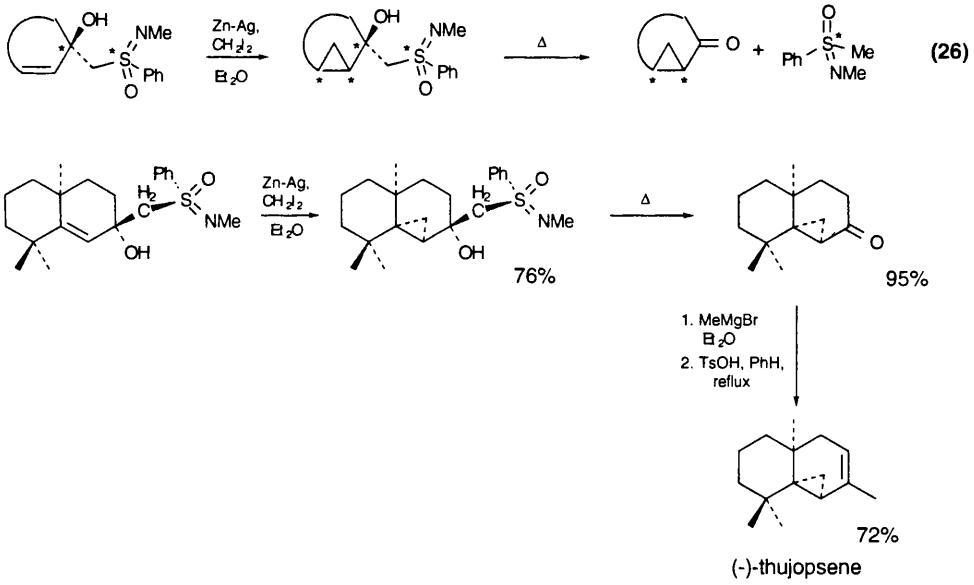
The asymmetric synthesis of cyclopropane carboxylic acid derivatives has been examined using an iron complex as the chiral auxiliary.[119,120] When [(η^5-C_5H_5)-Fe(CO)(PPh_3)] was complexed with a (*Z*)-α,β-unsaturated acyl ligand, and cyclopropanated using diethyl zinc and diiodomethane, in the presence of zinc chloride in toluene, the corresponding

cyclopropanes were isolated in 91% yield (Equation **(25)**). Stereoselectivity was found to increase with increasing size of the terminal alkene substituent. However, it was found that this method could not be used for the corresponding (*E*)-α,β-unsaturated acyl ligands, as these appeared to require a nucleophilic methylene transfer reagent.[120]



(25)

Optically active cyclopropyl ketones were accessed via the cyclopropanation of β-hydroxysulfoximines using a zinc-silver couple and diiodomethane, refluxing in diethyl ether for 72 hours (Equation **(26)**).[121] The cyclopropanation was found to occur *cis* to the hydroxyl group of the allylic β-hydroxysulfoximine. As both the enantiomers of the β-hydroxysulfoximine can be accessed, it is possible to synthesise both cyclopropane enantiomers. Removal of the β-hydroxysulfoximine group is achieved simply by a thermal elimination. This technology has been applied to the synthesis of (-) and (+)-thujopsene (**Scheme 35**).



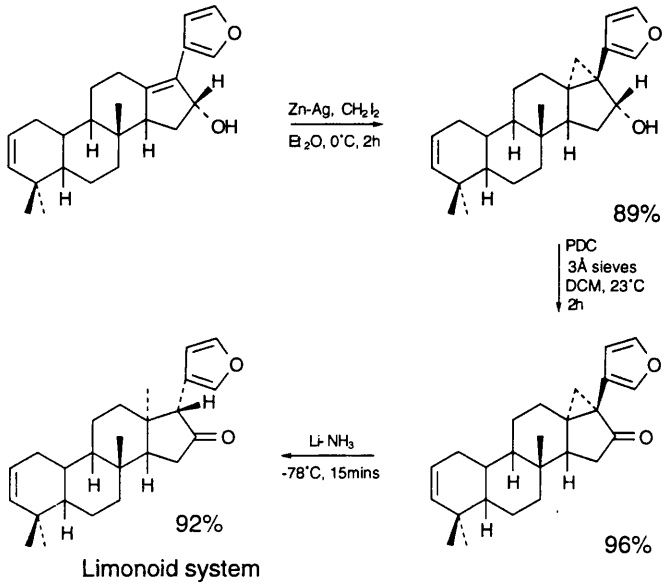
(26)

Scheme 35

Finally in this section, some of the more recent uses of the Simmons-Smith reaction in natural product synthesis will be outlined. Cyclopropanes feature in many important synthetic targets, and their introduction has also been used to furnish angular methyl groups via a ring cleavage protocol.

In the first total synthesis of the limonoid skeleton, Corey utilised a hydroxyl-directed Simmons-Smith reaction to stereospecifically generate a cyclopropane, which was then cleaved using lithium - liquid ammonia, to create the C/D angular methyl group (**Scheme**

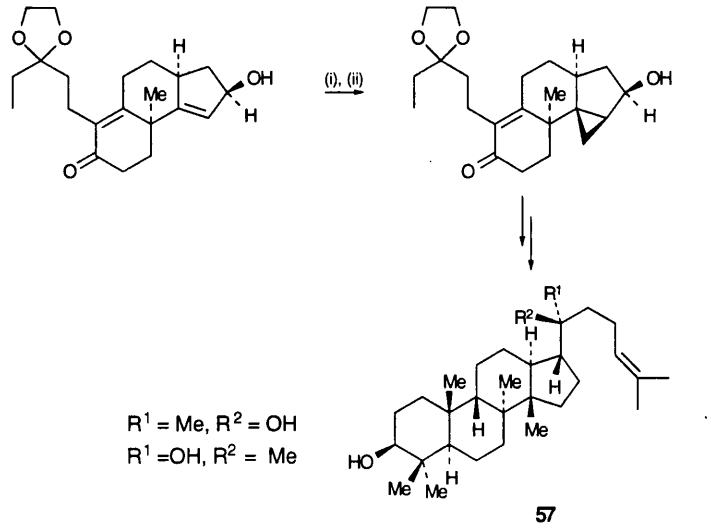
36).[122] Generally this group is difficult to introduce, and the Simmons-Smith methodology provides a useful entry.



Scheme 36

The same synthetic strategy for the introduction of the C/D angular methyl group was also applied in the synthesis of azadiradione, a tetracarbocyclic member of the limonoid family.[123]

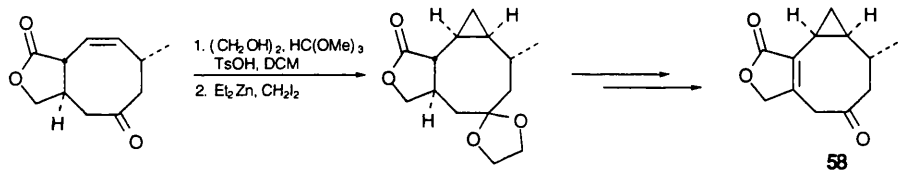
The first enantioselective total synthesis of 3β,20-dihydroxyprotost-24-ene **57**, a protostenediol of the protosterene system, again used a hydroxyl-directed cyclopropanation to furnish eventually an angular methyl group (**Scheme 37**).[124] In this instance, however, the yield in the cyclopropanation step was only moderate (66%).



Reagents: (i) 1eq. *n*-BuLi; (ii) 15eq. ICH_2ZnI, Et_2O, 23°C, 12h

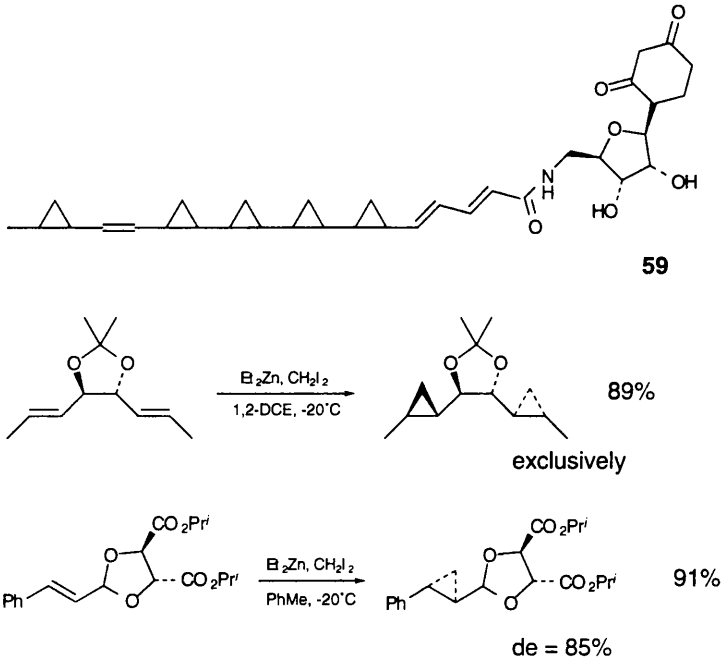
Scheme 37

The enantiospecific synthesis of ring system **58**, characteristic of the crenulide diterpenes was recently published.[125,126] In this instance, the cyclopropane moiety was introduced through reagent delivery from the least hindered face of the alkene, using diethyl zinc and diiodomethane to give a high yield (83%) of the desired product (**Scheme 38**).



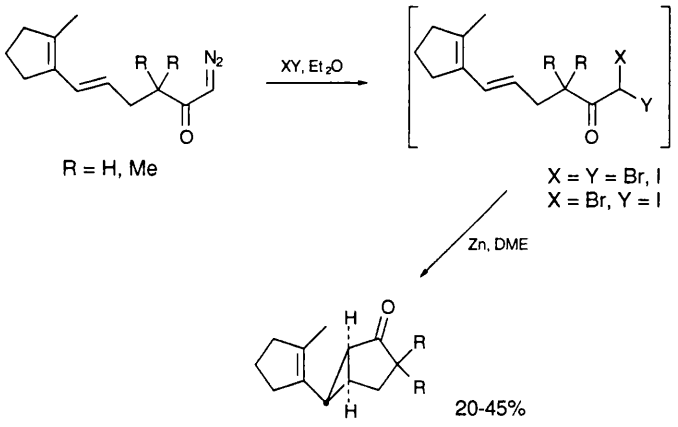
Scheme 38

Recently, in the course of studies directed towards the antifungal agent FR-900848 **59**, a structurally fascinating molecule with five cyclopropane units, Barrett has employed both dioxolanes[127] and homochiral ketals[128] derived from (+)-DET to achieve diastereoselective cyclopropanations (**Scheme 39**).



Scheme 39

As part of a strategy towards the linearly fused sesquiterpene hirsutene, Hudlicky and co-workers demonstrated the first example of an intramolecular Simmons-Smith reaction.[129] The reaction examined is illustrated in **Scheme 40**. Although the yields of the cyclopropanes were relatively low, the authors suggested that this was due to the purity of the precursor, which had to be generated *in situ* due to its instability.

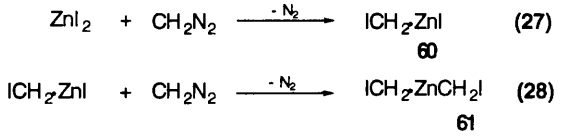


Scheme 40

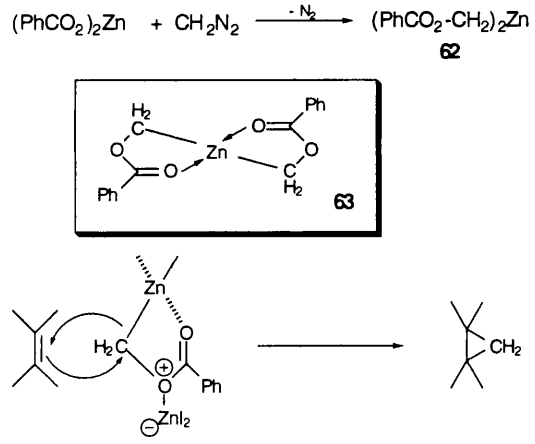
1.4 Simmons-Smith Reagents from the Reduction of a Zinc (II) Salt with a Diazoalkane

This method for the generation of Simmons-Smith type reagents for the cyclopropanation of olefins was first reported by Wittig,[130] and has since received relatively little attention. The active cyclopropanating species is formed by the addition of diazomethane or

aryldiazomethane to an ethereal suspension of a zinc (II) halide, Equations **(27)** and **(28)**, with the active species being either the 'monomer' **60** or 'dimer' **61**.

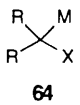


Wittig proceeded to publish a series of papers on this reaction,[131-135] where salt effects were examined, and the influence of other metals such as magnesium and lithium. It was possible to cyclopropanate alkenes with the reagent derived from diazomethane in moderate to good yields.[131] Whilst cyclohexene could only be cyclopropanated in 30% yield, aromatic substituted alkenes such as styrene and 4-propenylanisole gave far higher yields, 85% and 80% respectively. In a variant of this reaction[135] it was found that taking dibenzoyloxy zinc and diazomethane, an effective methylene insertion occurred to give the benzoyloxymethyl zinc derivative **62**. Characterisation by IR suggested structure **63**. This reagent could then be used to cyclopropanate alkenes in the presence of zinc (II) halides (**Scheme 41**).



Scheme 41

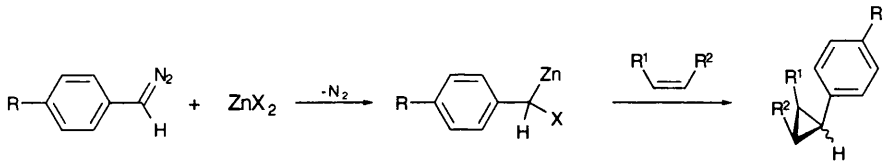
Apart from Wittig, few groups have examined this reaction, and it is primarily of academic interest. Closs[136] published a detailed study of the influences on the decomposition of aryldiazomethanes with lithium and zinc halides (Equation **29**). In effect, by considering the carbenoid generated by this method as having a general formulation **64**, the study examined the effect of the R (aryl only), M (metal) and X (leaving group).



64

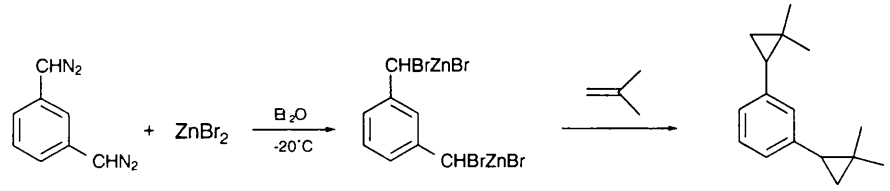
Zinc halide catalysis of the reaction (Equation **29**) was found to give excellent yields of cyclopropanes, with the *syn* isomer always predominating. The reaction also worked for catalytic quantities of zinc halide, although most results were for the use of stoichiometric

quantities. For any one olefin and zinc halide, increasing electron-donating ability of the *para*-substituent on the aromatic ring of the aryldiazomethane led to a marked increase in the *syn* to *anti* ratio of the resulting cyclopropane, although this was surprisingly mirrored by a decrease in yield, in contrast to the observations of Motherwell.[64] It would seem likely that this yield reduction was in fact due to increased substrate instability, and not inefficiency of carbenoid formation *per se*. Interestingly, a systematic study of the variation of the zinc halide used revealed that the chloride ion caused the smallest *syn* to *anti* ratio and iodide the largest (with bromide in between). The influence of the zinc halides on the reaction was measured using kinetic studies on the relative rates of additions of the various reactive intermediates to different olefins. Over all substrates, the rate increases markedly from chloride to bromide to iodide, with iodide being significantly faster. A substrate (olefin) dependency also became apparent from this study: the greater the degree of substitution around the olefin, the faster the addition; as a corollary to this, the greater the degree of substitution, the larger the rate difference across the series from chloride to bromide to iodide.



The influences of both the anion of the zinc halide and the *para* substituent on the aromatic ring were assigned to electronic effects affecting the charge density (i.e. electrophilic nature) of the carbenoid carbon in the transition state. However, for this explanation to be valid for the stereochemical outcome of the reactions, it assumes that charge transfer or dipolar interactions are responsible for the stereochemistry.

Extending this principle, Goh and co-workers[137] examined the formation of dicarbenoid species from the reaction of 1,3-*bis*(diazomethyl)benzene with zinc halides. Best results were obtained using isobutylene, with the decomposition of the diazocompound being carried out in the presence of zinc bromide at -20 °C in diethyl ether (**Scheme 42**). These reaction conditions gave a 62% yield of the dicyclopropane. In the absence of an alkene trap, the dicarbenoid was found to insert into the α-CH of diethyl ether (12%) and THF (34%), depending on the solvent employed for the reaction. Similar insertion reactions were also observed by Closs.[136] Attempted addition of the dicarbenoid to a diolefin (diallyl ether) failed to give any of the expected adduct.



Scheme 42

1.5 Conclusions

Organozinc carbenoids seem to occupy a rather curious position in metallocarbenoid chemistry, and despite their historical pedigree both in terms of the Clemmensen reduction and the Simmons-Smith cyclopropanation, their recognition as a discrete and useful class of reagents in their own right has yet to be fully appreciated. The very position of zinc in the Periodic Table, where it is, to some extent, shunned by the transition metal cognoscenti, may well be responsible.

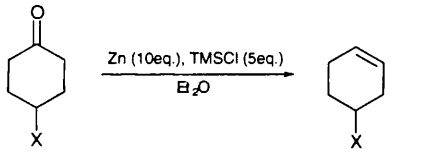
The foregoing review has attempted to tie some of these disparate threads together, and to highlight that these reactive intermediates display all of the classical features of carbene and carbenoid reactivity in terms of insertion reactions, ylide formation, and cyclopropanation. Moreover, their generation from readily available carbonyl compounds under mild reductive conditions, without recourse to diazo or *gem* dihalo precursors is an added advantage, which will hopefully enable organozinc carbenoids to increasingly serve as useful reagents for organic synthesis.

Chapter 2. Results and Discussion

2.1 Background

It is evident from the scope of the literature discussed in Chapter 1 that organozinc carbenoids have a significant role to play in organic synthesis. What is somewhat surprising is that the controlled reductive deoxygenation of carbonyl compounds in the presence of zinc and an electrophile - in the extreme case a proton - has been largely overlooked by the chemical community as a mild procedure to access these reactive intermediates. As this reaction (using a silicon electrophile) is the subject of the present work, it is perhaps instructive to provide a historical context, outlining what has been the simultaneous development of the synthetic and mechanistic aspects of the reaction.

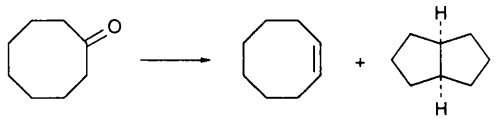
In 1973 Motherwell published a procedure for the reductive deoxygenation of alicyclic carbonyl compounds with zinc and chlorotrimethylsilane to give an olefin.[54] The reaction conditions are particularly mild, and the reaction itself very chemoselective, with both remote ester and bromide functionality tolerated (**Scheme 13**, reproduced here for clarity).



X = H 72%
X = Br 48%
X = OAc 60%

Scheme 13

From a mechanistic standpoint, this initial communication also provided several key insights. Firstly, when cyclooctanone had been exposed to the reaction conditions, although, as expected, *cis*-cyclooctene was isolated, bicyclo[3.3.0]octane was also formed as a result of a transannular interaction (**Scheme 12**, reproduced here for clarity). Such a reaction is characteristic of carbenoid reactivity, and is also exhibited by free carbenes in the Bamford-Stevens reaction.

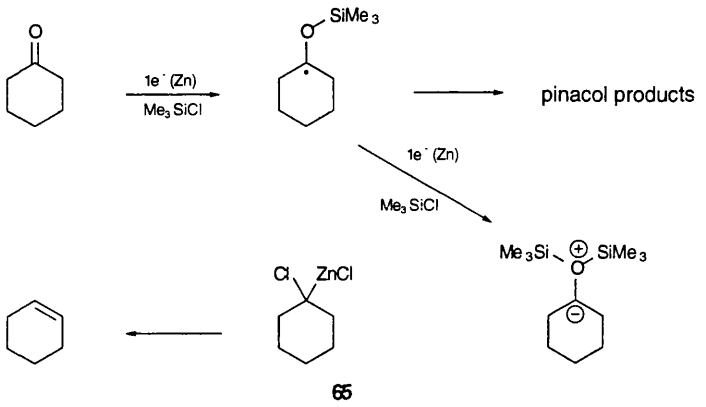


2 : 1

55% overall

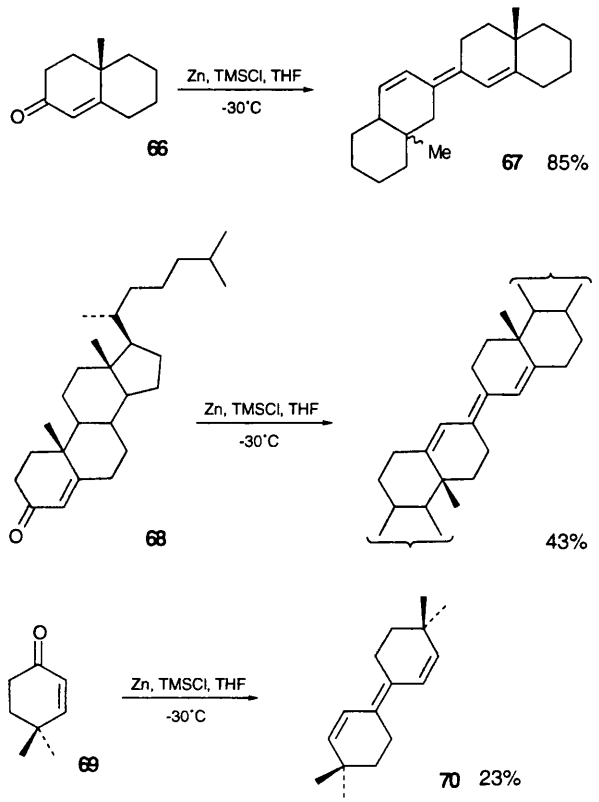
Scheme 12

The second piece of evidence supporting a carbenoid intermediate in the reactions came with the isolation of a 1:1 mixture of (±)- and *meso*-2,3-diphenyl-2,3-di(trimethylsiloxy)butane from the attempted deoxygenation of acetophenone. As silyl enol ethers were found to be inert to the reaction conditions (and hence not intermediates in the mechanism), this implied that the reaction pathway involved sequential one electron reductions, allowing a pinacol coupling reaction at the one electron reduction stage, particularly if the intermediate radical is stabilised. These facts allow a simplistic mechanism to be proposed, itself very similar to that one might propose for the Clemmensen reduction, only in this instance the intermediate organozinc carbenoid **65** is not further reduced to a geminal disilane (**Scheme 43**).



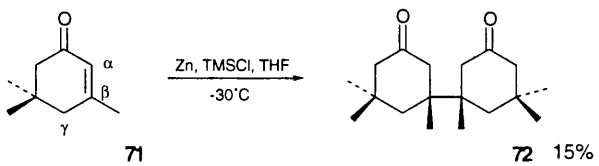
Scheme 43

The next significant development in the methodology was the discovery that under carefully controlled reaction conditions certain aryl and α,β-unsaturated carbonyl compounds could undergo a McMurry-like dicarbonyl coupling reaction.[58] Several illustrative examples are given in **Scheme 44**.



Scheme 44

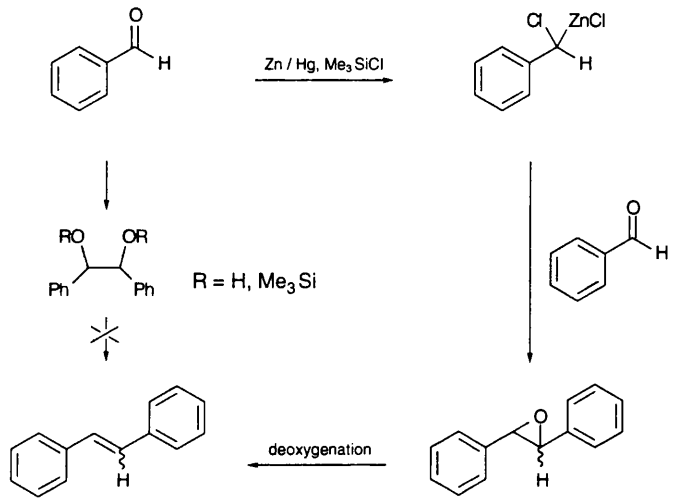
Thus, by the simultaneous addition of octalone **66** and chlorotrimethylsilane to a stirred suspension of zinc dust in tetrahydrofuran, the hydrocarbon dimer **67** was isolated in an excellent 85% yield. An identical coupling reaction was also found for cholest-4-en-3-one **68** and 4,4-dimethylcyclohex-2-enone **69**. Interestingly, when isophorone **71** was exposed to identical reaction conditions a complex product mixture resulted, from which the *meso* dimer **72** was isolated, formed through one electron induced dimerization at the softer β-carbon atom (**Scheme 45**). This substrate dependency found when comparing the results given in **Scheme 44**, and that of isophorone shown in **Scheme 45**, is curious. It suggests that it is the presence of additional substituents on the γ–carbon atom of the enone system which inhibits dimerization of the intermediate siloxyallyl radical (formed at the one electron reduction stage) at the β-carbon atom, and hence leads to reaction via the carbon atom of the original carbonyl group.



Scheme 45

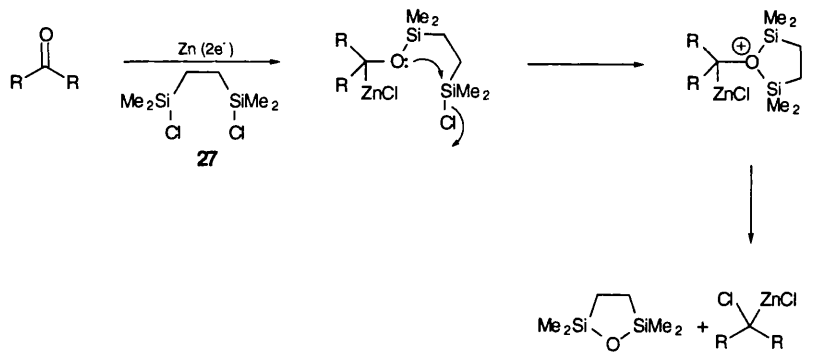
The mechanism of this reaction was of particular interest, as neither exposure of vicinal diols or their silylated derivatives to the reaction conditions resulted in olefins. These

results allowed the conclusion to be drawn that the mechanism was quite unlike that of the McMurry reaction.[62] Further evidence was gained through the dicarbonyl coupling of benzaldehyde. When benzaldehyde had been subjected to the reaction conditions, a mixture of benzpinacol (50%) and *cis*- and *trans*-stilbene (15%) had been isolated; exposure of *trans*-stilbene epoxide had also led to stilbene formation (30%), together with diphenylacetaldehyde (15%). Thus, it would appear reasonable to propose a pathway for the coupling reaction which involved the trapping of the intermediate organozinc carbenoid by a second molecule of carbonyl compound, followed by deoxygenation of the resulting epoxide to afford the 'dimeric' product (**Scheme 46**).



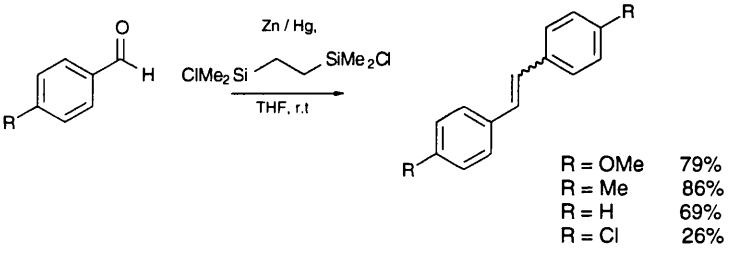
Scheme 46

The dicarbonyl coupling reaction was particularly illustrative of the complex mechanistic pathway which led to the intermediate organozinc carbenoid. In many instances the pinacol coupling of the carbon centred siloxy radical was becoming the dominant, if not the exclusive reaction. The problem was simply to try and favour the delivery of a second electron and / or silicon electrophile over the intermolecular pinacol coupling. Overall, formation of the carbenoid requires the delivery of two electrons, and sequential attack of two silicon electrophiles. From this standpoint an extremely elegant yet simple solution became apparent - effecting *intramolecular* delivery of the second silicon atom by the use of a *bis* silicon electrophile should favour carbenoid formation over the *intermolecular* reaction necessary for pinacol coupling. The *bis* electrophile chosen was 1,2-*bis*(chlorodimethylsilyl)ethane **27**,[60] with carbenoid formation occurring via the route shown in **Scheme 18** (reproduced here for clarity).



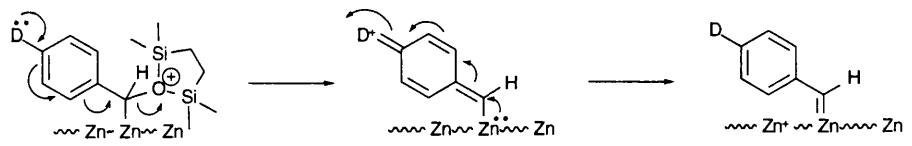
Scheme 18

There was a significant improvement in yield in the dicarbonyl coupling reaction through the use of this electrophile **27**, coupled with a slow addition of the carbonyl compound and **27** to the zinc suspension. (Later results indicated that the most efficient system involved the slow addition of a solution of the carbonyl compound to a suspension of zinc and the *bis* silicon electrophile in THF). The yield of coupled product **70** from 4,4-dimethylcyclohex-2-enone was increased to 76% from only 23% using chlorotrimethylsilane as the electrophile.[58] Of particular interest were the results from a series of aromatic aldehydes (**Scheme 47**).



Scheme 47

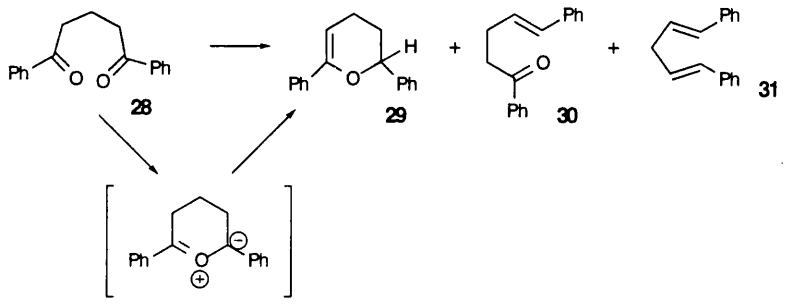
The yields in this reaction drop relatively uniformly with the decreasing electron-donating ability of the *para*-substituent on the aromatic ring, mirroring the yields obtained under classical Clemmensen reduction conditions. It seems likely that this trend is directly related to the ability of the *para*-substituent to provide an 'electronic push' to help expel the (siloxane) leaving group in the step prior to carbenoid formation. This is illustrated in **Scheme 19** (reproduced here for clarity).



Scheme 19

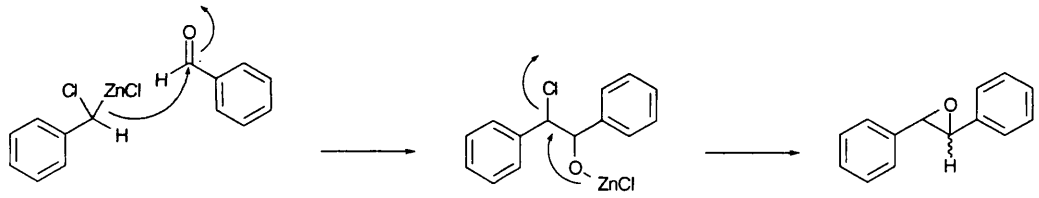
From a mechanistic standpoint, however, the most informative reaction was the attempted intramolecular dicarbonyl coupling of diketone **28**. The result was the formation of dihydropyran **29** (31%), and two open chain products, **30** (14%) and **31** (21%), formed via α-C-

H insertion of the carbenoid (**Scheme 20**, reproduced here for clarity). As shown in **Scheme 20**, the formation of dihydropyran **29** may be explained by the intermediacy of a carbonyl ylide, the ring closure of which to an epoxide is precluded, or at least retarded, due to a combination of ring strain and electronic effects.



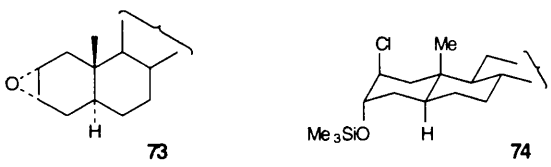
Scheme 20

This result served as proof of the carbenoid character of the reactive intermediate generated in this system. Ylide formation is a classic reaction of electrophilic metal carbenoids, and has been well documented.[138] Until this point it had not been possible to rule out a more Reformatsky-like behaviour of the carbenoid, where nucleophilic attack on the carbonyl compound, followed by ring closure, leads to the epoxide formed as an intermediate in the dicarbonyl coupling reaction (**Scheme 48**).

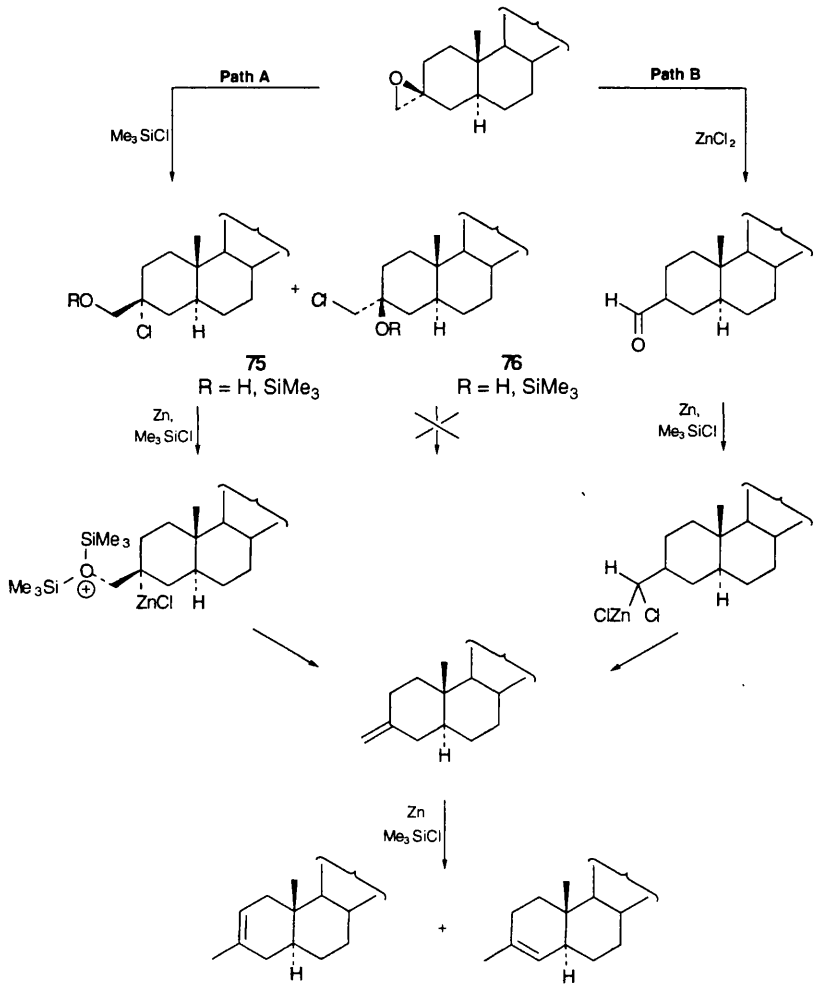


Scheme 48

The electronic requirements for, and mechanism of, epoxide deoxygenation in this system were still far from clear, with one obvious question being 'does this process require a doubly benzylic or allylic substrate to induce deoxygenation?' The answer to this question was found through a carefully designed series of epoxide deoxygenation experiments.[61] The first results indicated that for mono- or 1,2-disubstituted epoxides, alkene formation was not observed on exposure of the substrate to zinc and chlorotrimethylsilane. Instead, ring opening occurred to the trimethylsiloxychlorohydrins, and the use of 2α,3α-epoxy-5α-cholestane **73** indicated that ring opening was in a trans diaxial fashion (to afford **74**).



Using 1,1-disubstituted spiro epoxides as substrates, however, provided a greater insight. It appeared that two independent deoxygenation routes were occurring; one was via an aldehyde, formed by the Lewis acid ($ZnCl_2$) catalysed rearrangement of the epoxide (**Path B**), whist the other was via chlorohydrins (or siloxychlorohydrins) **75** and **76** (**Path A**). Independent synthesis of **75** and **76** indicated that only the siloxychlorohydrin **75** possessing a *tertiary* alkyl chloride would undergo zinc induced reductive elimination to the alkene. The results are summarised in **Scheme 49**.

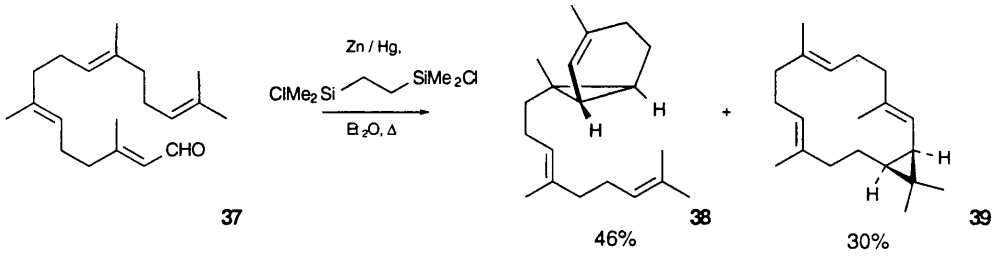


Scheme 49

Obviously, in the last stages of the mechanism it is debatable whether the processes involve zinc, or are simply occurring through the action of zinc chloride and chlorotrimethylsilane. More important though, was the finding that the chloride formed must be tertiary for further elimination to occur under these reaction conditions. Thus the benzylic and allylic substrates used in the dicarbonyl coupling reactions were clearly favoured.

