The Development and Application of New Methods for the Synthesis of Organozinc Carbenoids

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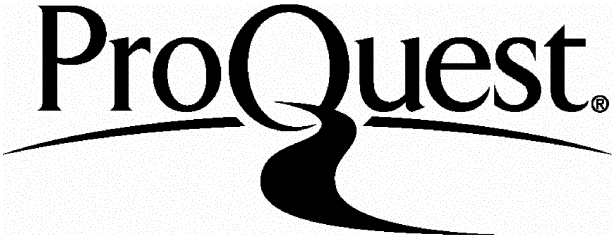

"I found this spoon."

Monty Python, 1981

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Abstract

This thesis concerns the generation of organozinc carbenoids and their subsequent reactions, particularly with alkenes to generate cyclopropanes. The thesis is divided into three major sections.

The first section comprises a review of the current methods available for the direct cyclopropanation of alkenes. The review focuses on the more controlled methods, and in particular on the different classes of precursor suitable for cyclopropanation.

The second chapter opens with an overview of the development of the generation of organozinc carbenoid *via* the reductive deoxygenation of carbonyl compounds. The generation of zinc carbenoids from a range of precursors is subsequently discussed in detail. The results are arranged to allow the reader to observe the chronological development of the chemistry. New observations on the formation of organozinc carbenoids from aldehydes and ketones are discussed first. The generation of organozinc carbenoids from acetals is then studied, and a series of new results presented. The generation of a novel class of α-alkoxyzinc carbenoids from simple orthoformates is then reported. A study into the generation of methylene organozinc carbenoids run concurrently with the aforementioned work is discussed and the chapter finishes with a brief insight into some attempts to generate other organozinc carbenoids and the range of unsuccessful precursors studied so far.

A concluding chapter summarises the results of the work described above, and full experimental details together with appropriate references are appended.

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Abbreviations

Ac	acetyl
Ar	aryl
Bn	benzyl
bpt	boiling point
br	broad
^{n}Bu	*n*-butyl
^{t}Bu	tert-butyl
cat	catalytic
Δ	heat
d	doublet
DCM	dichloromethane
de	diastereomeric excess
DME	dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
E	unspecified electrophile
ee	enantiomeric excess
EI	electron impact
equiv	molar equivalents
Et	ethyl
Et_2O	diethyl ether
EtOH	ethanol
EtOAc	ethyl acetate
FTIR	Fourier transform infra red
g	gram(s)
CG	gas chromatography
GCMS	gas chromatography coupled mass spectrometry

hr	hour(s)
IR	Infra red
L	unspecified ligand
lit.	literature value
m	*meta*
m	multiplet or medium as appropriate
Me	methyl
MeOH	methanol
mg	milligram
mins	minutes
ml	millilitres
mmHg	millimetres of mercury
mpt	melting point
NMR	nuclear magnetic resonance
Nu	unspecified nucleophile
o	*ortho*
p	*para*
P	polymer
Ph	phenyl
ppm	parts per million
^{i}Pr	*iso*-propyl
py	pyridine
quin	quintet
R	unspecified carbon substituent
rt	room temperature
s	singlet
t	triplet
t	tertiary
$t_{1/2}$	half life

THF	tetrahydrofuran
TLC	thin layer chromatography
Tl	*para*-methyphenyl
Tf	trifluoromethylsulfonyl
Ts	*para*-toluenesulfonyl
UV	ultra violet
X	unspecified substituent
	polymer
P	polymer
	microwave irradiation

1. Introduction

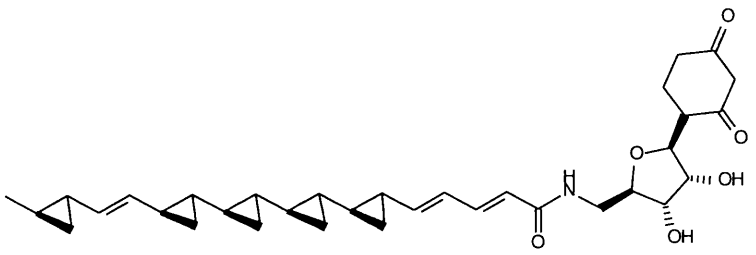
The Controlled Cyclopropanation of Alkenes

1. Introduction

This thesis is concerned with the generation and reactivity of organozinc carbenoids and in particular with their use as reagents in the cyclopropanation of alkenes.

It is therefore important to place our own work within the wider context of transition metal carbenoids and their use in the cyclopropanation of alkenes. At the same time, it is useful to reflect upon the broader field of alkene cyclopropanation and to consider some of the other methods available to the synthetic chemist for their preparation from alkenes.

Cyclopropanes constitute an unique and important class of alicyclic compounds arising in many common natural products, for example the important anti fungal agent FR-900648 **1**.[1] Equally, the proven ability of cyclopropanes to undergo ring opening reactions as a consequence of the relief of strain has allowed their widespread utilisation as key intermediates in many synthetic pathways to more complex natural products.



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The synthesis of cyclopropanes by the reaction of free carbenes with alkenes comprises in itself, an enormous body of work and is for the most part not included within this introduction. Rather, this introduction will focus on the more controlled methods of cyclopropanation and in particular metal mediated carbene transfer. At the same time it is important to show that the carbene [2 + 1] cycloaddition does not constitute the only means of direct cyclopropanation and thus other methods, particularly the cyclopropanation of electron poor alkenes with ylides, are included.

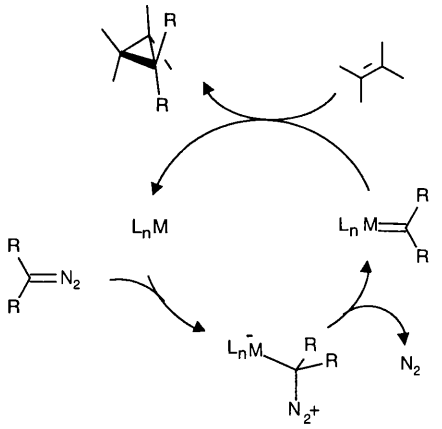
Emphasis has been placed upon the differing precursors which have been developed for cyclopropanation. Hence, this introduction will attempt to classify the most useful types of reagent that have emerged.

1.1. Metal Catalysed Cyclopropanation using Diazocompounds

In recent years, as a result of the development of new transition-metal catalysts and the design of effective strategies for their application, methods employing such metal catalysts have supplanted purely thermal and photochemical methods for the cyclopropanation of alkenes with diazocompounds. Some illustrative examples are included, but in the following review the aim is merely to highlight the general trends observed in this chemistry.

Although a metal catalysed decomposition of ethyl diazoacetate was originally described in 1906[2] it was many years before the value of this type of process for the cyclopropanation of alkenes was widely appreciated and reliable, efficient methods were developed. By the early 1960's however the reaction had become extremely important in organic synthesis. Whilst numerous transition metal compounds have been screened for catalytic activity in cyclopropanation, copper, rhodium and palladium compounds have emerged as the catalysts of choice. Today, the transition metal catalysed use of diazocompounds is the most generally employed approach to the formation of cyclopropanes.

As originally suggested by Yates,[3] there is now general agreement that transition metal catalysts react with diazo compounds, liberating nitrogen, to generate transient electrophilic carbenoids (scheme 1).



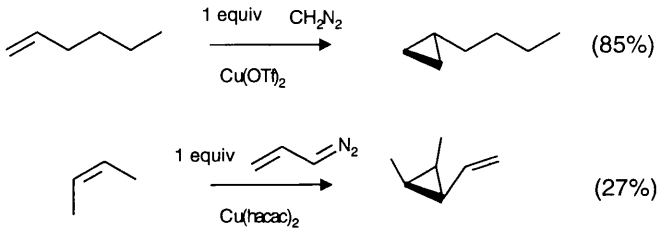
scheme 1

The catalytic activity of transition metal compounds depends on the co-ordinative unsaturation at the metal centre which allows them to act as electrophiles with diazocompounds. Electrophilic addition causes the loss of nitrogen and production of a metal stabilised carbene. Transfer of the carbene entity to an alkene completes the catalytic cycle.

Diazoalkanes as Cyclopropanating Reagents

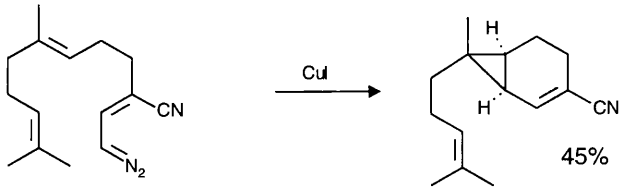
Diazoalkanes and in particular diazomethane can efficiently transfer an alkyl group to an alkene double bond *via* a metal catalysed process. The range of alkenes that may be cyclopropanated in this manner is vast and the efficiency of the cyclopropanation of various classes of alkenes can be highly dependant upon the catalyst chosen for the reaction.

Copper based catalysts are excellent for methyl cyclopropanation using diazomethane. For example, copper(II) sulfate and copper(II) triflate will catalyse the cyclopropanation of simple alkenes using diazomethane (scheme 6).[4,5] It has been postulated that the catalytic species is copper(I), produced *in situ* by the reduction of copper(II) salts by diazocompounds. Whilst cyclopropanation using diazomethane is smooth and efficient[4] the use of substituted diazoalkanes, for example vinyl diazomethane, often leads to cyclopropanation in lower yields (scheme 2).[5]



scheme 2

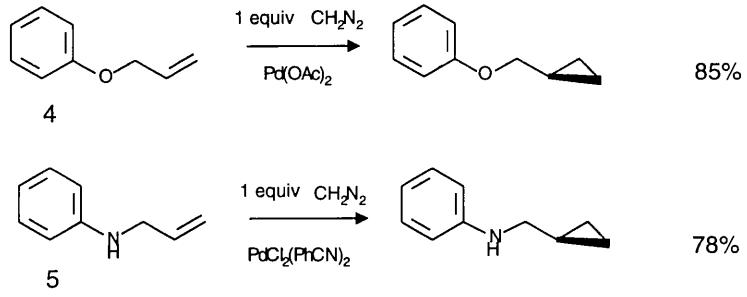
The activity of Cu(I) can be demonstrated by the case of the intramolecular cyclopropanation of diazocompound **2**, resulting in the bicycloadduct **3**.[6]



2 3

scheme 3

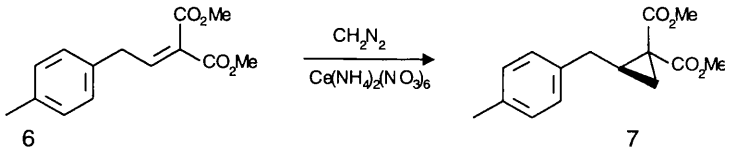
Palladium based catalysts, especially palladium(II) acetate and $PdCl_2.(PhCN)_2$ are highly active catalysts for the cyclopropanation of aliphatic and strained cyclic alkenes. For example, in the case of the cyclopropanation of the allylamine **5** and allylether **4** the cyclopropanation occurs efficiently and without evidence of ylide generation (scheme 4).[10,11,12] Since palladium(II) readily co-ordinates with alkenes[8,9] it has been suggested that palladium(II) catalysed processes may involve electrophilic addition of a palladium-alkene complex onto the diazoalkane.



scheme 4

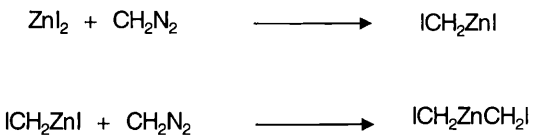
Palladium catalysts possess unique characteristics which make them suitable for efficient generation of cyclopropanes with diazoalkanes. Neither copper or rhodium have shown comparable reactivity with diazoalkanes, although both classes of catalyst are superior to palladium (II) compounds for the catalysis of cyclopropanation with diazocarbonyl compounds.

Although methylene transfer is generally less effective, electron poor alkenes can also be cyclopropanated using diazomethane. For example, ceric ammonium nitrate will catalyse the cyclopropanation of the alkene **6** by diazomethane (scheme 5).[13]



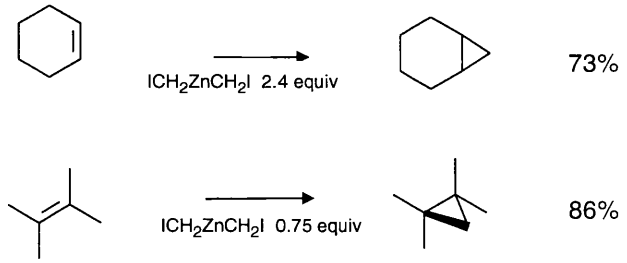
scheme 5

Diazoalkanes can also be used in the cyclopropanation of alkenes with zinc salts, generating organozinc carbenoids presumably identical to those encountered in the Simmons Smith reaction. This method for the generation of SimmonsSmith like reagents (*vide infra* 2.2.1) for the cyclopropanation of olefins was first reported by Wittig.[14] The active cyclopropanating species is formed by the addition of diazomethane to an ethereal suspension of a zinc (II) halide (scheme 6). As in the Simmons Smith reaction the active species may be either the monomer or the dimer (scheme 6).



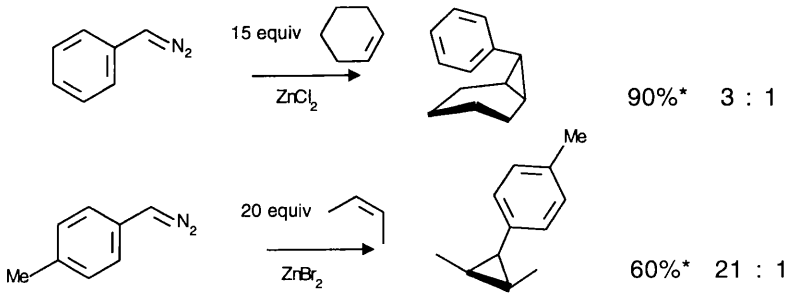
scheme 6

Wittig investigated the effects of the various zinc halides on the reaction as well as investigating the influence of other metals such as magnesium and lithium. It was possible to cyclopropanate alkenes in good yields, for example cyclohexene and tetramethylethylene in yields of 73% and 86% respectively relative to the zinc reagent (scheme 7).[14e]



scheme 7

Closs and Moss published a series of detailed studies on the cyclopropanation of simple alkenes using carbenoids derived from the reaction of aryl diazomethanes with zinc halides(scheme 8).[207, 208]

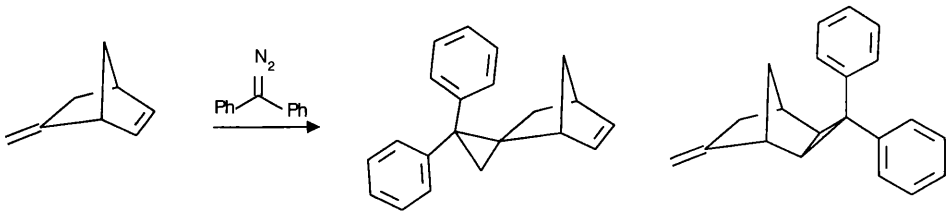


* relative to aryldiazomethane

scheme 8

In the same paper, the authors performed a comparison of the effects of other metal salts on the decomposition of the same aryl diazomethanes. Magnesium, lithium and cobalt halides were all shown to catalyse the cyclopropanation of simple alkyl substituted alkenes with 4-tolyldiazomethane although with lower efficiency than zinc halides.[208]

As is generally the case with cyclopropanes derived from diazocompounds, variation of the catalyst can have a profound effect on the reactivity of the carbenoid. Thus, the regioselectivity of the cyclopropanation of the diene **8** is completely reversed on replacing rhodium(II) tetraacetate with a palladium (II) complex.[15]



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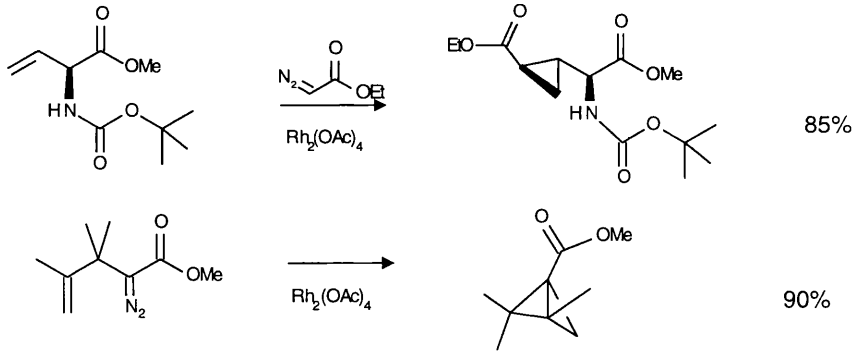
catalyst:	$Rh_2(OAc)_4$	100	:	1
	$PdCl_2(PhCN)$	1	:	50

Cyclopropanation using Diazocarbonyl Compounds

The metal catalysed decomposition of diazocarbonyl compounds in the presence of alkenes also provides an efficient means of constructing electrophilic cyclopropanes both in the intra- and intermolecular mode. Following the discovery of powerful group VIII metal catalysts, in particular the rhodium(II) derivatives, metal catalysed cyclopropanation using diazacarbonyl precursors is currently the most fertile area of cyclopropanation chemistry.

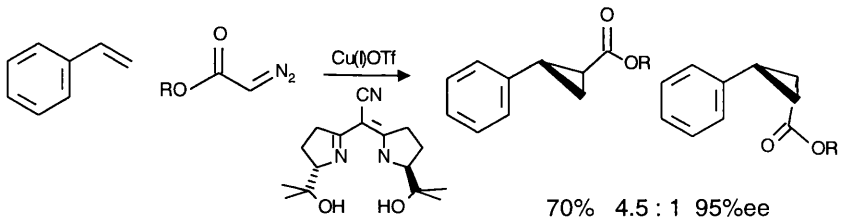
Cyclopropanation with Diazoesters

Catalysts containing a great array of metals including ruthenium,[16] rhodium,[17] palladium,[18] copper,[19,17b] cobalt,[20] osmium[21] and rhenium[22] have all been used widely in cyclopropanation with alkyldiazoesters. Among the transition metal based catalysts, rhodium(II) carboxylates appear to be the most generally effective in promoting the cyclopropanation of a wide range of alkenes with alkyl diazoacetates. The broad applicability of the rhodium acetate system to the synthesis of highly functionalised and highly strained molecules is emphasised by the examples in scheme 10. Intermolecular and intramolecular cyclopropanations can proceed in excellent yields.[24,25]



scheme 10

In recent years, much of the development of intermolecular cyclopropanation using diazoesters has focused on the catalytic asymmetric cylopropanation of alkenes.[26] Again, an exhaustive range of chiral transition metal catalysts have been extensively explored. Copper complexes modified with chiral bisoxazolines, such as the Pfalz catalyst **9** are good examples of the excellent enantioselectivity which can now be achieved with this chemistry (scheme 11).[22] Alternatively, the rhodium(II) bisoxazoline catalyst **10** developed by Evans has shown similar enantioselectivity in the cyclopropanation of *cis* but-2-ene (scheme 11).[22]



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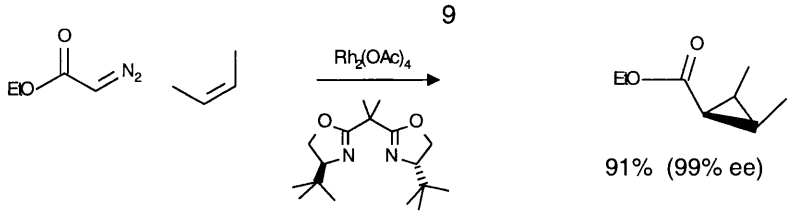

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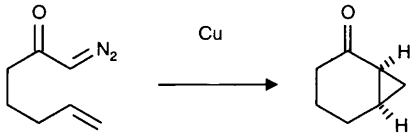
scheme 11

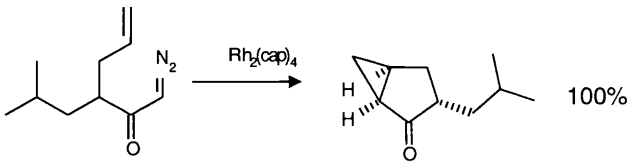
Cyclopropanation using Diazoketones

The first metal catalysed cyclopropanation of a diazoketone was reported by Stork in 1961 and used metallic copper (scheme 12).[27]



scheme 12

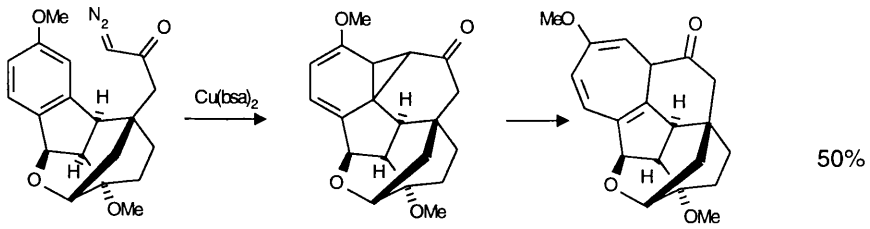
In the intervening decades, hundreds of examples of copper catalysed intramolecular cyclopropanations of diazoketones have been reported[28] although copper catalysts do require a relatively high reaction temperature and generally lack selectivity. As with diazoesters, rhodium carboxylates are the most active catalysts for cyclopropanation with diazoketones. The reactions may be carried out under ambient conditions to give cyclopropyl ketones in high yield. Thus the rhodium caprolactam catalyst will readily catalyse the intramolecular cyclopropanation of the homoallylketone **11** (scheme 13).[29]



11 12

scheme 13

Equally, the key step in the total synthesis of the tropone harringtonolide is the intramolecular copper bis(*N*-*t*butylsalicyl-aldiminato) catalysed cyclopropanation to afford the norcaradiene **14** which will isomerise to the ketone **15**.[30]



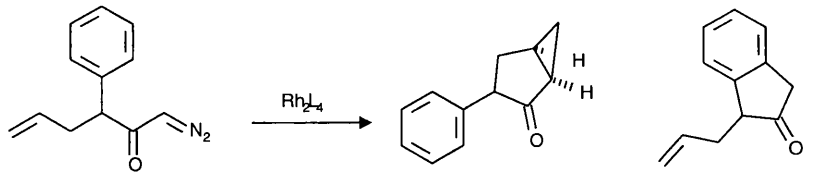
13 14 15

scheme 13

Electron withdrawing substituents greatly increase the stability of diazocompounds. For example, dicarbonyl diazomethanes which bear two carbonyl groups flanking the diazo carbon are even more stable than diazo compounds bearing only one carbon subsituent. As a consequence, diazodicarbonyl compounds require higher temperatures for carbenoid reactions than diazoesters. As with previous examples, rhodium(II) carboxylates are generally considered the best catalysts.

Chemoselectivity in Transition Metal Catalysed Diazocarbonyl Cyclopropanation

Carbenoids derived from the metal catalysed decomposition of diazo compounds undergo various chemical transformations beside cyclopropanation of alkenes and the ability to control chemoselectivity by selecting the appropriate catalyst has significantly increased their viability. Insertion reactions are very often a major pathway for carbenoid decomposition.[31] In the case of the rhodium(II) catalysed decomposition of the α-diazoketone **16**, variation of the ligands on the dirhodium catalyst can provide a switch which in some cases can turn competitive transformations on or off (scheme 14).



16 17 18

	catalyst	total yield (%)	**17**	**18**
1	$Rh_2(OAc)_4$	99	67	33
2	$Rh_2(pfb)_4$	95	0	100
3	$Rh_2(cap)_4$	73	100	0
4	$Rh_2(tpa)_4$	83	0	100

scheme14

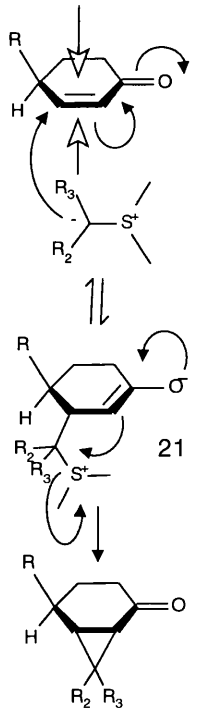
Hence, decomposition of diazoketone **16** with dirhodium caprolactamate (entry 3) provides only cyclopropane **17**. In contrast dirhodium perfluorobutyrate (entry 2) or dirhodium triphenylacetate (entry 4) gave the aromatic cycloaddition product **18**.[29,32] As previously explained, such manipulation of chemoselectivity by the screening of different catalysts remains a key feature of the carbenoid chemistry of diazocarbonyl compounds.

1.2. Cyclopropanation with Ylides

Although the first stable sulfur ylide was isolated by Ingold in 1930,[33] it was not until the pioneering work of Corey and Chaykowsky,[34,36] and later of Trost[35] that extensive synthetic activity in this area began. It has been noted that in many respects the reactions of sulfur ylides parallel those of carbenes. Both classes of intermediates form epoxides from aldehydes and ketones,[35,36] form cyclopropanes from olefinic compounds and undergo Wölff rearrangement upon photolysis. Since the early work by Corey however, the mechanism of ylide cyclopropanation, namely the stepwise addition of nucleophilic ylides to Michael acceptors and then ring closure, has been universally accepted.

Cyclopropanation of Michael Acceptors With Sulfur Ylides

Sulfur ylides can cyclopropanate unsaturated systems which are susceptible to Michael additions. Numbered amongst these are α,β-unsaturated ketones, esters, amides, nitriles, sulfones, sulfonamides, sulfoxides and nitro compounds.[36] Such reactions proceed best with more electron deficient olefins in contrast to the addition of carbenes and carbenoids.



scheme 15

The intermediacy of zwitterions or betaines in such systems has been generally accepted and thus the relative stereochemistry of the product may be predictable on the basis of the stepwise mechanism (scheme 15).[35,36] In essence, for an intermolecular ylide cyclopropanation the Michael addition of the ylide will occur predominantly from the less hindered face of the double bond. The subsequent cyclopropane closure will then take place in the most stable conformation of the betaine **21** (scheme 15).

α,β-Unsaturated carbonyls are ambident in their behaviour towards nucleophiles and as a consequence competing 1,2-ylide addition to the carbonyl can result in classical epoxide formation.[35,36] In general, highly reactive ylides will preferentially undergo carbonyl addition whereas stabilised ylides will add to the carbon-carbon double bond. As might be predicted, steric hindrance at the β-carbon results in enhanced 1,2-carbonyl addition whereas 1,4-addition and subsequent cyclopropanation are favoured by electron withdrawing substituents, alkyl substituents on the ylide carbon and steric hindrance at the carbonyl (table 1).

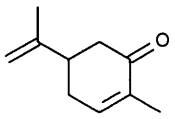
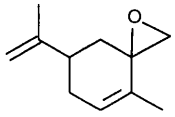
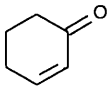
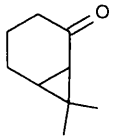
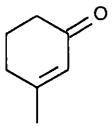
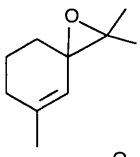
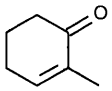
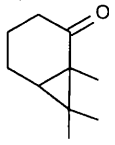
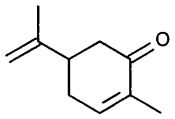
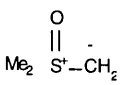
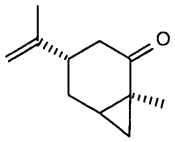
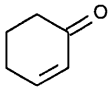
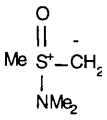
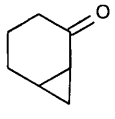
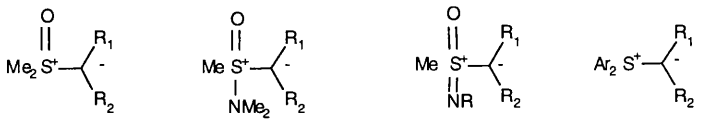
	alkene	ylide	product	ref
1				34
2				37
3				37
4				37
5				34
6				37

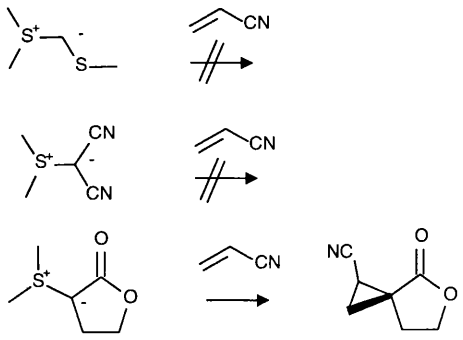
table 1

In addition to these factors it has been postulated that the reversibility of betaine formation plays a major role in product determination. With the unstabilised dimethyl sulfonium ylide (entry 1) betaine formation is thought to be essentially irreversible while in the case of the more stable ylides the 1,2-addition is reversible and hence thermodynamic control can operate (entries 3,4,5 and 6). The degree of stereospecificity thus depends upon the rate of cyclisation relative to the rate of rotation about the relevant single bond in the betaine.



scheme 16

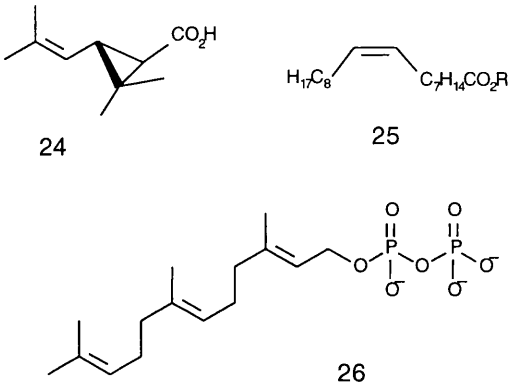
Some other typical sulfur ylides used in the cyclopropanation of Michael acceptors are shown in scheme 16. In general, the greater the stabilisation of the ylide the lower the degree of 1,2 carbonyl addition, although too highly stabilised ylides of low nucleophilicity will fail to undergo Michael addition (scheme 17). Nevertheless some stabilised species such as the lactone ylide in scheme 17 are still sufficiently reactive to act as cyclopropanating reagents.[36] Although the reaction tolerates a wide variety of functional groups, side reactions can sometimes interfere with the intermediate betaine.[38]



scheme 17

Cyclopropanation of Electron Rich Alkenes with Sulfur Ylides

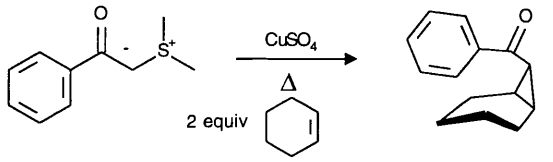
The biosynthesis of the cyclopropane ring in a number of natural products is known to occur by the transfer of a methylene group derived from the methyl of S-adenosylmethionine **22**[39] and it has been postulated that the cyclopropanation involves the corresponding ylide **23.**[40,36] Whilst sulfur ylides can readily be envisaged as the cyclopropanating species in the biosynthesis of compounds such as chrysanthemic acid **24**,[41] the methylene cyclopropanation of the unactivated oleic ester **25** or the reaction of farnesylpyrophosphate **26** with a sulfur ylide is contrary to the generally accepted reactivity profile of sulfur ylide species (scheme 18).



24 25 26

scheme 18

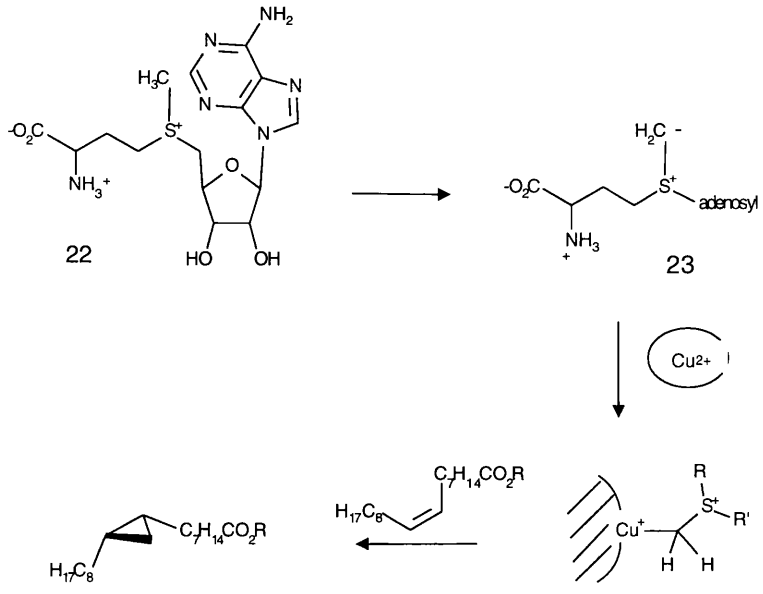
In view of this contradiction, Trost attempted the cyclopropanation of electron rich alkenes using sulphur ylides in the presence of a copper catalyst, since copper catalysis had previously been implicated in biological systems. He succeeded in achieving low yields of benzoyl norcarane **29** when performing the Cu(II) catalysed thermal decomposition of dimethysulfoniumphenacylide **28** in cyclohexene (scheme 19).[42]



28 29 5% stereochemistry not reported

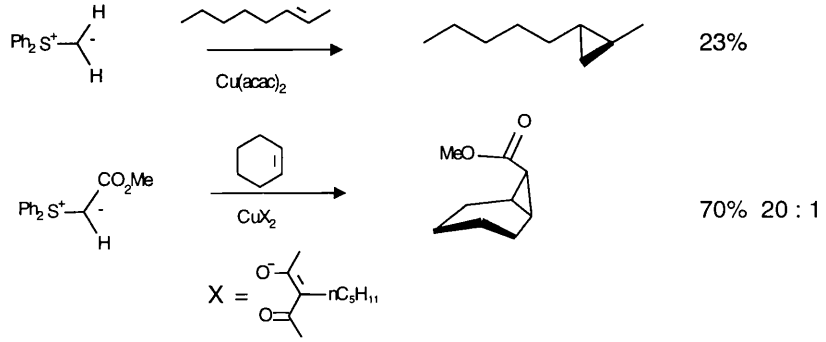
scheme 19

It was subsequently suggested by Cohen that cyclopropanation of unactivated alkenes in biological systems may occur through the formation of a copper-carbenoid formed by reaction between the S-adenosylmethionine ylide **22** and a copper containing enzyme (scheme 20).



scheme 20

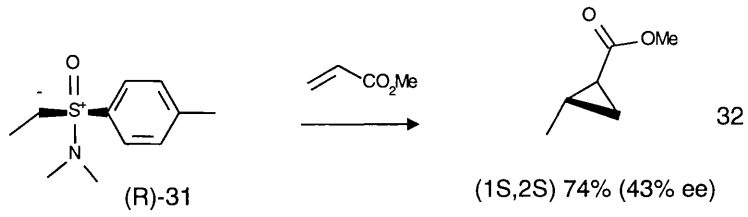
Cohen[43] reported that in the presence of Cu(II) bis-(acetylacetonate), the ylide generated from diphenylsulfonium tetrafluoroborate and sodium hydride would imitate the biological system and cyclopropanate an electron rich alkene (scheme 21). A further investigation of this reaction by Julia[44] found that copper bis-(^{n}pentylphenyl)acetylacetonate **30** could also be used as the catalyst for such reactions. The cyclopropanation of cyclohexene with the copper catalyst and diphenylsulfonium methylide proceeds in 86% yield (scheme 21.



scheme 21

Sulfur Ylides in Asymmetric Cyclopropanation

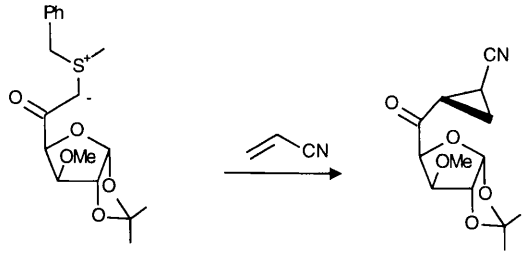
The thermodynamic control endemic in ylide cyclopropanation provides the opportunity for the highly asymmetric cyclopropanation of chiral functionalised electron poor alkenes.[45] Asymmetric methylene transfer from chiral sulphur ylides to achiral alkenes is also well known.[45] The asymmetric ylide cyclopropanation was reported as early as 1960,[46] and may be achieved *via* either of two approaches. Firstly, moderate enantioselectivity can be achieved using chiral sulfoxonium ylides which are enantiopure around the chiral sulphur centre. For example, asymmetric cyclopropanation using the chiral (R)-aminosulfoxonium ylide **31** enables the synthesis of the chiral cyclopropane **32** in good yield and moderate enantiomeric excess.



(R)-31 (1S,2S) 74% (43% ee)

scheme 22

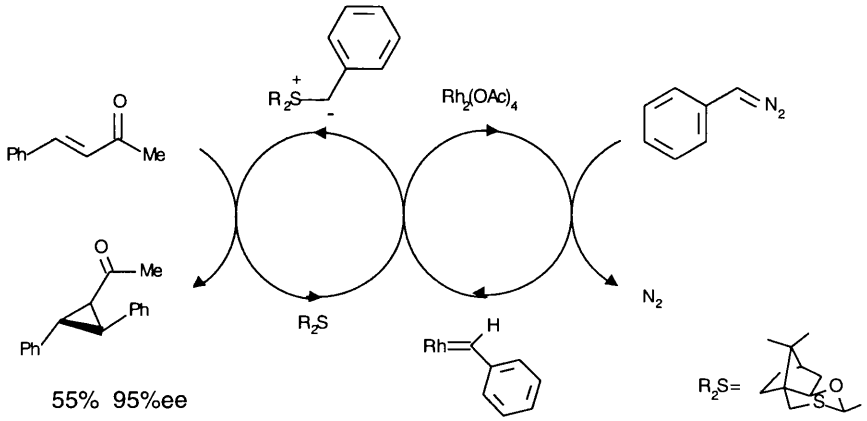
Alternatively, sulfur ylides containing pendant chirality can be employed in similar fashion, although to date with only limited success. For example, the sugar derived stabilised sulfonium ylide **33** can react with a range of Michael acceptors to give cyclopropanes in moderate yields with a low excess of one diastereoisomer (scheme 23).[47]



50% 7 : 3

33 scheme 23

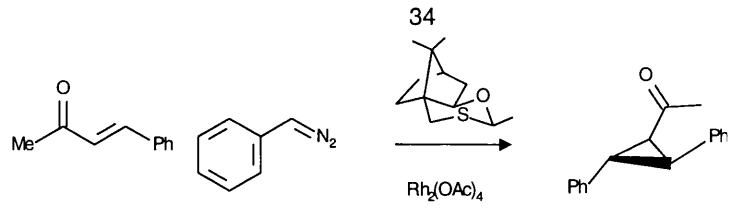
In an elegant study, Aggarwal has recently achieved the catalytic asymmetric cyclopropanation of enones using a catalytically generated chiral sulfur ylide. The rhodium carbenoid generated from phenyl diazomethane and dirhodium tetraacetate can be trapped by a chiral sulfide. The subsequent chiral ylide will then cyclopropanate α,β-unsaturated ketones in moderate yields and with high enantiomeric excess (scheme 24).[48]



55% 95%ee

scheme 24 34

The chiral sulphide **34** can give equally high enantioselectivities when used as a catalyst, but the corresponding chemical yields of cyclopropane are substantially reduced in such cases (scheme 25).



sulfide (equiv)	Yield (%)	isomer ratio	ee (%)
1.0	55	4 : 1	98
0.2	14	4 : 1	98

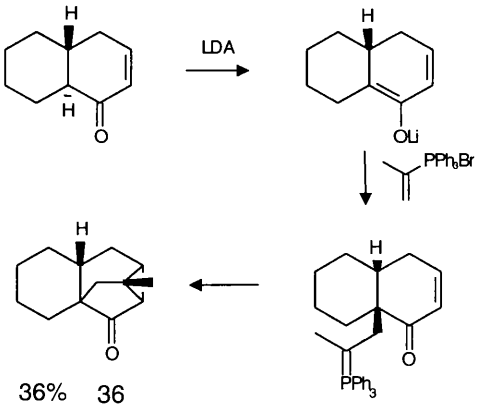
scheme 25

Cyclopropanation Involving Other Ylides

Although sulphur ylides are the most frequently employed reagents for the cyclopropanation of Michael acceptors, the development of phosphorus, arsenic,[49,50] selenium,[51] tellurium[52] and iodonium,[55] ylides as cyclopropanating reagents has also been explored.

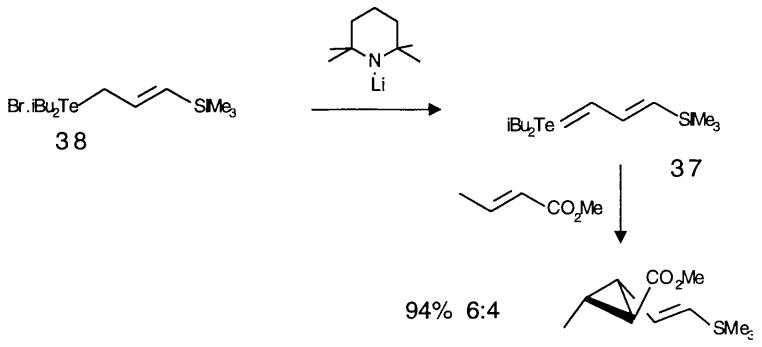
Phosphorus ylides are of course extensively utilised in the Wittig olefination reaction but their use in the cyclopropanation of Michael acceptors is less widely applied. Clearly, the exceptional ability of phosphorus ylides in alkene formation with aldehydes and ketones substantially limits their scope as cyclopropanating reagents. Nevertheless, phosphorus ylides have been utilised in the cyclopropanation of Michael acceptors.[53]

One significant application of phosphorus ylides has been in the synthesis of tricyclic compounds such as **36**. These cyclohexanones form the core unit required for the synthesis of trachyloban-19-oic acid. The phosphorus ylide is generated *in situ* by the addition of an enolate anion to a vinyl phosphonium salt (scheme 26).[54] The ylide can then undergo intramolecular Michael addition. The resultant betaine will close to give the cyclopropane **36**.



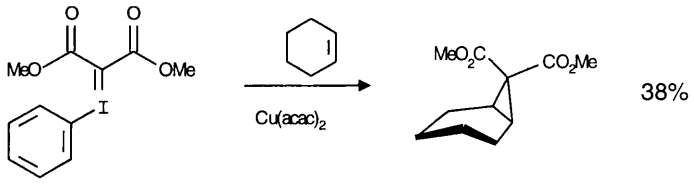
scheme 26

Equally, the tellurium ylide **37** generated from the corresponding bromide **38** reacts with a number of α,β–unsaturated esters to give vinyl cyclopropane derivatives in good yields (scheme 27).[52]



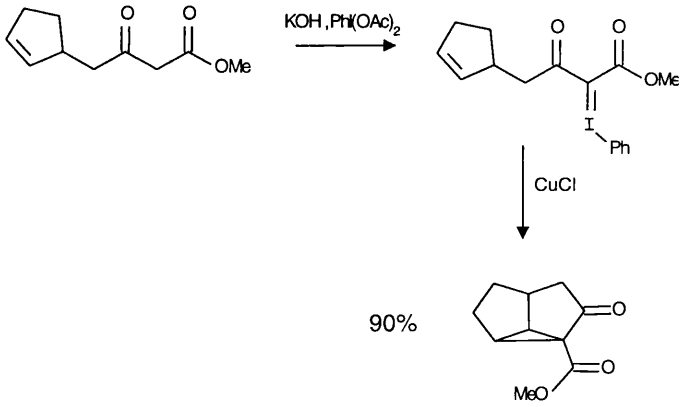
scheme 27

In contrast, iodonium ylides have been shown to be suitable precursors for the cyclopropanation of electron rich alkenes under copper catalysis. The resulting cyclopropanes are generated in moderate yield (scheme 28).[55]



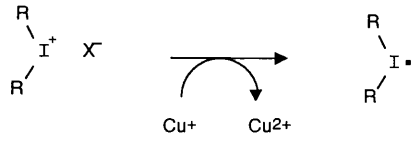
scheme 28

Moriarty and co-workers have recently published a series of reports detailing the cyclopropanation of electron rich alkenes using iodonium ylides.[56] They suggest that the usefulness of dicarbonyl-iodonium ylides could rival that of dicarbonyl-diazocompounds. Iodonium ylides can be generated by the reaction of an enolate with a hypervalent iodine species (scheme 29). In the presence of a copper catalyst this species can be used to cyclopropanate alkenes such as in the case of the intramolecular cyclopropanation shown (scheme 29).



scheme 29

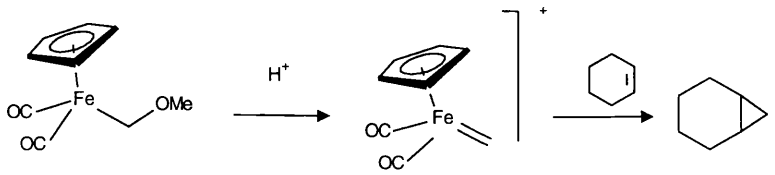
Surprisingly, the authors propose that the intermediate involved in the cyclopropanation is not a copper carbenoid (*vide supra* 1.2).[56a] They believe that the absence of Wölff type rearrangement products and the limited success of the reaction in the absence of catalyst indicates a probable cycloaddition mechanism. Alternatively, they propose that a radical mechanism may operate with Cu(I) as a catalytic electron transfer reagent. Cu(I) has been known to generate the iodino-aryl radical from diaryl iodonium salts (scheme 30).[57]



scheme 30

1.3. The Use of Transition Metal Carbene Complexes as Cyclopropanating Reagents

The first suggestion that transition metal carbenoid complexes might serve as carbene transfer reagents emerged from the work of Pettit and Jolly[58] who found that treatment of $CpFe(CO)_2CH_2OMe$ with acid in the presence of cyclohexene produced norcarane in 46% yield (scheme 31).



39

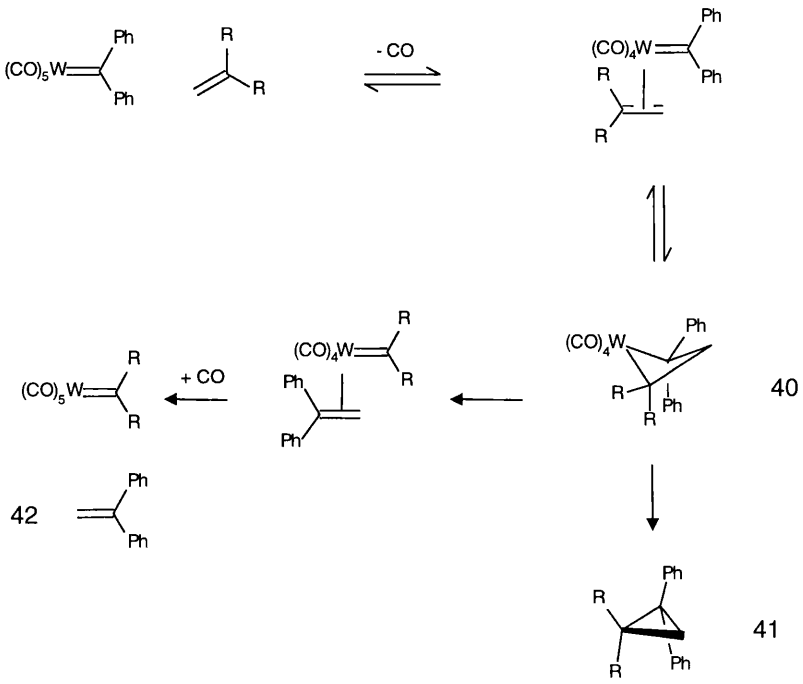
scheme 31

It was Fischer who reopened the field in the 1960's with the observation that the complexes $(CO)_5M=C(OMe)Ph$, where M was chromium, molybdenum or tungsten (the eponymous Fischer carbenes) react with some alkenes to give cyclopropanes, although he found that vigorous conditions were often required for the cyclopropanation.[59,60,61] Still further, he found that only activated alkenes could in fact be cyclopropanated. Both electron rich vinyl ethers and electron poor α,β-unsaturated esters would react readily, but intermediate species such as alkyl substituted alkenes showed low reactivity in cyclopropanation reactions.

Mechanistic Aspects of Transition Metal-Carbene Transfer to Alkenes

Transfer Involving Transition Metal Carbene-Alkene Complexes as Intermediates

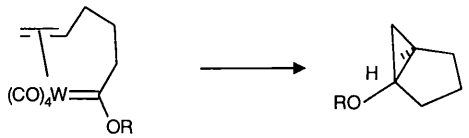
Early studies by Casey[62] suggested that in reactions of $(CO)_5W=CPh_2$ with alkenes, cyclopropanation occurred *via* initial loss of CO and subsequent formation of a carbene-alkene complex. Through equilibration with a metallocyclobutane **40** both cyclopropane **41** and metathesis **42** products could be generated (scheme 32).



scheme 32

Based on these results, Casey proposed an explanation for the unusual observations by Fischer that only highly activated or deactivated alkenes are reactive toward $(CO)_nM=C(OR)Ph$.[63] Casey postulated that two different reaction pathways may be involved. Vinyl ethers are sufficiently electron rich that they can undergo direct reaction, without CO loss, with the weakly alkoxy stabilised carbene complexes. This is in agreement with the observation that such reactions are favoured by high CO pressures that prevent metal-alkene complexation. On the other hand, α,β-unsaturated esters are only very weakly nucleophilic but are good π acid ligands for low valent metal complexes. Thus, they react only *via* CO loss and formation of intermediate metal carbene-alkene complexes.

This complexation and subsequent rearrangement mechanism was elegantly demonstrated by the X-ray structure of the tungsten carbene **43**. The complex is stable at room temperature and rearranges only on heating to give the cyclopropane **44** (scheme 33).[64]



43 44

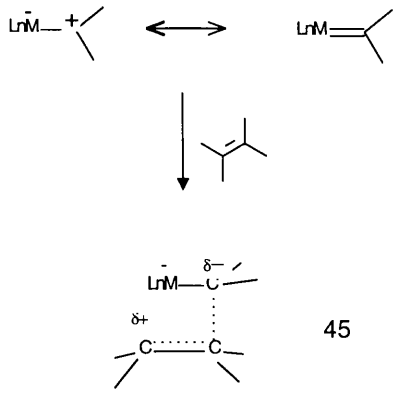
scheme 33

Cyclopropanation by Direct Transfer to Alkenes

The majority of carbene transfer reactions observed make use of highly electrophilic carbene complexes, such as $(CO)_5W{=}CHPh$ and $Cp(CO)(L)Fe{=}CR_2^+$. These species will react with alkenes at very low temperatures, far below those required for ligand dissociation. In addition, no metathesis products are generally observed. All available evidence points to direct reaction of the metal carbene complexes *via* ligand substitution.[65]

Substantial data relevant to the transfer mechanism is available including such aspects as the relative reactivities of a wide variety of alkenes with different carbene complexes, studies of the variation of *cis : trans* selectivities as a function of alkene structure,[67b] metal, ligands and substitution at the carbene carbon[65] and enantioselectivity observed using optically pure, chiral-at-the-metal carbene complexes.[66] To date however, there still exists no general mechanistic model which accounts unequivocally for all the data. Consequently, the following discussion must be considered purely hypothetical.[65]

It is widely accepted that the initial step in the reaction of an electrophilic metal carbene complex involves attack on the nucleophilic alkene, precipitating substantial charge development in the transition state45 (scheme 34).[65]



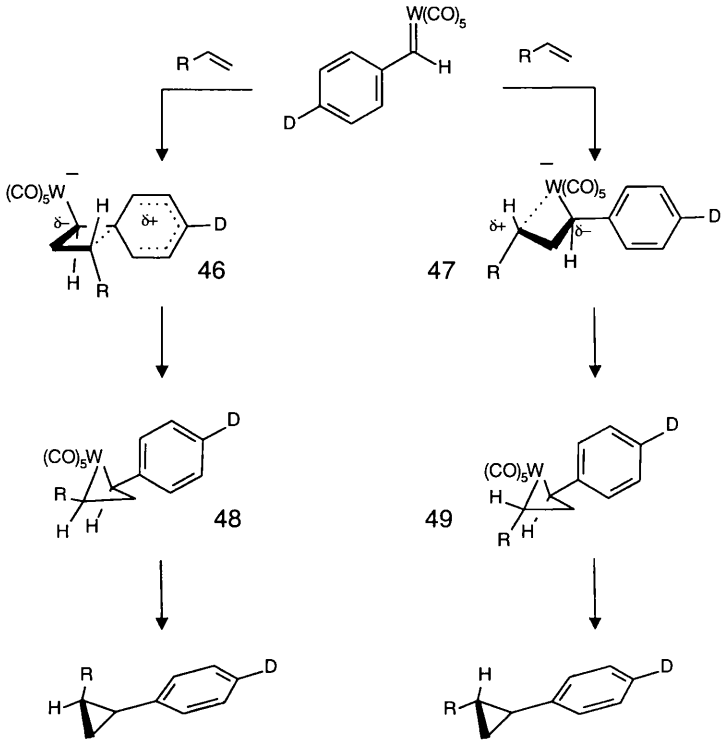
45

scheme 34

It is unclear as to whether the charge development proceeds as far as the formation of carbocationic intermediates. Such species are however considered unlikely to be intermediates, largely due to the observation that the stereochemistry of the alkene is maintained in the product cyclopropane.[67]

One of the most cognizant proposals for the mode of ring closure was originally advanced by Casey for cyclopropanations involving $(CO)_5W{=}CHPh$.[67b] Although initially metallo-cyclobutanes were presumed to be intermediates for the transition states of transfer reactions,[67a] later stereochemical results using an extensive array of substituted alkenes were sometimes incompatible with the puckered metallocycles proposed. The favoured mechanistic

model involves two competitive pathways, the relative rates of which are largely determined by the steric factors affecting each individual system (scheme 35).

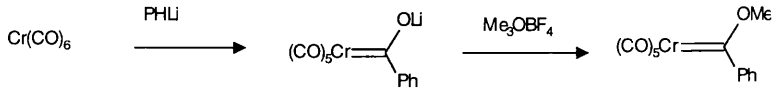


scheme 35

After initial nucleophilic attack by the alkene, the resulting polarised intermediate can adopt one of two conformations **46** and **47**, thus minimising the steric interaction between the transition metal and the alkene substituent R. In the case of **46** however, the positive centre on the alkene is further stabilised *via* an *ipso* interaction with the aromatic ring, stabilisation which will be increased if D is an electron donor. Each of these intermediates may then undergo closure to afford metallocyclobutanes of fixed geometry **48** and **49**, which can in turn undergo reductive elimination to give the cyclopropanes. As previously explained, there is evidence to suggest that for more highly substituted alkenes the formation of metallocyclobutanes never occurs, and there is direct ring closure from **46** and **47** to give the cyclopropanes.[65] For the monosubstituted alkenes as shown above however, a degree of metallocyclobutane formation is a prerequisite in order to explain the observed *cis* geometry.[67b]

Synthesis of Transition Metal-Carbene Complexes

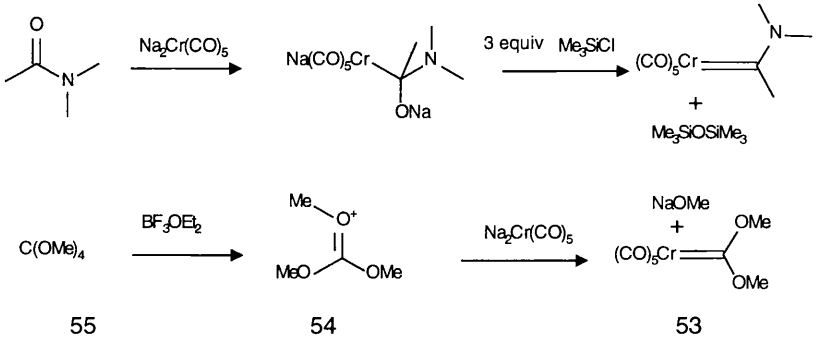
The most commonly applied method for the synthesis of transition metal carbene complexes is still the original Fischer procedure which involves the reaction of an organolithium reagent with a metal carbonyl complex and subsequent alkylation of the resulting alkoxide complex. For example, reaction of phenyl lithium with chromium hexacarbonyl followed by alkylation using Meerwein's salt gives the Fischer carbene complex **50** (scheme 36).



50

scheme 36

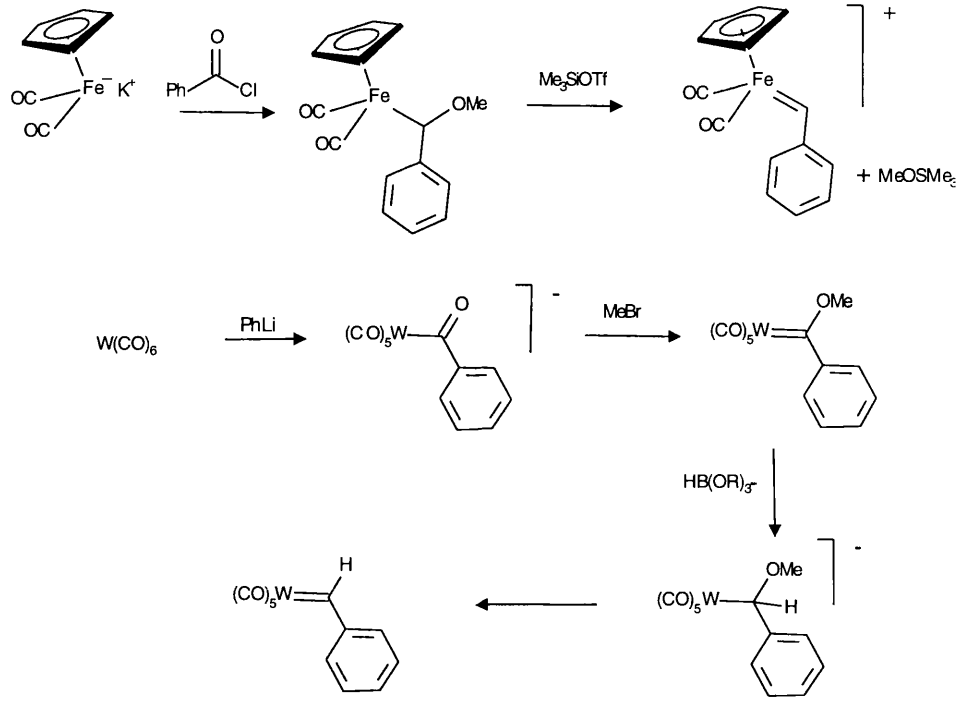
The major drawback of this methodology is that it restricts the β-substituent groups in Fisher carbenes to those available from organolithium reagents. Further elaboration of alkylcarbene complexes, for example by cycloaddition and displacement reactions widens the range of carbene complexes available *via* this route.[68] Recent work by Hegedus has demonstrated the utility of amides and metal carbonates as Fischer carbene precursors.[167] In this process, tertiary amides may be treated with the nucleophilic disodium chromium pentacarbonyl salt to generate the complex **51**. Treatment with chlorotrimethylsilane promotes deoxygenation of the complex to produce the neutral Fischer carbene **52**. A similar mechanism can be utilised to generate the dimethoxy chromium carbenoid **53** through reaction with the highly electrophilic oxonium salt **54** derived from tetramethyl carbonate **55** (scheme 37).



55 54 53

scheme 37

By far the most widely used technique for the synthesis of non-heteroatom stabilised transition metal carbene complexes is the ionisation of a leaving group located at the α–position of a metal-alkyl complex. The leaving group may be alkoxide, halide, sulphide or even hydride and its removal can be accomplished using Lewis acids or simply by thermal ionisation in polar solvents (scheme 38).[65] An alternative method is the direct hydride reduction of a Fischer carbene complex, followed by a similar acid catalysed α-ionisation (scheme 38).[69]

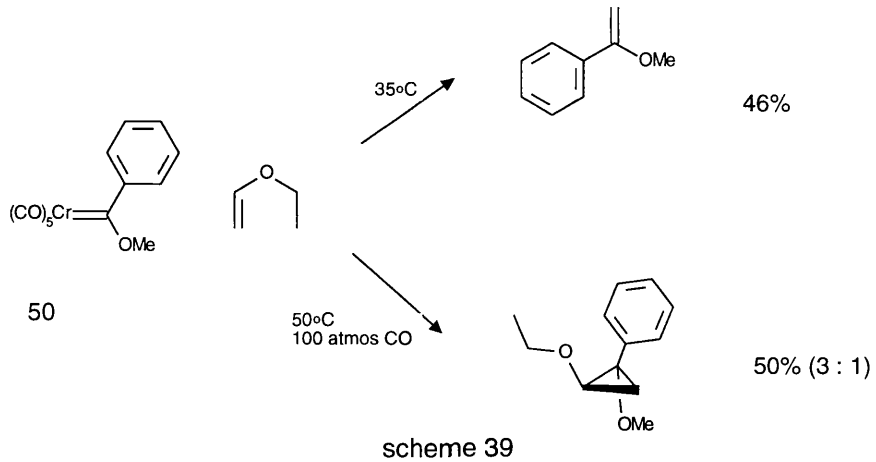


scheme 38

Cyclopropanation Reactions of Transition Metal Carbenes

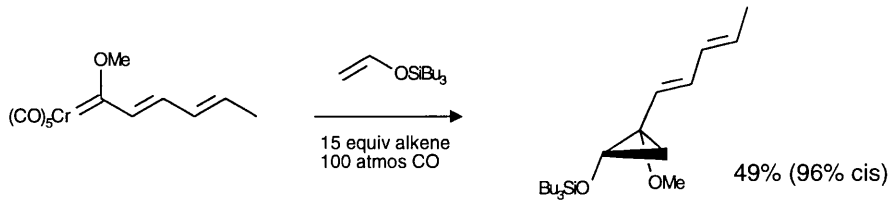
Cyclopropanation with Heteroatom Stabilised Carbenoids

As previously stated, only alkenes substituted by strongly electron withdrawing groups such as α,β-unsaturated esters or strongly electron donating groups such as vinyl ethers are readily cyclopropanated by Fischer carbenes. Simple alkyl substituted olefins are generally unreactive and metathesis products are commonly observed. The reactivity of a given catalyst can be altered by varying the temperature and the CO pressure of the system in order to favour cyclopropanation (*vide supra* 1.3). For example, in the reaction of the chromium carbene **50** with ethylvinylether, high CO pressures are required to suppress formation of the metathesis product (scheme 39).[60]



scheme 39

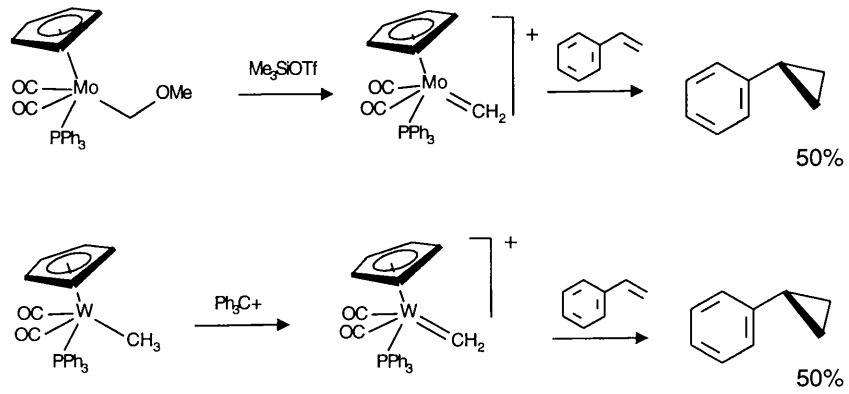
As a consequence of these problems, complex syntheses employing cyclopropanation with Fischer carbenes have yet to become commonplace in organic synthesis. Nevertheless there are plenty of examples of the cyclopropanation of simple systems, and a representative cyclopropanation which forms the key step in a synthesis of prostaglandin is shown in scheme 40.



scheme 40

Cyclopropanation with Non-Heteroatom Stabilised Transition Metal Complexes

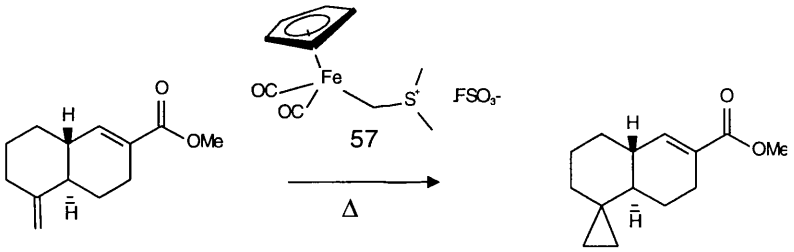
The synthesis of methyl cyclopropanes using transition metal methylene carbenoid complexes has received wide attention. The structurally simplest transition metal carbene system, methylene carbenoids were the first species investigated in alkene cyclopropanation. The method of Jolly and Pettit[58] (*vide supra* 1.3) has been used for the *in situ* generation and transfer of methylene from $Cp(CO)_2Fe{=}CH_2^{+}$[62], $Cp(diphos)Fe{=}CH_2^{+}$[62], $Cp(CO)_3Mo{=}CH_2^{+}$[70] and $Cp(CO)_2(PPh_3)Mo{=}CH_2^{+}$[70] amongst others (scheme 41). Only a limited range of alkenes have been studied and the yields reported were moderate.



scheme 41

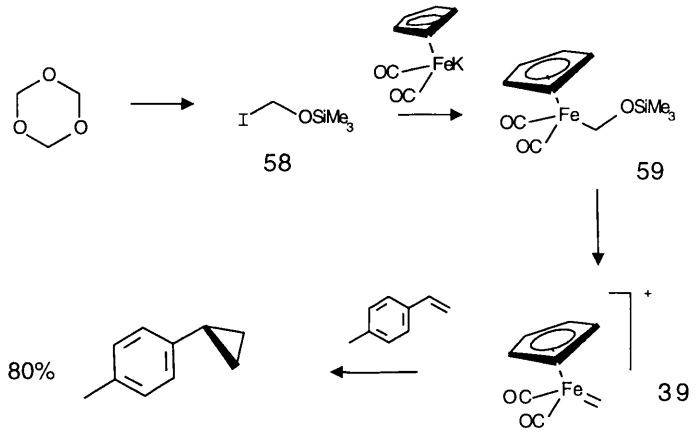
Hydride abstraction by trityl cation Ph_3C^{+} from the appropriate methyl complex was used to generate and spectroscopically characterise $Cp(CO)(PPh_3)W{=}CH_2^{+}$ and $Cp(CO)_2(PPh_3){=}CH_2^{+}$[70] (scheme 41) These species reacted with styrene to give cyclopropanes both in yields of 50%.[70,71b]

The most extensively studied methylene transfer to date involves thermolysis of the complex $Cp(CO)_2FeCH_2SMe_2^+$, with *in situ* generation of the corresponding methylene carbenoid **57**.[62] The reaction of this carbene complex with a variety of alkenes demonstrates that moderate to good yields of cyclopropanes may be obtained using this method and the ease of preparation, handling and storage of this complex add to its attractions as a reagent (scheme 42).[71b]



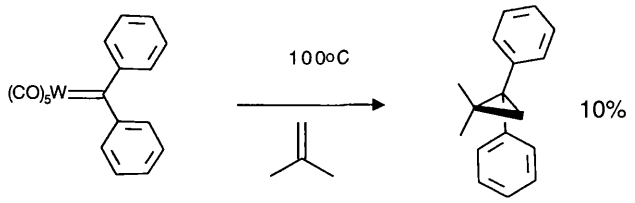
scheme 42

Hossain[72] has recently developed a novel method for the preparation of α-siloxymethyl iron complexes directly from paraformaldehyde or trioxane. The reaction of $Cp(CO)_2Fe$ anion with iodosiloxymethane **58** generated *in situ* from the reaction of paraformaldehyde and iodotrimethylsilane affords the alkyl-iron complex **59**. Treatment of the α–siloxymethyliron complex in the manner of Jolly and Pettit[58] provides the methylene iron carbene complex **39**. The generation of this species which will readily react with aryl alkenes allows for the one-pot synthesis of cyclopropanes from paraformaldehyde (scheme 43).



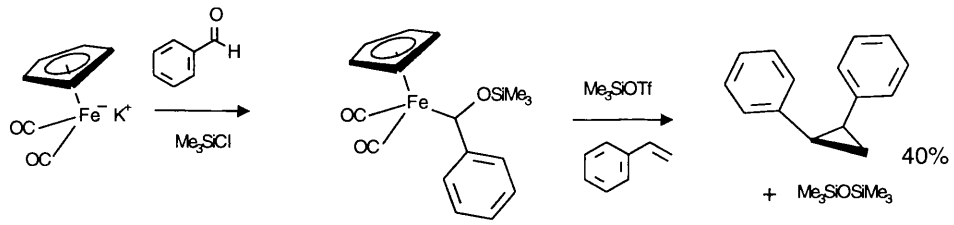
scheme 43

The requirement for a highly activated or deactivated olefin and forcing conditions places constraints on the use of alkoxy-Fischer carbene complexes in cyclopropane synthesis. In contrast Casey found that aryl transition metal carbenes such as $(CO)_5W{=}CPh_2$ which lack a stabilising heteroatom adjacent to the carbene carbon are more reactive toward simple activated olefins than the Fisher alkoxy carbene complexes. Unlike Fisher carbenes, transition metal carbenes are also reactive toward simple alkenes (scheme 44).[62] In many cases however, the major products of reaction with alkenes remain those of metathesis.



scheme 44

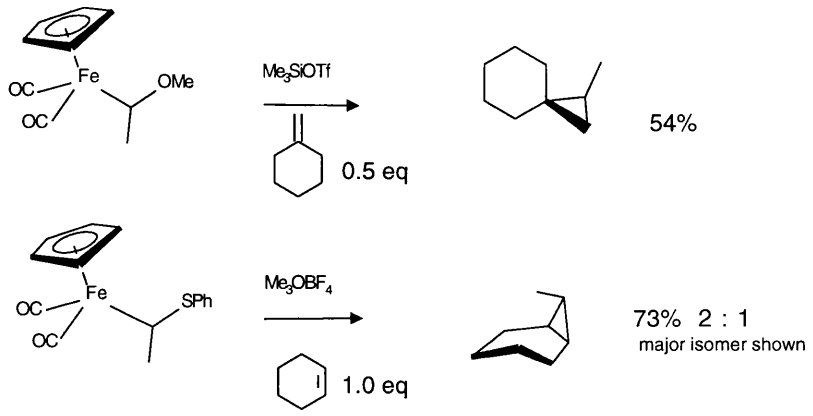
In an interesting development, Hossain has utilised phenyl-carbene complexes of cyclopentadienyl-iron dicarbonyl generated from aldehydes as cyclopropanating reagents. This two step, one-pot sequence traps the alkoxide generated by the nucleophilic attack of the anion on aryl aldehydes with chlorotrimethylsilane. Reaction with trimethylsilyltriflate generates the iron carbene complex, which may be trapped *in situ* to give cyclopropanes in reasonable yields (scheme 45).[73]



scheme 45

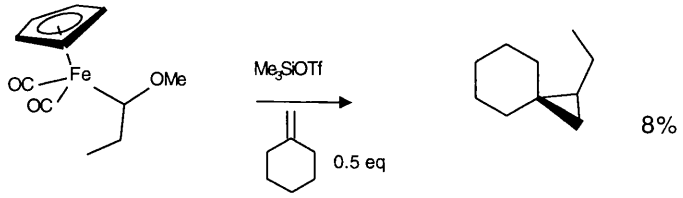
The synthesis of methylcyclopropanes using iron methylcarbene complexes has been the origin of much of the interest in the chemistry of carbene complex transfer reactions. In contrast to methylene transfer, where Simmons Smith reagents and metal catalysed diazomethane reagents are routinely used, techniques for transferring methyl carbene are much less successful. Rearrangement of the free carbene or carbenoid *via* α–hydride insertion to generate ethylene is often dominant relative to addition to alkenes.[65]

Brookhart observed that treatment of $Cp(CO)FeCH(OCH_3)CH_3$ with trimethylsilyltriflate in the presence of alkenes gave methylcyclopropanes.[69e] Kemer and Helquist have studied the methylcarbene transfer reactions of $Cp(CO)Fe\text{-}CH(SPhCH_3)CH_3^+$ (scheme 46).[74]



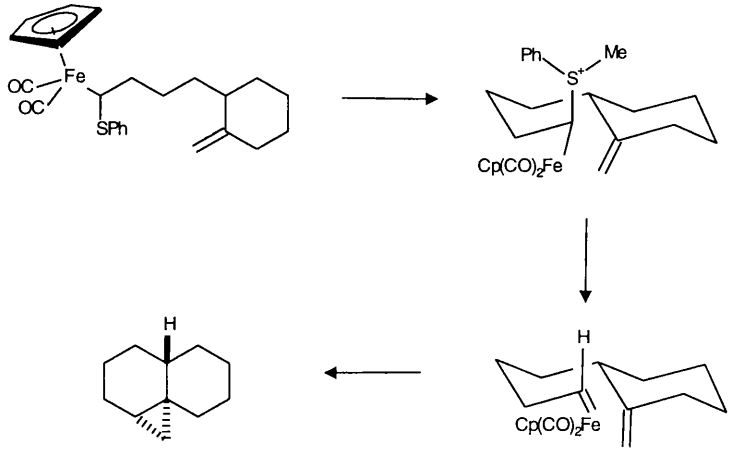
scheme 46

More highly alkylated species suffer from an even greater tendency for C-H insertion. This fact, coupled with increased steric hindrance, greatly reduces the transfer yields of such species. For example, *in situ* generation of $Cp(CO)_2Fe\text{-}CHCH_2CH_3^+$ gives cyclopropanes with *exo*-methylene cyclohexene in only 8% yield (scheme 47).[75]



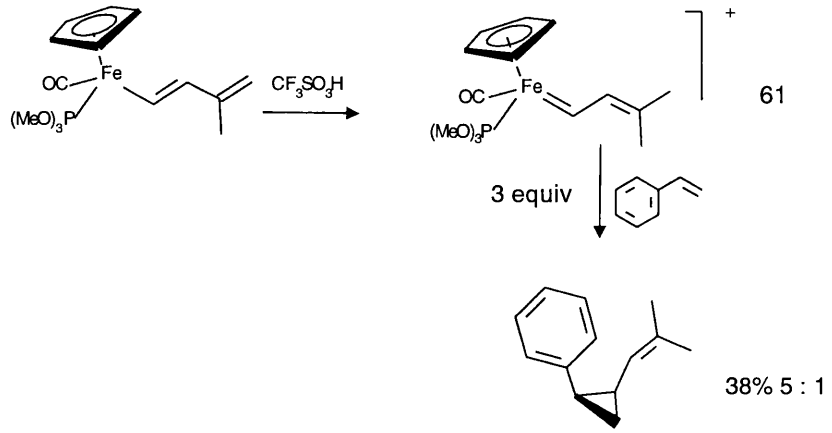
scheme 47

Helquist has demonstrated however, that intramolecular trapping can compete effectively with hydride migration in carbene complexes containing remote double bonds. The stereochemical control exhibited by such reactions therefore provides a useful synthetic method for constructing polycyclic ring systems (scheme 48).[76]



scheme 48

Generation and transfer reactions of stable mono-substituted carbene complexes of the type $Cp(CO)LFe{=}CHR^+$ have been reported for R=vinyl and cyclopropyl, both carbocation-stabilising substituents.[65] The vinyl complex **61** has been utilised in the cyclopropanation of styrene.[77,78]



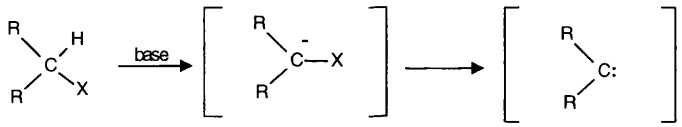
scheme 49

In summary, transition metal carbene complexes have shown that they are applicable as stoichiometric reagents for a wide range of cyclopropanations. Nevertheless, complex multistep procedures and forcing conditions are often required for the effective cyclopropanation of many alkenes. For simple unactivated alkenes in particular, transition metal-carbene complexes and alkoxy Fischer carbenes especially remain unsuitable as cyclopropanating reagents.

1.4. Cyclopropanation *via* Carbenoids derived from Alkyl Halides

Cyclopropanes from the Transfer of Halocarbenoids and Halocarbenes derived from α-Elimination of Alkyl Halides

Treatment of an appropriate substrate with a base can lead to a carbanionic intermediate that bears a leaving group on the carbanionic centre. Upon loss of this group, a carbene may be formed, the net overall process being called an α-elimination since both the hydrogen substituent and the leaving group are lost from the same carbon centre (scheme 50). Such species are usually considered to be the free carbene, but there is strong evidence to suggest that some form of co-ordinated carbenoid may be involved in some cases.[79] Most often the starting materials bear additional substituents, in particular electronegative groups, on the prospective carbene centres.



scheme 50

Haloforms as Cyclopropanation Reagents

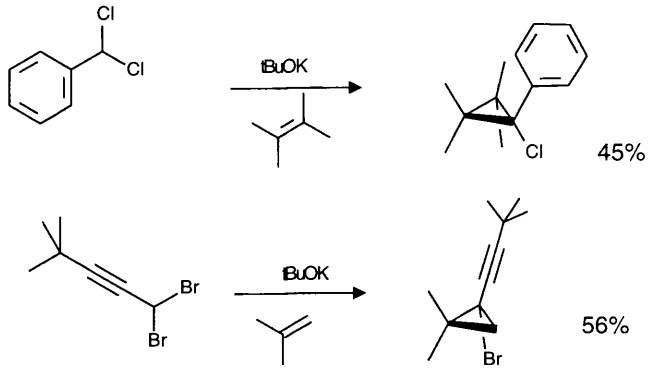
Haloforms were first recognised as suitable dihalocarbenoid and dihalocarbene precursors by Geuther as early as 1862[80] He suggested that chloroform is actually $HCl{\bullet}CCl_2$ from which hydrogen chloride might be removed by the addition of alkali to give "carbon dichloride". It was not until 1950 however that the mechanism of the basic α-elimination of chloroform to give dichlorocarbene was elucidated.[79]

Dihalocarbenoid addition to alkenes occurs stereospecifically with few exceptions to give dihalocyclopropanes.[81] These carbenoid species behave as electrophiles and consequently the reactivity of simple alkenes towards halocarbenoids decreases with decreasing substitution around the carbon-carbon double bond. In addition, the dihalocyclopropanes derived from strained alkenes are liable to undergo rearrangements, often defying the isolation of three membered ring products.[82]

Improvements in making dihalocyclopropanes *via* α-elimination under phase-transfer conditions have been reported.[83] In addition, other methods for making mixed dihalocarbenes and carbenoids have been extensively researched.[84]

Halocyclopropanes from the α-Elimination of Functionalised Dihalides

The propensity of methylene halides to undergo α-elimination is greatly enhanced by substituents which are capable of delocalising a negative charge. Hence, the reaction of benzal chloride with potassium *tert*-butoxide in excess alkene gives 1-phenyl-1-chlorocyclopropanes in yields from 50 to 90% (scheme 51).[84] The same procedure has been applied successfully to benzal bromide, and in the synthesis of fluorocyclopropanes with α-bromo-α-fluorotoluene and α-chloro-α-fluorotoluene.[87]

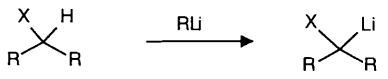


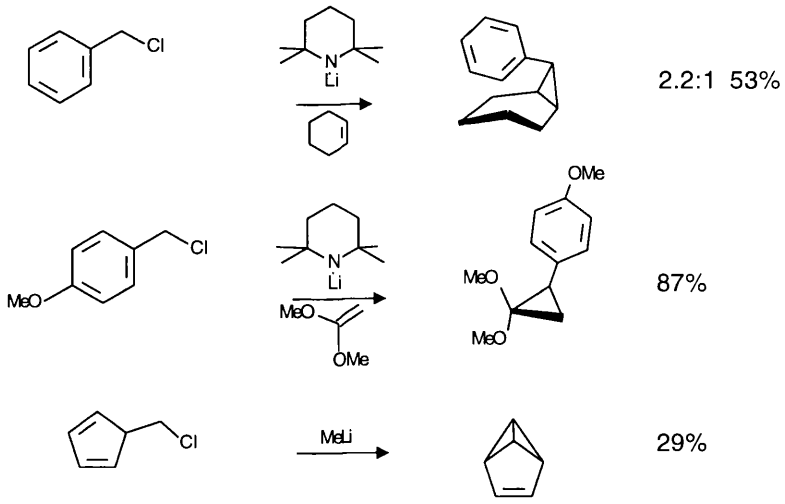
scheme 51

Similarly a series of 1,1-dihaloalk-2-ynes also serve as carbene precursors to form 1-alkynyl-1-halocyclopropanes in up to 90% yield (scheme 51).[87] In most of the examples above, the intermediate involved is normally assumed to be the free carbene rather than a carbenoid. The stabilisation afforded by a halide substituent on the carbene is substantial[79] and hence the presence of a metal centre in order to moderate reactivity is unnecessary. Nevertheless it is still possible to suppose that some metal salt is complexed at the carbenic carbon and hence these examples are included.

Cyclopropanation with Carbenoids Derived from the α-Elimination of Halo-Alkanes

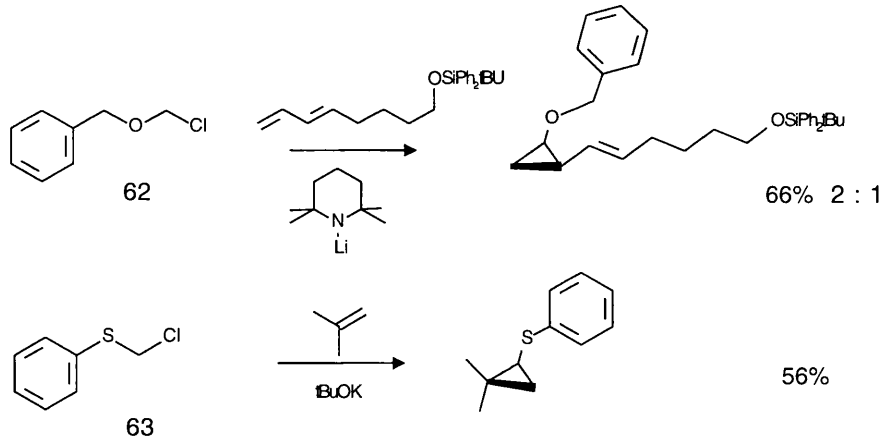
The α-elimination of monohaloalkanes with a lithium base to give carbenes and carbenoids is also facilitated by the presence of stabilising groups on the prospective carbenoid carbon. In the absence of ancillary halogens, this stabilisation is substantially reduced and thus there are only a small number of examples in which this approach has been utilised to form unfunctionalised cyclopropanes (scheme 54).[88,89] An organolithium carbenoid species is the probable intermediate in such reactions.





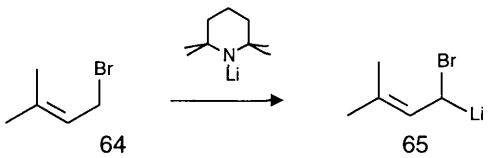
scheme 52

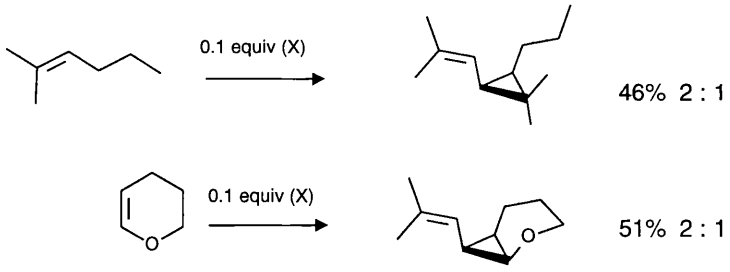
α-Haloethers are readily deprotonated to afford alkoxy carbenoids due to the added stabilisation afforded by the oxygen. Although with α-chloroethers this procedure provides good yields of oxycyclopropanes, the high toxicity of α-haloethers such as **62** has precluded its widespread adoption in synthesis (scheme 53).[90] Similarly, chloromethylphenyl sulfide **63** can be readily deprotonated with potassium *tert*-butoxide, thus transferring phenylthiocarbene to alkenes (scheme 53).[79]



scheme 53

Julia has shown that carbenoids can likewise be generated by the α-deprotonation of allyl halides with a strong, non nucleophilic lithium base. Thus treatment of either prenyl bromide **(64)** or prenyl chloride with lithium tetramethylpiperidide generates the lithium carbenoid species **65**. Subsequent reaction with electron rich alkenes generates predominantly the *cis* vinyl cyclopropanes (scheme 54).[91]

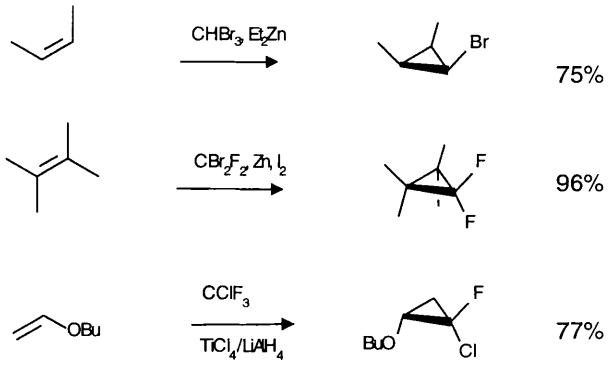




scheme 54

Perhalomethanes as Cyclopropanation Reagents

Perhalomethanes may also produce dihalocarbenoids *via* a number of mechanisms.[84] A zinc difluorocarbenoid generated from dibromodifluoromethane and zinc transfers difluoromethylene to alkenes in excellent yields (scheme 55).[92]The treatment of alkenes with trihalomethane and diethylzinc also affords monohalocyclopropanes in good yields.[93]

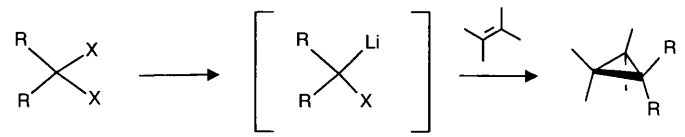


scheme 55

Dihalocarbenoids can also be generated *via* McMurry type conditions using low valent titanium, generated *in situ* by the reaction of titanium tetrachloride and lithium aluminium tetrahydride (scheme 55). The resulting low valent titanium species generates an organotitanium reagent capable of transferring the chlorofluoromethylene group to alkenes.[91]

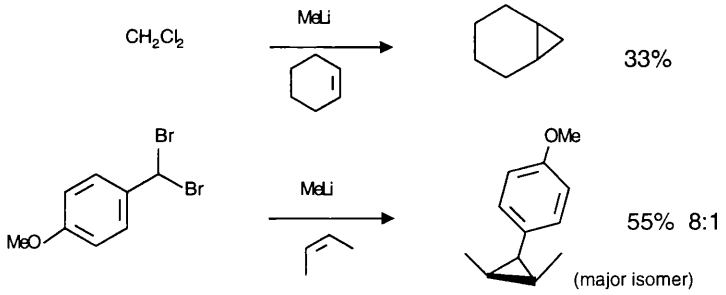
Cyclopropanation *via* Halogen-Lithium Exchange

A procedure closely related to the generation of carbenoids *via* α-elimination discussed earlier is the generation of geminal dihalides with alkyllithium reagents. Halogen lithium exchange occurs to give an α–haloalkyllithium carbenoid species which can then be effective in the cyclopropanation of alkenes (scheme 56).



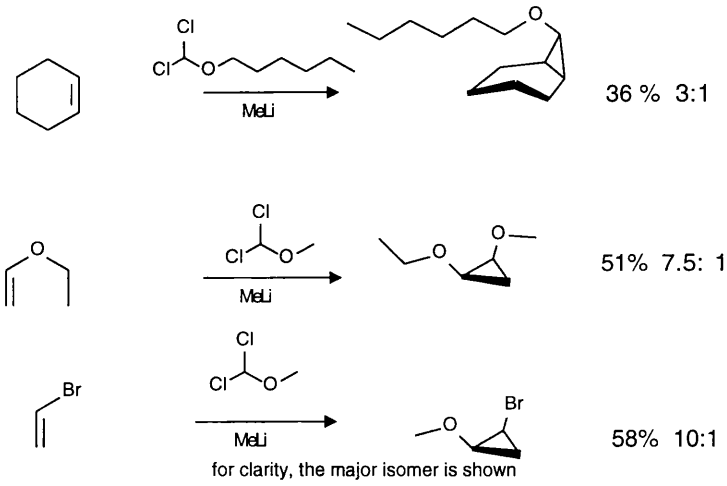
scheme 56

Thus, dichloromethane[94] and 4-methoxybenzalbromide,[95] in the presence of methyl lithium and an excess of alkene, can be used to generate cyclopropanes in reasonable yields (scheme 57).



scheme 57

Schöllkopf showed that α,α-dihaloethers could similarly serve as efficient precursors for alkoxycyclopropanes.[128] He demonstrated that the carbenoid generated in this manner would react with a variety of electron rich alkenes to give alkoxycyclopropanes (scheme 58). As in the case of the carbenoids derived from the α-elimination of haloethers previously described (*vide supra* 1.4), the use of α,α-dihaloethers as cyclopropanating reagents has not been widely utilised ostensibly as a consequence of their high toxicity.[92,96]

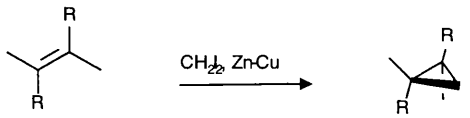


scheme 58

In order to generate alkoxycyclopropanes, Schöllkopf employed electron rich alkenes as solvent with two to three equivalents of methyllithium. Most cyclopropanes generated were *cis* although in some cases the *trans* cyclopropane was dominant (*vide infra* 2.4.4)

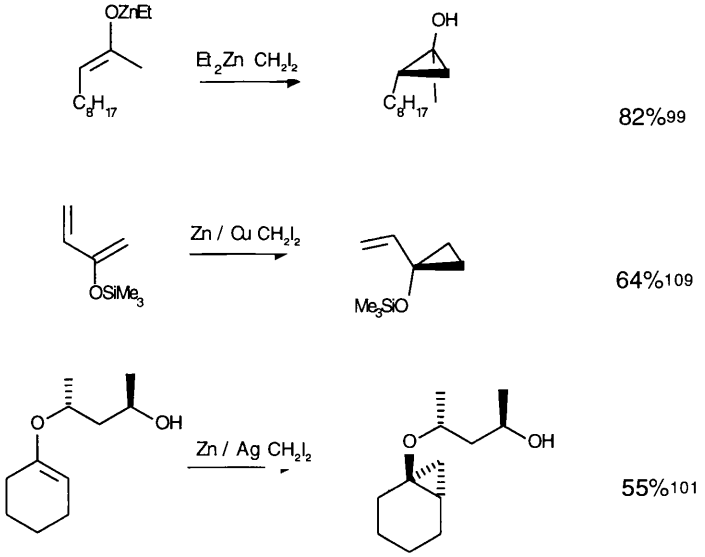
The Simmons Smith Reaction

The Simmons Smith reaction was first reported in 1958[97] and has since become one the most commonly used strategies in cyclopropanation.[98] The reaction, as it was originally published, involves the generation of a methylene organozinc carbenoid by the reaction of metallic zinc copper couple with methylene iodide. The zinc carbenoid will react with alkenes to generate cyclopropanes stereospecifically with respect to the alkene's geometry (scheme 59).



scheme 59

The Simmons Smith cyclopropanation has been extensively employed in synthesis and is effective with a wide range of alkenes. The conditions employed are mild and the Simmons Smith reaction has thus been effective in the presence of many functional groups (scheme 60). Cyclopropanation is subject to the directing effect of basic groups containing oxygen or nitrogen atoms which often enables the regio- and stereoselective cyclopropanation of functionalised substrates.[98] The reaction is not restricted solely to metallic Zn-Cu couple as the zinc source, as zinc-silver, zinc mercury and activated zinc are all suitable for the generation of zinc carbenoids from methylene iodide. In the reaction with metal couples, it has been assumed that the copper, silver and mercury do not play a role in the chemistry of the system and are simply present as a means of activation of the metal surface.[98] More recent work however, has since cast doubt on this assumption (*vide infra* 1.4).

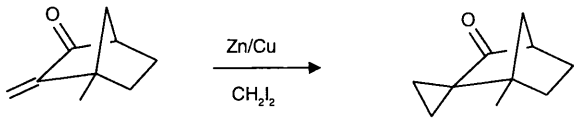


scheme 60

The Furukawa modification of the Simmons Smith reaction, first published in 1969, utilises diethyl zinc as an alternative to solid zinc metal.[102] The major advantage of this modification is that the reaction is then homogeneous and as a consequence yields of cyclopropanes are

usually improved relative to those obtained in the original protocol. The use of diethyl zinc reagents provides the added advantage of reducing the reaction time substantially.[103]

In general, the Simmons Smith cyclopropanation proceeds most smoothly with electron rich alkenes to afford cyclopropanes stereospecifically and without rearrangement. Although electron poor alkenes do not generally undergo successful cyclopropanation, there are examples of the reaction of α,β-unsaturated carbonyl compounds in the Simmons Smith Reaction.[98] 2-Methylenebornane-3-one **66** for example, can be cyclopropanated to give the spirocyclopropane **67.**[104]



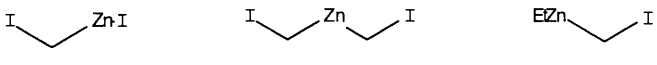
66 67

equiv CH_2I_2	yield
1.4	33 %
2.4	56 %
22	100 %

scheme 61

Although generation of the carbenoid under Simmons Smith conditions is assumed to be facile, in order to ensure high conversion of alkene to cyclopropane many workers employ a large excess of the zinc reagent.[98] For most systems two or three equivalents are employed but for some alkenes, such as 2-methylenebornane-3-one **66** the best results are found when an excess of zinc carbenoid as high as twenty two-fold is generated (scheme 61).[104]

The Simmons Smith methylene zinc carbenoid, once generated, may be stable in solution for several hours.[98] Nevertheless despite extensive investigation the exact structure of the reagent remains unclear. For the reagent produced *via* the reaction of diethylzinc with methylene iodide the structure of the cyclopropanating species is postulated to be one of the species shown in scheme 62.

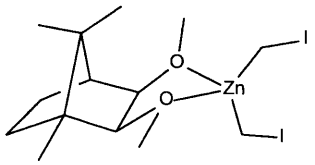


68 69 70

scheme 62

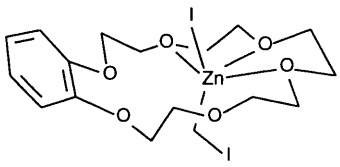
Recently the groups of Denmark[105] and Charette[106] have succeeded in crystallising zinc carbenoid species generated from the reaction of methylene iodide and diethyl zinc. In Denmark's study of the bis (iodomethyl)zinc species **69**, he succeeded in crystallising the (1S,2R,3S) bornanediol derived bisether complex **71** with the zinc carbenoid species formed by reaction of diethyl zinc with two equivalents of methylene iodide. He found the C-Zn-C bond

angle to be 138°, making the complex a distorted tetrahedron about zinc. The complex was also tetrahedral about each of the carbenoid carbons with the Zn-C-I bonds having bond angles of 107° and 116°.



71

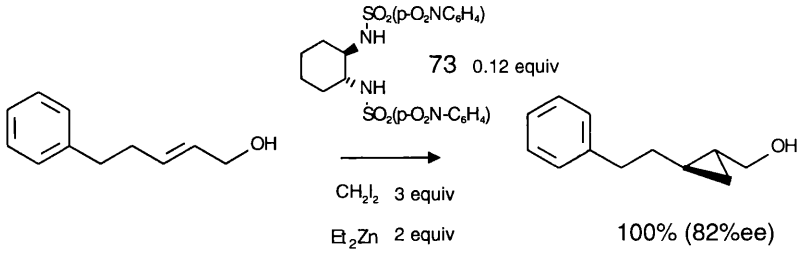
Charette generated the iodomethyl zinc complex **72** by the reaction of of ethylzinc iodide and methylene iodide in the presence of the crown ether benzo-18-crown-6. The resulting crystal structure of the IZnCH2I•benzo-18-crown-6 complex showed the zinc lying in a highly distorted trigonal bipyramidal environment within the crown ether with an I-Zn-C bond angle of 157°. The Zn-C-I of 118° shows that this complex is also approximately tetrahedral about the carbenoid carbon.



72

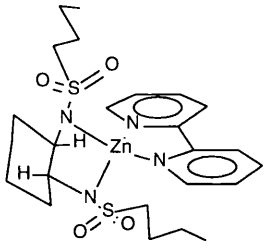
Solutions of both species were effective cyclopropanating reagents and whilst neither species may be definitively assigned as the actual Simmons Smith reagent, the common structural features of both provide strong evidence as to the nature of the zinc carbenoid species involved.

The strong directing effect of polar proximal groups in the Simmons Smith reaction has allowed for a wide variety of stereospecific cyclopropanations to be performed. Concurrent with this chemistry, several groups have developed methodologies for enantioselective Simmons Smith cyclopropanation using stoichiometrically generated chiral zinc carbenoid species.[200] More recently however, the Simmons Smith reaction has been utilised by Kobayashi in the catalytic enantioselective cyclopropanation of allylic alcohols.[107,108] In the presence of a catalytic quantity of the disulfonamide **73**, methylene iodide and diethyl zinc can be used to generate a chiral cyclopropanating reagent. The free hydroxyl group of the allylic alcohol was essential, and where ether derivatives were subjected to these reaction conditions racemic mixtures of cyclopropanes resulted (scheme 63).



scheme 63

Denmark[109] has published a comparison of various disulfonamide ligands as chiral catalysts for this system as well as an X-ray structure of the zinc-sulfonamide catalyst as a complex with bipyridine 74.[110] Interestingly, this complex is itself an active catalyst for the enantioselective cyclopropanation.



74

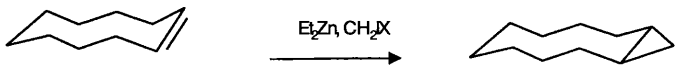
The relative lack of reactivity of dibromomethane has largely precluded its use as a carbenoid precursor in the Simmons Smith reaction, although it is both less expensive and easier to purify than methylene iodide. It has been found however, that by sonication of the heterogeneous reaction mixture[111] or by the addition of a small amount of titanium tetrachloride[112] or acetyl chloride,[113] the cyclopropanation using dibromomethane is markedly promoted. Simple alkenes can thus give cyclopropanes in yields as good or better than the simple Simmons Smith reaction involving methylene iodide (table 2). The authors propose that the function both of acetyl chloride and titanium tetrachloride is the liberation of HCl on reacting with traces of water.

yields (%) of cyclopropanes in the Simmons Smith reaction with CH_2X_2 and Zn-Cu					
alkene	CH_2I_2 not promoted	CH_2Br_2 not promoted	CH_2Br_2 sonication	CH_2Br_2 $TiCl_4$	CH_2Br_2 MeCOCl
1-octene	48	18	28	48	61
cyclohexene	57	38	60	58	61
cyclooctene	58	28	72	73	88

table 2

In a comparison of chloromethyl and iodomethyl zinc carbenoid reagents, Denmark has found that the former, derived from chloroiodomethane is generally the most reactive species.[114]

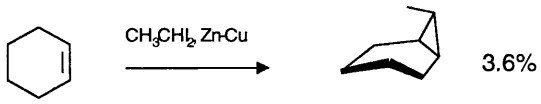
NMR spectra of the solution state reagents formed indicated that each gave rise to a different organometallic species (scheme 64).



equiv CH_2IX	X	yield
4	Cl	94%
2	I	12%

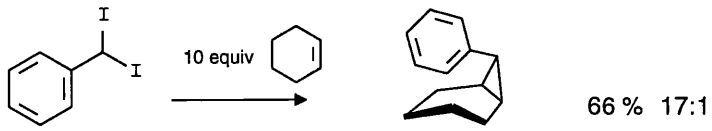
scheme 64

The use of other geminal dihalides with activated zinc was first investigated by Simmons and Smith themselves. They found that in the presence of zinc copper couple, a solution of 1,1-diiodoethane in cyclohexene could be used to generate methyl cyclopropanes in low yields (scheme 65).[115]



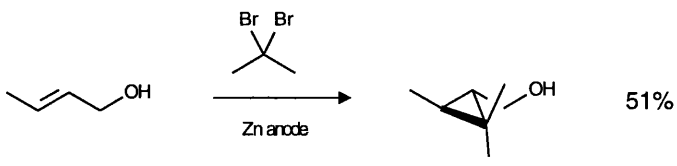
scheme 65

Since then although the use of *geminal* diodo compounds and zinc as Simmons Smith type precursors to functionalised cyclopropanes has been investigated,[101] their use has not become widespread. Furakawa showed that yields of cyclopropanes from diiodoalkanes could be enhanced by the use of diethylzinc. Reaction of 1,1-diiodoethane and diethylzinc with cyclohexene gave methylnorcarane in a yield of 66% based on cyclohexene. Similarly, benzaliodide gave 7-phenylnorcarane in 64% yield, predominately as the *cis* isomer (scheme 66).



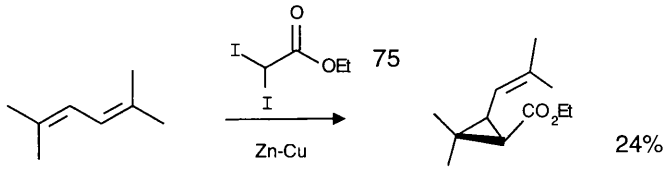
scheme 66

Recently, an efficient synthesis of dimethylcyclopropanes from 2,2-dibromopropane derived zinc carbenoids has been achieved in an electrolysis cell fitted with a sacrificial zinc anode.[116,117] Other examples of the use of electrolysis to propagate Simmons Smith type reactions have also been published (scheme 67).[118]



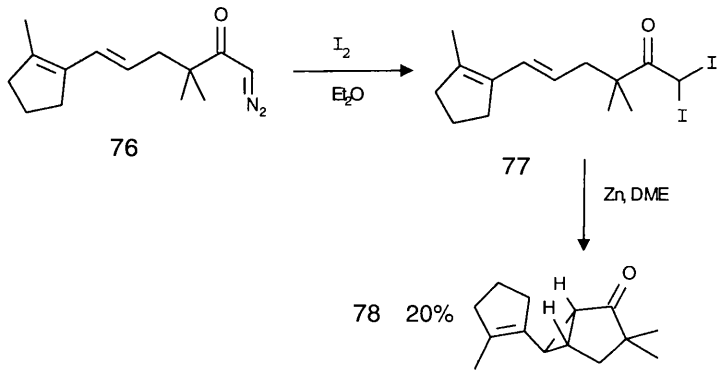
scheme 67

The Simmons Smith like cyclopropanation involving ethyl diiodoacetate **75** and zinc copper couple has also been performed successfully. Under these conditions 1,1,4,4-tetramethylbutadiene gave the corresponding vinyl cyclopropane in 24% yield (scheme 68).[119]



scheme 68

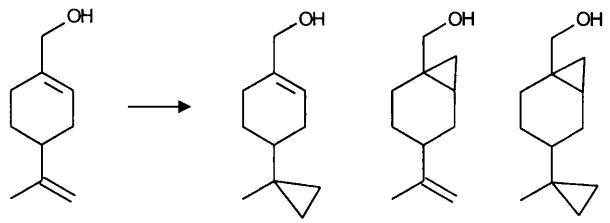
As part of a strategy towards the linearly fused sesquiterpene hirsutene, Hudlicky used a similar α,α-diiodo ketone **77** (scheme 69). The geminal diiodide was generated *in situ* by the reaction of iodine with the diazo ester **76** and the cyclopropanation was effected using zinc dust in DME. Although the yield was only moderate, the reaction is important in that it represents, to date, the only published example of an intramolecular Simmons Smith type procedure.[120]



scheme 69

Simmons Smith Related Cyclopropanation With Other Metals

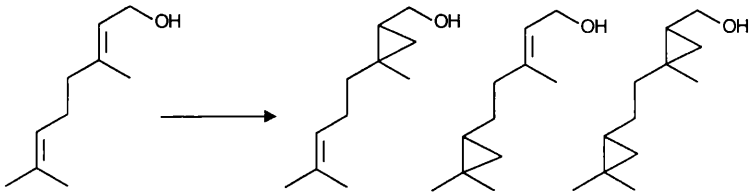
Treatment of alkenes with trialkyl aluminium and methylene iodide produces the corresponding cyclopropanes[121] stereospecifically and usually free from serious side reactions as is the case with the Simmons Smith reagent. This methodology however, exhibits a remarkable regioselectivity which is complimentary to that observed in the Simmons Smith reaction and its variants. Multiply unsaturated allylic alcohols for example undergo chemoselective cyclopropanation selectively at the olefinic site remote from the hydroxyl group (scheme 70).



% Yield:				
	1 equiv $^{i}Bu_3Al$ / CH_2I_2	79	0	0
	2 equiv Et_2Zn / CH_2I_2	3	49	8

scheme 70

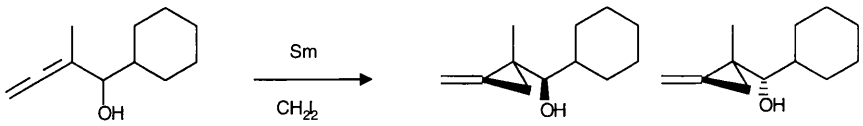
Methylene carbenoids are readily generated from the reaction of samarium metal with methylene iodide. The samarium reagent generated also exhibits very high regioselectivity. Like the Simmons Smith reagent, the samarium methylene carbenoid will preferentially cyclopropanate allylic alcohols.[122,123]



		yield %		
1 equiv	$^{i}Bu_3Al$ / CH_2I_2	0	76	0
2 equiv	Et_2Zn / CH_2I_2	74	2	3
4 equiv	Sm(Hg) / CH_2ICl	98	0	0

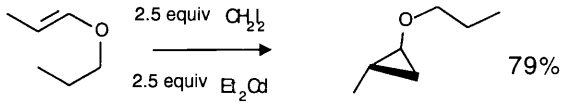
scheme 71

The directing effect of proximal oxygens is especially pronounced for samarium carbenoids. Neither simple alkenes nor double bonds separated from the hydroxyl group by more than 2 carbons appear to undergo cyclopropanation with samarium carbenoids. The extent of diastereoselectivity observed in the samarium based cyclopropanation of allylic alcohols is comparable to or higher than that found under Simmons Smith conditions.[124,125] For example, by exploiting the chemoselectivity of this reagent, highly substituted alkylidene cyclopropanes can easily be accessed *via* a regioselective cyclopropanation of α-allenic alcohols (scheme 72).[125]



66% 8 : 1
scheme 72

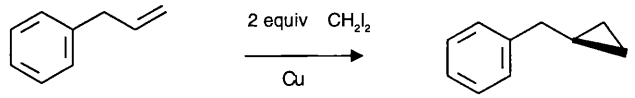
Methylene cyclopropanation has also been successful using organocadmium carbenoids. The reaction of methylene iodide with diethylcadmium was found to give an organocadmium reagent which could cyclopropanate electron rich alkenes.[127]



scheme 73

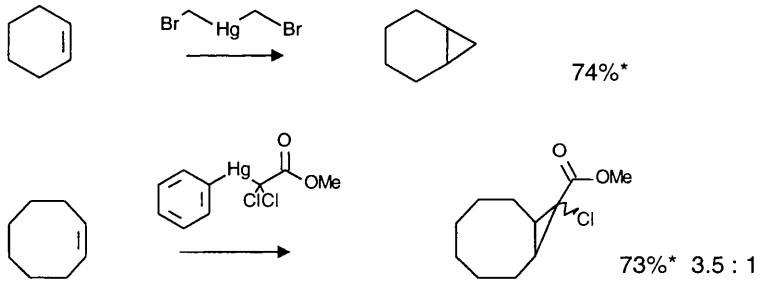
An organocopper reagent capable of transferring methylene to olefinc double bonds has been generated from methylene iodide and copper powder.[127] The treatment of the copper with iodine prior to the reaction is essential to the reactivity of the system. The reactivity of this reagent towards alkenes is similar to that of the Simmons Smith reagent, in that it gives

cyclopropanation of electron rich double bonds in preference to electron deficient ones. As in the Simmons Smith reaction, cyclopropanation is also stereochemically controlled by appropriately positioned oxygen functionality.



scheme 74

Organomercury compounds such as ICH_2HgI and $Hg(CH_2Br)_2$ may be prepared by the reaction of metallic mercury (II) salts with diazoalkanes. These mercury derivatives are similar to the intermediates that have been considered for the Simmons Smith reaction, and likewise they have been found to cyclopropanate alkenes (scheme 75).[129] Similarly, phenyl(dichloro-carbomethoxy)mercury can be prepared by the reaction of phenylmercuric chloride and methyl dichloroacetate. Cyclopropanation of an excess of cyclooctene with $PhHgCCl_2CO_2Me$ however, requires eleven days refluxing in chlorobenzene to afford the chlorocyclopropane (scheme 75).[130]



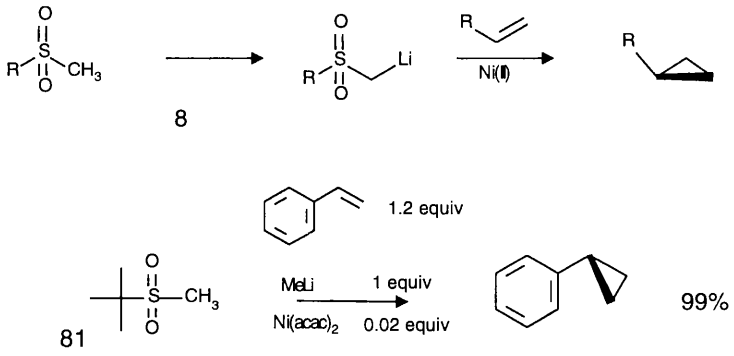
* relative to organomercury compound

scheme 75

1.5 Miscellaneous Cyclopropanating Reagents

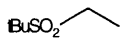
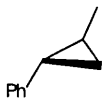
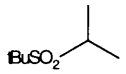
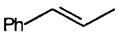
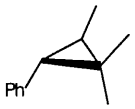
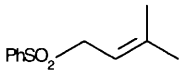
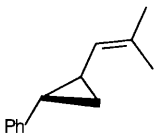
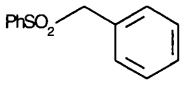
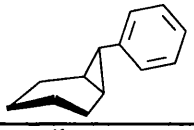
Cyclopropanation *via* α-Lithiated Sulfones

Lithiated alkyl sulfones can convert alkenes to cyclopropanes in the presence of Nickel catalysts. The facile deprotonation of the α-hydrogen generates a carbenoid species **80** which can effectively cyclopropanate electron rich alkenes.[131] Thus, styrene may be cyclopropanated in 99% yield relative to *tert*-butylmethylsulfone **8** (scheme 76).



scheme 76

With a primary alkyl sulfones (entry 1), the major product was the *trans* cyclopropane. A similar diastereoselectivity was observed for the reaction of allyl lithiated sulfones and benzyl lithiated sulfones (entries 3 and 4), with both substrates producing cyclopropanes in reasonable yields (table 3).

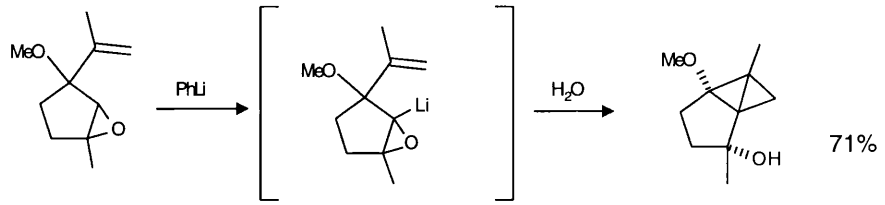
	sulfone	alkene	(equiv)	product	yield*	*trans / cis*
1			1.2		60%	5 : 4
2			5		31%	-
3			1.2		21%	5 : 1
4			10		22%	99 : 1

* relative to sulfone

table 3

Epoxides as Carbenoid Precursors for Intramolecular Cyclopropanation

The reaction of a lithium base and an epoxide has been shown to produce a carbenoid species which may undergo intramolecular cyclopropanation.[132] Thus the action of phenyl lithium on the cyclopentene oxide **82** produces a lithiated epoxide 83. This carbenoid will undergo stereospecific intramolecular cyclopropanation of the β-double bond to afford the highly strained tricyclo[4.1.0.$0^{2,6}$]heptane84.[132b]

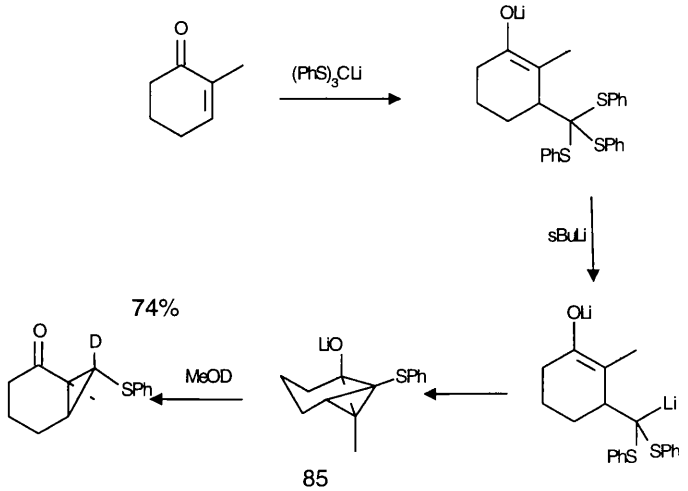


82 83 84

scheme 77

Cyclopropanation *via* Lithiated Trisulphides

Cyclopropanation of α,β-unsaturated ketones with "carbon trisulphide anions" and butyl lithium has been achieved *via* a stepwise sequence (scheme 78).



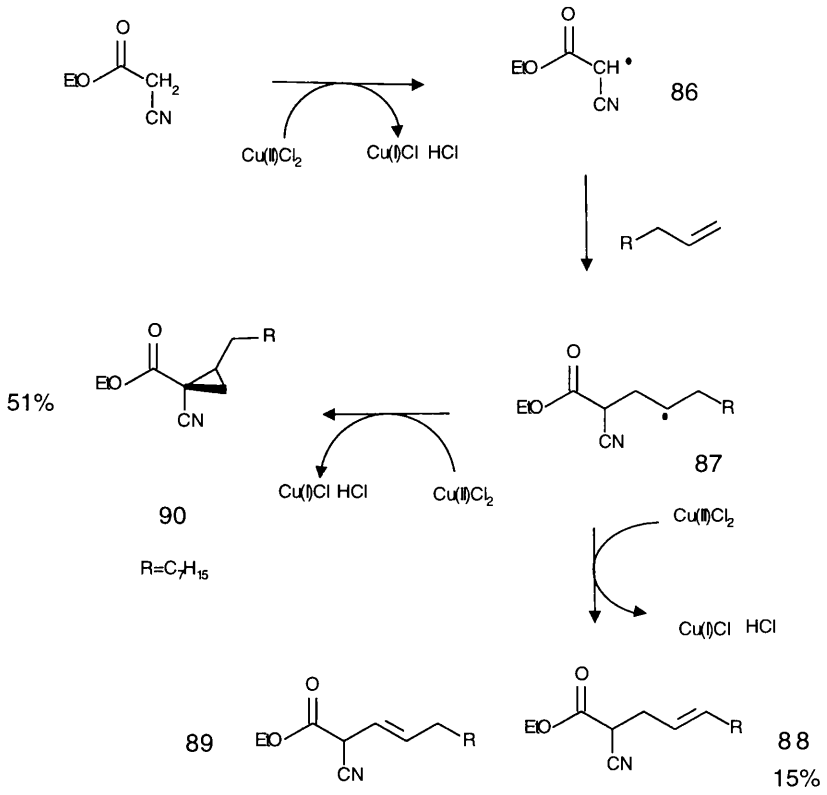
85

scheme 78

Sequential treatment of α,β-unsaturated ketones with $(PhS)_3CLi$ and a lithium base generates a cyclopropyl intermediate that may be electrophilically quenched to produce phenylthiocyclopropanes.[133] It is unclear as to the exact mechanism of ring closure, but it is postulated that intramolecular cyclopropanation with the lithiated thioacetal intermediate **85** may occur.

Cyclopropanation of Electron Rich Alkenes with Ethylcyanoacetate

In an interesting use of organocopper chemistry, Julia has shown that ethyl cyanoacetate and copper(II) chloride can cyclopropanate electron rich alkenes. It is understood that the copper reacts as a one electron oxidant to generate the intermediate free radical species **86.** In the presence of an alkene the free radical can then react intermolecularly to form the alkyl radical **87** which, on reaction with a further equivalent of copper(II) can form the carbocation and hence the alkenes **88** and **89** or the cyclopropane product **90** (scheme 79).[134]



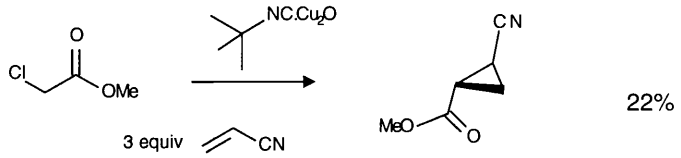
scheme 79

If the alkene is dec-1-ene, then the total formation of the alkene by-products amounts to 15%. Where there is no possibility of such a pathway, for example in the cyclopropanation of styrene the yield of cyclopropane is 66%. Cyclopropanes can also be generated from diethylmalonate although in lower yields.

The Cyclopropanation of Electron Poor Alkenes by means of Copper-Isonitrile Complexes

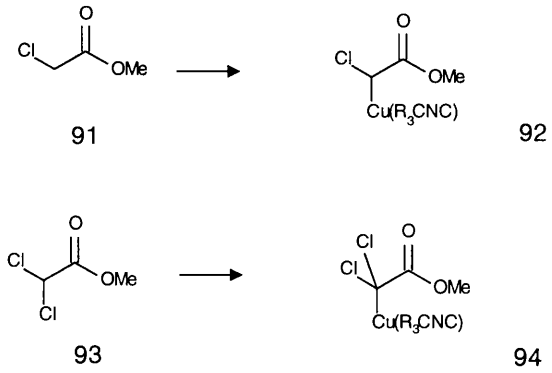
Copper(I)oxide-isonitrile and copper(0)-isonitrile systems will react with active methylene compounds and the resulting organocopper carbenoid intermediates can be trapped with electron deficient alkenes to make cyclopropanes.[135]

For example, copper(I)oxide-isonitrile complexes can react with α-dihaloacetates or α,α–dihaloacetates and acetonitriles to afford copper carbenoids which can be trapped by electron poor alkenes such as acrylonitriles to form cyclopropanes (scheme 80).[135a] The cyclopropane synthesis is stereoselective, with only the *trans* cyclopropane produced.



scheme 80

The cyclopropanation may be explained by the formation of the α-halomethylcopper(I)-isonitrile intermediate **92** and this species' subsequent addition to an alkene. In the case of the α,α-dihaloacetate **93**, the corresponding intermediate copper carbenoid **94** is produced and reaction with an electron deficient alkene affords the corresponding chlorocyclopropane. [135c]

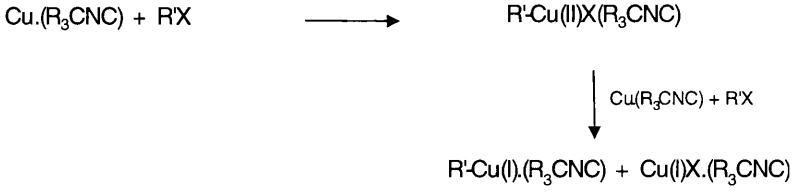


91 92

93 94

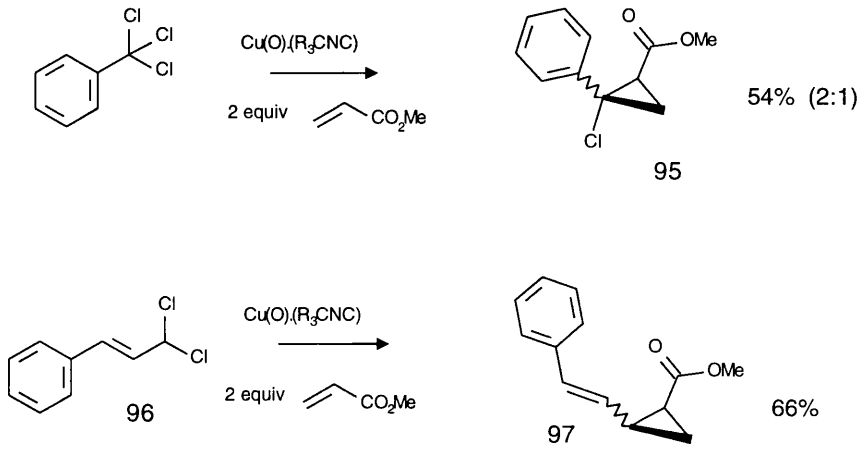
scheme 81

Similar active methylene compounds will react with copper(0)-isonitrile complexes to produce organocopper compounds in which an oxidative addition of the carbon-halogen bond followed by reduction of organocopper (II) to organocopper (I) would be involved (scheme 82).



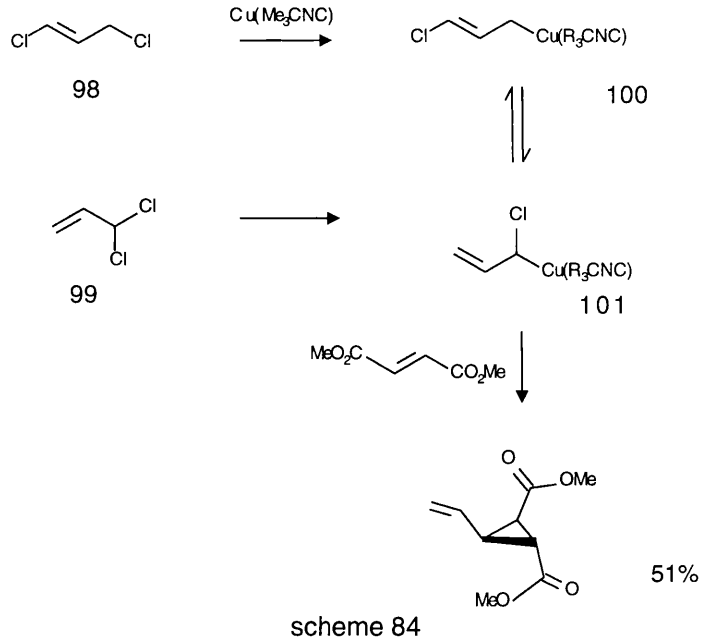
scheme 82

Thus, when a mixture of metallic copper and isonitrile was treated with trichlorotoluene and methyl acrylate, the cyclopropane **95** was produced in 54% yield. Similarly, the vinyl cyclopropane **97** was produced by treating the copper(0)-isonitrile complex with the phenylallylidene dichloride **96** and methyl acrylate (scheme 83)



scheme 83

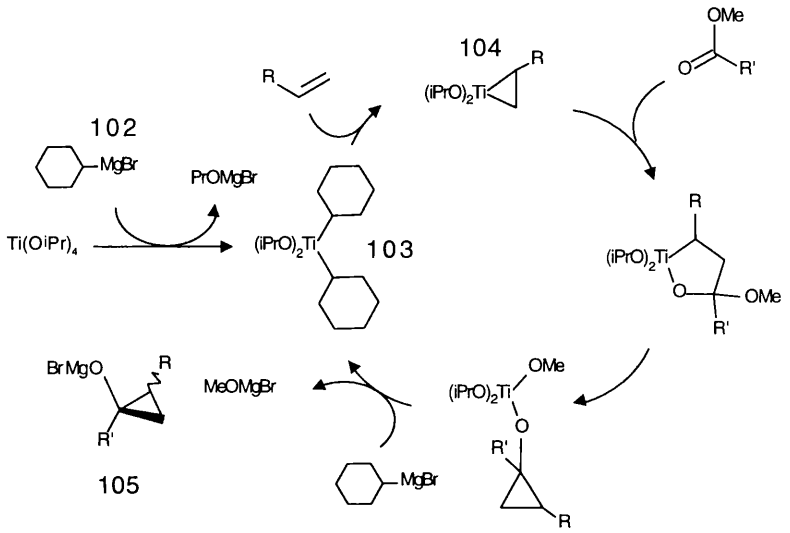
It is noteworthy that the reaction of 1,3-dichloropropene **98** with an α,β-unsaturated ester gives the same products in almost the same yields as those produced in the reaction with allylidene dichloride **99**.[135b] As a common reaction intermediate, the 1-chloro-2-propenylcopper-isonitrile complex **101** is proposed (scheme 84). The 3-chloro-2-propenylcopper-isonitrile complex **100** is probably formed initially but then isomerises to the same copper carbenoid intermediate **101** as is produced directly from allylidene dichloride **99**.



scheme 84

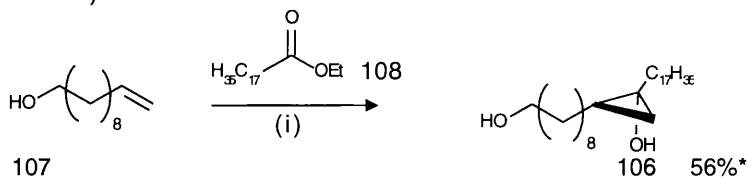
The Synthesis of Cyclopropanols *via* Titanium-Dialkane Complexes

A general approach to the synthesis of 1,2-disubstituted cyclopropanols by the reaction of esters with alkylmagnesium halides in the presence of $Ti(OiPr)_4$ has recently been discovered by Kulinkovich.[136] This exciting new chemistry takes advantage of the reaction between Gignard reagents such as cyclohexylmagnesium bromide **102** and $Ti(OiPr)_4$ which generates an organotitanium intermediate such as **103** (scheme 85). Reaction of the organotitanium species with an alkene generates a titanocycle **104** which can react with an ester to generate an oxycyclopropane **105** as shown. The reaction is catalytic in titanium.[136]



scheme 85

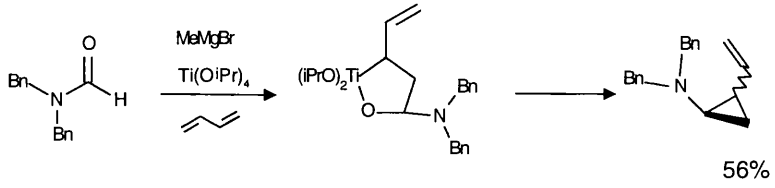
Thus Kulinkovich was able to prepare the hydroxycylopropane **106** by the reaction of 10-undecen-1-ol **107** with ethyl stearate **108** with six equivalents of cyclohexylmagnesium bromide and $Ti(O^iPr)_4$ (scheme 86).[137]



i). $Ti(O^iPr)_4$ (1 equiv), cyclohexylmagnesiumbromide (6 equiv), Et_2O
* based on 107

scheme 86

Amides will also react stoechiometrically with similar organotitanium intermediates to generate aminocyclopropanes as exemplified in scheme 87.[138]



scheme 87

1.6. Conclusions

The cyclopropanation of alkenes is an important synthetic transformation and rightly continues to be the focus of substantial research. The foregoing overview has attempted to loosely group the main areas of this chemistry and in particular to place emphasis on the categories of precursors commonly used in cyclopropanation.