Later papers capitalised on the optimised conditions for carbenoid generation from carbonyl compounds using zinc and 1,2-*bis*(chlorodimethylsilyl)ethane, and demonstrated the synthetic application of this system to the cyclopropanation of alkenes.[64,67] For a series of

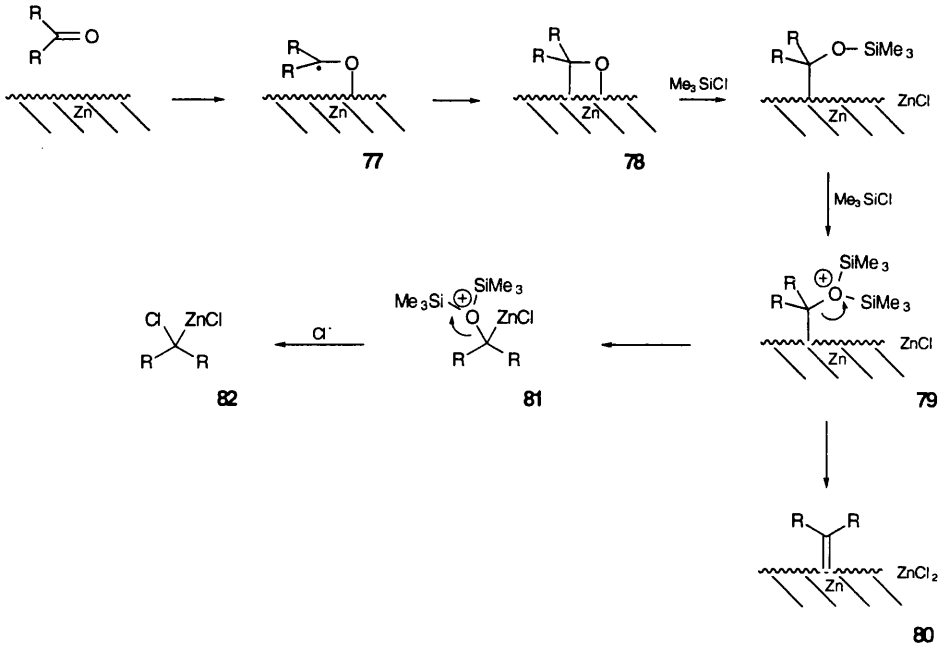
aromatic aldehydes, the yields were again found to decrease uniformly with the decreasing electron-donating ability of the *para* substituent on the aldehyde, and also the more sterically hindered cyclopropane was found to form preferentially. This selectivity will be discussed later in more detail (*vide infra* chapter 2.3). A wide range of alkenes were found to be suitable substrates: cyclohexene, styrene, electron-rich enol acetates, and of particular mechanistic interest, *trans*-5-decene, which cyclopropanated with retention of double bond geometry in the resultant cyclopropane, indicating a carbenoid singlet in nature. It was also found possible to cyclopropanate using certain α,β-unsaturated aldehydes and ketones; broadly speaking, successful substrates in this instance were identical, or very structurally similar to, those that had been successful in the dicarbonyl coupling reactions.[58] The successful generation and intramolecular trapping of the carbenoid derived from terpenoid enals was very dramatic, with geranylgeranial **37** cyclising to the prenyl homologue of sesquicarene **38** and the macrocycle casbene **39** (**Scheme 50**).



37 **38** 46% + **39** 30%

Scheme 50

In spite of the developments made in understanding mechanism for the reductive deoxygenation of carbonyl compounds using zinc and a silicon electrophile, there remain many significant questions unanswered, particularly with respect to the nature of the organozinc carbenoid. Simplistically, it may be said that it is either a heterogeneous entity, bound to the zinc surface, or a homogeneous species, akin perhaps to the Simmons-Smith intermediate (chapter 1.3.1). It is possible to draw a slightly more complex mechanism than the simple 'electron-count' given earlier (**Scheme 43**, chapter 2.1), that in the final stages could give rise to either a surface bound carbenoid, or a homogeneous species (**Scheme 51**).



Scheme 51

Thus the carbonyl compound approaches the zinc surface and coordinates (probably via oxygen) to give the surface bound ketyl radical **77**. This species would give rise to pinacol coupling products. Accepting a second electron from the zinc gives rise to the oxometallacycle **78**, although conceivably this could be drawn as a metallo-oxirane. Cleavage of the zinc - oxygen bond by the silicon electrophile, followed by reaction with a second molecule of chlorotrimethylsilane affords the carbenoid-type species **79**. This could then give rise to either the neutral metal-bound carbenoid **80** by the loss of hexamethyldisiloxane and concomitant production of zinc chloride, or alternatively a homogeneous species **81** or **82**, the latter formed via chloride ion displacement of hexamethyldisiloxane. Clearly either **81** or **82** could be considered as carbenoid intermediates.

A significant proportion of the work that is to be discussed is concerned with an attempt to elucidate the exact nature of the carbenoid intermediate, its electronic preferences, and the influences on the (numerous) reaction parameters on its reactivity. There are several significant and relevant publications, particularly those of Denmark[78,79] and Closs,[136] which provide strong circumstantial evidence about the nature of the carbenoid, but these will be discussed in the course of this chapter.

2.2 Mechanistic Studies

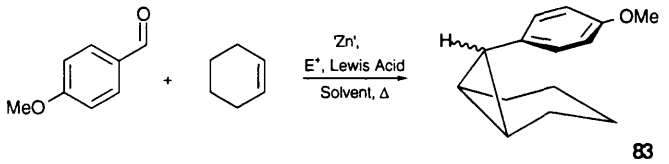
This section comprises of two main areas: (i) an in depth examination of the influence of all the variables in the zinc carbenoid system; (ii) a study to determine whether the zinc carbenoid is homo- or heterogeneous.

2.2.1 Influence of all Variables on the Course of a Standardised Reaction

2.2.1.1 The Standard Reaction

In choosing a standard reaction it was necessary to consider that whilst in effect carrying out an optimisation study on the reaction variables, the underlying theme was one of mechanistic appraisal. Obviously, the first criterion was that the reaction should proceed in moderate yield using non-standardised conditions. The other major factor influencing choice was that the reaction system should not preclude any type of carbenoid reactivity being observed (C-H insertion reactions (*vide infra* chapter 2.4), cyclopropanation and ylide-forming reactions (*vide supra* chapter 2.1)), as finding a method of controlling or channelling the reactivity of the carbenoid would be very significant.

For these reasons, the reaction shown in Equation **(30)** was chosen. Cyclopropanation would be the major reaction pathway expected, although ylide formation would be possible if the carbenoid was trapped by a second unreacted molecule of carbonyl compound, and C-H insertion reactions were known to occur in diethyl ether and tetrahydrofuran (*vide infra* chapter 2.4.1). If the reaction pathway was switched away from cyclopropanation, this should also provide useful information about the nature of the carbenoid. The reaction shown in Equation **(30)** was known to proceed in good yield,[139] and the formation of the cyclopropane would provide a second important piece of data apart from the yield - the *endo:exo* ratio of the diastereomers (also expressed as the diastereomeric excess, de). From this information, it was hoped that it would be possible to draw conclusions about the influences on the carbenoid in the transition state.



83 **(30)**

The reaction shown in **(30)** was used for all studies, except the initial examination of the type, quality and mesh size of the zinc used in the reaction (chapter 2.2.1.2). A standard set of conditions was defined, which provided the 'benchmark' result. This was 10 equivalents of zinc amalgam, 5 equivalents of chlorotrimethylsilane, 2 equivalents of cyclohexene and 1 equivalent of *p*-anisaldehyde, in refluxing diethyl ether. The aldehyde was then added over 12 hours via a motorised syringe pump, as a solution in the reaction solvent, to the other

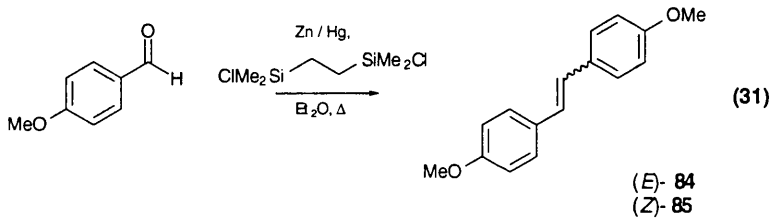
reagents. All reactions were carried out at identical concentrations, and on the same molar scale. The apparatus was always assembled in the same manner. Only one variable was ever altered from the standard reaction at a time.

As will become evident, the results provide an insight, but, as is often to be expected in studies of this nature, only provided even more questions to be asked than were answered.

2.2.1.2 Zinc Particle Size

Throughout the history of this reaction, the formation of zinc balls - when the finely divided zinc powder forms rapidly into one or several hard spheres in the reaction flask - had been a frustrating and puzzling problem. Whilst the use of a conical flask and vigorous off-centre stirring appeared to minimise the problem, it by no means solved it. As is frequently the case in such heterogeneous metallic systems, the zinc itself had never been the subject of any scrutiny, beyond the early observation that 'although commercial zinc dust is satisfactory, uniformly consistent results were obtained with amalgamated zinc.'[54] Thus, as at a very early stage in the course of this study it became apparent that mass balance in the reactions was a serious problem, and difficulties were being encountered in reproducing work carried out several years earlier, it was decided to examine the influence of zinc composition and particle size on the reactions.

Unlike the rest of the studies in this section, this work was carried out using the dicarbonyl coupling of *p*-anisaldehyde as the standard reaction (Equation **(31)**).



(31)

(*E*)- **84**
(*Z*)- **85**

Three samples of zinc (entries 1, 2 and 3) were amalgamated, and then if suitable, examined in the reaction. They were chosen particularly due to their varying purity and mesh size. Their compositions and particle sizes are listed in **Table 5**, with the data for Aldrich zinc dust provided for comparison.

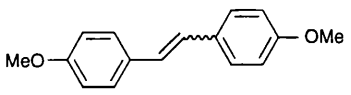
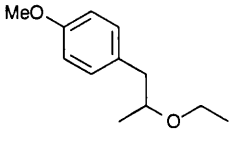
Table 5. Purity and particle size data for the samples of zinc assessed as an amalgam in the reaction

	Zinc Source*	Metallic Zn (%)	ZnO (%)	$ZnCl_2$ (ppm)	Sn (%)	Fe (%)	Pb (%)	Cd (%)	Average particle size (μm)
1	Pasminco Zn powder P120	99.00 (min)	-	-	0.001	0.002	0.003	0.003	~40
2	Pasminco Zn Dust CP75	95.0 (min.)	5.0 (max.)	-	-	0.003	0.1	0.005	6-10
3	Durham Chemicals Zn Dust Ultrafine	96	3.0 (max.)	<10	-	-	0.1	0.1	3.5
4	Aldrich Zn Dust	95-97	3-5	-	-	0.001-0.003	0.01-0.03	0.01-0.03	44

* - The samples from Pasminco (now Britannia Alloys) and Durham Chemicals were obtained directly from the companies, which are the UK's only zinc producers.

It proved almost impossible to amalgamate Durham Chemicals Zinc Dust Ultrafine (entry 3), as it formed exceedingly rapidly into zinc balls, in contrast to entries 1 and 2, which were found to amalgamate without zinc ball formation. From this simple test there was already a strong indication that the particle size of the zinc is crucial if the formation of zinc balls is to be minimised. Only the zinc amalgams from the zinc in entries 1 and 2 were used in the dicarbonyl coupling reaction. The rather surprising results are given in **Table 6**.

Table 6. Results from the attempted dicarbonyl coupling of *p*-anisaldehyde using different purity zinc amalgams

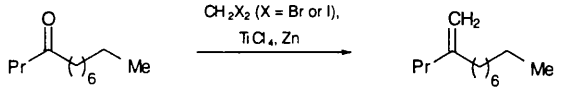
				Recovered Aldehyde
1	Pasminco Zn powder P120	8%	10%	-
2	Pasminco Zn Dust CP75	11%	6%	-

As can be seen, instead of the expected high yielding dicarbonyl coupling reaction, it was only occurring to a small degree, and a previously unobserved C-H insertion reaction was also occurring. This reaction will be discussed later (*vide infra* chapter 2.4.1). In essence though, the carbenoid reactivity was found to be independent of zinc purity (yields with both

samples were very similar), and carbenoid formation was quantitative even with the coarser sample (i.e. no aldehyde was recovered).

Thus, it was found that the problem of zinc balls was simply overcome by choosing zinc dust with a minimum particle size of 6μm, and that the reaction system did not appear to be affected by the purity of (or, more importantly, impurities in) the zinc. For all ensuing studies Pasminco zinc dust CP75 was used, reasoning that in any heterogeneous reaction, maximising surface area is important.

After the completion of this work, two interesting papers were published by a Japanese group concerning an $RCHX_2$ - $TiCl_4$ - Zn system they had developed for the methylenation of carbonyl compounds (**Scheme 52**).[140,141] It had become apparent that other groups had been unable to reproduce the results given in their initial report, and on investigation they found that the zinc they used contained a catalytic quantity of lead which had a dramatic accelerating effect on the reaction. They had proposed a mechanism for the overall transformation which involved initial formation of a zinc carbenoid, which they suggested was then trans-metallated by titanium to give what would presumably be a Tebbe-like intermediate. The actual reaction was proposed to proceed via this intermediate. The accelerating role of the lead was then suggested to be in the initial zinc carbenoid formation, with the zinc carbenoid presumably initially in the form XCH_2ZnX, which is converted into $CH_2(ZnX)_2$ accelerated by a trans-metallation with lead. It should perhaps be noted at this point that low valent titanium has been formed by the reaction of titanium tetrachloride with zinc powder.[142] Thus a mechanism in which some low valent titanium species forms before, and possibly in preference to, a zinc carbenoid, cannot be ruled out.



Scheme 52

What was perhaps more interesting in the context of this work were the results presented in their second paper, concerning the Simmons-Smith reaction.[141] In this instance they found that the zinc was deactivated towards iodoalkanes by the presence of a catalytic amount of lead, but that this effect was suppressed by the addition of a catalytic amount of chlorotrimethylsilane, and in fact resulted in an acceleration in the reaction rate. Auger electron spectroscopy studies of the zinc surface showed that both chlorotrimethylsilane and diethylzinc are extremely efficient at removing the oxide coating on the zinc surface, far more so than hydrochloric acid. (It should be noted that others previously have recorded the acceleration effect of chlortrimethylsilane on reactions involving zinc metal, and though intuitively one would put this effect down to a cleaning of the surface, this had never been proved).[15,143] However, it is not this process which causes the effect of the lead to be suppressed - this only occurs when the chlorotrimethylsilane is added to the reaction

mixture, and not when the zinc is pre-treated with it. The authors offered no explanation for this effect.

The two papers[140,141] indicate quite dramatically the difficulties in reproducibility that may be encountered especially when using a heterogeneous system, and how tracing the effects of impurities can be very complex. The results with chlorotrimethylsilane are especially relevant to this work, and it has been observed that on the addition of chlorotrimethylsilane to zinc amalgam suspended in dry diethyl ether, under rigorously anhydrous conditions, there is always rapid effervescence, even when every effort has been made to prepare essentially 'proton-free' electrophile. However, no dramatic rate changes have been observed, although presumably given that the silicon electrophile also has a crucial role to play in the reduction sequence, gains from a 'cleaner' zinc surface may be outweighed by, in this instance, a less 'efficient' electrophile.

2.2.1.3 Electrophile Variation

As had been highlighted in chapter 2.1, one of the more significant developments in the reaction system had been the use of 1,2-*bis*(chlorodimethylsilyl)ethane **27** as the silicon electrophile.[60] Its intramolecular delivery of the second silicon atom had precluded competing pinacol couplings at the one electron level, and had led to dramatic yield increases. The major drawback was that the oligomeric siloxanes produced at the end of the reaction were extremely difficult to remove from the products, and generally necessitated repeated chromatography. In parallel with the study of the zinc used in the reaction (*vide supra* chapter 2.2.1.2), the use of 1,2-*bis*(chlorodimethylsilyl)ethane as the electrophile was also examined.

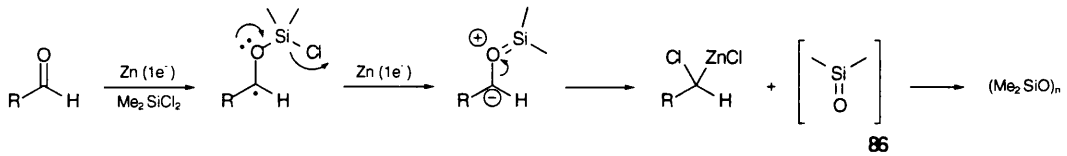
1,2-*Bis*(chlorodimethylsilyl)ethane is a low melting solid, which hydrolyses readily in air. As it was normally used as sold, it seemed appropriate to determine whether the degree of hydrolysis was affecting the reactions, and whether the storage method was important once a standard solution in a dry solvent had been prepared. Typically, a known concentration solution would be stored at 5 °C over PVP, and used indefinitely. NMR analysis of a sample concentrated *in vacuo* revealed that from either an ethereal or THF solution there had been extensive (complete) decomposition of the 1,2-*bis*(chlorodimethylsilyl)ethane into some undetermined (oligomeric?) product. Storage over sodium rather than PVP, or indeed in the absence of any acid scavenger, produced no change in this decomposition. Clearly, the decomposition product(s) of 1,2-*bis*(chlorodimethylsilyl)ethane was active in the reactions, but in the light of problems being experienced in reproducing reactions carried out by previous workers, the decomposition analysis was taken further.

To see if the decomposition was a result of hydrolysis by-products, a sample of the solid 1,2-*bis*(chlorodimethylsilyl)ethane was purified. This was achieved by dissolving in dry diethyl ether, and removing HCl by the addition of freshly cut sodium. The solution was

then transferred to a second flask by cannula, and concentrated *in vacuo*, releasing the vacuum to argon. Reduced pressure distillation afforded pure 1,2-*bis*(chlorodimethylsilyl)ethane whose ^{1}H NMR and melting point were correct in terms of reported literature values. Samples were then dissolved in an inert atmosphere in dry THF, and dry THF over sodium. After 1 hour, ^{1}H NMR indicated that the sample dissolved in THF had decomposed, with a 2:1 proton ratio of 1,2-*bis*(chlorodimethylsilyl)ethane to the decomposition product. The sample stored over sodium had decomposed completely. These results were then compared to unpurified 1,2-*bis*(chlorodimethylsilyl)ethane: the ^{1}H NMR of the reagent as sold appeared no different to the material obtained after purification. When dissolved in dry THF, after 1 hour ^{1}H NMR indicated decomposition, with a 1.5:1 proton ratio of 1,2-*bis*(chlorodimethylsilyl)ethane to the decomposition product. The sample stored over sodium as a solution in dry THF had decomposed completely. It should be noted that this method of proton removal poses no problems with chlorotrimethylsilane since Würtz coupling is very slow indeed.

Decomposition then appears to be independent of the purity of the initial sample of 1,2-*bis*(chlorodimethylsilyl)ethane. Storage of the solution over sodium accelerated the decomposition. The decomposition rate of a solution in diethyl ether was found to be much slower than that of a THF solution, but was still significant. Given the purification problems generally encountered when using 1,2-*bis*(chlorodimethylsilyl)ethane, and a general unease at using a reagent whose precise form in the reaction was unknown, it was decided to move back to the use of chlorotrimethylsilane, and also to examine the potential of dichlorodimethylsilane as the electrophile.

Dichlorodimethylsilane had already been reported as a suitable electrophile for this type of reductive deoxygenation by Smith and co-workers.[56] Mechanistically, a silicon dihalide should be a far more powerful electrophile in each of the two successive halogen displacement steps (**Scheme 53**). The high-energy dimethylsilanone **86** that would be displaced to give the carbenoid has been postulated in the base-catalysed decomposition of polydimethylsiloxanes, and would be anticipated to polymerise to other by-products.



86

Scheme 53

Initial results suggested an efficiency equal with, or at least very similar to, chlorotrimethylsilane.[144] In the current studies dichlorodimethylsilane was used predominantly (except in the following mechanistic appraisal), as the 'intramolecular' presence of the 'second' Si-Cl moiety was considered favourable over the intermolecular delivery necessary with chlorotrimethylsilane.

Thus, the influence of various silicon electrophiles on the course of the standard reaction, Equation **(30)**, was then investigated. The results for the nine electrophile systems examined are given in **Table 7**.

Table 7. Results of electrophile variation in the cyclopropanation of cyclohexene with *p*-anisaldehyde and zinc amalgam in diethyl ether

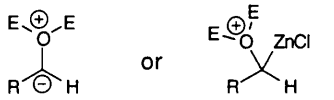
	Electrophile / no. of equivalents[#]	Yields and de / %			
		Cyclopropane[§]	de (endo / exo ratio)	Stilbene[§]	C-H Insertion[§]
1	Dichlorodisilane[*] (1.5eq)	85	92 (23:1)	-	2
2	TMSCl (5eq)	45	92 (25:1)	-	2
3	Me_2SiCl_2 (2eq)	37	93 (27:1)	-	3
4	TMSCl (4.75eq) + HCl (0.25eq) (i.e. 5% HCl in TMSCl)	32	93 (27:1)	4	-
5	TMSCl (2.5eq) + HCl (2.5eq)	49	93 (28.5:1)	-	2
6	HCl (5eq)	43 (47)[**]	92 (23:1)	-	1
7	HCl (5eq) + H_2O (2.5eq)	66	92 (24:1)	-	-
8	HCl (5eq) + H_2O (5eq)	49	93 (29:1)	-	2
9	H_2O (5eq)	0[***]	-	-	-

[#] - Number of mole equivalents with respect to the number of moles of aldehyde taken; [§] - Cyclopropane refers to 7-(4-methoxyphenyl)bicyclo[4.1.0]heptane; Stilbene refers to (*E*) and (*Z*)-1,1'-(1,2-ethenediyl)*bis*(4-methoxybenzene); C-H insertion refers to 3-(4-methoxyphenyl)-2-ethoxypropane; [*] - Dichlorodisilane refers to 1,2-*bis*(chlorodimethylsilyl)ethane; [**] - Based on recovered aldehyde; [***] - Aldehyde recovered quantitatively.

The first point to note with these results is that in all reactions, except entry 9, the aldehyde was completely consumed, presumably via the carbenoid, although alternative decomposition pathways cannot be ruled out. If it is the case that the aldehyde is quantitatively converted to the carbenoid, all electrophile systems examined are acting efficiently in the sense of formation of the reactive intermediate. A difference must then reside in how controlled the reactivity of the intermediate carbenoid is, i.e. does it cyclopropanate the alkene, or 'decompose'?

Comparing the three silicon electrophiles (entries 1, 2 and 3), the efficiency gain with the use of 1,2-*bis*(chlordimethylsilyl)ethane is evident - the yield of cyclopropane is approximately double that of both chlorotrimethylsilane and dichlordimethylsilane,

although the *endo:exo* ratio is a little lower than that for both of these reagents. The rather low yield with dichlorodimethylsilane (37%) is possibly indicative of the hyper-reactivity of the dimethylsilanone postulated as the leaving group in the carbenoid formation step. It is perhaps interesting to consider that the carbenoid may in fact be a species of the form **87** or **88**, in which case although a more 'potent' leaving group would imply a more reactive carbenoid, it may also suggest one that is far less discriminating in its reactivity.



or

87 **88**

If this is the case, a different electrophile would result in a different form of carbenoid, which could well account, at least in part, for the yield and de variations observed. Complexation of the carbenoid may also be important in the transition state, by solvent or another agent, although there is no direct evidence for this in these results. On a cautionary note, it is perhaps important to bear in mind that although some trends can be seen, the results also reinforce the idea that the reaction is extremely complex and subtle mechanistically, and finding a unifying explanation for all results is somewhat unlikely from such a preliminary study.

Finally, the reaction using 5 equivalents of HCl and 2.5 equivalents of water (entry 7) as the electrophile system, is worthy of comment. The yield of 66% was the second highest obtained in the series, and the *endo:exo* ratio is slightly higher than that found when 1,2-*bis*(chlorodimethylsilyl)ethane was used as the electrophile (entry 1). Such an electrophile system makes the reaction extremely cheap, and also 'environmentally friendly', increasing the viability of such a reaction industrially, particularly when compared to other alternatives.

2.2.1.4 Solvent Variation

The influence of the solvent on the standard reaction, Equation **(30)**, is shown by the results given in **Table 8**. The solvents chosen covered a range of polarities, envisaged complexation ability in terms of the intermediate carbenoid, and steric bulk. There is also considerable overlap with solvents examined by other groups working on zinc carbenoid chemistry, and particularly the Simmons-Smith reaction, which should provide useful comparisons.

Table 8. Results of solvent variation in the cyclopropanation of cyclohexene with *p*-anisaldehyde, zinc amalgam and chlorotrimethylsilane

	Solvent	Yields and de / %			
		Cyclopropane§	de (endo / exo ratio)	Stilbene§	C-H Insertion#
1	Et_2O	45	92 (25:1)	-	2
2	THF	31	88 (15:1)	1	9
3	DME	1*	90 (18:1)	-	-
4	$(Me_3Si)_2O$	3**	83 (11:1)	2	-
5	DCM	10	91 (20.5:1)	9	-
6	MeCN	20	92 (25:1)	-	-
7	Cyclohexene	16	87 (14:1)	5	-
8	PhMe	20	91 (21:1)	8	-

- C-H insertion is only relevant for entries 1 and 2, and refers to 3-(4-methoxyphenyl)-2-ethoxypropane and tetrahydro-2-(4-methoxyphenyl)furan respectively; § - Cyclopropane refers to 7-(4-methoxyphenyl)bicyclo[4.1.0]heptane; Stilbene refers to (*E*) and (*Z*)-1,1'-(1,2-ethenediyl)*bis*(4-methoxybenzene); * - 81% of aldehyde recovered; ** - zinc balls formed during the reaction, and yields are based on recovered aldehyde.

Thus, as can be seen, diethyl ether is the best solvent for the reaction in terms of yield and *endo*:*exo* ratio (entry 1). However, it is clear from the table that solvent is not the most crucial factor influencing the outcome of the reaction, although it does have a bearing on the outcome. In THF (entry 2), the solvent α-C-H insertion reaction (*vide infra* chapter 2.4) is far more important than in diethyl ether, presumably largely reflecting the relative ease of this reaction in the two solvents (for a dicussion of this point see chapter 2.4.1).

The use of DME as the solvent provided an interesting result (entry 3), as its use almost completely inhibited carbenoid formation. This may be due to the apparent insolubility of zinc chloride in DME: ordinarily, when chlorotrimethylsilane is added to zinc amalgam in dry diethyl ether, there is a modest amount of effervescence as, presumably, the zinc surface is cleaned (*vide supra* chapter 2.2.1.2), giving rise to a small amount of zinc chloride in solution; however, in DME this effervescence results in an immediate fine white precipitate. House has in fact published results showing that zinc chloride is only soluble in DME to a concentration of 0.05 M,[145] confirming this observation. Given the scale of the reaction (9.2 mmol of chlorotrimethylsilane in 10 ml of DME), only a tiny molar quantity of zinc chloride would be likely to remain in solution at saturation concentration. Thus, if zinc chloride complexation of the aldehyde is an important prelude to the reduction sequence, this would occur to a negligible degree in DME, with the result being no reaction. This effect is interesting, because Denmark has used DME extensively to stabilise the carbenoid formed from diethyl zinc and chloroiodomethane or diiodomethane.[79] It is then possible to envisage

using DME as a co-solvent with diethyl ether, so that the intermediate carbenoid could be stabilised a little and hence more efficient reactions achieved. Such suggestions should, however, be treated with caution, as it is also possible that a ligating solvent molecule may have to be displaced to allow the carbenoid to react (as commonly encountered in many transition metal systems), in which case if the solvent binds too tightly, this may be detrimental to reactivity.

Elphimoff-Felkin and Sarda had found, using zinc and boron trifluoride etherate to reductively deoxygenate aromatic aldehydes to zinc carbenoids, that the yield of cyclopropane formed from cyclohexene almost doubled when cyclohexene was used as the solvent rather than diethyl ether.[53] This is in contrast to the result obtained in the current system (entry 7), where the yield drops three-fold compared to diethyl ether. This reaction was also very slow, and took 40 hours to approach completion, in contrast to most of the reactions examined in chapters 2.2.1.3 - 2.2.1.7, which were invariably complete in approximately 15 hours.

2.2.1.5 Zinc Couple Variation

Throughout the history of the Simmons-Smith reaction, different groups have made use of different activation methods or zinc couples in the reaction. Consistently in this chemistry, zinc amalgam had been used. Thus several different couples, and simple acid washing as an activation process for zinc dust, were used in the standard cyclopropanation reaction, Equation **(30)**, with the results shown in **Table 9**.

Table 9. Results of zinc couple variation in the cyclopropanation of cyclohexene with *p*-anisaldehyde and chlorotrimethylsilane in refluxing diethyl ether

	Zinc	Yields and de / %			
		Cyclopropane§	de (endo / exo ratio)	Stilbene§	C-H Insertion#
1	Zn / Hg	45	92 (25:1)	-	2
2	Zn - Cu	35 (gc)	92 (25:1)	-	-
3	Zn - Ag	35	93 (28:1)	4	-
4	Zn_{act}	23	93 (30:1)	6	-

- C-H insertion refers to 3-(4-methoxyphenyl)-2-ethoxypropane; § - Cyclopropane refers to 7-(4-methoxyphenyl)bicyclo[4.1.0]heptane; Stilbene refers to (*E*) and (*Z*)-1,1'-(1,2-ethenediyl)*bis*(4-methoxybenzene); gc indicates that the yield was approximated using gc analysis.

The results from this series were a little surprising, both in terms of yields and *endo:exo* ratios. Clearly preparing a zinc couple does alter the property of the metallic system, and in

this case improve it with respect to the activated metal. Comparing then zinc amalgam (entry 1), and activated zinc (entry 4), the yield from the reaction almost halves, whilst the de increases quite dramatically. The zinc-copper couple (entry 2) and zinc-silver couple (entry 3) gave identical yields, both lower than that obtained using zinc amalgam. Interestingly though, the zinc-copper couple also led to the formation of an aromatic product, in a similar yield to the cyclopropane. However, the spectral complexity of this product prevented the elucidation of its structure.

At this stage there is no clear explanation for the results, and they can simply be regarded as an optimisation. There are many methods currently available for the activation of zinc, and as with many heterogeneous metallic systems, there are many 'tricks' involved in achieving optimal results - trial and error, rather than scientific fact, is frequently the defining principle in such circumstances.

2.2.1.6 Temperature Variation

To date, the large majority of these zinc carbenoid reactions, particularly cyclopropanations, had been carried out in refluxing solvent. Taking diethyl ether as the solvent in the standard reaction, Equation **(30)**, a 60°C temperature range was examined, and the results are presented in **Table 10**.

Table 10. Results of temperature variation in the cyclopropanation of cyclohexene with *p*-anisaldehyde, zinc amalgam and chlorotrimethylsilane in diethyl ether

	Temperature	Yields and de / %			
		Cyclopropane§	de (endo / exo ratio)	Stilbene§	C-H Insertion#
1	Reflux	45	92 (25:1)	-	2
2	Room temperature	59	95 (36:1)	2	-
3	0 °C	48	95 (38:1)	2.5	-
4	-30 °C	60	97 (64:1)	2	-

- C-H insertion refers to 3-(4-methoxyphenyl)-2-ethoxypropane; § - Cyclopropane refers to 7-(4-methoxyphenyl)bicyclo[4.1.0]heptane; Stilbene refers to (*E*) and (*Z*)-1,1'-(1,2-ethenediyl)*bis*(4-methoxybenzene).

The results found were very interesting. In all cases the aldehyde was completely consumed in a reaction time of approximately 15 hours. As can be seen, all temperatures below reflux (entry 1) give an improved yield and de. In fact, the de obtained by carrying the reaction out at -30°C is the highest ever observed in the cyclopropanation chemistry of the zinc - silicon electrophile system.

Considering first the yields from the reactions, they are not found to increase uniformly with temperature. At ambient temperature (entry 2) the yield is 14% higher than at reflux, but on cooling to 0°C (entry 3), the yield drops again to a level similar to that found at reflux. Cooling again to -30°C (entry 4) raises the yield again to 60%, just slightly higher than at ambient temperature. This non-linear sequence strongly indicates that there is an extremely energetically complex reaction profile necessary to form the carbenoid, with some steps being strongly temperature dependent. The result of this is the yield profile found with temperature. Overall, a lower temperature leads to a more discriminating carbenoid, and the highest yield of the sequence. From a preparative standpoint, it is very useful that the reaction can be done at both ambient and low temperatures, with approximately the same yield.

The diastereomeric excess (for *endo:exo*) in the reactions is found to increase dramatically with a decrease in temperature, as might be expected when kinetic control is dominating the transition state. On cooling the reaction mixture, the reduced reactivity of the carbenoid also presumably allows greater stereochemical differentiation. It would be interesting to see how far this reaction could in fact be cooled before carbenoid formation became too slow, and also what the effect of additional cooling would be on both the yield and de.

2.2.1.7 Lewis Acid Variation

Several related studies have used Lewis acids in the formation of zinc carbenoids, notably Wittig[130-135] and later Closs[136] using zinc (II) salts in the decomposition of aryldiazomethanes, and Elphimoff-Felkin[53,63] who reductively deoxygenated carbonyl compounds using zinc and boron trifluoride etherate. However, until recently, the influence of additional Lewis acids on the zinc - silicon electrophile system had not been considered. Zinc chloride is generated during the course of the reaction, and appears to be very important to the outcome of the reaction (*vide supra* chapter 2.2.1.4, *vide infra* chapter 2.2.2.5). It was recently found that adding zinc chloride to the reaction mixtures increases the reaction rate 100-fold in the conversion of hexadecanal to 1-hexadecene in diethyl ether, using chlorotrimethylsilane as the electrophile.[144] It is from this standpoint that the influence of Lewis acids on the course of the standard reaction, Equation **(30)** were investigated. The results are given in **Table 11**.

Table 11. Results of Lewis acid addition to the cyclopropanation of cyclohexene with *p*-anisaldehyde, zinc amalgam and chlorotrimethylsilane in refluxing diethyl ether

	Lewis Acid*	Yields and de / %			
		Cyclopropane§	de (endo / exo ratio)	Stilbene§	C-H Insertion#
1	None added	45	92 (25:1)	-	2
2	$ZnCl_2$ / 1 eq.	57	92 (25:1)	-	-
3	ZnI_2 / 1 eq.	37	93 (28:1)	5	-
4	$BF_3.OEt_2$ / 1 eq.	39	92 (25:1)	-	-
5	$MgBr_2$ / 1 eq.	4**	95 (40.5:1)	1.5**	-
6	$TiCl_4$ / 1 eq.	3	92 (23:1)	9	-

- C-H insertion refers to 3-(4-methoxyphenyl)-2-ethoxypropane; § - Cyclopropane refers to 7-(4-methoxyphenyl)bicyclo[4.1.0]heptane; Stilbene refers to (*E*) and (*Z*)-1,1'-(1,2-ethenediyl)*bis*(4-methoxybenzene); * - with respect to the aldehyde; ** - Based on recovered aldehyde.

The first important result is from the addition of zinc chloride to the reaction mixture (entry 2). When compared to the standard reaction where no Lewis acid was added (entry 1), there is an increase in yield, but no change in the *endo:exo* ratio. As the *endo:exo* ratio does not change, this indicates that zinc chloride chelation is not involved in the transition state, but that its role is much earlier in the reaction sequence. The yield increase may be caused by the faster release of a surface bound species into solution as a homogeneous carbenoid by the action of zinc chloride, which can of course then react rapidly. Alternatively, electron delivery from zinc to a carbonyl group - Lewis acid complex with zinc chloride could be faster and more efficient. These theories are discussed further in chapter 2.2.2.5.

Closs and co-workers had found in their studies that the *endo:exo* ratio of the cyclopropane formed by reaction of their zinc carbenoid increased when they moved from zinc chloride through zinc bromide to zinc iodide, although no yields were given.[136] Indeed, when zinc iodide is used in this system (entry 3) a modest increase in the *endo:exo* ratio over zinc chloride is observed. The temptation is then to say that zinc chloride results in a carbenoid such as **89**, and zinc iodide one such as **90**. From this viewpoint, using iodotrimethylsilane as the electrophile may be very instructive. However, the reaction of the carbonyl group with iodomethylsilane may also give a *gem* diiodide.

89

90

The use of boron trifluoride etherate (entry 4) led to a modest reduction in yield compared to a reaction in the absence of any Lewis acid, but the result was comparable in yield to that found by Elphimoff-Felkin,[53] although the *endo*:*exo* ratio was significantly better.