A wide range of such precursors are available with which the synthetic chemist may effect cyclopropanation. In the most part these are carbene or carbenoid species, many of which are transient intermediates the exact structure of which remains unknown. At the same time a large and distinguished body of work has been accumulated in which ylides and related compounds are exploited in cyclopropanation.

Nevertheless, scope still exists for the generation of new reagents which can cyclopropanate alkenes. In modern organic chemistry new emphasis is now placed on developing cyclopropanation methodologies employing only cheap, non toxic and environmentally sensitive reagents.

2. Results and Discussion

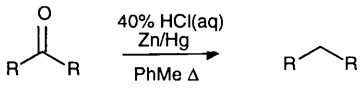
2.1. The Development of Methods for the Generation of Organozinc Carbenoids from Carbonyl Compounds

The foregoing review has hopefully provided some useful indications of the more commonly used methods for cyclopropane construction using carbenoids and highlighted the wide variety of metals and precursor reagents which are currently employed.

Before proceeding to the research carried out in the present thesis it is also however appropriate to set the stage by describing the evolution of the chemistry of organozinc carbenoids within our own group.

2.1.1. The Clemmensen Reduction of Carbonyl Compounds

The Clemmensen reduction of a carbonyl group to a methylene CH_2 is one of the most familiar reactions in organic chemistry (scheme 88). Since its discovery by Clemmensen[139] over 85 years ago, the original biphasic procedure involving amalgamated zinc and 40% aqueous hydrochloric acid has undergone considerable modification. Today's common procedures are suited to the reduction of highly functionalised compounds that would have proved exceedingly labile under the original conditions of Clemmensen's reaction.[140]



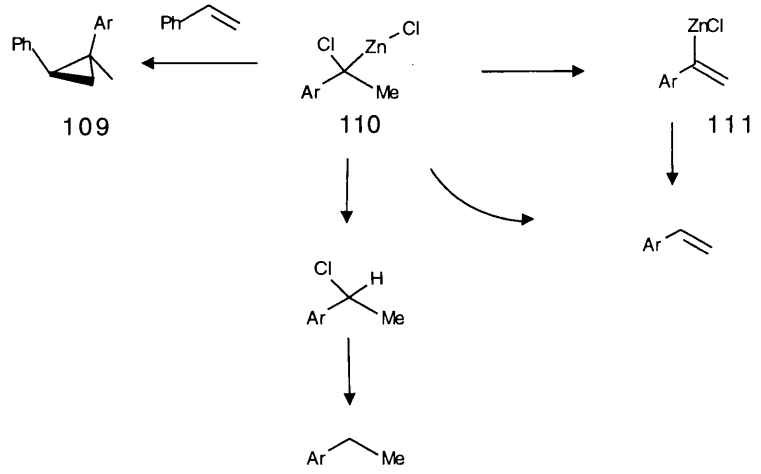
scheme 88

In early work Clemmensen had noted that the reduction of acetophenone in dilute acid gave styrene rather than ethyl benzene. The possible intermediacy of a zinc carbenoid however, was not considered and the assumption was that the alkene was in fact formed *via* the elimination of water in the acidic medium, rather than by the α-insertion of the carbenoid.[141]

One of the first detailed studies into the mechanism of the Clemmensen reduction was performed by Brewster.[142] He proposed that reduction of the carbonyl group took place following chemisorption of the aldehyde or ketone onto the zinc surface followed by delivery of two electrons and the formation of a covalently bonded organozinc species. Later work by Nakabayashi[143] supported this proposal concluding that reduction was a stepwise process, involving the generation of organozinc intermediates. As alcohols are not generally reduced under Clemmensen conditions Brewster suggested that free alcohols were not in fact intermediates in the Clemmensen reduction. In Nakabayashi's study, quenching the reduction of acetophenone after five minutes revealed a complex mixture including saturated, unsaturated and rearranged hydrocarbons, alcohols and pinacol derived coupling products. Experimental and kinetic data suggested that the rate determining step required zinc, chloride ion and the carbonyl group. Nakabayashi also noted that the formation of pinacols, the products of one

electron reduction, increases with decreasing zinc concentration in the amalgam used. At very low zinc concentrations this process predominates and he argued that the synthesis of pinacols was occurring *via* a separate pathway to the formation of alkanes.[143] It is worth noting that the Clemmensen reduction works only with zinc and not with other metals of similar redox potential.[143]

A more recent study by Burdon provides overwhelming evidence for the presence of zinc carbenoids in the Clemmensen reduction.[144] The reaction of 2- and 4-substituted acetophenones in 50% ethanolic hydrogen chloride gave the expected reduced alkanes along with styrenes and the self coupled cyclopropanes. In the presence of added styrene, *p*-bromoacetophenone gave primarily the cross-coupled cyclopropane **109** with drastic reductions in the yields of other carbenoid or Clemmensen products. Burdon proposed that all the products are derived from a zinc carbenoid intermediate **110** (scheme 89).

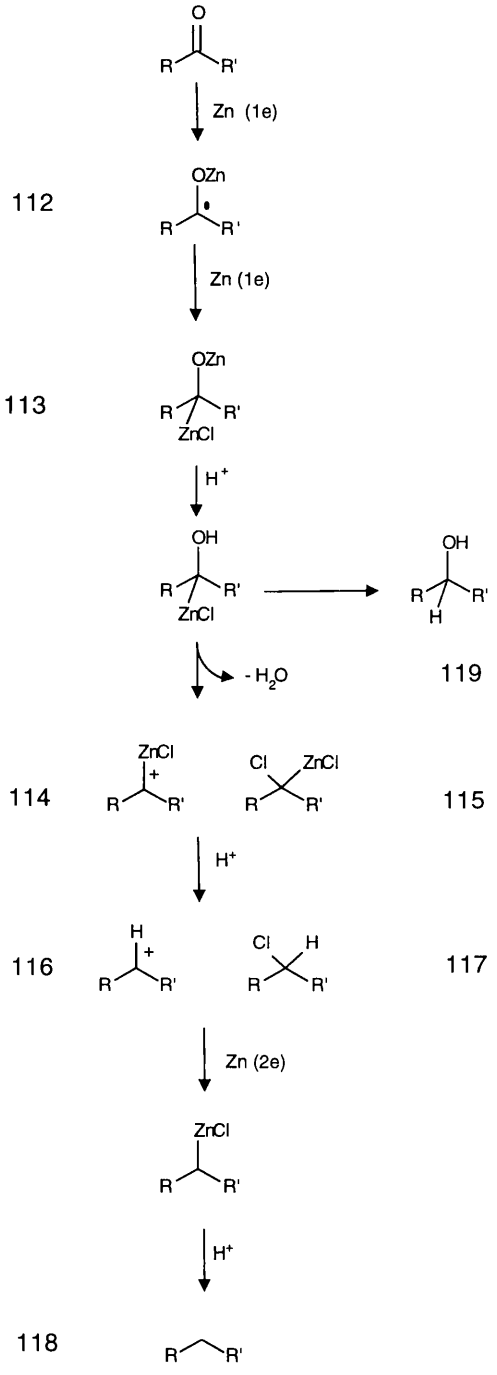


scheme 89

The utilisation of deuterated acetophenones identified a second mechanism for the production of styrenes *via* a proton loss from the zinc carbenoid **110** and subsequent quenching of the vinyl zinc intermediate **111**. Burdon suggests that the carbenoid is formed at the surface of the zinc particulates and is not homogenous in solution like the intermediates identified for the Simmons Smith reaction (*vide supra* 1.4).

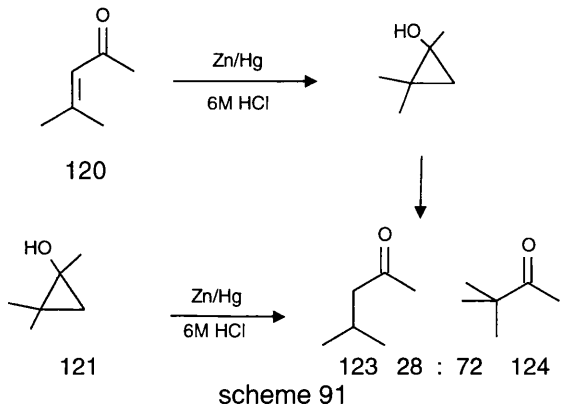
It was postulated that the formation of the zinc carbenoid occurs *via* sequential one electron reduction of the carbonyl at the zinc surface with initial formation of a zinc oxygen bond to generate the zinc bound radical species **112** (scheme 91). Further one electron donation will afford the chloro-zinc alkoxide species **113.** Protonation of the alkoxide and elimination of water affords a zinc-stabilised carbonium ion **114**, an intermediate which may also be represented as an organozinc carbenoid **115** If the carbenoid itself is subsequently protonated, the result is either the carbonium ion **116** or the chloroalkane **117.** In either case, further two electron

reduction by zinc and subsequent protonation will afford the methylene product **118**. Formation of the alcohol **119** was suggested to be merely the product of a minor side reaction.



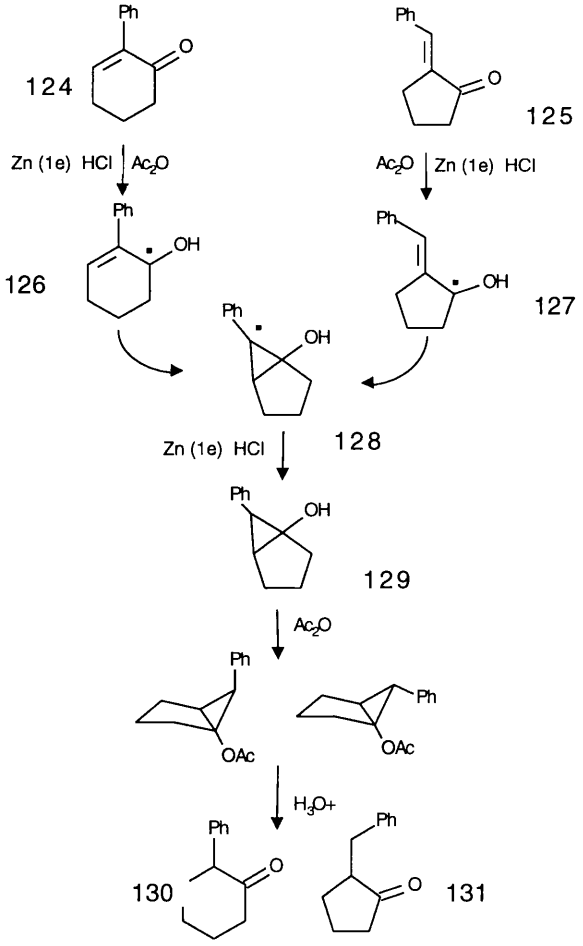
scheme 91

Strong evidence for initial one electron reduction was also provided by Davis and Woodgate who demonstrated that under Clemmensen conditions both 4-methylpent-3-ene-2-one **120** and 1,2,2-trimethylcyclopropanol **121** would generate an identical mixture of 3,3-dimethylbutan-2-one **122** and 4-methylpentan-2-one **123** (scheme 91).[145]



scheme 91

Similar evidence of one electron reduction was obtained by Elphimoff-Felkin who examined the behaviour of two α,β–unsaturated ketones which could be expected to undergo reduction *via* identical cyclopropanol intermediates.[146] The latter could be isolated from the reaction as their acetates by trapping with acetic anhydride, or subjected to solvolytic proton catalysed rearrangement to give the final product ketones **130** and **131** (scheme 92).



ketone:	**124**	**125**
yield (%):	87	13
	35	65

scheme 92

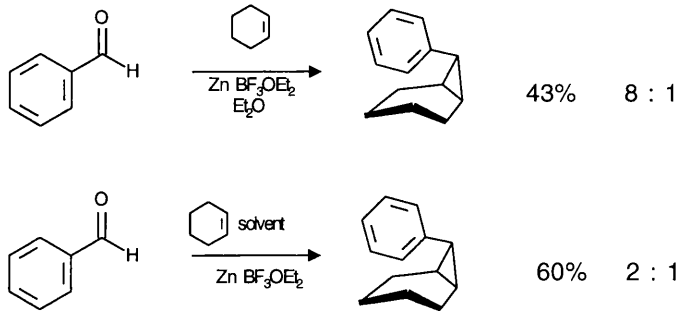
In a large study of various β phenyl enones, all were subjected to similar reducing conditions and in all cases a cyclopropanol acetate was isolated. The mechanism involves one electron reduction of the enone to form the radical species **126** and **127.** which with α,β-unsaturated carbonyls will undergo electrocyclic ring closure to give the benzylic cyclopropyl radical **128** Further reduction of the benzylic radical produced followed by protonation generates the cyclopropanol **129.**

2.1.2. The Controlled Generation of Organozinc Carbenoids from Carbonyl Compounds

Although it has become accepted that the Clemmensen reduction occurs *via* a zinc carbenoid, classical carbenoid reactivity is not routinely observed since the vigorous reaction conditions are also ideal for further protonation and two electron reduction to afford the methylene CH_2 group. In order to exploit the carbenoid synthetically, alternative reaction conditions are required which preclude these later steps.

2.1.2.1. The Generation of Organozinc Carbenoids from Arylaldehydes with Zinc and Boron Trifluoride Diethyletherate

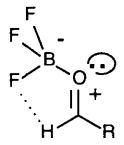
Two conceptually similar solutions both involving replacement of the proton have evolved. In the first of these reported by Elphimoff-Felkin in 1969,[215,147] the use of boron trifluoride diethyletherate as an electrophile in the presence of zinc allowed the carbenoid from benzaldehyde to be trapped by an alkene to give cyclopropanes (scheme 93). In the examples studied, whilst yields were moderate a notable feature was that cyclic alkenes gave the more hindered *cis* isomer preferentially. It was later to be shown by Burdon[144] that trapping of the carbenoids generated under Clemmensen conditions would similarly afford the *cis* cyclopropane as the major product.



scheme 93

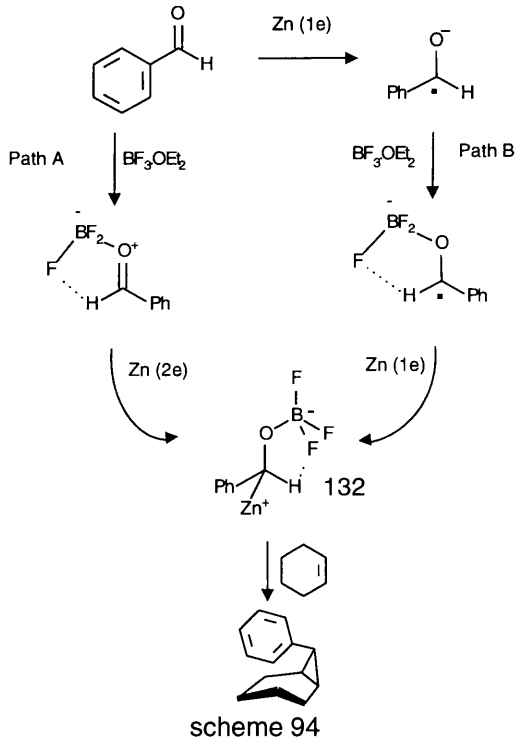
Also significant is that the use of cyclohexene as the reaction solvent gave a significant increase in yield. Since the Lewis acidity of boron trifluoride is significantly increased by the loss of the diethyl ether ligand it is possible to attribute the increase in yield to this, since the boron would be likely to be continually co-ordinated in ethereal solvent. This rationale is supported by the recent suggestion by Corey[148] that complexation of boron trifluoride to aldehydes is a far more favourable process than previously thought. Corey re-examined existing X-ray structures

and observed that in many cases there was an exceedingly short formyl H-F distance, postulating that there exists a C-H-F hydrogen bond. This suggestion was later quantified by molecular orbital calculations, as a result of which it was concluded that their also exists a substantial degree of anomeric overlap between the non-bonding oxygen lone pair and the σ* antibonding orbital of the C-H bond in the complex **131**.[149] Clearly, this will affect the reduction potential of the aldehyde.



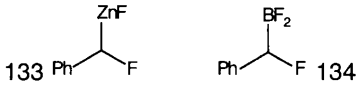
131

Whatever the exact nature of the interaction, it seems unlikely that the aldehyde will not be co-ordinated by the oxophilic boron especially in the cyclohexene system. Consequently, it is possible that Elphimoff-Felkin was accurate in the assumption that initial reduction of the aldehyde occurs *via* direct two-electron transfer (scheme 94).[215]



scheme 94

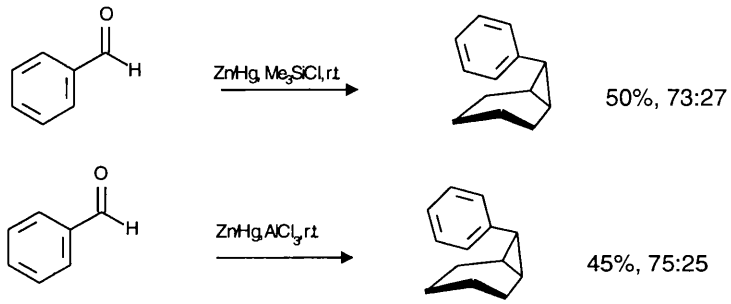
The authors suggest that the generation of the carbenoid can occur *via* direct two electron donation once the boron trifluoride has co-ordinated to the aldehyde (path A). Alternatively, and analogously to the mechanism of the Clemmensen reduction proposed by Burdon,[144] sequential transfer of two single electrons will provide the same zinc carbenoid **132** (path B). The structure of the active carbenoid is unknown and it is possible that if **132** itself is not the active species either the zinc carbenoid **133** or boron carbenoid **134** are involved.



The boron species **134** however, is considered as an unlikely candidate for the carbenoid intermediate as boron trifluoride diethyletherate is unable to catalyse the cyclopropanation of alkenes in the presence of diazomethane.[147] Furthermore, there are no literature examples of zinc fluoride catalysed carbenoid generation using diazocompounds, and indeed its applicability in such systems was not considered by Closs and Moss in their work on carbenoid generation from aryldiazomethanes and zinc halides (*vide supra* 1.4).[215]

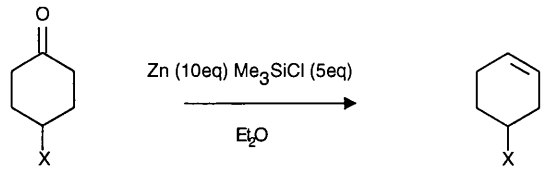
2.1.2.2 The Generation of Organozinc Carbenoids from Carbonyl Compounds using Zinc and Chlorotrimethylsilane

In their full paper in 1975, Elphimoff-Felkin and Sarda suggested that the use of metallic zinc and other oxophilic Lewis acids could generate carbenoids from benzaldehyde. They utilised both chlorotrimethylsilane and aluminium trichloride under the same reaction conditions to generate 7-phenylnorcarane in 50% and 45% yields respectively (scheme 95).[215]



scheme 95

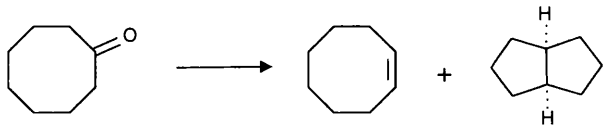
In 1973 Motherwell had also published in this area concerning the generation of organozinc carbenoids from alkyl ketones with chlorotrimethylsilane and zinc. He discovered that cyclohexanones could be converted to the corresponding cyclohexenes in good yields under these conditions and was able to rule out the intermediacy of silyl enol ethers from the reaction (scheme 96).[150] As in the Clemmensen reduction performed at low acid concentrations, alkene formation arises by α-insertion of the organozinc carbenoid into the adjacent C-H bond.



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

scheme 96

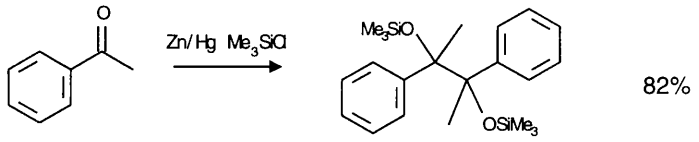
Particularly indicative of the intermediacy of a carbenoid species was the case of cyclooctanone which furnished not only *cis* cyclooctene, but also bicyclo[3.3.0]octane as a result of transannular insertion of the carbenoid (scheme 97).



2 : 1, 55% overall

scheme 97

Equally interesting was that the reaction of acetophenone provided the pinacolic product, 2,3-diphenyl-2,3-di(trimethylsilyloxy) butane **135** in 82% yield. This emphasises the similarity of the pathway to carbenoid generation with that proposed by Nakabayashi for the Clemmensen reduction (*vide supra* 2.1.1) (scheme 98).[143]

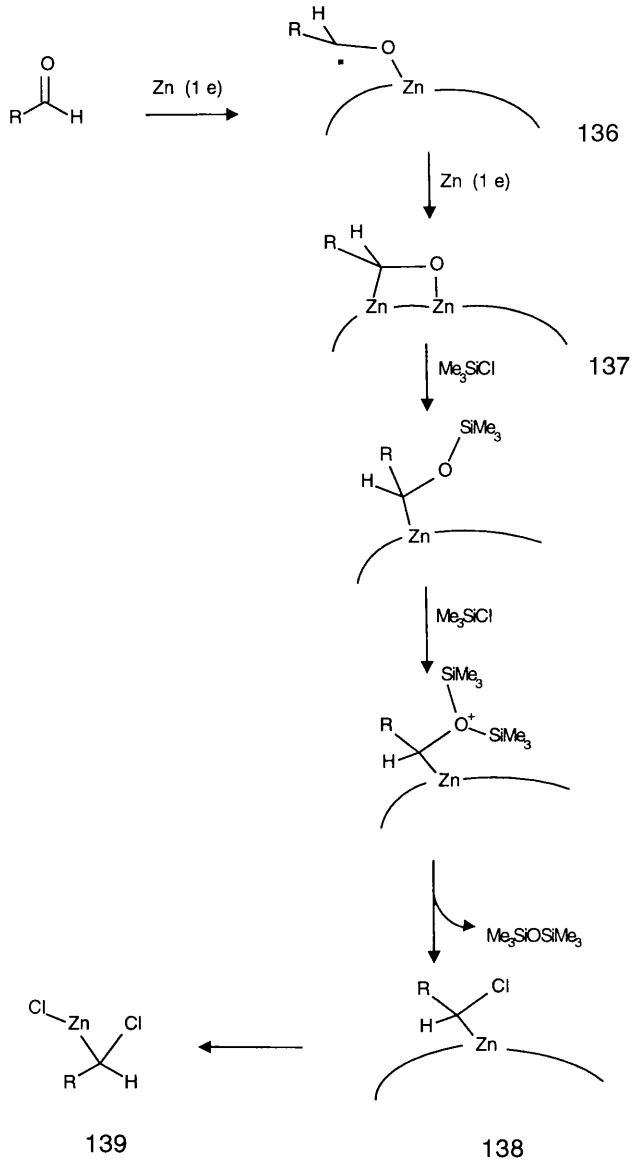


82%

135

scheme 98

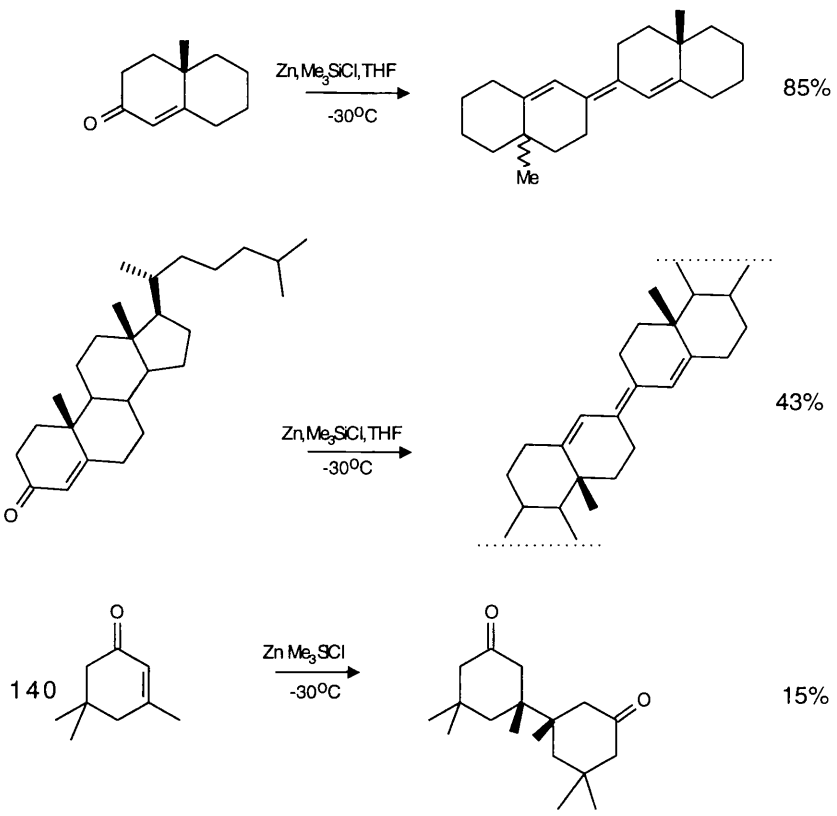
The formation of the organozinc carbenoid from a carbonyl in the presence of zinc and chlorotrimethylsilane will occur in a fashion similar to carbenoid formation in the presence of zinc and hydrochloric acid. Analogously to the mechanism proposed by Burdon[144] and Nakabayashi[143] for the Clemmensen reduction, the carbonyl may undergo one electron reduction at the zinc surface to generate the radical species **136** bound *via* the oxygen to zinc. A further electron donation from the zinc will generate an organozinc species **137**. The oxophilic chlorotrimethylsilane serves as a direct substitute for the proton in the mechanism of Clemmensen reduction. Two equivalents of chlorosilane are accordingly required to deoxygenate the carbonyl carbon, thus generating the surface bound, tetrahedral zinc type intermediate **138**. It was postulated by Burdon[144] that such a species could form a Fischer carbene-like zinc-carbon double bond, but there is no evidence for the formation of such a species in other zinc systems. It is also possible that the carbenoid could be dislodged from the zinc surface to form the homogenous species **139** exactly in accordance with the proposed mechanism of the Simmons Smith reaction with methylene iodide and solid zinc copper couple (*vide supra* 1.4).[98]



scheme 99

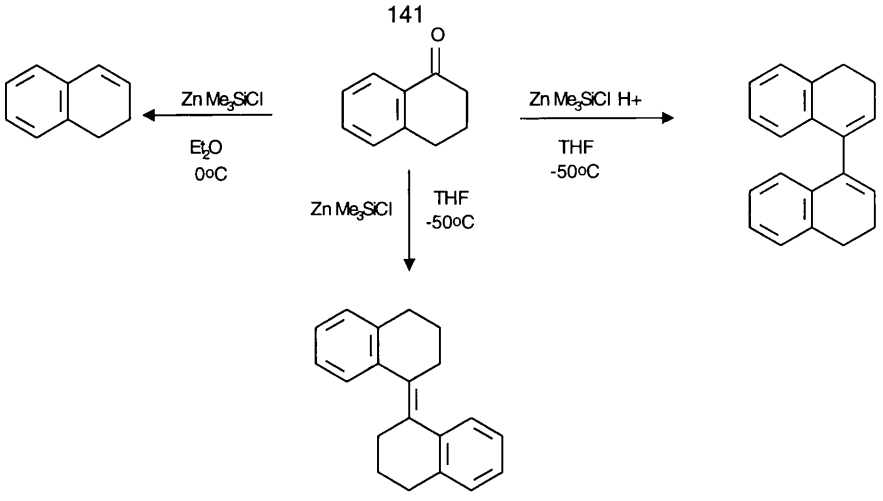
2.1.2.3. Dicarbonyl Coupling Reactions of Organozinc Carbenolds Generated using Chlorotrimethylsilane and Zinc

In their full paper of 1975, Elphimoff-Felkin and Sarda reported without comment that the reaction of benzaldehyde in the presence of zinc amalgam, chlorotrimethylsilane and no alkene produced stilbene.[147] Some years later Motherwell in collaboration with the group of Banerjee,[151] discovered that certain aryl and α,β-unsaturated carbonyl compounds could be induced to undergo a MacMurray-like coupling under Clemmensen conditions.[152] Although several coupling reactions could be achieved in very high yield using the chlorotrimethylsilane - zinc system, other substrates such as isophorone **140** yielded complex mixtures which included the product of one electron induced dimerisation at the β-carbon atom.



scheme 100

These results indicated that the coupling reactions were highly substrate specific and at the same time crucially influenced by the relative concentrations of substrate, reagents and the presence or absence of small amounts of hydrogen chloride.[151] The case of α-tetralone **141** where the reaction could be channelled to give unimolecular C-H insertion, pinacolic coupling followed by dehydration or dicarbonyl coupling is illustrative of these conclusions (scheme 101).

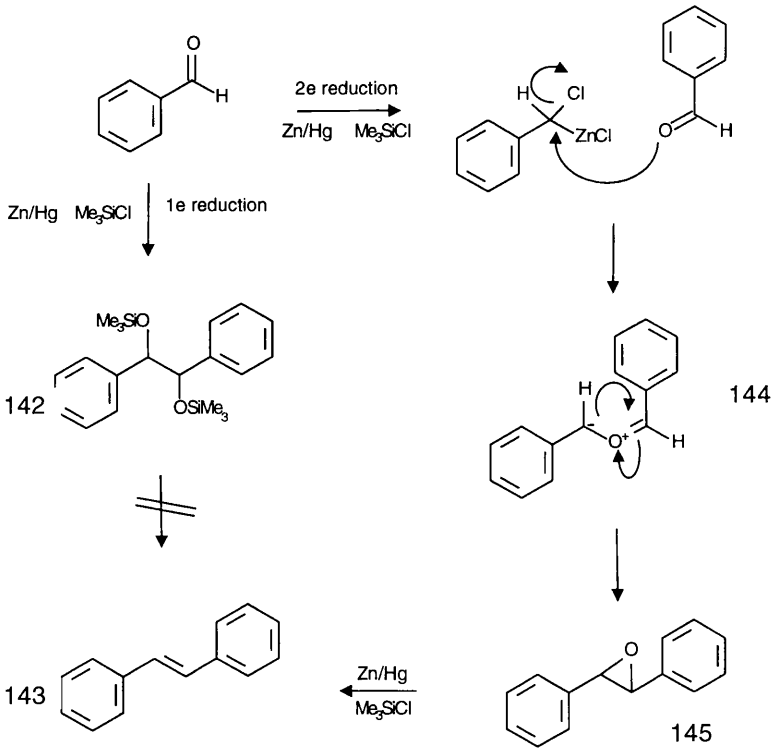


scheme 101

The zinc and silicon electrophile mediated coupling of carbonyl compounds has been shown to proceed *via* neither the pinacol product diol nor the diol derived bis-trimethylsilyl ether as these groups failed to yield alkenes when subjected to the reaction conditions.[152,153]

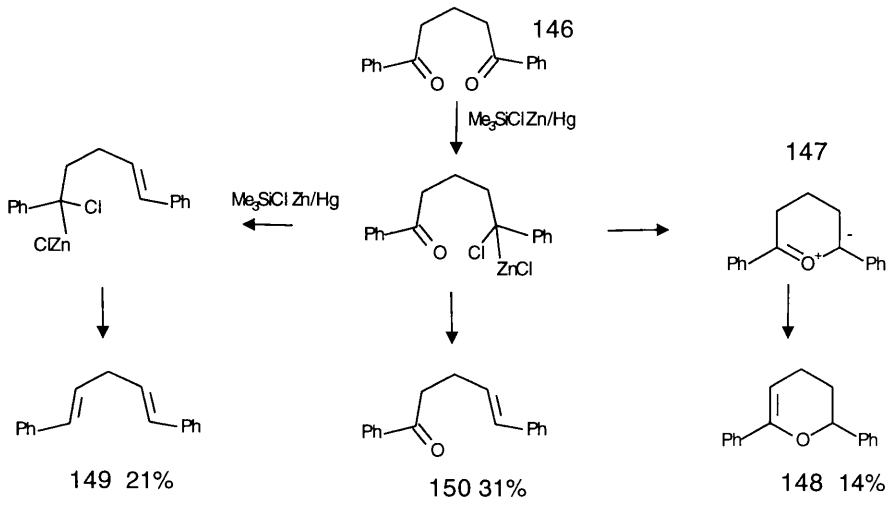
When benzaldehyde was used as a substrate a mixture of bistrimethylsilyl benzpinacol **142** (50%) and stilbene **143** (15%) had been isolated. When *trans*-stilbene oxide **144** was refluxed with zinc and chlorotrimethylsilane, alkene formation was also observed implying that the epoxide was a viable intermediate.[152,153]

It was later concluded that the mechanism for dicarbonyl coupling did indeed involve the generation of an epoxide intermediate. For the coupling of benzaldehyde the trapping of the zinc carbenoid species by a second molecule of the carbonyl compound affords an oxonium ylide intermediate **144**, which then closes to produce the stilbene oxide **145**. Carbonyl ylide formation is a classical reaction of metal carbenes and has been well documented.[79] The epoxide is further reduced under the reaction conditions to generate the alkene.[154]



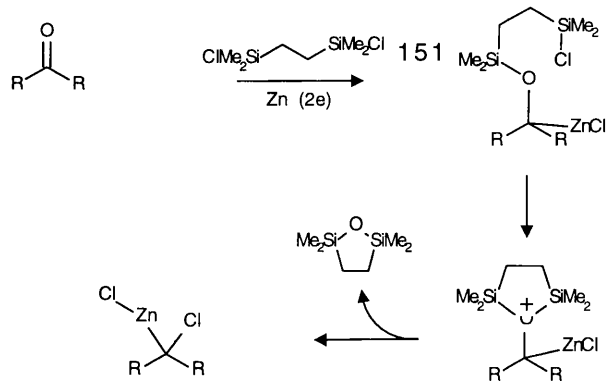
scheme 101

The intermediacy of the ylide in dicarbonyl coupling reactions was emphatically demonstrated by the case of the symmetric dicarbonyl precursor **146**. The result of the exposure of this diketone to zinc and chlorotrimethyl silane is the formation of a mixture of the dihydropyran **148** and the products of α-insertion, alkene **150** and diene **149**. Formation of the dihydropyran is rationalised as proceeding *via* the ylide **147**, which fails to close to the epoxide as a result of the benzylic nature of the substrate and the ring strain involved. (scheme 103)



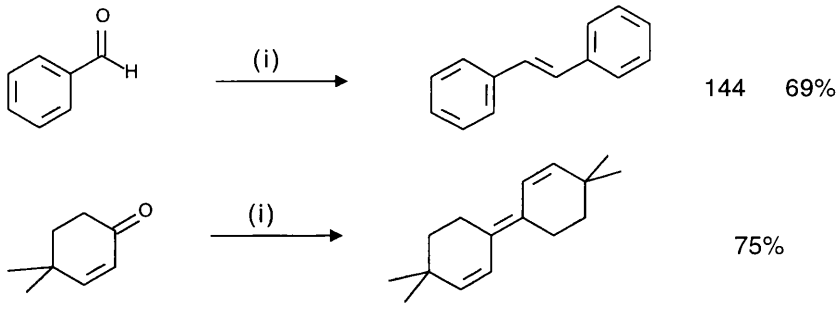
scheme 103

In many instances the pinacol coupling of the carbon centred siloxy radical was proving the dominant process and a method was sought to restrict the reaction *via* this pathway. It was reasoned that the solution might be simply to favour the delivery of a second electron and / or silicon electrophile over the pinacol coupling. Overall, formation of the carbenoid requires the delivery of two electrons and sequential attack of two silicon electrophiles. From this standpoint, an elegant but simple solution was devised, whereby the use of a bis-silicon electrophile would allow intramolecular delivery of the second silicon atom. Such a system should favour carbenoid formation over the intermolecular coupling reaction and as a consequence bis-(chlorodimethylsilyl)ethane **151** was selected as the electrophilic species. (scheme 104).[155]



scheme 104

The utilisation of this reagent in symmetrical dicarbonyl coupling led to a significant improvement in yields of alkenes[155] some examples of which are shown in scheme 105. The coupling of benzaldehyde is especially noteworthy, as the equivalent reaction in the presence of chlorotrimethylsilane afforded stilbene in only 15% yield.[151]



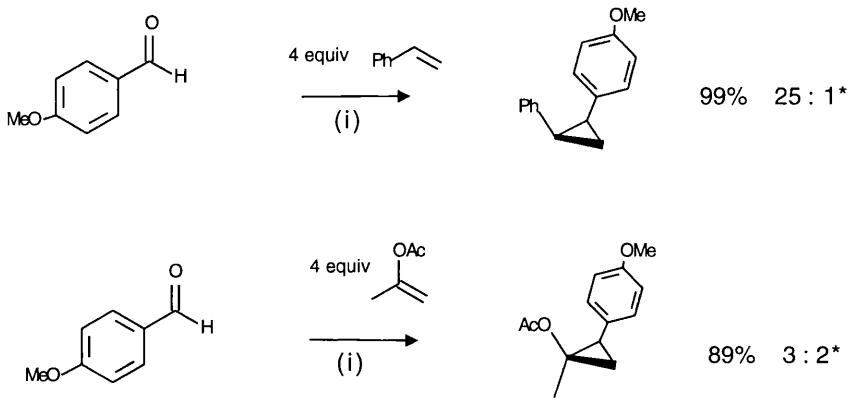
i). Zn/Hg, $ClMe_2SiCH_2CH_2SiMe_2Cl$, Et_2O

scheme 105

2.1.2.4 Cyclopropanation with Organozinc Carbenoids Generated using Zinc and Chlorotrimethylsilane

Having achieved good results in dicarbonyl coupling reactions with the bis-silicon electrophile, the focus within the Motherwell group turned to the application of the reagent in the intermolecular cyclopropanation of alkenes with carbenoids generation directly from carbonyls.

As earlier shown, the first controlled attempts at trapping an organozinc carbenoid with an alkene were made by Elphimoff Felkin and Sarda.[215,147] The authors had published a series of cyclopropanation reactions of a range of olefins with various *para*-substituted arylaldehydes.[147] A similar study was undertaken by Motherwell who found that simple alkenes could be readily cyclopropanated by the carbenoids derived from the reaction of arylaldehydes with zinc and chlorotrimethylsilane (scheme 106). As with the chemistry of Elphimoff-Felkin, the *cis* cyclopropanes were predominant.[156]

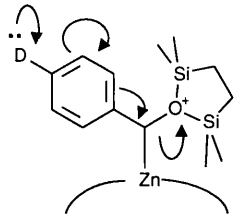


* major isomer

i). Zn/Hg, $ClMe_2SiCH_2CH_2SiMe_2Cl$, Et_2O

scheme 106

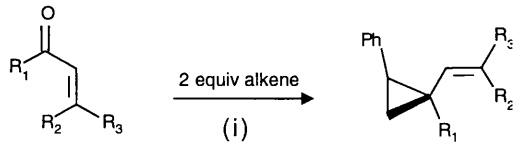
The virtually quantitative yields obtained for cyclopropanes derived from anisaldehyde are particularly noteworthy. Clearly, as the mechanism is understood an electron donating substituent such as the methoxy group in the 4-position of the arylaldehyde will promote expulsion of the siloxane leaving group as shown in scheme 107.



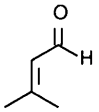
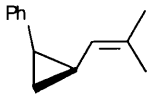
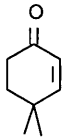
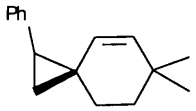
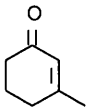
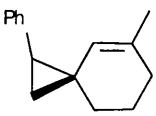
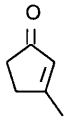
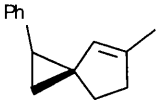
scheme 107

Similar arylaldehydes were screened for their effectiveness in the cyclopropanation of electron poor alkenes such as acrylonitrile, ethylacrylate, phenylvinylsulfone, maleic anhydride or diethylvinyl phosphate. All failed to provide any evidence for the formation of the corresponding cyclopropane adducts.[204]

The behaviour of non aromatic α,β-unsaturated organozinc carbenoids in cyclopropanation reactions has also been investigated within the Motherwell group[157,204] This proved a particularly interesting exercise as conventional wisdom relating both to the isolation of cyclopropanol acetates by Elphimoff-Felkin,[146] and to reductive ring contractions observed under Clemmensen conditions[145] suggests that carbenoid reactivity should not be observable. As shown below (table 4) this is clearly not the case with zinc carbenoids generated *via* the silicon electrophile method and in fact a useful range of cyclic and acyclic enones and enals may be trapped.



i). Zn/Hg, $ClMe_2SiCH_2CH_2SiMeCl$, Et_2O

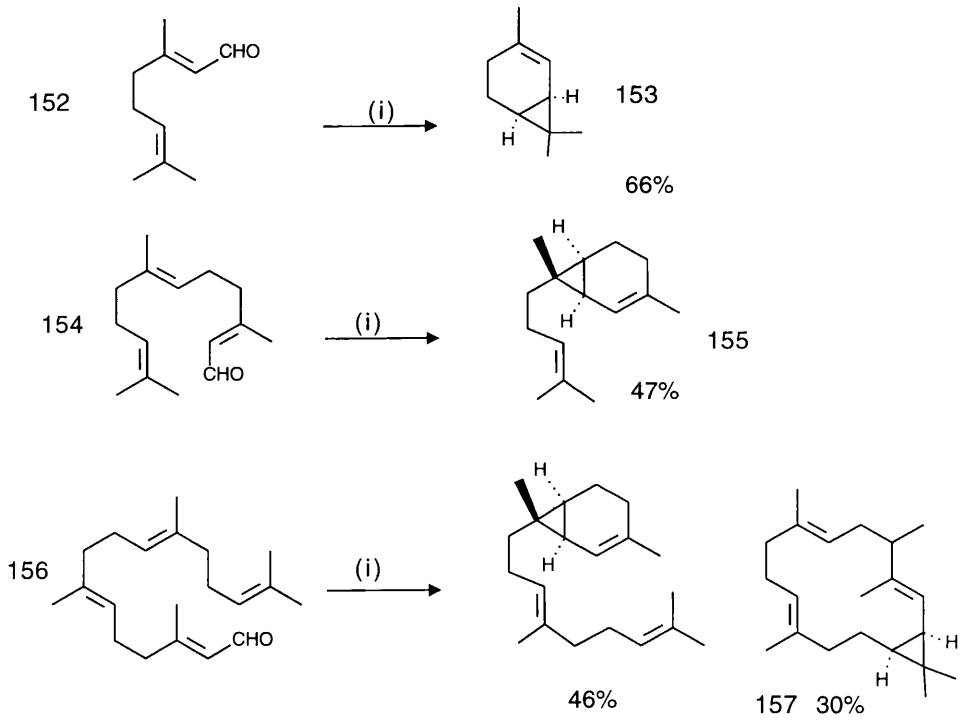
	substrate	product*	*cis/trans*	yield (%)
1			all *cis*	53
2			20 : 1	55
3			11 : 1	59
4			1 : 1	44

* major isomer shown

table 4

Curiously, a 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 enol. Thus, attempted cyclopropanation reactions using 'parent' systems such as cyclohexenone, cyclopentenone and cyclopenten-1-carboaldehyde were without success.[204] From a 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 (entry 1) and cyclohexenone substrates (entries 2 and 3).[157]

More recently, Motherwell has extended this work to intramolecular cyclopropanation reactions involving carbenoids (scheme 108).[158] Using high dilution conditions achieved by the slow addition of the terpenoid enals to other reagents geranial **152** could be cyclised to Δ-2-carene **153**, farnesal **154** cyclised to sesquicarene **155** and most impressively geranylgeranial **156** cyclised to the macrocycle casbene **157**.



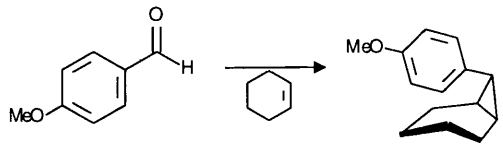
i). Zn/Hg, $ClMe_2SiCH_2CH_2SiMeCl$, Et_2O

scheme 108

Clearly, intramolecular cyclopropanation like other cyclizations, is at its least simple when the ring size is intermediate. Nonetheless, the chemistry has proved itself to be applicable to the synthesis of some complex and useful compounds.

2.2 Studies on the Generation of Organozinc Carbenoids from Aldehydes

As will be evident from the preceding summary, the generation of organozinc carbenoids from carbonyls has already been extensively explored within the Motherwell group. It is therefore ironic that even the reaction involving the very best carbenoid precursors, namely the aryl aldehydes, is still not properly understood. Recently, a systematic study of the cyclopropanation of cyclohexene with anisaldehyde was undertaken within our group. Variations in solvent, temperature, silicon electrophile, Lewis acid and most fundamentally the zinc source were all studied for their effect on the cyclopropanation of cyclohexene with anisaldehyde (scheme 109).[200]



scheme 109

Drawing the results together, it was possible to make some broad conclusions as to the optimal conditions for zinc carbenoid cyclopropanation reactions with aryl aldehydes.

- The best solvent tested for the reaction was diethyl ether, which was found to be superior even to utilising cyclohexene as the solvent. A wide range of solvents were also compatible including dichloromethane, acetonitrile and toluene. The stabilisation of the zinc carbenoid by ethereal solvent co-ordination is thought to be extremely important, especially in the light of the crystal structures of Simmons Smith type compounds recently published (*vide supr* 1.4).

- The yield was enhanced by the presence of one equivalent of zinc chloride which means, since it is a by-product of carbenoid generation, that the reaction is autocatalytic.

- Although bis(chlorodimethylsilyl)ethane remains the superior electrophilic, the use of four equivalents of chlorotrimethylsilane, dichlorodimethylsilane or even hydrogen chloride will also facilitate cyclopropanation in high yield.

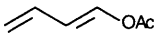
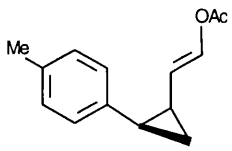
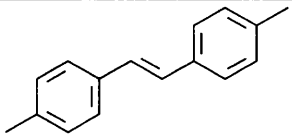
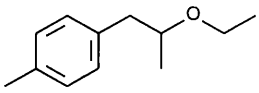
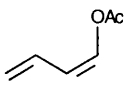
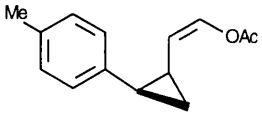
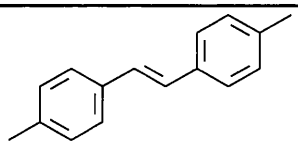
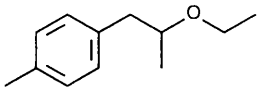
- Finally, the study showed that zinc-copper and zinc silver couples as used extensively in the Simmons Smith reaction are not as effective in the reaction with aryl aldehydes as the zinc mercury amalgam analogous to that employed in the Clemmensen reduction. Zinc dust itself was active, an important point when considering the potential for the reaction to be used industrially. It is also convenient that the reaction conditions require the addition of chlorotrimethylsilane, since chlorotrimethylsilane is routinely employed to activate zinc in Simmons Smith and related reactions.[159]

2.2.1. Some Recent Studies on the Cyclopropanation of Acetoxybutadienes

The present thesis begins with the chemistry involved in the generation of organozinc carbenoids from carbonyl compounds at an advanced stage. In order to acquire some level of familiarity with the techniques involved, my own personal experience with organozinc carbenoids began with the cyclopropanation of simple alkenes with arylzinc carbenoids.

We elected to study the cyclopropanation of *cis* and *trans* 1-acetoxy butadiene with arylzinc carbenoids derived from aryl aldehydes. This early study was a continuation of work begun within the group a few years previously.[204] The results we obtained extended those found earlier but more importantly perhaps they provide a good demonstration of the efficiency of cyclopropanation and an illustrative example of the side reactions inherent in this chemistry.

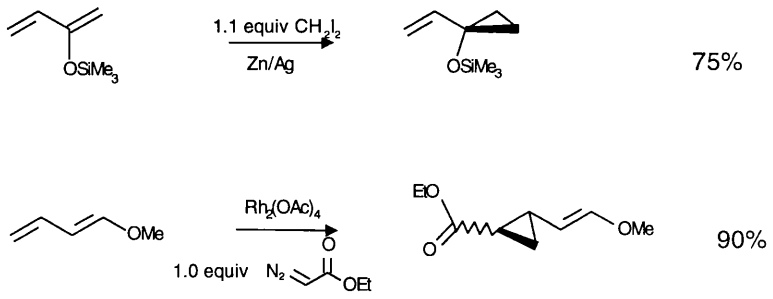
Cis- and *trans*-1-acetoxy butadiene were subjected to the optimal reaction conditions described above. Two equivalents of the diene were added to a flask containing diethyl ether, ten equivalents of zinc amalgam and four equivalents of chlorotrimethylsilane. The mixture was brought to reflux, and a solution of tolualdehyde in ether was added *via* syringe pump over twenty four hours. The results of the reactions are shown in table 5.

alkene (2 equiv)	cyclopropane *cis / trans* yield*	byproducts	yield*
	 159a 5 : 1 44%	 158  165	8% 10%
	 159b 3.6 : 1 37%	 158  165	12% 7%

* relative to tolualdehyde

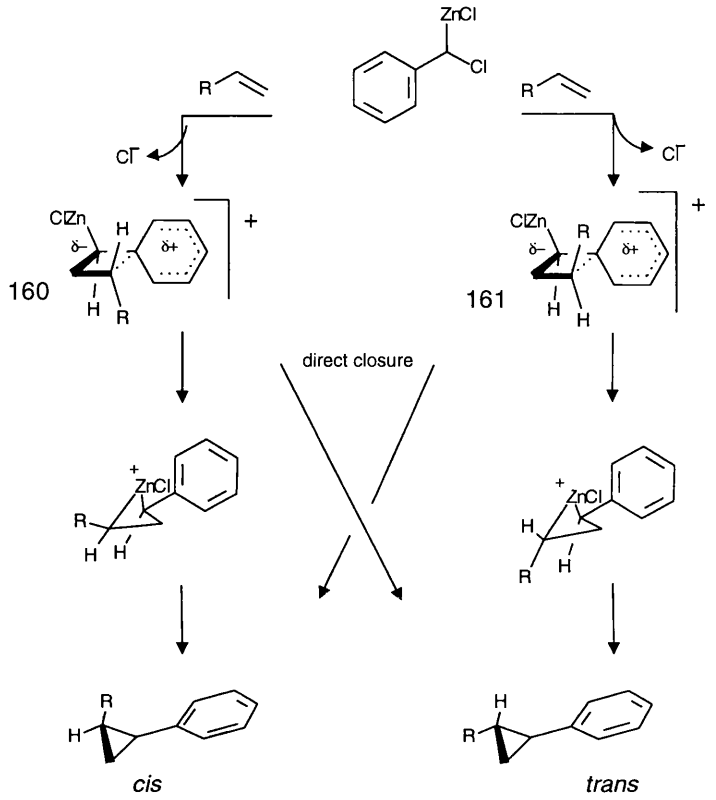
table 5

In accord with the earlier work within the group,[204] cyclopropanation was completely regioselective with only the terminal cyclopropanes being generated. This contrasts with the regioselectivity observed with the Simmons Smith reaction[196] (scheme 110) but is similar to the results obtained using rhodium carbenoids derived from α-diazoesters.[197] The yields of cyclopropane were at least as good as the Simmons Smith type cyclopropanation of similar substrates (scheme 110).



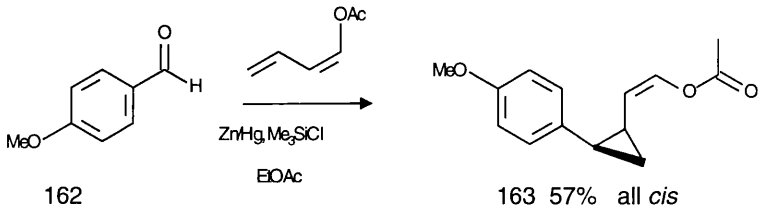
scheme 110

The diastereomeric preference for *cis* cyclopropanation with arylzinc carbenoids mirrors that observed for reaction of other benzylic. As previously shown (*vide supra* 1.3), this preference has been elegantly rationalised by Casey for tungsten aryl-carbene complexes.[67b] If this rationale is applied to arylzinc carbenoids, it implies that the carbenoid is first reacting as an electrophile with the alkene, with stabilisation of the positive centre thus produced by the aromatic ring (scheme 111). It is presumed that the metal centre and the major substituent on the alkene are automatically oriented away from one another in order to minimise steric interactions and thus **160** is favoured over **161**. The presence of the metallocyclobutane is crucial to the rationale - evidently direct closure of the intermediate **160** would result in the formation of the *trans* cyclopropane (scheme 111).



scheme 111

One solvent that had not been previously screened in the cyclopropanation of alkenes with zinc amalgam and chlorotrimethylsilane was ethyl acetate, and we were curious to see if the use of a solvent with similar co-ordination properties to the acetoxybutadiene would affect the regioselectivity of the cyclopropanation. It is also interesting to note that although our reaction conditions are known to be tolerant to esters, the Simmons Smith reaction is not commonly performed in ethyl acetate. In fact, generation of the carbenoid from *para*-anisaldehyde **162** in ethyl acetate gave the cyclopropane **163** in good yield (scheme 112) and of course without formation of any of the C-H insertion products.

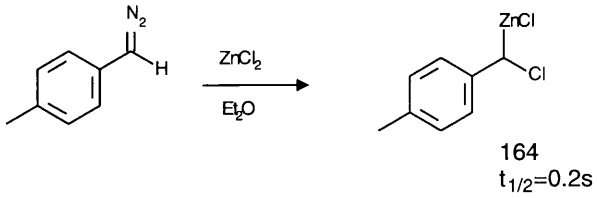


162 163 57% all *cis*

scheme 112

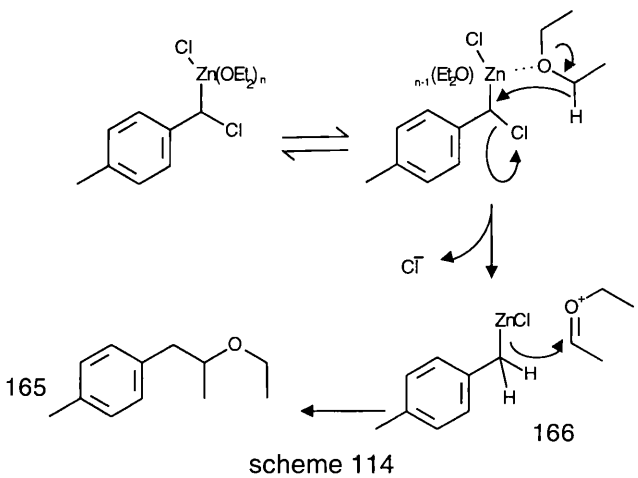
In the earlier study[204] the equivalent reaction performed in diethyl ether gave the same cyclopropane in 69% yield, as solely the *cis* diastereoisomer. It appears that when ethyl acetate is utilised as the solvent the regioselectivity remains just as pronounced. It is nevertheless a testament to the stability of esters under the reaction conditions that the reaction occurs in such a reasonable yield. The system was also interesting in that only the target cyclopropane was isolated, with no trace of stilbene formation.

The generation of homogenous zinc carbenoids from aryl diazomethanes was investigated by Closs and Moss (*vide supra* 1.4). They found that the reaction of aryl diazomethanes with ethereal solutions of zinc halide salts could be used to generate zinc carbenoids which the authors proposed were tetrahedral zinc species such as **164**. They discovered that cyclopropanation of alkenes under these conditions also gave the *cis* cyclopropanes. More interestingly, they utilised stop flow techniques to ascertain the lifetime of the carbenoid species. Their work allowed them to estimate the half life of the carbenoid derived from the reaction of zinc chloride and tolyldiazomethane in diethyl ether as being no more than 0.2 seconds (scheme 112). The corresponding carbenoid derived from phenyl diazomethane had an estimated half life of 10 seconds.[208] This is in stark contrast to the Simmons Smith methylene zinc carbenoids which have been shown to have a lifetime in the range of several hours (scheme 113).[98]



scheme 113

The same authors were also surprised to encounter relatively high yields of the ether insertion product **165**. In the cyclopropanation of the acetoxybutadienes reported in table 5, the yield of the insertion product is also relatively high despite the presence of a two-fold excess of alkene in the reaction. Similar insertion products arise in the Simmons Smith reaction though generally they are far less significant.[140] The formation of such species would evidently be expected to be concentration dependent and in the reaction mixture the ratio of solvent to alkene was approximately 10:1. Hence, given that the cyclopropane was formed in roughly five times the amount of the ether insertion product, it could be rationalised that the rate of reaction with the alkene is at least fifty times that of the insertion. On the other hand, if we assume that the zinc is at all times highly co-ordinated by the ether, this number is probably far higher. It is also worth noting that the zinc carbenoid half lives described above are the half lives of the species in ether.



scheme 114

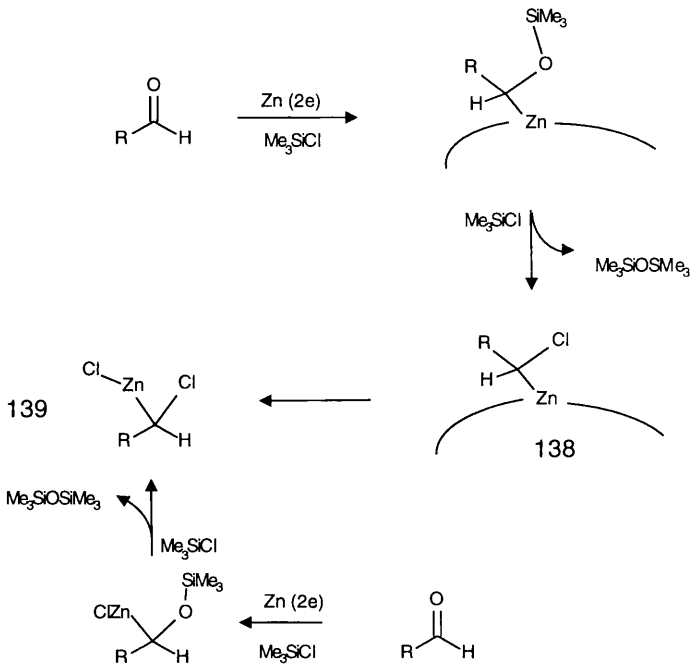
Although it is unclear as to what the exact mechanism of carbenoid insertion into ether might be, it is evident that the activation of the C-H bond by the α-oxygen exercises complete control over the regioselectivity. Thus, the generation of an oxonium intermediate **166** which remains associated with the zinc centre is the most likely pathway toward the insertion product.

Finally it should be recognised that even in the case of a twenty four hour syringe pump addition of tolualdehyde, a sizeable amount of dimethylstilbene was obtained (table 5). Whilst there is no absolute guarantee of the smoothness of the syringe pump addition, this seems to suggest a period of inertness, prior to reaction of the aldehyde with the zinc. This is perhaps to be expected in a system which, at this stage of the reaction at least, is heterogeneous. It is possible to infer that for the generation of organozinc carbenoids from aryl aldehydes the rate limiting step is the initial electron transfer from zinc to the carbonyl, in accordance with the proposal of Nakabayashi for the Clemmensen reduction (*vide supra* 2.1.1.).[143] The mechanism of dicarbonyl coupling has been discussed in detail in section 2.1.2.3.

In summary, the short study described above provides a clear example of both the positive and negative aspects of the cyclopropanation of alkenes with arylzinc carbenoids derived from aryl aldehydes. Clearly if our understanding of the mechanism of carbenoid generation is to progress further work which will shed light on the mechanism of carbenoid generation is necessary.

2.2.2. The Three Phase Test

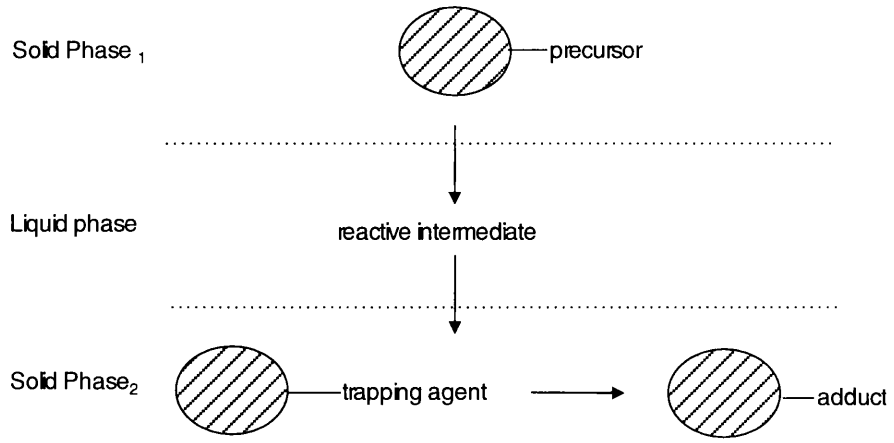
As previously stated, homogenous aryl zinc carbenoids have been studied extensively by Closs and Moss.[207,208] The similarity between the species generated from aryl diazomethanes and zinc chloride in ether and those carbenoids generated from aldehydes using zinc amalgam and a chlorosilane is evident from the comparison of the cyclopropane and ether insertion products formed from each. Nevertheless, the fundamental question remains - does the carbenoid form on the zinc surface, and if so does it remain bound there throughout the course of the reaction (scheme 115)?



scheme 115

In an attempt to answer these questions a study was undertaken by Motherwell and Nutley utilising a mechanistic probe known as "The Three Phase Test". The work, based on a concept first published by Rebek in 1974, would allow positive confirmation of homo- or heterogeneity provided it proved applicable to the reaction conditions utilised for the generation of organozinc carbenoids from carbonyls.