Using titanium tetrachloride in the reaction gave a result of little note (entry 6). However, it was of interest to find that on the addition of the titanium tetrachloride to the zinc amalgam and chlorotrimethylsilane in diethyl ether, the reaction mixture adopted a deep blue colour, which persisted (tinged with green) throughout the reaction. The possibility that such a system would be capable of quite different chemistry should not be ignored.[140] At the simplest level it is of note that the dicarbonyl coupling reaction occurred in 9% yield, over a 3% yield for the cyclopropanation. As a note of caution, though, McMurry's dicarbonyl coupling reaction should be borne in mind when considering this result (one of the earliest reported methods for the generation of low valent titanium involved the reaction of zinc dust with titanium tetrachloride).[142]

Drawing these results together, it is clear that this reaction system is both complex and subtle. The results found have certainly asked more questions than have been answered, although this perhaps should be expected in a study of mechanism. Several broad conclusions can nevertheless be drawn:

(i) The best solvent for the reaction is diethyl ether, although solvent does not have a dramatic influence on the course of the reaction. The presence of zinc chloride is important to the course of the reaction, and adding zinc·chloride to the reaction mixture elevates the yield.

(ii) Results from the electrophile variation were complex, but clearly showed the superiority of a *bis* silicon electrophile over one effecting intermolecular delivery of the second silicon atom.

(iii) Zinc amalgam is the best form of zinc for the reactions.

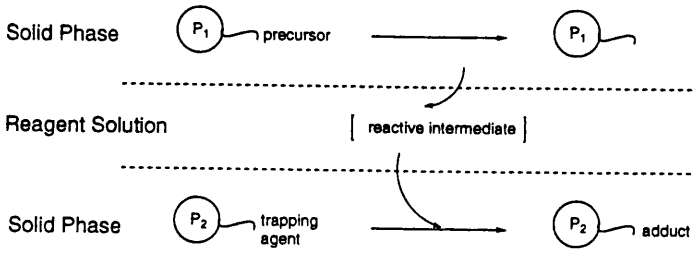
(iv) Lowering the reaction temperature increases both the yield and de of the product cyclopropane.

At this stage a programmed rate study would be particularly instructive, and at a much simpler level, varying the addition times of the aldehyde and following the rate of aldehyde consumption. Although a 12 hour addition time was used routinely in this work, and 36 hour for intramolecular systems, this is almost certainly unnecessary, and could be reduced considerably without causing competitive side-reactions, such as dicarbonyl coupling.

2.2.2 The Three-Phase Test

One of the most fundamental questions which had remained unaddressed about this reaction§ since its inception was whether the zinc carbenoid formed was homo- or heterogeneous. With such information appearing pivotal to the further development of this chemistry, a programmed investigation into this area was planned. The expectation was that, whatever the outcome, the knowledge gained would open new areas of research.

The first major problem to overcome was how such a transient intermediate could be detected, and how the detection would allow a positive confirmation of homo- or heterogeneity. In 1974, Rebek and co-workers, in a wave of popularity for solid phase synthesis[146], published results from a new mechanistic probe for the detection of reactive intermediates. They called it 'The Three-Phase Test'.[147,148] The concept was beautifully simple, and the results outstanding. As the name suggests, there were three phases to the reaction, two solid phases, and a liquid phase. For the purposes of Rebek's work, a precursor to the suspected intermediate was attached to one solid phase and liberated by a solution of an appropriate reagent, in the presence of a second solid phase bearing a trapping agent (**Scheme 54**). The detection of an adduct provided positive evidence for a free intermediate, as statistically a reaction between two solid phases is extremely unlikely (to the point of it never occurring).



Scheme 54

If this system is then applied to the zinc carbenoid reaction, the zinc amalgam acts as one solid phase, the aldehyde is the reagent solution, which then forms the carbenoid by reaction with the solid zinc, and the second phase would simply be a polymer bound alkene. If the carbenoid (which is known reliably to form with the action of zinc and chlorotrimethylsilane on an aromatic aldehyde) is in solution, it will react with the polymer bound alkene to afford a polymer bound cyclopropane. If, however, it is heterogeneous, no adduct will form. With this method of determination in hand, routes to a suitable polymer bound alkene were considered.

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§ Referring to the reductive deoxygenation of a carbonyl compound using zinc and a silicon electrophile.

2.2.2.1 Choosing the Polymer Bound Alkene

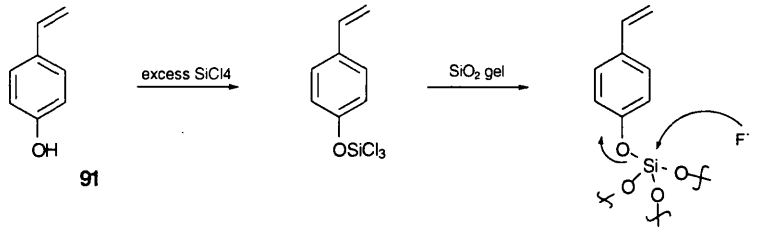
The choice made for the trapping agent had to fill several important criteria:

(i) As cyclopropanation reactions were very reliable in terms of yield and minimal by-product formation, an alkene was chosen, and more specifically, a styrene was selected, given the precedent for high yielding reactions[139] (*vide infra* Chapter 2.3.1). This factor was considered to be important by Rebek for the success of the test.[147] Using a styrene derivative had the second advantage that it would place the reactive site 4 atoms above the solid surface; the minimum in the Three-Phase Test had been 3 atom spacers, and this distance obviously could have a crucial influence on the outcome of the reaction. It is easy to imagine that if the reactive site was too close to the polymer surface, it becomes effectively inaccessible to any reagent.

(ii) The polymer should have a high surface area, as a successful reaction with a solution phase carbenoid is still heterogeneous, and as such, will be promoted by increased surface area.

(iii) Analysis of the polymer bound alkene / adduct had to be possible after the reaction, and beyond this it was decided that the most reliable results would be obtained if the alkene / adduct could be cleaved from the polymer support after the reaction and subjected to 'normal' analytical techniques (NMR, IR, mass spectrometry, and so on).

Thus, a *para*-substituted styrene attached to a solid phase seemed the most appropriate choice. Initially, the possibility of using silica gel as the solid support was examined. The basic synthetic strategy is outlined in **Scheme 55**. It relies on the synthesis of *p*-hydroxystyrene **91**, which is then supported onto silica gel in a two step sequence, reminiscent of the preparation of reverse-phase silica gel.[149,150] Cleavage of the alkene / adduct from the surface should then be accomplished using fluoride anion.



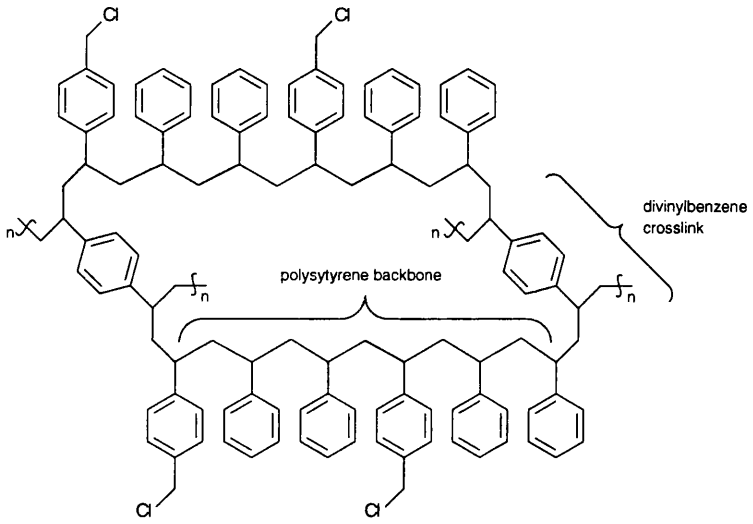
91

Scheme 55

However, extreme difficulties were encountered in the synthesis of **91**. which is prone to rapid polymerisation (and indeed is known industrially as a polymerisation agent). With only two rather tedious and inefficient literature syntheses known,[151,152] and given the

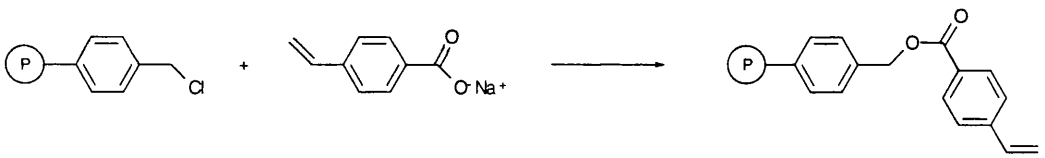
instability of **91**, this route to the polymer was abandoned, and a rather more conventional route considered.

Merrifield's resin was instead chosen as the polymer support. The resin is a polymer with a polystyrene backbone, 2% crosslinked with divinyl benzene (a cross-linked polymer is essential if it is necessary to mill it to a fine powder). The backbone is chloromethylated to the extent of one milli-equivalent of chlorine per gram (**Scheme 56**).



Scheme 56

It seemed reasonable to assume that the salt of *p*-vinylbenzoic acid would react with the polymer to afford the polymer supported alkene (**Scheme 57**), and that the ester link could be later saponified under basic conditions to yield the alkene / adduct. This strategy was adopted, and is described in the following sections. However, as a necessary prelude, initial work did not involve the polymer, but testing substrate suitability in a 'two-phase' system.

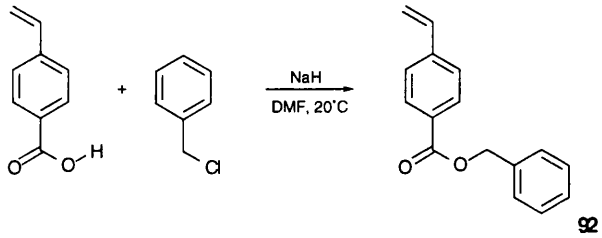


Scheme 57

2.2.2.2 Two Phase Analogue - Determination of Substrate Suitability

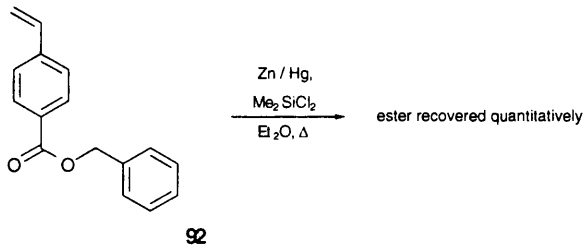
Thus, before the polymer system could be examined it was necessary to determine that (i) a styrene *para*-substituted with a benzyl ester would be stable to the zinc carbenoid reaction conditions - particularly that it did not decompose, or that the ester link was not cleaved, and (ii) that under standard 'two-phase' conditions the cyclopropanation of the styrene proceeded in a moderate yield.

If the polymer support is ignored in **Scheme 57**, the product of the reaction is benzyl-4-vinylbenzoate, which may then be used as a 'two-phase' mimic of the three-phase alkene. The ester **92** was prepared in a very clean reaction between the preformed sodium salt of *p*-vinylbenzoic acid and benzyl chloride (**Scheme 58**). However, the ester **92** decomposed rapidly on isolation and column chromatography, with an isolated yield of only 7%. That the product was so susceptible to what was presumably an alkyl-oxygen cleavage was worrying, as it suggested that the polymer ester link would be unstable to the zinc carbenoid reaction conditions.



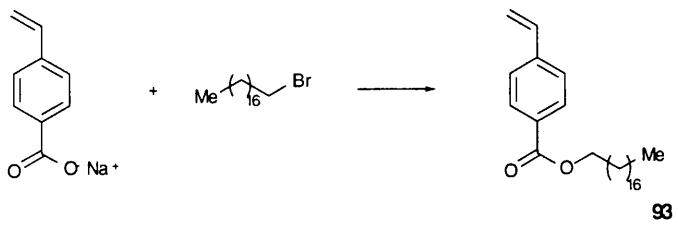
Scheme 58

In the event, when **92** was refluxed overnight in diethyl ether, in the presence of 10 mole equivalents of zinc amalgam and 2 mole equivalents of dichlorodimethylsilane (i.e. all the reactants required for the zinc carbenoid reaction except the carbonyl compound), the ester **92** was recovered quantitatively, indicating the ester link is stable to the reaction conditions (**Scheme 59**).



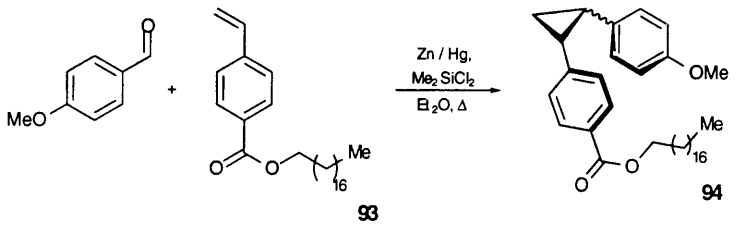
Scheme 59

It was still necessary to carry out a 'two-phase' cyclopropanation using a similar substrate to the polymer bound alkene. Due to the instability of the benzyl ester **92** and the difficulties encountered its isolation, a long chain alkyl ester **93** was prepared (**Scheme 60**), where arguably the C_{18} chain would act as something of a polymer mimic.



Scheme 60

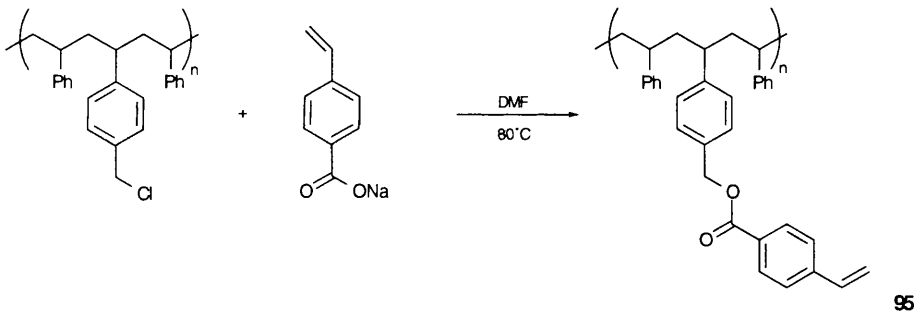
Under the conditions for cyclopropanation, using *p*-anisaldehyde as the carbenoid precursor, the cyclopropane adduct **94** was isolated in a moderate 40% yield (56% based on recovered alkene) (**Scheme 61**). This yield was high enough to allow work on the polymer system to proceed - in essence it was high enough to be confident that an adduct could be isolated from the Three-Phase Test, were one to form.



Scheme 61

2.2.2.3 Preparation of Polymer Supported Alkene

The polymer supported alkene was formed in an identical fashion to the 'two phase' analogue, by the reaction of the preformed sodium salt of *p*-vinylbenzoic acid with a suspension of Merrifield's resin in DMF at 80°C (**Scheme 62**). Cl analysis on the product polymer **95** suggested that the reaction had gone to 84% completion (i.e. only 16% of the chloromethyl residues on the Merrifield's resin remained). The polymer was characterised by IR, where the ester carbonyl stretch was clearly visible. It is important to note that the reaction was carried out in DMF: most polymer reactions are carried out in solvents such as DMF, DMSO, pyridine and benzene which swell the polymer, allowing all the reactive sites maximum freedom. Solvents such as dioxane, alcohols, diethyl ether and tetrahydrofuran are considerably less efficient.[146]



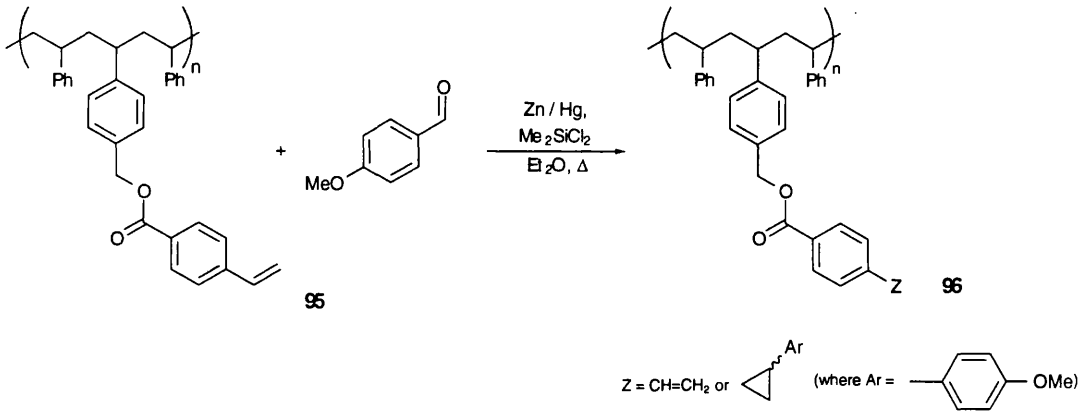
Scheme 62

Before the Three-Phase Test was conducted, it was necessary to establish that the ester link would not cleave under the reaction conditions, thus rendering the alkene homogeneous, and a false result arise. Exposure of this polymer **95** to the standard zinc carbenoid reaction conditions (10 mole equivalents of zinc amalgam, 1.5 mole equivalents of dichlorodimethylsilane and 0.5 mole equivalents of zinc chloride in refluxing diethyl ether) gave no cleavage of the ester link. Thus, as had been hoped, the polymer bound system

exhibited analogous stability to the 'two-phase' system (*vide supra* chapter 2.2.2.2). All control experiments having been performed, it was now possible to carry out the Three-Phase Test.

2.2.2.4 The Three-Phase Test

The Three-Phase Test on polymer **95** was carried by the slow addition (12 hour) of an ethereal solution of *p*-anisaldehyde to a refluxing suspension of zinc amalgam (10 mole equivalents), the polymer (1 mole equivalent) and dichlorodimethylsilane (2 mole equivalents) in diethyl ether (**Scheme 63**). On complete addition of the aldehyde, the zinc amalgam and polymer were filtered off under suction, and the filtrate quenched in the normal manner. The zinc was separated from the polymer by settling in diethyl ether (the less dense upper polymer layer may be pipetted from the surface of the zinc). Both the material isolated from the filtrate and the polymer were analysed.



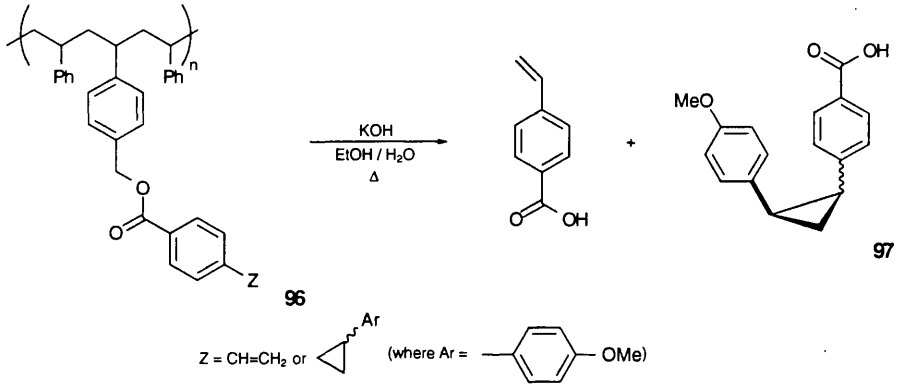
Scheme 63

NMR analysis of the residue from the filtrate indicated that there was material derived from dichlorodimethylsilane and from aromatic residues, but no identifiable products. The IR of the polymer had the same characteristics of the polymer before the reaction, but as the discrete C=C stretch of the alkene had not been visible, and little change could be expected in the aromatic C=C region (as the polymer itself is largely aromatic), this was not surprising. At this stage, before attempting to cleave the ester link in the recovered polymer , an attempt was made at ^{13}C NMR studies of the polymers in hand (i.e. Merrifield's resin, **Scheme 56**, and the product polymer **96**). Working on the principle that, at least in polymer **96**, the ester / cyclopropane segment of the polymer would be far enough away from the backbone to have enough rotational freedom to mimic the solution state, and thereby record a spectrum. Principally, it was hoped that if the cyclopropane had formed in **96**, the methoxy methyl group would be very clear on the spectrum. In the event, however, no reasonable spectrum could be recorded for any of the samples, suggesting that the backbone in this polymer is far too rigid to permit the 'flexing' necessary for solid-state polymer NMR.

The next stage thus involved saponification of the ester linkage, and analysis of the product mixture obtained.

2.2.2.5 Saponification of the Ester Linkage on the Polymer

Cleavage of the ester linkage was carried out in a 5% solution of potassium hydroxide in ethanol - water (**Scheme 64**). After stirring overnight at room temperature, tlc indicated the formation of two very faint UV active spots, one which was very non-polar, and a second which was considerably more polar, and appeared to be the acid. As this suggested that the saponification was very slow at room temperature, the reaction mixture was gently heated to 70 °C, although this resulted in a darkening of the reaction mixture, to a final deep red colour after 14 hours. On work up the filtrate afforded a small quantity of solid. The quantity isolated suggested that decomposition may have occurred during the saponification. This was then analysed without further purification.



Scheme 64

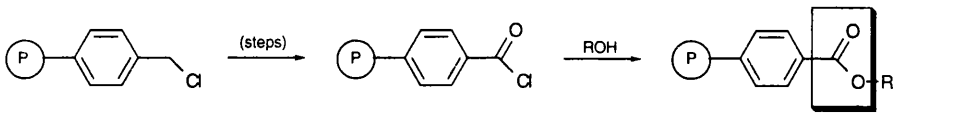
^{1}H NMR of the solid indicated that it was largely recovered *p*-vinylbenzoic acid, but there appeared to be baseline peaks that could be attributed to the cyclopropane. Thus, with possibly less than 5% of the sample being cyclopropane **97** (when the quantity of material recovered from the cyclopropanation represented only a 7-14% mass balance), GCMS was used to provide a positive identification, showing that the sample was principally a binary mixture of *p*-vinylbenzoic acid and the cyclopropane **97**.

Although isolating the cyclopropane **97** indicated the carbenoid's homogeneity, the extremely low yield was rather worrying. Several explanations for this should be considered:

(i) It is possible that the efficiency of the Three-Phase Test was considerably reduced because the reaction was carried out in diethyl ether, a solvent not used generally in polymer chemistry (as earlier discussed; *vide supra* chapter 2.2.2.3). If the reactive sites on the polymer were relatively inaccessible due to minimal swelling by the solvent, the reaction would only ever be low yielding, as only sites on the outside of the polymer would react. This

may account for the high recovery of *p*-vinylbenzoic acid, and the low overall recovery could also be related to point (ii).

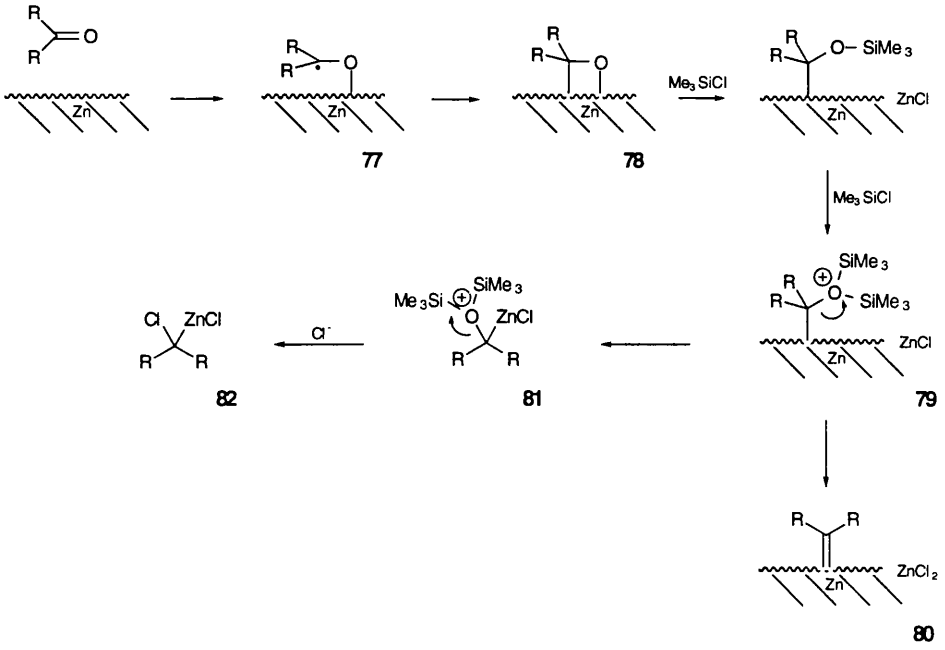
(ii) There appeared to be decomposition during the saponification sequence. The cyclopropane would be more susceptible to base catalysed decomposition than *p*-vinylbenzoic acid, which could explain the poor yield. It is also possible that the ester link does not cleave readily, and that the hydrolysis step is the problem. This is backed up circumstantially by that fact that in much polymer work where an ester linkage is used, the chloromethyl residue on the starting Merrifield's resin is first converted to an acid chloride, which is then reacted with an alcohol, so that in effect the ester link is reversed (**Scheme 65**). Such systems appear to cleave at room temperature using ammonium hydroxide solution.[153]



Scheme 65

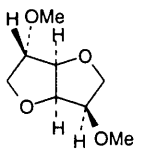
(iii) A more perplexing conclusion would be that the species is sometimes homogeneous and sometimes heterogeneous, and that, for instance, in the presence of zinc chloride, a homogeneous entity is formed. This would account for the low yield of cyclopropane (derived from a homogeneous carbenoid), as the zinc chloride concentration would have always been low (reaching 1 mole equivalent with respect to the aldehyde on complete aldehyde addition). It has indeed already been observed that the zinc carbenoid reaction undergoes a 100-fold rate increase on the addition of 2 mole equivalents of zinc chloride to the reaction mixture (in an aldehyde to alkene conversion), with the reaction profile strongly suggesting that the reaction is auto-catalytic with respect to zinc chloride.[144] This rate increase could be attributed to the formation of a homogeneous carbenoid rather than a heterogeneous one, the former reacting far more rapidly than the latter.

Returning then to the mechanism proposed for the reaction (**Scheme 51**), the rationale for the effect of zinc chloride remains plausible. Simply, in the presence of a stoichiometric quantity of zinc chloride, the route to the homogeneous Simmons-Smith - type species **81** or **82** would seem far more favourable if there was already zinc chloride in solution as well as the surface-bound material being formed during the reductive sequence. Beyond this role for zinc chloride in the mechanism, intuitively one would expect it to complex the carbonyl oxygen of unreacted carbonyl compound, thereby making the carbonyl carbon more electrophilic, and hence more susceptible to reduction. In fact, a structural study has been published on this complexation (between zinc chloride and benzaldehyde).[154] Although the complexation is apparently very poor, the complexed species does show some weakening of the carbonyl double bond and increased positive character of the carbonyl carbon.



Scheme 51

In conclusion, this mechanistic assay showed *de facto* that a homogeneous carbenoid was formed during the reaction. It remains, however, to be established whether this species is formed by the major mechanistic pathway, and is the 'normal' intermediate in these reactions, or whether it arises from a minor pathway. If the latter is the case, it should be possible to determine the factors controlling the operation of this mechanistic route, and thus generate a homogeneous species exclusively. In the case of the former, the opportunity now exists for an enantioselective zinc carbenoid reaction. Given the knowledge already gained about the influences of certain functional groups on the reaction (in terms of inhibiting carbenoid formation), it should be possible to devise a suitable chiral ligand for the carbenoid. Many of the systems used in the Simmons - Smith reaction (*vide supra* chapter 1.3.3) are ruled out due to the presence of free alcohol groups which would lead to hydrolysis of the silicon electrophile (although in a controlled fashion this is not necessarily detrimental to carbenoid generation - *vide supra* chapter 2.2.1.3). Nitrogenous systems would have to be ruled out as potential ligands due to their inhibition of carbenoid formation,[144] either as an additive in the reaction mixture, or as a functional group on the carbonyl compound. Given the apparent importance of ether complexation to the carbenoid (*vide supra* chapter 2.2.1.4), a chiral ether may well prove a suitable start point for any such investigation - isosorbide dimethyl ether **98** is a cheap commercially available example. Chiral esters are also a possibility.



98

At this stage it is also pertinent to recall that the generation of an organozinc carbenoid from the reaction of a diazo compound and zinc chloride has been described (*vide infra* chapter 1.4).[136] It would therefore perhaps be of interest to examine the homogeneity or otherwise of this species, and to attempt some form of comparison other than product analysis with the organozinc carbenoid generated by the reductive deoxygenation of a carbonyl compound. However, the reported lifetimes ($t_{1/2} \approx 0.2$ sec. for *p*-tolyldiazomethane)[136] of the carbenoids formed by the decomposition of diazo compounds might render such a task difficult.

Overall, these studies on the mechanism have served to further highlight its complexity. In the context of the Three Phase Test results, further work should be done on the saponification of the polymer ester link, and also on the influence of the addition of zinc chloride on the final result. The results have, to some degree, shown up the major failing of the Three Phase Test, in that although the result may prove that an intermediate exists, it gives little information about that intermediate.

One of the overriding features of this chemistry is the apparent rapidity with which the carbenoid is formed. This should be quantified by a rate study, and eventually the long reaction times currently used should become unneccessary.

2.3 Cyclopropanation Studies

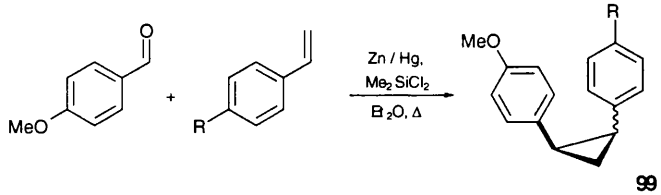
The synthetic utility of the cyclopropanation of alkenes using the zinc carbenoid formed by the reductive deoxygenation of an aldehyde in the presence of zinc amalgam and a silicon electrophile has already been clearly demonstrated.[64,67] The method has the clear advantage over procedures like the Simmons-Smith reaction and the transition metal catalysed decomposition of diazo compounds, in that it does not require the use of explosive intermediates. Furthermore, the carbenoid precursor - a carbonyl compound - is generally readily available.

The mechanism of cyclopropanation in this system is believed to be similar to that developed by Casey[65] to explain the stereoselectivities observed in the cyclopropanation of alkenes by tungsten carbene complexes. The following two sections (chapters 2.3.1 and 2.3.2) present the results from a series of reactions designed to provide further evidence for the Casey model, and to determine whether the zinc carbenoid formed in these systems is electrophilic, nucleophilic, or rather ambivalent in its reactivity.

2.3.1 Cyclopropanation of *para*-Substituted Styrenes

Earlier results from the cyclopropanation of styrene using various *para*-substituted aromatic aldehydes had led to the suggestion that Casey's mechanistic model[65] applied to this system.[139] It had been found that both the yield and diastereomeric excess (de) of the cyclopropane decreased with increasing electron-withdrawing ability of the *para* substituent on the aldehyde, a correlation which Casey's model would predict. Considering then the other partner in this cyclopropanation reaction, it was decided to investigate the influence of the *para* substituent on styrene on the course (yield and de) of the reaction. It was further hoped that by changing the electronic characteristics of the alkene, some information would be gained as to the (electronic) nature of the zinc carbenoid.

The general reaction under consideration is shown in **Scheme 66**. All reactions were carried out under identical conditions: a solution of the aldehyde in diethyl ether was added over 12 hour to a refluxing suspension of zinc amalgam (10 mole equivalents), dichlorodimethylsilane (2 mole equivalents), and the styrene (2 mole equivalents, except for the ester substituent, where only 1 equivalent was used)). **Table 12** gives the yields and de's for the substrates examined.



99

Scheme 66

Table 12. Results of the cyclopropanation of variously *para*-substituted styrenes with *p*-anisaldehyde, zinc amalgam and dichlorodimethylsilane

	R (in 99)	Yield of Cyclopropane, % (*cis*: *trans* isomer ratio, de)	Other Products
1	OMe	-	-
2	Me	58 (30:1, 94%)	-
3	H	58 (26:1, 93%)	stilbene§ 7%
4	Cl	48 (27:1, 93%)	stilbene§ 4%
5	F	58 (35:1, 94%)	-
6	CF_3	46 (38:1, 95%)	-
7	$CO_2(CH_2)_{17}Me$	40 (56 based on recovered alkene) (29:1, 93%)	stilbene§ 5%

§ - Stilbene refers to (*E*) and (*Z*)-1,1'-(1,2-ethenediyl)*bis*(4-methoxybenzene)

The yields in the series are explained by consideration of how electron rich or poor the alkene is, whilst a correlation of the diastereoselectivities is attempted using a mechanistic model. The variation in yield will be considered first.

p-Methoxystyrene (entry 1, **Table 12**) was found to be too electron rich to be stable under the reaction conditions, and indeed polymerised instantly in the presence of zinc amalgam and dichlorodimethylsilane. Considering entries 2-7, at a first glance it would appear that the zinc carbenoid exhibits little electronic discrimination - the yield from *p*-fluorostyrene is the same as that from *p*-methylstyrene, yet *p*-chlorostyrene is 10% lower. However, the yields correlate well to the Hammett substituent constants σ^0 for a *para* substituent on an aromatic ring. The relevant values are listed in **Table 13**,[155,156] with the sign and magnitude of σ^0 expressing the capability of a substituent to perturb its electronic environment; broadly speaking, a negative value implies an electron donating group, whilst a positive value implies an electron withdrawing group.

Table 13. Hammett substituent constants for linear free energy relationship use[155]

	Substituent (*para* position)	σ^0
1	Me	-0.14
2	OMe	-0.12
3	H	0
4	F	0.15
5	Cl	0.24
6	CO_2R	0.44
7	CF_3	0.53

As can be clearly seen from **Table 13**, the Hammett substituent constants do not correlate exactly with the popularly held beliefs that a fluorine substituent is more electron withdrawing than a chlorine (at least this is not so for an aromatic system), or that a methoxy group will be more electron donating than a methyl group. If **Table 13** is now modified to include the yields from **Table 12**, a strong correlation is seen between how electron rich the alkene is, and how high the yield is in the cyclopropanation (**Table 14**).

Table 14. Hammett substituent constants and yields from the cyclopropanation of variously *para*-substituted styrenes with the zinc carbenoid derived from *p*-anisaldehyde

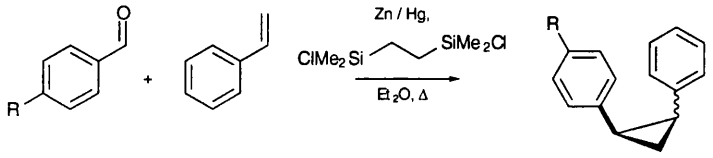
	Substituent (*para* position)	σ^0	Yield / %
1	Me	-0.14	58
2	OMe	-0.12	-
3	H	0	58
4	F	0.15	58
5	Cl	0.24	48
6	CO_2R	0.44	40 (56*)
7	CF_3	0.53	46

* - based on recovered alkene

Although the correlation is not perfect, the carbenoid can be seen to be expressing a distinct preference for a more electron rich alkene (and is hence rather electrophilic in its behaviour). Entry 6 may not represent a valid result as only one equivalent of alkene was used in the reaction, not two as with all the others, and also long alkyl chains (R = C_{18}) are known to be the cause of unusual properties and effects. The fact that *p*-fluorostyrene (entry

4) gave the same yield as both *p*-methylstyrene (entry 1) and styrene (entry 3), given the difference in the Hammett constants for these substituents, does suggest that stabilisation in the transition state, as well as influencing the de, also affects the yield.

It is also perhaps pertinent at this stage to re-examine the yields from the cyclopropanation of styrene with a series of variously *para*-substituted aldehydes.[139] Using again a Hammett substituent constant correlation, a trend is found, as with the variation in the *para*-substituent of the styrenes (see **Table 14**). Thus, in **Table 15** the yields from the cyclopropanation of styrene with the carbenoid derived from variously *para*-substituted aromatic aldehydes (**Scheme 67**) are given, together with the Hammett substituent constants.



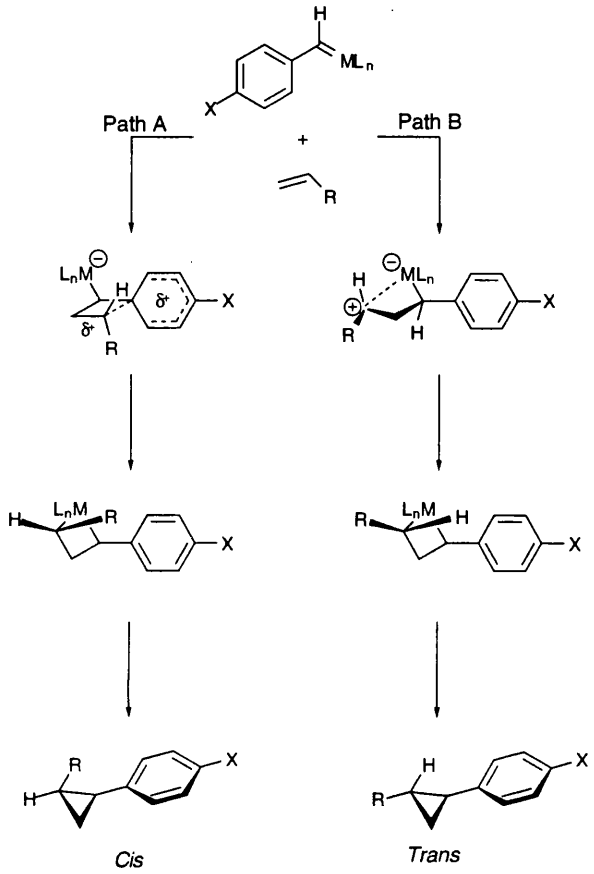
Scheme 67

Table 15. Hammett substituent constants and yields from the cyclopropanation of styrene with the zinc carbenoid derived from variously *para*-substituted aromatic aldehydes[139]

	Substituent (R in Scheme 67)	σ^0	Yield / %
1	Me	-0.14	87
2	OMe	-0.12	99
3	H	0	57
4	Cl	0.24	57

As found earlier with the variation of the *para*-substituent on the styrene, the correlation is not perfect, but is clear that a more electron-donating substituent on the aldehyde results in a higher yield of product cyclopropane. This presumably reflects the importance of the anchimeric assistance of the *para*-substituent on the aldehyde in the expulsion of the leaving group in the step prior to carbenoid formation (*vide supra* chapter 2.1).

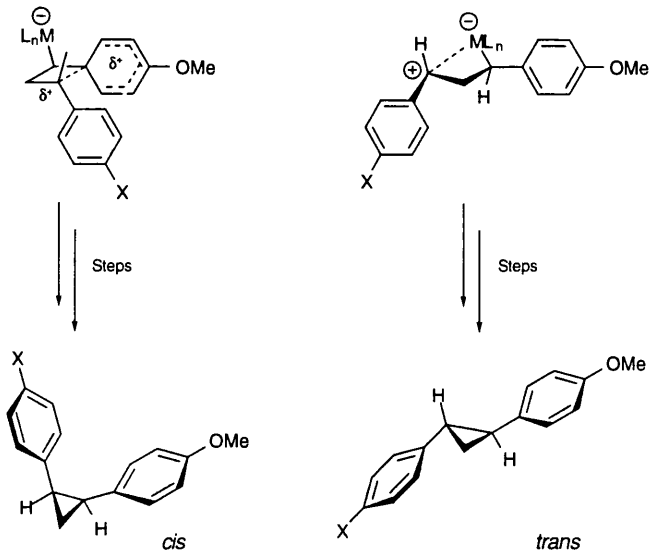
As earlier mentioned, the working mechanistic hypothesis for this reaction was based on a model developed by Casey.[65] The reaction can follow two distinctive mechanistic pathways - one, where steric considerations override any other, gives rise to the *trans* cyclopropane (Path B), and a second where *ipso* stabilisation of the developing positive charge on the alkene gives rise to the *cis* cyclopropane (Path A) (**Scheme 22**, reproduced here for clarity).



Scheme 22

When the substituent X was varied for a series of aromatic aldehydes (i.e. the zinc carbenoid portion), yields and de's were found to drop fairly uniformly with decreasing electron donating ability of the substituent X.[139] Thus, as the *ipso* stabilisation of the developing positive charge on the more substituted end of the alkene in Path A becomes less important (i.e. with a less electron-donating X group), the result is that steric consideration in the transition state becomes more important, and Path B occurs more frequently.

However, for the results in hand, where the *para*-substituent on the alkene portion is varied, the situation becomes a little more complex, and the fact that it is much more of a balance between several opposing factors becomes evident. Thus there is the tendency of the carbenoid to react with the alkene in the first instance, and stabilisation from the aldehyde portion in the transition state, juxtaposed with the electronic influence of the *para*-substituent on the styrene fragment. In **Scheme 68**, the two possible transition states in the Casey model before metallocyclobutane formation have been redrawn, showing the alkene substitution.

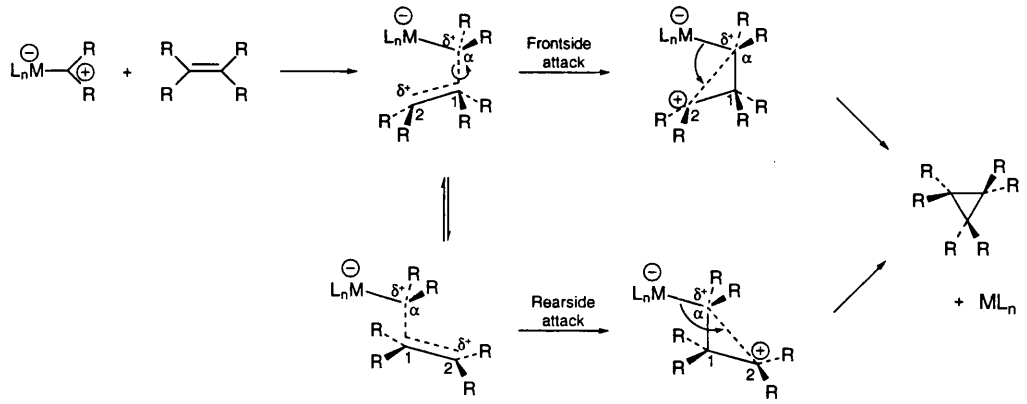


Scheme 68

Thus, the stabilisation from the aldehyde (carbenoid) portion is constant, as are steric considerations, except, perhaps for the case where X is the ester group ($CO_2(CH_2)_{17}Me$). The results then should derive only from the influence of the X group on the alkene portion.

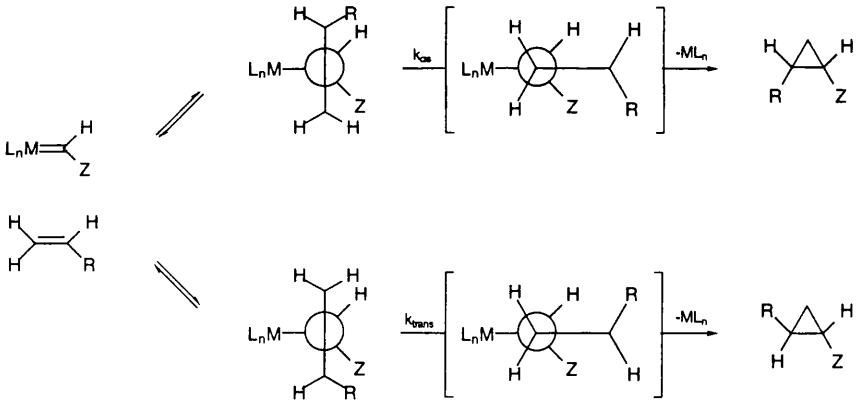
Considering then the transition state leading to the *cis* cyclopropane in **Scheme 68**, it is reasonable to assume that as X becomes more electron withdrawing, the developing positive charge on the α-carbon becomes more important, and hence the stabilisation from the carbenoid portion is more important, so this route is increasingly favoured. To an extent this is found with the results: more electron donating substituents such as the methyl group (*cis:trans* 30:1) neutralise the developing positive charge somewhat, and the *ipso*-stabilisation is less important; fluoro (*cis:trans* 35:1) and trifluoromethyl (*cis:trans* 38:1) substituents augment the developing charge, and make the route to the *cis* isomer, where the *ipso* stabilisation can occur, increasingly favoured. The result from the ester substituted styrene (*cis:trans* 29:1) is likely to be anomalous for the reasons discussed earlier. However, that the result from the chloro-substituted styrene (*cis:trans* 27:1) does not fit comfortably into the series is a little surprising.

It is perhaps important to note that in the general sphere of transition metal carbene cyclopropanation reactions, mechanisms are constantly undergoing reappraisal, with the ultimate goal to find a single unifying explanation for all results. Whilst this is an unrealistic prospect, there are principally two other mechanisms which are used as widely as Casey's model, although neither appears applicable to the system in hand. The first, proposed by Brookhart involves the nucleophilic attack of the alkene on the electrophilic carbene complex. No metallocyclobutane is formed, but there is substantial charge development in the transition state, with two stereochemically different modes of ring closure (frontside and backside) to afford the product cyclopropane (**Scheme 69**).[9] (Obviously for the example given both modes result in the identical cyclopropane).



Scheme 69

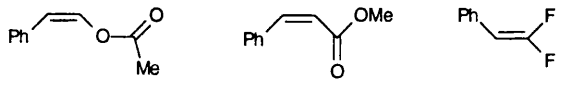
The second model is particularly surprising as it seems simply to account for the formation of a cyclopropane at the end of a reaction - it neither explains the stereochemical outcome, nor the influence of the ML_n on the outcome of the reaction. The mechanism, proposed by Doyle, invokes formation of π-complexes prior to backside closure in the transition state (**Scheme 70**).[12] Backside closure results in cyclopropane formation, with the *cis*:*trans* ratio in the cyclopropane product being explained through the rates of formation of the initial π-complexes.



Scheme 70

2.3.2 Electronic Influence of the Alkene on Cyclopropanations

Whilst the results from the cyclopropanation of the series of *para*-substituted styrenes discussed in chapter 2.3.1 provided some mechanistic insight, it was clear that in order to gain information about the electronic preferences of the zinc carbenoid, a more electronically extreme series of alkenes would be necessary. The carbenoid has already been shown to behave as an electrophile (*vide supra* chapter 2.3.1), but its reactivity had not been examined using alkenes which were more electronically 'extreme'. In an effort to probe this issue, the alkenes shown in **Scheme 71** were selected as substrates.

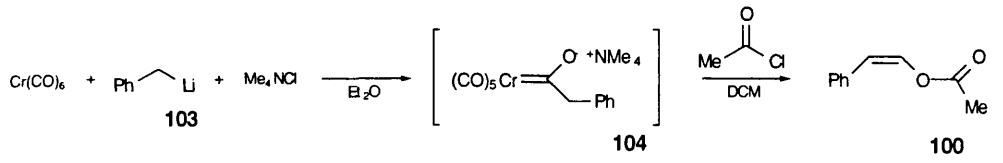


100 **101** **102**

Scheme 71

The first point to consider when choosing substrates was that, as far as possible, they should make equal steric demands on the transition state. Earlier studies indicated that *cis*-1,2-disubstituted alkenes are higher yielding in cyclopropanations than the corresponding *trans* isomer, and for these reasons the *Z* isomers of **100** and **101** were chosen.[144] The (Z)-enol ester **100**, accessible in a stereoselective manner via a chromium (acyloxy)carbene complex,[157] was selected as an electron-rich alkene. The electron-deficient alkene chosen was the (Z)-unsaturated ester **101**, in essence a substituted acrylate, which could be accessed using Still's modification of the Horner-Emmons olefination.[158] The *gem*-difluoroalkene **102** was selected because of its unique electronic properties due to the CF_2 group (*-I* effects result in an electron poor σ–framework, whilst p-π orbital overlap gives rise to an electron rich π-framework). **102** will also provide a useful comparison with styrene, as the *gem*-difluoro group is very compact, and would also be an interesting opening to 1,1-difluoro-cyclopropanes, species which may have biological activity.

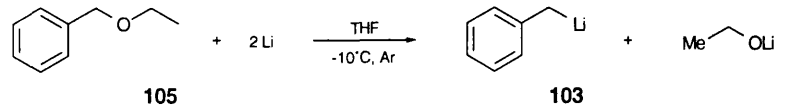
The only literature synthesis to afford (Z)-enol ester **100** stereoselectively was via the route shown in **Scheme 72**.[157]



103 **104** **100**

Scheme 72

Thus the preformed complex of tetramethylammonium pentacarbonyl(1-oxy-2-phenyl-ethylidene)chromate(0) is reacted in dichloromethane with one equivalent of acetyl chloride at -40 °C, and on slow warming to ambient temperature, an elimination occurs to afford the predominantly (Z)-enol ester. The formation of chromium carbene complex **104** required the preparation of benzyl lithium **103**.



105 **103**

Scheme 73

Benzyl lithium is not available by the more standard routes, such as lithiation of toluene by *n*-butyllithium, or the reaction of benzyl halides with lithium, although the former route gives a quantitative conversion if 1:1 complexes of *n*-butyllithium with *N,N,N',N'*-tetramethylethylenediamine (TMEDA) or 1,4-diazabicyclo[2.2.2]octane (DABCO) are

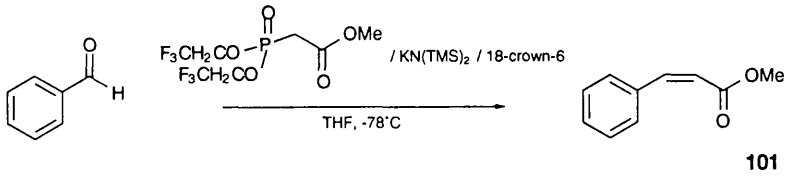
used.[159] As the influence of such additives in this reaction was unknown, benzyl lithium was prepared by the route shown in **Scheme 73**. Benzyl ethyl ether was synthesised in a Williamson-type procedure from sodium ethoxide and benzyl bromide, in a modest 58% yield. The product was fairly volatile, and this almost certainly accounts for the yield. The preparation of the organolithium did not proceed as expected, and afforded only a 0.5 M solution of benzyl lithium, as a result of significant decomposition. This was almost certainly the result of the long initiation period for the reaction whilst the oxide coating on the lithium was abraded by the glass chips, which was followed by too rapid a reaction, as a significant quantity of benzyl ethyl ether had, by then, been added.

The freshly prepared benzyl lithium was used directly in the preparation of the chromium carbene complex **104**. As no experimental procedure was described in the paper, standard Schlenk techniques for the synthesis of chromium carbenes were employed. When **104** had been generated as the salt, the solvent was removed *in vacuo* and the residue dissolved in dichloromethane and cooled to -40 °C. One equivalent of acetyl chloride was then added, and the reaction left to warm overnight. Unfortunately, chromatography of the crude product mixture afforded none of the desired enol ester.

This procedure almost certainly failed due to the instability of the intermediate carbene complex **104**, which would be powerfully nucleophilic. In hindsight, it was probably unnecessary to form the tetramethylammonium salt, but instead the intermediate could have been directly quenched by the addition of acetyl chloride. It is perhaps also important to note that enol esters of the type **100** are extremely unstable and moisture sensitive, and have been reported to decompose after two weeks storage at -18 °C.

Although the synthesis of enol ester **100** had been unsuccessful, compounds **101** and **102** were still prepared and their reactivity towards the zinc carbenoid probed.

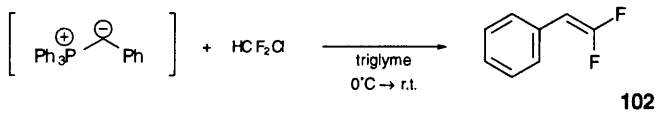
(*Z*)-Unsaturated ester **101** was prepared as shown in **Scheme 74**, using Still's trifluorophosphonate methodology,[158] affording the product in 82% yield, with the corresponding (*E*)-isomer not detectable by NMR. The coupling constant between the two alkenic protons appeared rather high for a *cis* alkene at 12.6 Hz, but comparison with that for the *trans* isomer, synthesised by another route, showed it to be considerably higher at 16.0 Hz.[160]



101

Scheme 74

β,β-Difluorostyrene **102** was accessed using the ylide-carbene reaction shown in **Scheme 75**.[161] Benzyltriphenylphosphonium chloride was deprotonated using phenyllithium, and then chlordifluoromethane condensed in excess into the reaction mixture. The desired product **102** was only isolated in a low 8% yield, but this was probably due to its extreme volatility.

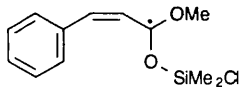


102

Scheme 75

With alkenes **101** and **102** in hand, cyclopropanation was attempted using the zinc carbenoid formed by the deoxygenation of *p*-anisaldehyde in the presence of zinc amalgam and dichlorodimethylsilane. The aldehyde was thus added over 12 hours to a vigorously stirred refluxing suspension of the alkene and other reagents in diethyl ether.

For the reaction with (Z)-methyl-3-phenylpropenoate, no cyclopropane was isolated. However, 40% of the alkene was recovered, together with a mixture of the (Z)-alkene, isomerised (*E*)-alkene, and 3-(4-methoxyphenyl)-2-ethoxypropane **106**, formed by the α C-H insertion of the carbenoid into diethyl ether. It was interesting to note that the unsaturated ester was not reduced under the reaction conditions, as it is easy to imagine that the formation of an intermediate such as **107** could occur quite readily under the reducing conditions.



107

The absence of any cyclopropane suggests, in keeping with previous findings, that the carbenoid is electrophilic in nature.

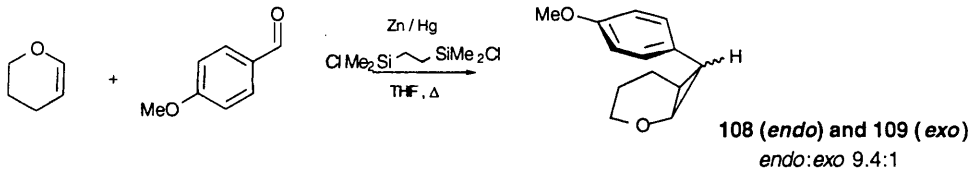
The attempted cyclopropanation of β,β-difluorostyrene **102** also afforded no identifiable products. The ^{19}F NMR of the crude product mixture appeared only to have signals corresponding to the starting alkene (signals for the alkene were found in the region -82 - -85ppm, whilst the signals for the cyclopropane would be expected in the region -135 - -155ppm),[162] whilst no recognisable products could be discerned on the proton NMR. The volatility of the alkene also prevented its isolation by column chromatography, which did not afford any other identifiable products. It was rather surprising to find that no cyclopropane had formed from β,β-difluorostyrene, as it would seem likely that the electron rich π–framework of the alkene would be nucleophilic enough to attack an electrophilic carbenoid. The most probable explanation is then that the curious electronics of the alkene prevented any reaction.

These results were interesting, if a little surprising. Obviously confirmation of the carbenoid's electrophilicity would be obtained if an alkene such as **100** could be synthesised and cyclopropanated, but this was precluded by time constraints.

2.3.3 Cyclopropanation of Cyclic Enol Ethers

Earlier work attempting to expand the range of olefins available as traps for the zinc carbenoid generated from an aldehyde and the zinc / silicon electrophile system had failed to produce any results, except with enol acetates and acetoxybutadienes.[139] Electron deficient olefins such as acrylonitrile or ethyl acrylate had either been insufficiently electron rich to react with the electrophilic carbenoid, or reduced at a faster rate than they could be trapped under the reaction conditions. Attempts at cyclopropanating electron rich olefins met with a similar degree of success - enol ethers such as ethyl vinyl ether, 3,4-dihydro-2*H*-pyran and 1-methoxycyclohexa-1,4-diene polymerised rapidly on introduction to the reaction mixture. Even with additives such as pyridine, collidine and calcium carbonate, the polymerisation could not be stopped. With the Simmons-Smith reaction or its later modifications working well for such olefins,[10] efforts were therefore directed again towards the cyclopropanation of cyclic enol ethers.

The cyclic enol ethers 3,4-dihydro-2*H*-pyran and 2,3-dihyrofuran were selected initially as substrates. The preliminary attempt at trapping the carbenoid generated from *p*-anisaldehyde met with success, the product cyclopropane *endo* **108** and *exo* **109** isomers (chromatographically separable) being isolated in overall 56% yield, *endo*:*exo* 9.4:1 (**Scheme 76**). Although the yield was modest, the successful isolation of the cyclopropanes strongly indicated that similar electron rich olefins were, contrary to earlier results, viable substrates in this reaction system.

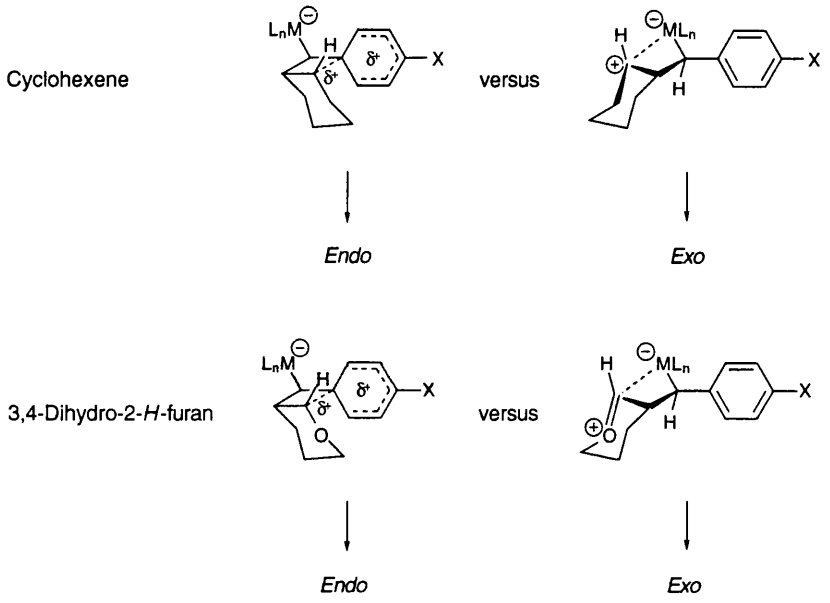


108 (*endo*) and 109 (*exo*)
endo:*exo* 9.4:1

Scheme 76

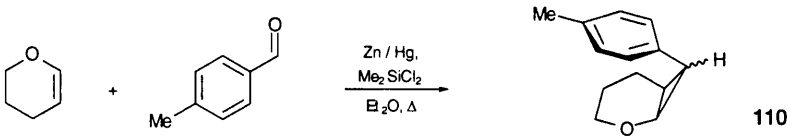
The *endo*:*exo* ratio found in this example is worthy of comment. In the cyclopropanation of cyclohexene in THF, using the carbenoid derived from *p*-anisaldehyde, and chlorotrimethylsilane as the electrophile, an *endo*:*exo* ratio of 15:1 was found (*vide infra* chapter 2.2.1.4). Considering then Casey's model[65] for the mechanism of the cyclopropanation (*vide infra* chapter 2.3.1, **Scheme 22**), the pathway (Path B) leading to the *trans*, or in this case *exo*, cyclopropane, involves a fully developed positive charge on the more substituted end of the alkene. In the case of a styrene or cyclohexene, this will be a high energy carbonium ion, in which case *ipso* stabilisation becomes very important, and the route leading to the *cis*, or in this case *endo*, cyclopropane (Path A) will predominate.

However, in the case of 3,4-dihydro-2-*H*-pyran, a much lower energy oxonium ion may be formed. There is thus less electronic discrimination between the two pathways, with the result being an increase in the amount of the exo isomer formed with respect to result obtained using cyclohexene. The question of synchronous versus asynchronous bond formation in the transition state is also raised by this result. The transition states are illustrated in **Scheme 77**.



Scheme 77

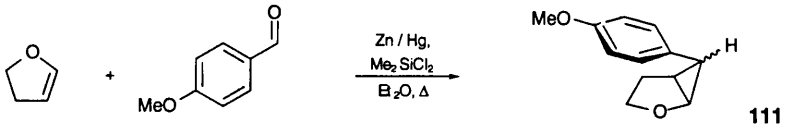
With this study being carried out in parallel with work on the electrophile used in the reaction (*vide supra* chapter 2.2.1.3), it was decided that 1,2-*bis*(chlorodimethylsilyl)ethane (which had been shown to decompose very rapidly in solvent) should be replaced with dichlorodimethylsilane. However, repeating the initial success proved rather difficult. Using *p*-methylbenzaldehyde as the carbenoid precursor, and 3,4-dihydro-2*H*-furan as the trap, led eventually to the isolation of the product cyclopropane **110** in a very modest 23% yield (**Scheme 78**). The product was also unstable, and decomposed rapidly on isolation, making characterisation difficult.



110

Scheme 78

2,3-Dihydrofuran proved, not surprisingly, to be even more difficult to work with than 3,4-dihydro-2*H*-pyran. From the many reactions attempted, the only success was using *p*-anisaldehyde as the carbenoid precursor (**Scheme 79**), where the cyclopropane **111** was isolated in 25% yield. As with **110**, the product from this reaction was very unstable making characterisation difficult.

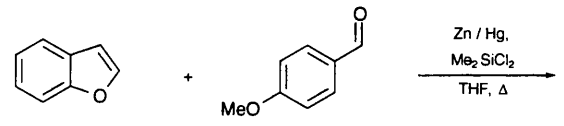


111

Scheme 79

It is clear from these results that these reactions are extremely capricious, probably due to the extreme sensitivity of these substrate alkenes to acidic (protic or Lewis) conditions. In all of the reactions which were unsuccessful, the products isolated appeared to be derived from the ring-opening of the enol ether in question.

In a final effort to explore the reactivity of cyclic enol ethers with the zinc carbenoid, 2,3-benzofuran was selected as a substrate, reasoning that it should be considerably more stable than either 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran. Indeed, in a stability test, where benzofuran was refluxed overnight under standard reaction conditions, with an added 0.5 mole equivalents of zinc chloride, but without the addition of an aldehyde, it was recovered intact (THF decomposition products, were, however, isolated). Confident that benzofuran would then prove a suitable substrate, the reaction shown in **Scheme 80** was attempted.



Scheme 80

However, several attempts at this reaction led only to the quantitative recovery of the aldehyde. The zinc amalgam used was separately tested, and found to be active. Thus, in a most curious twist for which no rationale can be provided, benzofuran appears to inhibit this reaction. 2,3-Dihydrobenzofuran (as a substrate in C-H insertion reactions) was also found to have a similar effect, though to a slightly lesser degree (*vide infra* chapter 2.4.1).

In conclusion, the cyclopropanation of cyclic enol ethers such as 2,3-dihydrofuran and 3,4-dihydro-2*H*-pyran met with limited success. It is presently unclear whether the instability of these substrates derives from slightly protic reaction conditions, or Lewis acidity. In either case, it seems likely that a reinvestigation of this system, not using a silicon electrophile, may be more fruitful.

2.4 C-H Insertion Studies

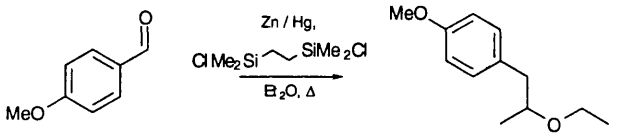
X-H insertion reactions (where X = C, N, O, S and so on), although one of the three most important possible reaction pathways for a carbene or carbenoid, had not really been a synthetic pathway examined for the zinc carbenoid system. The reaction was known to occur, primarily as an α-C-H insertion, where for instance a cyclic ketone would be reductively deoxygenated to the carbenoid, which would then insert into the neighbouring C-H bond to afford an alkene (*vide supra* chapter 1.2.2.2).[54] A transannular C-H insertion had also been found in the reductive deoxygenation of cyclooctanone. More recently, and concurrently with the present study, the synthetic utility of an aliphatic aldehyde to terminal alkene transformation has been demonstrated using the zinc / chlorotrimethylsilane system, and a wide range of functional groups found to be tolerated.[144]

However, these systems were all relatively simple, and the following sections describe efforts made to exploit this reaction in more complex systems.

2.4.1 Intermolecular C-H Insertion Reactions

It is frequently the case in metallo-carbenoid chemistry that one of the by-products of any reaction will be a small quantity of material derived from the C-H insertion of the carbenoid into the solvent. The start point for this investigation was that, in many cases, the solvent C-H insertion product was the only product being isolated from reactions where other transformations were expected (no previous workers had observed this reaction). These insertions were then optimised to some degree, and other potential C-H insertion substrates investigated.

The insertion of a zinc carbenoid into the C-H α- to oxygen (which will be referred to as α-C-H insertion) in diethyl ether had been the side-reaction both Closs and Elphimoff-Felkin had separately noted. Closs, whose carbenoids were formed by the zinc halide catalysed decomposition of aryldiazomethanes, had found that he could isolate the α-C-H insertion product in up to 20% yield.[136] Elphimoff-Felkin, who had generated zinc carbenoids by the reductive deoxygenation of carbonyl compounds using zinc and boron trifluoride etherate, had found that in a control experiment, the yield of α-C-H insertion product would not exceed 10%.[163] These yield levels were mirrored in the current work, and using the conditions shown in **Scheme 81** (12 hour addition of the aldehyde), and the carbenoid derived from *p*-anisaldehyde, the product **106** of α-C-H insertion would be isolated in typically 10% yield, often with the formation of the dicarbonyl coupling reaction product in a similar yield.

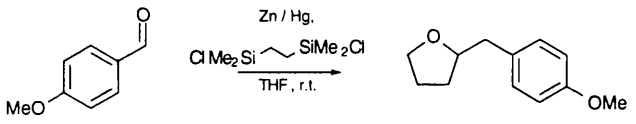


106

Scheme 81

Although at a first glance a 10% yield appears exceptionally modest, when it is considered that diethyl ether is generally chosen as a solvent because of its stability, the insertion actually occurs into a relatively unactivated C-H bond. It seems likely that the zinc carbenoid is closely coordinated by the oxygen of the diethyl ether molecules (given the solvent dependence of the reaction, *vide supra* chapter 2.2.1.4), and the proximity of the C-H bond α- to oxygen, which is slightly activated, allows the insertion reaction to occur.

When THF was employed as the substrate for α-C-H insertion, yields were dramatically increased when compared to the reaction with diethyl ether. The highest yield for this reaction was obtained by adding the aldehyde over 1 hour to the silicon electrophile and zinc amalgam in THF at room temperature (**Scheme 82**). The C-H insertion product **112** was isolated in 39% yield, with 9% of the dicarbonyl coupling product. The elevated yield compared to diethyl ether is probably explained through the balance of two factors: the ability of the ether to complex to the carbenoid, and the inherent reactivity of the ether as a reagent towards the carbenoid.



112

Scheme 82

However, extending the range of substrates for this intermolecular reaction proved difficult. No C-H insertion reaction was observed using tetrahydropyran (THP) as the ether. The only likely explanation for this lack of reactivity of the carbenoid towards THP is that the lone pairs on the oxygen in THP are less available than in the more planar THF, resulting in poor complexation of the carbenoid, and hence no α-C-H insertion (**Scheme 83**).

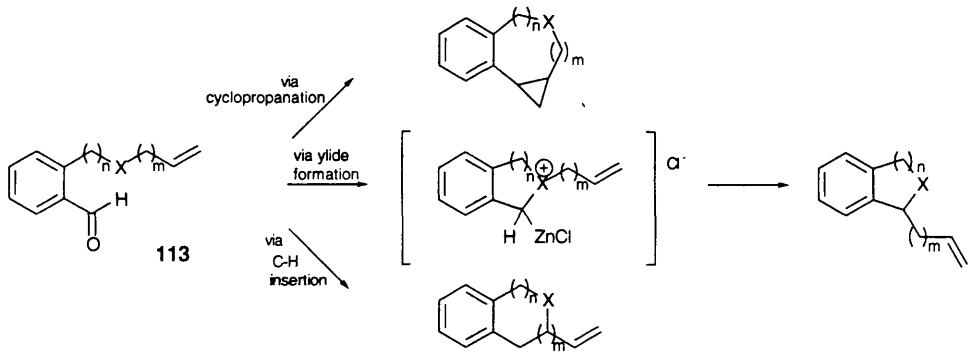
Scheme 83

As with THP, attempts to use 2,3-dihydrobenzofuran as a substrate met with little success, with no α-C-H insertion product being isolated from any reaction. In this instance, the 2,3-dihydrobenzofuran was used as a substrate with THF as the solvent, whereas in all previous reactions, the reagent was also the solvent. Interestingly, as had been noted with benzofuran (*vide supra* chapter 2.3.3), 2,3-dihydrobenzofuran appeared to suppress carbenoid formation,

although to a far lesser degree than benzofuran (only ~30% of aldehyde recovered). A stability test indicated that 2,3-dihydrobenzofuran did not decompose under the reaction conditions. This unusual inhibition of the reductive sequence necessary for carbenoid formation by the benzofuranoid nucleus is extremely curious, if without explanation.

2.4.2 *o*-Allyloxybenzaldehyde - Attempts at an Intramolecular Reaction

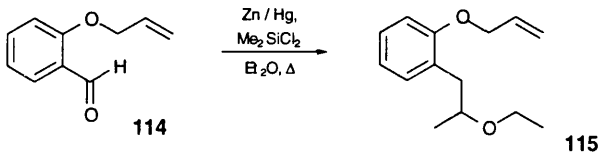
As a much greater level of success is often found in an intramolecular system rather than an intermolecular one (in terms of reaction yield), it was decided to examine a simple intramolecular system. The system **113** was devised such that m and n could be systematically varied by an easy synthetic route, and such that X could also be varied. Choosing a 1,2-disubstituted aromatic system also entropically favoured the intramolecular reaction, and had the added benefit that substituents on the ring could be added should an extra electronic 'push' be necessary. The object then was to try and define the parameters controlling intramolecular C-H insertion reaction, cyclopropanation and ylide formation (**Scheme 84**).



Scheme 84

The first substrate synthesised was *o*-allyloxybenzaldehyde **114**, prepared in 77% yield by reaction of the sodium salt of salicylaldehyde with allyl bromide. To minimise the possibility of an intermolecular reaction between two molecules of **114**, high dilution conditions were applied in the zinc reaction. Thus the aldehyde was added over 36 hours to a refluxing suspension of zinc amalgam and dichlorodimethylsilane in diethyl ether. It was with considerable surprise, however, that instead of affording a product from an intramolecular reaction, the only product isolated, **115** (14%), was formed via an intermolecular α-C-H insertion of the carbenoid into the solvent (**Scheme 85**). Repeating the reaction under the same conditions gave an identical result, and also when the addition time was altered. Using dichloromethane as the solvent (where insertion was precluded) afforded no identifiable products. When a zinc-copper couple was used rather than zinc amalgam, with dichloromethane as the solvent, only starting aldehyde was recovered, although neither of these results are now surprising in the light of subsequent experiments discussed earlier (*vide supra* chapter 2.2.1). Interestingly, when the zinc-copper couple was used in diethyl ether, only unreacted aldehyde was recovered. The activity of the zinc-

copper couple was confirmed in the cyclopropanation of cyclohexene using diiodomethane. The reaction was also carried out in THF, and afforded two major products, which although apparently pure by tlc, were very complex spectroscopically. It did appear, though, that the product mixture contained the solvent C-H insertion product in a moderate yield.



114 115

Scheme 85

Although both the ylide and cyclopropanation pathways were less likely in **114**, it was rather surprising that the C-H insertion had not occurred. However, when the intermediate carbenoid is considered, it is clear the system's geometry is perfectly aligned to provide intramolecular chelation of the carbenoid through the lone pairs on the oxygen in the allyloxy side chain. Thus, considering **Figure 2**, a representation of this complexation, with a zinc carbon length of 1.96 Å,[37] the side chain is held too far away to react. As the carbenoid is almost certainly still complexed by other diethyl ether molecules, it is then possible to envisage how the intermolecular product is formed.

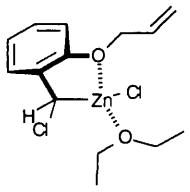


Figure 2

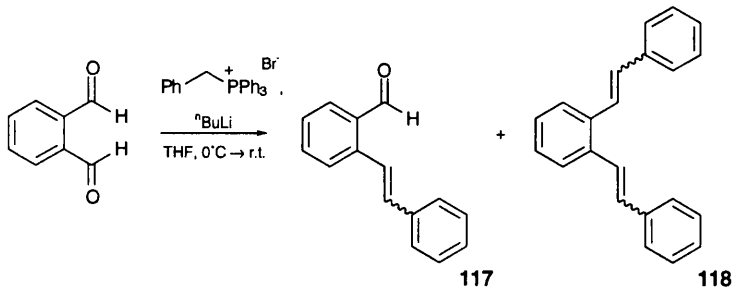
Given the potential importance of this intramolecular chelation, attempts were made to prove that this effect was preventing the intramolecular reaction. If it was possible to provide extra evidence to support this theory, consideration could then be given to introducing a chiral pendant side chain to induce enantioselection in the carbenoid's reactions. This would be equally valid for either a homogeneous or a heterogeneous carbenoid, but particularly so for the latter, as enantiocontrol by the addition of chelating ligands to the reaction mixture would be impossible.

2.4.3 A Heteroatom-Free Intramolecular System

To ascertain whether intramolecular chelation of the carbenoid was preventing intramolecular reaction, it was decided to try and carry out an intramolecular C-H insertion reaction in a system free from heteroatoms which could complex the carbenoid. As the carbenoid would be unlikely to insert into an unactivated C-H bond, i.e. an aliphatic C-H, the system would require a benzylic CH_2 group suitably positioned in the molecule to favour C-H insertion of the carbenoid. Taking these requirements into account, 2-

(phenethyl)benzaldehyde **116** was chosen as a suitable target, available in two steps from phthalic dicarboxaldehyde.

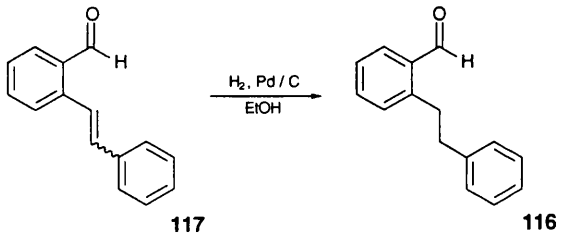
The Wittig reaction of phthalic dicarboxaldehyde with the preformed ylide from benzyltriphenylphosphonium bromide and *n*-butyllithium, afforded a mixture of the mono- and di-stilbenes **117** and **118** in 69% and 11% yields respectively (**Scheme 86**).



117 **118**

Scheme 86

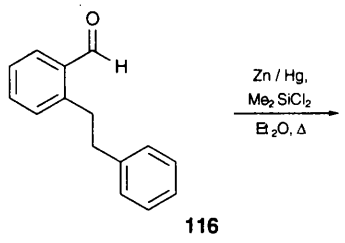
The mono-stilbene **117** was then hydrogenated at atmospheric pressure over palladium on carbon to afford the desired aldehyde **116** in a modest 59% yield (**Scheme 87**).



117 **116**

Scheme 87

Thus, the aldehyde **116** was reductively deoxygenated using zinc amalgam and dichlorodimethylsilane (**Scheme 88**), under identical reaction conditions and concentrations to those used for the original intramolecular system **114**.