The Three Phase Test utilises the elegant concept of performing a reaction in the presence of a liquid phase and two solid phases.[163] 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. The second solid phase would bear a trapping agent, and hence the detection of an adduct would provide positive evidence of a free intermediate in solution as statistically any reaction between the two solid phases would be impossible (scheme 116).



scheme 116

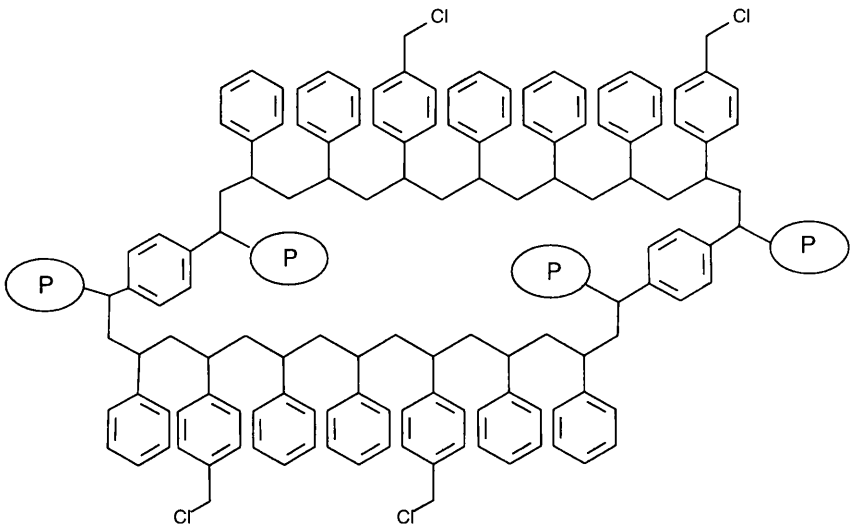
If the system is applied to the generation of organozinc carbenoids then the solid zinc amalgam will act as one solid phase and the ether, as solvent, the liquid phase. The second solid phase hence needs to contain an alkene which, after quenching the reaction, may be chemically cleaved from the solid support. If the alkene has been cyclopropanated then the conclusion has to be that the carbenoid is homogeneous. If the reaction is in fact heterogeneous and the zinc carbenoids are confined to the zinc surface, only the parent alkene will be isolated.

2.2.2.1 Previous Work on the Three Phase Test

Although the concept is simple, in undertaking the three phase test with aryl aldehyde derived organozinc carbenoids Motherwell and Nutley encountered several problems.[200]

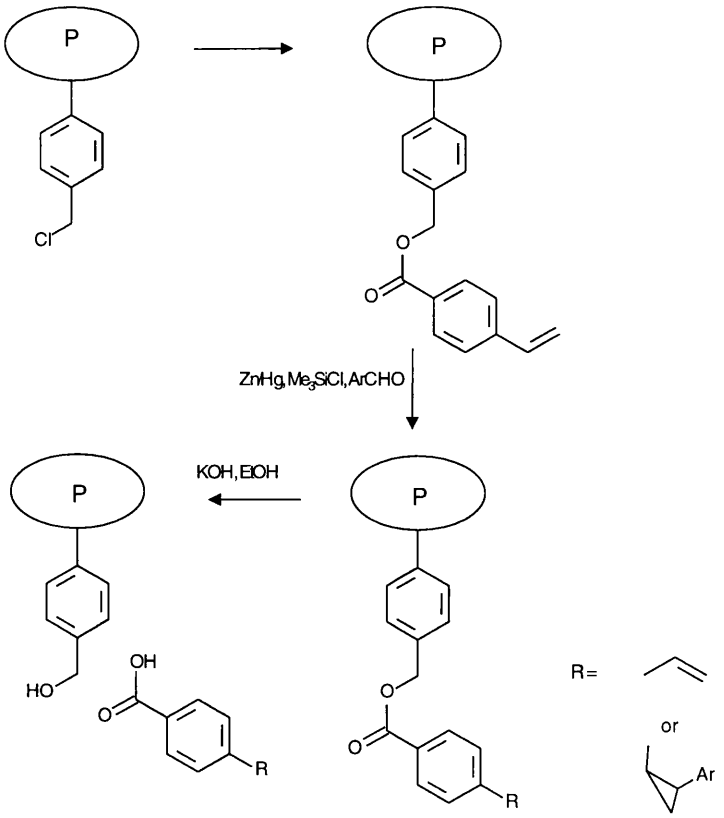
Styrene was selected as the parent alkene utilised to trap the carbenoid intermediates, given the precedent for high yielding cyclopropanation (*vide supra* 2.1.2.4). Using styrene as the trap would present the carbenoid with a reactive target some way distant from the solid phase "surface", an essential prerequisite according to Rebek's findings. He reported that a minimum of three atom spacers between the solid phase and the reactive centre were necessary for good results.

Merrifield's resin was 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 in order that it be milled to a fine powder. The backbone is chloromethylated to the extent of one milli-equivalent of chlorine per gram (scheme 117).



scheme 117

In order to attach a removable styrene onto the polymer, the chloromethylated residues were to be functionalised by coupling with a *para*-vinylbenzoate moiety. It was reasoned that the ester linkage thus formed should be stable to the reaction conditions necessary for zinc carbenoid generation and would be readily saponified when necessary under conditions to which the cyclopropane or parent alkene would be stable (scheme 118).



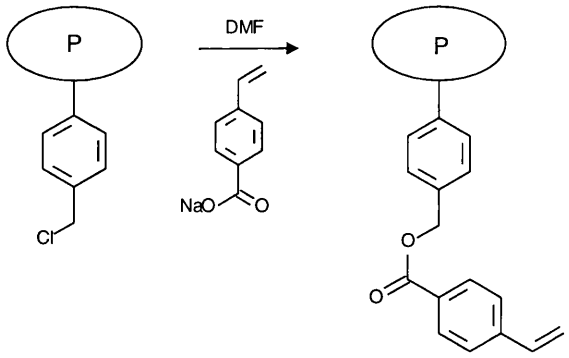
scheme 118

After substantial testing of an analogous two phase system, Motherwell and Nutley succeeded in forming the resin bound alkene by the reaction of the sodium salt of *para*-vinylbenzoic acid with the polymer. Cl analysis of the resulting polymer suggested that the coupling was 80% complete, and the IR stretch of the carbonyl carbon was clearly visible in the polymer infrared spectrum.[200]

Subsequent reaction with *p*-anisaldehyde in the presence of zinc amalgam and chlorotrimethylsilane was performed. The polymer was then purified, and the saponification attempted using ethanolic potassium hydroxide. Unfortunately, only a trace of material was obtained from the saponification process and although analysis of this by GCMS showed that it contained some of the alkene and also the adduct cyclopropane, no firm conclusions could be drawn. Due to the constraints of time, no further investigation of the carbenoid species *via* the Three Phase Test was performed.

2.2.2.2. Recent Work on the Three Phase Test

In order to quantify and resolve the problems encountered in the three phase test performed by Nutley, it was first necessary to prepare the appropriate coupled polymer. To this end, a DMF solution of the sodium salt of vinylbenzoic acid was added to a suspension of Aldrich Merrifield resin in DMF and the whole system heated at 80°C for 24 hours. It should be noted that the use of DMF as the reaction solvent is essential to the success of the coupling. Most polymer reactions are carried out in solvents such as DMF, DMSO, pyridine and benzene which swell the polymer in order to allow accessibility to all the reactive sites (scheme 119).[163a]



scheme 119

It was clearly important to ensure that when the coupling procedure was complete, any resident acid had been washed from the polymer. Any residual vinylbenzoic acid trapped within the polymer could of course trap an homogenous zinc carbenoid especially if, as the results of Nutley seem to show, the degree of carbenoid infiltration into the polymer phase is likely to be low at best. This introduces one of the major complications inherent in all polymer work, namely the purification and characterisation of polymeric systems.

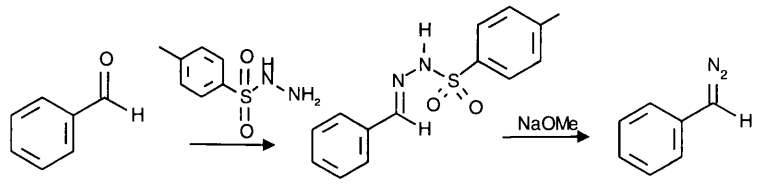
Having filtered the polymer from the reaction mixture, repeated washing first with DMSO and then with acetone was performed. Thorough washing was continued until no trace of organic material could be recovered from the filtrate. The resin was then dried and the resulting solid examined. The polymer resembled the original free flowing fine powder, and in the infra-red spectrum showed a strong carbonyl stretch at 1710 cm^{-1}. Chlorine microanalysis of the original resin had shown the chlorine content to be 3.7%, equivalent to 1.07 milli-equivalents of chlorinated residues per gram of polymer. The new microanalysis showed that the chlorine content was now 1.5% suggesting that the coupling had been reasonably effective. Given that the molecular weight of styrene is 104$gmol^{-1}$ and the degree of crosslinker quite small, the frequency of chlorinated residues in the initial polymer can be estimated as roughly 1 in every 10. Thus, as the increase in weight due to the coupling is small, the amount of coupled vinylbenzoic acid can be estimated by the change in chlorine content of the polymer. Hence it can be estimated that the total coupling of vinylbenzoic acid accounted for roughly 60% of all the chlorinated residues, or 0.6$mmolg^{-1}$ of alkene.

Given this microanalytical data, the polymer was titrated to ascertain firstly if the saponification could be achieved efficiently and secondly to test the accuracy of the characterisation of the system. Hence, stirring 0.5g of resin overnight with potassium hydroxide in 9:1 ethanol-water gave 50 mg of a cream solid which was 90% vinylbenzoic acid mixed with some unidentified aromatic compounds.

2.2.2.3. The Three Phase Test with Homogenous Zinc Carbenoids

As previously documented (*vide supra* 2.2.1.) the work of Closs and Moss with aryldiazomethanes had demonstrated that homogenous zinc carbenoids can be readily generated by the reaction of compounds such as phenyldiazomethane with zinc chloride in ether. In order to test whether the system we had devised was suitable for the formation and isolation of cyclopropane adducts of the polymer bound vinylbenzoic acid, we elected to first investigate the efficiency of the acknowledged homogenous reagent. Bearing in mind that the effectiveness of our strategy was dependent on the carbenoid, acknowledged to have a half life of the order of 10 seconds, being sufficiently miscible with the polymer to encounter the alkene, it was vital that this reaction was successful.

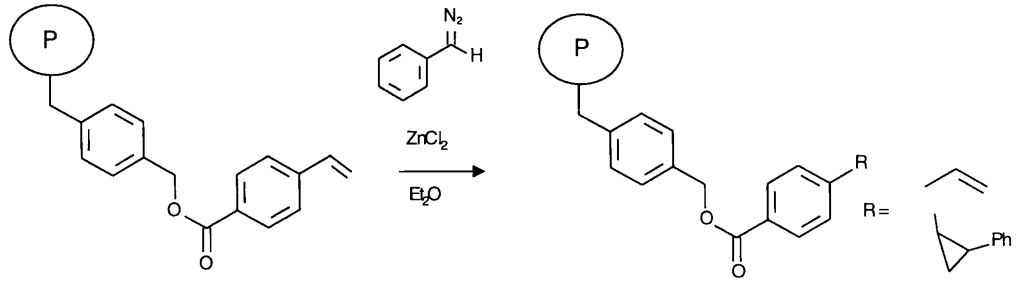
Phenyldiazomethane was prepared by reaction of the tosylhydrazine 168 according to the method of Closs and Moss. The tosylhydrazine was readily prepared from benzaldehyde (scheme 120).



92% 168

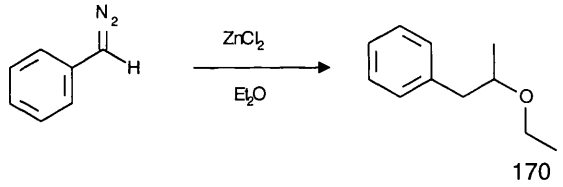
scheme 120

The phenyldiazomethane was generated just prior to reaction with the polymer, by treatment of the tosylhydrazone **168** with sodium methoxide. The deep red solution isolated from the mixture was added *via* dropping funnel to a suspension of the polymer resin in an ethereal solution of zinc chloride . The polymer was then filtered and washed (scheme 121).



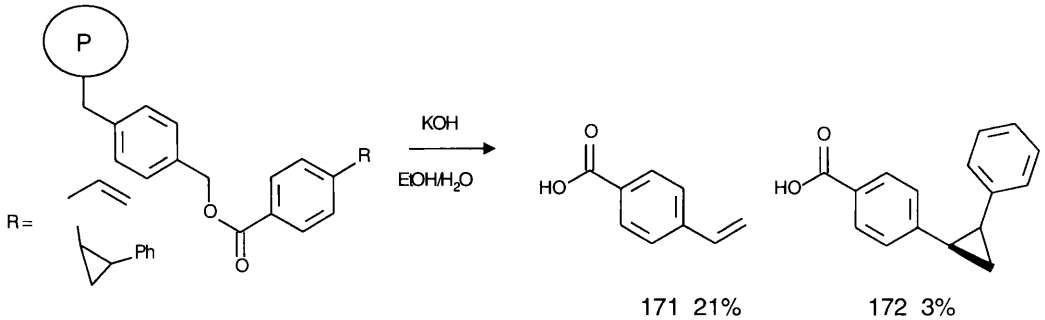
scheme 121

Analysis of the washings presented ample evidence of the formation of the zinc carbenoid species as well as a large amount of unidentified aromatic residues. The major component was the product of ether insertion, 170 isolated in 6% yield relative to phenyldiazomethane. Equally encouraging was that no vinyl benzoic acid (or cyclopropane adduct) were present in the washings.



170

The polymer residue was dried before saponification, similarly to the earlier titration, with potassium hydroxide in ethanol-water. ^{1}H NMR of the resulting solid suggested that it was a mixture of unidentified aromatic compounds, vinylbenzoic acid, and the desired cyclopropane **171** Chromatography afforded 20mg of a mixture of the vinyl acid and the desired cyclopropane **172** in a ratio of approximately 10 : 1. This amounts to about 21% vinylbenzoic acid recovery from the polymer, giving roughly 0.13mmol, and more vitally a 3% yield of cyclopropane relative to the amount of alkene present in the reaction (scheme 122).



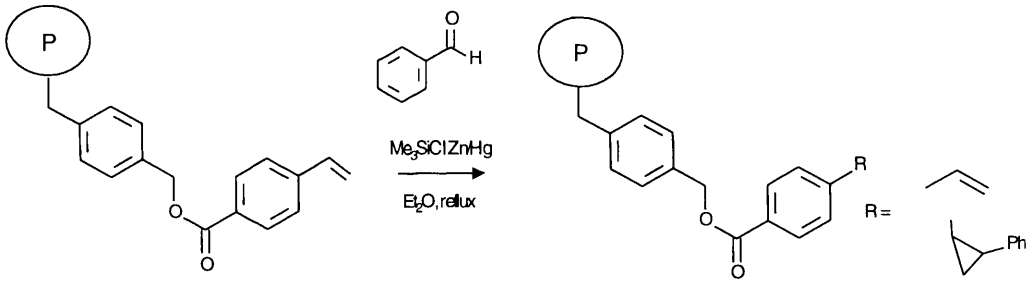
171 21% 172 3%

scheme 122

The low yield of cyclopropane was a disappointment, although not a surprise given the measured lifetime of the arylzinc carbenoid in ether. It is also probable that, as was envisaged from the outset, there is a problem with the swelling of the polymer in the unsuited diethyl ether solvent. It is also interesting to speculate on the fate of the majority of the zinc carbenoid, since the level of insertion into ether was relatively low. It is likely that the compound simply inserted into the activated C-H bonds in the polymer or alternately was trapped as highly strained cyclopropane adducts with the polymeric aryl rings.[164]

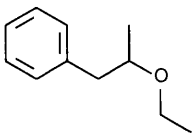
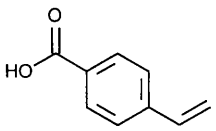
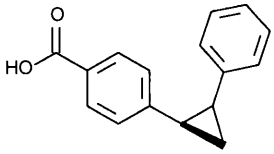
Despite these setbacks, the cyclopropane was isolated and clearly the challenge now lay in repeating the reaction with the chlorotrimethylsilane, benzaldehyde and zinc amalgam system. It was also now apparent as to why Nutley had been unable to satisfactorily isolate the cyclopropane during the previous study. The task was to duplicate if possible the results obtained with the phenyldiazomethane system, and in so doing demonstrate conclusively that the zinc carbenoids produced were homogenous entities.

2.2.2.4. The Three Phase Test Employing Benzaldehyde



scheme 123

Exposure of the coupled Merrifield resin to the standard zinc carbenoid conditions was performed in the presence and absence of zinc chloride. Two similar resins (here labelled A and B) were employed and all the reactions were performed at reflux in ether, with the standard zinc mercury amalgam as the second solid phase. In contrast to the reaction with phenyl diazomethane, benzaldehyde was utilised in excess to the calculated amount of polymer-bound alkene. Each reaction used syringe pump addition of the aldehyde, after which time the system was filtered and then thoroughly washed. The washings contained a large amount of unidentified material, vinylbenzoic acid and the adduct cyclopropane. The results are summarised in table 6

	PhCHO (equiv)*	electrophile (equiv)†	P	Lewis acid			
					Products of washings yield %†		
1	14	Me_3SiCl (4)	A	-	3	(13)*	2 & (30*)
2	5	Me_3SiCl (4)	B	$ZnCl_2$	4	(9%)*	3 & (14%)*
3	3	Me_3SiCl (4)	A	-	15	0	0
4	5	BF_3OEt_2 (2)	B	-	2	1 & (11)*	2 & (11)*

* relative to alkene on polymer

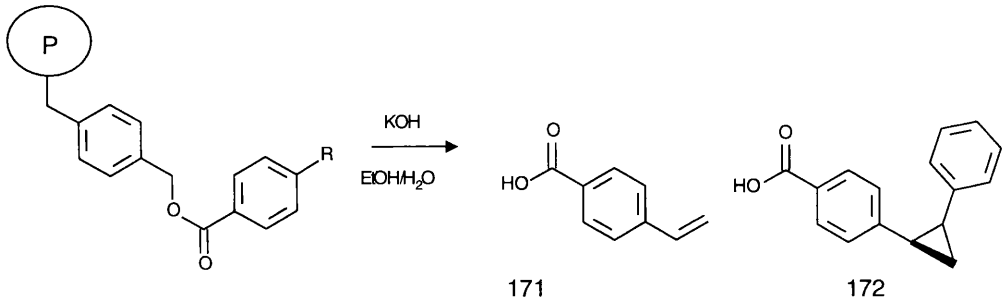
† relative to PhCHO

table 6

It was immediately apparent that under the reaction conditions and contrary to the findings of Nutley,[200] the ester linkage was undergoing at least partial cleavage. It is especially surprising, given the overwhelming evidence for the stability of esters to the reaction conditions employed (*vide supra* 2.2.1.). In accordance with the optimal reaction conditions for cyclopropanation with benzaldehyde a four fold excess of chlorotrimethylsilane relative to the aldehyde was being utilised in the reaction. This implies that there was a 20 to 50 fold ratio of chlorotrimethylsilane to alkene for entries 1 and 2 and as such the lability of the ester is not surprising. As can be seen in entry 3, with the silane present in lower concentrations the cleavage became minimal. This implies that the Three Phase Test may be frustratingly balanced such that under the conditions required for generation of a large excess of zinc carbenoid the ester linkage is labile, whereas the use of milder conditions generates insufficient carbenoids to properly probe the homogeneity of the species.

The Three Phase Test was also undertaken with the zinc carbenoid generated under Elphimoff-Felkin conditions (entry 4), again inducing cleavage of the alkene from the polymer. The nature of the carbene generated using boron trifluoride diethyletherate is even less well understood than that generated with chlorotrimethylsilane. The question of the homogeneity or heterogeneity of the carbenoid species is also, therefore, a mystery.

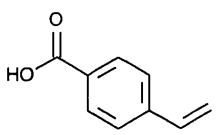
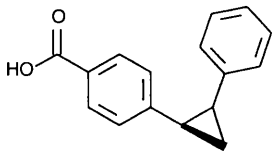
2.2.2.5. Saponification of the Ester linkage



171 172

scheme 124

The zinc and the polymer were separated by repeated sedimentation in ether, with the polymer being decanted as a suspension in the solvent. Once the polymer was visibly clear of zinc amalgam following 5 to 10 such purifications it was further washed with acetone. The dried polymer was then saponified under conditions identical to those previously described. After workup of the saponification reactions the mixtures were examined by ^1H NMR. Where the process had provided sufficient material, purification was undertaken by flash chromatography (table 7).

entry	P	KOH* (equiv)	products of saponification (yield %)* 	
1.1	A	30	trace	trace
1.2	B	4	22	22
1.3	A	15	40	10
1.4	B	5	10	0

* relative to alkene on polymer

table 7

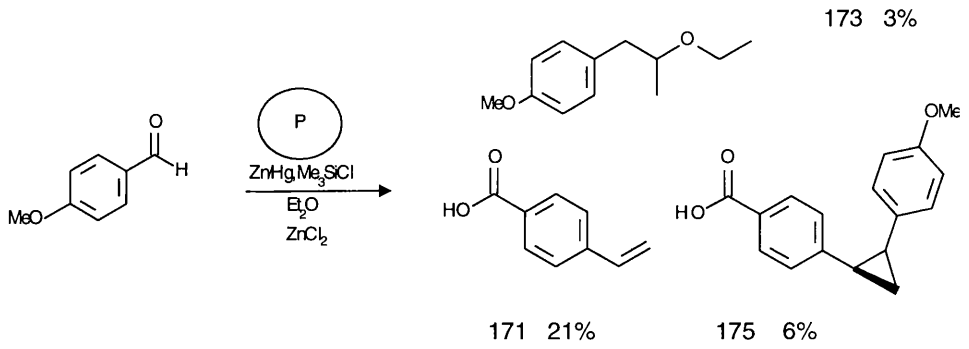
The results obtained were interesting. In the case of the system where benzaldehyde had been employed in a 14-fold excess (and chlorotrimethylsilane in a 50 fold excess) (entry 1.1), the saponification provided only the smallest trace of vinyl benzoic acid and the corresponding cyclopropane. This is unsurprising, as purification of the washings from the Three Phase Test had delivered a combined yield of 43% of vinylbenzoic acid and the cyclopropane adduct. It is probable that under such extreme conditions only very little of the alkene remained attached to

the polymer to undergo saponification. However, entries 1.2 and 1.3 where a five- and three-fold excess of the aldehyde had been utilised provided both the cyclopropane and the acid in reasonable yields relative to the total amount of alkene present. It is interesting to note that the cyclopropanation has occurred both in the presence and absence of added zinc chloride. In comparison with the results obtained using zinc chloride and diazomethane the results are excellent and appear to show conclusively that the organozinc carbenoid generated from benzaldehyde is homogenous.

One note of caution however must be sounded. As previously explained, one of the drawbacks of using polymers as mechanistic probes is that ensuring their purity is often difficult. In this case, it is impossible to guarantee that, following the Three Phase Test, all the cleaved acid and cyclopropane were removed from the resin. It is however unlikely, following the stringent washing of the polymer and the subsequent sedimentation to remove the zinc, that the level of trapped compounds was anywhere near the amount of compound isolated following saponification.

As support to this assumption, the reaction performed in the presence of boron trifluoride diethyletherate gave only the parent alkene after saponification (entry 1.4). Bearing in mind that the boron trifluoride system also cleaved the ester linkage under the reaction conditions, it can be assumed that if alkene and cyclopropane were indeed trapped within the resin after the Three Phase Test then cyclopropanes would have been isolated during the saponification. That they were not suggests the results obtained with the chlorosilane system are accurate and moreover that the Elphimoff-Felkin system generates only zinc-surface bound carbenoids. The latter of these two assumptions is of course highly tenuous, since it could simply be a measure of the lifetime of the carbenoid generated under Elphimoff-Felkin conditions. Given more time, a thorough study of these carbenoids might produce evidence to the contrary and also show homogeneous carbenoids.

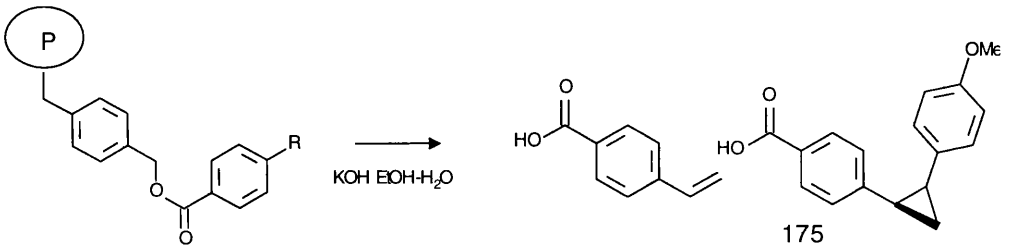
2.2.3.6. The Three Phase Test with Anisaldehyde



scheme 125

In a repeat of the work of Nutley, the same experiment was also conducted with anisaldehyde as the carbenoid source. The reaction was performed in the presence of zinc chloride with

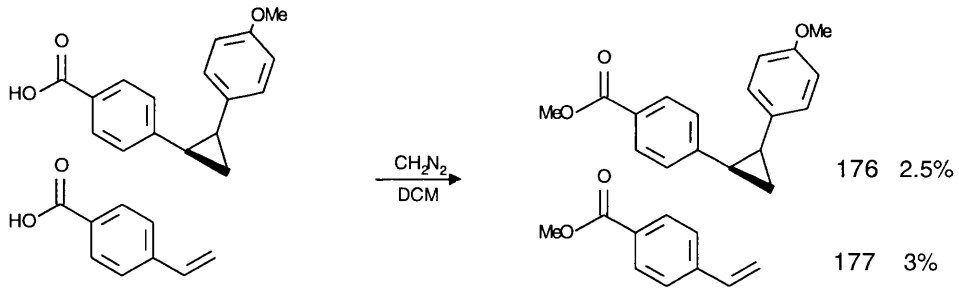
three equivalents of anisaldehyde relative to the estimated coupled alkene. Analysis of the crude washings again suggested that substantial cleavage of the ester linkage had occurred as the vinyl benzoic acid was clearly present. In contrast to the findings of Nutley however, a second highly insoluble acid species, namely the cyclopropane **175,** was also present in an estimated yield of 6% relative to the total coupled alkene.



175

scheme 126

Saponification of the polymeric ester from the Three Phase Test with anisaldehyde was also effected using potassium hydroxide in ethanol-water. Similarly to the crude from the cyclopropanation reaction the resulting 50mg of residue proved highly insoluble but clearly contained some of the cyclopropane. In order to facilitate identification the crude mixture was subjected to diazomethane esterification, affording a mixture of the cyclopropane and alkene methyl esters in low yield relative to the coupled alkene (scheme 127).

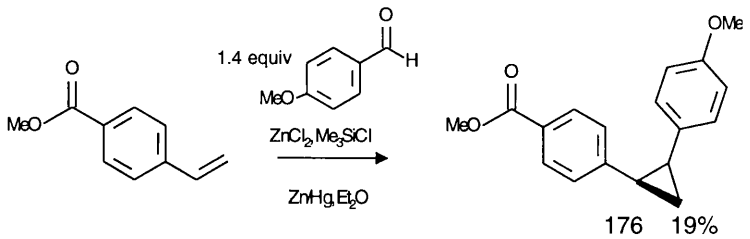


176 2.5%

177 3%

scheme 127

This esterification led to the isolation of 10mg of the cyclopropane and 6mg of the vinylbenzoate ester. This effectively duplicates the results of Nutley, who had found a similar low yield of a roughly even mixture of the cyclopropane and parent alkene.[200]



176 19%

scheme 128

Attempted cyclopropanation of vinylbenzoate methyl ester gave the same cyclopropane in 19% yield, plus a 5% yield of the insertion product. It is unfortunate that only a 19% trapping of the carbenoid even by the free alkene was possible. As was found by Nutley, the results obtained

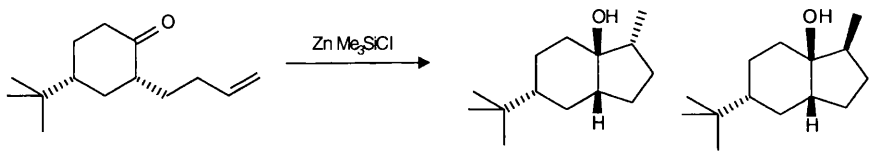
using the Three Phase Test with anisaldehyde were disappointing. It is possible that the carbenoid produced is even more short lived than the corresponding species derived from benzaldehyde and hence that penetration into the polymer is insufficiently rapid for the carbenoid to encounter the polymer bound alkene. Although the lifetime of the carbenoid might be extended by cooling the reaction mixture, this would probably lead to an even less efficient swelling of the polymer by the ether solvent. Despite involving a poor substrate for the Three Phase Test however, our results and those of Nutley concur in showing that the carbenoid derived from anisaldehyde exists homogeneously.

In summary, it would appear that, reservations aside, the carbenoid produced from aromatic aldehydes using zinc and chlorotrimethylsilane is an homogenous entity, analogous to that found in the Simmons Smith reaction and similar to that produced by the reaction of zinc chloride with aryl diazomethanes. In the case of the carbenoid generated using boron trifluoride diethyletherate the Three Phase Test suggests that the opposite is true, with the carbenoid reacting at the zinc surface only. This hypothesis has only been briefly explored however, and further experimentation with different ratios of aldehyde and boron trifluoride are required before a more definitive conclusion can be drawn for the Elphimoff-Felkin system.

2.3.The Use of Acetals as Organozinc Carbenoid Precursors

Whilst organozinc carbenoids may readily be produced from a variety of aldehydes and ketones, a large body of work exists which demonstrates that the mechanistic pathway is not as simple as would be ideal. As was shown in section 2.1 it is likely that the reductive generation of carbenoids from carbonyl compounds proceeds *via* sequential one electron delivery from the zinc.

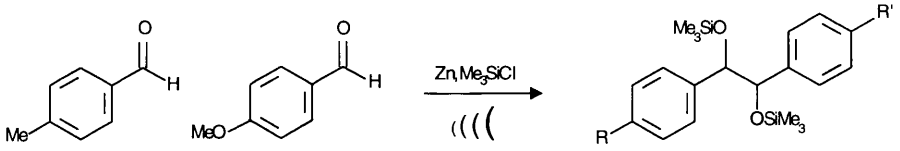
Further proof of this fact comes from the work of Corey who has shown that the zinc chlorotrimethylsilane system can be used to generate and trap the siloxyalkyl radicals derived from carbonyls. The bicyclic species formed are evidently produced directly from intramolecular trapping of the radical formed by one electron reduction of the carbonyl compound (scheme 129).[161]



66% 7%

scheme 129

Similarly the exposure of aryl aldehydes to zinc and chlorotrimethylsilane under sonication has been used to produce high yields of cross-coupled aromatic pinacols.[160] Evidently, the lifetime of the one electron species is very brief (scheme 130).



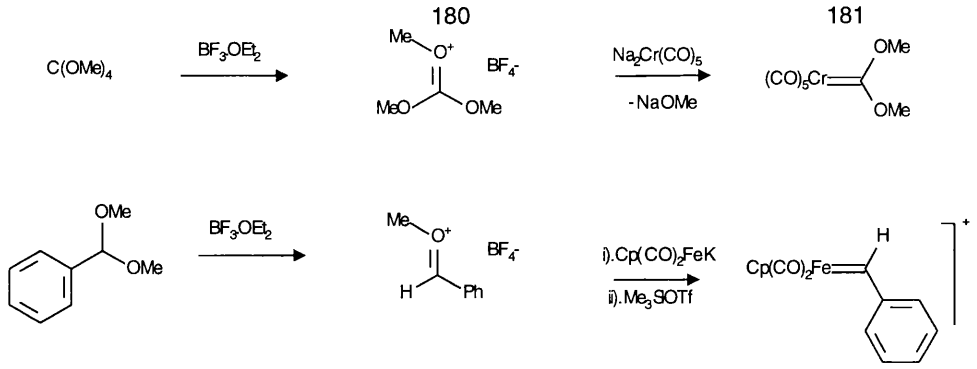
95%, mixture of R, R'=Me and OMe

scheme 130

It is evident that the reaction conditions need to be carefully controlled in order to ensure that the zinc-bound radical intermediates are unable to react. Hence, a process that facilitates direct two electron reduction of the carbonyl might lead to improved efficiency in zinc carbenoid generation.

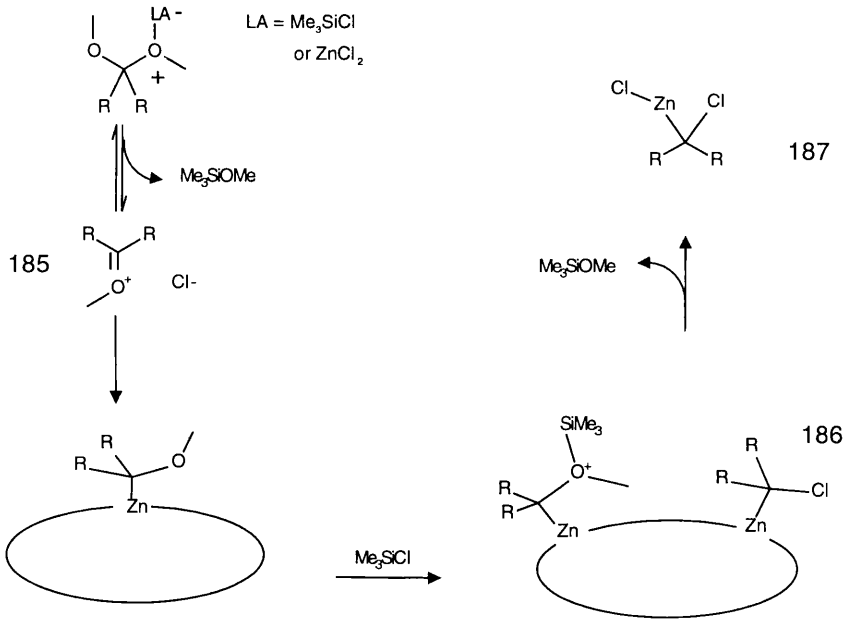
The direct formation of Fisher type metal carbenes from carbonyl groups was recently realised by Hegedus in the synthesis of aminocarbene chromium complexes (*vide supra* 1.3).[167] In the same paper, he describes the formation of the dimethoxycarbene complex **181** by the reaction of disodium chromium pentacarbonyl with the oxonium ion **180** generated from tetramethyl-carbonate and boron trifluoride diethyletherate In a related procedure Hossain later showed that a similar reaction could be performed using potassium cyclopentadienyliron dicarbonyl and the oxonium intermediates derived from acetals.[168] Although these systems use nucleophilic metal

complexes, the idea of the direct reduction of an oxonium intermediate to give a carbenoid species is clearly one that could be applied to metallic zinc.



scheme 131

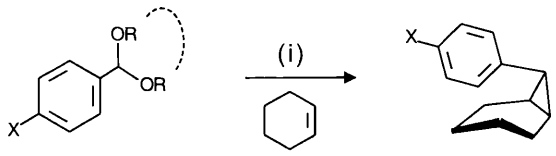
For the reaction of acetals with zinc in the presence of a silicon electrophile the oxonium ion **185** generated *via* Lewis acid cleavage of an acetal should be readily reduced by zinc (scheme 131). Since the reducible species is a positively charged intermediate it is likely that, in analogy to the work of Hossain and Hegedus, the zinc carbenoid could be produced *via* direct two electron reduction (scheme 132). Similarly to the carbenoids generated directly from aldehydes and ketones, a surface bound carbenoid such as **186** or a similar homogenous species **187** could both be the result. The major advantage of such a pathway is that it precludes formation of any intermediate radical with a zinc oxygen bond.



scheme 132

2.3.1. Observations on the use of Acetals as Organozinc Carbenoid Precursors

The trapping of organozinc carbenoids derived from a series of *para*-substituted aryl acetals with cyclohexene was selected for initial study by Motherwell and O'Mahony.[199] Examination of the tabulated results in table 8 confirms the above hypothesis, with the relative efficiencies of carbenoid generation and the observed diastereomeric preference for *cis* adduct formation tending to mirror those already noted and rationalised for the free aldehyde (*vide supra* 2.1.2.4).



i). Reagents and Conditions: Zn/Hg (10 equiv), Me_3SiCl (4 equiv), $ZnCl_2$ (1 equiv), Et_2O reflux.

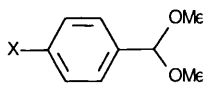
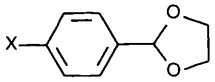
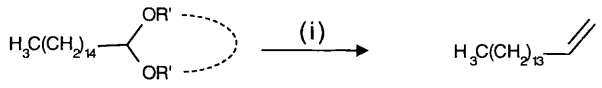
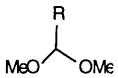
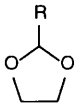
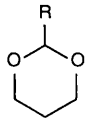
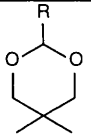
	acetal	X	yield (%)	*cis / trans*
1		Me	34	5.6 : 1
2		OMe	40	24 : 1
3		Me	38	6.1 : 1
4		H	36	3.3 : 1
5		Cl	30	2.9 : 1

table 8

Aliphatic ketals and acetals were also studied for their suitability as carbenoid precursors with zinc and chlorotrimethylsilane. Initial studies by O'Mahony with some common acetal protecting groups showed that such species could act effectively as organozinc carbenoid precursors with zinc amalgam in the presence of chlorotrimethylsilane (table 9). The carbenoid thus generated from acetals of pentadecanal will readily undergo α-insertion to produce the corresponding alkene.



(i) Reagents and Conditions: Zn/Hg (10 equiv), Me_3SiCl (4 equiv), Et_2O reflux.

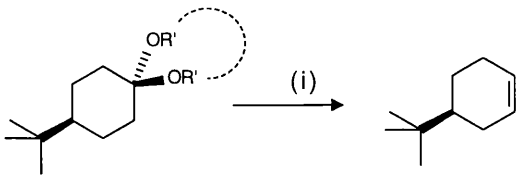
$R=H_3C(CH_2)_{14}$				
entry	1	2	3	4
time (h)	20	17	36	60
yield*	62	86	6 (84)	14 (80)

* Yields in parenthesis are of recovered starting material

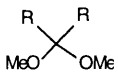
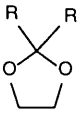
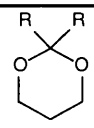
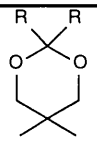
table 9

Inspection of the results in table 9 indicates that the nature of the acetal can clearly play a determining role in the reaction. Thus, while the 1,3-dioxolane and dimethyl acetal derivatives (entries 1 and 2 respectively) gave the alkene in preparatively useful yield, the corresponding six membered ring, 1,3-dioxane acetals (entries 3 and 4) were essentially inert under the reaction conditions.

The paramount importance of the substrate structure in facilitating oxonium ion formation was further reinforced through a study of the corresponding series of ketals derived from 4-^{t}butyl cyclohexanone (table 10) where, in marked contrast to the aliphatic aldehyde derivatives, all four ketals yielded the alkene in essentially comparable yield.[199]



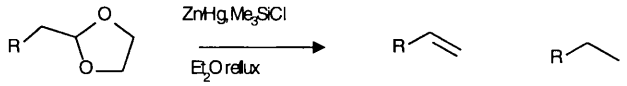
(i) Reagents and Conditions: Zn/Hg (10 equiv), Me_3SiCl (4 equiv), Et_2O reflux.

R-R = 4-^{t}Butylcyclohexyl				
entry	1	2	3	4
time (h)	16	16	14	17
yield*	56	59	50	52

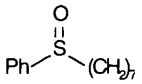
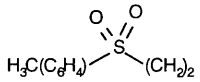
*Isolated as the dibromide

table 10

As a functional group interconversion in its own right, the direct generation of an alkene from an acetal or ketal is worthy of note. In order to study the applicability of this interconversion to more functionalised substrates, a range of acetals carrying remote functionality were synthesised[199] In all cases, exposure of the acetal to standard conditions gave the alkene and in some cases, the fully reduced Clemmensen product as well (table 11).



(i) Reagents and Conditions: Zn/Hg (10 equiv), Me_3SiCl (4 equiv), Et_2O reflux.

	R	alkene (%)	alkane (%)
1	$EtOC(CH_2)_6$	75	2
2	$HO_2C(CH_2)_6$	42	8
3	$HO(CH_2)_7$	24	10
4		23*	-
5		4 (68)§	20

* sulphide product isolated
§yield of recovered starting material

table 11

All of the above observations are in keeping with a mechanistic rationalisation in which cleavage to an oxonium ion is the rate limiting step which is strongly influenced by the nature of the substrate, both in terms of the ability of the structure of the parent carbonyl compound, aldehyde or ketone, to stabilise the positive charge, and also, for the acetal or ketal, in terms of relief of ring strain and entropic factors. An obvious parallel can be drawn with the faster rates of hydrolysis of ketals relative to acetals, and with the known relative rates as a function of the cyclic or acyclic nature of the protecting group.[172]

2.3.2. New Observations on the Generation and Trapping of Organozinc Carbenoids Derived from Acetals

The initial studies within the Motherwell group had demonstrated that like their aldehyde congeners, aromatic aldehydes were good precursors for the intermolecular cyclopropanation of electron rich alkenes.[199] Equally, and again in similar fashion to aldehydes and ketones, the efficiency of α-insertion reactions of alkyl acetals had been demonstrated.

One area of zinc carbenoid chemistry previously investigated with carbonyl compounds was the cyclopropanation reactions of carbenoids derived from α,β-unsaturated aldehydes and ketones. Although a range of such compounds had previously been shown to be effective in the cyclopropanation of some simple alkenes and styrenes, a variety of related systems had been shown to be ineffectual in carbenoid reaction (*vide supra* 2.1.2.4..). The work of Davis and Woodgate had demonstrated that some α,β-unsaturated carbonyl systems will rearrange to give cyclopropanols after one electron reduction.[145] Thus, it seemed plausible that the use of acetals rather than the parent carbonyl species might suppress such side reactions and facilitate cyclopropanation. With this in mind, we synthesised the ketals and acetal shown in table 12. The compounds were subjected to slow addition to a refluxing mixture of zinc amalgam, zinc chloride and dichlorodimethylsilane in the presence of four equivalents of the alkene.

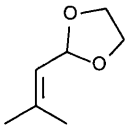
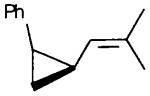
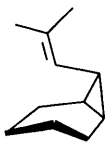
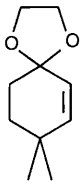
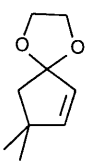
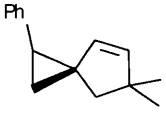
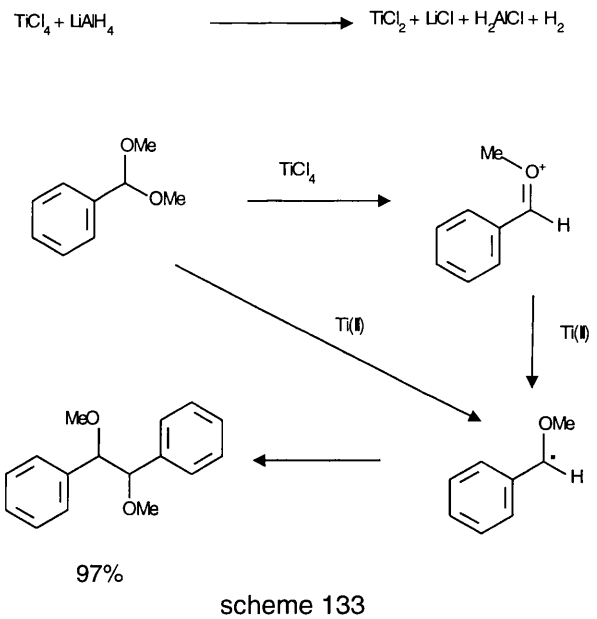
	acetal		alkene	product		yield (%)
1		178a	styrene		179a	10
			cyclohexene		179b	trace
2		178b	styrene	none		
			cyclohexene			
3		178c	styrene		179c	16

table 12

The selection of dichlorodimethylsilane as the electrophile and the formation of 1,3-dioxolane acetals was intended to facilitate the intramolecular delivery of the second silicon electrophile in a process that mirrored the action of the bis-silicon electrophile with the parent carbonyl compounds (*vide supra* 2.1.2.4.)

Although some success was obtained, it swiftly became apparent that the generation of cyclopropanes from acetals and ketals derived from α,β-unsaturated compounds was not as facile a process as for the parent carbonyl species. A further possibility was that the acetals were merely precursors for the regeneration of the carbonyl species under the reaction conditions employed. If that were the case, the poor results could again simply be a consequence of the absence of the pseudo bis-silicon electrophile.

The original rationale which favoured the use of acetals as zinc carbenoid precursors, namely that two electron reduction of the oxonium intermediate could be facilitated was also unproven. Work by Ishikawa[250] with aryl acetals has shown that one electron reduction is possible. Ishikawa demonstrated that the reduction of dialkyl acetals derived from aromatic aldehydes and ketones with titanium tetrachloride and lithium aluminium hydride gave the coupling products, pinacolic ethers, in high yields (scheme 133). He proposed that titanium (II) was the reactive species and that the reaction proceeded *via* pinacolic coupling of a radical intermediate in a mechanism analogous to the McMurray coupling of carbonyls.[190]

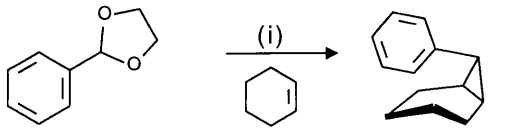


97%

scheme 133

2.3.3. Mechanistic Studies on the Generation of Organozinc Carbenoids from Simple Acetals

In hindsight, our initial foray into the use of α,β-unsaturated acetals as zinc carbenoid precursors appeared somewhat over ambitious and a more readily accessible reaction was sought in order to further probe the mechanism of carbenoid formation from acetals. In view of this, it was decided that the cyclopropanation of cyclohexene with acetals derived from benzaldehyde would be further studied. Some key results are summarised in table 13.



188 189

i). Slow addition of acetal to Zn/Hg (10 equiv), Me_3SiX, Et_2O and cyclohexene (4 equiv)

	electrophile (equiv)	solvent (temp)	add^n (hrs)	Lewis acid (equiv)	7-phenyl norcarane yield % (*cis/trans*)
1	Me_3SiCl (4)	Et_2O -30°C	24	$ZnCl_2$ (1)	15 (4.7:1)
2	Me_3SiCl (4)	Et_2O reflux	24	$ZnCl_2$ (1)	51 (3.8 :1)
3	Me_3SiCl (4)	Et_2O reflux	1*	$ZnCl_2$ (1)	28 (3.3;1)
4	Me_3SiOTf (4)	Et_2O reflux	12	-	26 (3.3:1)
5	Me_3SiBr (3)	Et_2O reflux	30	$ZnCl_2$ (1)	25 (3.3:1)

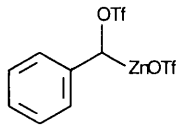
*total reaction time 2 hours

table 13

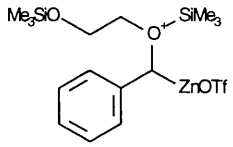
Zinc carbenoids can clearly be generated from acetals at lower temperatures than are commonly employed (entry 1). Unsurprisingly, although the yield of cyclopropanation at -30°C was lower, the diastereoselectivity had increased. Equally interesting was that the yield of cyclopropane under standard conditions (entry 2) exceeded that reported by O'Mahony in his earlier study. If the primary pathway of carbenoid generation is one of acetal cleavage to the aldehyde (*vide infra* 2.3.4), the use of a more electrophilic silane would perhaps be expected to facilitate carbenoid generation. In the case of the bromotrimethylsilane (entry 5) however, the yield of cyclopropane was actually reduced. Equally, if the aldehyde was an intermediate in the reaction, then a faster addition of the acetal to the reaction mixture might be expected to result in significant levels of either pinacolic or dicarbonyl coupling (*vide supra* 2.1.2.3.). In the event of one hour addition of the acetal however (entry 3) only the desired product was formed, albeit in lower yield. Whilst it is possible that the lack of stilbene was a function of the ratio of

carbenoid to carbonyl at any one time, the reaction does clearly demonstrate that the opportunity exists to substantially lower the reaction times involved. Most interesting of all however, the use of trimethylsilyltriflate as the electrophile demonstrates that the presence of a halide ion is not a prerequisite for carbenoid generation (entry 4).

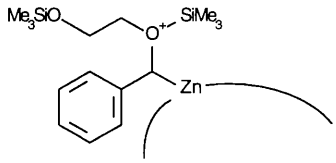
It is interesting to speculate on the nature of the species involved in the cyclopropanation. In the absence of any halide anions, the tetrahedral carbenoid analogous to the Simmons Smith reagent heretofore postulated as the relevant zinc species cannot be present. It is possible that the reactive intermediate is one of several analogous species, such as any of **190**, **191** and **192** below (scheme 134).



190



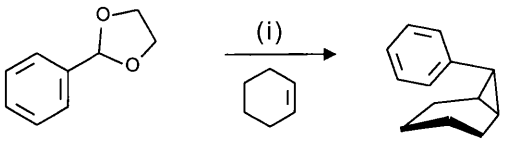
191



192

scheme 134

If the mechanism of zinc carbenoid generation from acetals is primarily *via* electron donation into an oxonium intermediate, then aryl oxonium species generated from acetals using alternative Lewis acid systems should also be active as carbenoid precursors. Foremost amongst these, the oxonium ions produced by reaction of aryl acetals with boron trifluoride diethyletherate should be amenable to reduction by zinc. Such a system, a hybrid of the work of Hossain (section 2.3) and Elphimoff-Felkin (section 2.1) would be ideal in that the oxonium could theoretically be preformed thus simplifying at least by one step the supposed pathway to carbenoid generation.[168]

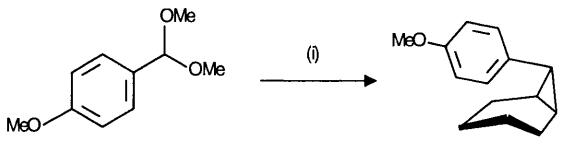


i). Zn/Hg (10 equiv), BF_3OEt_2, cyclohexene (4 equiv)

	electrophile (equiv)	solvent	addition (hours)	yield % (*cis/trans*)
1	BF_3OEt_2 (2)	r.t.	0.1	2 (>99:1)
2	BF_3OEt_2 (2)	Et_2O r.t.	1	1.2 (49:1)
3	BF_3OEt_2 (3)	Et_2O refux	24	15 (>99:1)

scheme 135

The use the dioxolane acetal of benzaldehyde under the conditions described as optimal by Elphimoff-Felkin (entry 1) provides only a minor yield of the desired cyclopropane, the major product being the starting material. However, in accordance with the reported[215] reaction with aldehydes the yield with ether as the solvent is slightly lower. Interestingly, the usefulness of zinc as the electron source in such cases appears to be highly temperature dependent, as the yield of cyclopropane at reflux is far higher (entry 3). Whatever the source of the carbenoid, the reaction is self evidently less efficient, at the temperatures investigated at least, than the reaction employing chlorotrimethylsilane.



193 194

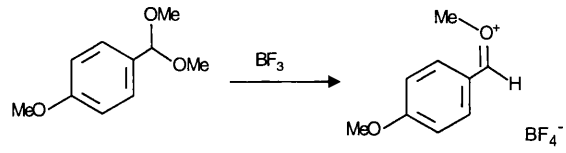
i). Zn/Hg (10 equiv), BF_3OEt_2,(1 equiv) cyclohexene (4 equiv)

	solvent (temp)	addition (hr)	yield % (*cis* /*trans*)
1	r.t.	0.1	13 (17:1)
2	Et_2O r.t.	1	21 (32:1)

scheme 136

For the dimethyl acetal **193**, the yield of the cyclopropane obtained in ether at ambient temperature was the highest isolated and the efficiency of the reaction performed in cyclohexene was actually lower.

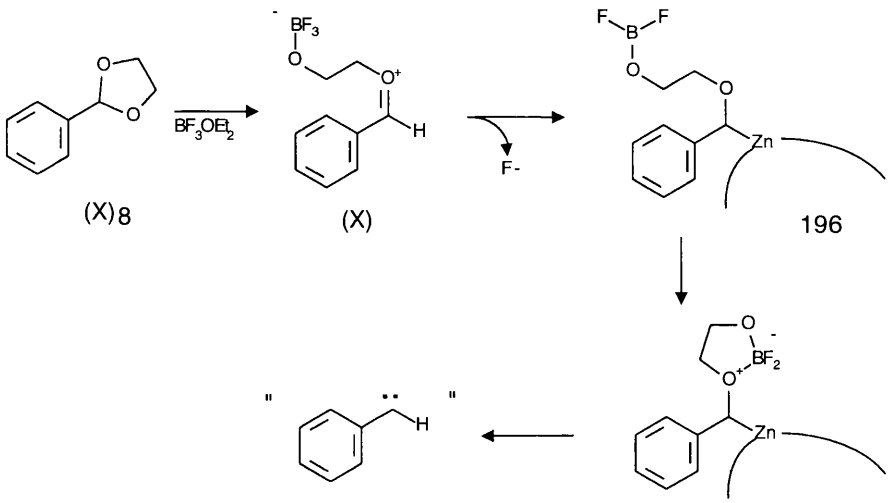
Furthermore Rabinovitz and Bruck had found that the oxonium ion **195** could be readily formed by the addition of BF_3 to a chloroform solution of the acetal **193**.[171] They reported that the resulting salt was stable even at 50°C (scheme 137). It is therefore unlikely that in this case formation of the zinc carbenoid occurs *via* the aldehyde.



193 195

scheme 137

It is, as always, fruitful to speculate as to the exact mechanism of carbenoid generation under these conditions. Even if the aforementioned aldehyde is discounted, the nature of the zinc carbenoid as well as the pathway to its generation still remain unknown.

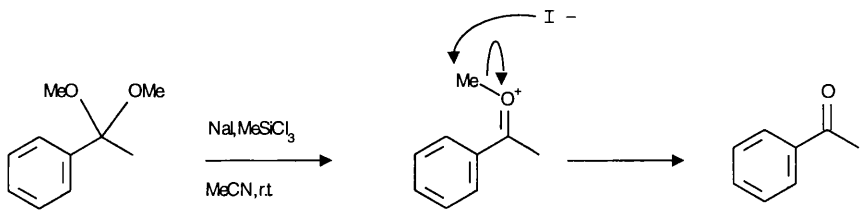


scheme 138

For the dioxolane acetal in particular, one possible mechanism which can be envisaged is analogous to that postulated for the reaction of the bis-silicon electrophile with aldehydes (*vide supra* 2.1.2.3.) in that deoxygenation by the removal of the second acetal oxygen can actually occur intramolecularly (scheme 138). Unlike the silicon electrophile however, the corresponding difluoroboronate **196** would be expected to show significantly lower electrophilicity than the parent trifluoride, and hence intramolecular delivery of this species as the "second" electrophile might be disfavoured relative to an intermolecular process. Whatever the truth, this chemistry is patently worth further investigation.

2.3.4. Observations on the Possible *in situ* Generation of Aldehydes from Acetals

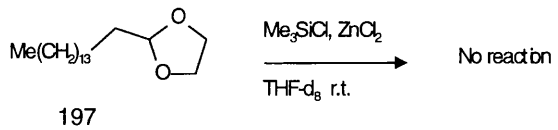
In his original study with acetals O'Mahony had noted that it was possible that the carbonyl compound had been formed from the acetal prior to reduction by the zinc. The work of Olah[174] has shown that dimethyl acetals can be deprotected to the carbonyl compound by an iodosilane generated *in situ via* the reaction of sodium iodide and trichloromethylsilane in acetonitrile (scheme 139).



scheme 139

In the absence of such a potent electrophile however, O'Mahony[199] postulated that aryl acetals, especially the more hindered cyclic species, would be unlikely to undergo similar cleavage. In order to demonstrate this he had performed a series of NMR experiments on the

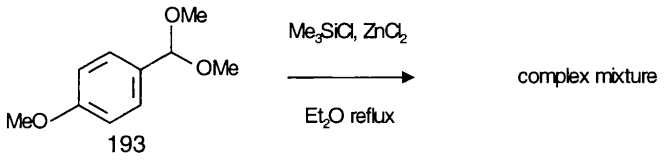
reaction of **197** with chlorotrimethylsilane and with zinc chloride chlorotrimethylsilane in THF-$_{d8}$. Neither reaction showed production of any of the carbonyl compound after 20 hours at room temperature.



197

scheme 140

In order to further substantiate his findings, we undertook a similar experiment with the dimethoxy acetal **193**. In contrast to the observed stability of 2-pentadecyl-1,3-dioxolane in tetrahydrofuran, we found that after three hours at reflux in ether the aryl acetal-electrophile mixture showed a complex array of different compounds by TLC.

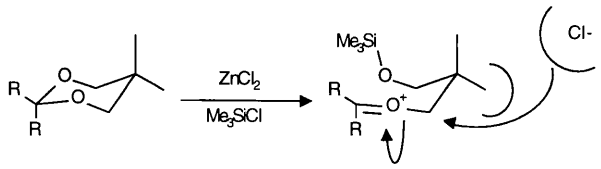


193

scheme 141

Investigation by NMR showed that although most of the acetal remained, there was clearly some of the aldehyde present as well. The two examples above probably demonstrate the two possible extremes of acetal stability, with the *para*-methoxy group on **193** facilitating oxonium formation[214] and it is plausible that the stability of most acetals lies somewhere in between. Whatever the case, further investigation as to the possibility of *in situ* aldehyde regeneration was considered important.

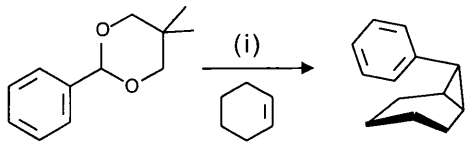
It was postulated that generation of an aryl zinc carbenoid from more hindered acetals such as the neopentylic 5,5-dimethyl-1,3-dioxane acetal (scheme 142) would reduce the likelihood of oxonium ion cleavage by halide ions. The added steric bulk would mask the necessary angle of nucleophilic attack at the ethereal carbon, hence reducing the rate of carbonyl regeneration.[199]Chlorotrimethylsilane has not been reported as effective in the cleavage of ethers.[165]



scheme 142

If this were indeed the rate limiting step in zinc carbenoid generation then the manipulation of the electrophile might be expected to induce an increase in the efficiency of cyclopropanation.[165] In the event, cyclopropanation of cyclohexene with the neopentyl-acetal of

benzaldehyde **198** was achieved in reasonable yield with both chloro- and bromotrimethylsilane as electrophiles (scheme 143).



198 189

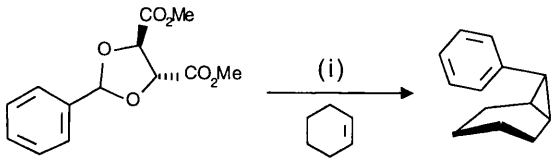
i). Slow addition, Zn/Hg (10 equiv), cyclohexene (4 equiv), Et_2O reflux

Me_3SiCl (5 equiv)	44%
Me_3SiBr (5 equiv)	49%

scheme 143

The use of the bromosilane (in contrast to the reaction with the 1,3-dioxane acetal) gives a slightly higher yield than the usual chlorotrimethylsilane. This might appear to favour the argument for aldehyde regeneration being at least partly responsible for carbenoid generation, although the difference is minimal. At the same time bromotrimethylsilane is reported as being unable to cleave acetals.[165] On the basis of these results it still remains impossible to interpret decisively whether or not the aldehyde forms an intermediate in the pathway toward carbenoid generation. It is again worthy of note that the yields of cyclopropane exceed those found with other acetals of benzaldehyde by O'Mahony, despite utilising the same reaction procedure.[199]

In the case of the even more hindered chiral acetal **199** derived from the protection of benzaldehyde with (*L*)- dimethyltartrate, the production of the carbenoid proved impossible with chlorotrimethylsilane as the electrophile, affording only the starting material. With bromotrimethylsilane 7-phenylnorcarane **189** is produced in 12% yield, with a lower than expected *cis / trans* ratio (scheme 144).



199 189

i). Slow addition, Zn/Hg (10 equiv), cyclohexene (4 equiv), Et_2O reflux

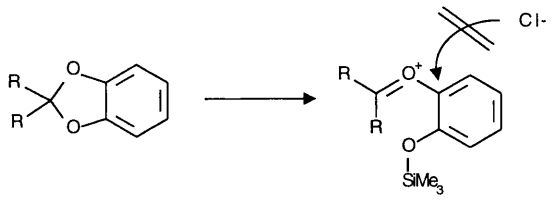
Me_3SiCl (5 equiv)	0%	
Me_3SiBr (5 equiv)	12%	2.7 : 1

scheme 144

2.3.5. Catechol-Acetals as Organozinc Carbenoid Precursors

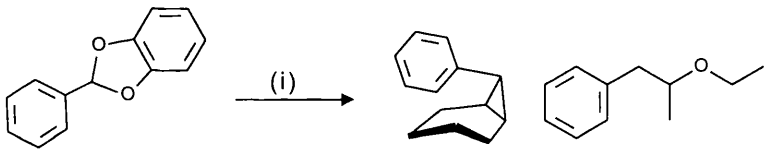
One further class of acetals not previously considered as possible carbenoid precursors, were those derived from the protection of carbonyl compounds with catechol. For catechol derived acetals, cleavage of the oxonium ion intermediate (scheme 145) to form the aldehyde would require an *ipso*-type substitution on the catechol aromatic ring, and this pathway may hence be

discounted.[165] On the minus side, the catechol acetals may be poor precursors for the oxonium ion intermediate presumed necessary in the transition state since delocalisation of the oxygen electrons reduces their ability to facilitate acetal opening (scheme 145).



scheme 145

In the event, the most difficult aspect of the reaction of the catechol acetal of benzaldehyde lay in its synthesis. Although the synthesis under Dean and Stark conditions exists in the literature,[217] protection under the reported reaction conditions yielded large quantities of unidentified polymeric material thus making the acetal **201** exceedingly hard to purify. Eventually, synthesis of a small amount was achieved by the reaction of catechol with phenyldichloromethane **200**



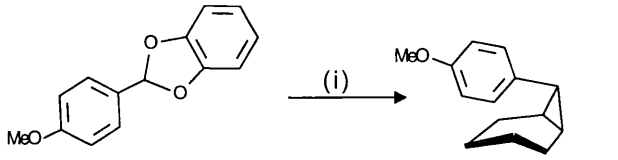
201 189 20%, 3.3:1 170 16%

i). Slow addition, Zn/Hg (20 equiv), $ZnCl_2$ (1.3 equiv), Me_3SiCl (10 equiv), cyclohexene (10 equiv), Et_2O

scheme 146

The catechol acetal **201** gave the desired cyclopropane **189** in 20% yield, along with a 16% yield of the ether insertion product **170** (scheme 146). The ratio of *cis* and *trans* isomers is the same as for other acetals and for the free aldehyde. Also interesting is the relatively high yield of the ether insertion product **170**. This may be due to the small amount of acetal utilised, since the reaction was consequently performed at higher dilution than is ideal.

A similar problem was encountered in the synthesis of the catechol acetal of anisaldehyde **202** In this case however, Dean and Stark conditions produced the desired acetal albeit in low yield. In contrast to all the previous work undertaken with both acetals and aldehydes however, the anisaldehyde derived acetal gave cyclopropane **194** in only the same yield as the benzaldehyde analogue (scheme 147)



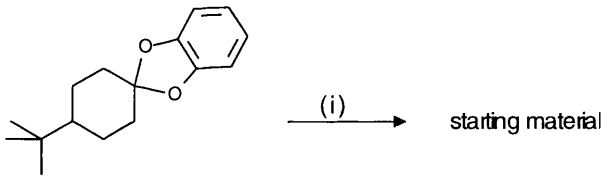
202 194 20%, 15:1

i). Slow addition, Zn/Hg (14 equiv), $ZnCl_2$ (1.3 equiv), Me_3SiCl (10 equiv), cyclohexene (9 equiv), Et_2O

scheme 147

Also surprising, as the reaction was performed at a similar low concentration as that of the benzaldehyde catechol-acetal, was the absence of the product of ether insertion. The implication is that for the carbenoid derived from the *para*-methoxy acetal **202** the efficiency of generation is lower than for the analogous unsubstituted benzaldehyde acetal **201**. This runs contrary to all the previous carbenoid work with aryl acetals and aldehydes and hence it is tempting to dismiss the result as an anomaly. Nevertheless, the results prove that catechol acetals themselves are applicable as direct precursors to arylzinc carbenoids.