116

Scheme 88

Two spectrally complex products were isolated from the reaction, pure by tlc. HPLC purification was attempted on both samples. The more polar sample separated into two components, but the less polar fraction could not be further resolved by HPLC. Mass spectra of

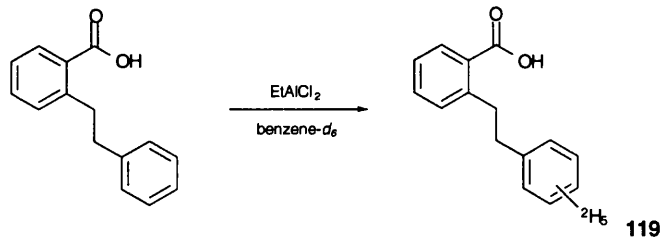
the products indicated that the products were neither dimeric, nor the result of a solvent α-C-H insertion reaction. With the complexity and form of the NMR spectra suggesting that, in at least one product, there had been no reaction at the bridging linker between the two aromatic rings, but that the disubstituted aromatic ring may have been involved in the reaction, it was decided to synthesise a specifically deuterated system. It was envisaged that with the extreme simplification of the proton NMR that would follow, it would be possible to elucidate what had happened in the reaction.

2.4.3.1 Specifically Deuterated System

Although several different types of labelling study were considered, the most worthwhile appeared to be the complete deuteration of the lower ring in 2-(phenethyl)benzaldehyde. In this way, any changes in the very characteristic proton NMR pattern of the *ortho*-disubstituted aromatic would be seen. Furthermore, given the data acquired for the non-deuterated system, it seemed likely that after the reaction the result would be a nine proton system, which again should not be too complex to analyse.

In the early 1970's a procedure had been published for the selective and rapid deuteration of aromatic compounds using catalytic ethylaluminium dichloride in d_6-benzene.[164] The reaction, obviously an equilibrium process, was complete in minutes, which was a distinct advantage over the other available methods, which frequently took days and required elevated temperatures. The authors also reported that neither alkenes, alkanes, and nitrogen- or oxygen-containing compounds exchanged. Assuming then that inhibition of the reaction by oxygenated functionality only occurred at the aromatic ring bearing the oxygenated functionality, starting with a substrate such as 2-phenethylbenzoic acid, it should be possible to selectively deuterate the lower, non-oxygen substituted, aromatic ring. If this reaction worked, simple functional group manipulation would afford the aldehyde required.

Indeed, the deuteration hypothesis was borne out in a small-scale reaction, where the lower ring of 2-phenethylbenzoic acid was completely and selectively per-deuterated (as judged by proton NMR). On scale-up, 2g of this material **119** were made, in three sequential deuterations. Repeating the deuteration three times was considerably more economical in d_6-benzene: as the reaction was an equilibrium process, to take it to completion in one step required a vast excess of d_6-benzene, whereas in three steps, considerably less d_6-benzene was required. The reaction is shown in **Scheme 89**.

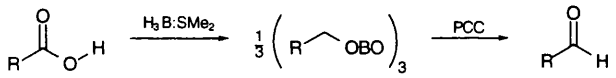


119

Scheme 89

The mechanism for this reaction is suggested to involve the catalyst (ethylaluminium dichloride) acting as a proton-transfer agent, with the two aromatic compounds undergoing exchange in turn. It is possible that the aromatic compounds complex with the metal atoms of ethylaluminium dichloride through a π-associative species.

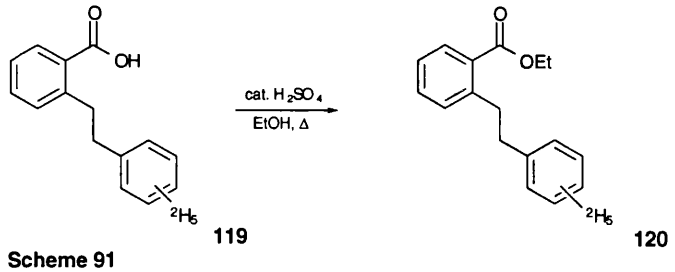
Having obtained the acid **119**, it was hoped that lithium aluminium hydride reduction to the alcohol, followed by manganese dioxide oxidation, would afford the desired aldehyde. However, an attempted lithium aluminium hydride reduction of **119** resulted in complete decomposition of the starting material. Brown's method for the conversion of carboxylic acids to aldehydes via formation of the trialkoxyboroxine,[165] which is oxidised without isolation using pyridinium chlorochromate (PCC) (**Scheme 90**), was very attractive as a one-pot sequence that would afford the aldehyde.



Scheme 90

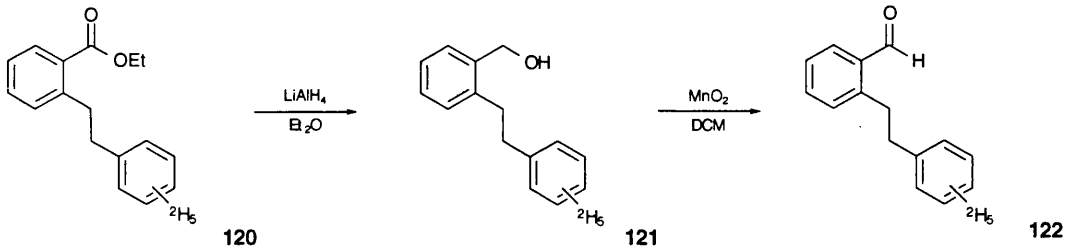
When this sequence was carried out using the acid **119**, although the product mixture included the aldehyde, starting acid remained. It also appeared that some scrambling of the deuteriums had occurred, or loss of isotopic integrity, presumably due to the harshly Lewis acidic reaction conditions. As it seemed likely that more 'conventional' transformations would afford the desired aldehyde in a cleaner, high yielding sequence without compromising the isotopic integrity of the deuterated ring, this route was abandoned.

Returning instead to a simple reduction - oxidation sequence, the acid **119** was first esterified in ethanol, in the presence of catalytic concentrated sulfuric acid. The reaction was quantitative on a small-scale, but on scale-up there was extensive decomposition, and the ester **120** was isolated in only 43% yield (**Scheme 91**).



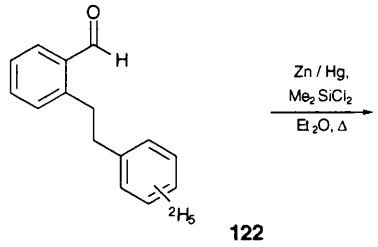
Scheme 91

Ester **120** was then cleanly reduced to alcohol **121** with lithium aluminium hydride, in 92% yield. Manganese dioxide oxidation of **121** afforded the desired aldehyde **122** in only 46% yield (**Scheme 92**), which was again disappointing when compared to the quantitative reaction in the small scale sequence.



Scheme 92

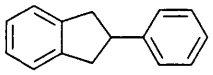
The aldehyde **122** was then reductively deoxygenated using zinc amalgam and dichlorodimethylsilane (**Scheme 93**), under identical reaction conditions and concentrations to those used for the non-labelled system **116**.



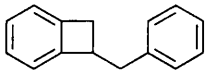
Scheme 93

Three products were isolated from the reaction - the major one was extremely non-polar, and two minor ones, of higher polarity, which appeared by proton NMR to be some sort of decomposition products. As might have been expected, the major product appeared, both by tlc and proton NMR, to be very similar to the major product isolated from the non-deuterated system. The mass spectrum of the sample suggested that the product was neither dimeric, nor derived from a solvent α-C-H insertion reaction. The proton NMR indicated that the *ortho* substitution pattern of the upper ring had not been disrupted in the reaction, but the collapsing together of the signals compared to the aldehyde's spectrum indicated that substitution did not involve any strongly electron withdrawing or donating group. Examination of the normal ^{13}C NMR spectrum indicated that the carbonyl carbon had been

lost, while the ^{13}C off-resonance decoupled spectrum revealed that the deuterated ring had not been affected by the reaction. The first conclusion then is that this extremely non-polar material does not result from the reaction of the carbenoid at either aromatic ring. The proton NMR indicated 4-5 protons in the aliphatic region 3.0 - 2.6 ppm. The pattern was complex, indicating that the product was not symmetrical. In the ^{13}C NMR the quaternary carbons all appeared to have a second smaller signal at slightly lower field, suggesting either two distinct constitutional or conformational isomers. To try and distinguish which of these two possibilities was actually the case, a sample of the analogous non-deuterated product was heated to 50 °C in $CDCl_3$ in the NMR probe. It was anticipated that if two conformers were present, the result would be a simplification in the aliphatic region of the proton NMR spectrum, but no change was observed compared with the spectrum recorded at ambient temperature. This then suggested that the sample was in fact two constitutional isomers. The structure, then, remains unresolved. The two obvious structures which could be drawn, **123** and **124** do not correspond unambiguously with the data collected, particularly to the extent that there are evidently two isomers in the sample, and the product is not symmetrical.



123

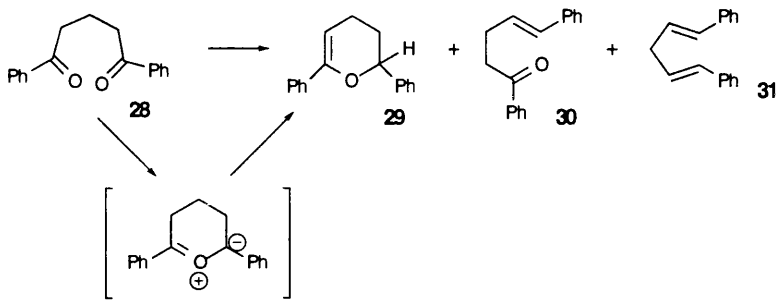


124

In conclusion, there is almost certainly some type of intramolecular reaction occurring in this system, but it is not possible to conclusively assign a structure to the product at this stage. To determine the nature of the reaction it is necessary to introduce some polar functionality into the system, probably on the lower ring, so that HPLC purification of the sample becomes possible.

2.5 Attempted Ylide Studies

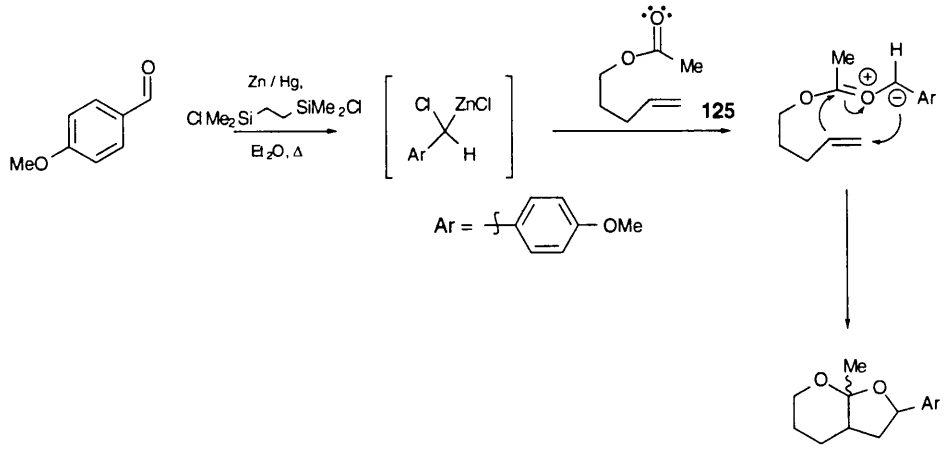
Ylide formation was one area of carbenoid chemistry that had not been exploited using the zinc / silicon electrophile system. Since the discovery of the dicarbonyl coupling reaction,[58] for which some evidence of an ylide mechanism was obtained when **28** was exposed to the reaction conditions (**Scheme 20**, reproduced here for convenience), this area of reactivity had been ignored. Given the literature precedent for this type of carbenoid reaction in other transition metal systems,[138] attempts were made to extend to scope of this reaction using zinc carbenoids.



Scheme 20

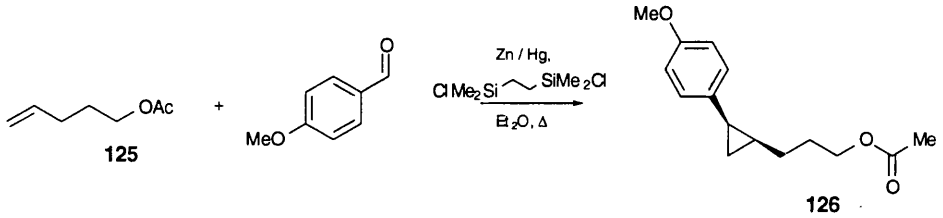
2.5.1 Carbonyl Ylides

As the only examples of ylide formation using the zinc / silicon electrophile system to generate the carbenoid had been carbonyl ylides, this was the first system examined. The very simple substrate 4-penten-1-yl acetate **125** was chosen, and was prepared in modest yield (28%) by the acetylation of 4-penten-1-ol. The low yield was almost certainly due to the volatility of the product. It was anticipated either that simple cyclopropanation would ensue, or that if the carbenoid was trapped by the carbonyl group in **125**, the intramolecular rearrangement shown in **Scheme 94** would occur.



Scheme 94

In the event, however, when a solution of *p*-anisaldehyde was added over 12 hours to a refluxing suspension of zinc amalgam, **125** and 1,2-*bis*(chlorodimethylsilyl)ethane in diethyl ether, the only product isolated was cyclopropane **126**, in 27% yield (**Scheme 95**). The low yield of cyclopropane is simply an indication that monosubstituted aliphatic alkenes are not good substrates in this system, as they are not particularly electron rich, and the carbenoid formed in these reactions appears to be electrophilic (as is often the case with transition metal carbenoids[11,12]). By NMR, only the more sterically hindered *cis* isomer could be detected, in keeping with the trends discussed earlier (*vide supra* chapter 2.3). The result, however, was disappointing, as it strongly suggested that cyclopropanation would always occur faster than any other type of carbenoid reaction.

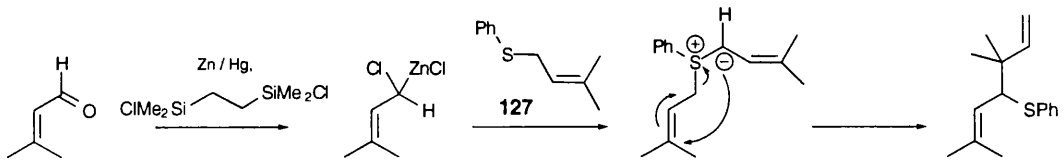


Scheme 95

2.5.2 Sulfur Ylides

The lack of success with this prelude to carbonyl ylide chemistry prompted an investigation into the potential of sulfur ylides, formed by the reaction of carbenoid with a sulfide. Sulfur ylides are known to be far more stable and readily formed than analogous ylides with other heteroatoms due to the stabilising effect of the sulfur d orbitals.

The reaction chosen to provide an entry into this area was the head-to-tail coupling of prenyl units, achieved via the formation of a sulfur ylide from an allyl sulfide **127** and the carbenoid derived from prenal (**Scheme 96**). This type of ylide rearrangement is well-documented in the literature,[138,166-169] and with synthetic utility of the zinc carbenoid derived from prenal already demonstrated,[64] a straightforward trapping and [2,3]-sigmatropic rearrangement was anticipated. Obviously any reaction would have to be carried out under conditions which minimised the potential side-reactions, including an iterative sequence of trapping and rearrangement leading to an oligomeric / polymeric product, since the product of any sequence is also an allyl sulfide.



Scheme 96

Allyl sulfide **127** was made in high yield (89%) from the reaction of sodium thiophenoxide with 4-bromo-3-methyl-2-butene. However, as with the attempted carbonyl ylide chemistry, the desired rearrangement was not observed, and in fact in all reactions the starting allyl sulfide was recovered. An extensive range of reaction conditions were examined, including concomitant addition of the aldehyde and allyl sulfide in case the sulfide was poisoning the zinc surface. In a last attempt activated zinc rather than zinc amalgam was employed to see if the sulfide's affinity for mercury was inhibiting the reaction. Once again, however, the allyl sulfide was recovered at the end of the reaction.

It is unclear why this chemistry was unsuccessful, although sulfur poisoning of the zinc surface seems most likely.[167]

Chapter 3. Conclusions and Perspectives

Although an attempt has been made to present the foregoing Results and Discussion section within some kind of logical and mechanistic framework, it should nevertheless be appreciated that many elements of this multifaceted problem were being studied in parallel. Whilst the findings have provided some insight into what is an exceptionally complex system, the outcome has been that, not unexpectedly, many more questions have been asked than answered.

On a simple preparative level, there have been several important findings. Considering firstly the reaction variables (solvent, electrophile and so on) studied in the standard reaction (Equation **(30)**):

(i) The purity of the zinc in the reaction had little influence on the outcome of the reaction, although the particle size of the zinc is crucially important, and should be in the range 6-10 μm. Using zinc of this size almost completely eliminates what had been a common problem of zinc ball formation. The highest yields were found using zinc amalgam in preference to other commonly used methods of zinc activation.

(ii) Diethyl ether was found to be the most efficient solvent, with DME completely inhibiting the reaction.

(iii) Using 1,2-*bis*(chlorodimethylsilyl)ethane as the electrophile gave the highest yields, although it was found to decompose extremely rapidly in diethyl ether and THF. Furthermore, the oligomeric siloxanes that are a by-product of the reaction are exceptionally hard to remove from the reaction products. Surprisingly, using 5 equivalents of HCl and 2.5 equivalents of water as the electrophile system was found to be the next most efficient electrophile after 1,2-*bis*(chlorodimethylsilyl)ethane. The low cost, coupled with the 'environmental friendliness' of this system, should make it of interest to industry.

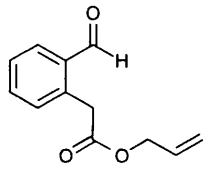
(iv) Lowering the reaction temperature to -30 °C brought about a dramatic increase in both yield of the reaction and de of the product cyclopropane. The de of 97% obtained at this temperature is the highest ever recorded to date for this chemistry. It would be of interest to know how far the temperature could be lowered before carbenoid formation becomes too slow, and if this results in further increases in both yield and de. The preparative use of a reaction which works equally well at ambient and sub-ambient temperatures cannot be overstated.

(v) The addition of 1 equivalent of zinc chloride to the reaction mixture was found to elevate yields, with no influence on the de of the product cyclopropane compared to the control reaction. However, the use of zinc iodide elevated the de slightly, whilst the yield remains similar to that of the control reaction.

In terms of cyclopropanation chemistry, the potential to vary the styrene coupling partner in cyclopropanation reactions has been demonstrated. The work has also been extended to the cyclopropanation of cyclic enol ethers, contrary to earlier results which indicated that such electron-rich alkenes decomposed under the reaction conditions.[139]

Other areas of carbenoid reactivity have also been explored, with the most notable success in the area of C-H insertion reactions. Novel intermolecular α-C-H insertion reactions of the carbenoids derived from both *p*-anisaldehyde and *o*-allyloxybenzaldehyde into diethyl ether and THF have been found. Attempts to extend this reactivity to intramolecular systems gave rather complex results that warrant further investigation.

Whilst ylide formation from the organozinc carbenoid seemed a realistic possibility, attempts at both carbonyl ylide and sulfur ylide formation met with no success, although the importance of this area of carbenoid chemistry suggests that it should be pursued further. It is perhaps more likely that such reactivity would be observed in a carefully designed intramolecular system, such as **128**.



128

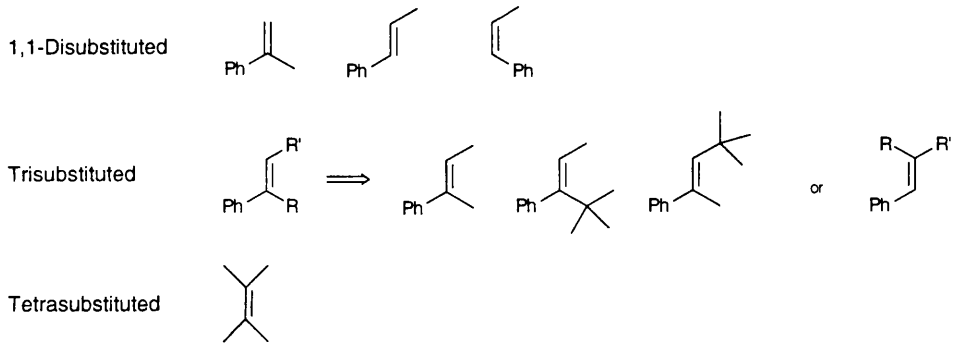
In terms of the mechanism of both organozinc carbenoid formation, and cyclopropanation reactions, several interesting results have been found, although clearly much work remains. Of particular note was the finding that zinc chloride chelation is not involved in the transition state, indicating that its involvement is much earlier in the reaction sequence. The same study also indicated the possibility that the use of zinc iodide as a Lewis acid gives rise to a subtlely different carbenoid to that obtained when zinc chloride was used. At this stage it would be pertinent to see if iodotrimethylsilane is a suitable electrophile for the reactions, and if so what its influence is on the yield and de of the standard reaction (Equation **(30)**). However, of greater importance is a programmed rate study, particularly if carried out in parallel with a study on the species generated by the zinc halide catalysed decomposition of aryldiazomethanes. The results should give more information on the nature of the reactive intermediate formed in both of these reactions, and the rate limiting steps in its formation. At this stage it is most important that the nature of the organozinc carbenoid formed is elucidated.

The results from the Three Phase Test were interesting, and indicated that, at least in some instances, or by the action of some reagent, the carbenoid is homogeneous. Taken at face value, this was a very pleasing result, as the potential for enantioselective reactions was opened up, by, for instance, the addition of chiral ligands to the reaction mixture. The practicalities of the test also indicated that solid-phase synthetic techniques are

applicable to this system. However, the low yield of product cyclopropane after cleavage from the polymer support was worrying, and explanation of this poor mass balance requires further investigation. In the first instance the method for cleavage of the ester linkage binding the alkene onto the polymer should be examined, such that the method chosen gives quantitative recovery. The Three Phase Test should then be repeated *per se*, and then with the addition of zinc chloride to see if the result is altered. Perhaps the simplest explanation for the poor efficiency of the test is that diethyl ether is completely unsuitable as a solvent for the polymer, not swelling it enough to allow the reactive sites to be accessed.

The studies on the cyclopropanation of variously *para*-substituted styrenes provided further evidence for the working mechanistic hypothesis, based on a model developed by Casey.[65] The results also correlated well with the Hammett substituent constants for the *para* substituent on the styrene. The yields over the series suggest that the organozinc carbenoid is electrophilic in its tendencies, and fairly electronically discriminating. Further efforts should, however, be made to attempt reactions with more electronically demanding alkenes, such that a true picture of the carbenoid's reactivity can be built up.

Whilst elucidation of the mechanism clearly requires much more work, there are several other areas which warrant exploration. To date, there has been no programmed study on the steric and geometric demands of the transition state in the cyclopropanation reaction. A series of alkenes, such as those shown in **Scheme 97**, would provide a valuable insight.



Scheme 97

It would also be of interest to see if a similar type of chemistry is possible using metals other than zinc - titanium, samarium, or samarium diiodide, for instance. Although preliminary ventures into this area gave no results of note, a more detailed investigation should be carried out. With electrochemical methods becoming more widely used in organic synthesis, attempting the zinc carbenoid reaction using such techniques may lead to more efficient reactions.

Given the clear advantages in terms of cost and safety of this reaction system over the Simmons-Smith using *gem*-dihalo compounds, the potential to extend the scope of this reaction to the formation of a methylene carbenoid should be explored. Precursors such as

1,3,5-trioxane are a obvious start point, given the precedent for organozinc carbenoid chemistry from acetals and trimeric aldehydes.[144]

Chapter 4. Experimental Procedures

4.1 General Information

Unless otherwise stated, IR spectra were recorded on either a Perkin Elmer 943G spectrometer or a Perkin Elmer 1600 FTIR. ^{1}H spectra were recorded on a 270 MHz Jeol GSX 270 instrument, and ^{1}H and ^{13}C NMR spectra recorded at 500 MHz and 125 MHz respectively on a Bruker AM 500 instrument, or at 400 MHz and 100 MHz respectively on a Varian VXR 400 instrument, with residual protic solvent as the internal standard for ^{1}H spectra and $CDCl_3$ for ^{13}C spectra. Spectra were recorded in the solvent specified, with chemical shifts expressed in parts per million (δ) relative to the internal standard, and coupling constants J measured in Hertz (Hz). Mass spectra were recorded by EI or CI on a VG Micromass 7070 B Extended Geometry or AutoSpecQ, and by EI on a VG ZAB SE Double Focussing machine. CI coupled GC mass spectra were recorded on a Finnigan Magnum instrument (30 m x 0.2 mm, 0.25 μm film), and EI coupled GC mass spectra on a Finnigan ITS40 instrument (SE54 column, 50 m x 0.2 mm, 0.33 μm film). All GC's were recorded on a Hewlett-Packard 5890A machine (flame-ionisation detector), with a 25 m x 0.32 mm BPX5 column (crosslinked 95% polydimethylsiloxane / 5% polydiphenylsiloxane, 0.5 μm film). Melting points were recorded on Reichert hot-stage apparatus, and are uncorrected.

Petroleum ether (b.pt. 40-60 °C and 30-40 °C) were distilled prior to use. Diethyl ether and tetrahydrofuran (sodium and benzophenone), dichloromethane (phosphorus pentoxide), and acetonitrile (calcium hydride) were distilled under an atmosphere of nitrogen immediately prior to use. N,N-Dimethylformamide and dimethyl sulfoxide (calcium hydride at reduced pressure), and pyridine (potassium hydroxide) were distilled and stored over 4 Å molecular sieves under argon. Hexamethyldisiloxane was distilled from lithium aluminium hydride under nitrogen immediately before use. 1,2-*Bis*(chlorodimethylsilyl)ethane was prepared and stored as a solution in dry solvent as specified. Chlorotrimethylsilane and dichlorodimethylsilane (sodium) were distilled under an atmosphere of nitrogen immdiately prior to use. All other solvents and reagents were purified by standard means.

Analytical thin layer chromatography (tlc) was performed on pre-coated glass backed plates (Merck Kieselgel 60 F_{254}) and visualised using ultra violet light (254 nm), iodine, potassium permanganate [add 62.5 g of Na_2CO_3 in water (1.25 l) to 12.5 g of $KMnO_4$ in water (1.25 l)] or acidic ammonium molybdate (IV) [concentrated H_2SO_4 (250 ml), ammonium molybdate.$4H_2O$, water (2.25 l)] as appropriate. Preparative chromatography was performed at low positive pressure on Merck Kieselgel 60 (230-400 mesh). High pressure liquid chromatography was performed using a 250 mm x 10 mm Partisil silica gel column on a Varian 5000 machine with a UV (254 nm) detector.

All glassware was oven-dried and cooled under nitrogen before use unless otherwise stated. The apparatus for all zinc reactions was assembled as follows: the zinc amalgam was

preweighed into the conical flask, a stirrer bead placed in the flask, and a condender fitted. The joints were then sealed with teflon tape, and the apparatus flushed with argon or nitrogen before flame drying, maintaining the inert atmosphere.

Zinc dust (Delaville Standard CP75, average particle size 6-10 μm, minimum metallic zinc content 95%) was obtained from Britannia Alloys and Chemicals Ltd.. Mercury (II) chloride (> 99.5%; also referred to as mercuric chloride) was purchased from Aldrich, and used as sold.

Zinc Amalgam - A solution of mercuric chloride (2.0 g, 7.37×10^{-3} mol) in concentrated hydrochloric acid (2.0 ml) was added with rapid stirring to water (30 ml). With continued vigorous stirring zinc dust (Delaville Standard CP75 ex. Pasminco) (10.0 g, 0.15 mol) was added, and stirring continued for a further 10 minutes. The finely divided powder was then filtered off under suction, and washed successively with water (75 ml), acetone (75 ml), ethanol (75 ml), and diethyl ether (75 ml), the solid collected, dried, and stored *in vacuo*.

Zinc-Copper Couple (LeGoff's Couple)[22] - Zinc dust (3.02 g, 4.59×10^{-2} mol) was added to a rapidly refluxing solution of copper (II) acetate hydrate (301 mg, 1.50×10^{-2} mol) in acetic acid (5 ml). After 5 minutes stirring at reflux, the suspension was allowed to cool to room temperature, diluted with THF (35 ml), and stirring continued for a further 5 minutes. The couple was then filtered off under suction, washed with THF (2 x 50 ml), collected, dried, and stored *in vacuo*.

Zinc-Silver Couple - Zinc dust (10.0 g, 1.53×10^{-2} mol) was added to a vigorously stirred refluxing solution of silver acetate (104 mg, 6.0×10^{-4} mol) in acetic acid (20 ml). After stirring for 1 minute the suspension was rapidly cooled, and the zinc-silver couple filtered off under suction. The couple was then rinsed sucessively with acetone (3 x 30 ml) and diethyl ether (6 x 50 ml), collected, dried, and stored *in vacuo*.

Acid-Washed Zinc[170] - A suspension of zinc dust (5.02 g, 7.5×10^{-2} mol) was stirred vigorously in 2% v/v dilute hydrochloric acid (15 ml) for 10 minutes. The finely divided powder was then filtered off under suction, and washed successively with water (30 ml), acetone (30 ml), ethanol (30 ml), and diethyl ether (30 ml), before collecting the solid, drying and storing *in vacuo*.

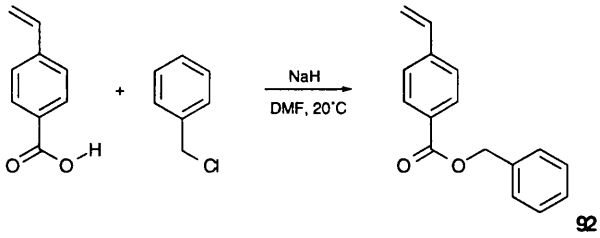
Activated MnO_2 on Carbon[171] - Potassium permanganate (24.4 g, 0.15 mol) was dissolved with stirring in boiling water (300 ml) in a 1l beaker. The solution was then removed from the heat and activated charcoal (7.50 g) added portionwise with stirring. On complete addition the suspension was reheated until the purple colouration discharged. The mixture was then allowed to cool, the solid collected by filtration under suction. The residue was washed with water (4 x 50 ml) and dried under suction. The resultant cake was then suspended in toluene (150 ml) in a 250 ml round-bottomed flask, and residual water was

azeotropically removed using a Dean-Stark apparatus. On complete removal of water, the finely divided black solid was collected and dried under suction. The activated MnO_2 on carbon was finally dried under high vacuum at 50 °C overnight to yield a free-flowing black powder (22.0 g; ~20% C).

Purification of 18-Crown-6 via the Acetonitrile Complex[172] - A slurry of 18-crown-6 (18 g) in acetonitrile (50 ml) was heated with stirring to effect solution, in a 100 ml round bottomed flask protected with a calcium chloride guard tube. The solution was then left to cool with rapid stirring overnight, finally cooling the white suspension in an ice-bath for 15 minutes. The precipitate was then rapidly filtered off under suction and collected into a dry 100 ml round bottomed flask, equiped with a magnetic stirrer bead. The solid was then heated (t ~ 40 °C) with stirring *in vacuo* (P ~ 5 mmHg) for ~3 h to yield 18-crown-6 as a finely divided white powder.

4.2 Syntheses

Preparation of *Benzyl-4-vinylbenzoate* **92**

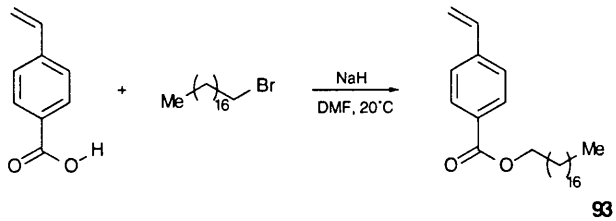


92

A solution of *p*-vinylbenzoic acid (757 mg, 5.07×10^{-3} mol) in DMF (7.5 ml) was added dropwise over several minutes to a stirred suspension of sodium hydride (248 mg, 5.60×10^{-3} mol as a 55% dispersion in mineral oils, prewashed with diethyl ether) in DMF (15 ml) at room temperature under nitrogen. After 30 minutes benzyl chloride (760 µl, 6.60×10^{-3} mol) was introduced dropwise to the reaction mixture, and stirring continued for a further 6 h before quenching under nitrogen with water (10 ml). The reaction mixture was then poured into diethyl ether (25 ml), and the phases separated. The aqueous phase was extracted (3 x 25 ml Et_2O), and then the combined organic extracts washed successively with water (3 x 50 ml) and brine (50 ml), before drying ($MgSO_4$) and concentrating *in vacuo* to yield a mobile yellow oil. The oil was chromatographed (silica, Et_2O (0-5%) / petroleum ether (40-60 °C)) to give *benzyl-4-vinylbenzoate* **92** (79 mg, 7%) as a clear colourless oil.

υ_{max} (NaCl plates, neat)/ cm^{-1} 3035, 2956 ($-CH_2-$), 1717 (C=O), 1625 (phenyl conj. C=C), 1608 (C=C aromatics), 1455, 1272 (C-O), 1178, 1104; δ_H (400 MHz, $CDCl_3$) 8.04 (2H, $aa'bb'$, *m*), 7.51 (2H, $aa'bb'$, *m*), 7.43-7.35 (5H, m), 6.76 (1H, dd, *J* 10.7, 17.4), 5.87 (1H, d, *J* 17.7), 5.39 (1H, d, *J* 11.2), 5.37 (2H, s); δ_C (100 MHz, $CDCl_3$) 166.2, 142.0, 136.0, 135.97, 130.0, 129.2, 128.6, 128.2, 128.1, 126.1, 116.6, 66.5; *m/z* 238 (19%, M^+), 131 (100%, M^+-[$PhCH_2O$]), 103 (16%), 91 (73%, tropylium), 77 (29%, $[C_6H_5]^+$). (Found: M^+, 238.0990. $C_{15}H_{14}O$ requires *M*, 238.0994).

Preparation of n-*Octadecyl-4-vinylbenzoate* **93**



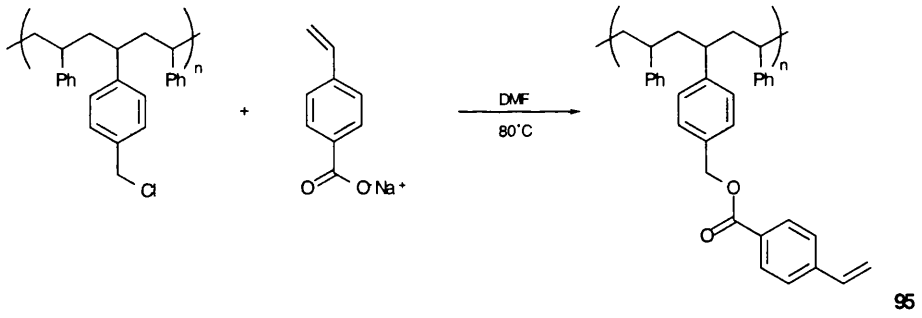
93

A solution of *p*-vinylbenzoic acid (503 mg, 3.40×10^{-3} mol) in DMF (5 ml) was added dropwise over several minutes to a stirred suspension of sodium hydride (169 mg, 3.70×10^{-3} mol as a 55% dispersion in mineral oils, prewashed with diethyl ether) in DMF (5 ml) at room temperature. After 20 minutes a solution of octadecyl bromide (1.25 g, 3.70×10^{-3} mol) in DMF

(10 ml) was introduced dropwise to the reaction mixture, and after 40 minutes the reaction mixture warmed to 60 °C for a further 6 h. On cooling to room temperature the reaction mixture was quenched with stirring into water (20 ml) and diethyl ether (25 ml). The phases were then separated, and the aqueous phase was extracted (3 x 50 ml Et_2O). The combined organic extracts were then washed successively with water (3 x 50 ml) and brine (30 ml), before drying ($MgSO_4$) and concentrating *in vacuo* to yield an off-white solid. The residue was chromatographed (silica, Et_2O (0-10%) / petroleum ether (40-60 °C)) to afford *n-octadecyl-4-vinylbenzoate* **93** (810 mg, 68%) as white plates, m.pt. 41-42 °C (from Et_2O - petroleum ether (40-60 °C)).

υ_{max} (NaCl plates, neat)/ cm^{-1} 2953 (-CH_3 str.), 2916 (=CH), 2849 (-CH_2-), 1717 (C=O), 1609 (C=C aromatics), 1472, 1294 (C-O), 1129; δ_H (400 MHz, $CDCl_3$) 7.98 (2H, dd, *J* 1.9, 8.6), 7.44 (2H, d, *J* 8.6), 6.73 (1H, dd, *J* 10.9, 17.6), 5.84 (1H, d, *J* 17.7), 5.36 (1H, d, *J* 11.0), 4.29 (2H, t, *J* 6.6), 1.74 (2H, t, *J* 7.4), 1.42-1.21 (30H, m, CH_2 envelope), 0.86 (3H, t, *J* 6.8); δ_C (100 MHz, $CDCl_3$) 166.4, 142.8, 136.0, 129.8, 129.6, 126.0, 116.3, 65.1, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 28.7, 26.0, 22.7, 14.1; *m/z* 400 (16%, M^+), 150 (100%), 131 (48%), 103 (20%), 83 (16%). (Found: M^+, 400.3346. $C_{27}H_{44}O_2$ requires *M*, 400.3341).

Preparation of the Solid Phase Alkene **95**



95

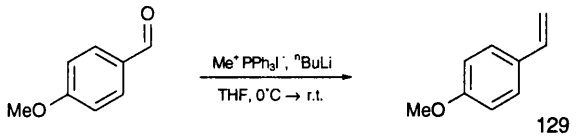
A solution of *p*-vinylbenzoic acid (749 mg, $5.00x10^{-3}$ mol) in DMF (5 ml) was introduced dropwise over 5 minutes to a stirred suspension of sodium hydride (247 mg, $5.50x10^{-3}$ mol as a 55% dispersion in mineral oils, prewashed with diethyl ether) in DMF (10 ml) at room temperature under nitrogen. After 20 minutes the suspension of the acid salt was poured with stirring into a suspension of Merrifield's resin (5.01 g, $5.01x10^{-3}$ mol of Cl, 2% cross-linked) in DMF (50 ml) at room temperature under nitrogen. The reaction mixture was then heated to 80 °C for 24 h, protected from light, and then cooled to room temperature before filtering off the polymer under suction. The collected polymer was then washed successively with DMSO (4 x 15 ml) and acetone (4 x 20 ml), and dried *in vacuo* for 24 h to yield the desired polymer **95** (5.41 g).

υ_{max} (KBr) / cm^{-1} (quoted values are those exclusive to the polymer product, i.e. not derived from the starting Merrifield resin) 1710 (C=O ester), 1094 (C-O ester), 688 (C-Cl from original Merrifield resin).

Cl analyses: **Merrifield's resin** - Found: Cl 3.94%. $1x10^{-3}$ mol Cl/g requires Cl 3.55%. Hence Merrifield's resin taken was $1.11x10^{-3}$ mol Cl/g.

Product polymer - Found: Cl 0.96%. Quantitative reaction requires Cl 0.40%. Thus there was 84% reaction at the chloromethyl residue on the resin.

Preparation of *p-Methoxystyrene* **129**

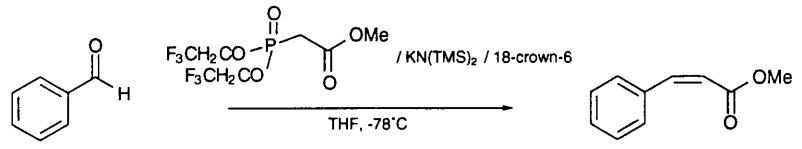


129

n-Butyllithium (46 ml, 0.11 mol as a 2.5 M solution in hexanes) was added dropwise with stirring to a suspension of methyltriphenylphosphonium iodide (45.9 g, 0.11 mol) in THF (200 ml) at 0 °C under nitrogen. After 1 h a solution of *p*-anisaldehyde (13.8 ml, 0.11 mol) in THF (35 ml) was added dropwise, the reaction mixture allowed to warm to room temperature, and then stirred for a further 65 h before pouring into water (300 ml). The phases were then separated, and the aqueous phase extracted (3 x 150 ml Et_2O). The combined organic extracts were then dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by reduced pressure bulb-to-bulb distillation to give *p*-methoxystyrene[173] **129** (11.7 g, 79%, b.p. 130 °C, 18 mmHg) (lit.,[173] 74-75 °C, 3.5 mmHg) as a clear colourless oil.

υ_{max} (NaCl plates, neat)/ cm^{-1} 3086 (=C-H), 3003, 2956, 2836, 1628 (phenyl conj. C=C), 1607 (C=C aromatics), 1510, 1463, 1301, 1248 (C-O), 1174, 1033; δ_H (400 MHz, $CDCl_3$) 7.37 (2H, dd, *J* 2.2, 6.7), 6.88 (1H, dt, *J* 2.0, 6.7), 6.68 (1H, dd, *J* 10.9, 17.5), 5.63 (1H, dd, *J* 0.9, 17.6), 5.14 (1H, dd, *J* 0.9, 10.4), 3.83 (3H, s).

Preparation of *(Z)-Methyl-3-phenylpropenoate*[158] **101**



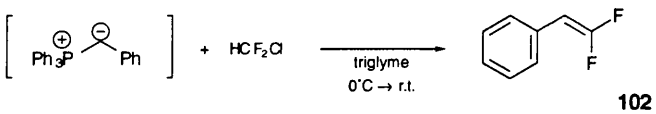
101

A solution of 18-crown-6 (12.6 g, $4.77x10^{-2}$ mol) and *bis*(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate (1.6 ml, $7.56x10^{-3}$ mol) in THF (100 ml) was cooled to -78 °C under nitrogen, in a 250 ml round-bottomed flask, and a solution of potassium bis(trimethylsilyl)amide (15.1 ml, $7.56x10^{-3}$ mol as a 0.5 M solution in PhMe) introduced dropwise to this mixture over 10 minutes. After stirring at -78 °C for a further 20 minutes benzaldehyde (780 µl, $7.7x10^{-3}$ mol) was added dropwise to the resultant yellow solution. The reaction mixture was then quenched after a further hour by the addition of

saturated ammonium chloride solution (20 ml) at -78 °C under nitrogen. On warming to room temperature the precipitated 18-crown-6 was filtered off under suction and rinsed thoroughly with petroleum ether (40-60 °C). The phases in the filtrate were then separated, and the aqueous phase extracted (2 x 50 ml Et_2O). The combined organic extracts were then washed with saturated potassium chloride solution (40 ml), dried ($MgSO_4$), and concentrated *in vacuo* to yield a mobile yellow oil. Chromatography (silica, EtOAc (0-10%) / petroleum ether (40-60 °C)) afforded (Z)-methyl-3-phenylpropenoate **101** (1.00 g, 82%) as a pale yellow oil.

υ_{max} (NaCl plates, neat)/ cm^{-1} 3058 (=CH aromatic), 3028 (CHR=CHR' cis), 2950, 1724 (C=O α,β-unsaturated ester), 1631 (C=C aromatics), 1573, 1495, 1436, 1200 (C-O), 1169, 1005; δ_H (400 MHz, $CDCl_3$) 7.58 (2H, d, *J* 7.3), 7.37-7.30 (3H, m), 6.94 (1H, d, *J* 12.6), 5.95 (1H, d, *J* 12.6), 3.70 (3H, s); δ_C (100 MHz, $CDCl_3$) 166.5, 144.4, 134.7, 129.7, 129.0, 128.0, 119.2, 51.3; *m/z* 162(70%, M^+), 131 (100%, M^+-OMe), 103 (85%, M^+-CO_2Me), 77 (62%, $[C_6H_5]^+$), (Found: M^+, 162.0684. $C_{10}H_{10}O_2$ requires *M*, 162.0681).

Preparation of *β,β-Difluorostyrene*[161] **102**

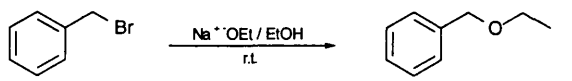


102

Phenyllithium (18.5 ml, $3.30x10^{-3}$ mol, as a 1.8 M solution in cyclohexane - diethyl ether, 7:3) was added dropwise with rapid stirring to an ice-cooled suspension of benzyltriphenylphosphonium chloride (13.0 g, $3.30x10^{-2}$ mol) in triglyme (50 ml), under nitrogen, in a 250 ml 3-necked round-bottomed flask equiped with a cold-finger condenser. On complete addition the resultant orange-brown solution was allowed to warm to room temperature and left stirring for 1 h before condensing an excess of chlorodifluoromethane into the reaction mixture, which brought about an immediate lightening of the reaction mixture to an orange colour. After stirring overnight at room temperature the precipitated benzyltriphenylphosphonium chloride was filtered off under suction and rinsed thoroughly with triglyme. The filtrate was then poured into diethyl ether (75 ml) and water (75 ml), and the phases separated. The organic phase was then washed with water (2 x 60 ml H_2O) and dried ($MgSO_4$). The diethyl ether was then removed by distillation at atmospheric pressure, and the residue twice purified by bulb to bulb distillation to yield β,β-difluorostyrene[174] **102** (175 mg, 8%, b.pt. 50 °C, 27 mmHg) as a volatile clear colourless oil, which was stored at -18 °C.

υ_{max} (NaCl plates, neat)/ cm^{-1} 2926, 2877, 1730 ($C=F_2$), 1662, 1598 (C=C aromatics), 1451, 1241, 1109 (C-F), 1019; δ_H (400 MHz, $CDCl_3$) 7.39-7.15 (5H, m), 5.26 (1H, dd, *J* 3.9, 26.3);
δ_F (376 MHz, $CDCl_3$, referenced to internal standard $CFCl_3$) -84.76 (1F, d, *J* 29.0), -82.85 (1F, t, *J* 29.0); *m/z* 140 (14%, M^+), 105 (78%), 79 (53%), 77 (100%, $[C_6H_5]^+$).

Preparation of *Benzyl Ethyl Ether* **105**

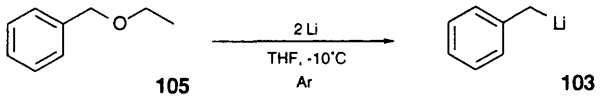


105

Benzyl bromide (7.0 ml, 6.1×10^{-2} mol) was added dropwise with stirring to a preformed solution of sodium ethoxide in ethanol (1.5 g, 6.5×10^{-2} mol of Na in 150 ml EtOH) under nitrogen. After 14 h the reaction mixture was poured into water (20 ml) with stirring, diethyl ether added (50 ml) and the phases separated. The aqueous phase was then extracted (3 x 50 ml Et_2O), the combined organic extracts dried ($MgSO_4$), concentrated *in vacuo*, and the residue purified by reduced pressure distillation to yield benzyl ethyl ether[175] **105** (4.62 g, 58%, b.pt. 76-81 °C, 26 mmHg) as a clear colourless mobile oil.

υ_{max} (NaCl plates, neat)/ cm^{-1} 3064, 3030 (C=C-H), 2976 (-CH_3), 2863 (-CH_2 -str.), 1598(C=C aromatics), 1454, 1373, 1354, 1101 (C-O), 1019; δ_H (400 MHz, $CDCl_3$) 7.38-7.30 (5H, m), 4.54 (2H, s), 3.75 (2H, q, *J* 7.0), 1.28 (3H, t, *J* 7.0); δ_C (100 MHz, $CDCl_3$) 138.5, 128.3, 127.6, 127.4, 72.7, 65.5, 15.2; *m/z* 136 (10%, M^+), 135 (44%), 105 (76%), 91 (93%, tropylium), 77 (100%, $[C_6H_5]^+$).

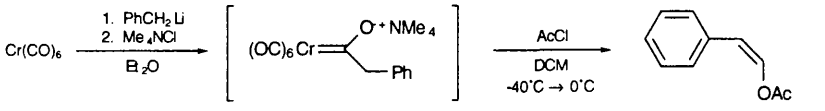
Preparation of *Benzyl Lithium*[159] **103**



105 **103**

A solution of benzyl ethyl ether (2.0 g, 1.47×10^{-2} mol) in diethyl ether (3 ml) was added dropwise with stirring over 30 minutes to a suspension of freshly cut small pieces of lithium (207 mg, 2.94×10^{-2} mol) and glass shards in THF (6 ml) at -10 °C under argon, in a 50 ml Schlenk tube. After 1 h a bright orange colouration appeared, and the solution darkened over the next 3 h to a brown colour. Titration[176] gave a concentration of 0.47 M. The organolithium was used directly.

Attempted Preparation of *(Z)-2-Phenyl-1-ethen-1-ol Acetate*[157] **100**

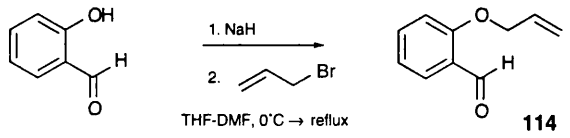


100

Benzyl lithium **103** (9.0 ml, 4.23×10^{-3} mol as a 0.47 M solution in THF - Et_2O) was added dropwise to a stirred suspension of chromium hexacarbonyl (940 mg, 4.26×10^{-3} mol) in diethyl ether (15 ml) at room temperature under argon, in a 50 ml round-bottomed Schlenk flask.

After 45 minutes no suspended solid remained, and solid tetramethylammonium chloride (469 mg, 4.28×10^{-3} mol) was added in one portion to the reaction mixture, and left stirring for a further 30 minutes before removing the solvent *in vacuo*. The residue was dissolved in DCM (30 ml) and cooled to -40 °C. Acetyl chloride (300 µl, 4.23×10^{-3} mol) was then added dropwise with stirring, and the reaction mixture left to warm slowly to room temperature overnight. The reaction mixture was then adsorbed directly onto silica gel and chromatographed (silica, Et_2O (0-20%) / petroleum ether (40-60° C)). No identifiable products were isolated.

Preparation of *o-Allyloxybenzaldehyde* **114**

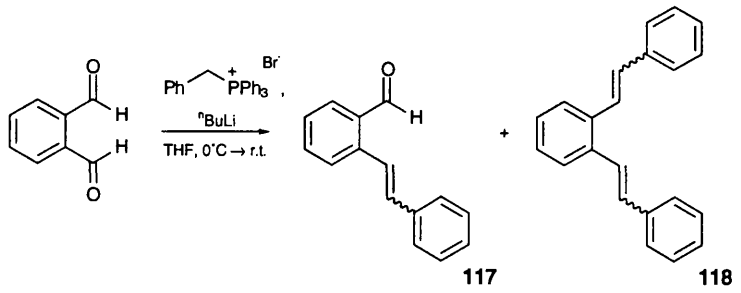


114

Salicylaldehyde (4.4 ml, 4.09×10^{-2} mol) was added slowly with stirring to a suspension of sodium hydride (2.23 g, 5.11×10^{-2} mol, as a 55% dispersion in mineral oils, prewashed with diethyl ether) in THF-DMF (170 ml, 7.5:1) at 0 °C under nitrogen. After stirring for 1 h at 0 °C, allyl bromide (4.4 ml, 5.11×10^{-2} mol) was added dropwise to the suspension. The reaction mixture was then allowed to warm to room temperature, and heated to ~80 °C. After 20 h the reaction mixture was cooled to room temperature and quenched under nitrogen with saturated ammonium chloride solution (40 ml). The reaction mixture was then poured into diethyl ether (150 ml), the phases separated, and the aqueous phase extracted (3 x 50 ml Et_2O). The combined organic phases were then washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to yield a mobile yellow oil. This was purified by reduced pressure bulb-to-bulb distillation to give *o*-allyloxybenzaldehyde[177] **114** (5.11 g, 77%, b.pt. 150 °C, 21 mmHg) (lit.,[177] 142 °C, 17 mmHg) as a clear colourless oil.

υ_{max} (NaCl plates, neat)/ cm^{-1} 3078 (=C-H), 2864 ($-CH_2$), 1682 (C=O), 1598 (C=C aromatics), 1483, 1466, 1397, 1286, 1240, 1163; δ_H (400 MHz, $CDCl_3$) 10.52 (1H, s), 7.82 (1H, dd, *J* 1.8, 7.7), 7.51 (1H, dt, *J* 1.9, 8.8), 7.01 (1H, t, *J* 7.5), 6.95 (1H, d, *J* 7.9), 6.05 (1H, tdd, *J* 5.2, 10.6, 17.2), 5.43 (1H, dd, *J* 1.4, 17.3), 5.32 (1H, dd, *J* 1.4, 10.6), 4.64 (2H, td, *J* 1.5, 5.1); δ_C (100 MHz, $CDCl_3$) 189.2, 160.6, 135.6, 132.1, 127.9, 124.7, 120.5, 117.6, 112.6, 68.8; *m/z* 162 (22%, M^+), 121 (94%, M^+-allyl), 105 (32%, M^+-allyloxy), 41 (100%, $[CH_2CH{=}CH_2]^+$), 28 (57%). (Found: M^+, 162.0672. $C_{10}H_{10}O_2$ requires *M*, 162.0681).

Preparation of 2-(2-*Phenylethenyl)benzaldehyde* **117**



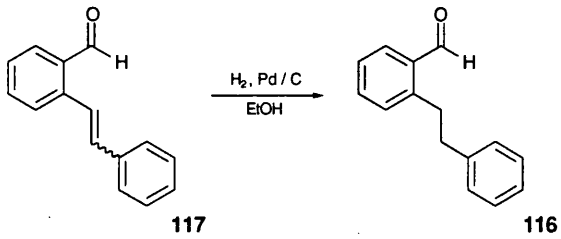
117 **118**

n-Butyllithium (13.3 ml, 0.03 mol as a 2.29 M solution in hexanes) was added dropwise with stirring to a suspension of benzyltriphenylphosphonium bromide (13.1 g, 0.03mol) in THF (75 ml) at 0 °C under nitrogen. After 20 minutes the suspension was added via a cannula to a stirred solution of phthalic dicarboxaldehdye (4.08 g, 0.03 mol) in THF (75 ml) at 0 °C under nitrogen. The reaction mixture allowed to warm slowly to room temperature, and left stirring for 30 h before pouring into water (100 ml). The phases were then separated, and the aqueous phase extracted (3 x 75 ml Et_2O). The combined organic extracts were then dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed (silica, Et_2O (0-20%) / petroleum ether (40-60 °C)) to afford, in order of elution, 1,2-*bis*(2-phenylethenyl)benzene[178] **118** (0.89 g, 11%, an inseparable mixture of (*E*,*E*)-, (*E*,*Z*)- and (*Z*,*Z*)- isomers) as a yellow crystalline solid and 2-(2-phenylethenyl)benzaldehdye[179] **117** (4.33 g, 69%, an inseparable mixture of *Z*- and *E*- isomers in a ratio of 3:2 by NMR) as a viscous yellow oil.

1,2-*Bis*(2-phenylethenyl)benzene: υ_{max} (NaCl plates, thin film)/ cm^{-1} 3056 (=C-H), 3024 (CHR=CHR'), 1598 (C=C aromatics), 1493, 1446, 961; δ_H (400 MHz, $CDCl_3$) 7.70-6.60 (18H, m); δ_C (100MHz, $CDCl_3$) 131.3, 130.7, 130.1, 139.7, 129.3, 129.0, 128.9, 128.7, 128.6, 128.0, 127.7, 127.6, 127.5, 127.4, 127.1, 127.0, 126.96, 126.8, 126.64, 126.6, 126.56, 125.6; *m/z* 282 (30%, M^+), 191 (100%), 165 (47%), 91 (84%, tropylium), 77 (79%, $[C_6H_5]^+$). (Found: M^+, 282.1406. $C_{22}H_{18}$ requires *M*, 282.1409).

2-(2-Phenylethenyl)benzaldehdye: υ_{max} (NaCl plates, neat)/ cm^{-1} 3059 (=C-H), 3023 (CHR=CHR'), 2743 (C-H str. RCHO), 1693 (C=O aryl RCHO), 1596 (C=C aromatics), 1567, 1491, 1446, 1291, 1195; δ_H (400 MHz, $CDCl_3$; integral values not given due to spectral complexity, except where signals may be definitively assigned to one isomer) 10.23 (1H, s), 10.17 (1.5H, s), 7.98 (1H, d, *J* 16.3, *trans*), 7.82 (dd, *J* 1.5, 7.7), 7.75 (dd, *J* 1.37, 7.7), 7.63 (d, *J* 7.9), 7.51-7.47 (m), 7.35-7.28 (m), 7.24-7.20 (m), 7.16-7.05 (m), 7.00-6.95 (m), 6.90 (1.5H, d, *J* 12.1, *cis*), 6.75 (1.5H, d, 12.2, *cis*); δ_C (100MHz, $CDCl_3$) 192.5, 191.9, 140.8, 139.8, 136.8, 135.7, 133.8, 133.6, 133.3, 133.2, 132.8, 135.3, 130.4, 129.2, 129.1, 128.7, 128.2, 127.6, 127.5, 127.4, 127.0, 126.9, 126.4, 124.5; *m/z* 208 (56%, M^+), 191 (38%), 178 (56%), 165 (31%), 131 (28%), 91 (22%, tropylium), 77 (54%, $[C_6H_5]^+$), 51 (64%), 39 (66%), 28 (100%). (Found: M^+, 209.0962 . $C_{15}H_{12}O$ requires *M*, 209.0966).

Preparation of 2-(2-*Phenylethyl)benzaldehyde* **116**

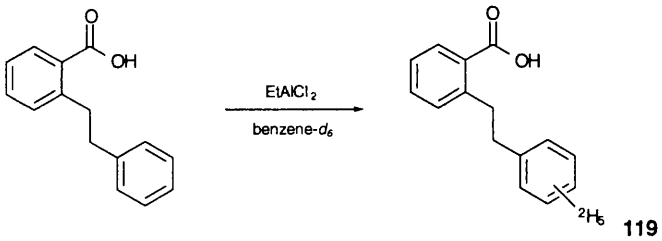


117 **116**

A degassed suspension of 5% palladium on carbon (203 mg, 10 mol%) and 2-(2-phenylethenyl)benzaldehyde **117** (994 mg, 4.70 mmol) in ethanol (10 ml) was stirred at room temperature under a positive hydrogen pressure for 2 h. The catalyst was then filtered off under suction through Celite, and the residue rinsed thoroughly with diethyl ether. The filtrate was then concentrated *in vacuo* to yield a clear colourless oil, which was chromatographed to yield 2-(2-phenylethyl)benzaldehyde[180] **116** (581 mg, 59%) as a clear colourless oil.

υ_{max} (NaCl plates, neat)/ cm^{-1} 3026, 2925 ($-CH_2-$), 2860 ($-CH_2-$), 2735 (C-H str. RCHO), 1694 (C=O), 1600 (C=C aromatics), 1496, 1453, 1292, 1192; δ_H (400 MHz, $CDCl_3$) 10.21 (1H, s), 7.84 (1H, dd, *J* 1.4, 7.6), 7.51 (1H, dt, *J* 1.5, 7.5), 7.41 (1H, dt, *J* 1.1, 7.4), 7.30 (1H, dt, *J* 1.8, 6.4), 7.25-7.20 (5H, m), 3.34 (2H, t, *J* 8.0), 2.92 (2H, t, *J* 8.0); δ_C (100 MHz, $CDCl_3$) 192.3, 144.3, 141.1, 133.8, 132.4, 131.2, 128.6, 128.5, 128.4, 126.7, 126.2, 126.1, 38.2, 34.9; *m/z* 210 (15%, M^+), 107 (56%), 91 (100%, tropylium), 77 (40%, $[C_6H_5]^+$), 65 (81%), 51 (44%), 39 (65%). (Found: MH^+ (FAB matrix), 211.1126. $C_{15}H_{14}O$ requires *M*, 211.1123).

Preparation of 2-(2-([$^2H_5$]*Phenyl)ethyl)benzoic acid* **119**



119

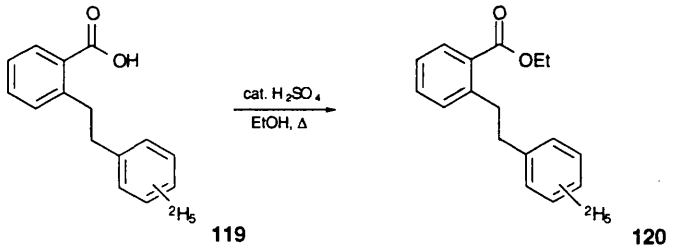
Ethylaluminium dichloride (1.4 ml, $1.33x10^{-2}$ mol) was added dropwise to an ice-cooled suspension of 2-phenethylbenzoic acid (2.01 g, $8.84x10^{-3}$ mol) in benzene-d_6 (6 ml) under nitrogen. On addition of the ethylaluminium dichloride the reaction mixture clarified to give an orange solution, from which there was a rapid precipitation of a cream solid after ~5 minutes. The reaction mixture was then stirred overnight for 15.5 h, and subsequently quenched by the cautious addition, with cooling, of water (5 ml) to the reaction mixture, under nitrogen. The reaction mixture was then poured into diethyl ether and brine, the phases separated, and the aqueous phase extracted (3 x 20 ml Et_2O). The combined organic extracts were then washed successively with 2 M HCl (50 ml), water (50 ml), and brine

(50 ml), dried ($MgSO_4$), and concentrated under reduced pressure to yield an off-white solid (2.07 g).

This process was repeated twice futher to yield 2-(2-([$^2H_5$]*phenyl*)*ethyl*)*benzoic acid* **119** (1.96 g, 96% over 3 steps) as white needles, m.pt. 129.5-131 °C (from diethyl ether), which was used without further purification.

υ_{max} (KBr disc)/ cm^{-1} 3446 (O-H), 3067 (=CH), 2944, 2862 (-CH_2-), 1692 (C=O), 1600 (C=C aromatics), 1574, 1303, 1272, 1256; δ_H (400 MHz, $CDCl_3$) 8.11 (1H, dd, *J* 1.3, 7.8), 7.49 (1H, dt, *J* 1.5, 7.5), 7.33 (1H, dt, *J* 1.2, 7.6), 7.29-7.25 (1H, m, superimposed on residual $CHCl_3$), 3.37-3.33 (2H, m), 2.98-2.94 (2H, m); δ_C (100 MHz, $CDCl_3$) 172.7, 144.8, 141.7, 133.0, 131.8, 131.5, 128.1, 128.0, 126.2, 38.0, 37.1; *m/z* 231 (18%, M^+), 212 (24%), 135 (18%, M^+-$C_7[^2H_5]H_2$), 96 (100%, [$^2H_5$]-tropylium), 77 (14%, $[C_6H_5]^+$). (Found: M^+, 231.1319. $C_{15}H_9[^2H_5]O_2$ requires *M*, 231.1385).

Preparation of *Ethyl* 2-(2-([$^2H_5$]*phenyl*)*ethyl*)*benzoate* **120**

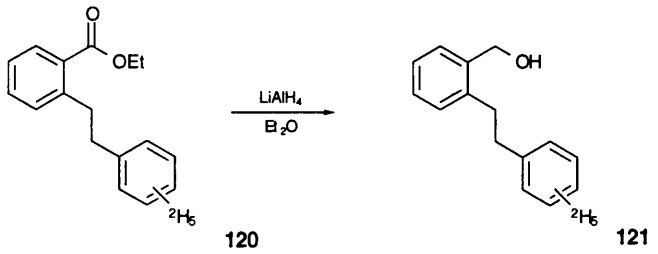


119 **120**

A solution of acid **119** (1.48 g, $6.43x10^{-3}$ mol) in absolute ethanol (150 ml) in the presence of catalytic concentrated sulfuric acid was heated under reflux for 16.5 h, under a slow nitrogen flow. The reaction mixture was then cooled to room temperature and quenched with stirring into ice (150 g). The quenched reaction mixture was then poured into diethyl ether (150 ml), the phases separated, and the aqueous phase extracted (2 x 100 ml Et_2O). The combined organic extracts were then washed successively with saturated aqueous sodium bicarbonate solution (2 x 100 ml) and water (100 ml), dried ($MgSO_4$), and concentrated *in vacuo* to yield *ethyl* 2-(2-([$^2H_5$]*phenyl*)*ethyl*)*benzoate* **120** as a mobile yellow oil (720 mg, 43%), which was used without further purification.

υ_{max} (KBr disc)/ cm^{-1} 3062, 2980, 2929 (-CH_2-), 2863, 1718 (C=O), 1619, 1601 (C=C aromatics), 1447, 1252 (C-O str.), 1129, 1079; δ_H (400 MHz, $CDCl_3$) 7.96 (1H, d, *J* 7.8), 7.44 (1H, t, *J* 7.5), 7.31 (1H, t, *J* 7.6), 7.25 (1H, d, *J* 7.7), 4.42 (2H, q, *J* 7.1), 3.34-3.30 (2H, m), 2.99-2.95 (2H, m), 1.44 (3H, t, *J* 7.1); δ_C (100 MHz, $CDCl_3$) 167.7, 143.5, 141.8, 131.9, 131.2, 131.0, 130.7, 130.0, 128.3, 128.1, 127.9, 126.1, 60.9, 38.1, 36.8, 14.4; *m/z* 259 (2%, M^+), 212 (14%), 149 (27%, M^+-$(CH_2)_2$-$C_6[^2H_5]$), 135 (44%), 96 (100%, [$^2H_5$]-tropylium), 77 (46%, $[C_6H_5]^+$), 69 (26%). (Found: M^+, 259.1625. $C_{17}H_{13}[^2H_5]O_2$ requires *M*, 259.1621).

Preparation of 2-(2-([$^2H_5$]*Phenyl)ethyl)benzyl alcohol* **121**

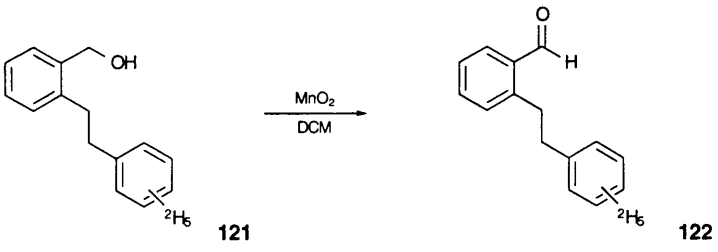


120 **121**

A solution of the ester **120** (561 mg, 2.59×10^{-3} mol) in diethyl ether (20 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (103 mg, 2.70×10^{-3} mol) in diethyl ether (80 ml) at room temperature under nitrogen. After stirring overnight the reaction mixture was quenched under nitrogen by the slow addition of water (20 ml) with stirring. The phases were then separated, the aqueous phase extracted (3 x 20 ml Et_2O), and the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo* to yield 2-(2-([$^2H_5$]*phenyl)ethyl)benzyl alcohol* **121** (516 mg, 92%) as a clear viscous oil which crystallised on standing as white needles, m.pt. 51-54°C (diethyl ether). The product was used without further purification.

υ_{max} (KBr disc)/ cm^{-1} 3334 and 3251 (O-H), 3015, 2923 (-CH_2-), 2862, 1605 (C=C aromatics), 1451, 1431, 1359, 1215, 1010 (C-O str.); δ_H (400 MHz, $CDCl_3$) 7.38 (1H, d, *J* 7.0), 7.31-7.23 (3H, m), 4.65 (2H, s), 3.03-2.99 (2H, m), 2.96-2.92 (2H, m), 1.52 (1H, s, br.); δ_C (100 MHz, $CDCl_3$) 141.5, 139.9, 138.4, 129.6, 128.4, 128.2, 128.1, 126.4, 63.1, 37.7, 34.4; *m/z* 217 (1%, M^+), 199 (66%, M^+-H_2O), 184 (45%), 119 (67%), 96 (84%, [$^2H_5$]-tropylium), 91 (100%, tropylium), 77 (70%, [C_6H_5]$^+$). (Found: M^+-H_2O, 199.1407. $C_{15}H_9[^2H_5]$ requires *M*, 199.1409).

Preparation of 2-(2-([$^2H_5$]*phenyl)ethyl)benzaldehyde* **122**

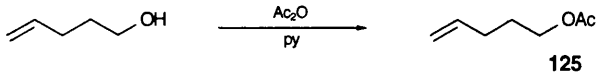


121 **122**

Activated manganese dioxide on carbon (2.44 g, 2.24×10^{-2} mol, ~20% C) was added in one portion to a stirred solution of the alcohol **121** (485 mg, 2.24×10^{-3} mol) in DCM (70 ml) at room temperature under nitrogen. After 14.5 h the manganese dioxide was filtered off under suction through Celite, and the residues rinsed thoroughly with DCM. The filtrate was then concentrated *in vacuo* to yield a clear mobile oil which was chromatographed (silica, Et_2O (0-2.5%) / petroleum ether (40-60 °C)) to give 2-(2-([$^2H_5$]*phenyl)ethyl)benzaldehyde* **122** (220 mg, 46%) as a clear colourless oil.

υ_{max} (KBr disc)/ cm^{-1} 3067, 2925 (-CH_2-), 2862, 2860, 2736 (C-H str. RCHO), 1694 (C=O), 1600 (C=C aromatics), 1574, 1452, 1359, 1208, 1192; δ_H (400MHz, $CDCl_3$) 10.2 (1H, s), 7.85 (1H, dd, *J* 1.4, 7.7), 7.51 (1H, aa'bb', m), 7.41 (1H, aa'bb', m), 7.25 (1H, aa'bb', m), 3.37-3.33 (2H, m), 2.94-2.90 (2H, m); δ_C (100MHz, $CDCl_3$) 192.3, 144.3, 141.0, 133.8, 133.7, 132.4, 131.2, 126.7, 38.2, 34.9; *m/z* 215 (7%, M^+), 135 (20%), 96 (100%, [$^2H_5$]-tropylium), 77 (30%, $[C_6H_5]^+$). (Found: M^+, 215.1355. $C_{15}H_9[^2H_5]O$ requires *M*, 215.1358).

Preparation of 4-*Penten*-1-*yl Acetate* **125**



125

A prepared mixture of acetic anhydride (14.2 ml, 0.15 mol) in pyridine (25 ml) was added with stirring over 10 minutes to a mixture of 4-penten-1-ol (4.8 ml, $4.65x10^{-2}$ mol) and DMAP (29 mg, $2.34x10^{-4}$ mol) at 0 °C under argon. On complete addition the reaction mixture was allowed to warm to ambient temperature, and stirred for a further 4.5 h before pouring into diethyl ether (100 ml). The ethereal solution was then separated and washed successively with water (50 ml), saturated copper sulphate solution (6 x 50 ml), 2 M HCl (50 ml), water (50 ml), saturated sodium bicarbonate solution (50 ml), and saturated sodium chloride solution (50 ml), dried ($MgSO_4$), and concentrated under reduced pressure to yield a clear colourless oil. The product was purified by reduced pressure distillation to give 4-penten-1-yl acetate **125** (1.69 g, 28%, b.pt. 37 °C, 200 mmHg) (lit.,[181] 150-151°C) as a clear colourless oil.

υ_{max} (NaCl; neat)/ cm^{-1} 3079 and 2956 (vinylic / aliphatic -C-H), 1742 (C=O), 1642 (non-conjugated C=C), 1448 (C-CH_3, C-H asymmetric deformation), 1242 (C-O stretching vibration of acetate); δ_H (270 MHz, $CDCl_3$) 5.78 (1H, ddd, *J* 6.6, 10.0, 17.1), 5.07-5.01 (1H, m), 5.00-4.96 (1H, m), 4.07 (2H, t, *J* 6.6), 2.16-2.10 (2H, m), 2.04 (3H, s), 1.74 (2H, dt, *J* 6.7, 13.3).

Preparation of 3-*Methyl*-1-*phenylthio*-2-*butene* **127**

127

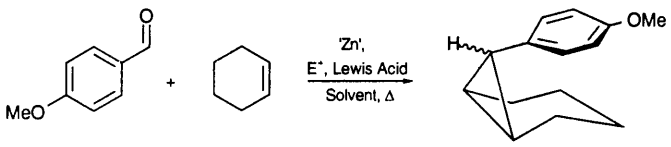
Thiophenol (3.6 ml, $3.53x10^{-2}$ mol) was added slowly with stirring to a suspension of sodium hydride (1.56 g, $3.60x10^{-2}$ mol as a 55% dispersion in mineral oils, pre-washed with diethyl ether) in DMF (75 ml), at room temperature under argon. After 15 minutes, 4-bromo-3-methyl-2-butene (3.9 ml, $3.4x10^{-2}$ mol) was added in one portion to the reaction mixture, and stirring continued for a further 3.5 h. The reaction mixture was then quenched under an argon blanket with water (50 ml), and extracted (3 x 50 ml diethyl ether). The combined organic

extracts were then washed successively with 2 N NaOH (5 x 40 ml), water (50 ml) and brine (50 ml). The organic phase was then dried ($MgSO_4$), and concentrated under reduced pressure to yield a mobile yellow oil which was purified by reduced pressure bulb to bulb distillation to give 3-methyl-1-phenylthio-2-butene[182] **127** (5.41 g, 89%, b.pt. 75 °C, 0.35 mmHg) as a colourless mobile oil.

υ_{max} (NaCl plates, neat)/ cm^{-1} 3058, 2975, 2914 (vinylic / aliphatic -C-H), 1668 (non-conjugated trisubstituted C=C), 1584 (C=C in plane vibration), 1482, 1376, 1089 (C-S stretching vibration); δ_H (270 MHz, $CDCl_3$) 7.36-7.24 (5H, m), 5.35-5.27 (1H, m), 3.53 (2H, d, *J* 7.8), 1.71 (3H, s), 1.59 (3H, s); δ_C (125 MHz, $CDCl_3$) 136.8, 136.0, 129.5, 128.5, 125.7, 119.3, 32.0, 25.6, 17.5.

4.3 Mechanistic Analysis

Typical Experimental for the Cyclopropanation of Cyclohexene With the Carbenoid Derived From *p*-Anisaldehyde



83

A solution of *p*-anisaldehyde (223 µl, 1.84×10^{-3} mol) in solvent (1.5 ml) was added over 12 h via a motorised syringe pump to a vigorously stirred heated (reflux for diethyl ether, DCM and THF; 53 °C for all other solvents) suspension of 'zinc' (1.84×10^{-2} mol), the Lewis acid (number of mole equivalents as specified), cyclohexene (370 µl, 3.68×10^{-3} mol) and the electrophile (number of mole equivalents as specified) in solvent (10 ml), under nitrogen, in a previously flame-dried 25 ml conical flask equiped with a condenser. On complete comsumption of the aldehyde as indicated by tlc the reaction mixture was cooled to room temperature and quenched under nitrogen with saturated aqueous sodium bicarbonate solution (10 ml for all electrophiles except chlorotrimethylsilane, where 20 ml is required). The solid residues were then filtered off under suction through Celite, diethyl ether added to the filtrate (20 ml), the phases separated, and the aqueous phase extracted with diethyl ether (3 x 20 ml). The combined organic extracts were then dried ($MgSO_4$), concentrated *in vacuo*, and the residue was chromatographed (silica, Et_2O (0-30%) / petroleum ether (40-60 °C)) to give, in order of elution, an inseperable mixture of *endo*- and *exo*-7-(4-methoxyphenyl)bicyclo[4.1.0]heptane[163] **83** as a colourless oil (isomer ratio determined by GC), mixtures of (*E*) and (*Z*)-1,1'-(1,2-ethenediyl)*bis*(4-methoxybenzene)[183] **84** and **85**, and solvent C-H insertion products (where the solvent is diethyl ether or THF).