The catechol-ketal of *tert*-butylcyclohexanone **203** was also investigated in a direct comparison with the ketals studied by O'Mahony (*vide supra* 2.3) Synthesis under Dean and Stark conditions was facile, and the ketal was exposed to the same reaction conditions as utilised for the earlier α-insertion The results and conditions used are summarised in scheme 148.



203

i). Zn/Hg, Me_3SiX

	solvent (reflux)	Lewis acid (eq)	time (days)	electrophile (eq)
1	Et_2O	-	2	Me_3SiCl (5)
2	Et_2O	$ZnCl_2$ (1)	6	Me_3SiCl (5)
3	THF	$ZnCl_2$ (1)	7	Me_3SiCl (5)
4	Et_2O	-	2	Me_3SiOTf (5)

scheme 148

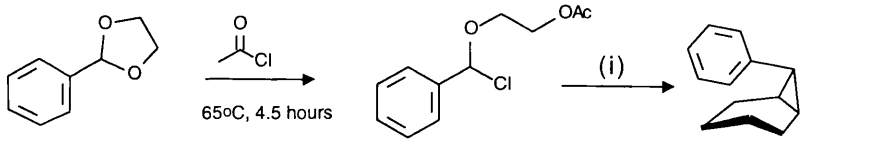
In all cases, only the starting material was isolated after workup. The stability of the ketal to the reaction conditions is total, a surprising discovery given the results of O'Mahony with alkyl ketals. The stability of acetals and ketals to hydrolysis generally increases in the order

$CH_2(OR')_2$ > $CHR(OR')_2$ > $CR_2(OR')_2$ due to the lower stabilisation of the oxonium ion intermediate.[175] The high stability of the catechol ketal **203** relative to the acetal is also perhaps a factor of the increased strain inherent in the transition state leading to the oxonium species. Equally opening to an oxonium ion is facilitated by anomeric overlap between the ketal oxygens.[172] The planar nature of the catechol acetal will clearly reduce this overlap.

In summary, the use of catechol-acetals has shown that acetals can react as zinc carbenoid precursors without recourse to regeneration of the parent aldehyde. The ketal derived from *tert*-butylcyclohexanone was completely stable to the reaction conditions. Whilst this is disappointing from the point of view of expanding the range of precursors available for the production of zinc carbenoids, it does imply excellent chemoselectivity under the reaction conditions.

2.3.6. α-Chloro Ethers as Carbenoid Precursors with Zinc

Acetals, although useful as zinc carbenoid precursors, have so far proved inferior to the parent carbonyl compounds as precursors for carbenoid formation. If the rate limiting step were assumed to be cleavage to the oxonium ion we reasoned that facilitating this process might increase the efficiency of carbenoid generation. In order to achieve this, one possibility was the use of the α-chloroether **204** derived from the reaction of an acetal with an acid chloride (scheme 149).[176]



188 204 189 26% 2.8:1

i). Slow addition, Zn/Hg (10 equiv), Me_3SiCl (5 equiv), cyclohexene (4 equiv), Et_2O reflux

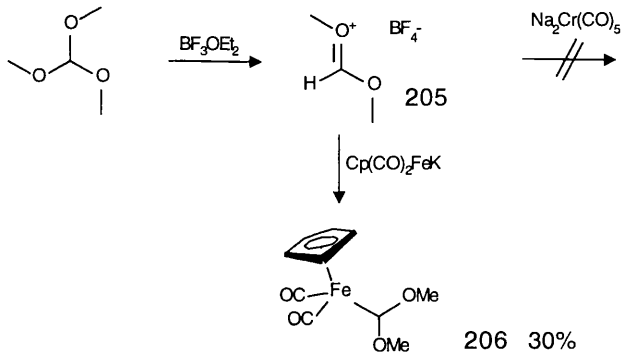
scheme 149

Thus, the acetal **188** was heated with acetyl chloride for 4.5 hours to give 98% formation of the α-chloroether **204**. Reaction of the resultant ether under standard conditions gave 7-phenyl norcarane **189** in 26% yield.

Although the compound may also simply be a precursor to the aldehyde under the reaction conditions, the reaction is interesting because it suggests that all α-chloroethers might be active as carbenoid precursors in the presence of zinc and chlorotrimethylsilane. They are however notoriously carcinogenic and would thus preferably be generated *in situ* from acetals.

2.4. The Generation of α-Alkoxyzinc Carbenoids from Orthoformates

The studies with acetals described earlier demonstrated the feasibility of organozinc carbenoid generation by electron delivery into stabilised oxonium ions. In common with the previously described work of Hegedus[167] utilising disodium chromium pentacarbonyl, we postulated that the oxonium species derived from the reaction of a Lewis acid with an orthoformate could act as a zinc carbenoid precursor. Hegedus and co-workers had generated the oxonium species **205** from the reaction of trimethylorthoformate with boron trifluoride but had found that nucleophilic addition of the chromium anion would not occur. In emulating this process with potassium cyclopentadienylirondicarbonyl, Hossain had later found that he could successfully generate the carbenoid precursor **205** from the same oxonium ion (scheme 150).[168]

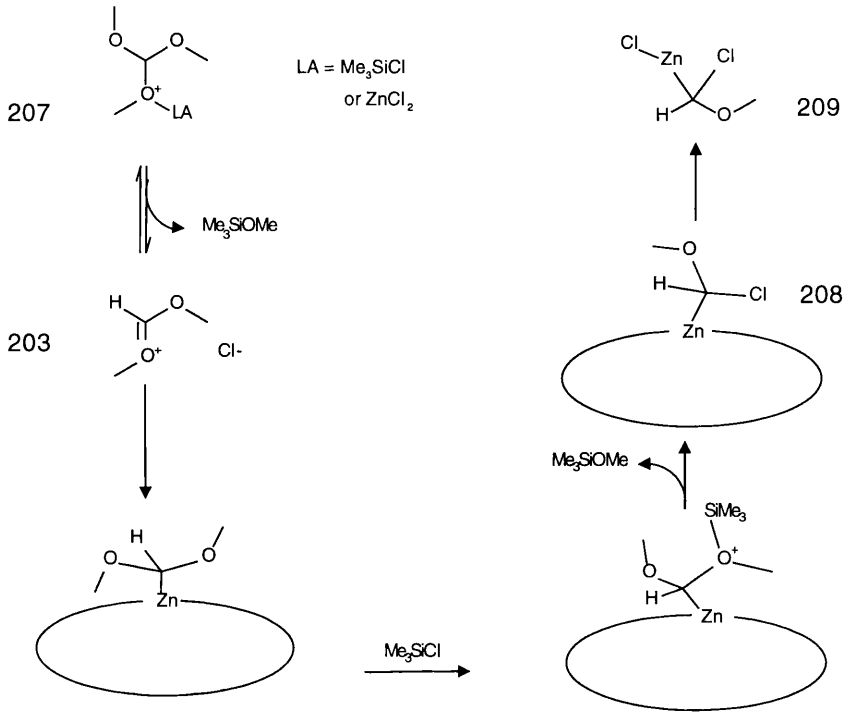


206 30%

scheme 150

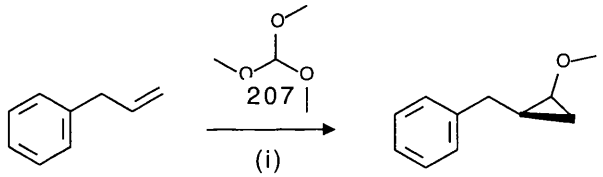
2.4.1. Preliminary Investigation of the Alkoxycyclopropanation of Simple Alkenes

By analogy to the generation of carbenoids from acetals, zinc and chlorotrimethylsilane it was supposed trimethylorthoformate **207** might be a suitable precursor for alkoxyzinc carbenoids. Lewis acid induced cleavage to the oxonium ion **205**, subsequent two electron transfer from zinc and further deoxygenation should thus generate an alkoxyzinc carbenoid **208** (scheme 150). In common with the previously generated zinc carbenoids, the alkoxyzinc carbenoid might be either a surface bound species such as **208** or an homogeneous alkoxyzinc carbenoid such as **209**. It was also hoped that the α-alkoxy substituent might profoundly affect the stability of the zinc carbenoid, as both free carbenes[192] and Fischer carbenes[65] are substantially stabilised by oxygen substituents. This generation of an α-alkoxyzinc carbenoid would represent the first synthesis of such a species.



scheme 151

Hence, in conjunction with my colleague Dr Rodney Fletcher, a preliminary investigation into the reaction of allylbenzene with trimethyl orthoformate, zinc amalgam and chlorotrimethylsilane was undertaken (table 14). It quickly became apparent that alkoxy cyclopropanes were being formed.



210 211

i). Zn/Hg (10 equiv), Me_3SiCl (4 equiv), Et_2O reflux, 48 hours

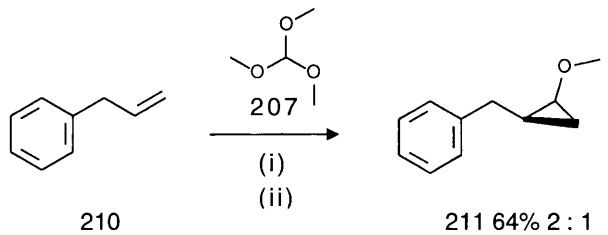
	207 equiv	other conditions	yield **211**	*cis / trans*
1	1	$ZnCl_2$ (1 equiv)	16	2 : 1
2	5	4 hr§	14	2 : 1
3	4	slow addition of **207**	30	2 : 1
4	2 + 2*	slow addition of **207**	37	2 : 1

* 2nd addition after 24 hr
§total reaction time 4 hr

table 14

The moderate yields of methoxycyclopropanes obtained were very encouraging and in common with previous cyclopropanations involving zinc carbenoids a *cis* diastereoselectivity was

evident. The use of ultrasound did not appear to increase the yield of the cyclopropanation. Interestingly, it was found that addition of further portions of orthoformate to the reaction mixture could increase the yield of cyclopropane and hence optimal reaction conditions for the cyclopropanation were sought along such lines.



210 211 64% 2 : 1

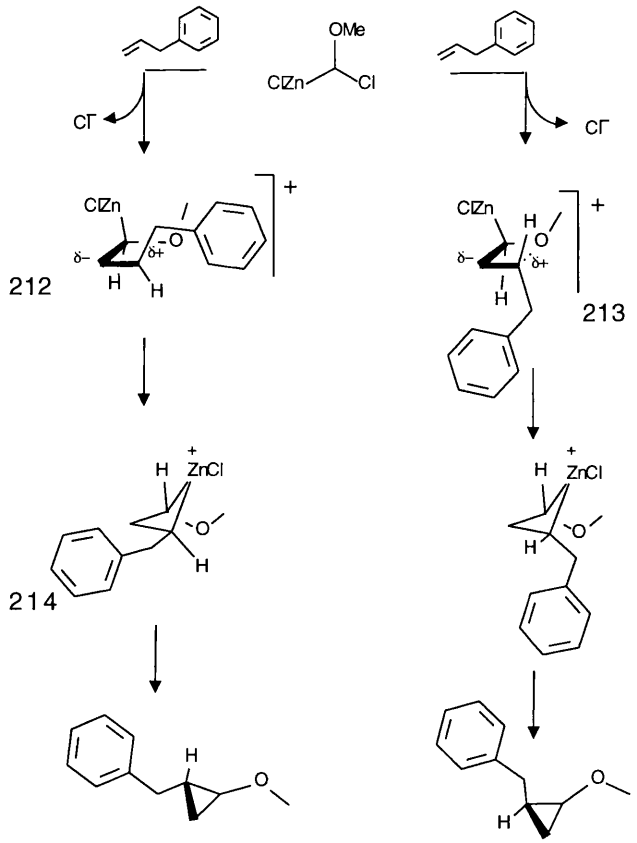
i). Zn/Hg (5 equiv), Me_3SiCl (8.5 equiv), **207** (6 equiv) Et_2O reflux, 24 hours

ii). Me_3SiCl (5 equiv), **207** (6 equiv) Et_2O reflux, 48 hours

scheme 152

It was found that the syringe pump addition of a large excess of trimethyl orthoformate to the reaction mixture, followed by a further similar addition after 24 hours gave the methoxy cyclopropane in good yield.

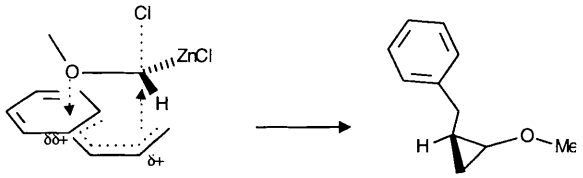
That the diastereoselectivity mirrors that found for all organozinc carbenoids generated from acetals and carbonyls is unsurprising. This diastereoselectivity also mirrors that found in most cyclopropanations with alkoxy Fischer carbenes (*vide supra* 1.3).



scheme 152

It is possible to envisage two intermediates, **212** and **213** in the cyclopropanation, both of which involve stabilisation of the developing positive centre by the α-oxygen of the carbenoid. Assuming there is a steric repulsion between the zinc and the benzyl substituent of the alkene the preference for the *cis* cyclopropane formation can be rationalised by imaging the closure of **212** to the metallocyclobutane **214**. This is analogous to the formation of metallocyclobutane intermediates suggested by Casey (*vide supra* 1.3)[67b] for tungsten carbenes.

Alternatively, the cyclopropanation might occur *via* a more concerted mechanism. Generation of the intermediate **215**, analogous to that proposed by Closs and Moss for aryl lithium carbenoids, involves the electrostatic stabilisation of the positive charge developing on the alkene by interaction with the methoxy substituent. The metal centre meanwhile remains remote.[207]



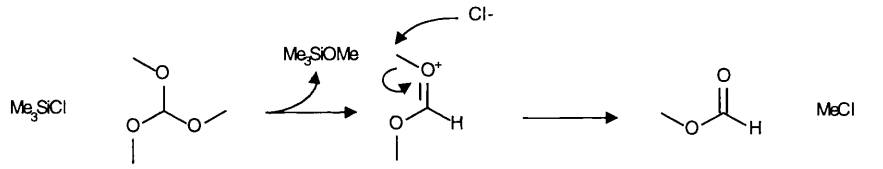
215 211

scheme 153

Thus, with the assistance of Dr Fletcher a series of preliminary experiments established the ideal conditions for the alkoxycyclopropanation of simple alkenes with trimethylorthoformate. The following section describes the subsequent expansion of these early studies. Some of the alkoxycyclopropanes described hereafter were first prepared by Dr Fletcher, but full characterisation and analyses were performed by the author of this thesis.

2.4.2 Further Studies into the Generation of Alkoxyzinc Carbenoids

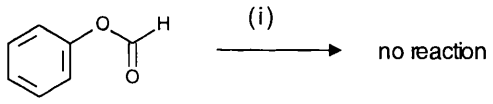
It was clear that the trimethyl orthoformate was being readily consumed by the reaction mixture, although no progress was made in identifying the fate of the majority of the intermediates thus generated. It is possible that carbenoid generation is a highly efficient process, but that the majority of the carbenoids produced are inserting into the solvent. Alternatively, the electron transfer might constitute the rate limiting step, and the oxonium intermediate **203** might simply be cleaved as shown to give the inert and volatile chloromethane **216** and methyl formate **217** (scheme 154).



203 217 216

scheme 154

It was also thought possible that formates themselves might be reactive in the presence of zinc and chlorotrimethylsilane. In order to test this hypothesis, phenyl formate **218** was submitted to the reaction conditions, but the compound proved completely inert (scheme 156).

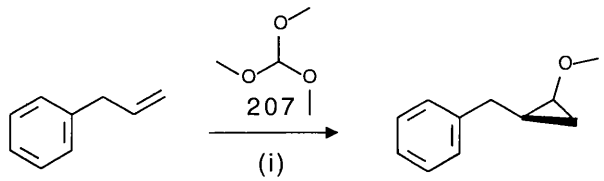


218

i). Zn/Hg, allylbenzene, $ZnCl_2$, Me_3SiCl

scheme 155

The use of boron trifluoride diethyletherate as the electrophile was also studied (scheme 156). Generation of the carbenoid with an excess of allyl benzene produced the alkoxycyclopropane **211** in low yield. The reaction proved more complex than for the corresponding experiment with chlorotrimethylsilane.

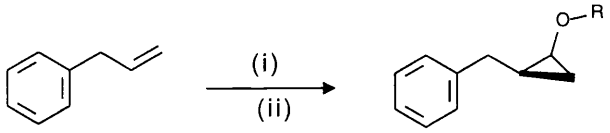


210 211 9% 1 : 1

i). Zn/Hg (10 equiv), $BF_3.OEt_2$ (1.3 equiv), allylbenzene (4 equiv), Et_2O reflux, 48 hours

scheme 156

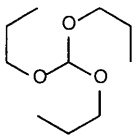
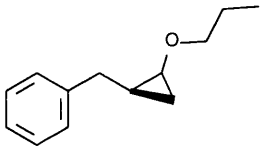
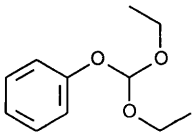
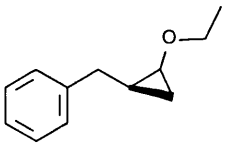
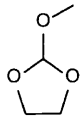
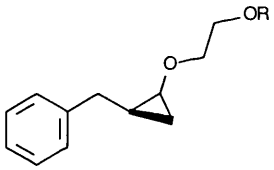
The ideal reaction conditions devised by Fletcher were applied to the synthesis of oxycylopropanes derived from a series of commercially available orthoformates and allylbenzene **210**. The results are given in table 15.



210 219

i). Zn/Hg (5 equiv), Me_3SiCl (8.5 equiv), orthoformate (6 equiv), Et_2O reflux, 24 hours

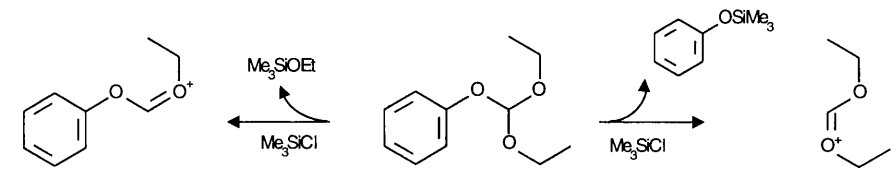
ii). Me_3SiCl (5 equiv), **207** (6 equiv,) Et_2O reflux, 48 hours

	orthoformate	product*	No.	yield	*cis / trans*
1			219a	43%	2 : 1
2			219b	67%	2 : 1
3			219c	R=OSiMe$_3$ 38%	3 : 1
			219d	R=H 17%	3 : 1

* for clarity, only the major isomer is shown

table 15

The tripropyl orthoformate (entry 1) gives the propyloxycyclopropane in good yield although significantly less than its trimethyl congener. This is presumably as a result of increased steric hindrance for oxonium ion formation and electron delivery. An improved yield however, was obtained with diethylphenylorthoformate **220** (entry 2), an unsymmetrical orthoformate with improved leaving group ability which afforded only the ethoxycyclopropane in good yield. The clear implication for this is that the oxonium directly generated *via* cleavage of the acetal is likely to be **222** rather than **221**, the phenoxy silane representing the best leaving group.

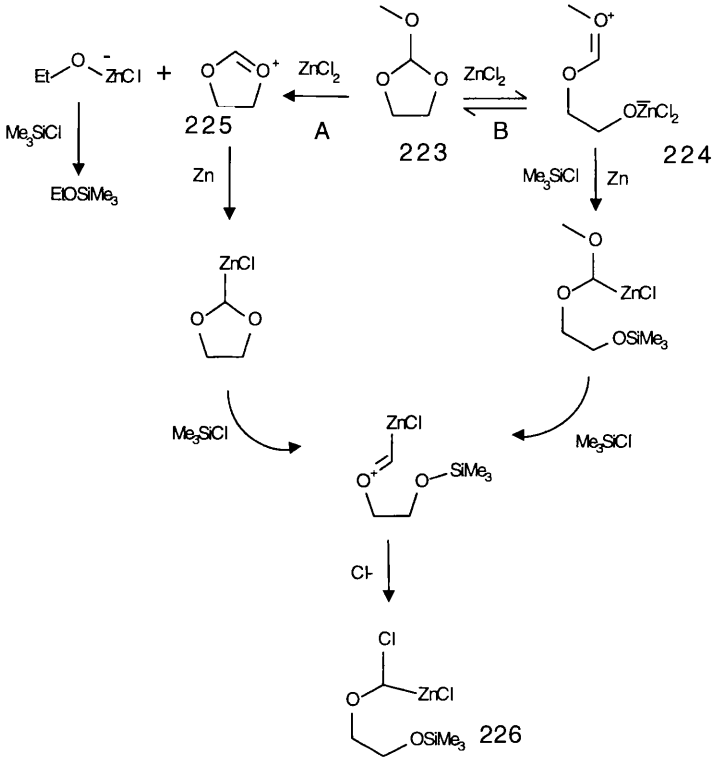


221 220 222

scheme 157

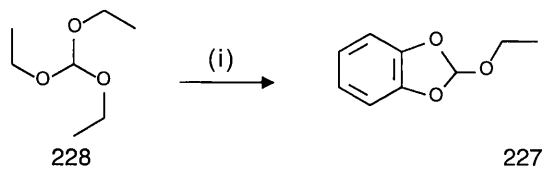
Most interestingly of all, the methoxydioxolane **223** gave only the hydroxyethoxycyclopropane (entry 3). In order to rationalise this result, it is necessary to consider in detail the various factors controlling the hydrolysis of cyclic orthoformates.

Zinc chloride induced cleavage of the orthoformate **223** may favour the release of ring strain and hence the synthesis of **224** *via* path B. As the silyloxy species is still attached however, the internal return to give **223** might be important. Hence the formation of oxonium **225** *via* pathway A would be favoured.[172] The formation of **225** is also associated with the greater increase in entropy. If cleavage and reduction do proceed *via* pathway B then the second deoxygenation can again occur in either of two fashions, and thus the observed carbenoid **226** is favoured statistically.



scheme 158

In order to further probe the selectivity of carbenoid formation from unsymmetrical orthoformates, we synthesised the catecholic orthoester **227** by the reaction of triethylorthoformate **228** and catechol. The orthoformate is formed in high yield (scheme 159).

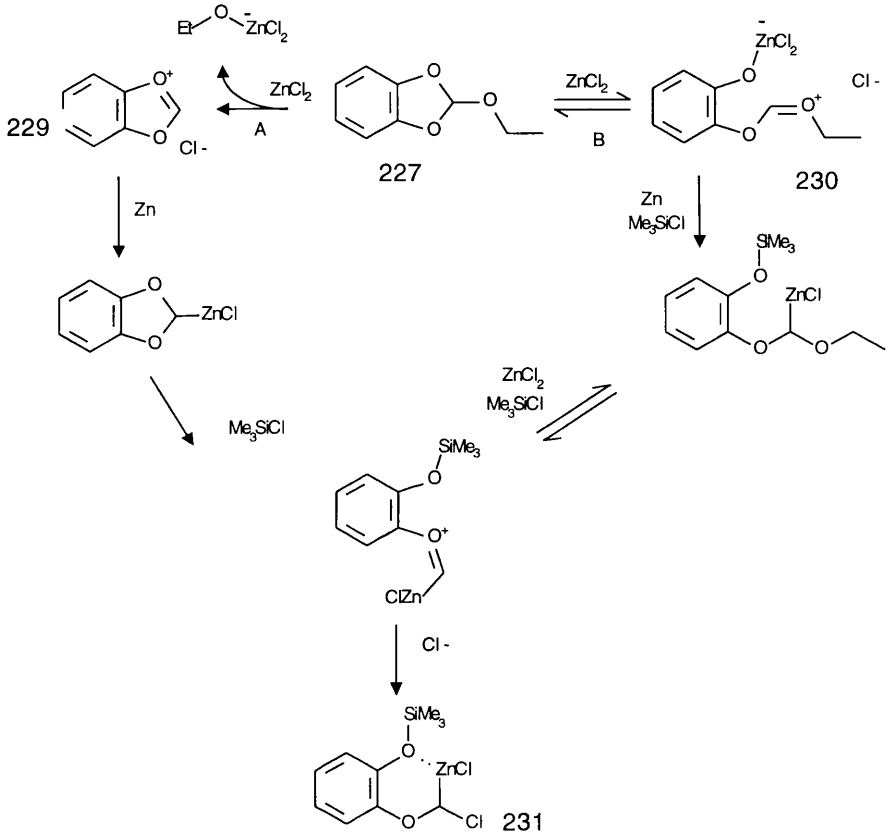


228 227

i). catechol, HCl cat, reflux, 96%

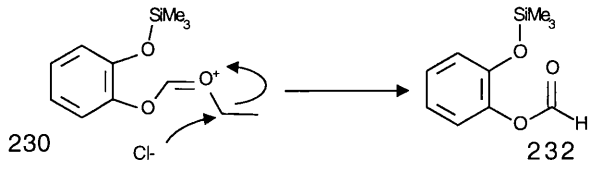
scheme 159

It could again be argued that there are two possible routes toward carbenoid formation beginning either with zinc chloride induced cleavage to the dioxolane oxonium **229** or the acyclic oxonium **230**. Relief of ring strain and the good leaving group ability of the silyl catecholate would seem to favour pathway B (scheme 160).



scheme 160

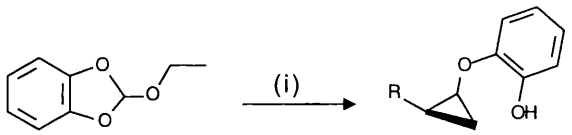
However formation of the oxonium **230** is reversible and thus the original equilibrium might favour formation of the dioxolane oxonium **229** *via* pathway A. In the initial cleavage to the oxonium ion **229** the loss of the ethoxysilane is favoured due to the greater basicity of the ethoxy oxygen and the oxonium ion **229** thus formed is also stabilised by delocalisation. Subsequent steps can only generate the carbenoid **231**, a species whose generation might be favoured thermodynamically by the intramolecular stabilisation afforded by co-ordination of zinc by the phenolic oxygen as shown in scheme 160.



scheme 191

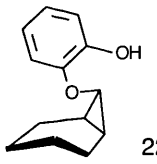
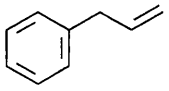
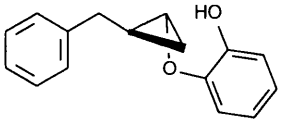
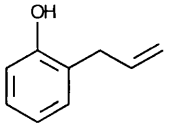
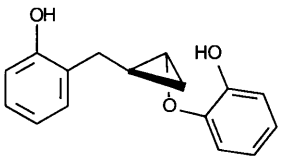
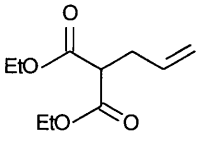
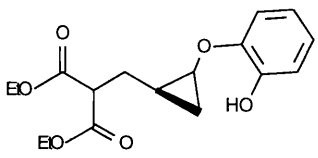
An alternative might be that the oxonium ion **230** produced through pathway B does not react primarily *via* zinc reduction, but is instead quickly cleaved to the inert catechol formate **232** (scheme 161). Such cleavage is known to occur in the Lewis acid hydrolysis of catecholic orthoesters in the presence of a nucleophilic species (*vide infra* 2.4.8.).[247]

Ethylcatechol orthoformate **227** was screened as a zinc carbenoid precursor with a variety of simple alkenes, as shown in table 16. The alkenes were employed in excess and the resulting cyclopropane yields are stated relative to the amount of orthoformate used.



227 228

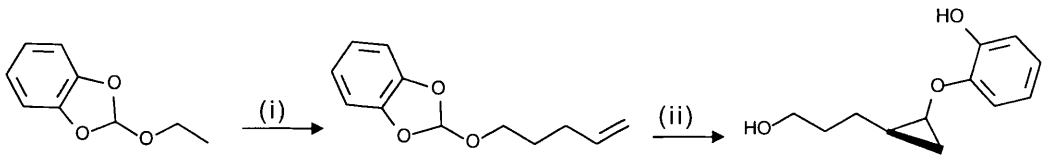
i). slow add^{n} of **227**, Zn/Hg (10 equiv), Me_3SiCl (5 equiv), $ZnCl_2$ (1 equiv,) alkene (4 equiv), Et_2O reflux

	alkene	product*	yield	*cis / trans*
1		 228a	14%	2. 5 : 1
2		 228b	23%	1 : 1.2
3		 228c	5%	1 : 1.1
4		 228d	19%	10 : 1

* for clarity, only the major isomer is shown

table 16

The aryloxycarbenoid **231** is evidently the only product of ethylcatechol orthoformate reduction by zinc, in accordance with the preference demonstrated by the methoxydioxolane acetal. Yields are all moderate, with the phenolic alkene derivative (entry 3) providing the lowest yield of cyclopropane. The diastereo-preference varies widely and is self evidently substrate dependent. Entries 2 and 3 show only marginal diastereoselectivity, both in favour of the *trans* cyclopropane. Contrastingly the cyclopropanation of diethylallylmalonate (entry 4) however appears to proceed with high diastereoselectivity for the *cis* isomer.



227 233 32% 234 15% 2 : 1

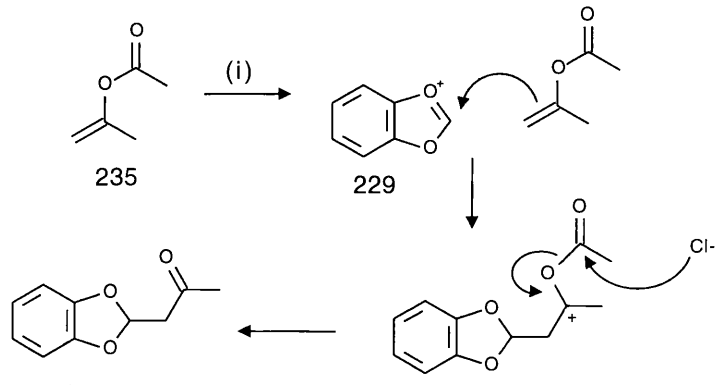
i) 4-penten-1-ol, reflux,

ii).slow addition to Zn/Hg (17 equiv), Me_3SiCl (4 equiv), Et_2O reflux 24 hours

scheme 162

The alkoxy cyclopropanation of simple alkenes evidently requires the use of an excess of orthoformates for efficient organozinc carbenoid generation and trapping. This is reflected in the (potentially intramolecular) aryloxycyclopropanation of the unsaturated orthoformate **233** (scheme 162). Only one molar equivalent of alkoxycarbenoid can be produced and the orthoformate **233**, derived from the transesterification of ethyl catechol orthoformate with 4-penten-1-ol, reacts to give solely the aryloxy cyclopropane **234** in the expected yield.

Further insight into the relative rates of zinc carbenoid generation *via* ketones, acetals and orthoesters was gained from the attempted cyclopropanation of isopropenyl acetate **235** with ethyl catechol orthoformate **227** (scheme 163). The reaction of enol acetates with orthoformates in the presence of Lewis acids is well known.[193]



235 229

236 20%

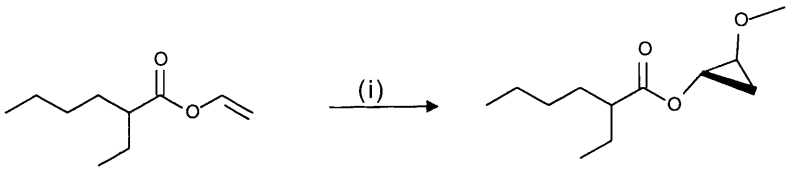
i). slow addition of ethylcatechol orthoformate (0.3 equiv),

Zn/Hg Me_3SiCl (1.1 equiv), Et_2O reflux 24 hours

scheme 163

The isopropenyl acetate reacts as a nucleophile, trapping the oxonium intermediate **229** to form the keto-acetal **236** which was then isolated in moderate yield. The isolation of **236** from the reaction mixture suggests that electron transfer from zinc into the dioxolane oxonium **229** is probably the rate limiting step in the carbenoid generation. It is also of note that the product contains two centres which might act as carbenoid precursors under the reaction conditions. Even after refluxing under the standard conditions for twenty four hours however, the compound **236** was recovered intact. The isolation of this supports the conclusions of earlier work with catechol acetals (*vide supra* 2.3.5) and alkyl ketones (*vide supra* 2.1.2.2.) which had previously shown such species to be only partially effective as organozinc carbenoid precursors.

Successful cyclopropanation of a more hindered enol acetate was achieved in the reaction of ethylhexanoate vinyl ester **240** with trimethyl orthoformate. Utilising a large excess of orthoformate allowed for the synthesis of the highly functionalised cyclopropane **241** in a *cis / trans* ratio of 1 : 2.6.

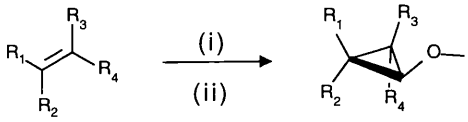


240 241 46% 2.6 : 1

i). Zn/Hg (5 equiv), Me_3SiCl (8.5 equiv), **207** (6 equiv), Et_2O reflux,48 hours
then Me_3SiCl (5 equiv), **207** (6 equiv), Et_2O reflux, 48 hours

scheme 164

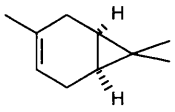
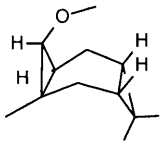
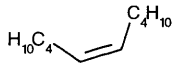
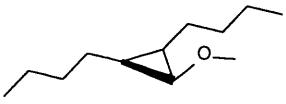
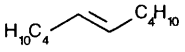
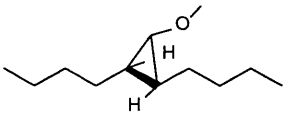
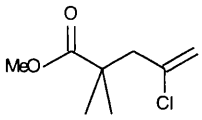
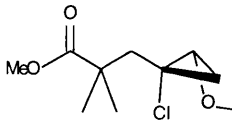
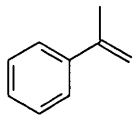
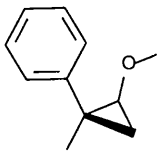
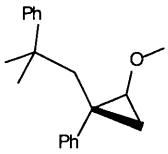
The cyclopropanation of other electron rich alkenes was investigated under the standard conditions devised by Motherwell and Fletcher. The results of the cyclopropanation of some alkenes with trimethylorthoformate are summarised in table17.



238

i). trimethyl orthoformate **207** (6 equiv), Zn/Hg (5 equiv), Me_3SiCl (8.5 equiv), Et_2O reflux, 24 hours;

ii). trimethyl orthoformate **207** (6 equiv), Me_3SiCl (5 equiv), Et_2O reflux, 48 hours

	alkene	product*	yield (5)	*cis / trans*
1		 238a	65%	5 : 2
2		 238b	53%	6 : 1
3		 238c	56%	-
4		 238d	46%	4 : 1
5		 238e	56%	1.7 : 1
		 238f	9%	3 : 1

* for clarity, only the major isomer is shown

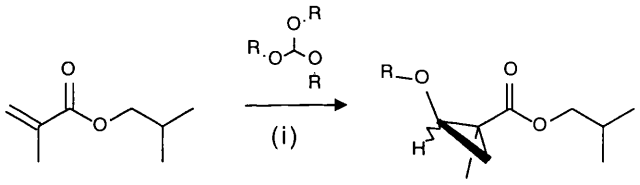
table 17

As with monosubstituted alkenes, the cyclopropanation of electron rich disubstituted and trisubstituted alkenes proceeds in good yields. Once again, it is evident that a diastereomeric preference for the *cis* isomer is dominant.

It is interesting to note that both the *cis* and *trans* decene (entries 2 and 3) give methoxycyclopropanes with complete retention of alkene geometry, suggesting that the addition is a concerted process. It is also noteworthy that the yield of methoxycyclopropane is the same for both the *E* and *Z* isomers, a result not mirrored in the reactivity of other zinc carbenoids.[e8] The highly functionalised vinyl chloride ester (entry 4) is also stable to the reaction conditions. The methoxcylopropane (entry 5) derived from α-methyl styrene presumably stems from the Lewis acid-catalysed dimerisation of the styrene prior to cyclopropanation.

2.4.3. The Alkoxycyclopropanation of Electron Poor Alkenes

The cyclopropanation of electron poor alkenes was also investigated using orthoformates. Attempted cyclopropanation of ethyl acrylate gave no cyclopropanes and it was apparent that ethyl acrylate was undergoing polymerisation under the reaction conditions. Isobutyl methacrylate **242** was however stable to the reaction conditions, and could be cyclopropanated to generate the ethoxy- and methoxycyclopropane derivatives.



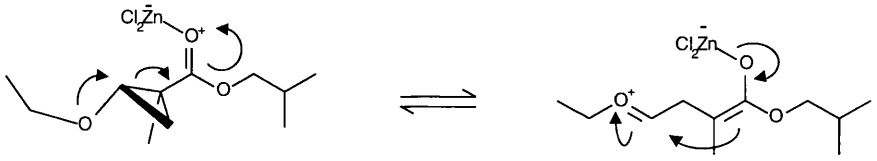
242 343a R= Me 4% 1 isomer only

243b R= Et 16% 1 isomer only

i). Zn/Hg (5 equiv), Me_3SiCl (4 equiv), orthoformate (2 equiv,) Et_2O reflux, 24 hours

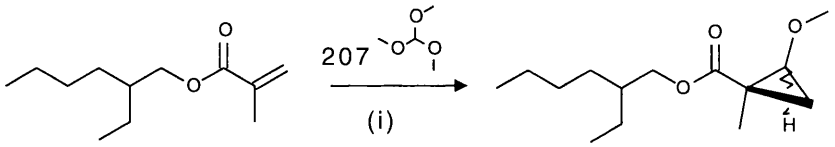
scheme165

The cyclopropanation occurs in moderate yield with triethylorthoformate **228** and in poor yield with trimethylorthoformate **207**. Interestingly, both cyclopropanations produce only one diastereoisomer. This could be explained by the reversibility of the Lewis acid catalysed ring opening shown in scheme 166, and hence one may assume that the product observed is the thermodynamic one.



scheme 166

Conversely, the cyclopropanation of 2-ethylhexylmethacrylate proceeded in good yield, affording the methoxycyclopropane **245** as a mixture of diastereoisomers (scheme 167) as yet unassigned.



245 43% 3 : 1

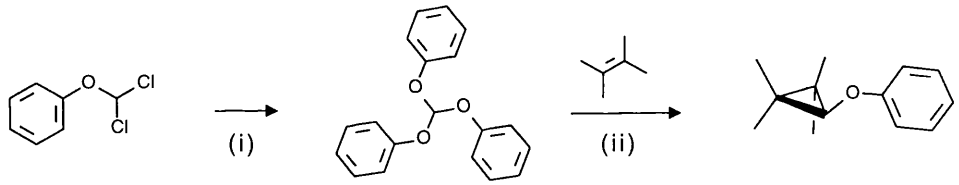
i). Zn/Hg (5 equiv), Me_3SiCl (8.5 equiv), **207** (6 equiv), Et_2O reflux, 24 hours

then Me_3SiCl (5 equiv), **207** (6 equiv), Et_2O reflux, 48 hours

scheme 167

2.4.4. The Synthesis of Aryloxycyclopropanes from Triarylorthoformates

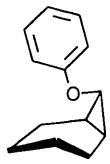
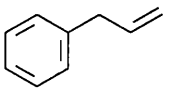
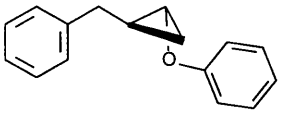
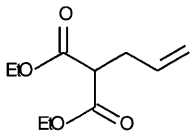
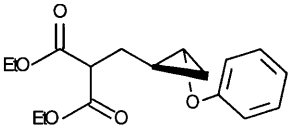
It was postulated that a triarylorthoformate might produce carbenoids more effectively than a trialkyl species as elimination to generate formates would not readily occur. It was also suggested that a triarylorthoformate might act as an efficient carbenoid precursor because all three phenoxy substituents represent good leaving groups. The synthesis of triphenyl orthoformate was readily achieved *via* the reaction of phenoxydichloromethyl ether **245** with sodium phenoxide. The crystalline triphenyl orthoformate **246** was utilised effectively in the cyclopropanation of some electron rich alkenes (table 18).



244 246 71% 255

i). PhONa, (2 equiv)

ii). slow add^n. Zn/Hg (10 equiv), Me_3SiCl (5 equiv), $ZnCl_2$ (1 equiv), alkene (4 equiv), Et_2O

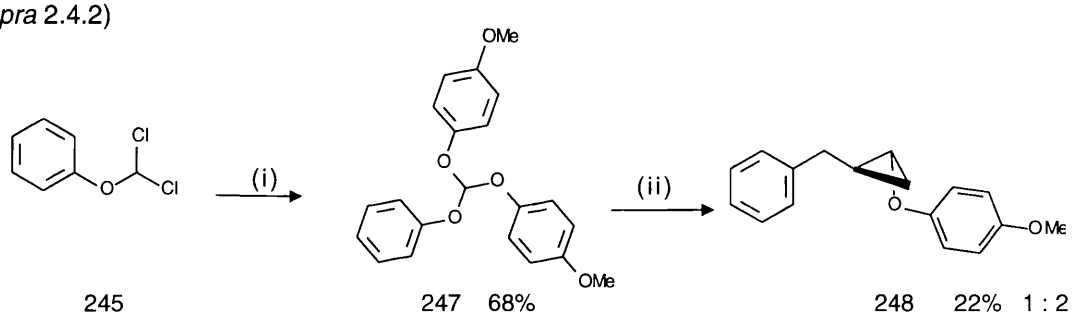
	alkene	product*	yield§ (%)	cis / trans
1		 255a	50	1.6 : 1
2		 255b	24	1 : 3
3		 255c	30	1 : 1.2

* for clarity, only the major isomer is shown

§relative to triphenylorthoformate

table 18

Although the yields were moderate, the cyclopropanation products from the reaction with diethyl allyl malonate (entry 3) and allybenzene (entry 2) were interesting in that both generated the *trans* phenoxycyclopropane as the major product. The formation of the *trans* cyclopropane with allylbenzene is in accord with the results of the cyclopropanation with ethylcatechol orthoformate. The isolation of an excess of the *trans* phenoxycyclopropane with diethylallylmalonate however, is the reverse of the reaction of ethylcatechol orthoformate (*vide supra* 2.4.2)



245 247 68% 248 22% 1 : 2

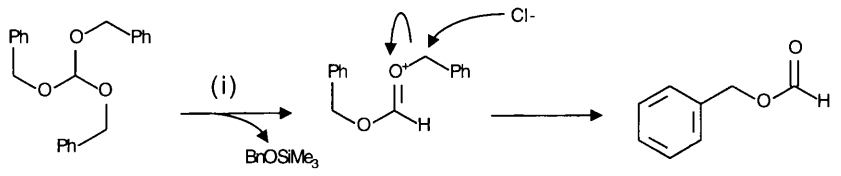
ii). $MeOC_6H_4ONa$, (2 equiv)

i). slow add^n of **247**, Zn/Hg (10 equiv), Me_3SiCl (5 equiv), $ZnCl_2$ (1 equiv), alkene (4 equiv)

scheme 168

Similarly, the non-symmetric orthoformate **247** also synthesised from dichlorophenylether, gave predominantly the *trans* cyclopropane **248** on reaction with an excess of allylbenzene. Only the *para*-methoxy aryloxy zinc carbenoid has formed. This in agreement with the concept of the phenolate forming a superior leaving group compared to the *para*-methoxyphenolate.

By way of contrast the use of tribenzyl orthoformate **249** gave no trace of cyclopropanes at all, the major product being the benzyl formate **250**. This again confirms that formates are inert under the reaction conditions and implies that the generation of formates from oxonium ions is likely to be a major pathway of orthoformate decomposition (scheme 169) particularly when alkyl oxygen cleavage occurs at a potentially low energy carbocation site such as a benzylic position.



249 250 30%

i). slow add^n of **249** Zn/Hg (10 equiv), Me_3SiCl (5 equiv), $ZnCl_2$ (1 equiv), alkene (4 equiv), Et_2O reflux

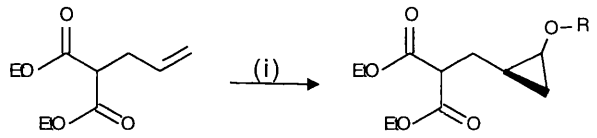
scheme 169

The stereochemistry of cyclopropanation is clearly less predictable for aryloxyzinc carbenoids than for the organozinc carbenoids derived from aryl aldehydes and acetals. The structures of both the carbenoid precursor and the alkene play important roles in determining the

stereochemical outcome of cyclopropanation. Each case still has to be considered individually in order to attempt a rationalisation of the observed stereochemistry although most probably steric rather than electronic effects are important.

2.4.5. Observations on the Alkoxy- and Aryloxycyclopropanation of Diethylallylmalonate

The difficulties inherent in the prediction of the stereochemical outcome of alkoxycyclopropanation can be exemplified by considering the cyclopropanation of diethylallylmalonate (table 19). Under identical conditions triethyl orthoformate (entry 1), ethylcatechol orthoformate (entry 2) and triphenyl orthoformate (entry 3) all produce *cis* and *trans* cyclopropanes with differing diastereoselectivity.



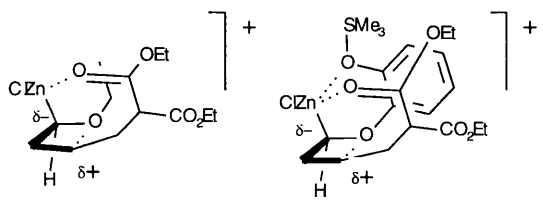
i). slow add^{n} of orthoformate, Zn/Hg (10 equiv), Me_3SiCl (5 equiv), $ZnCl_2$ (1 equiv), alkene (4 equiv), Et_2O reflux

entry	R	No.	yield*	*cis / trans*
1	Et	253	22%	3.5 : 1
2	2-hydroxyphenyl	228d	19%	10 : 1
3	Ph	255c	30%	1 : 1.2

* relative to alkene

table 19

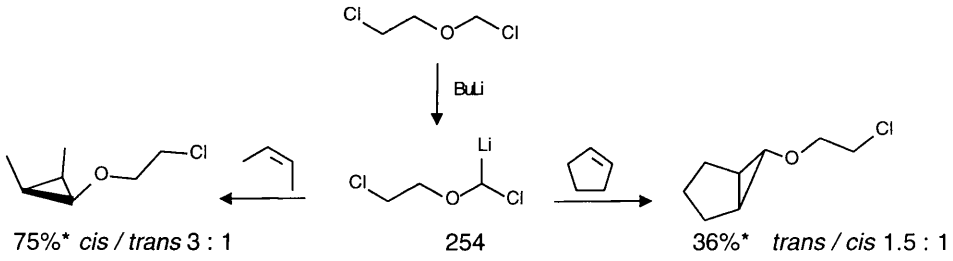
It is possible to visualise how the ethoxy carbenoid produces the *cis* diastereoismer with reasonable diastereoselectivity *via* the transition state **251**. The intermediate is stabilised by interaction between the developing positive centre, the alkoxy group and a co-ordination between malonate and zinc. In order to generate the *cis* cyclopropane, direct closure of **251** to the cyclopropane without formation of the intermediate metallocyclobutane is required. For the catecholic carbenoid it can be imagined that the *ortho* oxygen is able to chelate the zinc centre, and thus tight control exists in the transition state **252.** Consequently a high diastereoselectivity in the cyclopropanation with ethylcatechol orthoformate is observed. Contrastingly, the phenoxyzinc carbenoid appears to favour *cis* and *trans* cyclopropanation equally.



251 252

scheme 17

In his early work on the synthesis of alkoxy cyclopropanes *via* lithium carbenoids Schöllkopf also observed that the diastereospecificity of cyclopropanation was often substrate specific. He found that reaction of the lithium chloroethoxy carbenoid **254** with cyclopentene gave mostly the *trans* isomer, whereas a similar reaction with 2-butene gave the *cis* isomer as the major product (scheme 171).[90]



75%* *cis* / *trans* 3 : 1 254 36%* *trans* / *cis* 1.5 : 1

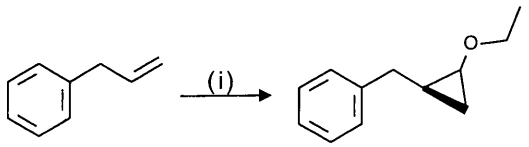
* for clarity the major isomer is shown

scheme 171

Whatever the considerations as to the mechanism involved, a note of caution is necessary. Under the reaction conditions commonly utilised, especially in the presence of a large excess of chlorotrimethylsilane, it is possible that some degree of alkoxycyclopropane decomposition may be occurring. Although cyclopropanes have always previously proved stable to the reaction conditions, the oxygen substituent on the cyclopropane makes the carbocycle more prone to opening in the presence of an electrophile. Consequently, it is possible that more highly strained cyclopropanes such as the *cis*-phenoxy compounds[239] are decomposing under the reaction conditions. Although no decomposition products have so far been identified, the reaction clearly requires investigation as to this possibility.

2.4.6. Further Optimisation of Reaction Protocol for Alkoxycyclopropanation

The slow addition of the orthoformate to the reaction system allows for the synthesis of oxycyclopropanes in good yields. It was reasoned however, that the slow addition might be unnecessary as the alkoxyzinc carbenoid produced should not react with the parent orthoformate or the intermediate oxonium species. Consequently, dropwise addition over a few minutes of an excess of triethyl orthoformate **228** to allylbenzene was utilised in the synthesis of the ethoxycyclopropane **255**. The cyclopropanation occurred in good yield, and clearly demonstrates that there is scope for the lowering of reaction times.



210 219b 69% 2 : 1

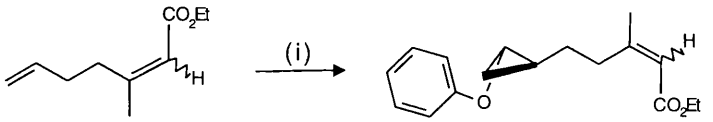
* relative to allylbenzene

i). dropwise addition of triethylorthoformate (3.5 equiv), Zn/Hg (19 equiv), Me_3SiCl (16 equiv), Et_2O reflux 24 hours

scheme 172

2.4.7. Chemoselective Alkoxy- and Aryloxy-Cyclopropanation

The alkoxyzinc carbenoids derived from orthoformates are evidently ambiphilic in nature, able to cyclopropanate both electron rich and electron poor alkenes. Free alkoxycarbenes[194] have been shown to be highly nucleophilic in nature, and Fisher carbenes also react as nucleophiles with electron deficient olefins (*vide supra* 1.3).[65] When triphenyl orthoformate **246** was reacted with an excess of the diene ester **256** the only product of the cyclopropanation was the terminal phenoxycyclopropane **257**, with the *trans* diastereoismer in a slight excess (scheme 173). The yield is relative to the amount of orthoformate used.



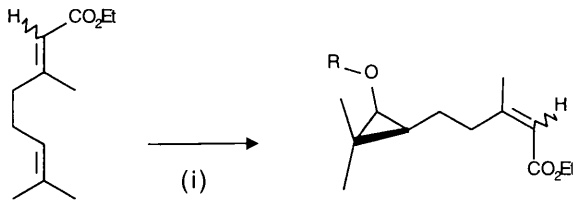
256 (*Z* / *E* 2 : 1) 257 (*Z* / *E* 2 : 1) 34% *cis* / *trans* 1 : 1.2

i). slow addition of triphenylorthoformate **246** (0.5equiv), alkene (1 equiv), Zn/Hg (5 equiv), Me_3SiCl (2 equiv), Et_2O reflux, 18 hours

scheme 173

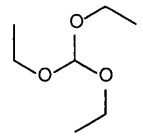
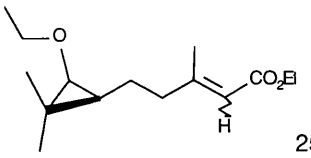
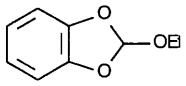
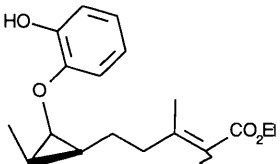
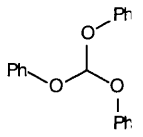
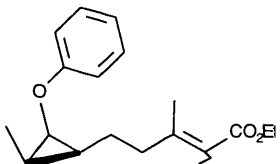
It was postulated that as the terminal alkene was the less highly substituted, the comparison with the more hindered trisubstituted electron poor α,β-unsaturated olefin was unfair.

Consequently, in order to afford a more direct comparison, the diene ester **258** was synthesised and cyclopropanation investigated with a range of orthoformates. After much initial work in which very little could be satisfactorily isolated from the reaction mixtures, it was discovered that the ideal conditions required a slow addition of a four-fold excess of the orthoformate. The reaction nevertheless afforded as the major product only moderate yields of monocyclopropanes. In all cases, a range of other, as yet unidentified compounds were also produced.



258 (*Z* / *E* 3 : 1) 259

i). orthoformate (4 equiv), Zn/Hg (40 equiv), Me_3SiCl (20 equiv), Et_2O reflux, 48 hours

	orthoformate	product*	yield§	*cis / trans*
1		 259a	44%	2 : 1
2		 259b	17%	4 : 1
3		 259c	12%	4 : 1

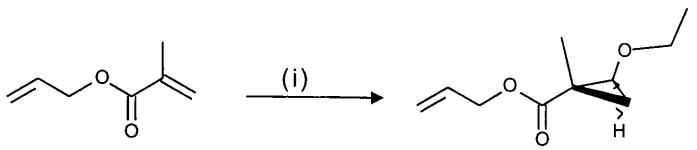
* for clarity, only the major isomer is shown

§ yields relative to alkene

table 20

All the reactions gave primarily the *cis* cyclopropanes shown. The reaction of triphenyl orthoformate in particular proved complex, a fact reflected in the low isolated yield. Nevertheless, the results seemed to show conclusively that the carbenoids being produced will chemoselectively cyclopropanate the electron rich double bonds in such chemically differentiated dienes.

In complete contrast to the above results however, the cyclopropanation of an excess of allylmethacrylate **260** with triethylorthoformate provided exclusively the cyclopropane **261** Employing an excess of the orthoformate generated a highly complex mixture, the constituents of which remain unidentified.



260 261 12% 1 isomer only

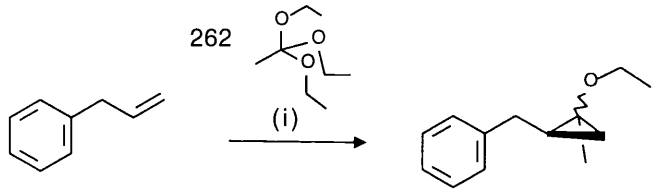
i). triethylorthoformate (0.4 equiv), Zn/Hg (4 equiv), Me_3SiCl (2 equiv), Et_2O reflux, 24 hours

scheme 174

In summary, chemoselective alkoxy- and aryloxycyclopropanation is generally observed. Further investigation is necessary however, if a full understanding of the factors which influence the chemoselectivity of alkoxyzinc carbenoids is to be acquired

2.4.8. Alkoxy- and Aryloxyzinc Carbenoids Derived from Orthoesters

The utilisation of orthoesters to produce highly functionalised alkoxyzinc carbenoids was also investigated. In early work, Fletcher had found that the slow addition of a four-fold excess of triethylorthoacetate **262** to allylbenzene 210 gave only a 2% yield of the alkoxycyclopropane **263** (scheme 175).[198]

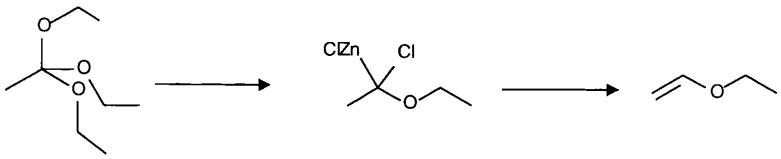


210 263 2%, 2 : 1

i). triethylorthoacetate **262** (4 equiv), Zn/Hg (20 equiv), Me_3SiCl (20 equiv), Et_2O reflux, 48 hours

scheme 175

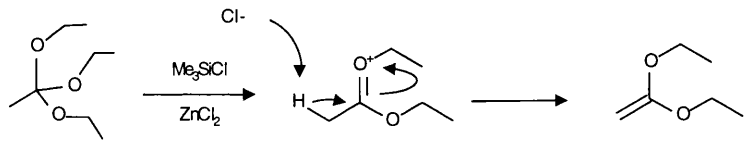
It is probable, in common with the reactivity of carbenoids derived from dihalolkanes[98] and alkyl Fischer carbenes[65] that the majority of the carbenoid is lost to α-insertion with formation of the volatile enol ether **263** (scheme 176).



262 263

scheme 174

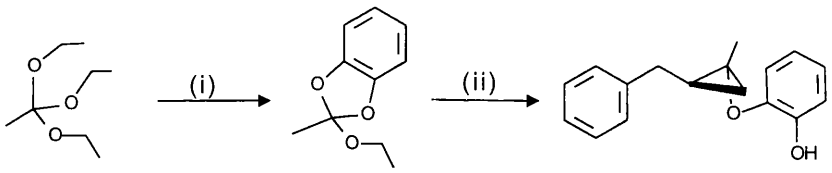
Alternatively, the orthoacetate could be acting as the precursor for the generation of a ketene acetal **264** by the elimination of of an α-acetate proton. It is however unusual to observe the production of ketene acetals from orthoesters lacking activating α-substituents such as CN, CO_2R or Ph (scheme 175).[193] The reactivity profile of ketene acetals under the reaction conditions is unknown.



262 264

scheme 177

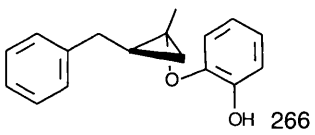
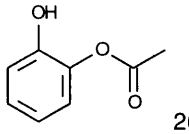
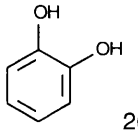
In order to further investigate the utility of simple orthoacetates in cyclopropanation, the catecholic derivative **264** was synthesised, and its efficiency in the cyclopropanation of allylbenzene studied (scheme 178).



262 265 *trans* isomer 266

i). catechol (1 equiv) 110°C 3hrs, 59%

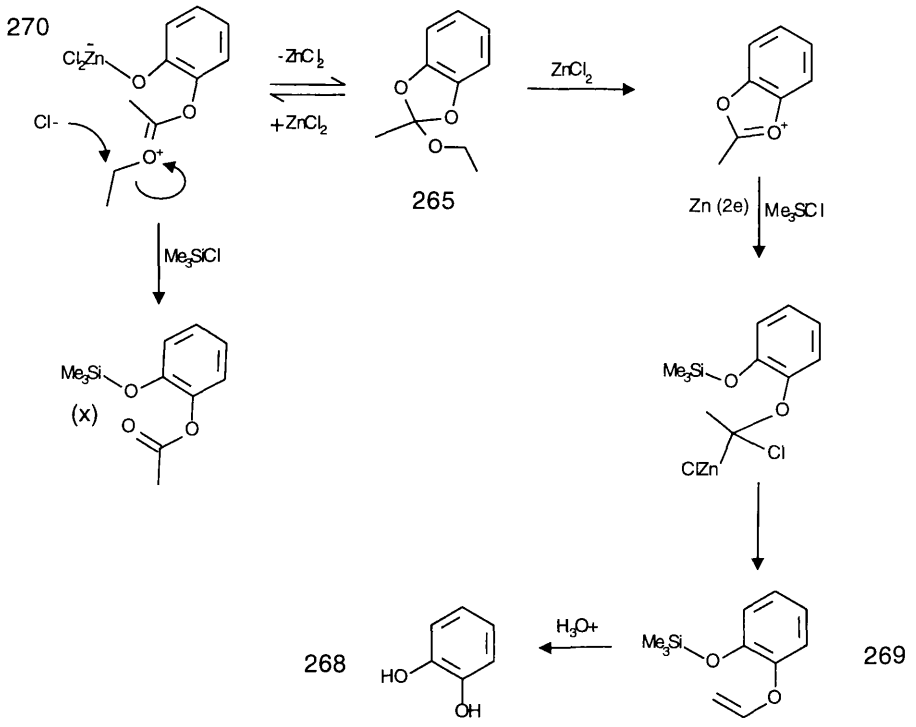
ii). allylbenzene (3 equiv), Zn/Hg (100 equiv), Me_3SiX (4 equiv), Et_2O reflux, 48 hours

	products		
electrophile	 266	 267	 268
Me_3SiCl	0 %	39%	16%
Me_3SiOTf	6% (1 : 2)*	4%	49%

* *cis / trans*

scheme 178

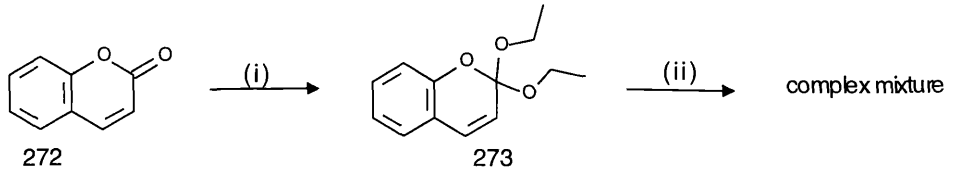
The use of chlorotrimethylsilane as the electrophile fails to produce any cyclopropane. The major product, catecholmonoacetate **267**, is presumably the product of cleavage of the oxonium ion **270** by chloride ion (scheme 179.)[247] Since the ester of **267** is stable under the reaction conditions, the yield of catechol **268** is almost certainly due to the hydrolysis on work up of **269**, the product of α-insertion (scheme 179).



scheme 179

The use of trimethylsilyltriflate however, allows for the generation of the aryloxycyclopropane **266** albeit in low yield. The compound is predominantly the *trans* diastereoisomer. Of further interest is that the yield of catechol monoacetate **268** is now very low, confirming the previous hypothesis that the formation of **268** was a function of the cleavage of the oxonium ion **270** by chloride ion.[247] Catechol **268** is now the major product suggesting that, as predicted, α-insertion is the dominant pathway of carbenoid decomposition.

An orthoester immune to α-insertion **273** was synthesised from coumarin **272**. Reaction with zinc and trimethylsilyltriflate however produced a highly complex mixture from which no identifiable products could be isolated (scheme 180)



272 273

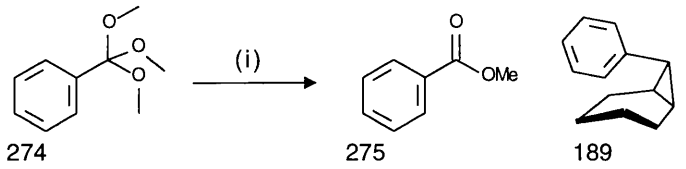
I). Me_3OBF_4 then NaOEt, 30%.

ii). Zn/Hg, Me_3SiOTf, allylbenzene, Et_2O reflux.

scheme 180

The loss of the carbenoid *via* α-insertion is also impossible for the methoxy-phenyl carbenoid derived from trimethylorthobenzoate **274**. The reaction of trimethylorthobenzoate with cyclohexene was hence investigated (table 21). Even the use of trimethylsilyltriflate as the electrophile however produced none of the target cyclopropane, the main product in all cases

being methyl benzoate **275**. In an unexpected twist however, the reactions did afford 7-phenylnorcarane **189** in low yield (table 21).