7-(4-Methoxyphenyl)bicyclo[4.1.0]heptane: υ_{max} (NaCl plates, neat)/ cm^{-1} 3002, 2932, 2860 (-CH_2- str.), 1608 (aromatic C=C), 1512, 1447 (-CH_2 skeletal), 1243, 1176, 1039; δ_H (400 MHz, $CDCl_3$) 7.20 (2H, dd, *J* 1.0, 8.7), 6.86 (2H, d, *J* 8.7), 3.80 (3H, s), 1.93-1.85 (3H, m), 1.69-1.63 (2H, m), 1.25-1.20 (2H, m), 1.12-1.05 (2H, m), 0.72-0.64 (2H, m); δ_C (100 MHz, $CDCl_3$) 157.6, 132.1, 130.6, 113.6, 55.2, 30.3, 21.8, 21.2, 20.2, 12.6; *m/z* 202 (93%, M^+), 134 (53%), 121 (100%), 91 (39%, tropylium), 77 (27%, $[C_6H_5]^+$), 39 (27%).

(*E*)- and (*Z*)-1,1'-(1,2-Ethenediyl)*bis*(4-methoxybenzene): υ_{max} (KBr disc)/ cm^{-1} 3015 (CHR=CHR' trans), 2954 (-CH_3 str.), 2913, 2841, 1605 (aromatic C=C), 1514, 1267, 1250, 1180, 1031; δ_H (400 MHz, $CDCl_3$) 7.44 (4H, dd, *J* 2.1, 6.8, (*E*-)), 7.21 (4H, dd, *J* 2.1, 6.7, (*Z*-)), 6.94 (2H, s, (*E*-)), 6.90 (4H, dd, *J* 2.0, 6.7, (*E*-)), 6.78 (4H, dd, *J* 2.1, 6.7, (*Z*-)), 6.45 (2H, s, (*Z*-)), 3.84 (6H, s, (*E*-)), 3.80 (6H, s, (*Z*-)).

For all reactions where 1,1'-(1,2-ethenediyl)*bis*(4-methoxybenzene) was obtained as a product, ^{1}H NMR data consistent with either single isomers or variously proportioned isomeric mixtures of **84** and **85**.

3-(4-*Methoxyphenyl*)-2-*ethoxypropane*: ^{1}H NMR data consistent with the product **106** (*vide infra* chapter 4.5).

***Tetrahydro*-2-(4-*methoxyphenyl*)*furan*:** ^{1}H NMR data consistent with the product **112** (*vide infra* chapter 4.5).

General Notes: the NMR data for all products tabulated corresponded with those given above. For each section, as appropriate, the 'constants' of the reactions are listed, and a note made of any other experimental conditions additional to the general procedure.

TABLE 7. Electrophile Variation:

Solvent	Diethyl ether
Zinc	Zinc amalgam
Lewis Acid	None added

Protic conditions were achieved by the precise hydrolysis of chlorotrimethylsilane, according to the following equation:

$$2Me_3SiCl + H_2O \rightarrow Me_3Si\text{-}O\text{-}SiMe_3 + HCl$$

Previously distilled 1,2-*bis*(chlorodimethylsilyl)ethane was weighed immediately before the reaction and dissolved in a small volume of diethyl ether for introduction into the reaction flask. Dichlorodisilane refers to 1,2-*bis*(chlorodimethylsilyl)ethane (Entry 1).

	Electrophile / no. of equivalents[#]	Yields and de / %			
		Cyclopropane[§]	de (endo / exo ratio)	Stilbene[§]	C-H Insertion[§]
1	Dichlorodisilane (1.5eq)	85	92 (23:1)	-	2
2	TMSCl (5eq)	45	92 (25:1)	-	2
3	Me_2SiCl_2 (2eq)	37	93 (27:1)	-	3
4	TMSCl (4.75eq) + HCl (0.25eq) (i.e. 5% HCl in TMSCl)	32	93 (27:1)	1	-
5	TMSCl (2.5eq) + HCl (2.5eq)	49	93 (28.5:1)	-	2
6	HCl (5eq)	43 (47)[*]	92 (23:1)	-	1
7	HCl (5eq) + H_2O (2.5eq)	66	92 (24:1)	-	-
8	HCl (5eq) + H_2O (5eq)	49	93 (29:1)	-	2
9	H_2O (5eq)	0[**]	-	-	-

[#] - Number of mole equivalents with respect to the number of moles of aldehyde taken

[§] - Cyclopropane refers to 7-(4-methoxyphenyl)bicyclo[4.1.0]heptane (*endo* and *exo* **83**)
Stilbene refers to (*Z*)- and (*E*)-1,1'-(1,2-ethenediyl)*bis*(4-methoxybenzene) **85** and **84**
C-H insertion refers to 3-(4-methoxyphenyl)-2-ethoxypropane **106**

[*] - Based on recovered aldehyde

[**] - Aldehyde recovered quantitatively

TABLE 16. Solvent Variation:

Electrophile	TMSCl
Zinc	Zinc amalgam
Lewis Acid	None added

All solvents were freshly distilled immediately prior to use except for DME, which was an Aldrich SureSeal™ solvent, and cyclohexene, which was used without further purification (GPR grade, no stabiliser present).

	Solvent	Yields and de / %			
		Cyclopropane§	de (endo / exo ratio)	Stilbene§	C-H Insertion#
1	Et_2O	45	92 (25:1)	-	2
2	THF	31	88 (15:1)	1	9
3	DME	1*	90 (18:1)	-	-
4	DCM	10	91 (21:1)	9	-
5	MeCN	20	92 (25:1)	-	-
6	Cyclohexene	16	87 (14:1)	5	-
7	PhMe	20	91 (21:1)	8	-
8	$(SiMe_3)_2O$	3**	83 (11:1)	2	-

#- C-H insertion is only relevent for entries 1 and 2, and refers to 3-(4-methoxyphenyl)-2-ethoxypropane **106** and tetrahyro-2-(4-methoxyphenyl)furan **112** respectively

§- Cyclopropane refers to 7-(4-methoxyphenyl)bicyclo[4.1.0]heptane (*endo* and *exo* **83**) Stilbene refers to (*Z*)- and (*E*)-1,1'-(1,2-ethenediyl)*bis*(4-methoxybenzene) **85** and **84**

*- 81% of aldehyde recovered

**- Based on recovered aldehyde - zinc balls formed mid-way through reaction

TABLE 17. Zinc Variation:

Solvent Et_2O
Electrophile TMSCl
Lewis Acid None added

	Zinc	Yields and de / %			
		Cyclopropane§	de (endo / exo ratio)	Stilbene§	C-H Insertion#
1	Zn / Hg	45	92 (25:1)	-	2
2	Zn - Cu*	35	92 (25:1)	-	-
3	Zn - Ag	35	93 (28:1)	4	-
4	Zn_{act}	23	93 (30:1)	6	-

#- C-H insertion refers to 3-(4-methoxyphenyl)-2-ethoxypropane **106**

§- Cyclopropane refers to 7-(4-methoxyphenyl)bicyclo[4.1.0]heptane (*endo* and *exo* **83**)
Stilbene refers to (*Z*)- and (*E*)-1,1'-(1,2-ethenediyl)*bis*(4-methoxybenzene) **85** and **84**

* Large quantity of unidentified aromatic product also obtained

TABLE 18. Lewis Acid Variation:

Solvent Et_2O
Electrophile TMSCl
Zinc Zinc amalgam

	Lewis Acid / no. of equivalents*	Yields and de / %			
		Cyclopropane§	de (endo / exo ratio)	Stilbene§	C-H Insertion#
1	None added	45	92 (25:1)	-	2
2	$ZnCl_2$ / 1 eq.	57	92 (25:1)	-	-
3	ZnI_2 / 1 eq.	37	93 (28:1)	5	-
4	$MgBr_2$ / 1 eq.	4**	95 (40.5:1)	1.5**	-
5	$BF_3.OEt_2$/ 1 eq.	39	92 (25:1)	-	-
5	$TiCl_4$ / 1 eq.	3	92 (23:1)	9	-

#- C-H insertion refers to 3-(4-methoxyphenyl)-2-ethoxypropane **106**

§- Cyclopropane refers to 7-(4-methoxyphenyl)bicyclo[4.1.0]heptane (*endo* and *exo* **83**)
Stilbene refers to (*Z*)- and (*E*)-1,1'-(1,2-ethenediyl)*bis*(4-methoxybenzene) **85** and **84**

* - With respect to aldehyde

** - Based on recovered aldehyde

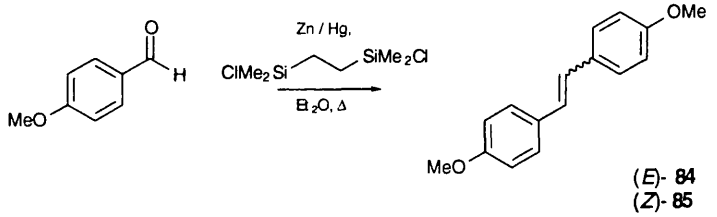
TABLE 19. Temperature Variation: *Solvent* Et_2O; *Electrophile* TMSCl; *Zinc* Zinc amalgam

	Temperature / °C	Yields and de / %			
		Cyclopropane§	de (endo / exo ratio)	Stilbene§	C-H Insertion#
1	Reflux	45	92 (25:1)	-	2
2	Room temperature (~20)	59	95 (26:1)	2	-
3	0	48	95 (38:1)	2	-
4	-30	60	97 (64:1)	2	-

#- C-H insertion refers to 3-(4-methoxyphenyl)-2-ethoxypropane **106**

§- Cyclopropane refers to 7-(4-methoxyphenyl)bicyclo[4.1.0]heptane (*endo* and *exo* **83**)
Stilbene refers to (*Z*)- and (*E*)-1,1'-(1,2-ethenediyl)*bis*(4-methoxybenzene) **85** and **84**

Typical Experimental for the Attempted Dicarbonyl Coupling the Carbenoid Derived From *p*-Anisaldehyde - Influence of Zinc Type on the Reaction



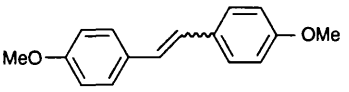
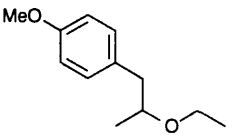
(*E*)- **84**
(*Z*)- **85**

A solution of *p*-anisaldehyde (450 µl, $3.67x10^{-3}$ mol) in diethyl ether (510 µl) was added over 18 h via a motorised syringe pump to a vigorously stirred refluxing suspension of zinc amalgam (zinc source as specified in **Table 20**, 2.45 g, $3.67x10^{-2}$ mol) and 1,2-*bis*(chlorodimethylsilyl)ethane (4.8 ml as a 1.0 M solution in diethyl ether) in diethyl ether (20 ml), in a previously flame-dried 50 ml conical flask equiped with a condenser, under argon. After 88 h the reaction mixture was cooled to room temperature and quenched under argon with saturated aqueous sodium bicarbonate solution (20 ml). The solid residues were then filtered off under suction through Celite, the phases separated, and the aqueous phase extracted with diethyl ether (3 x 20 ml). The combined organic extracts were then dried ($MgSO_4$), concentrated *in vacuo*, and the residue was chromatographed (silica, Et_2O (0-20%) / petroleum ether (40-60 °C)) to give, in order of elution, 3-(4-methoxyphenyl)-2-ethoxypropane **106**, and mixtures of (*E*) and (*Z*)-1,1'-(1,2-ethenediyl)*bis*(4-methoxybenzene)[183] **84** and **85**.

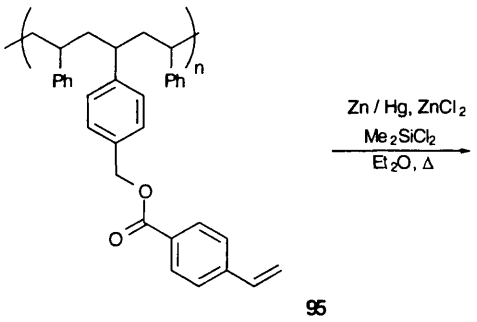
3-(4-*Methoxyphenyl*)-2-*ethoxypropane*: ^1H NMR data consistent with the product **106** (*vide infra* chapter 4.5).

(*E*)- and (*Z*)-1,1'-(1,2-Ethenediyl)*bis*(4-methoxybenzene): ^{1}H NMR data consistent with either single isomers or variously proportioned isomeric mixtures of **84** and **85** (*vide supra*).

Table 20. Zinc Source Variation

		 (*E*)- **84** (*Z*)- **85**	 **106**
1	Pasminco Zn powder P120	8%	10%
2	Pasminco Zn Dust CP75	11%	6%

Stability Test for the Solid Phase Alkene **95** to the Reaction Conditions for Zinc Carbenoid Generation



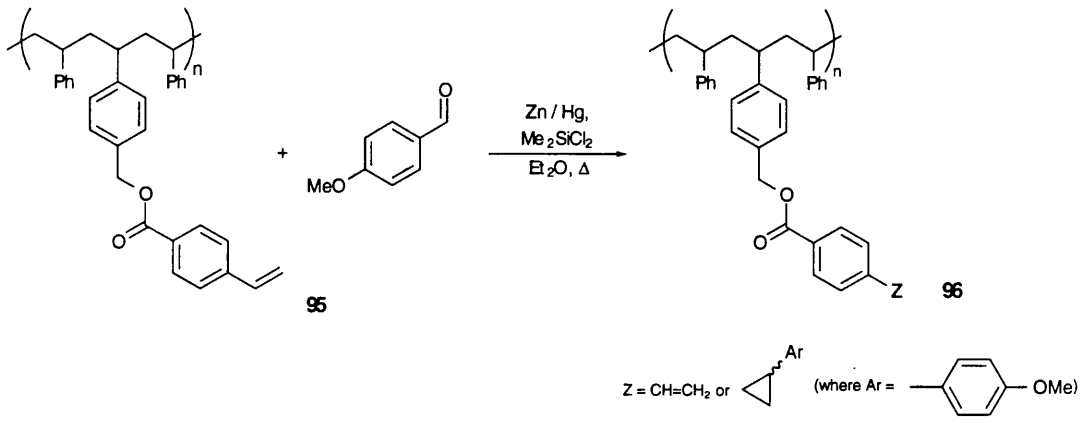
95

A vigorously stirred refluxing suspension of zinc amalgam (71 mg, 1.0 x10^{-3}mol), zinc chloride (8 mg, 5x10^{-5}mol), the polymer **95** (102 mg, 1.0x10^{-4} mol) and dichlorodimethylsilane (18 µl, 1.5x10^{-4} mol) in diethyl ether (1.5 ml), was heated for 15.5 h under nitrogen, in a previously flame-dried 5 ml conical flask equiped with a condenser. The reaction mixture was then cooled to room temperature and the solids filtered off under suction, rinsed thoroughly with diethyl ether, collected and dried *in vacuo*. The filtrate was then quenched by the addition of saturated aqueous sodium bicarbonate solution (5 ml) with stirring. After stirring for 10 minutes the solid residues were filtered off under suction through Celite, diethyl ether added to the filtrate (10 ml), the phases separated, and the aqueous phase extracted with diethyl ether (3 x 15 ml). The combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo* to yield small white needles.

Polymer: υ_{max} (KBr) / cm^{-1} (quoted values are those exclusive to the polymer product, i.e. not derived from the starting Merrifield resin) 1718 and 1700 (C=O ester), 1095 (C-O ester), 688 (C-Cl from original Merrifield resin).

Material Recovered from Filtrate: δ_H (400 MHz, $CDCl_3$) no aromatic signals corresponding to any of the aromatic residues in the polymer; spectrum predominantly signals from decomposed dichlorodimethylsilane.

Attempted Reaction of the Solid Phase Alkene **95** with the Carbenoid Derived from *p*-Anisaldehyde



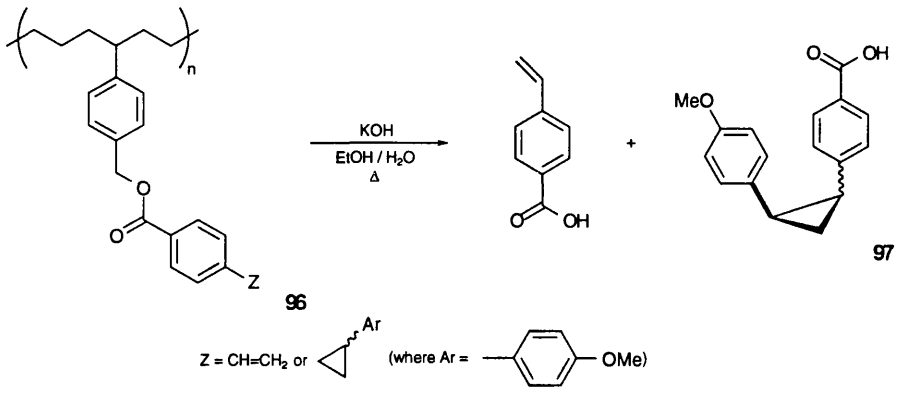
A solution of *p*-anisaldehyde (122 µl, $1.0x10^{-3}$ mol) in diethyl ether (1.5 ml) was added over 12 h via a motorised syringe pump to a vigorously stirred refluxing suspension of zinc amalgam (655 mg, $1.0x10^{-2}$ mol), the polymer **95** (1.03 g, $1.0x10^{-3}$ mol) and dichlorodimethylsilane (245 µl, $2x10^{-3}$ mol) in diethyl ether (11 ml), under N_2, in a previously flame-dried 25 ml conical flask equiped with a condenser. After 18 h the reaction mixture was cooled to room temperature and the solids filtered off under suction, rinsed thoroughly with diethyl ether, collected and dried *in vacuo*. The filtrate was then quenched by the addition of saturated aqueous sodium bicarbonate solution (10 ml) with stirring. After stirring for 10 minutes the solid residues were filtered off under suction through Celite, diethyl ether added to the filtrate (20 ml), the phases separated, and the aqueous phase extracted with diethyl ether (3 x 20 ml). The combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo* to yield an oily yellow solid (205 mg).

The zinc was separated from the polymer by settling in diethyl ether. The collected polymer **96** was then carried directly through to the following experiment.

Polymer: υ_{max} (KBr) / cm^{-1} quoted values are those exclusive to the polymer product, i.e. not derived from the starting Merrifield resin) 1718 and 1700 (C=O ester), 1097 (C-O ester), 688 (C-Cl from original Merrifield resin).

Product mixture from Liquid Phase: δ_H (400 MHz, $CDCl_3$) no identifiable products; NMR indicates aromatic residues and material derived from dichlorodimethylsilane.

Saponification of the Ester Linkage of the Polymer Supported Substrate Post Exposure to Carbenoid Reaction Conditions



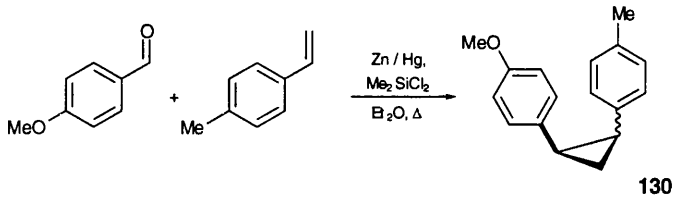
A solution of potassium hydroxide (493 mg, 8.8×10^{-3} mol) in water (1 ml) was added dropwise with rapid stirring to a suspension of the polymer **96** (935 mg; post-carbenoid reaction - The Three Phase Test[147]) in absolute ethanol (9 ml). After stirring overnight at room temperature, the reaction mixture was then heated to ~70 °C, rapidly darkening in colour, with the polymer appearing dark red after 14 h at this temperature. The reaction mixture was then cooled to room temperature, the polymer filtered off under suction, rinsed thoroughly with EtOH / H_2O (9:1), and collected. The filtrate was then evaporated to dryness *in vacuo*, and dilute HCl (50 ml, 1 M) added. After stirring the aqueous solution was extracted (3 x 30 ml EtOAc), and the combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo* to yield a mixture of *p*-vinylbenzoic acid and 1-(4-*benzoic*)-2-(4-*methoxyphenyl*)*cyclopropane* **97** as a powdery brown solid (21 mg, 10:1 acid:cyclopropane by ^1H NMR integrals). This product mixture was analysed directly (without purification).

***p*-Vinylbenzoic acid:** δ_H (400 MHz, $CDCl_3$) 8.08 (2H, d, *J* 8.1), 7.51 (2H, d, *J* 8.1), 6.78 (1H, dd, *J* 10.9, 17.4), 5.91 (1H, d, *J* 17.4), 5.43 (1H, d, *J* 10.7); EI GCMS: t_R 48:40 minutes, *m/z* 148 (82%, M^+), 131 (100%, M^+-OH), 103 (55%, M^+-CO_2H), 77 (48%, $[C_6H_5]^+$), 51 (33%), 45 (26%), 40 (32%).

1-(4-*benzoic*)-2-(4-*methoxyphenyl*)*cyclopropane*: δ_H (400 MHz, $CDCl_3$) peaks visible on baseline attributable to cyclopropane, notably 3.82 (s, -OMe), 2.41-2.37 (m, C*H*Ar), 1.69-1.66 (m); EI GCMS: t_R 98:47 minutes, *m/z* 268 (26%, M^+), 240 (29%, M^+-CO), 225 (24%), 121 (100%, M^+-$PhCO_2H$), 91 (19%, tropylium), 77 (43%, $[C_6H_5]^+$), 51 (18%); CI GCMS: t_R 81:20 minutes, *m/z* 268 (31%, M^+), 121 (100%, M^+-$PhCO_2H$).

4.4 Cyclopropanation Reactions

Reaction of the Carbenoid Derived From *p*-Anisaldehyde with *p*-Methylstyrene

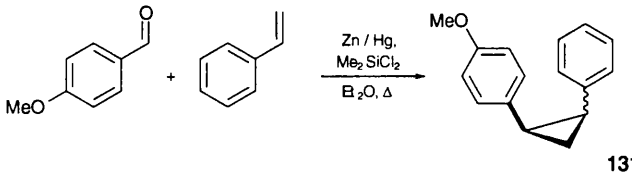


130

A solution of *p*-anisaldehyde (225 µl, 1.84×10^{-3} mol) in diethyl ether (1.5 ml) was added over 12 h via a motorised syringe pump to a vigorously stirred refluxing suspension of zinc amalgam (1.21 g, 1.84×10^{-2} mol), dichlorodimethylsilane (445 µl, 3.68×10^{-3} mol) and *p*-methylstyrene (485 µl, 3.68×10^{-3} mol) in diethyl ether (10 ml) under nitrogen, in a previously flame-dried 25 ml conical flask equiped with a condenser. After 21 h the reaction mixture was cooled to room temperature and quenched under nitrogen with saturated aqueous sodium bicarbonate solution (10 ml), and stirred for 10 minutes before the solid residues were filtered off under suction through Celite and rinsed thoroughly with diethyl ether. Diethyl ether (15 ml) was added to the filtrate, and the phases separated. The aqueous phase was then extracted (3 x 20 ml Et_2O), and the combined organic extracts dried ($MgSO_4$), and concentrated *in vacuo* to afford a mobile yellow oil, which was chromatographed (silica, DCM (0-30%) / petroleum ether (40-60 °C)) to give an inseparable diastereomeric mixture of *cis* and *trans* 1-(4-methoxyphenyl)-2-(4-methylphenyl)cyclopropane[184] **130** (254 mg, 58%, 30:1 *cis:trans* by GC) as a white opaque oil.

υ_{max} (NaCl plates, neat)/ cm^{-1} 3005, 2835, 1582 (C=C aromatics), 1515, 1464 (C-CH_3 C-H deformation), 1249, 1179, 1036; δ_H (400 MHz, $CDCl_3$) 6.90-6.85 (4H, m), 6.80 (2H, d, *J* 8.1), 6.65 (2H, dd, *J* 2.1, 6.5), 3.70 (3H, s, -O*Me*), 2.40-2.35 (2H, m, 2 x C*H*Ar), 2.21 (3H, s, -Me), 1.40 (1H, dt, *J* 5.3, 8.7, H_α), 1.26-1.19 (1H, m, H_β); δ_C (100 MHz, $CDCl_3$) 154.5, 135.5, 134.8, 130.5, 130.0, 128.6, 128.4, 113.1, 55.1, 23.5, 21.0, 11.5. *m/z* 238 (100%, M^+), 223 (99%, M^+-Me), 207 (43%, M^+-OMe), 115 (75%), 91 (46%, tropylium). (Found: M^+, 238.1354. $C_{17}H_{18}O$ requires *M*, 238.1358).

Reaction of the Carbenoid Derived From *p*-Anisaldehyde with Styrene



131

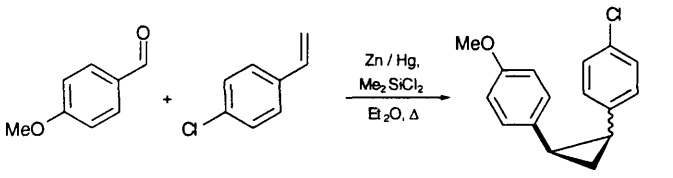
A solution of *p*-anisaldehyde (225 µl, 1.84×10^{-3} mol) in diethyl ether (1.5 ml) was added over 12 h via a motorised syringe pump to a vigorously stirred refluxing suspension of zinc

amalgam (1.20 g, 1.84×10^{-2} mol), dichlorodimethylsilane (450 µl, 3.68×10^{-3} mol) and styrene (420 µl, 3.68×10^{-3} mol) in diethyl ether (10 ml) under nitrogen, in a previously flame-dried 25 ml conical flask equiped with a condenser. After 19 h the reaction mixture was cooled to room temperature and quenched under nitrogen with saturated aqueous sodium bicarbonate solution (10 ml), and stirred for 10 minutes before the solid residues were filtered off under suction through Celite and rinsed thoroughly with diethyl ether. Diethyl ether (15 ml) was added to the filtrate, and the phases separated. The aqueous phase was then extracted (3 x 20ml Et_2O), and the combined organic extracts dried ($MgSO_4$), and concentrated *in vacuo* to afford a mobile yellow oil, which was chromatographed (silica, DCM (0-30%) / petroleum ether (40-60 °C)) to give, in order of elution, an inseparable diastereomeric mixture of *cis* and *trans* 1-(4-methoxyphenyl)-2-phenylcyclopropane[185] **131** (237 mg, 58%, 26:1 *cis:trans* by GC) as a white opaque oil, and (*E*)-1,1'-(1,2-ethenediyl)*bis*(4-methoxybenzene) **84** (16 mg, 7%) as white needles.

1-(4-Methoxyphenyl)-2-phenylcyclopropane: υ_{max} (NaCl plates, neat)/ cm^{-1} 3026 (=C-H), 3003, 2955, 2833 , 1610, 1581 (C=C aromatics), 1515, 1457, 1301, 1249, 1179, 1035; δ_H (400 MHz, $CDCl_3$) 7.20-7.04 (3H, m, Ph), 6.94-6.92 (2H, m, Ph), 6.88 (2H, dd, *J* 2.0, 6.5), 6.66 (2H, dd, *J* 2.2, 6.7), 3.71 (3H, s), 2.43 (2H, m, 2 x C*H*Ar), 1.44 (1H, dt, *J* 5.2, 8.7, H_α), 1.30 (1H, q, *J* 6.3, H_β); δ_C (100 MHz, $CDCl_3$) 157.5, 138.7, 130.3, 130.1, 128.8, 127.6, 125.4, 113.1, 55.8, 23.9, 23.7, 11.5. *m/z* 224 (100%, M^+), 209 (27%, M^+-Me), 193 (37%, M^+-OMe), 115 (73%), 91 (40%, tropylium), 77 (30%, $[C_6H_5]^+$). (Found: M^+, 224.1206. $C_{16}H_{16}O$ requires *M*, 224.1201).

(*E*)-1,1'-(1,2-Ethenediyl)*bis*(4-methoxybenzene): ^1H NMR data consistent with **84** earlier described (chapter 4.3).

Reaction of the Carbenoid Derived From *p*-Anisaldehyde with *p*-Chlorostyrene



132

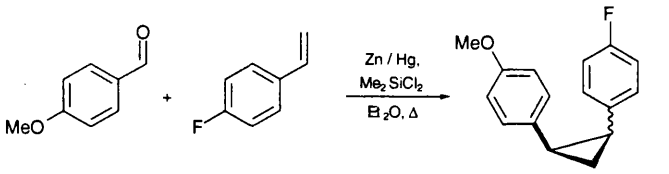
A solution of *p*-anisaldehyde (225 µl, 1.84×10^{-3} mol) in diethyl ether (1.5 ml) was added over 12 h via a motorised syringe pump to a vigorously stirred refluxing suspension of zinc amalgam (1.21 g, 1.84×10^{-2} mol), dichlorodimethylsilane (450 µl, 3.68×10^{-3} mol) and *p*-chlorostyrene (440 µl, 3.68×10^{-3} mol) in diethyl ether (10 ml) under nitrogen, in a previously flame-dried 25 ml conical flask equiped with a condenser. After 27 h the reaction mixture was cooled to room temperature and quenched under nitrogen with saturated aqueous sodium bicarbonate solution (10 ml), and stirred for 10 minutes before the solid residues were filtered off under suction through Celite and rinsed thoroughly with diethyl ether. Diethyl ether (15 ml) was added to the filtrate, and the phases separated. The aqueous phase was then extracted (3 x 20 ml Et_2O), and the combined organic extracts dried ($MgSO_4$) and

concentrated *in vacuo* to afford a turbid pale yellow oil, which was chromatographed (silica, DCM (0-30%) / petroleum ether (40-60 °C)) to give, in order of elution, an inseparable diastereomeric mixture of *cis* and *trans* 1-(4-chlorophenyl)-2-(4-methoxyphenyl)cyclopropane[185] **132** (229 mg, 48%, 27:1 *cis:trans* by GC) as a turbid pale yellow oil, and (*E*)-1,1'-(1,2-ethenediyl)*bis*(4-methoxybenzene) **84** as white needles (9 mg, 4%).

1-(4-Chlorophenyl)-2-(4-methoxyphenyl)cyclopropane: υ_{max} (NaCl plates, neat)/ cm^{-1} 3026 (=C-H), 3004, 2955, 2834, 1612, 1581 (C=C aromatics), 1515, 1494, 1248, 1179, 1092 (C-Cl aromatic str. vib.), 1036; δ_H (400 MHz, $CDCl_3$) 7.05 (2H, dd, *J* 1.9, 6.6), 6.87 (2H, dd, *J* 2.1, 6.6), 6.83 (2H, dd, *J* 1.8, 6.7), 6.68 (2H, dd, *J* 2.1, 6.7), 3.73 (3H, s), 2.45 (1H, dt, *J* 6.4, 8.9, C*H*Ar), 2.36 (1H, dt, *J* 6.3, 8.8, C*H*Ar),1.45 (1H, dt, *J* 5.5, 8.7, H_α), 1.26 (1H, q, *J* 6.0, H_β); δ_C (100 MHz, $CDCl_3$) 157.7, 137.3, 131.1, 130.1, 130.0, 129.7, 127.7, 113.3, 55.1, 23.8, 23.2, 11.6. *m/z* 258 and 260 (100% and 34%, M^+), 223 (42%, M^+-Cl), 121 (32%, $[C_7H_6(OMe)]^+$), 115 (40%), 91 (16%, tropylium), 77 (16%, $[C_6H_5]^+$). (Found: M^+, 258.0810. $C_{16}H_{15}O^{35}Cl$ requires *M*, 258.0811).

(*E*)-1,1'-(1,2-Ethenediyl)*bis*(4-methoxybenzene): ^1H NMR data consistent with **84** earlier described (chapter 4.3).

Reaction of the Carbenoid Derived From *p*-Anisaldehyde with *p*-Fluorostyrene

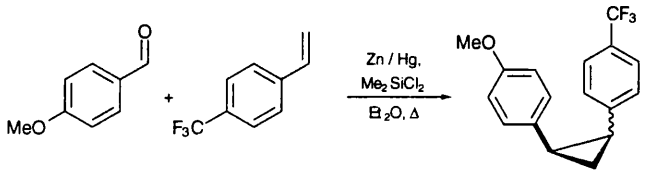


133

A solution of *p*-anisaldehyde (225 µl, $1.84x10^{-3}$ mol) in diethyl ether (1.5 ml) was added over 12 h via a motorised syringe pump to a vigorously stirred refluxing suspension of zinc amalgam (1.21 g, $1.84x10^{-2}$ mol), dichlorodimethylsilane (450 µl, $3.68x10^{-3}$ mol) and *p*-fluorostyrene (440 µl, $3.68x10^{-3}$ mol) in diethyl ether (10 ml) under nitrogen, in a previously flame-dried 25 ml conical flask equiped with a condenser. After 17 h the reaction mixture was cooled to room temperature and quenched under nitrogen with saturated aqueous sodium bicarbonate solution (10 ml), and stirred for 10 minutes before the solid residues were filtered off under suction through Celite and rinsed thoroughly with diethyl ether. Diethyl ether (15 ml) was added to the filtrate, and the phases separated. The aqueous phase was then extracted (3 x 20 ml Et_2O), and the combined organic extracts dried ($MgSO_4$), and concentrated *in vacuo* to afford a turbid yellow oil, which was chromatographed (silica, DCM (0-30%) / petroleum ether (40-60 °C)) to give an inseparable diastereomeric mixture of *cis* and *trans* 1-(4-*fluorophenyl*)-2-(4-*methoxyphenyl*)*cyclopropane* **133** (260 mg, 58%, 35:1 *cis:trans* by GC) as a clear colourless oil.

υ_{max} (NaCl plates, neat)/ cm^{-1} 3037 (=C-H), 3005, 2956, 2835, 1611, 1582 (C=C aromatics), 1514, 1465, 1302, 1249, 1180, 1159 (C-F aromatic str. vib.), 1036; δ_H (400 MHz, $CDCl_3$) 6.90-6.84 (4H, m), 6.79 (2H, ddd, *J* 2.2 ($^4J_{H-H}$), 6.6 ($^3J_{H-H}$), 11.0 ($^3J_{H-F}$)), 6.66 (2H, dd, *J* 2.1, 6.6), 3.73 (3H, s), 2.45-2.35 (2H, m, 2 x C*H*Ar), 1.44 (1H, dt, *J* 5.5, 8.7, H_α), 1.25 (1H, q, *J* 6.1, H_β); δ_C (100 MHz, $CDCl_3$) 161.0 (d, *J* 243 ($^1J_{C-F}$)), 157.6, 134.2, 130.2 (d, *J* 8 ($^3J_{C-F}$)), 130.0, 129.9, 114.4 (d, *J* 21 ($^2J_{C-F}$)), 113.2, 55.1, 22.4, 22.1, 11.4. *m/z* 242 (100%, M^+), 211 (42%, M^+-OMe), 133 (35%, M^+-$[C_7H_6(F)]^+$), 121 (24%, $[C_7H_6(OMe)]^+$), 109 (17%, $[C_7H_6(F)]^+$), 91 (14%, tropylium), 77 (18%, $[C_6H_5]^+$). (Found: M^+, 242.1110. $C_{16}H_{15}OF$ requires *M*, 242.1107).

Reaction of the Carbenoid Derived From *p*-Anisaldehyde with *p*-(Trifluoromethyl)styrene

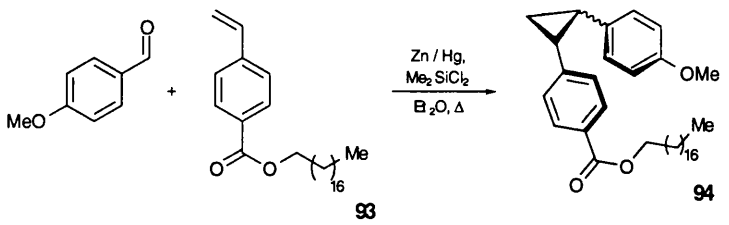


134

A solution of *p*-anisaldehyde (225 µl, $1.84x10^{-3}$ mol) in diethyl ether (1.5 ml) was added over 12 h via a motorised syringe pump to a vigorously stirred refluxing suspension of zinc amalgam (1.21 g, $1.84x10^{-2}$ mol), dichlorodimethylsilane (450 µl, $3.68x10^{-3}$ mol) and *p*-(trifluoromethyl)styrene (550 µl, $3.68x10^{-3}$ mol) in diethyl ether (10 ml) under nitrogen, in a previously flame-dried 25 ml conical flask equiped with a condenser. After 16 h the reaction mixture was cooled to room temperature and quenched under nitrogen with saturated aqueous sodium bicarbonate solution (10 ml), and stirred for 10 minutes before the solid residues were filtered off under suction through Celite and rinsed thoroughly with diethyl ether. Diethyl ether (15 ml) was added to the filtrate, and the phases separated. The aqueous phase was then extracted (3 x 20 ml Et_2O), and the combined organic extracts dried ($MgSO_4$), and concentrated *in vacuo* to afford a mobile pale yellow oil, which was chromatographed (silica, DCM (0-30%) / petroleum ether (40-60 °C)) to give an inseparable diastereomeric mixture of *cis* and *trans* 1-(4-*methoxyphenyl*)-2-(4-(*trifluoromethyl*)*phenyl*)*cyclopropane* **134** (246 mg, 46%, 38:1 *cis:trans* by GC) as a turbid white oil.

υ_{max} (NaCl plates, neat)/ cm^{-1} 3007, 2958, 2837, 1618, 1582 (C=C aromatics), 1515, 1326 (-CF_3 C-F deformation), 1250, 1164, 1121; δ_H (400 MHz, $CDCl_3$) 7.34 (2H, d, *J* 8.1), 6.99 (2H, d, *J* 8.2), 6.91 (2H, d, *J* 8.8), 6.69 (2H, d, 8.6), 3.74 (3H, s), 2.55 (1H, dd, *J* 6.2, 9.0, C*H*Ar), 2.44 (1H, dd, *J* 6.2, 8.9, C*H*Ar), 1.52 (1H, dt, *J* 5.5, 8.4, H_α), 1.36 (1H, q, *J* 6.2, H_β); δ_C (100 MHz, $CDCl_3$) 157.8, 143.3, 130.3, 129.3, 128.6, 124.4 (q, J_{C-F} 4), 113.3, 55.1, 24.5, 23.5, 12.0. *m/z* 292 (100%, M^+), 121 (44%, $[C_7H_6(OMe)]^+$), 115 (63%), 108 (46%), 91 (37%, tropylium), 77 (41%, $[C_6H_5]^+$), 69 (74%, CF_3^+). (Found: M^+, 292.1078. $C_{17}H_{15}OF_3$ requires *M*, 292.1075).

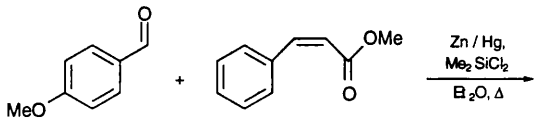
Reaction of the Carbenoid Derived From *p*-Anisaldehyde with *n*-Octadecyl-4-vinylbenzoate **93**



A solution of *p*-anisaldehyde (93 µl, $7.5x10^{-4}$ mol) in diethyl ether (1.5 ml) was added over 12 h via a motorised syringe pump to a vigorously stirred refluxing suspension of zinc amalgam (491 mg, $7.5x10^{-3}$ mol), dichlorodimethylsilane (182 µl, $1.5x10^{-3}$ mol) and *n*-octadecyl-4-vinylbenzoate **93** (301 mg, $7.5x10^{-4}$ mol) in diethyl ether (10 ml) under nitrogen, in a previously flame-dried 25 ml conical flask equiped with a condenser. After 23 h the reaction mixture was cooled to room temperature and quenched under nitrogen with saturated aqueous sodium bicarbonate solution (10 ml), and stirred for 10 minutes before the solid residues were filtered off under suction through Celite and rinsed thoroughly with diethyl ether. Diethyl ether (15 ml) was added to the filtrate, and the phases separated. The aqueous phase was then extracted (3 x 20 ml Et_2O), and the combined organic extracts dried ($MgSO_4$), and concentrated *in vacuo* to afford a white crystalline solid, which was chromatographed (silica, Et_2O (0-30%) / petroleum ether (40-60 °C)) to give, in order of elution, recovered *n*-octadecyl-4-vinylbenzoate **93** (90 mg) as white plates, and an inseparable diastereomeric mixture of *cis* and *trans* 1-(4-(*octadecyloxycarbonyl*)*phenyl*)2-(4-*methoxyphenyl*)*cyclopropane* **94** (154 mg, 40% (56% based on recovered *n*-octadecyl-4-vinylbenzoate), 28:1 *cis:trans* by GC) as white plates, m.pt. 58-58.5 °C (diethyl ether - petroleum ether (40-60 °C)).

υ_{max} (NaCl plates, neat)/ cm^{-1} 2945, 2849 (-CH_2- str.), 1745 (C=O), 1700, 1653, 1610 (C=C aromatics), 1515, 1471, 1280 (C-O), 1243, 1149, 1102; δ_H (400 MHz, $CDCl_3$) 7.85 (2H, dd, *J* 1.8, 8.5), 7.03 (2H, d, *J* 8.4), 6.99 (2H, dd, *J* 1.5, 8.2), 6.75 (2H, dd, *J* 2.1, 8.7), 4.33 (2H, t, *J* 6.7), 3.81 (3H, s), 2.63 (1H, dt, *J* 6.5, 8.8, C*H*Ar), 2.54 (1H, dt, *J* 6.4, 8.8, C*H*Ar), 1.81 (2H, quin, *J* 6.9), 1.60 (1H, dt, *J* 5.5, 8.6, H_α), 1.48-1.20 (31H, m, CH_2 envelope and H_β), 0.98 (3H, t, *J* 6.9); δ_C (100 MHz, $CDCl_3$) 167.0, 157.8, 144.6, 130.2, 129.4, 128.9, 128.3, 127.5, 113.3, 64.9, 55.1, 31.93, 29.7, 29.6, 29.5, 29.4, 29.3, 28.7, 26.0, 24.7, 23.8, 22.7, 14.1, 12.0. *m/z* 520 (17%, M^+), 240 (100%), 225 (83%), 165 (58%), 153 (48%), 121 (37%), 83 (56%), 71 (41%), 55 (95%). (Found: M^+, 520.3911. $C_{35}H_{52}O$ requires *M*, 520.3916).

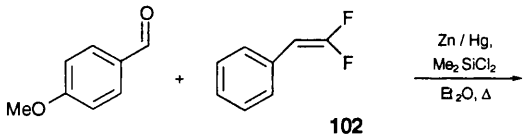
Reaction of the Carbenoid Derived From *p*-Anisaldehyde with (Z)-Methyl-3-phenylpropenoate **101**



101

A solution of *p*-anisaldehyde (175 µl, 1.43×10^{-3} mol) in diethyl ether (1.5 ml) was added over 12 h via a motorised syringe pump to a vigorously stirred refluxing suspension of zinc amalgam (933 mg, 1.43×10^{-2} mol), dichlorodimethylsilane (350 µl, 2.68×10^{-3} mol) and (Z)-methyl-3-phenylpropenoate **101** (237 mg, 1.43×10^{-3} mol) in diethyl ether (10 ml) under nitrogen, in a previously flame-dried 25 ml conical flask equiped with a condenser. After 16 h the reaction mixture was cooled to room temperature and quenched under nitrogen with saturated aqueous sodium bicarbonate solution (10 ml), and stirred for 10 minutes before the solid residues were filtered off under suction through Celite and rinsed thoroughly with diethyl ether. Diethyl ether (15 ml) was added to the filtrate, and the phases separated. The aqueous phase was then extracted (3 x 20 ml Et_2O), and the combined organic extracts dried ($MgSO_4$), and concentrated *in vacuo* to afford a mobile yellow oil, which was chromatographed (silica, Et_2O (0-30%) / petroleum ether (40-60 °C)) to afford recovered alkene (94 mg), and a small amount of the corresponding *E*-isomer.

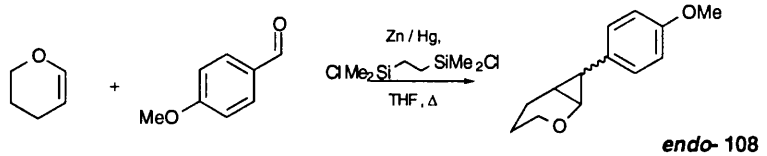
Reaction of the Carbenoid Derived From *p*-Anisaldehyde with β,β–Difluorostyrene **102**



102

A solution of *p*-anisaldehyde (105 µl, 8.64×10^{-4} mol) in diethyl ether (1.5 ml) was added over 12 h via a motorised syringe pump to a vigorously stirred refluxing suspension of zinc amalgam (565 mg, 8.64×10^{-3} mol), dichlorodimethylsilane (210 µl, 1.73×10^{-3} mol) and β,β–difluorostyrene **102** (121 mg, 8.64×10^{-4} mol) in diethyl ether (6 ml) under nitrogen, in a previously flame-dried 25 ml conical flask equiped with a condenser. After 20 h the reaction mixture was cooled to room temperature and quenched under nitrogen with saturated aqueous sodium bicarbonate solution (10 ml), and stirred for 10 minutes before the solid residues were filtered off under suction through Celite and rinsed thoroughly with diethyl ether. Diethyl ether (15 ml) was added to the filtrate, and the phases separated. The aqueous phase was then extracted (3 x 20ml Et_2O), and the combined organic extracts dried ($MgSO_4$), and concentrated *in vacuo* to afford a mobile pale yellow oil, which was chromatographed (silica, Et_2O (0-30%) / petroleum ether (40-60 °C)). No identifiable products were isolated.

Reaction of the Carbenoid Derived From *p*-Anisaldehyde with 3,4-Dihydro-2*H*-pyran .



***endo*- 108**
***exo*- 109**

A solution of *p*-anisaldehyde (225 µl, 1.84×10^{-3} mol) in dry THF (1.3 ml) was added over 12 h via a motorised syringe pump to a vigorously stirred refluxing suspension of zinc amalgam (0.99 g, 1.52×10^{-2} mol), 3,4-dihydro-2*H*-pyran (170 µl, 1.84×10^{-3} mol) and 1,2-*bis*(chlorodimethylsilyl)ethane (2.3 ml, 2.4×10^{-3} mol as a 1.07 M solution in THF) in THF (10 ml), at reflux under argon, in a previously flame-dried 25 ml conical flask equiped with a condenser. After 24 h the reaction mixture was cooled to room temperature, and quenched under argon with saturated aqueous sodium bicarbonate solution (10 ml), and stirred for 10 minutes before the solid residues were filtered off under suction through Celite and rinsed thoroughly with diethyl ether. Diethyl ether (20 ml) was added to the filtrate, and the phases separated. The aqueous phase was then extracted (3 x 20 ml Et_2O), and the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo* to yield a mobile yellow oil, which was chromatographed (silica, Et_2O (0-40%) / petroleum ether (40-60 °C)) to give, in order of elution, *endo* 2-(4-*methoxyphenyl*)-7-*oxabicyclo*[4.1.0]*heptane* **108** (175 mg, 47%) and *exo* 2-(4-*methoxyphenyl*)-7-*oxabicyclo*[4.1.0]*heptane* **109** (33 mg, 9%) as colourless oils.

Endo* 2-(4-*methoxyphenyl*)-7-*oxabicyclo*[4.1.0]*heptane: υ_{max} (NaCl plates, neat)/ cm^{-1} 2952 (-CH_2- str.), 2856 (-Me str.), 1610 (C=C aromatics), 1514, 1463, 1288, 1244, 1174, 1038; δ_H (500 MHz, $CDCl_3$) 7.28 (2H, d, *J* 8.8), 6.85 (2H, d, *J* 8.7), 3.82-3.79 (1H, m) and 3.79 (3H, s) (superimposed), 3.46 (1H, td, *J* 3.6, 10.8), 3.28 (1H, dt, *J* 2.1, 11.2), 1.97-1.89 (1H, m, C*H*Ar), 1.82 (2H, q, 6.3), 1.26-1.20 (2H, m), 1.12 (1H, tdd, *J* 2.6, 5.1, 12.5); δ_C (125 MHz, $CDCl_3$) 157.7, 132.2, 128.4, 113.4, 64.3, 55.1, 53.3, 22.4, 22.0, 17.1, 13.2; *m/z* 204 (100%, M^+), 173 (29%), 161 (36%), 147 (53%), 121 (73%). (Found: M^+, 204.1142. $C_{13}H_{16}O_2$ requires *M*, 204.1150).

Exo* 2-(4-*methoxyphenyl*)-7-*oxabicyclo*[4.1.0]*heptane: υ_{max} (NaCl plates, neat)/ cm^{-1} 2933 (-CH_2- str.), 2855 (-Me str.), 1612 (C=C aromatics), 1465, 1248; δ_H (500 MHz, $CDCl_3$) 6.92 (2H, dd, *J* 2.1, 8.7), 6.80 (2H, dd, *J* 2.2, 8.7), 3.77 (3H, s), 3.65 (1H, dtd, *J* 1.4, 4.0, 6.7), 3.60 (1H, dd, *J* 2.2, 7.3), 3.37 (1H, td, *J* 3.5, 10.4), 2.10-2.07 (1H, m), 2.01-1.99 (1H, m), 1.95 (1H, dd, *J* 2.3, 6.5, C*H*Ar), 1.59-1.53 (2H, m), 1.35 (1H, dd, *J* 6.4, 12.8); δ_C (125 MHz, $CDCl_3$) 157.7, 133.5, 126.7, 113.8, 64.4, 59.9, 55.3, 28.1, 22.3, 21.1, 19.5. *m/z* 204 (100%, M^+), 173 (33%), 161 (40%), 147 (59%), 135 (54%), 121 (72%), 91 (22%, tropylium). (Found: M^+, 204.1142. $C_{13}H_{16}O_2$ requires *M*, 204.1150).

Reaction of the Carbenoid Derived From *p*-Tolualdehyde with 3,4-Dihydro-2*H*-pyran

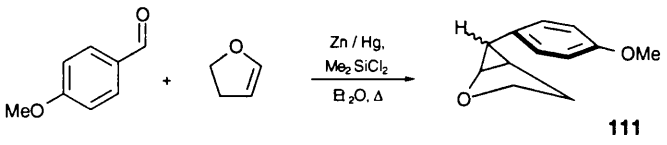
110

A solution of *p*-tolualdehyde (220 µl, 1.84×10^{-3} mol) in dry THF (1.3 ml) was added over 12 h via a motorised syringe pump to a vigorously stirred refluxing suspension of zinc amalgam (1.20 g, 1.84×10^{-2} mol), 3,4-dihydro-2*H*-pyran (170 µl, 1.84×10^{-3} mol) and dichlorodimethylsilane (445 µl, 3.68×10^{-3} mol) in THF (10 ml), under nitrogen in a previously flame-dried 25 ml conical flask equiped with a condenser. After 19 h the reaction mixture was cooled to room temperature, and quenched under nitrogen with saturated aqueous sodium bicarbonate solution (10 ml), and stirred for 10 minutes before the solid residues were filtered off under suction through Celite and rinsed thoroughly with diethyl ether. Diethyl ether (20 ml) was added to the filtrate, and the phases separated. The aqueous phase was then extracted (3 x 20 ml Et_2O), and the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo* to yield a clear colourless oil, which was chromatographed (silica, DCM (0-50%) / petroleum ether (40-60 °C)) to give, in order of elution, a mixture of (*E*) and (*Z*)-1,1'-(1,2-ethenediyl)*bis*(4-methoxybenzene) **84** and **85** (9 mg, 5%), and an inseparable mixture of *endo* and *exo* 2-(4-*methylphenyl*)-7-*oxabicyclo*[4.1.0]*heptane* **110** (81 mg, 23%) as a clear colourless oil, which decomposed rapidly on isolation.

(*E*) and (*Z*)-1,1'-(1,2-Ethenediyl)*bis*(4-methoxybenzene): ^1H NMR data consistent with **84** and **85** earlier described (chapter 4.3).

Endo* and *Exo* 2-(4-*Tolylphenyl*)-7-*oxabicyclo*[4.1.0]*heptane: υ_{max} (NaCl plates, neat)/ cm^{-1} 2962 (-CH_3 str.), 2922, 2852 (-Me str.), 1678, 1613 (C=C aromatics), 1420, 1284, 1261, 1094 (br.), 1021; δ_H (400 MHz, $CDCl_3$) 7.26 (2H, d, *J* 6.8), 7.11 (2H, d, *J* 7.1), 3.82 (1H, t, *J* 6.5), 3.48-3.44 (1H, m), 3.28 (1H, dt, *J* 1.9, 11.2), 2.33 (3H, s), 1.96-1.82 (3H, m), 1.27-1.22 (2H, m), 1.15-1.10 (1H, m); δ_C (100 MHz, $CDCl_3$) 131.2, 130.2, 129.6, 129.2, 64.4, 53.4, 22.5, 21.8, 21.2, 17.1, 13.2. *m/z* 188 (9%, M^+), 136 (71%), 119 (91%), 105 (40%), 91 (100%, tropylium), 65 (28%), 49 (29%), 39 (27%). (Found: M^+, 188.1205. $C_{13}H_{16}O$ requires *M*, 188.1201).

Reaction of the Carbenoid Derived From *p*-Anisaldehyde with 2,3-Dihydrofuran



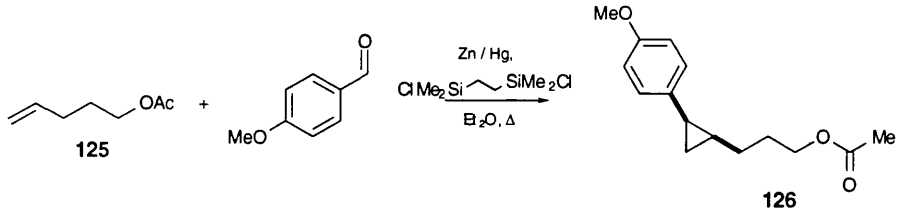
111

A solution of *p*-anisaldehyde (225 µl, 1.84×10^{-3} mol) in dry THF (1.5 ml) was added over 12 h via a motorised syringe pump to a vigorously stirred refluxing suspension of zinc amalgam

(1.19 g, 1.84×10^{-2} mol), 2,3-dihydrofuran (140 µl, 1.84×10^{-3} mol) and dichlorodimethylsilane (450 µl, 3.68×10^{-3} mol) in THF (11 ml), under nitrogen, in a previously flame-dried 25 ml conical flask equiped with a condenser. After 16 h the reaction mixture was cooled to room temperature, and quenched under nitrogen with saturated aqueous sodium bicarbonate solution (10 ml), and stirred for 10 minutes before the solid residues were filtered off under suction through Celite and rinsed thoroughly with diethyl ether. Diethyl ether (20 ml) was added to the filtrate, and the phases separated. The aqueous phase was then extracted (3 x 20 ml Et_2O), and the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo* to yield a clear yellow oil, which was chromatographed twice (silica, EtOAc (0-15%) / petroleum ether (40-60 °C) and then silica, Et_2O (0-30%) / petroleum ether (40-60 °C)) to give an inseparable mixture of *endo* and *exo* 2-(*4-methoxyphenyl*)-*6-oxabicyclo*[3.1.0]*hexane* **111** (87 mg, 25%) as a clear colourless oil which decomposed rapidly on isolation.

υ_{max} (NaCl plates, neat)/ cm^{-1} 3037, 2956 (-CH_2- str.), 1610 (C=C aromatics), 1515, 1457, 1283, 1244, 1106, 1039; δ_H (400 MHz, $CDCl_3$) 7.24 (2H, d, *J* 8.7), 6.83 (2H, dd, *J* 2.1, 8.7), 3.77 (3H, s), 3.69-3.63 (2H, m), 3.55 (1H, dt, *J* 2.0, 6.6), 2.12-2.07 (1H, m), 1.88-1.85 (2H, m), 1.79-1.72 (1H, m); δ_C (100 MHz, $CDCl_3$) 158.1, 131.1, 127.4, 113.8, 70.1, 62.2, 55.1, 26.9, 25.8, 21.3. *m/z* 190 (81%, M^+), 161 (61%), 159 (39%), 134 (100%), 121 (49%), 91 (100%, tropylium). (Found: M^+, 190.1004. $C_{12}H_{14}O_2$ requires *M*, 190.0994).

Reaction of the Carbenoid Derived From *p*-Anisaldehyde with 4-Penten-1-yl Acetate **125**

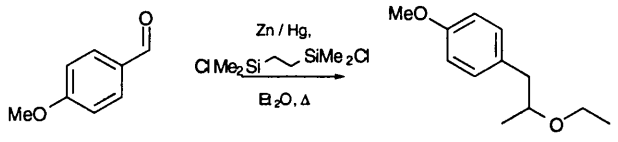


A solution of *p*-anisaldehyde (285 µl, 2.34×10^{-3} mol) in diethyl ether (1.7 ml) was added over 12 h via a motorised syringe pump to a vigorously stirred refluxing suspension of zinc amalgam (1.53 g, 2.34×10^{-2} mol), 4-penten-1-yl acetate **125** (303 mg, 2.34×10^{-3} mol) and 1,2-*bis*(chlorodimethylsilyl)ethane (3.4 ml, 2.8×10^{-3} mol as a 0.83 M solution in diethyl ether) in diethyl ether (7 ml) under argon, in a previously flame-dried 25 ml conical flask equiped with a condenser. After 17 h the reaction mixture was cooled to room temperature and quenched under argon with saturated aqueous sodium bicarbonate solution (10 ml), and stirred for 10 minutes before the solid residues were filtered off under suction through Celite and rinsed thoroughly with diethyl ether. Diethyl ether (15 ml) was added to the filtrate, and the phases separated. The aqueous phase was then extracted (3 x 20 ml Et_2O), and the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo* to yield an oil, which was chromatographed (silica, DCM (0-70%) / petroleum ether (40-60 °C)) to afford *cis* 3-[2-(*4-methoxyphenyl*)*cyclopropyl*]*propan-1-yl acetate* **126** (155 mg, 27%) as a colourless oil.

υ_{max} (NaCl plates, neat)/ cm^{-1} 2955, 2836 (aromatic / aliphatic C-H), 1739 (aliphatic ester), 1613 (aromatic C=C), 1515, 1466 (C-CH_3, C-H asymmetric deformation), 1366, 1248 (C-O stretching vibration of acetate); δ_H (400 MHz, $CDCl_3$) 7.10 (2H, dd, *J* 1.5, 8.2), 6.15 (2H, dd, *J* 2.2, 8.7), 3.95 (2H, ddd, *J* 4.1, 13.7, 13.7), 3.79 (3H, s), 2.05 (1H, dd, *J* 6.1, 8.6 , C*H*Ar), 2.03 (3H, s), 1.62-1.57 (2H, m), 1.05-0.88 (4H, m), 0.55 (1H, dd, *J* 5.1, 10.8); δ_C (100 MHz, $CDCl_3$) 171.1, 157.6, 131.0, 129.9, 113.3, 64.3, 55.2, 28.3, 24.9, 20.9, 20.0, 18.0, 9.5; *m/z* 248 (27%, M^+), 188 (52%), 160 (100%), 147 (99%), 134 (30%), 121 (43%) (Found: M^+, 248.1409. $C_{15}H_{20}O_3$ requires *M*, 248.1412).

4.5 C-H Insertion Reactions

C-H Insertion of the Carbenoid Derived From *p*-Anisaldehyde into Diethyl Ether



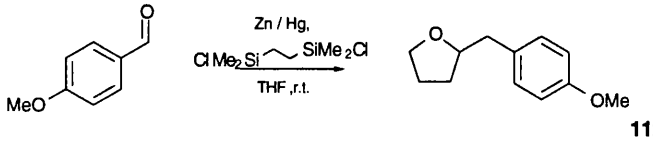
106

A solution of *p*-anisaldehyde (450 µl, 3.67×10^{-3} mol) in diethyl ether (510 µl) was added over 18 h via a motorised syringe pump to a vigorously stirred refluxing suspension of zinc amalgam (2.44 g, 3.67×10^{-2} mol) and 1,2-*bis*(chlorodimethylsilyl)ethane (4.8 ml, 4.8×10^{-3} mol as a 1.0 M solution in Et_2O) in diethyl ether (20 ml), under argon, in a previously flame-dried 50 ml conical flask equiped with a condenser. After 88 h the reaction mixture was cooled to room temperature and quenched under argon with saturated aqueous sodium bicarbonate solution (20 ml). The solid residues were then filtered off under suction through Celite, diethyl ether added to the filtrate (20 ml), the phases separated, and the aqueous phase extracted (3 x 20 ml Et_2O). The combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo* to yield a yellow oil, which was chromatographed (silica, Et_2O (0-30%) / petroleum ether (40-60 °C)) to afford, in order of elution, the 3-(4-*methoxyphenyl*)-2-*ethoxypropane* **106** as a colourless oil (66 mg, 10%), and (Z)-1,1'-(1,2-ethenediyl)*bis*(4-methoxybenzene) **85** (72 mg, 8%) as a colourless oil.

3-(4-*Methoxyphenyl*)-2-*ethoxypropane*: υ_{max} (NaCl plates, neat)/ cm^{-1} 2974, 2930 (aromatic / aliphatic -C-H), 1613, 1584 (aromatic C=C), 1463, 1374, 1339, 1108; δ_H (500 MHz, $CDCl_3$) 7.12 (2H, dd, *J* 2.1, 8.7), 6.83 (2H, dd, *J* 2.1, 8.7), 3.79 (3H, s), 3.50-3.59 (2H, m), 3.43 (1H, dq, *J* 7.0, 14.0), 2.86 (1H, dd, *J* 6.0, 13.6), 2.56 (1H, dd, *J* 6.8, 13.6), 1.17 (3H, t, *J* 7.0), 1.12 (3H, d, *J* 6.2); δ_C (125 MHz, $CDCl_3$) 157.9, 131.2, 130.3, 113.6, 76.5, 63.9, 55.2, 42.1, 19.5, 15.5; *m/z* 194 (29%, M^+), 121 (44%, M^+-Et_2O), 73 (100%, M^+-[C_7H_6(OMe)]), 45 (88%). (Found: M^+, 194.1327. $C_{12}H_{18}O_2$ requires *M*, 194.1307).

(Z)-1,1'-(1,2-ethenediyl)*bis*(4-methoxybenzene): ^1H NMR data consistent with **85** earlier described (chapter 4.3).

C-H Insertion of the Carbenoid Derived From *p*-Anisaldehyde into THF



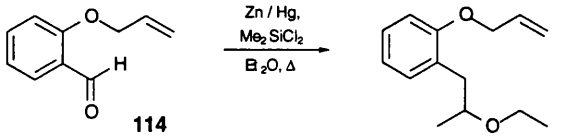
112

A solution of *p*-anisaldehyde (230 µl, 1.88×10^{-3} mol) in THF (6 ml) was added over 1 h via a motorised syringe pump to a vigorously stirred suspension of zinc amalgam (1.26 g, 1.88×10^{-2} mol) and 1,2-*bis*(chlorodimethylsilyl)ethane (3.5 ml, 3.8×10^{-3} mol as a 1.07 M solution in THF) in THF (8.5 ml), at room temperature under argon, in a previously flame-dried 25 ml conical flask equiped with a condenser. After 112 h the reaction mixture was quenched under argon with saturated aqueous sodium bicarbonate solution (10 ml). The solid residues were then filtered off through Celite under suction, diethyl ether added to the filtrate (20 ml), the phases separated, and the aqueous phase extracted (3 x 20 ml Et_2O). The combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo* to yield a yellow oil / solid, which was chromatographed (silica, Et_2O (0-50%) / petroleum ether (40-60 °C)) to give, in order of elution, a mixture of (*Z*) and(*E*)-1,1'-(1,2-ethenediyl)*bis*(4-methoxybenzene) **85** and **84** (3:1) as an oily white solid (12 mg, 5%), (*Z*)-1,1'-(1,2-ethenediyl)bis(4-methoxybenzene) **85** as white needles (10 mg, 4%), and *tetrahydro*-2-(4-*methoxybenzyl*)*furan* **112** as a colourless oil (139.8mg, 39%).

(*E*)-1,1'-(1,2-ethenediyl)*bis*(4-methoxybenzene) and (*Z*)-1,1'-(1,2-ethenediyl)*bis*(4-methoxybenzene): ^1H NMR data consistent with **84** and **85** earlier described (chapter 4.3).

Tetrahydro-2-(4-methoxyphenyl)furan: υ_{max} (NaCl plates, neat)/ cm^{-1} 2932, 2861 (aromatic / aliphatic -C-H), 1612, 1584 (aromatic C=C), 1463, 1301, 1247, 1178, 1062; δ_H (270 MHz, $CDCl_3$) 7.13 (2H, dd, *J* 2.2, 8.8), 6.83 (2H, dd, *J* 2.2, 8.8), 4.07-3.98 (1H, m), 3.93-3.71 (2H, m) and 3.78 (3H, s) (superimposed), 2.85 (1H, dd, *J* 6.4, 13.7), 2.68 (1H, dd, *J* 6.6, 13.7), 1.97-1.81 (3H, m), 1.59-1.51 (1H, m); δ_C (125 MHz, $CDCl_3$) 158.0, 131.1, 130.1, 113.7, 80.2, 67.9, 55.2, 41.0, 30.9, 25.6; *m/z* (CI, carrier gas NH_3) 402 (6%, $[2M+NH_4]^+$), 385 (37%, $[2M+H]^+$), 210 (45%, $[M+NH_4]^+$), 193 (76%, $[M+H]^+$), 192 (100%, M^+), 121 (60%, $[C_7H_6(OMe)]^+$), 91 (9%, tropylium), 71 (77%). (Found: $M-H^+$, 193.1235. $C_{12}H_{17}O_2$ requires *M*, 193.1229).

C-H Insertion of the Carbenoid Derived From *o*-Allyloxybenzaldehyde **114** into Diethyl Ether

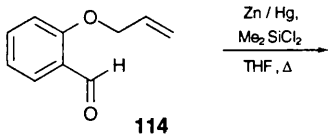


114 **115**

A solution of *o*-allyloxybenzaldehyde **114** (258 mg, 1.58×10^{-3} mol) in diethyl ether (9.6 ml) was added over 36 h via a motorised syringe pump to a vigorously stirred refluxing suspension of zinc amalgam (1.00 g, 1.53×10^{-2} mol) and dichlorodimethylsilane (420 µl, 3.07×10^{-3} mol) in diethyl ether (20 ml), under nitrogen, in a previously flame-dried 50 ml conical flask equiped with a condenser. After 96 h the reaction mixture was cooled to room temperature and quenched under nitrogen with saturated aqueous sodium bicarbonate solution (10 ml). The solid residues were then filtered off under suction through Celite, diethyl ether added to the filtrate (20 ml), the phases separated, and the aqueous phase extracted (3 x 20 ml Et_2O). The combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo* to yield a viscous yellow oil, which was chromatographed (silica, Et_2O (0-80%) / petroleum ether (40-60 °C)) to afford 3-(2-*allyloxybenzyl*)-2-*ethoxypropane* **115** as a clear colourless oil (49 mg, 14%).

3-(2-*Allyloxyphenyl*)-2-*ethoxypropane*: υ_{max} (NaCl plates, neat)/ cm^{-1} 2974, 2925 (-CH_2- str.), 2862, 1601, 1585 (aromatic C=C), 1463, 1452, 1242, 1103 (aliphatic C-O-C vib.); δ_H (400 MHz, $CDCl_3$) 7.18-7.14 (2H, m), 6.87 (1H, dt, *J* 1.1, 7.7), 6.81 (1H, dd, *J* 1.0, 9.6), 6.05 (1H, tdd, *J* 5.2, 10.4, 17.1), 5.41 (1H, qd, *J* 1.7, 17.5), 5.26 (1H, ddd, *J* 1.5, 3.0, 12.1), 4.52 (2H, td, *J* 1.6, 5.0), 3.71-3.66 (1H, m), 3.54-3.46 (2H, m), 3.03 (1H, dd, *J* 5.4, 13.1), 2.60 (1H, dd, *J* 7.6, 13.0), 1.15 (3H, t, *J* 7.0), 1.10 (3H, d, *J* 6.2); δ_C (100 MHz, $CDCl_3$) 157.5, 133.5, 131.4, 127.8, 127.2, 120.4, 116.8, 111.4, 74.8, 68.6, 63.8, 37.5, 19.9, 15.6; *m/z* 220 (13%, M^+), 147 (25%), 73 (100%), 45 (69%). (Found: M^+, 220.1453. $C_{14}H_{20}O_2$ requires *M*, 220.1463).

C-H Insertion of the Carbenoid Derived From *o*-Allyloxybenzaldehyde **114** into THF

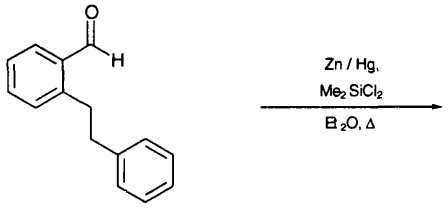


114

A solution of *o*-allyloxybenzaldehyde **114** (257 mg, 1.53×10^{-3} mol) in THF (9.6 ml) was added over 36 h via a motorised syringe pump to a vigorously stirred refluxing suspension of zinc amalgam (1.00 g, 1.53×10^{-2} mol) and dichlorodimethylsilane (420 µl, 3.07×10^{-3} mol) in THF (20 ml), under nitrogen, in a previously flame-dried 50 ml conical flask equiped with a condenser. After 110 h the reaction mixture was cooled to room temperature and quenched under nitrogen with saturated aqueous sodium bicarbonate solution (10 ml). After stirring for

10 minutes the solid residues were filtered off under suction through Celite and rinsed thoroughly with diethyl ether. Diethyl ether added to the filtrate (20 ml), the phases separated, and the aqueous phase extracted (3 x 20 ml Et_2O). The combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo* to yield a clear mobile oil, which was chromatographed (silica, Et_2O (0-20%) / petroleum ether (40-60 °C)) to give several products apparently pure by tlc. However, spectral complexity prevented characterisation.

Intramolecular C-H Insertion of the Carbenoid Derived From 2-(2-Phenethyl)benzaldehyde **116** in Diethyl Ether

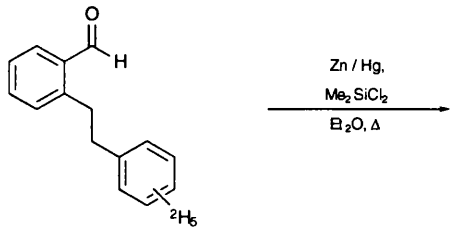


116

A solution of 2-(2-phenethyl)benzaldehyde **116** (300 mg, $1.40x10^{-3}$ mol) in diethyl ether (4.6 ml) was added over 36 h via a motorised syringe pump to a vigorously stirred refluxing suspension of zinc amalgam (927 mg, $1.43x10^{-2}$ mol) and dichlorodimethylsilane (350 µl, $2.9x10^{-3}$ mol) in diethyl ether (10 ml), under nitrogen, in a previously flame-dried 25 ml conical flask equiped with a condenser. After 42 h the reaction mixture was cooled to room temperature and quenched under nitrogen with saturated aqueous sodium bicarbonate solution (10 ml) and stirred for 10 minutes. The solid residues were then filtered off under suction through Celite, diethyl ether added to the filtrate (20 ml), the phases separated, and the aqueous phase extracted (3 x 20 ml Et_2O). The combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo* to yield a viscous yellow oil, which was chromatographed (silica, DCM (0-25%) / petroleum ether (40-60 °C)) to give two clear colourless oils which were further purified by HPLC.

Although the products isolated were apparently pure by tlc, spectral complexity prevented characterisation.

Intramolecular C-H Insertion of the Carbenoid Derived From 2-(([^{2}H$_5$]Phenyl)ethyl)benzaldehyde **122** in Diethyl Ether



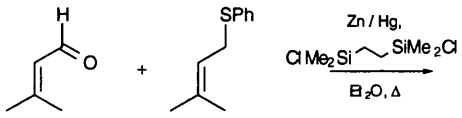
122

A solution of 2-(([^{2}H$_5$]phenyl)ethyl)benzaldehyde **122** (198 mg, 9.2×10^{-4} mol) in diethyl ether (4.6 ml) was added over 36 h via a motorised syringe pump to a vigorously stirred refluxing suspension of zinc amalgam (601 mg, 9.2×10^{-3} mol) and dichlorodimethylsilane (225 µl, 1.85×10^{-3} mol) in diethyl ether (6 ml), under nitrogen, in a previously flame-dried 25 ml conical flask equiped with a condenser. After 39 h the reaction mixture was cooled to room temperature and quenched under nitrogen with saturated aqueous sodium bicarbonate solution (10 ml) and stirred for 15 minutes. The solid residues were then filtered off under suction through Celite, diethyl ether added to the filtrate (20 ml), the phases separated, and the aqueous phase extracted (3 x 20 ml Et_2O). The combined organic extracts were then dried ($MgSO_4$) and concentrated *in vacuo* to yield a slightly turbid oil, which was chromatographed (silica, DCM (0-25%) / petroleum ether (40-60 °C)) to afford one major product and two minor ones, all as clear colourless oils.

Although the products isolated were apparently pure by tlc, spectral complexity prevented characterisation.

4.6 Attempted Ylide Rearragement Reactions

Typical Procedure for the Prenyl S-Ylide Rearrangement



127

A solution of 3-methyl-2-butenal (135 µl, $1.4x10^{-3}$ mol) in diethyl ether (2.3 ml) was added via a motorised syringe pump over 36 h to a vigorously stirred suspension of zinc amalgam (941 mg, $1.4x10^{-2}$ mol), 3-methyl-1-phenylthio-2-butene **127** (251 mg, $1.4x10^{-3}$ mol) and 1,2-*bis*(chlorodimethylsilyl)ethane (1.8 ml, $1.8x10^{-3}$ mol as a 1.0 M solution in Et_2O) in diethyl ether (8 ml) at reflux under argon, in a previously flame-dried 25 ml conical flask equiped with a condenser. After 43 h the reaction mixture was cooled to room temperature, and quenched under argon with saturated aqueous sodium bicarbonate solution (10 ml). The solid residues were then filtered off through Celite under suction and rinsed with diethyl ether. The phases of the filtrate were then separated, and the aqueous phase extracted with diethyl ether (3 x 20 ml). The combined organic extracts were then dried ($MgSO_4$) and concentrated under reduced pressure to yield a clear oil, which was chromatographed (silica, DCM (0-20%) / petroleum ether (40-60 °C)) to yield only recovered 3-methyl-1-phenylthio-2-butene.

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Corrigenda

p. 103, line 3	'with respect to result' should read 'with respect to the result'
p. 158, line 2	'Diethyl ether added to the filtrate' should read 'Diethyl ether was added to the filtrate'