274 275 189

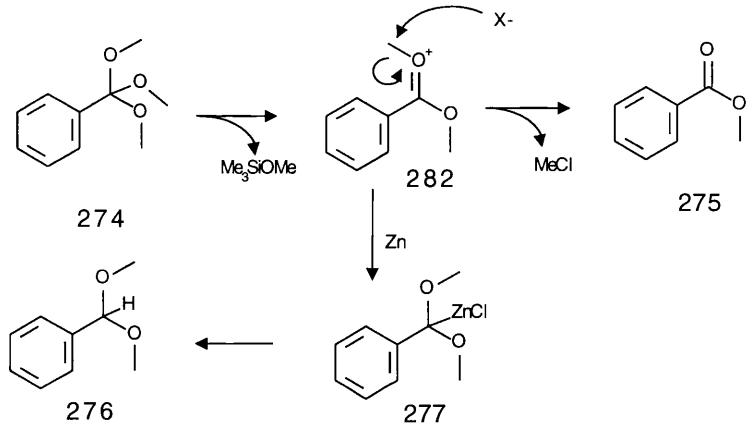
i). cyclohexene (4 equiv), Zn/Hg (10 equiv), electrophile (5 equiv)

	Lewis ac. (equiv)	electrophile	solvent (temp)	products %* 275	189
1	$ZnCl_2$ (1)	Me_3SiCl	Et_2O (r.t.)	45	6
2	$ZnCl_2$ (1)	Me_3SiCl	Et_2O (reflux)	63	8
3	-	Me_3SiOTf	Et_2O (reflux)	56	5
4	-	Me_3SiCl	EtOAc (r.t.)	48	6

* relative to orthoester

table 21

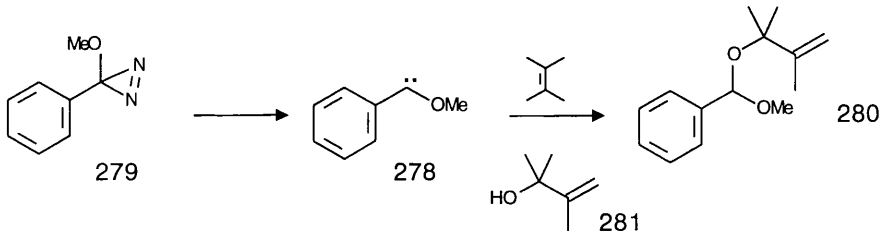
The isolation of phenylnorcarane **189** came as a complete surprise. Assuming the stability of the ester **275** for which there is strong evidence, one possible route to phenylnorcarane first involves the production of the acetal **276** by reduction of the zinc intermediate **277**. The acetal could simply be a product of the protic quench of the carbon zinc bond, although this does imply an extended lifetime of the intermediate **277**. This is in fact analogous to the generation of alcohols as byproducts in the Clemmensen reaction of carbonyls (*vide supra* 2.1.).



274 282 275 276 277

scheme 180

Interestingly the free methoxyphenylcarbene **278** , when generated from 3-methoxy-3-phenyldiaziridine **279** showed low reactivity in the cyclopropanation of simple alkenes.[195] In the attempted cyclopropanation of tetramethylethylene utilising the alkene as solvent, the acetal **280** was isolated. It was concluded, in the absence of any alternative explanation, that the carbene was reacting extremely selectively with traces of the alchohol **281** present as a minor impurity (scheme 181).



scheme 181

Whatever the route to phenylnorcarane **189**, the results confirm that the major pathway is cleavage of the oxonium ion **282** to the ester. The predominance of this reaction, even in the presence of trimethylsilyltriflate as the electrophile suggests that the reduction of the oxonium ion **282** by zinc is unfavourable, and the reaction casts new light on the range of precursors applicable in the generation of organozinc carbenoids.

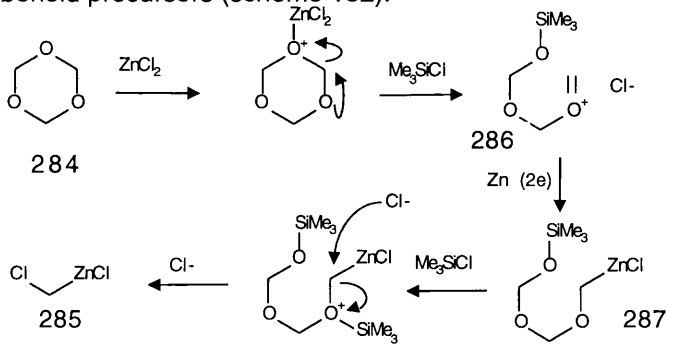
In summary, the above results exemplify a simple and inexpensive method for the preparation of alkoxy- and aryloxycyclopropanes under mild neutral conditions *via* a novel class of organozinc carbenoids. Furthermore, in comparison to traditional methods for the generation of alkoxycarbenoids, the present method obviates the necessity for handling toxic α-halo- and α,α-dihalo-ether precursors, or the multistep procedures involved in the preparation of stoichiometric Fischer carbenoids.

2.5. Studies into the Generation of Methyiene Organozinc Carbenoids

Concurrently with the work described previously, we also conducted a limited study into the generation of new reagents for the transfer of methylene carbenoids to simple alkenes. The following chapter describes the discoveries that we made in this field.

The simple cyclopropanation of alkenes with a methylene carbenoid is also routinely performed in the laboratory with a wide range of reagents. Methylene Fisher carbene-type complexes, methylene dihalides, diazomethane and ylides are all commonly employed as precursors for addition of the methylene unit in cyclopropanation. The cyclopropanation of electron rich alkenes however, still represents a challenge to the repertoire of the organic chemist because all of the available methodologies possess significant shortcomings. Fisher carbene complexes, reactivity profile aside, are more difficult to prepare and handle and do not allow atom efficient methylene transfer. Equally, utilisation of methylene dihalides becomes less useful for cyclopropanation on a large scale due to toxicity and purification problems. Lastly, diazomethane, for all its great efficiency in transition metal catalysed methylene cyclopropanation is an explosive reagent and thus an unsuitable precursor for cyclopropanation on a large scale.

Evidently there is scope for the introduction of new methylene carbenoid precursors suited to the efficient cyclopropanation of electron rich alkenes. Prospective reagents, in order to surpass the existing methodologies will be required to be amenable to cyclopropanation of alkenes on a large scale utilising only cheap, non hazardous reagents. The generation of methyl carbenoids from formaldehyde derived acetals using zinc and chlorotrimethylsilane would clearly meet such stipulations. The use of readily available acetal precursors such as trioxane **284** or paraformaldehyde would be infinitely preferable to the use of methylene diiodide as a methylene zinc carbenoid precursors (scheme 182).

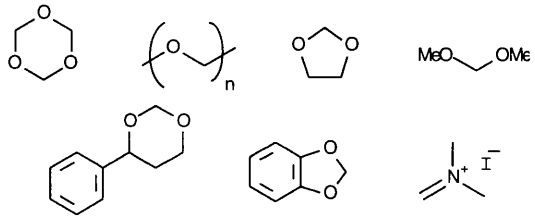


scheme 182

The theoretical pathway for the generation of a methylene zinc carbenoid such as **285** would first involve opening of the acetal to the oxonium ion **286**. Just as for the acetals in section 2.3 two electron transfer from zinc is required to generate an organozinc intermediate **287**.

Subsequent loss of the remaining oxygen bond to the methylene carbene would lead to the desired zinc carbenoid species **285**.

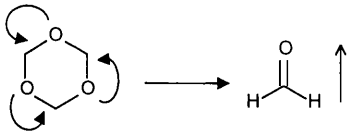
To this end a series of common methylene acetals were studied as potential methylzinc carbenoid precursors for the cyclopropanation of allylbenzene and α-methylstyrene. In general, the compounds were screened by reaction with zinc mercury amalgam and chlorotrimethylsilane in ether. In a similar vein Eschenmoser's salt was also examined.



scheme 183

Under standard conditions with slow addition of a five-fold excess of the acetals to the alkene-zinc-silane reaction mixture no cyclopropane formation was observed. The system was screened at a range of temperatures using other electrophiles and Lewis acids, but under no conditions was even a trace of cyclopropane recovered. It was subsequently considered that this failure to generate cyclopropanes could have any of several causes. It is possible that the zinc species generated in the reaction is unsuitable as a cyclopropanating reagent although the work of Denmark suggests that were the proposed zinc carbenoid generated it would prove effective.[114]

In many of the reactions, the deposition of a fine white solid on the condensers was observed. This was later identified as para-formaldehyde and indicates that, under the reaction conditions, depolymerisation of the methylene acetals to give gaseous formaldehyde was occuring. Formaldehyde was then repolymerising outside the reaction vessel.



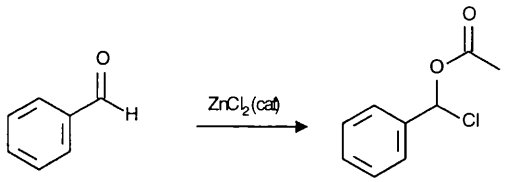
It is probable that the greatest obstacle to zinc carbenoid formation is that electron transfer from zinc to the oxonium species **288** is not occuring. In contrast to the benzylic oxonium species **289** derived from the opening of an arylacetal the oxonium species is unstabilised. This implies that that opening to the oxonium will be a more difficult process[172] and at the same time that the reduction potential of the oxonium species will be very different and electron transfer from zinc may be disfavoured.

288 289

scheme 184

2.5.1. The Generation and Reactivity of Geminal-Haloacetates Derived from Carbonyl Compounds

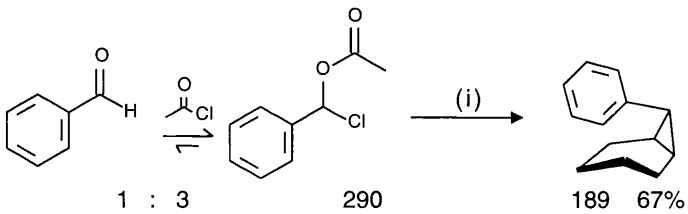
It was thought that the unstabilised oxonium ion would require activation in some manner to facilitate electron donation from the zinc. In a procedure related to this the use of adducts of aryl aldehydes as carbenoid precursors was investigated. Using the procedure of Ulich and Adams[177] we generated the geminal chloroacetate **290** by the zinc chloride catalysed reaction of acetyl chloride and benzaldehyde (scheme 185).



290

scheme 185

The highly exothermic production of **290** appeared to occur readily, although obtaining a high yield of **290** without using an excess of acetyl chloride proved difficult. Purification by distillation afforded a mixture of acetyl chloride, benzaldehyde and the chloro-acetate **290** as the major part. Nevertheless, direct reaction of this crude mixture with cyclohexene, zinc amalgam and chlorotrimethylsilane gave phenylnorcarane in 67% (scheme 186). It is noteworthy that this yield is equal to that obtained using the bis-chlorosilane with benzaldehyde (*vide supra* 2.1.2.4.), and actually surpasses that previously described for the cyclopropanation with chlorotrimethylsilane and benzaldehyde.[204,215]

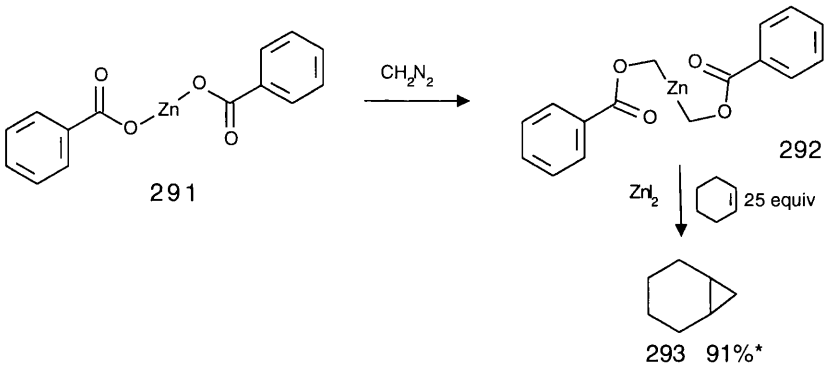


1 : 3 290 189 67%

i). Slow addition, Zn/Hg (10 equiv), Me_3SiCl (5 equiv), cyclohexene (4 equiv), Et_2O reflux

scheme 186

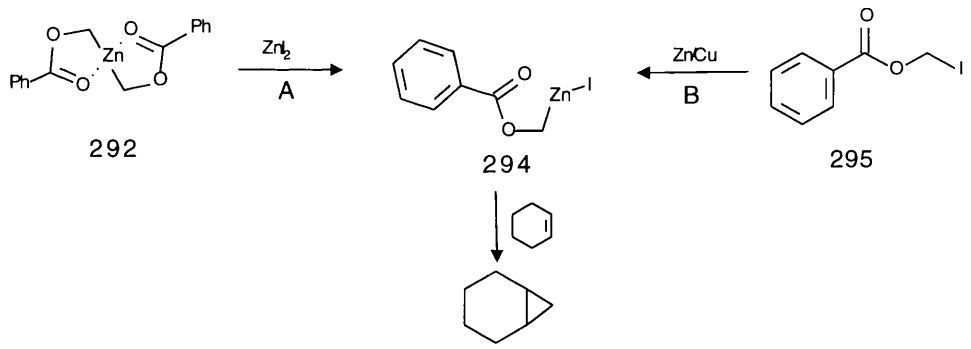
Whether the *geminal*-chloro acetate **290** is indeed an active precursor, or whether the activation by acetyl chloride takes another form is unclear (*vide supra* 1.4). It was hoped that a similar activation of formaldehyde might provide a species suitable as a zinc carbenoid precursor, despite the absence of benzylic stabilisation. Investigation as to the plausibility of this approach led us to re-examine the work of Wittig (scheme 187).



*relative to 291

scheme 187

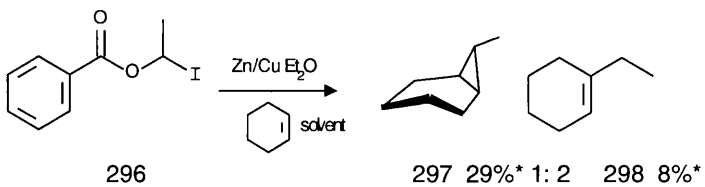
In the course of his original investigations into the use of diazomethane as a cyclopropanating reagent with zinc salts, Wittig found that bis(benzoyloxymethyl)zinc **292** could readily be produced by the reaction of zinc benzoate **291** and diazomethane.[228] In the presence of metal halide salts in refluxing ether this reagent was able to cyclopropanate cyclohexene to give norcarane **293** in good yields. Further careful investigation of the reaction led Wittig to conclude that the cyclopropanating reagent was in fact the benzoyloxymethylzinc iodide species **294**produced by the reaction with the zinc halide. In order to test this hypothesis, iodomethyl benzoate **295** was reacted with a zinc-copper couple in ether at reflux, and the resulting species was also shown to cyclopropanate cyclohexene in 86% yield (scheme 188).



yield of cyclopropane:		A	91%
relative to precursor	B		86%

scheme 188

Wittig had also synthesised the methyl analogue, 1-benzoyloxyethylzinc iodide generated from the corresponding iodoalkyl ester, and demonstrated that this too was an active cyclopropanating reagent (scheme 189).[228]

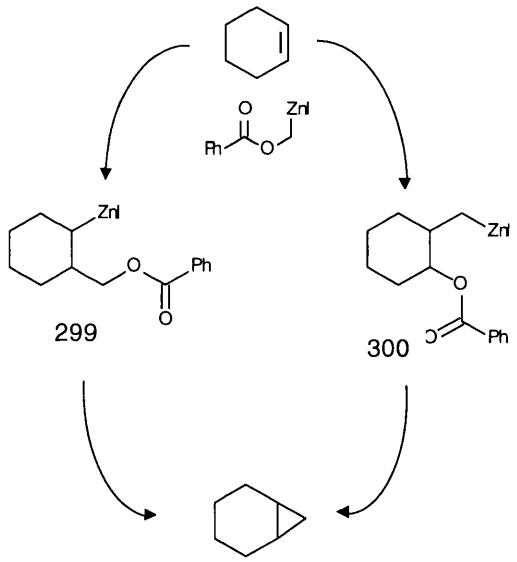


* relative to 296

scheme 189

The synthesis of the methyl norcarane **297** provided a further product, 2-ethylcyclohexene **298**. Wittig demonstrated that under the reaction conditions the *cis* methylnorcarane readily isomerised to give the alkene. Hence, the primary product of the reaction of the 1-benzoyloxyethylzinc iodide is actually a 1:1 mixture of *cis* and *trans* methylnorcarane in 37% yield.[228]

Wittig's work was intriguing on several levels. Since no further examples of iodoalkyl benzoate compounds as cyclopropanation reagents have since been published, it was thought possible that the untested reagent itself could be utilised in the cyclopropanation of a diverse range of alkenes. The reagent also represents a step in the correct direction toward our stated goal of finding an alternative methylene carbenoid transfer reagent. On a more fundamental level, benzoyloxymethylzinc iodide itself is clearly an intriguing species. Wittig asked the question as to whether the cyclopropanation was in fact a carbene-type concerted methylene transfer as is postulated for the Simmons Smith reaction, or in fact the reaction of a nucleophilic metal reagent which generates a second organozinc species that subsequently closes to give the cyclopropane (scheme 190).

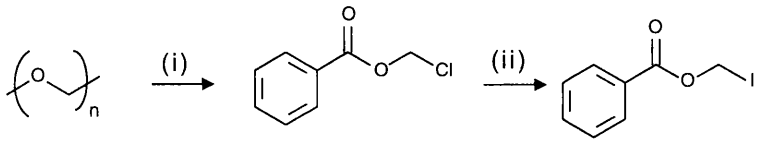


scheme 190

Wittig was unable to isolate the intermediate esters derived from the aqueous quenching of **299** or **300** and consequently suggested that the concerted mechanism was in operation, at least for the reaction with cyclohexene.[228]

2.5.2. Observations on the Synthesis and Chemistry of Halomethyl Acetates

Reaction of paraformaldehyde with benzoyl chloride and a catalytic amount of zinc chloride delivers chloromethylbenzoate **301** in moderate yield. Finkelstein reaction with sodium iodide in acetone affords iodomethyl benzoate **295**. The resulting solid can be recrystallised from petrol and stored in the freezer for at least one year without loss of reactivity (scheme 191).



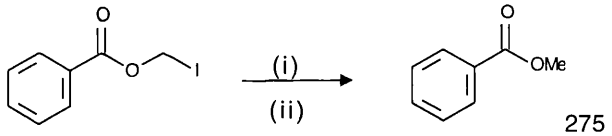
301 295

i). PhCOCl, $ZnCl_2$, 100°C 2 hrs, 35%.

ii). NaI, acetone, r.t. 4.5 hours 43%.

scheme 191

Reaction of **295** with zinc copper couple was straightforward and quenching after 3 hours gave methyl benzoate **275** in 83% yield. Wittig had noted that in a series of quenching experiments, methyl benzoate was isolated after one hour in 90% yield, in 92% yield after 2 hours and in only 82% yield after 4 hours implying some deterioration of the benzoyloxymethylzinc iodide reagent with time (scheme 192).[228]

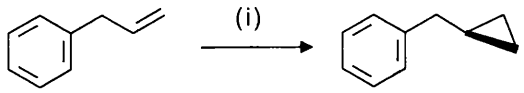


275

i). Zn/Cu, I_2 (cat) Et_2O reflux 3hr; ii). H_2O, 83%

scheme 192

The efficiency of the reagent in the cyclopropanation of allylbenzene was subsequently investigated. In order to facilitate the study of the reaction on a small scale, the yield of cyclopropane **303** was calculated by GC analysis of the reaction mixture. A standard sample of benzyl cyclopropane **303** was first prepared by the Simmons Smith cyclopropanation of allylbenzene under sonication (scheme 193). It is worthy of note that even in the presence of an excess of methylene diiodide, the yield of cyclopropane is low.



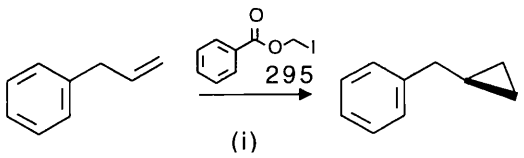
210 303 27%

i). Zn-Cu (4 equiv) CH_2I_2 (4 equiv), $ClCH_2CH_2Cl$ 6 hr ((((

scheme 193

The cyclopropanation of allyl benzene with benzoyloxymethylzinc benzoate was investigated utilising the *in-situ* trapping of the reagent with an excess of alkene. A typical reaction would thus involve dropwise addition of the reagent **295** to a refluxing suspension of the zinc source

and in ether, immediately followed by the addition of the alkene and whatever additive was required. Some of the results are summarised in table 22.



i). Zinc (10 equiv), Et_2O, 24 hours

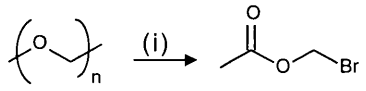
	zinc source	equiv **295**	solvent (reflux)	additives (equiv)	yield*
1	Zn (on TiO_2)	0.2	Et_2O	Me_3SiCl (4)	15%
2	Zn-Cu	0.2	Et_2O (((	Me_3SiCl (3)	6%
3	Zn-Cu	0.2	Et_2O	Me_3SiCl (3)	10%
4	Zn/Hg	0.2	Et_2O	Me_3SiCl (3)	7%
5	Zn/Cu	0.2	Et_2O	ZnI_2 (1)§	1%
6	Zn-Cu	0.2	Et_2O	$ZnBr_2$ (1)§	0%
7	Zn-Cu	0.2	Et_2O	$ZnCl_2$ (1)§	2%
8	Zn-Cu	0.2	Et_2O	CuI (1)§	1%
9	Zn-Cu	0.2	Et_2O	I_2 (0.1)	3%

* by comparison with GC standard, relative to **295**
§ halide salts were added with the zinc and flame dried

table 22

Analysis of the reaction mixtures by GC and comparison with the standard mixture produced in the Simmons Smith reaction allows an estimation of the yield of cyclopropane (table 22). As is immediately evident, the reagent does not give good yields of benzylcyclopropane, with only two examples producing cyclopropanes in yields above 10% (entries 1 and 3). The GC showed that the major product from the analysis was usually methyl benzoate, suggesting that the benzoyloxymethylzinc iodide although forming readily was unreactive towards allyl benzene. At the same time, the zinc source also appears to play a role in the success of the reaction. This finding is in conjunction with Wittig's observation that activation with iodine was necessary. The additive plays a role too and surprisingly the use of excess zinc halide appears to hinder the reaction. Although NMR of the crude reaction mixtures confirmed the ratios of cyclopropane to alkene, in general the crude mixture contained other compounds. Since the estimation of the

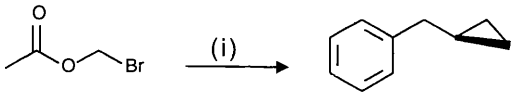
yield was based on the alkene consumed, it is possible that the yields are actually lower than those quoted above.



304

i). AcBr, $ZnCl_2$, 50°C, 2.52 hrs, 65%.

In order to investigate whether other haloacetates are suitable for methylene cyclopropanation we also synthesised bromomethylacetate **304** from paraformaldehyde. When exposed to identical reaction conditions as those used for iodomethylbenzoate **295** the compound was also effective in the cyclopropanation of allylbenzene although in lower yield (scheme 194).



304 303

i). Zn-Cu (5 equiv), Me_3SiCl (2 equiv), allylbenzene (1.6 equiv), Et_2O reflux

2 hours 6%,

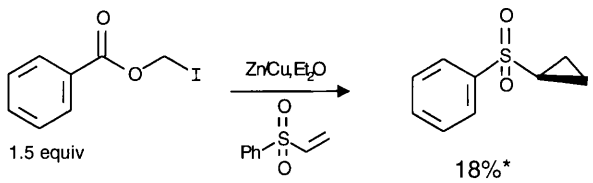
48 hours 8%

scheme 194

Given however that cyclopropanation of allylbenzene under Simmons Smith conditions gave only a 27% yield of cyclopropane with a four-fold excess of methylene iodide, this is an encouraging observation.

2.5.3. Reaction Of Benzoyloxymethylzinc Iodide with Other Alkenes

In order to further examine Wittig's work the reaction of iodomethylbenzoate and zinc with phenylvinylsulfone was also investigated. Wittig had found that reaction of the olefin with an excess of the reagent **295** had produced the cyclopropane in 18% yield (scheme 195) in conjunction with the recovery of 47% of methyl benzoate **275.** Phenyl vinyl sulfone is inert to cyclopropanation under Simmons Smith conditions.



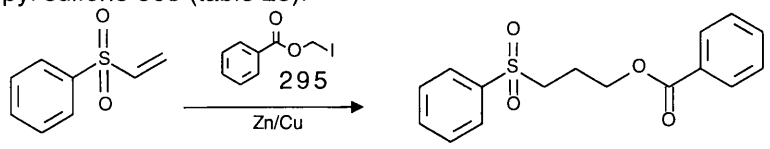
1.5 equiv 18%*

* relative to pheneylvinyl sulfone

scheme 195

On attempting to reproduce this work, we obtained quite different results. Addition of iodomethylbenzoate to a suspension of zinc-copper couple and an excess of the

phenylvinylsulfone in refluxing ether gave no trace of the cyclopropane, but instead phenyl-(3-benzoyloxy)propyl sulfone **305** (table 23).



305

	equiv **295**‡	solvent (reflux)	additives (equiv)	yield* **305**
1	0.3	Et_2O	ZnI_2 (1)	18§
2	0.3	Et_2O	I_2 (0.1)	4
3	0.2	Et_2O	Me_3SiCl (4)	0
4	0.8	Et_2O	$ZnCl_2$ (1)	4

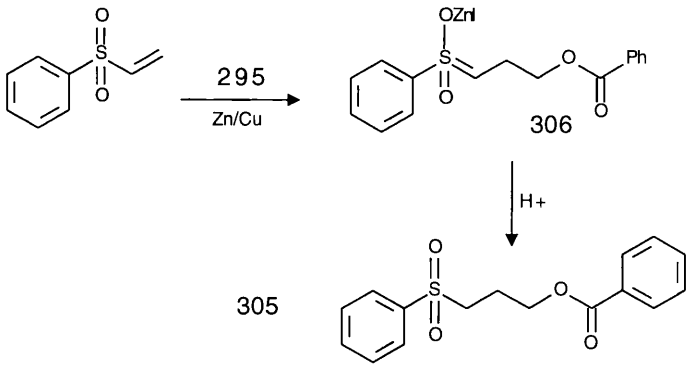
‡ relative to phenylvinyl sulfone

* relative to iodomethyl benzoate

§ 62% of methylbenzoate isolated

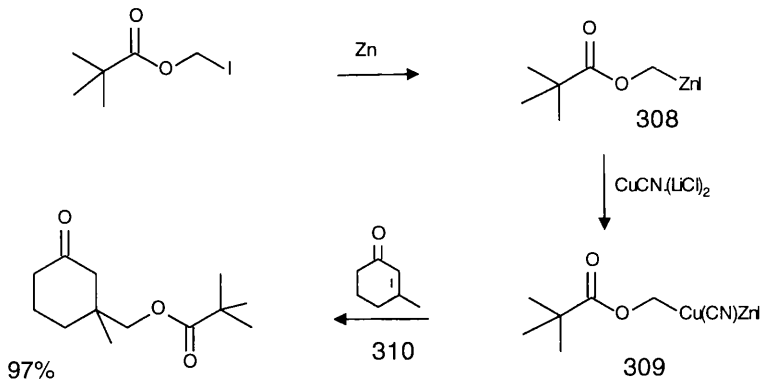
table 23

The reaction with phenylvinylsulfone is illustrative as it demonstrates that Wittig's original suggestion that the reagent can react as an organometallic nucleophile was accurate at least for the case of the Michael acceptor phenyl vinyl sulfone. The isolated product **305** is obtained *via* quenching of the zinc sulfonate intermediate **306** (scheme 196).



scheme 196

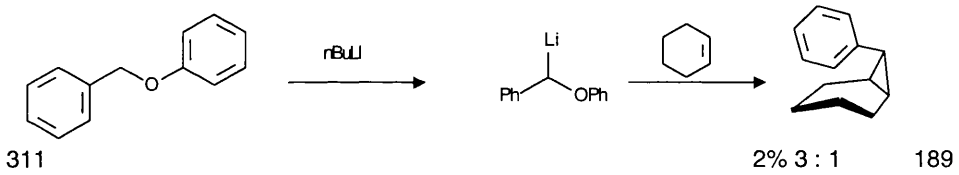
It is of interest to discern whether or not the reagent reacts with the copper in the zinc source to produce some form of organocuprate. The use of such organozincs has been shown by Knochel to give organocopper reagents suitable for nucleophilic addition in this manner (scheme 198).[178]



scheme 197

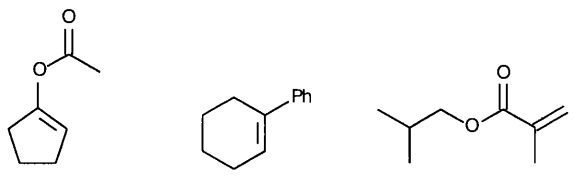
Hence preparation of the cuprate ester **309** can be achieved by generation of the organozinc species **308** followed by transmetallation with copper. The cuprate **309** will react readily with electrophiles such as acid chlorides, aldehydes and allylic halides but most effectively of all with enones such as **310** to give the Michael addition products in high yields (scheme 197).

Conversely, and in support of the carbenoid nature of the reagent **294**, it was reported by Schöllkopf in 1963 that phenyl benzyl ether **311** in the presence of butyl lithium could react with cyclohexene to give the cyclopropane **189** in low yield (scheme 198) in a reaction which formally requires the loss of lithium phenoxide to generate "phenyl carbene."[179]



scheme 198

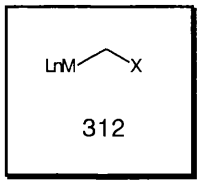
Benzoyloxymethyl zinc iodide was also investigated in the cyclopropanation of several other alkenes (scheme 199). All the reactions however, afforded complex mixtures with no trace of the target cyclopropane. Although the results with the benzoyloxymethyl zinc iodide system were generally disappointing, they did provide some insight into the nature of the reagent. The results seem to indicate that the reagent is not widely applicable as a cyclopropanating species which may explain in part why only Wittig's original paper appears to utilise this chemistry.



scheme 199

It is possible in the light of the contrasting evidence that the reagent benzoyloxymethylzinc iodide **294** lies somewhere between an alkylzinc reagent and a Simmons Smith type carbenoid species. The reagent has the ability to add in nucleophilic fashion to some electron poor

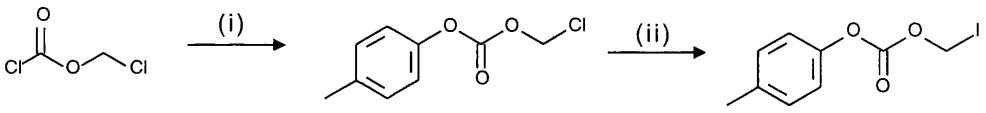
Michael acceptors and at the same time cyclopropanate electron rich alkenes. Whatever its exact nature, it is illustrative of the fine balance that must be obtained for the generation of new methylene organozinc carbenoids. It also lends weight to the simplistic rationale that a carbenoid might be represented as any species possessing the generic structure **312** where a metal and leaving group are attached to the same carbon. This hypothesis, formulated by Wittig for iodomethylzinc iodide[202] and reiterated by Julia for some important biological transformations[180] infers that other, readily available species may be applicable as cyclopropanation reagents.



312

2.5.4 The Use of Iodomethyltolylcarbonate as a Methylenezinc Carbenoid Precursor

An analogous compound with potentially improved leaving group ability which by the same rationale might display reactivity towards alkenes in the presence of zinc amalgam is the iodomethyltolylcarbonate **315** shown in scheme 207. The synthesis of this species is readily achieved *via* the chloro-analogue **314**, which is in turn generated *via* standard means from chloromethyl chloroformate **313** in good yield. The compound **315** is solid below 0°C and is stable when stored in the freezer for long periods.



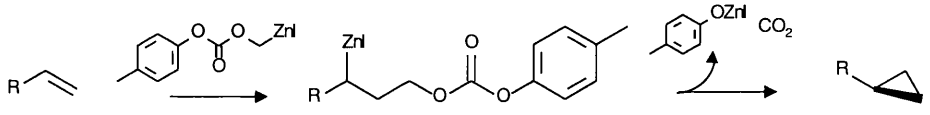
313 314 75% 315 61%

i). *p*-cresol, pyridine

ii) NaI, acetone

scheme 201

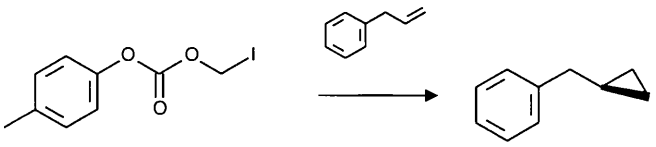
It is possible that the efficiency of the Wittig-iodomethylbenzoate reagent in the cyclopropanation of electron rich alkenes is a function of the leaving group ability of the benzoate moiety. If that were the case the substitution of an aryl carbonate for the benzoate leaving group might increase the carbene-like nature of the zinc reagent. If, as was postulated by Wittig, an intermediate such as **316** is involved, the presence of a carbonate might simply improve the efficiency of ring closure in the generation of cyclopropanes (scheme 202).



316

scheme 202

Hence, iodomethyltolylcarbonate **315** was screened as a precursor for the cyclopropanation of allyl benzene. The reagent was added to a solution containing zinc and an excess of allylbenzene in a range of solvents (table 24). As with the Wittig-iodomethylbenzoate reagent, the yields, relative to the amount of iodomethyltolylcarbonate **315**, were estimated by GC.



315 303

	Zinc source	**315**‡ (equiv)	solvent (reflux)	additives (equiv)‡	yield*
1	Zn-Cu	0.5	Et_2O	I_2 (0.05)	4%
2	Zn-Cu	0.5	Et_2O	Me_3SiCl (0.55)	17%†
3	Zn-Cu	0.2	Et_2O	I_2 (0.05)	20%
4	Zn/Hg	0.2	Et_2O	-	0%
5	Zn/Hg	0.5	Et_2O	$ZnCl_2$ (0.55)	3%
6	Zn/Hg	0.5	PhMe	-	5%
7	Zn/Hg	0.5	PhMe	I_2 (0.05)	5%

* by comparison with GC standard

† confirmed by ^1H NMR of the crude reaction mixture

‡ relative to allylbenzene

table 24

Table **24** shows that the reagent afforded cyclopropanes in low yields, although superior to those obtained in the reaction of allyl benzene with the Wittig-iodomethylbenzoate reagent. Again the zinc source seems important, suggesting perhaps that copper can play a role in the reaction mechanism.

The yields estimated in the table were validated by the repetition of the result in entry 2, as a result of which a fuller analysis of the other products of the reaction was also obtained.

Thus, the reaction of iodomethyltolylcarbonate **315** with zinc copper couple in the presence of five equivalents of allyl benzene and chlorotrimethylsilane gave 16% of the target cyclopropane, roughly equivalent to the yield previously calculated by GC.

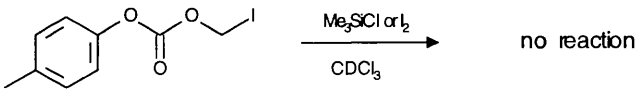
303 16% 318 29% 319 20%

i). Zn/Cu (15 equiv), allyl benzene (5 equiv), Me_3SiCl (1.5 equiv), Et_2O reflux 24 hrs

scheme 203

The presence of the carbonate **319**, derived from quenching of the zinc reagent implies that reaction with the alkene is a slow process. Most importantly however on a molar reagent basis we have now surpassed the efficiency of the Simmons Smith reagent.

One potential source of cyclopropanes would be the *in situ* decomposition of the iodomethyl carbonate under the reaction conditions to generate either methylene iodide or chloroiodomethane. Subsequent reaction with zinc would then generate a Simmons Smith-type methylene zinc carbenoid. In a series of NMR experiments in $CDCl_3$ however, (table 25) no formation of methylene diiodide or chloroiodomethane was observed in the ^1H NMR spectrum, with the starting material remaining stable in all cases. Hence it is possible to conclude that the reagent **315** does not simply act as an exotic source of methylene iodide or chloroiodomethane. Equally interestingly, the results also imply that insertion of the zinc into the C-I bond is required to facilitate departure of the leaving group.



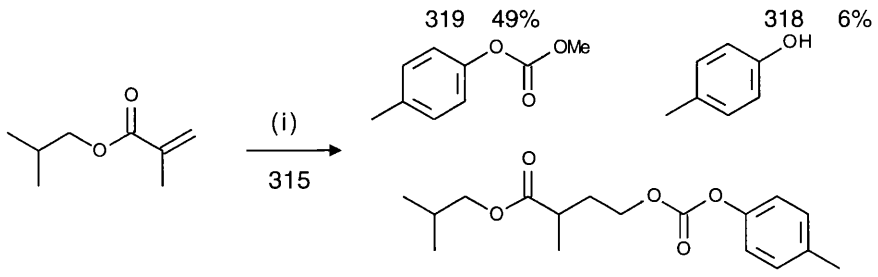
315

	time	solvent (temp)	additives (equiv)*
1	3 days	$CDCl_3$ (r.t.)	Me_3SiCl (1.7)
2	5 hours	$CDCl_3$ (50°C)	Me_3SiCl (2)
3	2 hours	$CDCl_3$ (50°C)	I_2 (1)
4	6 hours	$CDCl_3$ (50°C)	ZnI_2 (2)

* relative to iodomethyltolyl carbonate

table 25

The iodomethyltolyl carbonate **315** was studied in the reaction with the Michael-acceptor isobutyl methacrylate. In this case the zinc source used was zinc amalgam thus precluding the possibility of any organocopper species forming (scheme 204).

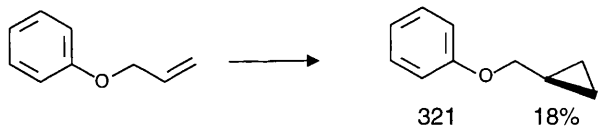


i). Zn/Hg (10 equiv), isobutylmethacrylate (1.2 equiv), Me_3SiCl (1 equiv), Et_2O reflux 24 hrs

scheme 204

The large recovery of methyl tolylcarbonate **317** and the low yield of the Michael addition product implies that, as for the Wittig benzoyloxymethylzinc iodide reagent the organozinc species derived from iodomethyltolylcarbonate **315** has only low reactivity toward Michael acceptors. In contrast to the Wittig reagent however, reaction under similar conditions with phenyl vinyl sulfone gave no adduct formation whatsoever.

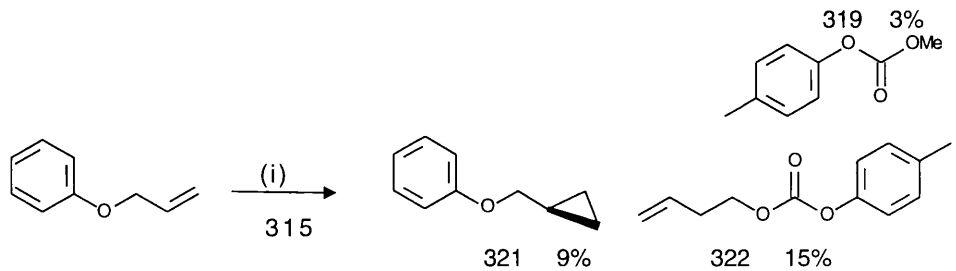
The cyclopropanation of allylphenylether was also studied. In order to obtain a sample of the target cyclopropane, cyclopropanation was first studied using the Furakawa-modified Simmons Smith reagent derived from methylene iodide and diethylzinc. As with allylbenzene it is noteworthy that even a large excess of methylene iodide does not guarantee a high yield of the cyclopropane **321** (scheme 205).



i). Et_2Zn (2 equiv), CH_2I_2 (2 equiv), allylphenyl ether (1 equiv), Et_2O, 0°C 5hrs

scheme 205

Attempted cyclopropanation using iodomethyltolylcarbonate **315** and zinc copper couple again gave a complex mixture of products (scheme 206). The cyclopropane was formed in 9% yield and some methyltolyl carbonate **319** was also recovered. Surprisingly however, the major product was the carbonate **322**.

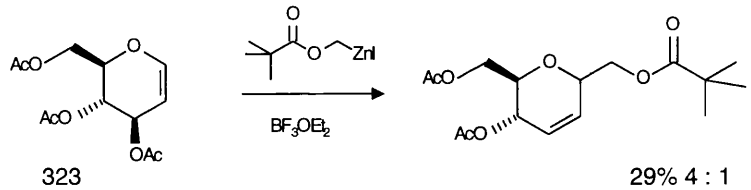


i). Zn/Hg (10 equiv), allylphenylether (1.2 equiv), Me_3SiCl (1 equiv), Et_2O reflux 24 hrs

scheme 206

Although the yield of cyclopropane is low, the classical cyclopropanation of allylphenyl ether under Furakawa conditions was no more efficient. This again suggests that iodomethyl-tolylcarbonate is at least as efficient a carbenoid precursor as methylene iodide.

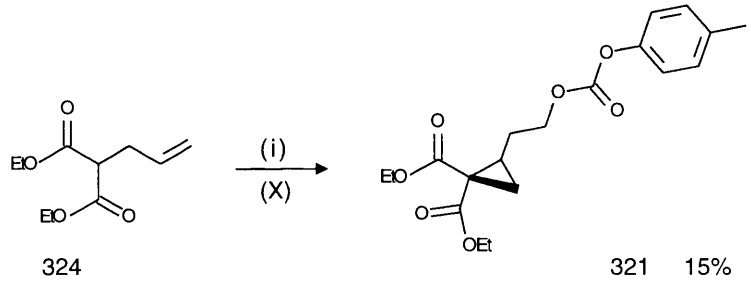
Formation of the alkene **322** may simply be viewed as the reaction of an organozinc reagent with an alkene bearing an allylic leaving group. Similar reactivity has been observed by Gallagher, in the reaction of the pivaloyl based organozinc reagent **308** with 3,4,6-tri-*O*-acetyl-D-glucal **323** (scheme 207).[184]



323 29% 4 : 1

scheme 297

Iodomethyltolylcarbonate was also tested against diethyl allyl malonate **324**. Reaction, once more with zinc mercury amalgam and utilising a slight excess of the iodomethyltolyl carbonate **295** gave, as the major product, a compound identified as the cyclopropane **325** with no trace of the target cyclopropane (scheme 208).

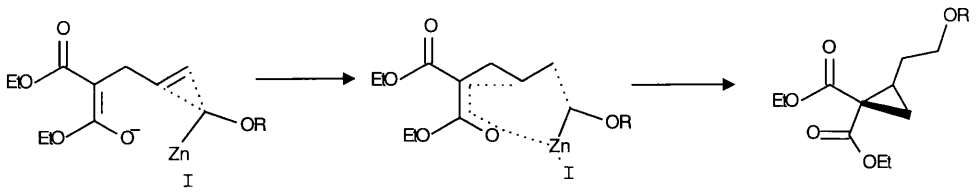


324 321 15%

i). Zn/Hg (13 equiv), diethylallylmalonate (0.91 equiv), Me_3SiCl (1 equiv), Et_2O reflux 48 hrs

scheme 208

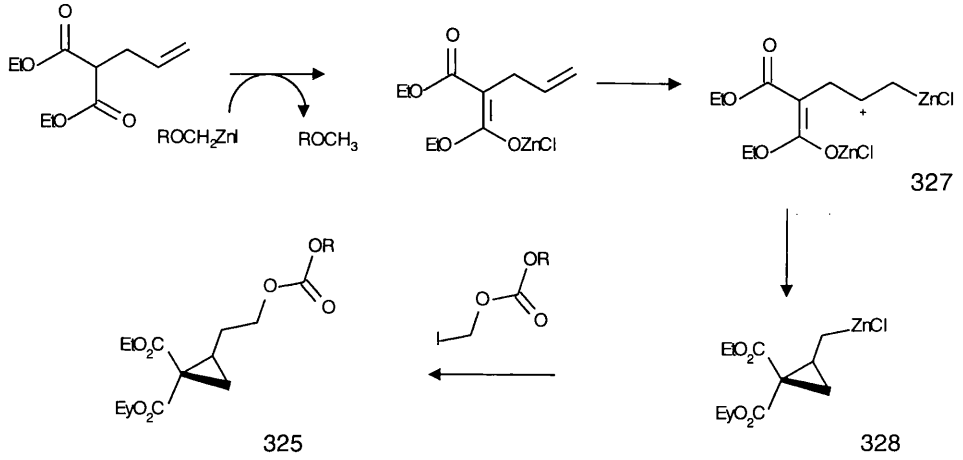
While it is likely that the first reaction with diethyl allylmalonate **324** is deprotonation of the acidic malonate proton to form a zinc enolate, subsequent generation of the cyclopropane **325**however is much harder to rationalise. If the zinc reagent is truly a carbenoid species, then a concerted intermediate such as **326** analogous to that rationalised for the Simmons Smith reaction might be envisaged. Interference by the internal nucleophile might generate the product (scheme 209).



326 325

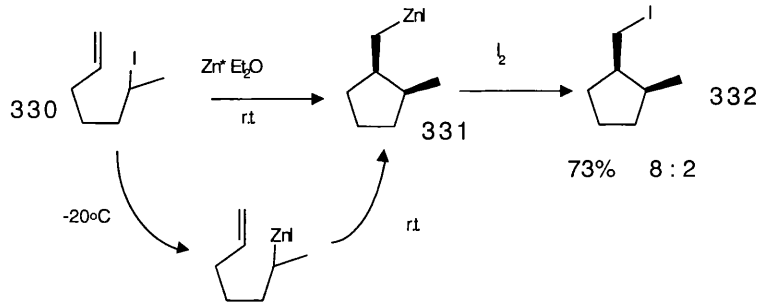
scheme 209

Another possible explanation, and one that has implications for all of the cyclopropanations previously described, is that a zinc halide salt is acting as an electrophile with the alkene to generate the carbocation **327**. For diethyl allyl malonate, the internal nucleophile provided by alkylzinc deprotonation of the malonate can close to form the cyclopropane **328**. This species is in itself a zinc nucleophile and S_N2 reaction with the iodomethyl zinc carbonate could generate the isolated product (scheme 210). Zinc chloride however is a mild Lewis acid, and electrophilic reaction with a primary alkene is highly unlikely.



scheme 210

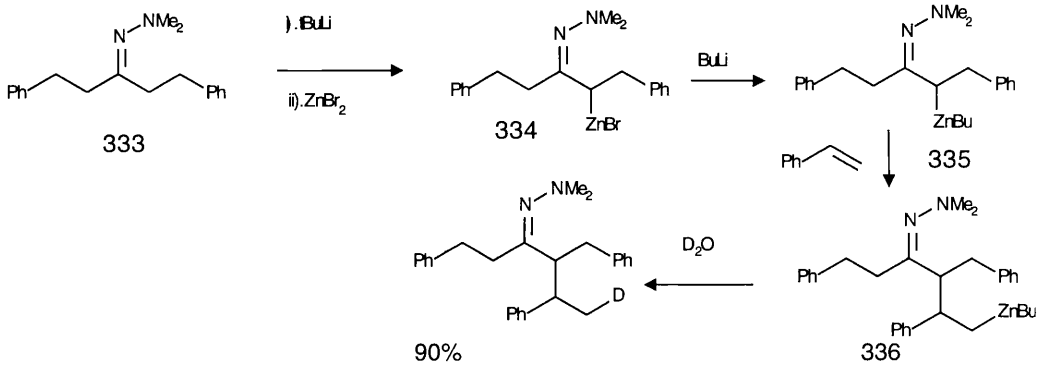
The reaction of alkylzinc species with unactivated alkenes has been previously observed. Normant has shown that in the presence of Reike zinc, the iodoalkene **330** will undergo an intramolecular cyclisation to afford the organozinc carbocycle **331**, trapping of which with iodine can generate the iodoalkane **332**. As can be seen in scheme 211, the zinc moiety reacts with the alkene only on warming to room temperature.[182]



scheme 211

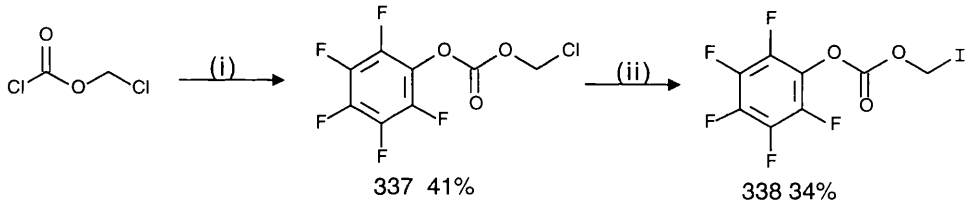
The intermolecular addition of a zinc hydrazone species to an unactivated alkene has also been reported. Nakamura has demonstrated that hydrazones such as **333** can be converted to an organozinc species such as **334** by base induced deprotonation followed by transmetallation with a zinc halide. The organozinc bromide **334** was unreactive toward alkenes, and the dialkyl zinc species **335** had first to be generated by reaction with butyl lithium prior to reaction with an alkene. The resulting zinc hydrazone **335** will add to electron rich alkenes such as styrene and

the resulting organozinc **336** can then be captured by an electrophile. Aliphatic alkenes were also reactive, albeit less so (scheme 212).[184]



scheme 212

If the iodomethyl carbonate-zinc species is showing any carbene-like reactivity at all, then increasing the leaving group ability of the carbonate substituent should render the species an even better cyclopropanating reagent. Consequently, the chloromethylcarbonate **337**. was prepared by the reaction of chloromethylchloroformate with pentafluorophenol. Finkelstein reaction with sodium iodide gave the iodomethylpentafluorophenyl carbonate **338** as a solid stable at room temperature.



i) Pentafluorophenol, pyridine
ii) NaI, acetone

scheme 213

Attempted cyclopropanation of allyl benzene under a variety of conditions however, gave no identifiable products. The reagent afforded highly complex mixtures and there clearly remains further scope for its investigation.

At this moment in time it remains impossible to judge which mechanism is responsible for the formation of cyclopropanes. The possibility remains that all the zinc reagents described display a reactivity profile that encompasses both nucleophilic and carbenoid-like activity. If it is this ambiphilicity that allows for the reaction with isolated double bonds, then clearly scope exists for the development of new organozinc species with similar reactivity.

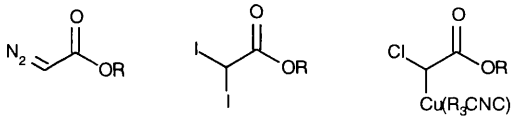
At the very least the work described above has shown that the cyclopropanation of simple alkenes with zinc and iodomethyltolylcarbonate is at least as efficient a process as using methylene diiodide under Simmons Smith conditions. In this respect we have partially fulfilled our stated goal of developing alternative precursors to methylzinc carbenoids.

2.6 Studies on the Attempted Generation of Other Organozinc Carbenoids

At this stage of the discussion we briefly mention several largely unsuccessful attempts to generate other organozinc carbenoids from different precurors. The examples are all illustrative of some of the future work that might be possible with zinc and simple carbenoid precursors.

2.6.1. Observations on the Generation of New Carboxy-methylzinc Reagents

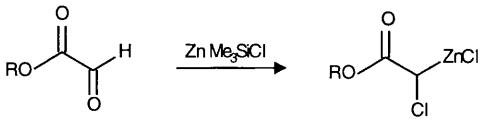
The carboxymethyl cyclopropanation of alkenes is currently the most widely studied area of carbenoid chemistry (*vide supra* 1.1.). Carboxymethylene cyclopropanes are routinely prepared from α-diazo esters such as **340**. The extensive use of chiral transition metal catalysis has further widened the usefulness of this methodology and numerous examples of cyclopropanes generated in this manner continue to be published. Equally, the synthesis and application of α,α-dihalo Simmons Smith-type reagents such as **341** has also been demonstrated including one isolated example of an intramolecular reaction. (*vide supra* 1.4.). Lastly, a broad family of organocuprate carbenoids such as **342** have shown the ability to cyclopropanate electron poor alkenes (*vide supra* 1.5.).



340 341 342

Despite the range of methods already available for the carboxymethylene cyclopropanation of alkenes, a system employing only cheap, readily prepared and non-hazardous starting materials is not yet available.

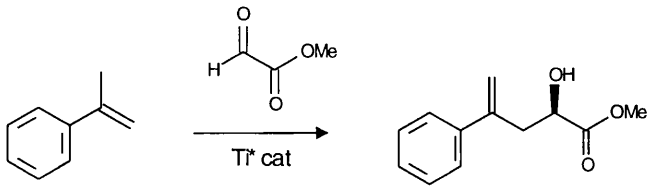
For this reason, the synthesis of new organozinc reagents for the carboxymethylene cyclopropanation of alkenes from carbonyl compounds was considered. A glyoxylate compound such as 343, if applicable to direct reductive carbenoid generation with zinc and chlorotrimethylsilane would be ideal (scheme 214).



343

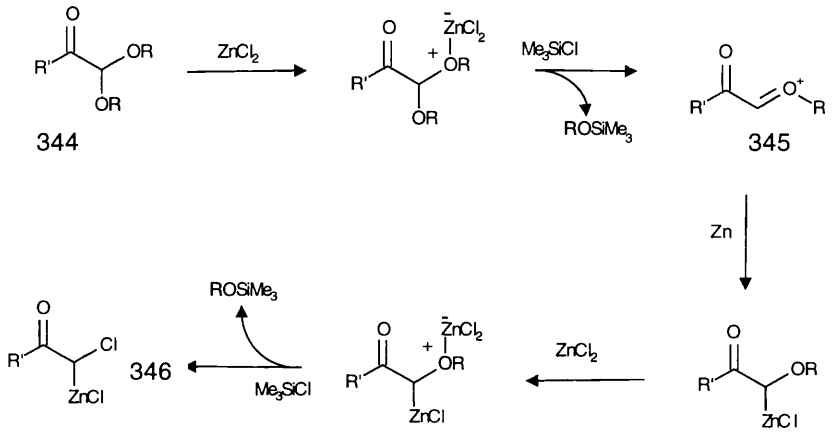
scheme 214

Glyoxolates, although readily prepared, will undergo the glyoxylate-ene reaction in the presence of alkenes and are hence unsuitable precursors for the direct generation of organozinc carbenoid species. Furthermore the ene reaction is catalysed by a wide range of Lewis acids (scheme 215).[185,186]



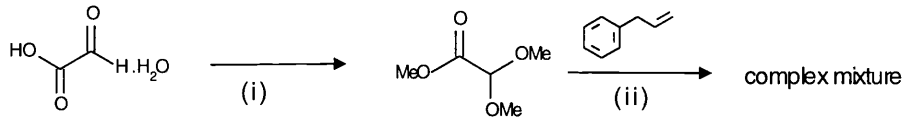
scheme 215

In the light of earlier success in the generation of organozinc carbenoids from acetals it was reasoned that an acetal species such as **344** might be a carbenoid precursor in the presence of zinc and a silicon electrophile. As with the earlier examples, delivery of two electrons from zinc might be facilitated by the positive charge of the oxonium ion **345** (*vide supra* 2.3.).



scheme 216

Methyldimethoxy acetate **347** is readily available *via* the reaction of glyoxylic acid monohydrate **348** with methanol in the presence of concentrated sulfuric acid and anhydrous copper sulfate. The acetal can be generated in reasonable yield after a long reaction time (scheme 217).[219]



348 347 65%

i). methanol, concentrated H_2SO_4, anhydrous $CuSO_4$, 1 2 days

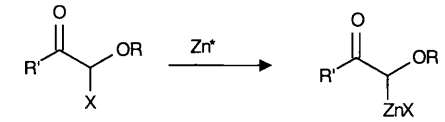
ii) Zn/Hg (10 equiv), allyl benzene (2 equiv), $ZnCl_2$ (1 equiv), Me_3SiCl (4 equiv), Et_2O reflux

scheme 217

The attempted cyclopropanation of allylbenzene with methyldimethoxy acetate **347** was unsuccessful. Purification of the complex reaction mixture did not provide a trace of the target cyclopropane. Instead, the reaction gave a complex mixture of products. A similar reaction with boron trifluoride diethyletherate as the electrophile was also unsuccessful.

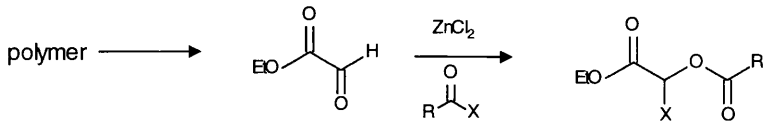
Instead of beginning with the acetal it was reasoned that, analogously to the chemistry employed successfully in the methylene cyclopropanation of alkenes (*vide supra* 2.5.) and also

to the Simmons Smith reagent **341** above, the synthesis of an α-halo species such as **349** would allow for the generation of an organozinc species with carbenoid reactivity.



349 346

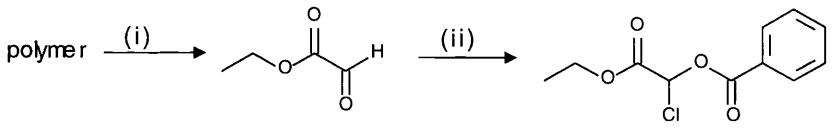
A new synthesis of species such as **349** from ethyl glyoxolate was subsequently developed. Ethyl glyoxolate **350** is a polymeric material at room temperature, and is supplied as a 50:50 mixture by weight in toluene. The compound may be de-polymerised on heating, and the monomer distilled. The monomer will re-polymerize in a few hours at room temperature but it was hoped that it would prove sufficiently stable to be trapped, under zinc chloride catalysis, as the halo-acetate using an acyl chloride (scheme 218)



350 351

scheme 218

It was found that although heating the ethylgyloxolate polymer to 150°C could cause de polymerisation, better results were obtained using microwave irradiation. Thus, the polymer-toluene mixture was distilled at 150°C to remove the toluene and then subjected to 600W microwave irradiation for 5 minutes. The resulting oil was then distilled, and the distillate reacted with benzoyl chloride under zinc chloride catalysis (scheme 219).



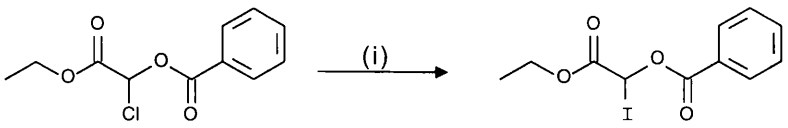
352

i) 150°C then 600W microwave irradiation, 100°C/40mmHg

ii). PhCOCl (1 equiv), $ZnCl_{2\ (cat)}$ 7% overall

scheme 219

The resulting chlorobenzoate **352** proved extremely difficult to purify by distillation alone. Flash chromatography however, afforded a small amount of the pure compound which was subjected to Finkelstein iodination to give the α-iodobenzoate **353**.

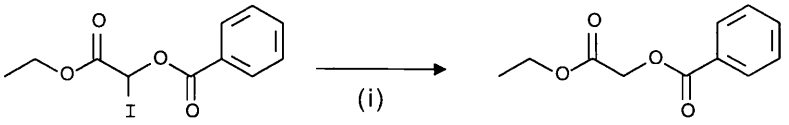


352 353

i). NaI, acetone 68%

scheme 220

Cyclopropanation of allylbenzene was attempted with the α-iodobenzoate **353** under standard conditions. In the event only the reduced diester **354** was isolated from the reaction mixture (scheme 221)

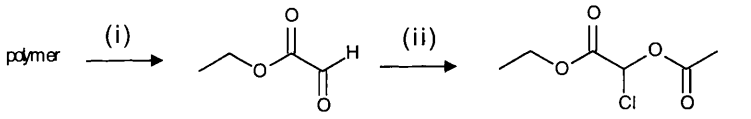


353 354

i). Zn/Hg (20 equiv), Me_3SiCl (10 equiv), allylbenzene (10 equiv,) Et_20 reflux 24 hr

scheme 221

Due to the difficult purification of the α-chlorobenzoate **352**, a similar species was synthesised which could be purified simply by distillation. Hence, ethylglyoxolate **350** was again distilled to remove the toluene and de-polymerised with microwave irradiation. The distilled glyoxolate was then reacted with acetyl chloride to give the chloroacetate **355** which was readily purified scheme 222).



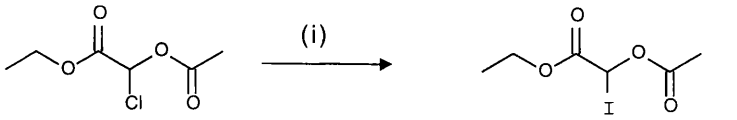
352 355

i). 150°C, microwave then 100°C/40mmHg

ii). AcCl (1 equiv) $ZnCl_2$ (cat), 16% overall

scheme 222

Halide exchange to give the iodide **356** also proceeded in reasonable yield. Using this methodology ethyl(acetoxyiodoacetate) **356** could be prepared on a gram scale.

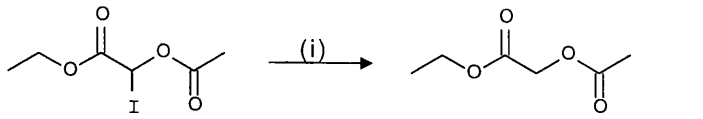


355 356

i).NaI acetone 67%

scheme 223

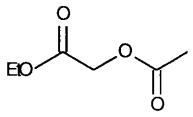
The results of the reaction of the iodoacetate **356** with zinc and a variety of Lewis acids are summarised in table 24. Zn/Hg was utilised as the zinc source and the reactions were all performed at reflux in ether. Zinc insertion is evidently occurring efficiently, but the organozinc-compound is failing to demonstrate carbene-like behaviour and cyclopropanate either allylbenzene or cyclohexene. The major product from most of the reactions is diester **357** formed on quenching the zinc species (table 26).



356 357

i). Zn/Hg (10 equiv), allylbenzene (4 equiv), Et_2O relux 24 hr

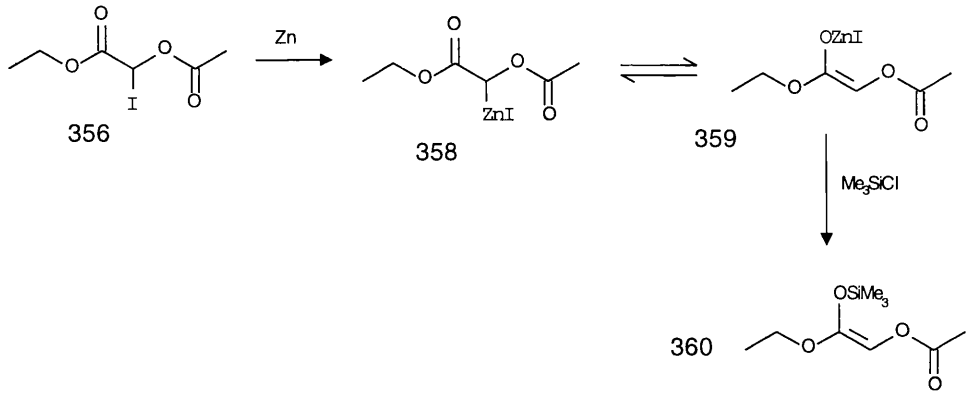
scheme 224

	solv	electrophile (equiv)	add^n (hrs)	L.A. (equiv)	alkene (equiv)	
1	Et_2O	Me_3SiCl (2)	0	-	 2	48
2	Et_2O	-	6	$ZnCl_2$	 2.5	30
3	Et_2O	Me_3SiCl (1.5)	6	-	 2	12
4	PhMe	-	0	-	 6	22
5	Et_2O	Me_3SiCl (3)	6	$ZnCl_2$	 5	32
6	Et_2O	BF_3OEt_2 (1)	6	-	 4.5	39
7	Et_2O	-	0	$MeAlCl_4$	 4.5	43
8	Et_2O	-	0	$TiCl_4$	 4.5	0*
9	Et_2O	-	0	$Pd(Ph_3)_4$	 4.5	0‡

* only identifiable product was 2-chloro-3-phenyl propane‡ no identifiable products

table 26

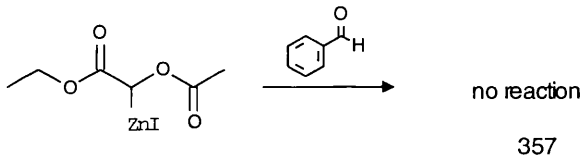
Under the standard conditions with zinc and chlorotrimethylsilame it is possible that the reagent exist primarily as a more Reformatsky type species **359** or even as the silyl ester enolate **360**. In the presence of other Lewis acids zinc-metal exchange can occur, and hence compound **358** can form titanium (entry 8), aluminium (entry 7) or boron enolates (entry 6).



356 358 359 360

scheme 225

Whatever the case, the reagent fails to exhibit carbene-like characteristics and hence it was decided to attempt a simple Reformatsky reaction with benzaldehyde (scheme x). In the event it would seem that the organozinc compound, at least at room temperature, does not show Reformatsky-like behaviour. Work up of the reaction provided only a 1:1 mixture of benzaldehyde and the reduced diester **357** equivalent to 79% recovery of the starting materials.



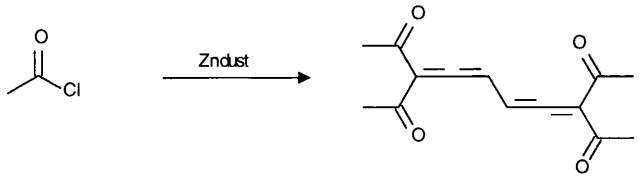
358 357

scheme 226

It is ironic then that having achieved the concise construction of a highly functionalised zinc reagent **358**, the same species appears to show neither carbene-like or Reformatsky-like behaviour, at least in the initial investigation above. It is possible however, that the transmetallation of the zinc reagent particularly to a copper species might provide reagents capable of either pattern of reactivity.

2.6.2. Observations on the Generation of Organozinc Carbenoids from Acid Fluorides

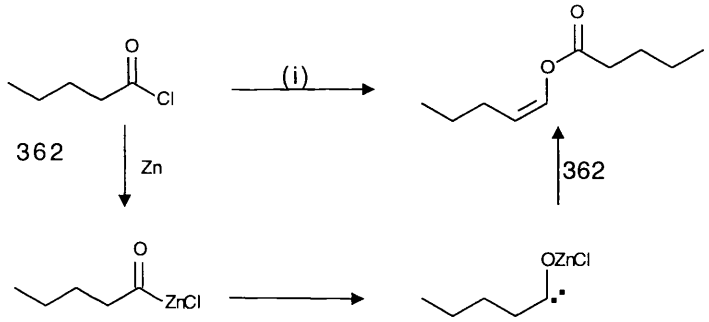
The reduction of acyl halides themselves by zinc has been little studied in the past, but interesting work has been published which shows that some acid halides are amenable to reaction with metallic zinc. Acetyl chloride will react with zinc dust to give 1,1,6,6-tetraethyl-3,4-dimethyl-1,2,4,5-hexatetraene **361**, in a remarkable reaction whose mechanism is not known.[187]



361

scheme 227

Recently Chemla and Normant have published a report on the reaction of some acyl chlorides with activated zinc in ethyl acetate. Reaction of acyl chlorides such as the alkyl species **362** gives enol-acetates in high yield. The reaction appears quite general, and it is suggested that the product might occur *via* trapping of the zinc carbene species **363** formed after insertion of zinc into the carbon-chlorine bond.[188]

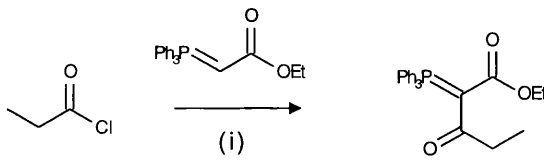


363

i). Zn (0.5equiv), EtOAc reflux 88%

scheme 228

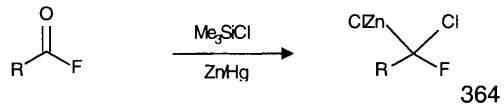
Simple acyl halides have also been utilised in the zinc promoted acylation of ylides at the α-carbon.[189] Reaction of zinc dust with an acyl chloride at room temperature has been shown to generate a species that will acylate stable phosphonium ylides in a few hours and in high yields (scheme 229) *via* an unknown mechanism.



i), Zn dust, toluene 10 mins then ylide (1 equiv) 2 hr, 80%

scheme 229

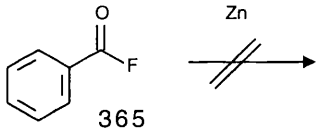
In contrast, nothing at all is known about the reactivity of acyl fluorides with zinc. It was reasoned that zinc could not insert into the strong carbon fluorine bond of an acyl fluoride, but instead might induce direct reduction of the carbonyl group to give the fluorocarbenoid species **364** in a mechanism analogous to that of simple carbonyl compounds (scheme 230).



364

scheme 230

The presence of the fluorine should stabilise the carbenoid and the system could in theory be utilised in the generation of fluorocyclopropanes. In order to probe this rationale, benzoyl fluoride was subjected to a range of reagents in the attempted cyclopropanation of cyclohexene. The acid fluoride however, proved stable to the reaction conditions, some of which are summarised in table 27.

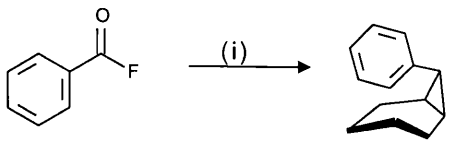


365

	solvent (reflux)	zinc	electrophile (3 equiv)	time (hr)	alkene (4 equiv)
1	Et_2O	Zn/Hg	Me_3SiCl	24	cyclohexene
2	Et_2O	Zn/Hg	Me_3SiI	24	cyclohexene
3	EtOAc	Zn/Hg	Me_3SiI	24	allylbenzene
4	Et_2O	Zn/Hg	Me_3SiOTf	24	cyclohexene
5	toluene	Zn	Me_3SiCl	144	cyclohexene
6	Et_2O	Zn/Hg	$BF_3.OEt_2$	24	cyclohexene

table 27

The addition of titanium trichloride however, changed the reaction completely, consuming the benzoyl fluoride entirely and generating a complex mixture. Low valent titanium has also been utilised in the generation of carbenes from alkyl halides.[91] One compound isolated from the reaction was 7-phenylnorcarane, albeit in low yield (scheme 231).



a). Zn (4 equiv), Me_3SiCl (4 equiv), cyclohexene (2.5 equiv), aq$TiCl_3$ in HCl (0.05 equiv) 1%

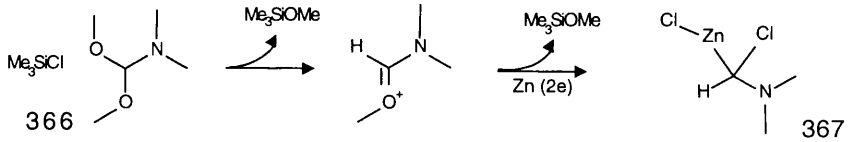
b). Zn (4 equiv), Me_3SiCl (4 equiv), cyclohexene (2.5 equiv), $TiCl_3$ (0.05 equiv) 3%

scheme 231

Although clearly not a synthetically useful transformation, it may be inferred that under the modified MacMurray conditions used, acyl fluorides may now be reduced. The mechanism of the MacMurray coupling of carbonyls with active titanium reductively generated using zinc and a silicon electrophile is not fully understood.[190] and in this case it is unclear at which point the carbon-fluorine bond is reduced. Nevertheless, the reaction suggests that it could be possible to generate carbenoids from acyl fluorides, and that the use of an alternative electrophile such as boron trifluoride diethyletherate in conjunction with zinc and titanium could allow for the generation of fluorocarbenoids.

2.7.2 The Attempted Generation of Organosamarium Carbenoid Species

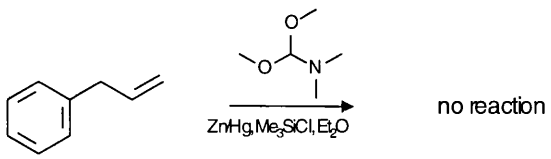
Given the efficiency of alkoxyzinc carbenoid generation from orthoformates, it was postulated that nitrogen analogues, such as dimethylformamide dimethyl acetal **366** might also serve as zinc carbenoid precursors for aminocyclopropanation. The superior electron push delivered by the nitrogen coupled with the thermodynamic preference for silicon oxygen bond formation would presumably lead to the generation of aminozinc carbenoids such as **367**.



366 367

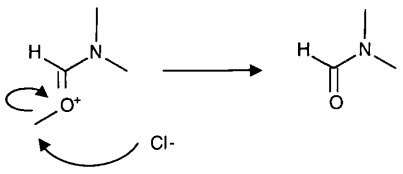
scheme 232

In the event, in the presence of zinc amalgam and chlorotrimethylsilane, the cyclopropanation of allyl benzene with dimethylformamide dimethylacetal **366** proved impossible. No adducts derived from allylbenzene were isolated from the reaction mixture.



scheme 233

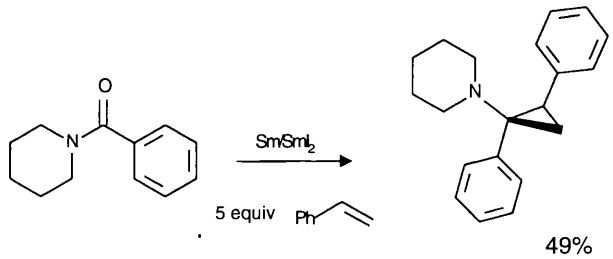
It is probable that in the presence of chlorotrimethyl silane, the acetal is simply being cleaved to give the parent formamide **369**, which is not prone to reduction by zinc. In order to ensure that dimethylformamide **368** would not itself be liable to reduction by zinc under the reaction conditions, **368** was also screened as a carbenoid precursor. Similar reaction conditions to those employed for the dimethylacetal however, failed to yield any amino-cyclopropane.



369

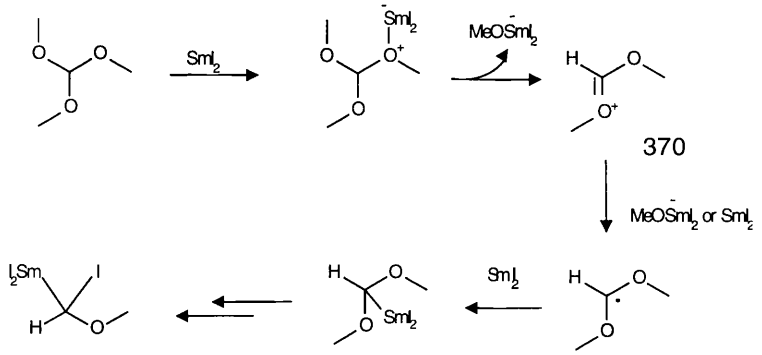
scheme 234

Substitution of solid samarium for zinc has been shown to generate Simmons-Smith type carbenoids from methylene iodide (*vide supra* 1.4), a reaction that is supposedly catalysed by the addition of chlorotrimethylsilane. Samarium carbenoids have also been generated directly from *N,N*-disubstituted aromatic amides with Sm/SmI_2. The resulting samarium carbenoids can be trapped if generated in the presence of styrene to produce cyclopropanes in moderate yields (scheme 235).[191]



scheme 225

It is possible that a samarium iodide species itself might act as the Lewis acid for opening an acetal or orthoformate. Sequential one electron transfer from samarium iodide or the methoxy samarium "ate" complex into the oxonium ion **370** will form an organosamarium such as **371** Further reduction of this species could then generate a samarium carbenoid such as the alkoxy samarium species **372** in scheme 236.



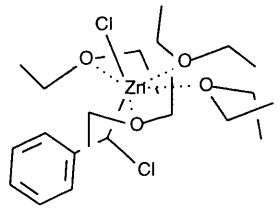
scheme 236

Preliminary studies with triethyl orthoformate, samarium iodide and allylbenzene again produced no cyclopropanes, but it is likely that scope for extending this chemistry to samarium and other metals exists.

3. Conclusions

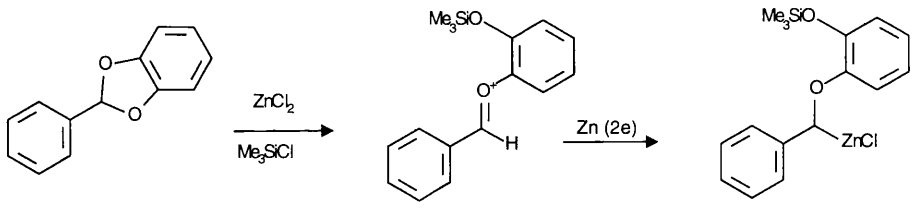
The preceding thesis has hopefully provided an insight into the recent advances made with organozinc carbenoid chemistry. The early chapters describe the results obtained as a continuation of work begun previously within the Motherwell group.

Prior to the commencement of this thesis, the chemistry by which organozinc carbenoids are generated from carbonyl compounds was at an advanced stage. We have now gained greater insight into the nature of the carbenoids produced from these precursors. A careful study using the Three Phase Test has established that the arylzinc carbenoids derived from aryl aldehydes, zinc amalgam and chlorotrimethylsilane exist homogeneously in solution, analogously with the methylene zinc carbenoids produced in the Simmons Smith reaction. The carbenoid possibly exists as the highly co-ordinated species **380**, analogous to the methylene zinc carbenoid produced in the aforementioned Simmons Smith reaction.



380

We have shown through new cyclopropanation reactions with catechol acetals that regeneration of the parent carbonyl compound is not a prerequisite for carbenoid generation. Zinc amalgam can generate organozinc carbenoids *via* two electron reduction of an oxonium species such as **381**.

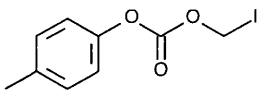


381

Extending the principal of carbenoid generation *via* electron transfer into an oxonium ion, a new species of alkoxyzinc carbenoid was generated directly from orthoformates. The alkoxyzinc carbenoids thus produced proved efficient in the cyclopropanation of a range of functionalised electron rich and electron poor alkenes. Alkoxyzinc carbenoids generated in this manner were also able to show chemoselectivity for electron rich alkenes over electron poor alkenes in a direct competition experiment.

382

The limited study into the generation of methylene zinc carbenoids from new precursors showed some success. Although the simple methylene acetals such as trioxane were completely ineffective as zinc carbenoid precursors, a new methylene zinc carbenoid species derived from iodomethyltolylcarbonate **315** at least as efficient in the cyclopropanation of simple alkenes as methylene diiodide, was synthesised. Further work is needed to more fully probe the limitations of this reagent, and related iodomethylcarbonates could also be examined.



315

In conclusion, the chemistry of organozinc cabenoids generated from unusual precursors is at an exciting stage. New organozinc carbenoid precursors have been found, and it is possible to envisage the use of other trivial compounds to produce these versatile reactive intermediates.

4. Experimental

4.1 General Information

IR spectra were recorded on a Perkin Elmer 1600 FTIR. ^1H spectra were recorded on a Varian XL-200 MHz, a Varian VXR-400 MHz or a Bruker AC300 MHz instrument in the stated solvent using residual protic solvent as the internal standard. Mass spectra were recorded under electron impact conditions unless otherwise stated, at the University of London School of Pharmacy mass spectrometry service. Gas chromatography was performed on a Hewlett-Packard 5890A machine (flame ionisation detector) with a 2.5m x 0.32mm BPX5 column using helium or hydrogen as the carrier gas. Boiling points for Kugelrohr bulb to bulb distillations refer to uncorrected air temperatures. Pressure was recorded on a standard Gallenkamp manometer. Melting points were recorded on Reichert hot-stage apparatus and are uncorrected. Microanalyses were performed in the University College Chemistry Department.

All chemical reactions were performed in flame dried glassware under an atmosphere of nitrogen, unless otherwise stated. Solvent transfer was performed either by canula or using syringes. Glass syringes and needles were stored at 120°C, disposable syringes were stored under vacuum in a dry dessicator. Molecular sieves were activated by microwave irradiation.

40-60° Petroleum ether and diethyl ether for flash chromatography were used as supplied by the manufacturers. Dimethylsulfoxide, methanol, pentane, absolute ethanol and acetone when used experimentally were also used as supplied by the manufacturers. When used under anhydrous conditions, all solvents were distilled under an atmosphere of dried nitrogen. Diethyl ether, DME and tetrahydrofuran were distilled from sodium and benzophenone. Benzene and toluene were ditilled from sodium. Dichloromethane was distilled either from phosphorous pentoxide or calcium hydride. Dimethylformamide was distilled under reduced pressure from calcium hydride and stored over 4Å molecular sieves. Chlorotrimethylsilane was distilled from calcium hydride immediately prior to use. Acetone for experimental purposes was distilled immediately prior to use from either 4Å molecular sieves or anhydrous sodium carbonate. Ethyl acetate was distilled from anhydrous potassium carbonate. Ethanol and methanol were distilled from magnesium turnings and iodine.

Analytical thin-layer chromatography was performed on pre-coated aluminium backed plates (Merck Kieselgel 60 F_{254}). Visualization was afforded either under ultraviolet light (254nm), basic potassium permanganate (add 6.25g of Na_2CO_3 in water (1.25l) to 12.5g of $KMnO_4$ in water (1.25l) acidic ammonium molybdate (IV) (concentrated H_2SO_4 (250ml), ammonium molybdate.$4H_2O$ in water (2.25l)) or anisaldehyde (15ml anisaldehyde dissolved in EtOH with concentrated H_2SO_4 (25ml)). Flash chromatography was performed using BDH flash silica gel (40-60nm), with a silica to crude mass ratio of 10 to 1. Unless otherwise stated, elution was afforded by a graduated solvent system beginning with 40-60° petroloeum ether and terminating with diethylether.

All compounds were used as supplied by the manufacturers unless otherwise stated.

Zinc Mercury Amalgam

Mercury (II) Chloride (1.80g) was dissolved in concentrated HCl. The solution was added to a flask of distilled water (30ml) and to this solution, zinc powder (10g) was added. The flask was vigorously stirred for 10 minutes, and any zinc aggragates were crushed with a glass rod. The aqueous layer was decanted and the amalgam was transferred to a sintered funnel. The metal was washed with distilled water (3 x 20ml) acetone (3 x 20ml), ethanol (3 x 20ml) and finally ether (3 x 20ml) before being dried under high vacuum. The amalgam was thereafter stored under vacuum, and was always flame dried under a stream of nitrogen immediately prior to use.[200]

Zinc Copper Couple

Zinc (3.5g) was placed on a sintered funnel, and washed with 1M HCl (3 x 5ml) water (3 x 5ml) 3% copper sulfate solution (2 x 5ml) water (3 x 5ml) ethanol (3 x 5ml) and finally ether (2 x 10ml). The couple was dried and stored under vacuum, and was always flame dried under a stream of nitrogen immediately prior ro use.[201]

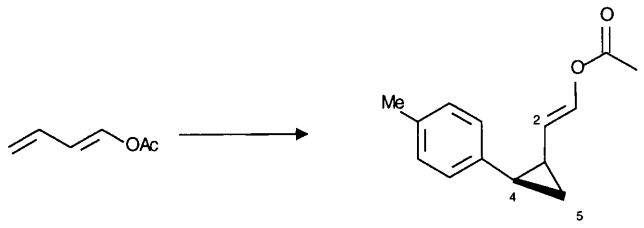
Activated Zinc on Titanium Dioxide

To dry titanium dioxide under nitrogen (2.5g) sodium (0.17g) was added. The mixture was stirred at 150^{o}C for 15minutes. The resulting grey solid was cooled, and a solution of fused zinc chloride (0.80g) in dry ether (10ml) was added. After 30 minutes stirring the suspension may be used.[202]

Samarium Diiodide

Tetrahydrofuran was refluxed over sodium and benzophenone overnight, before collecting (250ml) directly in a dropping funnel. The funnel was placed over a flask containing samarium powder (3g, Strem Chemicals), weighed out in a glove bag. To the THF solution, diiodoethane (2.82g, 0.010mol, pre-purified by dissolving in ether and washing with1M sodium thiosulfate) was added, and the solid dissolved by bubbling with nitrogen. The solution of diiodoethane was added to the solid samarium as a steady drip over one hour. The presence of a deep blue turquoise colour after 2 minutes indicated the formation of the air sensitive solution. Following complete addition of the THF solution, stirring was continued for one hour. After stirring ceased and the unreacted samarium metal settled out, the dropping funnel was replaced by a dry suba seal and the resulting deep turquoise 0.04M solution of samarium iodide could be stored under nitrogen for at least one week.[203]

4.2 *E*-2-[2-(4-Methylphenyl)cyclopropyl]ethen-1-ol Acetate 159a



A solution of distilled 4-tolualdehyde (0.24g, 2.0mmol) in dry ether (1.8ml) was added *via* syringe pump over 36 hours to a vigorously stirred mixture of flame dried Zn/Hg amalgam (1.3g, 20mmol), dry ether (10ml), *E*-1-acetoxy-1,3-butadiene (0.45g, 4mmol) and chloro-trimethylsilane (1ml, 8mmol) at reflux. The cooled mixture was quenched by the addition of saturated sodium bicarbonate (10ml) then filtered through celite and the residue washed with ether (50ml). The washings were separated and the ethereal solution was washed with saturated aqueous sodium bicarbonate solution (10ml) and brine (5ml). The combined organic phase was dried over $MgSO_4$ then concentrated *in vacuo*. The crude product was purified by flash chromatography to give the *title compound* **159a** (160mg, 0.74mmol, 37%, *cis* / *trans* 3:6:1 GC) as a colourless oil, 4,4'-dimethylstilbene **158** (50mg, 0.24mmol, 12%) and phenyl-2-ethoxypropane **165** (24mg, 0.14mmol, 7%).

4,4'-dimethylstilbene 158[204] mpt 180°C

^{1}H NMR($CDCl_3$ / ppm): 8.50-8.40(4H, d, H2,2',6,6'), 7.20-7.108(4H, d, H3,3',5,5'), 7.06(2H, 2 x s, **H**C=C**H**), 2.36(6H, s, 2 x C**H**$_3$).

(4-methylphenyl)-2-ethoxypropane 165[205]

^{1}H NMR ($CDCl_3$ / ppm) 7.41(2H, d, aryl), 6.95(2H, d, aryl), 3.62-3.45(m, 3H, C**H**OC**H**$_2$), 2.92 and 2.60 (2H, 2 x dd, PhC**H**$_2$), 1.38(3H, t, C**H**$_3$), 1.30(3H, d, C**H**$_3$).

***E*-2-[2-(4-methylphenyl)cyclopropyl]ethen-1-ol acetate 159a**

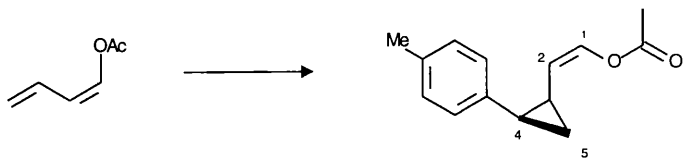
IR (*cis* / *trans* 3:6:1, thin film / cm^{-1}): 2920(s), 1754(s), 1667(s), 1514(s), 1372(s), 1223(s), 1120(s), 930(s), 822(s), 726(m), 652(m), 601(w).

^{1}H NMR (*cis* / *trans* 3.6:1, $CDCl_3$ / ppm); 7.3-6.9(4H, m, aryl), 7.19(0.75H, d, J=12.4, H1 *cis*), 7.14(0.25H, d, J=12.4, H1 *trans*), 5.30(0.25H, dd, J=12.4, 8.5, H2 *trans*) 5.25(0.75H, dd, J=13.0 9.6, H2 *cis*) 2.34 and 2.33(3H, 2 x s, 4:1, Me *cis* and *trans*) 2.4-1.75(2.75H, m, H3, H4, and *trans* H5), 2.13 and 2.04(3H, s, 4:1, Ac *cis* and *trans*), 1.55(0.25H, m, H5 *trans*),1.3-1.2(0.75H, m, H5β *cis*), 1.05(0.25H, m, H5 *trans*), 0.95(0.75H, q, J=6.1, H5α *cis*)

^{13}C NMR (*cis* / *trans* 3:6:1, thin film / cm^{-1}) 168.0, 135.5, 135.2, 135.0, 129.0, 128.8, 126, 117, 115, 24.4, 22.1, 21.2, 21.0, 20.6, 17.2, 16.0, 11.0.

Mass Spectrum: calculated for $C_{14}H_{16}O_2$ (M^+) 216.1150; found 216.1140.

_Z_-2-[2-(4-Methylphenyl) cyclopropyl]ethen-1-ol Acetate 159b



A solution of distilled 4-tolualdehyde (0.27g, 2.25mmol) in dry ether (1.8ml) was added *via* syringe pump over 36 hours to a vigorously stirred mixture of flame dried Zn/Hg amalgam (1.3g, 20mmo), dry ether (10 ml) *Z*-1-acetoxy-1,3-butadiene (0.45g, 4mmol) and chlorotrimethylsilane (1ml, 8mmol) under nitrogen at reflux. The cooled mixture was quenched by the addition of saturated sodium bicarbonate (10ml) then filtered through celite and the residue washed with ether (50ml). The washings were separated and the ethereal solution was washed with saturated aqueous sodium bicarbonate solution (10ml) and brine (5ml). The combined organic phase was dried ($MgSO_4$) then concentrated *in vacuo*. The crude product was purified by flash chromatography to give the *title compound* **159b** (160mg, 0.74mmol, 44% , *cis* / *trans* 5: 1 GC) as a colourless oil, 4,4'-dimethylstilbene **158**[204] (38mg, 0.18mmol, 8%) and (4-methylphenyl)-2-ethoxypropane **165**[205] (41mg, 0.23mmol, 10%).

IR (*cis*, thin film / cm^{-1}); 3006(m), 2920(m), 2846(m), 1754(s), 1573(w), 1516(m), 1368(m), 1217(s), 1157(m), 1061(w), 1045(m), 1013(w), 965(w), 933(w), 885(w), 837(w), 822(m), 756(w), 724(w), 655(w).

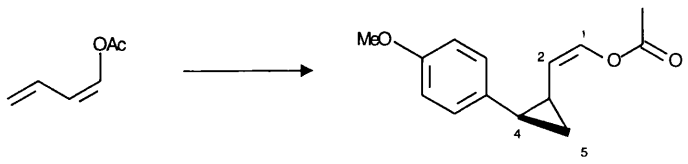
^1H NMR (*cis*, $CDCl_3$ / ppm): 7.20-7.07(4H, m, aryl), 7.01 (1H, d, J=6.4, H1), and 4.17 (1H, 2 x dd, 1:5 J=6.4, 9.7, H2), 2.45(1H, q, J=6.5, H4), 2.34(3H, s, CH_3), 2.2(1H, m, obscured, H3) 2.19 (3H, s, OAc), 1.32(1H, m, H5β), 0.99(1H, q, J=6.5, H5α).

^{13}C NMR (*cis*, $CDCl_3$ / ppm)168.0, 134.6, 129.0, 128.9, 128.8, 125.7, 113.6, 22.7, 21.0, 20.8, 15.0, 12.1.

^1H NMR (*trans*, $CDCl_3$ / ppm); 7.20-7.07(4H, m, aryl), 7.04(1H, d, J=6.4, H1), 4.50(1H, dd, 1:5 J=6.4 9.7, H2), 2.35(1H, m, obscured, H4), 2.34(3H, s, CH_3), 1.95(1H, m, obscured, H3) 2.16 (3H, s, OAc), 1.30(1H, m, H5), 1.06(1H, m, H5).

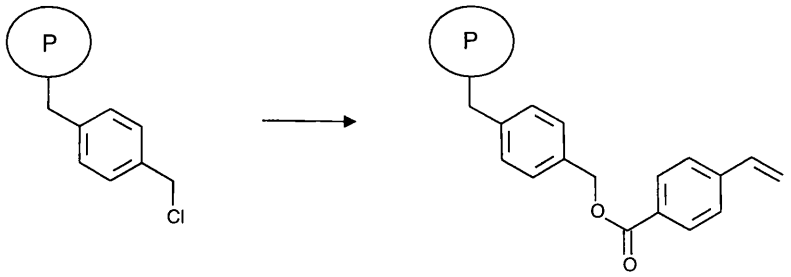
Mass Spectrum: calculated for $C_{14}H_{16}O_2$ (M^+) 216.1150; found 216.1140.

Preparation of *Z*-2-[2-(4-Methoxylphenyl)cyclopropyl]ethen-1-ol Acetate 163



A solution of anisaldehyde (0.294g) in ethyl acetate (1.8ml) was added *via* syringe pump over 36 hours to a vigourosly stirred mixture of flame dried Zn/Hg amalgam (1.3g, 20mmol), *Z*-1-acetoxy-1,3-butadiene (0.45g, 4mmol) and chlorotrimethylsilane (1.0ml, 8mmol) in freshly dried ethyl acetate (8ml) at reflux. Saturated sodium bicarbonate was added to the cooled mixture, which was then filtered through celite and the separated zinc washed with ether (50ml). The ethereal solution was washed with saturated aqueous sodium bicarbonate solution (20ml) and the aqueous layer was extracted with ether (25ml). The combined organic extracts were washed with brine (10ml), dried over $MgSO_4$ then concentrated *in vacuo*. The crude product was purified by flash chromatography, to give the *title compound* **163** as a clear oil (270mg, 1.2mmol, 57%).[204]
IR (thin film / cm^{-1}): 3002(s), 1754.(s), 1732(s), 1614(m) 1504(s), 1454(s), 1372(s), 1218(s), 1031(s), 836(s), 760(s), 586(m).
^1H NMR($CDCl_3$ / ppm) 7.16(1H, d, J 12.5, H1), 7.11 (2H, d, J=8.8, aryl), 6.38 (2H, d, J=8.8, aryl), 4.78 (1H, dd, J=12.5, 9.5, H2), 3.79(3H, s, OMe), 2.29 (1H, dt, J=6.3, 8.3, H4), 2.03 (3H, s, OAc), 1.74 (1H, ddt, J 9.5, 8.8 and 5.4, H3), 1.23(1H, dt, J =8.3, 5.4, H5β) and 0.90(1H, q, J=5.7, H5α).

Coupling of *p*-vinylbenzoic acid 171 to Merrifield's resin



Merrifield's resin A: A solution of *p*-vinylbenzoic acid **171** (0.749g, 5.0mmol) in DMF (5ml) was introduced dropwise over 5 minutes to a stirred suspension of sodium hydride (0.247mg, 5.50mmol as a 55% dispersion in mineral oils, prewashed with diethyl ether) in DMF (10ml) After 20 minutes the suspension of the acid salt was poured with stirring into a suspension of Merrifield's resin (5.01g of Aldrich resin Cl 3.7%, equivalent to 5.3mmol Cl) in DMF (50ml) also at room temperature. The reaction mixture was then heated to 80°C for 24 hours whilst protecting from light. After cooling to room temperature, the polymer was filtered under suction. The collected polymer was washed successively with DMSO (4 x 15ml), and acetone (4 x 20ml). The polymer was stirred in DMSO for 2 hours and the solvent filtered off. The washing was repeated before final rinsing of the polymer with acetone (4 x 20ml), and drying *in vacuo* for 24 hours to afford polymer **A** .[200]

IR (KBr disc / cm^{-1}) 1710 (carbonyl, ester) 1094 (C-O ester);

Microanalysis: found: Cl 1.35%, implies 6% coupling to polymer (0.6mmolg^{-1} of alkene).

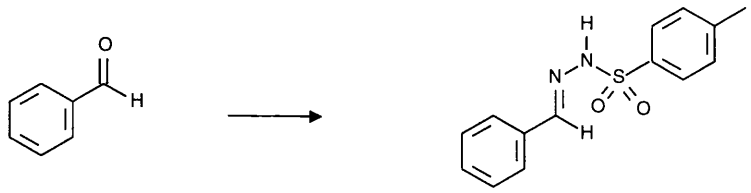
Titration of the polymer (0.5g,), in ethanol / water (10ml, 9:1), with KOH (250mg), afforded, after acid / base work-up a buff solid, which ^1H NMR showed to be a mixture of vinyl benzoic acid and unidentified aromatic compounds (50mg).

Merrifield's resin B: A solution of *p*-vinylbenzoic acid (1.50, 10.0 mmol) in DMF (10ml) was introduced dropwise over 5 minutes to a stirred suspension of sodium hydride (440mg, 11.0mmol as a 55% dispersion in mineral oils, prewashed with diethyl ether) in DMF (2ml). After 20 minutes the suspension of the acid salt was poured with stirring into a suspension of Merrifield's resin (4.0g of Lancaster resin, Cl 8.22%, 2.4mmolg^{-1} of Cl, 8.8mmol Cl in total) in DMF (50ml) at room temperature. The reaction mixture was protected from light and then heated to 80°C for 24 hours. The mixture was cooled to room temperature before filtering off the polymer under suction. The collected polymer was washed successively with DMSO (4 x 15ml), and acetone (4 x 20ml). The polymer was stirred in DMSO for 2 hours and the solvent filtered off. The washing was repeated, before final rinsing of the polymer with acetone (4 x 20ml), and drying *in vacuo* for 24 hours to afford polymer **B**.[200]

IR (KBr disc / cm^{-1}) 1710 (carbonyl, ester) 1094 (C-O ester);

Microanalysis: found: Cl 2.68%, implies 68% coupling to polymer (1.6mmolg^{-1} of alkene).

Phenyl-(*N*-(4-methylphenyl))sulphonyl)hydrazone 168



4-Toluenesulfonylhydrazone (7.4g, 40mmol) was dissolved in methanol (10ml) at reflux. The solution was taken up in a syringe and added to a solution of benzaldehyde (4.0ml, 40mmol), in methanol (30ml). After 5 minutes the flask was cooled to -78°C. After 2.5 hours, the solution was filtered, and the filtrate was collected and washed with methanol. The white solid was recrystallized from methanol, to afford white needles of the *title compound* **168** (10.1g, 37mmol 92%), mpt 137-139°C.[206]

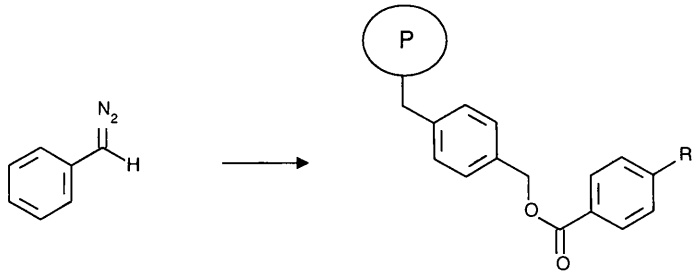
IR (thin film / cm^{-1}) 3197(s), 3058(m), 2922(w), 2736(w), 1598(w), 14929w), 1445(s), 1363(s), 1327(s), 1310(s), 1223(w), 1164(s), 1087(m), 1047(s), 951(m), 814(m), 757(m), 730(m), 688(m), 669(s), 584(s), 548(s).

^{1}H NMR ($CDCl_3$ / ppm): 8.22(1H, bs, N**H**), 7.89(2H, d, J=8.4, aryl), 7.78(1H, s, PhC(N)**H**), 7.58 and 7.36(2H and 3H, 2 x m, Ph), 7.33(2H, d, J=8.4, aryl), 2.41(3H, s, Me).

^{13}C NMR ($CDCl_3$ / ppm) 147.9, 144.3, 133.2, 130.5, 129.7, 128.7, 128.0, 127.4, 21.7.

Microanalysis: calculated for $C_{14}H_{14}N_2SO_2$ C61.30 H5.14 N10.22 S11.69; found C 61.22 H5.04 N10.38 S11.77.

Cyclopropanation of Resin A with Phenyldiazomethane

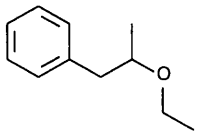


To a suspension of sodium methoxide (810mg, 5eq, 15mmol) in dry diglyme (6ml), phenyl-(*N*-4-(methylphenyl)sulphonyl)hydrazone **168** (810mg, 3 mmol) was added, and the solution was stirred at 60°C for 40 minutes under a vacuum of approximately 20 mmHg (rotary pump). After 10 minutes, bubbling had subsided and the solution had turned a rich orange. The solution was poured into ice water and extracted with pentane (2 x 20ml). The pentane was cooled to -78°C

for 5 minutes during which time a pale yellow precipitate formed. The solid was removed by filtration through a sintered funnel (CAUTION), and the pentane removed *in vacuo* (water bath at 0°C). The resulting red oil[207] was dissolved in ether (7ml), and placed in a dry-ice cooled droppping funnel over a round bottom flask containing a solution of fused zinc chloride (450mg, 3.30mmol), polymer resin **(A)** (1.0g, implying 0.63mmol of alkene), and ether (20ml). The phenyldiazomethane solution was added over 15 minutes, and vigorous production of N_2 was observed. Stirring was continued overnight, after which time the solution was filtered to afford the polymer which was washed with ether (5 x 30ml), and acetone (2 x 20ml), before being dried *in vacuo.*

Analysis of the washings showed that they contained a large amount of unidentifiable aromatic species and the product of insertion of the carbenoid (30mg, 0.18mmol, 6%) 2-ethoxy-1-phenyl propane **170**

Phenyl-2-ethoxypropane 170[209]

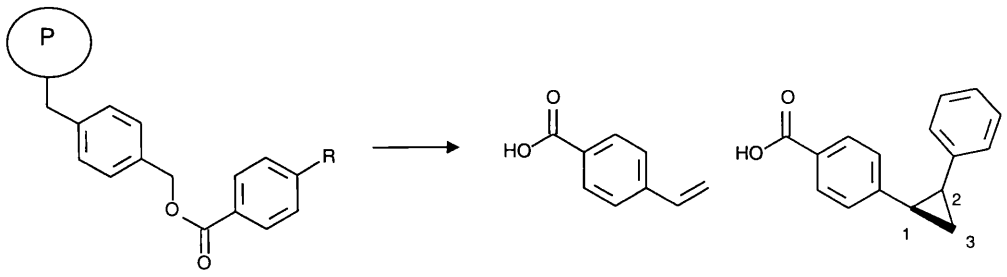


IR (thin film / cm^{-1}) 2924(s), 2850(s), 2673(w), 1683(s), 1600(m), 1453(m), 1419(m), 1378(w), 1321(m), 1287(s), 1175(m), 1123(m), 1123(m), 1098(m), 1067(m), 1025(w), 934(m), 802(w), 750(w), 705(s), 667(m).

^1H NMR ($CDCl_3$ / ppm): 7.5-7.1(5H, m, Ph), 3.62-3.40(3H, m, MeC**H**OC**H**2), 2.92(1H, dd, J-11.0, 6.0, PhC**H**), 2.60(1H, dd, J=13.5, 7.0, PhC**H**), 1.16(3H, t, J=7.0, $OCH_2C\mathbf{H}_3$), 1.11(3H, d, J=6.14, $OCH(Bn)C\mathbf{H}_3$),

^{13}C NMR ($CDCl_3$ / ppm) 139.2, 137.3, 127.6, 128.7, 76.4, 63.9, 43.1, 19.7, 15.0.

Saponification of Polymer A



The dried polymer filtrate was stirred for 2 days in a solution of potassium hydroxide (2.4g) in water (5ml) and ethanol (45ml). The polymer was then filtered, washing with copious ethyl acetate. The resulting solution was acidified with 1M HCl (50ml), and transferred to a separating funnel. The layers were separated, and the aqueous layer was washed with ethyl acetate (3 x

100ml). The combined organic extracts were washed with brine (50ml), dried over $MgSO_4$, and the solvent removed *in vacuo* to afford a pale cream solid (326mg).

^1H NMR of the solid suggested that it was a mix of unidentified aromatic compounds, vinyl benzoic acid, and the desired cyclopropane **172**. Chromatography afforded a mixture of the vinyl acid **171** and the desired cyclopropane **172** in a ratio of approximately 20:1 (20mg in total, 0.13mmol, 21% vinylbenzoic acid recovery, 0.023mmol, 3% yield of cyclopropane).

4-(2-phenylcyclopropyl) benzoic acid 172 mpt 203-206^{o210}

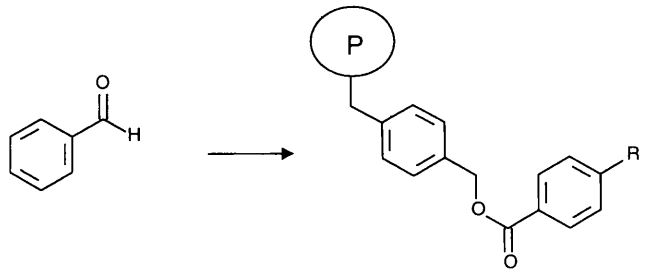
IR (thin film / cm^{-1}) 3439(s), 2925(s), 2858(w), 2567(w), 1628(s), 1649(s), 1609(s), 1452(w), 1420(m), 1312(m), 1287(s), 1171(m), 1121(m), 1087(m), 1020(m), 924(w), 835(w), 778(w), 756(w), 728(w), 699(m), 672(m), 543(w), 520(w).

^1H NMR ($CDCl_3$ / ppm): 7.81(2H, d, J=7.6, aryl), 7.30-6.92(7H, m, aryl, 2.61 and 2.80(2 x q, AB pattern, J=6.6, H1, H2), 1.56-1.40(1H, m, H3) 1.45(1H, q, J=6.2, H3).

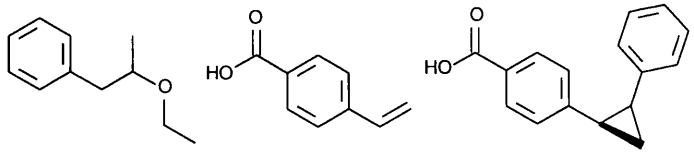
^{13}C NMR ($CDCl_3$ / ppm) 172.4, 145.5, 137.3, 130.4, 128.5, 127.8, 126.0, 29.7, 25.5, 11.8.

Mass Spectrum: calculated for $C_{16}H_{14}O_2$ (M^+): 238.0994; found 238.0998.

The 3 Phase Test Employing Benzaldehyde



To a suspension of coupled Merrifield's resin (1g), Zn/Hg amalgam (2g, 31mmol) and chlorotrimethylsilane (see table) in ether (20ml), a solution of benzaldehyde (see table), in ether (2ml), was added *via* syringe pump over 12 hours. The mixture was refluxed overnight, alowed to cool and then filtered, washing with ether (3 x 20ml). The filtrate was quenched by addition of saturated sodium bicarbonate (6ml). The filtrate was filtered through celite and transferred to a separating funnel where the layers were separated. The ethereal layer was washed with brine (10ml) and dried over $MgSO_4$. The ether was removed *in vacuo* to afford a brown solid. Purification by flash chromatography afforded a mixture of vinyl benzoic acid **171** the desired cyclopropane **172** and the product of carbenoid insertion into the solvent, 2-ethoxy-3-phenylpropane **170** (see table 6):

	PhCHO* (equiv)	electro-phile (eq)†	P	Lewis acid			
1	14	Me_3SiCl (4)	A	-	3	(13)*	2 & (30)*
2	5	Me_3SiCl (4)	B	$ZnCl_2$	4	(9%)*	3 & (14%)*
3	3	Me_3SiCl (4)	A	-	15	0	0
4	5	BF_3OEt_2 (2)	B	-	2	1 & (11)*	2 & (11)*

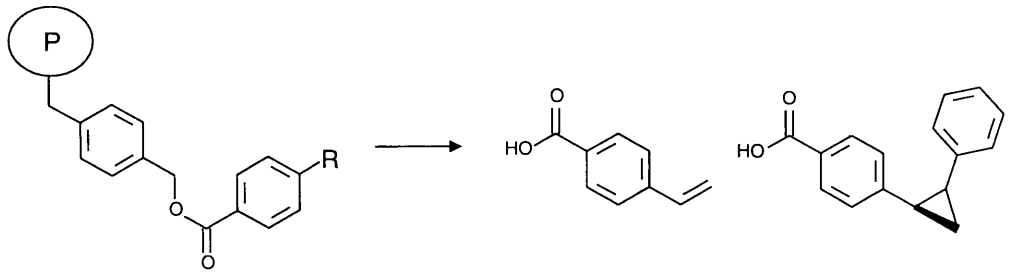
Products of washings (yield %)†

* relative to alkene on polymer

† relative to PhCHO

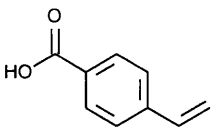
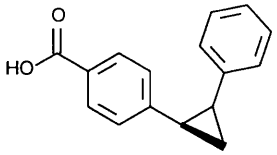
table 6

Saponification of Merrifield's Resin



The polymer and zinc mixture from the previous reaction was washed with ether and ethanol. Evaporation of the washings provided only a trace of material, and so the polymer and Zn/Hg amalgam were separated by repeated sedimentation in ether. Each time, the polymer-zinc mixture was suspended in a flask containing ether (10ml), allowed to settle, and the top layer of polymer was carefully decanted *via* pipette. After 5 separations the polymer was dried *in vacuo*.

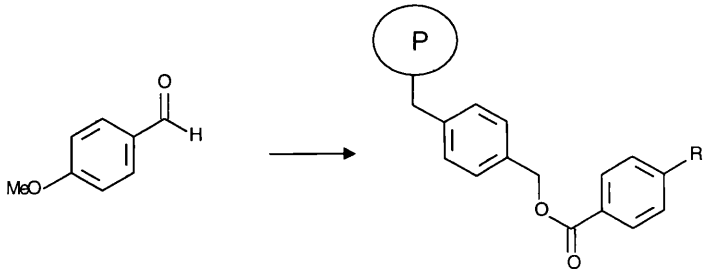
To the dried polymer, potassium hydroxide (see table), in 10:1 ethanol / water (10ml), was added, and the mixture allowed to stir at room temperature for 2 days. After this time, the polymer was filtered off, and the filtrate was acidified to pH 2 by dropwise addition of 1M HCl. The mixture was transferred to a separating funnel, and ether (100ml) was added. The layers were separated, and the aqueous layer was back titrated with ether (50ml). The combined organic extracts were dried over $MgSO_4$, and the solvent reomved *in vacuo* to afford a brown solid which was investigated by ^1H NMR. Where the saponification provided sufficient material, this was purified by flash chromatography (see table 7).

No.	P	No of eq KOH*	Products of Saponification (yield %)* 	
1.1	A	30	trace	trace
2.1	B	4	22	22
3.1	A	15	40	10
4.1	B	5	10	0

* relative to alkene on polymer

table 7

The Three Phase Test employing Anisaldehyde

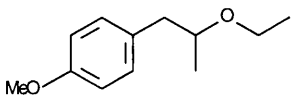


To a suspension of coupled Merrifield's resin (1g, resin B 68% coupled with vinyl benzoic acid, implying 1.62mmolg^{-1}of alkene), $ZnCl_2$ (560mg, 4mmol), Zn/Hg amalgam (2g, 31mmol) and chlorotrimethylsilane (4.0ml, 32mmol) in ether (20ml), a solution of anisaldehyde (0.60 ml 0.67g, 5mmol), was added *via* syringe pump over 12 hours. The mixture was refluxed overnight, alowed to cool and then filtered, washing with ether (3 x 20ml). The filtrate was quenched by addition of saturated sodium bicarbonate (6ml) filtered through celite and transferred to a separating funnel, where the layers were separated. The ethereal layer was washed with brine and dried over $MgSO_4$. The ether was removed *in vacuo* to afford a brown solid which was examined by ^1H NMR.

The residue contained a mixture of insoluble polymeric compounds, unidentified aromatic compounds, and what appeared to be the acid cyclopropane (230mg) **175**. After drying *in vacuo,* trituration provided a brown oil, which was a mixture of unidentifiable aromatic

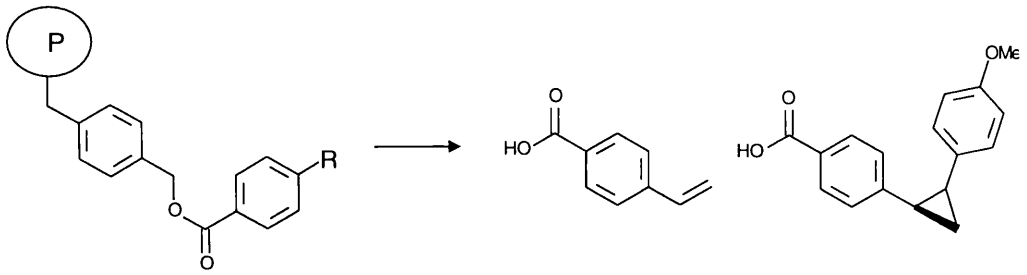
compounds, the product of ether insertion 3-(4-methoxyphenyl)-2-ethoxypropane **173** (20mg, 0.13mmol, 3%) vinyl benzoic acid **171** (50mg, 0.34mmol 21% relative to the coupled vinylbenzoic acid) and the cyclopropane acid **175** (20mg, 0.06mmol, 6%relative to the coupled vinylbenzoic acid). Attempted column chromatography led to substantial decomposition of the product, and identification was made by comparison to the product from the saponification.

(4-methoxyphenyl)-2-ethoxypropane 173[200]



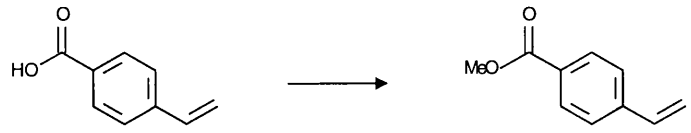
^{1}H NMR ($CDCl_3$ / ppm): 7.12(2H, d, J=8.7 aryl), 6.83(2H, d, J=8.7, aryl), 3.79(3H, s, OMe), 3.50-3.59(2H, m, OC**H**2), 3.43(1H, dq, J=14.0, 7.0, OC**H**), 2.86(1H, dd, J=6.0, 13.6, PhC**H**), 2.56(1H, dd, J=6.8, 13.6, PhC**H**), 1.17(3H, t, J=7.0, C**H**3), 1.12(3H, d, J=6.2, C**H**3).
^{13}C NMR ($CDCl_3$ / ppm): 157.9, 131.2,130.3, 113.6, 76.5, 63.9, 55.2, 42.1, 19.5, 15.5.

Cleavage of Merrifield's Resin



The polymer and zinc mixture from the previous reaction was washed with ether and ethanol. Evaporation of the washings provided only a trace of material, and so the polymer and zinc amalgam were purified by repeated sedimentation in ether. Each time, the polymer-zinc was suspended in a flask containing ether (10ml), and allowed to settle. The top layer of polymer was carefully decanted using a pasteur pipette After 5 separations the polymer was dried *in vacuo*.
To the dried polymer, potassium hydroxide (620mg, 11mmol), in 10:1 ethanol/water (10ml), was added, and the mixture allowed to stir at room temperature for 2 days. After this time, the polymer was filtered off, and the filtrate was acidified to pH 2 by dropwise addition of 1M HCl. The mixture was transferred to a separating funnel, and ether (100ml) was added. The layers were separated, and the aqueous layer was back titrated with ether (50ml). The combined organic extracts were dried over $MgSO_4$, and the solvent removed *in vacuo* to afford a brown solid (50mg) ^{1}H NMR of the crude suggested that this contained unidentified aromatic residues and a 1:1 mixture of vinyl benzoic acid **171** and *cis*-4-(2-(4-methoxyphenyl)cyclopropyl)benzoic acid **175**. The solid was only partially soluble in $CDCl_3$.

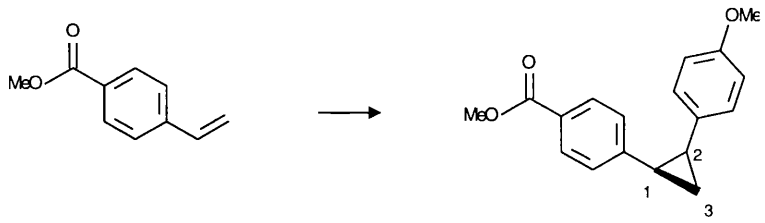
Vinylbenzoic Acid Methyl Ester 177



4-Toluenesulfonic acid monohydrate (64mg, 0.34mmol) was flame dried under vacuum. To the same flask, vinylbenzoic acid (1.0g, 6.8mmol) and dry methanol (10.0ml) were added. The mixture was heated to reflux for 4 hours, and then cooled. The methanol was removed *in vacuo,* and the residue was dissolved in ether (100ml). The ethereal solution was washed with saturated sodium bicarbonate (10ml), brine (10ml) and dried over $MgSO_4$. The solvent was removed *in vacuo* to afford an oil, which was purified by flash chromatography to afford the *title compound* **177** as a clear oil (0.50g, 3.1mmol, 46%).[211]

^1H NMR ($CDCl_3$ / ppm): 7.98(2H, d, J=8.4, aryl), 7.44(2H, d, J=8.4, aryl), 6.73(1H, dd, J=9.1, 18.6, C**H**=CH_2), 5.90 and 5.36(2H, 2, x, d, J=18.6 and 9.1, CH=C**H**$_2$). 3.90(3H, s, OC**H**$_3$).

***cis*-4-(2-(4-Methoxyphenyl)cyclopropyl)benzoic acid methyl ester 176**



To a flame dried suspension of zinc amalgam (1.5g), chlorotrimethylsilane (1.8ml), and vinyl benzoic acid methyl ester (450mg, 2.8mmol), in ether (10ml), anisaldehyde (0.49ml, 4mmol), in ether (2ml), was added over 24 hours. The reaction was quenched by the addition of saturated sodium bicarbonate (5ml), and then filtered through celite. After transferring to a separating funel with ether (50ml), the layers were separated and the ethereal layer was washed with brine (10ml), dried over $MgSO_4$ and the solvent evaporated *in vacuo* to afford a brown oil which was purified by flash chromatography to afford the cyclopropyl methyl ester **176**, (131mg, 0.52mmol, *cis /trans* 12:1 19%), and the product of ether insertion (4-methoxyphenyl)-2-ethoxypropane173, (40mg. 0.21mmol, 5%).

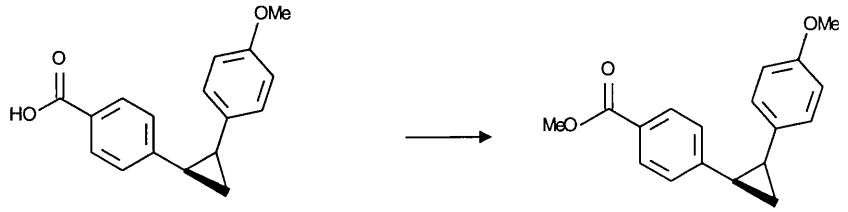
IR (thin film / cm^{-1}) 3302(m), 2954(s), 2837(m), 2253(w), 2066(w), 1720(s), 1611(s), 1579(m), 1436(s), 1367(m), 1279(s), 1248(s), 1180(s), 1108(s), 1035(s), 967(w), 911(m), 831(s), 798(m), 778(s), 706(s), 685(w), 624(w), 570(w), 530(s).

^1H NMR ($CDCl_3$ / ppm): 7.75(2H, d, J=8.2, aryl), 6.94(2H, d, J=8.4, aryl), 6.89(2H, d, J=8.7, aryl), 6.65(2H, d, J=8.8, aryl), 3.85(3H, s, CO_2C**H**$_3$), 3.72(3H, s, OC**H**$_3$), 2.58-2.40(2H, m, H1, H2), 1.50(1H, td, J=12.0, 5.5, H3α), and 1.38(1H, m, H3).

^{13}C NMR ($CDCl_3$ / ppm): 167.2, 157.7, 144.8, 130.3, 129.7, 129.3, 128.3, 113.2, 55.1, 51.9, 24.7, 23.8, 11.9.

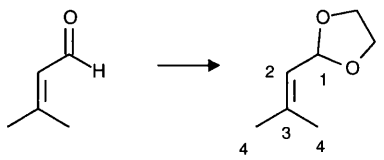
Mass Spectrum: calculated for $C_{18}H_{18}O_3$ 282.1266 found 282.1270.

cis-4-(2-(4-Methoxyphenyl)cyclopropyl)benzoic acid methyl ester 176.



The residue from the saponification was dissolved in dichloromethane (5ml) in an open vial, and diazomethane was bubbled slowly into the solution using a stream of nitrogen.[212] The diazomethane was generated in a separate flask by the dropwise addition of 1M sodium hydroxide to a solution of diazald (*N*-Methyl-*N*-nitroso-4-toluenesulfonamide 43mg, 0.2mmol) in ethanol (10ml). After the addition of 1ml of the sodium hydroxide solution the yellow colour of the diazald had completely disappeared. After stirring for a further 30 minutes, the dichloromethane solution was concentrated *in vacuo*, and the resulting oil was purified by flash chromatography to produce the desired cyclopropane methyl ester 176, (10mg, 0.05mmol, 2.5%, relative to the coupled alkene) and the methyl ester of vinyl benzoic acid **177** (6mg, 0.04mmol, 3% relative to the coupled alkene), both spectroscopically identical to material already produced.

Preparation of 2-(2-methyl-1-propenyl)-1,3-dioxolane 178a

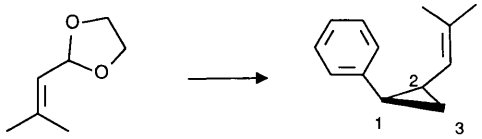


Trimethylsilytrifluoromethanesulfonate (93µl, 0.48mmol) was dissolved in dichloromethane (3ml), and the solution cooled to -78°C. Bis(trimethylsilyloxy) ethane (6.18ml, 25mmol) and 3-methyl-2-butenal (2.29ml, 24mmol) were added in succesion and the mixture stirred at -78°C overnight.[e13] TLC (4:1 petrol/EtOAc) indicated complete loss of the starting material. The reaction was quenched by addition of a few drops of pyridine. The reacton mixture was poured into saturated aqueous sodium bicarbonate solution (20ml), and extracted with ether (2 x 20ml). The combined extracts were dried over a 1:1 mixture of sodium carbonate and sodium sulfate, and the solvent was removed *in vacuo* to afford a crude oil. The oil was purified by flash chromatography to afford the *title compound* as a clear oil (1.88g, 14.7mmol, 61%).[213]

^{1}HNMR ($CDCl_3$ / ppm): (5.40(1H, d, J=7.5, H1), 5.15(1H, d, J=7.5, H2), 3.9-3.8(4H, m, OCH_2CH_2O), 1.7(6H, s, Me4).

^{13}C ($CDCl_3$ / ppm): 141.0, 121.3, 100.4, 64.6, 26.3.

Preparation of *cis*-[2-(2-methyl-1-propenyl)cyclopropyl]benzene 179a

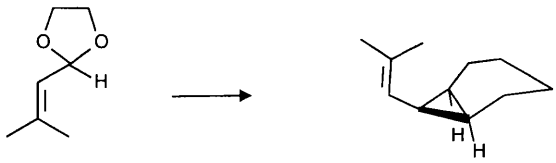


Zn/Hg amalgam (1.3g, 20mmol), zinc chloride (280mg, 1.0 equiv.), dichlorodimethylsilane (0.49ml, 4mmol, 2 equiv.) and styrene (1.10ml, 10mmol, 5 equiv.) were stirred at relux in ether (9ml). A solution of the acetal (0.20g, 2mmol) in ether (1.0ml) was added over 22 hours. The reaction was quenched by addition of saturated sodium bicarbonate solution (10ml). After 15 minutes stirring, the solids were removed by filtration through celite, and the aqueous solution was extracted with ether (2 x 20ml). The combined organic extracts were washed with brine (10ml), dried over $MgSO_4$, and the solvent removed *in vacuo* to afford a viscous yellow oil which was purified by flash chromatography (petrol) to afford, the *title compound* as a clear oil (31 mg, 0.20mmol, 10%, *cis* / *trans* 5:1).[204]

IR (thin film / cm^{-1}) 3060, 3025, 2958, 1937, 1861, 1795, 1749, 1601, 1493, 1447;

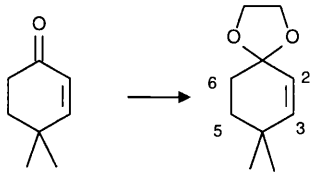
^{1}HNMR ($CDCl_3$ / ppm): 7.28-7.07(5H, m, Ph), 4.43(H, d, J=7.8, H4), 2.22(1H, dt, J =7.8, 6.2, H1), 1.82(1H, ddt, J=8.7, 7.8 and 5.2, H2), 1.64(3H, s, Me), 1.47(3H, s, Me), 1.18(1H, td, J=8.5, 4.9, H3α), 0.90(1H, q, J=5.7, H3β).

Preparation of 7-(2-methylpropenyl)norcarane 179b



To a stirred suspension of zinc amalgam (1.32g, 20mmol), zinc chloride (280mg, 2mmol), chlorotrimethylsilane (1.0ml, 8mmol), and cyclohexene (1.0ml, 10mmol) in refluxing ether (9ml) a solution of the acetal **(x)** was added **(x)** (0.256g, 2mmol) over 22 hours. The reaction was quenched by addition of saturated sodium bicarbonate solution (10ml). After 15 minutes stirring, the solids were removed by filtration through celite, and the aqueous solution was extracted with ether (2 x 20ml). The combined organic extracts were washed with brine (10ml), dried over $MgSO_4$, and the solvent removed *in vacuo* to leave a viscous yellow oil which was purified by flash chromatography (petrol) to afford a mixture (56mg, not pure, ~0.7mmol, 17%). ^1H NMR of the major fractions suggested that the desired compound had formed, but it proved impossible to separate the compounds to allow accurate assignment of the spectra. The presence of the *title compound* of the product was confirmed by GC-MS (isomer ratio 4:1, elution times 6.4min, 7.2min). Both spectra (electrospray) were identical: (MNH_4^+ 78%) 168, (MH^+, 100%) 151, (M^+, 90%),150.

1,3-Dioxolane acetal of 4,4-Dimethylcyclohexenone 178c



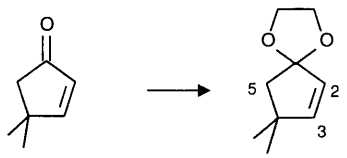
Trimethylsilyltrifluoromethanesulfonate (0.060ml, 0.32mmol) was dissolved in DCM (1ml), and the solution cooled to -78°C. Bis(trimethylsilyloxy) ethane (3.90ml, 16mmol) and 4,4-dimethylcyclohexenone (2.0g, 16mmol) were added in succession and the solution was stirred overnight at -78°C. The reaction was quenched by addition of a few drops of dry pyridine, and poured into saturated sodium bicarbonate (20ml).[213] The aqueous layer was extracted with ether (2 x 30ml) and the combined extracts were dried over a 1.1 mixture of sodium carbonate and sodium sulfite. The solvent was removed *in vacuo* to afford a yellow oil which was purified by flash chromatography to afford the *title compound* as a clear oil (0.713g, 4.2mmol, 26%).

IR (thin film / cm^{-1}): 2956, 2869, 1470, 1453, 1402, 1376, 1361, 1292, 1255, 1223, 1178, 1156, 1105, 1028, 1014, 996, 954, 936, 897, 884, 756, 722;

^1H NMR ($CDCl_3$ / ppm): 5.6(1H, d, H1), 5.3(1H, d, H2), 3.95(4H, m, OCH_2CH_2O), 1.8-1.6(4H, m, H5, H6), 1.0(3H, s, Me).

Mass spectrum: 169 (75%, M^+).

1,3 Dioxolane acetal of 4,4-dimethylcyclo-2-pentenone 178c

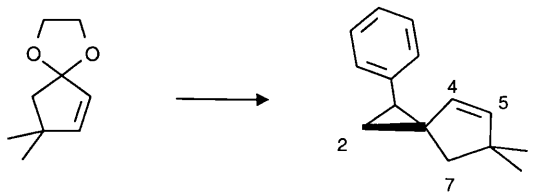


Trimethylsilyloxy trifluoromethanesolfonate (0.013ml, 0.066mmol) was dissolved in DCM (1ml), and the solution cooled to -78°C. Bis(trimethylsilyloxy)ethane (0.80ml, 3.3mmol) and 4,4-dimethylcyclopentenone (0.360g, 3.27mmol) were added in succession and the solution was stirred overnight at -78°C.[e13] The reaction was quenched by addition of a few drops of dry pyridine, and poured into saturated sodium bicarbonate (10ml). The aqueous layer was extracted with ether (2 x 20ml) and the combined extracts were dried over a 1.1 mixture of sodium carbonate and sodium sulfate. The solvent was removed *in vacuo* to afford a yellow oil which was purified by flash chromatography (9:1 petrol / EtOAc) to afford the *title compound* as a clear oil (43mg, 0.35mmol, 10%).

IR (thin film / cm^{-1}): 2926, 2854, 1722, 1541, 1466, 1375, 1363, 1350, 1287, 1192, 1144, 1072, 858, 774, 728;

^{1}HNMR ($CDCl_3$ / ppm): 5.7(1H, d, H2), 5.5(1H, d, H3), 3.8(4H, s, OCH_2CH_2O), 1.9(2H, s, H5), 1.1(6H, s, 2 x Me).

Synthesis of 6,6-Dimethyl-1-phenylspiro[2.4]hept-4-ene 179c



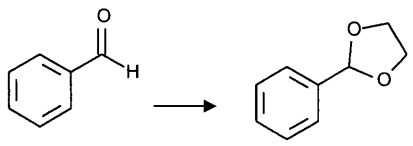
To a suspension of Zn/Hg amalgam (0.2g, 3mmol), zinc chloride (43mg, 0.32mmol), chlorotrimethylsilane (0.16ml, 1.3mmol) and styrene (0.18ml, 1.5mmol) in ether (2ml) at reflux, a solution of the acetal (0.040g, 0.32mmol) was added *via* syringe pump as a solution in ether (1ml) over 20 hours. The reaction was quenched by addition of saturated sodium bicarbonate (10ml). The solids were removed by filtration through celite, and the aqueous layer was extracted with ether (2 x 20ml). The combined extracts were washed with brine (5ml) dried over $MgSO_4$ and the solvent removed *in vacuo* to give a yellow oil, which was purified by flash chromatography (petrol) to afford the *title compound* as a clear oil (10mg, 0.051mmol, 16% 1isomer only).[204]

IR (thin film / cm^{-1}): 3027, 2924, 2856, 1602, 1494, 1155, 745.

^{1}H NMR ($CDCl_3$ / ppm): 7.28-7.06(5H, m, Ph), 5.5(m, 2H, H4), 5.2-5.0(m, H5), 2.18(m, 1H, PhC**H**), 1.80-0.92(4H, m, H7), 1.2(4H, 2 x s, 2 x Me).

Mass Spectrum: 197 (21%, $(M-H)^+$).

2-Phenyl-1,3-dioxolane 188



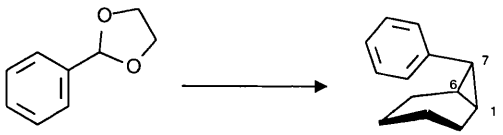
A solution of benzaldehyde (4.7g, 44mmol), ethylene glycol (5.6ml, 66mmol) and *p*-toluenesulfonic acid (600mg) in dry benzene (70ml) were heated at reflux for 5 hours in a Dean-Stark apparatus containing 4Å sieves. The solution was cooled to ambient temperature, and poured into 10ml of 1M sodium hydroxide. The sodium hydroxide was extracted with ether (2 x 20ml), and the combined organic extracts were washed with water (2x10ml), brine (10ml) and dried over $MgSO_4$. The solution was filtered and the solvent removed *in vacuo* to afford the *title compound* **188** as a pale yellow oil which was distilled (110°C/17mmHg) to afford the pure acetal as a clear oil (3.93g, 26mmol, 67%).[214]

IR (thin film / cm^{-1}): 3066, 3045, 2955, 2887, 1458, 1395, 1312, 1293, 1220, 1174, 1094, 1070, 1028, 967, 944, 915, 849, 759, 699 and 639.

^{1}HNMR ($CDCl_3$ / ppm): 7.51-7.35(5H, m, Ph), 5.81(1H, s, H2), 4.17-4.08 and 4.06-3.98(2H, m, OCH_2CH_2O).

Mass Spectrum 150(16%, M^+).

7-Phenylbicyclo-[4.1.0]heptane (7-phenyl norcarane) 189



A typical procedure

Zn/Hg amalgam (1.3g, 20mmol) and Lewis acid (see table) were flame dried under a stream of nitrogen. Ether (9.0ml), the elctrophile (see table) and cyclohexene (0.9ml, 8mmol) were added. A solution of the acetal **188** (0.30g, 2.0mmol) in ether (3.0ml) was added *via* syringe pump over several hours (see table). After a further twelve hours, the reaction was quenched by addition of saturated aqueous sodium bicarbonate solution (10ml). After 15 minutes stirring, the solids were removed by filtration through celite, and the aqueous solution was extracted with ether (2 x 20ml). The combined organic extracts were washed with brine (10ml), dried over $MgSO_4$, and the solvent removed *in vacuo* to afford a viscous yellow oil which was purified by flash

chromatography to afford, in order of elution, a mixture of cis and *trans* 7-phenyl norcarane· **189**.[215]

No.	electrophile (eq)	solvent (temp)	add^n (hrs)	Lewis acid.(eq)	7-phenyl norcarane yield % (*cis/trans*)
1	Me_3SiCl (4)	Et_2O -30°C	24	$ZnCl_2$ (1)	15 (4.7:1)
2	Me_3SiCl (4)	Et_2O refux	24	$ZnCl_2$ (1)	51 (3.8 :1)
3	Me_3SiCl (4)	Et_2O refux	1	$ZnCl_2$ (1)	28 (3.3;1)
4	Me_3SiOTf (4)	Et_2O refux	12	-	26 (3.3:1)
5	Me_3SiBr (3)	Et_2O refux	30	$ZnCl_2$ (1)	25 (3.3:1)
6	BF_3OEt_2 (2)	 r.t.	0.1	-	2 (>99:1)
7	BF_3OEt_2 (2)	Et_2O r.t.	1	-	1.2 (49:1)
8	BF_3OEt_2 (3)	Et_2O refux	24	-	15 (>99:1)

***cis*-7-phenyl norcarane**

IR (thin film / cm^{-1}): 3080, 3057, 2932, 2865, 1602, 1497, 1462, 1449, 1358, 1348, 1340, 1246, 1184, 1132. 1073, 1030, 966, 912, 848, 810, 777, 730, 718, 701, 668, 658.

^1H NMR ($CDCl_3$ / ppm): 7.34-7.16(5H, m, Ph), 1.96-1.84(2H, m, alkyl H), 1.95(1H, t, J=9.4, H7), 1.72-1.63(2H, m, alkyl H), 1.31-1.22(2H, m, alkyl H), 1.12-1.01(2H, m, alkyl H), 0.71-0.60(2H, m, H1,6);

Mass spectrum 172 (M^+ 86%).

***trans*-7-phenyl norcarane**

IR (thin film / cm^{-1}): 3085, 3062, 3010, 2927, 2852, 1606, 1581, 1500, 1486, 1456, 1448, 1355, 1348, 1280, 1255, 1220, 1200, 1174, 1150, 1098, 1080, 1064, 1032, 1015, 972, 908, 845, 788, 727, 696.

^1HNMR ($CDCl_3$ / ppm): 7.27-7.21(2H, m, H3',5), 7.14-7.07(2H, m, H4), 7.02-6.97(2H, m, H2',6'), 2.02-1.91(2H, m, alkyl H), 1.82-1.72(2H, m, alkyl H), 1.57(1H, t, J=4.6, H7), 1.38-1.24(6H, m, alkyl H).

Mass spectrum 172 (M^+ 91%).

Preparation of 4-Methoxybenzaldehyde dimethyl acetal 193

A solution of *p*-anisaldehyde (10.0g, 73.5mmol), trimethyl orthoformate (16ml, 147mmol, 2.0 equiv.) and *p*-toluenesulfonic acid monohydrate (190mg) were stirred overnight at reflux in methanol. The solution was cooled to ambient temperature and poured into saturated aqueous sodium bicarbonate (20ml) and ether (40ml). The layers were separated, and the aqueous layer extracted with ether (2 x 20ml). The combined organic extracts were washed with water (20ml) and brine (10ml), dried over $MgSO_4$, and the solvent removed *in vacuo* to afford a pale yellow oil, which was distilled (157°C/13mmHg) to afford the *title compound* **193** as a clear oil (9.3g, 51.0mmol, 69%).[216]

IR (thin film / cm^{-1}): 2994, 2938, 2902, 2833, 1614, 1587, 1513, 1466, 1443, 1353, 1303, 1250, 1209, 1171, 1102, 1075, 1052, 1036, 983, 912, 824 and 786;

^{1}HNMR ($CDCl_3$ / ppm): 7.34(2H, d, J=8.5, H2,6), 6.90(2H, d, J=8.5, H3,5), 5.36(1H, s, C**H**$(OMe)_2$), 3.81(3H, s, ArOC**H**$_3$), 3.31(6H, s, ArCH(OC**H**$_3)_2$).

Preparation of 7-(4-Methoxyphenyl)norcarane 195 using Borontrifluoride Diethyletherate

No	solvent (temp)	addition (hours)	yield of 7-(4-methoxyphenyl) norcarane % (*cis*/*trans*)
1	 r.t.	0.1	13 (17:1)
2	Et_2O r.t.	1	21 (32:1)

To a stirred suspension of Zn/Hg amalgam (1.3g, 20mmol), cyclohexene (see table) and boron trifluoride diethyl etherate (0.25ml, 1.8mmol) at room temperature, the acetal **193** (0.36g, 2mmol) was added slowly. After 24 hours the system was quenched by addition of saturated sodium bicarbonate solution. After 10 minutes the reaction mixture was filtered and poured into a mixture of ether (20ml) and saturated sodium bicarbonate (10ml). The layers were separated and the ether layer was washed with brine (5ml), dried over $MgSO_4$ and the solvent removed *in*

vacuo to afford a pale yellow oil (103mg). The oil was purified by flash chromatography (petrol) to afford the *title compound* **195** as a clear oil (54mg, 0.21 mmol, 13%, *cis / trans* 16.5:1).[215]

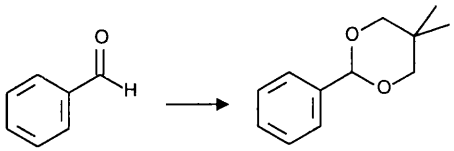
IR (thin film, cm^{-1}): 3001, 22932, 2863, 2834, 1610, 1577, 1511, 1462, 1449, 1358, 1340, 1289, 1242, 1180, 1171, 1109, 1039, 968, 928, 02, 831, 810, 799, 773, 745, 729.

^1H NMR, ($CDCl_3$ / ppm): 7.20(2H, dd, J 8.8 and 2.9 H3',5'), 6.87 (2H, dd, J 8.8 and 2.9, H2',6'), 3.78 (3H, s, OMe) and 1.92-0.90 (9H, m, 4 x CH_2 and H1), 0.64(2H, m, H1, H6)

^{13}C NMR (CDCl3 / ppm): 157.6, 132.1, 130.6, 113.6, 55.2, 30.3, 21.8, 21.2, 20.2, 12.6.

Mass spectrum: 202 (100% M^+).

Synthesis of 2-Phenyl-5,5-dimethyl-1,3-dioxane 198

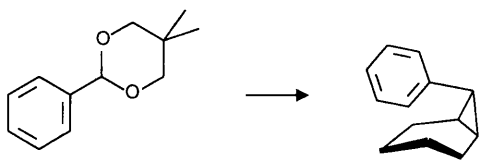


Benzaldehyde (4.62g, 30mmol), 2,2-dimethylpropan-1,3-diol (6.24g, 60mmol) and *p*-toluenesulfonic acid monohydrate (600mg) were refluxed in benzene (150ml) in a Dean Stark apparatus containing 4Å molecular sieves for 24 hours. The reaction was poured into saturated sodium bicarbonate and extracted with ether (3 x 50ml). The combined ethereal extracts were dried over $MgSO_4$ and the solvent removed *in vacuo* to leave a pale yellow oil which was purified by bulb to bulb distillation (85°C, 1mmHg) to afford the title compound **198** as a white solid (9.0g, 0.047mol, 78%) mpt 39-42°C.[222]

^1H NMR ($CDCl_3$ / ppm): 7.56-7.53(2H, m, Ph), 7.43-7.38(3H, m, Ph), 5.42(1H, s, PhC**H**), 3.83-3.64(4H, m, 2 x O**CH**$_2$), 1.33(3H, s, Me), 0.81(3H, s, Me).

Microanalysis: calculated for $C_{12}H_{16}O_2$ C74.98 H17.53; found C74.73 H17.48.

Synthesis of 7-Phenylnorcarane (X) from 2-Phenyl-5,5-dimethyl-1,3-dioxane 189



i). Preparation of 7-phenyl norcarane using chlorotrimethylsilane

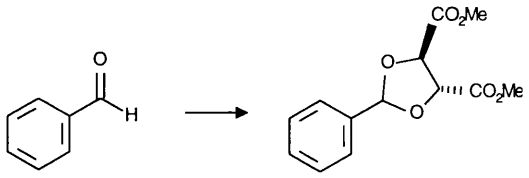
2-Phenyl-5,5-dimethyl-1,3-dioxane **198** (0.38g, 2mmol) in ether (2ml) was added *via* syringe pump over 36 hours to a suspension of Zn/Hg amalgam (1.3g, 20mmol), zinc chloride (280mg, 2mmol), chlorotrimethylsilane (1.0ml, 10mmol), and cyclohexene (0.9ml, 8mmol) in ether (6ml). After complete addition, the reaction was quenched by stirring with saturated sodium

bicarbonate solution (10ml) for 15 minutes. The solids were removed by filtration through celite, and the aqueous solution was extracted with ether (2x20ml). The combined extracts were washed with brine (10ml), dried over $MgSO_4$, and the solvent removed *in vacuo* to afford a viscous yellow oil. The oil was purified by flash chromatography to afford 7-phenylnorcarane **189**as a clear oil (150mg, 0.87mmol, 44%), spectroscopically identical to material already prepared.

ii). Preparation of 7-phenyl norcarane using bromotrimethylsilane

2-Phenyl-5,5-dimethyl-1,3-dioxane **198** (0.38g, 2mmol) in ether (2ml) was added *via* syringe pump over 36 hours to a suspension of Zn/Hg amalgam (1.3g, 20mmol), zinc chloride (280mg, 2mmol), bromotrimethylsilane (0.8ml, 6mmol), and cyclohexene (0.9ml, 8mmol) in ether (6ml). After complete addition, the reaction was quenched by stirring with saturated sodium chloride solution (10ml) for 15 minutes. The solids were removed by filtration through celite and the aqueous solution was extracted with ether (2 x 20ml). The combined extracts were washed with brine (10ml), dried over $MgSO_4$, and the solvent removed *in vacuo* to afford a viscous yellow oil. The oil was purified by flash chromatography to afford 7-phenylnorcarane **189** as a clear oil (170mg, 1.0 mmol, 49%), spectroscopically identical to material already prepared.

Preparation of (*R*)-4-(*S*)-5-Dimethoxycarboxy-2-phenyldioxane 199



A solution of benzaldehyde (9.4ml, 88mmol), dimethyl-(*L*)-tartrate (20.4g, 114.4mmol), and p-toluenesulfonicacid monohydrate (1g, 5.3mmol), was refluxed in benzene under Dean-Stark conditions. After 20 hours, the reaction was allowed to cool and the solution was transferred to a separating funnel containing ether (200ml), and sodium hydroxide (20ml). the layers were separated, and the aqueous layer was extracted with ether (2 x 20ml). The combined organic extracts were washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo* to afford a yellow oil. The oil contained traces of benzaldehyde, which were removed by distillation (95°C, 0.5mmHg), to leave a solid, which was recrystallized from methanol, to afford the *title compound* **199** as white crytals (10.1g, 43%), mpt 72-74°C^{225} α_D [-40.3°].

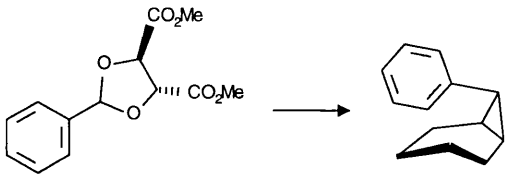
IR (KBr disc / cm^{-1}): 2955(m), 1753(s), 1636(m), 1428(m), 1398(m), 1368(m), 1315(w), 1262(m), 1239(s), 1107(s), 1034(w), 1000(w), 971(m), 925(w), 859(w), 764(m), 706(m).

^1H NMR ($CDCl_3$/ ppm): 7.6(2H, m, Ph), 7.4(3H, m, Ph), 6.12(1H, s, C**H**$_2$O), 5.00 and 4.88(1H, 2 x d, 2 x C**H**CO_2), 3.9 and 3.83(6H, 2 x s, 2 x CO_2C**H**$_3$).

Microanalysis: calculated for $C_{13}H_{14}O_6$ C58.65 H5.31; found C58.56 H5.23.

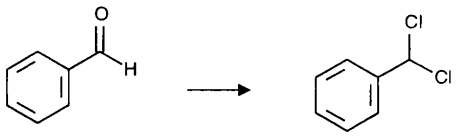
Mass spectrum: calculated for $C_{13}H_{15}O_6$ 267.0868; found 267.0880.

Synthesis of 7-Phenylnorcarane 189 from (R)-4-(S)-5-Dimethoxycarboxy-2-phenyldioxane 199



2-Phenyl-5,5-dimethyl-1,3-dioxane **199** (0.53g, 2mmol) in benzene (2ml) was added *via* syringe pump over 12 hours to a suspension of Zn/Hg amalgam (1.3g, 20mmol), bromotrimethylsilane (1.4ml, 10mmol), and cyclohexene (0.9ml, 8mmol) in ether (6ml). After complete addition, the reaction was quenched by stirring with saturated sodium bicarbonate solution (10ml) for 15 minutes. The solids were removed by filtration through celite, and the aqueous solution was extracted with ether (2 x 20ml). The combined extracts were washed with brine (10ml), dried over $MgSO_4$, and the solvent removed *in vacuo* to afford a viscous yellow oil. The oil was purified by flash chromatography to afford the *title compound* **189** as a clear oil (41 mg, 0.27mmol, 12% *cis / trans* 2.7:1 GC), spectroscopically identical to material already prepared.

Phenyldichloromethane

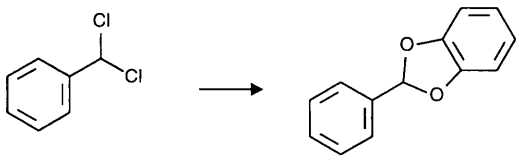


Benzaldehyde (2.03ml, 20mmol) was added dropwise to phosphorus pentachloride (4.16g, 20mml) at 0°C. After stirring for 2 hours, the resulting yellow solution was purified by bulb to bulb distillation of the crude (120°C, 40mmHg) to afford the *title compound* as a clear oil (2.06, 62%).[223]

^1H NMR ($CDCl_3$ / ppm): 7.60(2H, d, aryl), 7.42(3H, m, aryl), 6.74(1H, s, $CHCl_2$).

^{13}C NMR ($CDCl_3$ / ppm): 129.9, 128.7, 128.7, 126.1, 71.8.

Preparation of the Benzalehyde Catechol Acetal 201



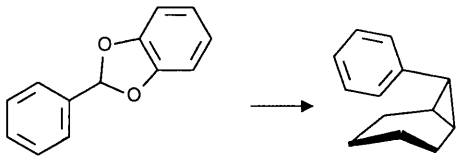
To a solution of catechol (1.10g, 0.01mmol), in pyridine (10ml), a solution of dichlorophenyl methane (2.0g), in pyridine (5ml) was added. The mixture was refluxed for 5 hours. Aftr cooling

to ambient temperature the pyridine was removed *in vacuo* to afford the *title compound* **201** as a clear oil which solidified on standing. The solid was recrystallized from petrol to give pale pink ctystals (327mg, 1.65mmol, 17%) mpt 48-50°C.[217]

^{1}H NMR ($CDCl_3$ / ppm): 7.60(2H, m, Ph), 7.50(3H, m, Ph), 6.99(1H, s, PhC**H**Cl), 6.88(4H, m, catechyl).

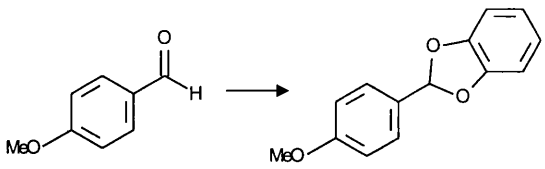
^{13}C NMR ($CDCl_3$ / ppm): 146.6, 136.2, 130.2, 128.7, 126.4, 121.7, 109.9, 108.6.

Synthesis of 7-Phenylnorcarane 189 using benzaldehyde catechol acetal 201



Benzaldehyde catechol acetal **201** (173mg, 0.87mmol) in ether (2ml) was added *via* syringe pump over 12 hours to a suspension of zinc amalgam (1.0g, 15mmol,), zinc chloride (149mg, 1mmol), chlorotrimethylsilane (1.0ml, 10mmol), and cyclohexene (0.9ml, 8mmol) in ether (8ml). After complete addition, the reaction was quenched by stirring with saturated sodium bicarbonate solution (10ml) for 15 minutes. The solids were removed by filtration through celite, and the aqueous solution was extracted with ether (2 x 20ml). The combined extracts were washed with brine (10ml), dried over $MgSO_4$, and the solvent removed *in vacuo* to afford a viscous yellow oil. The oil was purified by flash chromatography (petrol) to afford 7-phenyl-norcarane **189** as a clear oil (31mg, 0.17mmol, 20% *cis/trans* 3.3:1), and 2-ethoxy-1-phenyl propane **170** (26mg, 16%), spectroscopically identical to material already prepared.

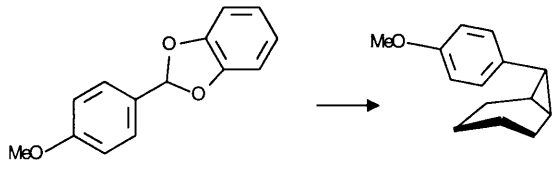
Preparation of Anisaldehyde Catechol Acetal 202



Freshly distilled anisaldehyde (4.0g, 0.029mol),p-toluenesulfonic acid monohydrate (30mg) and catechol (3.2g, 0.029mol) were refluxed under Dean-Stark conditions in benzene (40ml). After 16 hours, the reaction was allowed to cool, and then transferred to a separating funnel containing ether (300ml) and 1M sodium hydroxide (100ml). The layers were separated, and the ethereal layer was washed with one further portion of 1M sodium hydroxide (50ml), brine (50ml), dried over $MgSO_4$ and the solvent removed *in vacuo* to afford a viscous red oil. Purification of the oil proved difficult, but after repeated column chromatography, the *title compound* **202**was delivered as a pale pink oil (300mg, 1.3mmol, 5%).[217]

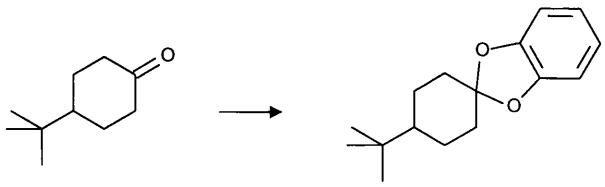
^{1}H NMR ($CDCl_3$ / ppm): 7.53(2H, d, J=8.5, aryl), 6.97(2H, d, J=8.4, aryl), 9.93(1H, s, CHO_2), 6.88(4H, s, catechol), 3.85(3H, s, OMe).
^{13}C NMR ($CDCl_3$ / ppm): 161.1, 147.7, 129.7, 128.3, 128.0, 121.6, 114.0, 110.0, 108.5, 55.3.
Mass spectrum: (FAB), 228 (100%, M+).

Synthesis of 7-Phenylnorcarane using Anisaldehyde Catechol Acetal 194



Anisaldehyde catechol acetal **(x)** (130mg, 0.57mmol) in ether (2ml) was added *via* syringe pump over 12 hours to a suspension of Zn/Hg amalgam (1.0g, 15mmol,), zinc chloride (100mg, 0.66mmol), chlorotrimethylsilane (0.5ml, 5mmol), and cyclohexene (0.5ml, 4.5mmol) in ether (6ml). After complete addition, the reaction was quenched by stirring with saturated sodium bicarbonate solution (10ml) for 15 minutes. The solids were removed by filtration through celite, and the aqueous solution was extracted with ether (2 x 20ml). The combined extracts were washed with brine (10ml), dried over $MgSO_4$, and the solvent removed *in vacuo* to afford a viscous yellow oil. The oil was purified by flash chromatography (petrol) to afford 7-(4-methoxyphenyl)norcarane **194** spectroscopically identical to material already prepared (23mg, 0.11mmol, 20% *cis/trans* 15:1 by GC).

Preparation of the catechol acetal of 4-*tert*butylcyclohexanone 203



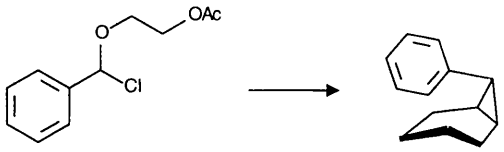
4-^{t}Butylcyclohexanone (2g, 0.013mol), p-toluenesulfonic acid monohydrate (50mg) and catechol (1.50g, 0.13mol) were refluxed in benzene under Dean-Stark conditions for 3 hours. TLC showed no trace of the starting material. The reaction was cooled, and the solution transferred to a separating funnel containing ether (100ml). The ethereal solution was washed with 1M sodium hydroxide (20ml), water (2 x 20ml) and brine (10ml), dried over $MgSO_4$, and the solvent removed *in vacuo* to give an orange solid, which was purified by recrystallization (40-60 petrol) to give the *title compound* **203** as white crystals (1.96g, 7.7mmol, 61%), mpt 100-101°C.[224]

IR (KBr disc / cm^{-1}): 2954(s), 2856(m), 1627(w), 1486(s), 1480(s), 1360(w), 1305(w), 1278(w), 1234(s), 1175(w), 1093(m), 1066(s), 100(w), 924(w), 893(m), 856(m), 826(w), 804(w), 732(s), 668(w).

^1H NMR ($CDCl_3$ / ppm): 7.8(4H, m, catechol), 2.20, 1.85-1.37 and 1.20-1.10(8H, 3 x m, alky), 0.95(9H, s, $C(CH_3)_3$).

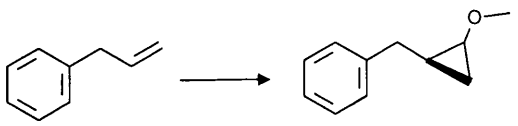
^{13}C NMR ($CDCl_3$ / ppm): 147.5, 147.3, 120.8, 118.2, 108.5, 108.3, 46.7, 32.3, 32.3, 27.7, 27.0, 24.0.

Synthesis of 7-Phenyl norcarane *via* (2-Acetoxyethoxy)chlorophenylmethane 204



The dioxalane acetal of benzaldehyde **188** (0.30g, 2.0mmol) was stirred for 4 hours at 70°C with acetyl chloride (140ml, 1.0 equiv). ^1H NMR showed >95% formation of the α-chloro ether (^1H NMR, $CDCl_3$) 7.6-7.1(m, 5H, Ph), 6.6(s, 1H, PhC**H**), 4.12-4.4(m, 4H, OCH_2CH_2O), 2.1(s, 3H, OAc). The brown solution was dissolved in ether (2.5ml) and added *via* syringe pump over 24 hours to a suspension of flame-dried zinc amalgam (1.3g, 20 mmol), chlorotrimethylsilane (1.0ml, 8mmol) and cyclohexene (0.9ml, 8mmol) in ether (8ml) over 12 hours. After complete addition, the reaction was quenched by stirring with saturated sodium bicarbonate solution (10ml) for 15 minutes. The solids were removed by filtration through celite, and the aqueous solution was extracted with ether (2 x 20ml). The combined extracts were washed with brine (10ml), dried over $MgSO_4$, and the solvent removed *in vacuo* to afford a viscous yellow oil. The oil was purified by flash chromatography (petrol) to afford, in order of elution, a mixture of *cis* and *trans* 7-phenyl norcarane (89mg 26%, 2.7:1) **189**, spectroscopically identical to material already prepared.

2-Benzyl-1-methoxycyclopropane 211

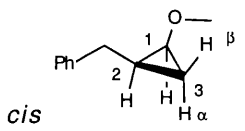


Zn/Hg amalgam (2.5g, 50mmol), chlorotrimethylsilane (2.2ml, 17mmol) and allylbenzene (0.25ml, 2mmol) were heated to reflux in ether (10ml). Trimethylorthoformate (1.40ml, 12mmol) was added *via* syringe pump over 48 hours. A further portion of trimethyl orthoformate (1.4ml, 12.0mmol) and chlorotrimethylsilane (1.0ml, 7.9mmol) were added and the mixture was refluxed for a further 2 days. The reaction was allowed to cool, and was quenched by the addition of saturated sodium bicarbonate (10ml). After stirring for 10 minutes, the mixture was filtered through celite and transferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography to afford 2-benzyl-1-methoxycyclopropane **211** as a clear oil (208mg, 1.3mmol, 64%, *cis* / *trans* 2:1).[238]

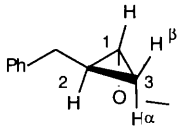
Generation with BF_3OEt_2

To a suspension of Zn/Hg amalgam (1.3g, 15mmol), allylbenzene (0.90ml, 8mmol) and trimethylorthoformate (0.22ml, 2mmol) in ether (10ml), borontrifluoride diethyletherate (0.32ml, 2.6mmol) in ether (1ml) was added over 6 hours. Tthe solution was stirred overnight at room temperature and was quenched by the addition of saturated sodium bicarbonate (10ml). After stirring for 10 minutes, the mixture was filtered through celite, and transferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography to afford 2-benzyl-1-methoxycyclopropane as a clear oil (26mg, 0.17mmol, 9% *cis* / *trans* 1:1).[238]

IR (mixture of *cis* and *trans* 2:1, thin film / cm^{-1}): 3063(m), 3027(m), 2999(m), 2932(s), 2827(m), 1604(m), 1496(s), 1453(s), 1434(m), 1386(w), 1354(m), 1230(s), 1143(m), 1103(m), 1089(m), 1075(s), 1062(m), 1031(w), 1015(m), 996(w), 967(w0, 828(w), 804(w), 763(w), 732(s), 699(s).



cis



trans

***cis*-2-benzyl-1-methoxycyclopropane**

^1H NMR ($CDCl_3$ / ppm): 7.31-7.18(5H, m, Ph), 3.39(3H, s, OMe), 3.29(1H, td, J=6.2, 3.3, H1), 2.89(1H, dd, J=15.0, 6.7, PhC**H**), 2.68(1H, dd, J=15.7, 7.4, PhC**H**), 1.11-1.04(1H, m, H2), 0.71(1H, m, H3β), 0.35(1H, td, J=6.2, 3.3, H3α).

^{13}C NMR ($CDCl_3$ / ppm): 142.2, 128.3, 128.2, 125.7, 58.5, 58.4, 32.6,18.5, 11.1.

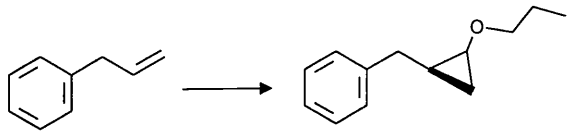
***trans*-2-benzyl-1-methoxycyclopropane**

^{1}H NMR ($CDCl_3$ / ppm): 7.31-7.18(5H, m, Ph), 3.27(3H, s, OMe), 3.07(1H, dt, J=6.2, 3.1, H1), 2.53(2H, dd, J=7.2, PhC**H**$_2$), 1.27-1.18(1H, m,), 1.11-1.04(1H, m, H2), 0.80 and 0.45(2H, m, H3), 0.45(1H, q, J=6.2, H3).

^{13}C NMR ($CDCl_3$ / ppm): 141.0, 128.4, 128.3, 128.2, 125.9, 60.7, 57.9, 37.4, 19.8,12.6

Mass Spectrum: calculated for $C_{11}H_{15}O$ (M^+) 163.1123; found 163.1130.

1-Propyloxy-2-benzylcyclopropane 219a



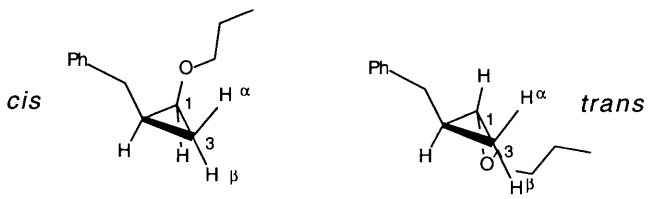
Zn/Hg amalgam (2.5g, 50mmol), chlorotrimethylsilane (2.2ml, 9mmol) and allyl benzene (0.25ml, 2mmol) were heated to reflux in ether (10ml). Tripropylorthoformate (1.72ml, 8mmol) was added *via* syringe pump over 24 hours. After a further day at reflux, the reaction was allowed to cool, and was quenched by the addition of saturated sodium bicarbonate (10ml). After stirring for 10 minutes, the mixture was filtered through celite, and transferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography to afford *cis*-1-propyloxy-2-benzylcyclopropane **219a** (100mg, 0.53mmol, 26%) and *trans*-1-propyloxy-2-benzylcyclopropane (64mg, 0.33mmol, 17%).

***cis*-1-propyloxy-2-benzylcyclopropane**

IR (thin film / cm^{-1}): 3004(m), 3037(m), 3000(m), 2963(s), 2936(m), 2879(m), 1943(w), 1603(w), 1496(m), 1453(s), 1378(w), 1350(m), 1219(s), 1162(w), 1075(s), 1021(m), 958(w), 913(w), 826(w), 732(s), 698(s).

^{1}H NMR ($CDCl_3$ / ppm): 7.36-7.19(5H, m, aryl), 3.50(2H, m, OC**H**$_2$), 3.35(1H, td, J=6.4, 3.31, H1), 2.93 and 2.69(1H, dd, J=6.7, 4.9, and 1H, dd, J=7.6, 4.9, PhC**H**$_2$), 1.63(2H, td, J=14.1, 7.4, OCH_2C**H**$_2$), 1.07(1H, m, H2), 0.97(3H, t, J=7.4, Me), 0.72(1H, dt, J=9.1, 6.1, H2β), 0.39(1H, td, J=6.1, 3.3, H2α).

^{13}C NMR ($CDCl_3$ / ppm): 142.2, 128.2, 128.0, 125.2, 72.5, 56.5, 32.6, 22.8, 18.4, 11.1, 10.6.



***trans*-1-propyloxy-2-benzylcyclopropane**

IR (thin film / cm^{-1}): 3065(w), 3027(m), 3001(w), 2962(s), 2939(s), 2876(s), 2363(w), 1604(w), 1496(m), 1454(s), 1380(m), 1337(w), 1197(s), 1173(s), 1146(m), 1087(s0, 1029(w), 1000(w), 976(m), 869(w), 801(w), 698(s).

^1H NMR ($CDCl_3$ / ppm): 7.30-7.17(5H, m, aryl), 3.35(2H, t, J=6.7, OCH_2), 3.09(1H, dt, J=6.5, 2.8, H1), 2.57 and 2.47(1H, dd, J=16.8, 7.1, and1H, dd, J=14.7, 7.1, $PhCH_2$), 1.51(2H, m, OCH_2CH_2), 1.23(1H, m, H2), 0.86(3H, t, J=7.4, Me), 0.74(1H, ddd, J=12.9, 5.7, 3.0, H3α), 0.43(1H, q, J=6.0, H3β).

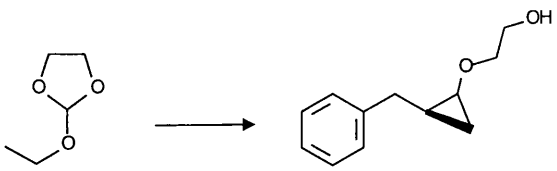
^{13}C NMR ($CDCl_3$ / ppm): 140.9, 128.1, 125.7, 72.1, 58.8, 37.3, 22.5, 19.7, 12.5, 10.3.

Mass Spectrum: (FAB) calculated for $C_{13}H_{19}O$ (MH^+),191.2940; found 191.2950.

2-benzyl-1-ethoxycyclopropane 219b

Zn/Hg (2.5g, 50mmol), chlorotrimethylsilane (2.1ml, 49mmol) and allylbenzene (025ml, 1.9mmol), were heated to reflux in ether (10ml). To this mixture, a solution of phenyldiethylorthoformate (2.8ml, 14.7mmol), in ether (2ml) was added *via* syringe pump over 24 hours. Afer 24 hours at reflux, a further portion of phenyldiethylorthoformate (2.8ml, 14.7mmol), and chlorotrimethylsilane (1.0ml, 7.9mmol) was added and the mixture was refluxed for another 2 days. The reaction was allowed to cool, and was quenched by the addition of saturated sodium bicarbonate (10ml). After stirring for 10 minutes, the mixture was filtered through celite and transferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography to afford *cis*-2-benzyl-1-ethoxycyclopropane (144mg, 0.82mmol, 41%) and *trans*-2-benzyl-1-ethoxycyclopropane (92mg, 0.52mmol, 26%), both spectroscopically identical to material already prepared.

1-(2-Hydroxyethoxy)-2-benzylcyclopropane



Zn/Hg amalgam (2.5g, 50mmol), chlorotrimethylsilane (1.2ml, 9 mmol) and allylbenzene (0.25ml, 2mmol) were heated to reflux in ether (10ml). 2-Methoxydioxolane **223** (0.70ml, 4.0mmol) in ether (1ml) was added *via* syringe pump over 24 hours. A further portion of 2-methoxydioxolane

(0.7ml, 4mmol) and chlorotrimethylsilane (1.0ml, 7.9mmol) was added. After a further 3 days at reflux the reaction was allowed to cool and was quenched by the addition of saturated sodium bicarbonate (10ml). After stirring for 10 minutes, the mixture was filtered through celite, and transferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography to afford 1-(2-trimethylsilyloxyethoxy)-2-benzyl cyclopropane, **219c** (203mg, 0.77mmol, 38%, *cis* / *trans* 3:1), and 1-(2-trimethylsilyloxy)ethoxy 1-(2-hydroxyethoxy)-2-benzyl cyclopropane **219d** (65mg, 0.34mmol, 17%, *cis* / *trans* 3:1).

(2-trimethylsilyloxyethoxy)-2-benzylcyclopropane 219c

IR (mixture of *cis* and *trans*, thin film / cm^{-1}): 3064(w), 3027(w), 3001(w), 2958(s), 2922(m), 2868(m), 1728(w), 1604(w), 1496(m), 1453(m), 1386(w), 1343(w), 1291(w), 1251(s), 1219(w), 1198(w), 1169(m), 1105(s), 1017(m), 978(m), 842(s), 734(m), 698(s).

***cis*-1-(2-trimethylsilyloxyethoxy)-2-benzylcyclopropane**

^{1}H NMR ($CDCl_3$ / ppm): 7.30-7.19(5H, m, Ph), 3.74(2H, m, C**H**$_2$O), 3.69(2H, t, J=5.4, C**H**$_2$O), 3.42(1H, td, J=6.4, 3.5, H1), 3.34(1H, dd, J=14.9, 6.8, PhC**H**), 2.89(1H, dd, J=14.9, 7.7, PhC**H**), 1.00(1H, m, H2), 0.65(1H, dt, J=15.7, 5.9, H3β), 0.33(1H, td, J=6.4, 3.3, H3α), 0.06(1H, s, (SiC**H**$_3$)$_3$).

^{13}C NMR ($CDCl_3$ / ppm): 142.4, 128.5, 128.3,125.8, 72.4, 61.9, 61.8, 57.3, 32.8, 18.8, 11.5, 0.30.

***trans*-1-(2-trimethylsilyloxy)ethoxy-2-benzylcyclopropane**

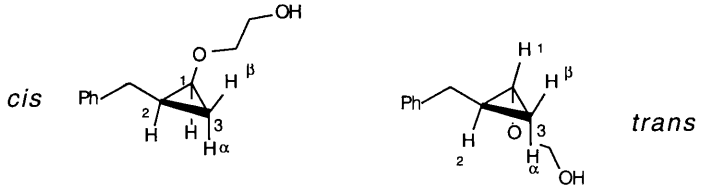
^{1}H NMR ($CDCl_3$ / ppm): 7.24-7.17(5H, m, Ph), 3.59(2H, t, J=5.1, C**H**$_2$O), 3.42(2H, m, C**H**$_2$O), 3.39(1H, m, H1), 2.49(1H, dd, J=14.7, 7.1, PhC**H**), 2.42(1H, dd, J=14.6, 7.1, PhC**H**), 1.19(1H, m, H2), 0.84(1H, m, H3), 0.38(1H, q, J=6.2, H3), 0.33(1H, td, J=6.4, 3.3, H3), 0.04(1H, s, (SiC**H**$_3$)$_3$).

^{13}C NMR ($CDCl_3$ / ppm): 141.0, 128.3, 128.2,125.7, 71.8, 61.9, 59.5, 57.2, 37.4, 19.9, 12.8, -0.43.

Mass Spectrum: (FAB) calculated for $C_{15}H_{24}O_2Si$ (MH^+) 264.1549; found 264.1540.

1-(2-hydroxyethoxy)-2-benzylcyclopropane 219d

IR (mixture of *cis* and *trans*, thin film / cm^{-1}): 3406(s), 3062(m), 3026(m), 3000(m), 2923(s), 1603(w), 1496(s), 1452(s), 1343(s), 1219(s), 1157(m), 1072(s), 888(w), 812(w), 734(s), 699(s).



***cis*-1-(2-hydroxyethoxy)-2-benzyl cyclopropane.**

^{1}H NMR ($CDCl_3$ / ppm): 7.31-7.17(5H, m, Ph), 3.74(2H, t, J=5.1, C**H**$_2$O) 3.62(2H, m, C**H**$_2$O), 3.40(1H, td, J=6.4, 3.3, H1), 2.87(1H, dd, J= 15.1, 6.8, PhC**H**), 2.27(1H, bs, O**H**),1.08(1H, m, H2), 0.75(1H, dt, J=9.2, 6.2, H3β), 0.401H, td, J=6.2, 3.9, H3α).

^{13}C NMR ($CDCl_3$ / ppm): 142.1, 128.3, 125.8, 72.1, 61.8, 57.2, 32.8, 18.6, 11.4.

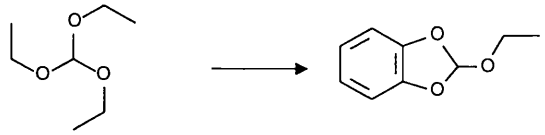
***trans*-(1-(2-hydroxyethoxy)-2-benzyl cyclopropane.**

^{1}H NMR ($CDCl_3$ / ppm): 7.31-7.17(5H, m, Ph), 3.63(2H, m, C**H**$_2$O), 3.51(2H, m, C**H**$_2$O), 3.16(2H, m, C**H**OMe), 2.52(1H, dd, J=14.2, 7.0, PhC**H**$_2$), 1.25(1H, m, H2), 0.84(1H, m, H3), 0.44(1H, q, J=6.0, H3).

^{13}C NMR ($CDCl_3$ / ppm): 140.9, 128.4, 126.1, 71.7, 61.6, 59.5, 57.2, 37.4, 20.1, 12.9.

Mass Spectrum: (FAB) calculated for $C_{12}H_{16}O_2Na$ (MNa^+) 215.1048, found 215.1040.

Ethylcatechol orthoformate 227



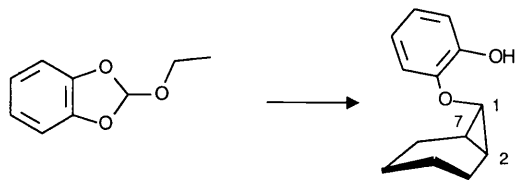
Catechol (2.2g, 20mmol) and triethylorthoformate (10.0ml, 91mmol) were placed in a distillation apparatus. A few drops of 1M HCl in dioxane were added, and the mixture was heated to reflux with a heat gun. The vapour temperature was carefully monitored and the ethanol was removed. After this, the excess triethylorthoformate was distilled out to leave the impure orthoformate as a blue oil. The oil was distilled (150°C/20mmHg) to afford the *title compound* **227** as a clear oil (3.19g, 19mmol, 96%).[243]

IR (thin film / cm^{-1}): 3067(m), 2982(s), 2940(m), 26049w), 2464(w), 2228(w), 2014(w), 1873(m), 1754(w), 1631(m), 1606(m), 1486(s), 14639s), 1448(m), 1394(m), 1359(s), 1300(m), 1279(m), 1239(s), 1131(s), 1094(s), 1038(s), 926(s), 903(s).

^{1}H NMR ($CDCl_3$ / ppm): 6.90-6.88(5H, m, aryl and O_3C**H**), 3.74(2H, q, J=7.5, OC**H**$_2$), 1.28(3H, t, J=7.1, Me).

Microanalysis: calculated for $C_9H_{10}O_3$ C 65.04 H 6.10; found C 64.92 H 5.97.

7-(2-Hydroxyphenoxy)norcarane 228a



A suspension of Zn/Hg amalgam (1.36, 15mmol), chlorotrimethylsilane (1.0ml, 8mmol), cyclohexene (0.90ml, 8mmol), and $ZnCl_2$ (280mg, 2mmol) in ether (10ml) was brought to reflux. A solution of ethylcatechol orthoformate (0.58g, 3.5mmol) in ether (10ml) was added *via* syringe pump over 12 hours. After a further 12 hours at reflux the reaction was allowed to cool, and was quenched by the addition of saturated sodium bicarbonate (10ml). After stirring for 10 minutes, the mixture was filtered through celite and transferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo.* The residue was purified by flash chromatography to afford *trans*-7-(2-hydroxy-phenoxy)norcarane **228a** (29mg, 0.14mmol, 4%) mpt 62-64°C, and *cis*-7-(2-hydroxyphenoxy)-norcarane (69mg, 0.34mmol, 10%) mpt 65-68°C.

***trans*-7-(2-hydroxyphenoxy)norcarane**

IR (thin film / cm^{-1}): 3450(s) 2932(s), 28449s), 1635(s), 1499(s), 1447(m), 13545(w), 1260(m), 1223(m), 1147(w), 1109(w), 1066(w), 1039(w), 742(s), 699(s).

^1H NMR ($CDCl_3$ / ppm): 7.04(1H, m, aryl), 6.90-6.86(3H,m), 5.48(1H, s, O**H**), 3.46(t, 1H, J=2.6, H1), 2.00-1.80(2H, m, alkyl), 1.78-1.76(2H, m, alkyl), 1.36-1.16(5H, m, alkyl and H7), 0.88(1H, m, H2).

^{13}C NMR ($CDCl_3$ / ppm): 145.9, 145.4, 121.34, 120.1, 114.5, 112.7, 62.3, 21.9, 21.56, 18.1

***cis*-7-(2-hydroxyphenoxy)norcarane**

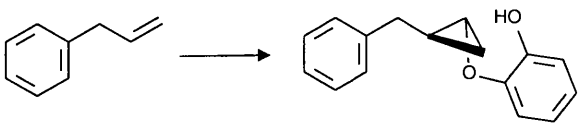
^1H NMR ($CDCl_3$ / ppm): 7.20-7.16(1H, m, aryl), 6.97-6.79(3H,m), 5.56(1H, s, OH), 3.68(t, 1H, J=6.7, H1), 1.93-1.86(2H, m, alkyl), 1.60-1.54(2H, m, alkyl), 1.32-1.14(5H, m, alkyl and H7), 0.80(1H, q, J=6,7, H2).

^{13}C NMR ($CDCl_3$ / ppm): 146.5, 146, 121.4, 120.2, 114.4, 112.2, 57.0, 20.1, 17.8, 11.6

Mass Spectrum: (FAB) calculated for $C_{13}H_{16}O$ (M^+) 204.1150, found 204.1140.

Microanalysis: calculated for $C_{13}H_{16}O_2$ C76.42 H7.89; found C76.83 H 8.11.

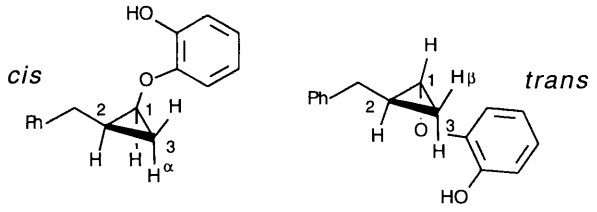
2-Benzyl-1-(1-hydroxyphenyl)cyclopropane 228b



A mixture of Zn/Hg amalgam (1.3g, 15mmol), chlorotrimethylsilane (1.0ml, 8mmol) allylbenzene (0.90ml, 8mmol) and zinc chloride (280mg, 2mmol) were heated to reflux in ether (8ml). Ethylcatechol orthoformate 330mg, 2mmol) was added *via* syringe pump over 16 hours. and the mixture was refluxed for a further 24 hours. The reaction was allowed to cool and was quenched by the addition of saturated sodium bicarbonate (10ml). After stirring for 10 minutes, the mixture was filtered through celite and transferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo.* The resulting oil was purified by flash

chromatography to afford 2-benzyl-1-(1-hydroxyphenyl)cyclopropane **228b** as a clear oil (110mg, 0.46mmol, 23%, *cis* / *trans* 1:1.2).

IR (mixture of *cis* and *trans*, 1:1.2, thin film / cm^{-1}): 3442(s), 3069(m), 2930(s), 2557(s), 1958(w), 18929w), 1824(w), 1732(w), 15899m), 14699(m), 1453(m), 1426(w), 1384(m), 1358(m), 1306(w), 1259(w), 1206(w), 1125(s), 1028(m), 939(w), 913(w), 824(m), 740(m), 699(s).



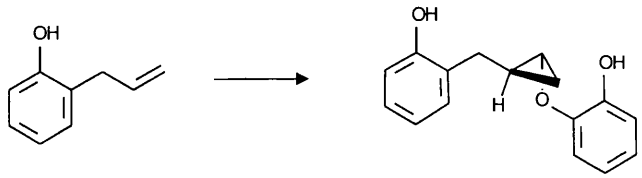
^1H NMR (mixture of *cis* and *trans*, $CDCl_3$ / ppm): 7.4-7.2(5H, m, Ph), 7.0-6.7(4H, m, catechyl), 5.48(0.45H, s, O**H**, *cis*), 5.47(0.55H, s, O**H**, *trans*), 3.91(0.45H, td, J=5.5, 3.2, H1, *cis*), 3.64(0.55H, dt, J=6.2, 2.8, *trans*), 2.93(0.44H, dd, J=15.2, 6.7, PhC**H**, *cis*), 2.77(0.44H, dd, partially obscured, J=17.6, 7.1, PhC**H,** *cis*), 2.75 and 2.69(1.1H, 2 x dd, J=14.8, 3.8 and J=14.6, 7.0, PhC$\mathbf{H}_2$, *trans*), 1.53-1.40(1H, m, H2, *cis* and *trans*), 1.15-1.04(1H, m, H3), 0.81(0.55H, q, J=6.4, H3β *trans*), 0.68(0.45H, td,J=6.6, 3.2, H3α *cis*).

^{13}C NMR (mixture of *cis* and *trans*, $CDCl_3$ / ppm): 145.6, (145.4), (141.3), 140.1, 128.54, 128.49, 12.4, 125.3, 126.3,126.1, 121.8, 121.7, 120.2, 120.0, 114.6, 114.6, 112.6, 56.9, (55.1), 37.1, (33.0), 20.2, (18.3), 13.3, (12.2).

Mass Spectrum: calculated for $C_{16}H_{16}O_2$ (M^+) 240.1150; found 240.1140.

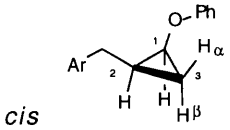
Micro Analysis: calculated for $C_{16}H_{16}O_2$: C79.70 H6.71; found C79.64, 6.67.

2-(2-Hydroxybenzyl)-1-(2-hydroxyphenyl)cyclopropane 228c

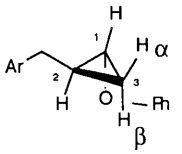


To a suspension of Zn/Hg amalgam (1.3g, 19mmol), chlorotrimethylsilane (1.0ml, 8mmol) and 2-allylphenol (0.60ml, 4mmol) in ether (10ml) at reflux, a solution of ethylcatechol orthoformate (0.33g, 2mmol) was added *via* syringe pump over 16 hours. After a further 8 hours at reflux the reaction was allowed to cool, and was quenched by the addition of saturated sodium bicarbonate (5ml). After stirring for 10 minutes, the mixture was filtered through celite, and transferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography, but separation from catechol could not be achieved. Eventually, the compound 2-(2-hydroxybenzyl)-1-(2-hydroxyphenyl)-cyclopropane **228c** was characterized as a 4:1 mixture with catechol (26mg, 0.10mmol, 5%, *cis* / *trans* 1:1.1).

^{1}H NMR ($CDCl_3$ / ppm): 7.26-6.74(8H, m, aryl), 6.17, 5.77, 5.51 and 4.95(4H, 4 x bs, 4 x O**H**), 3.83(0.45H, td, J=6.1, 3.3, H1, *cis*), 3.65(0.55H, dt, J=6.1, 2.6, H1, *trans*), 2.93(0.45H, dd, J=15, 5.3, PhC**H** *cis*), 2.83(0.45H, dd, J=15, 9.8, PhC**H**, *cis*), 2.73(1.1H, dd, J=9.3, 7.3, PhC**H**$_2$ *trans*), 1.58-1.40(1H, m, H2 *cis* and *trans*), 1.10-0.95(1H, m, cyclopropyl, *cis* and *trans*), 0.79(0.55H, q, J=6.4, cyclopropyl C**H** *trans*), 0.60(1H, td, J=6.1, 3.3, H3α, *cis*).



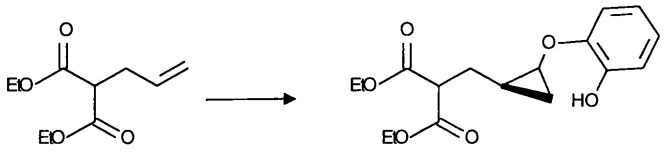
cis



trans

^{13}C NMR ($CDCl_3$ / ppm): (mixture of isomers, partially obscured by catechol) 130.5, 130.0, 127.5, 127.5, 121.0, 120.5, 120.0, 115.0 113.0, 112, 57, 21.5, 19.0, 13.0, 12.0.
Mass Spectrum: calculated for $C_{16}H_{16}NaO_3$ (MNa^+): 279.0997; found 279.0980.

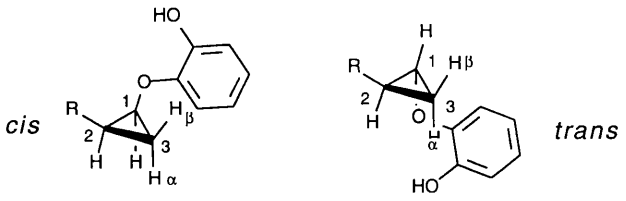
Diethyl (2-(2-hydroxyphenoxy)cyclopropyl)methyl malonate 228d



Zn/Hg amalgam (1.3g, 15mmol), chlorotrimethylsilane (1.0ml, 8mmol), diethylallylmalonate (1.6g, 8mmol) and zinc chloride (280mg, 2mmol) were heated to reflux in ether (8ml). Ethylcatechol orthoformate (300mg, 1.8mmol) was added *via* syringe pump over 6 hours and the mixture was then refluxed for a further 16 hours. The reaction was allowed to cool, and was quenched by the addition of saturated sodium bicarbonate (10ml). After stirring for 10 minutes, the mixture was filtered through celite, and transferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo.* The resulting oil was purified by flash chromatography to afford 2-benzyl-1-methoxycyclopropane **228d** as a clear oil (110mg, 0.34mmol, 19%, *cis* / *trans* 10:1).

diethyl *cis*-(2-(2-Hydroxyphenoxy)cyclopropyl)methyl malonate

IR (thin film / cm^{-1}): 3446(s), 2984(s), 2255(w), 1730(s), 1601(m), 1501(s), 1447(m), 1372(m), 1337(m), 1265(s), 1229(s), 1197(s), 1096(m), 1033(s), 912(m), 859(m), 793(m), 746(s), 594(w).
^{1}H NMR ($CDCl_3$ / ppm): 6.75-7.1(4H, m, aryl), 6.25(1H, s, OH), 4.23(4H, m, $CO_2C\mathbf{H}_2$), 3.74(1H, td, J=6.4, 3.3, H1), 3.53(1H, dd, J=7.9, 5.8, $(EtO_2C)_2C\mathbf{H}$), 2.35(1H, dt, J=14.3, 5.6, $(EtO_2C)_2CHC\mathbf{H}$), 1.99(1H, m ddd, J=14.3, 9.3, 8.1, $(EtO_2C)_2CHC\mathbf{H}$), 1.25(6H, t, 2xMe), 1.15(1H, m, H2), 1.02(1H, dt, J=9.4, 6.1, H3β), 0.44(1H, td, J=6.4, 3.2, H3α).
^{13}C NMR ($CDCl_3$ / ppm): 170.6, 196.2, 145.8, 145.7, 121.8, 119.7, 115.0, 112.3, 91.8, 54.1, 52.2, 30.9, 27.4, 15.6, 15.1, 12.6, 12.3.



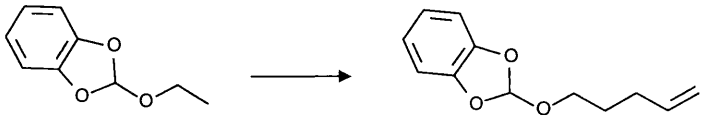
***trans*-2-benzyl-1-methoxycyclopropane**

^{1}H NMR (partially obscured by *cis* isomer, $CDCl_3$ / ppm): 3.03(1H, dt, J=6, 3, H1), 0.80(1H, m, H3), 0.30(1H, q, J=6.1Hz, H3).

Mass Spectrum: $C_{11}H_{17}O_4$ ((M-C_6H_6O)$^+$) 228 (32%).

Microanalysis: calculated for $C_{17}H_{22}O_6$ C63.35 H 6.88; found C63.94 H 6.84.

Catechol-(pent-4-enyl)-orthoformate 233



Ethylcatechol orthoformate (1.0g, 6.0mmol), 4-penten-1-ol (0.60g, 7.0mmol) and a drop of 4M HCl in dioxane were heated to reflux with a heat gun. The vapour temperature was held at 78°C for several minutes, and heating was continued until it reached 136°C. ^{1}H NMR of the crude suggested that ethylcatechol orthoformate remained. A further 0.50ml of pentenol was added and the system heated to reflux again. The mixture was transferred to a Kugelrohr, and distilled at 125°C/30mmHg. The residue of the distillation was purified by column chromatography to afford the *title compound* **233** as a clear oil (400mg, 1.9mmol, 32%).

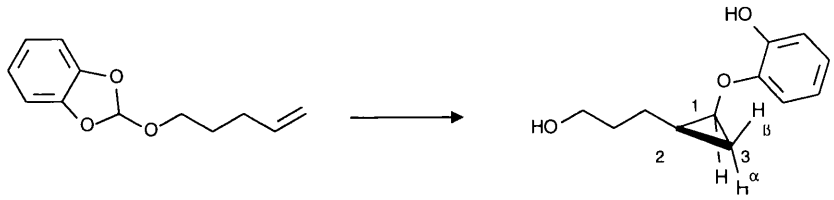
IR (thin film / cm^{-1}): 3077(m), 2942(s), 1728(w), 1641(m), 1478(s), 1395(w), 1359(s), 1240(s), 1137(s), 1096(s), 1044(s), 908(s), 777(w), 733(s), 652(w), 630(w), 548(w), 521(w).

^{1}H NMR ($CDCl_3$ / ppm): 6.88-6.86(4H, m, aryl), 6.88(1H, s, O_3C**H**), 5.86-5.76(1H, m, C**H**=CH_2), 5.14-5.01(CH=C**H**$_2$), 3.68(2H, t, J=6.5, OC**H**$_2$), 2.15(2H, q, J=6.5, C**H**$_2$CH=CH_2), 1.71(2H, m, CH_2C**H**$_2$).

^{13}C NMR ($CDCl_3$ / ppm): 145.9, 137.7, 121.6, 118.7, 115.1, 108.3, 62.7, 29.9, 28.4.

Mass Spectrum: (FAB) 207 (46%, MH$^+$) .

1-(2-Hydroxyphenoxy)-2-(3-hydroxypropyl)-cyclopropane 234



A suspension of Zn/Hg amalgam (1g, 15mmol), chlorotrimethylsilane (0.30ml, 2.4mmol) and zinc chloride (84mg, 1mmol) in ether (5ml) was heated to reflux. A solution of catecholpent-4-enyl orthoformate **233** (120mg, 0.58mmol) in ether (2ml) was added dropwise. After refluxing overnight, the reaction was quenched by the addition of saturated sodium bicarbonate (3ml). Ether (50ml) was added, and the layers were separated. The ethereal layer was washed with brine (5ml), dried over $MgSO_4$ and the solvent removed *in vacuo* to afford a yellow oil. The oil was purified by flash chromatography to afford the *title compound* **234** as an oil (18mg, 15%, *cis* / *trans* 2:1).

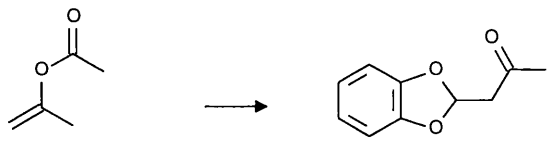
IR (*cis*, thin film / cm^{-1}): 3394(s), 2932(s), 1597(m), 1499(s), 1394(m), 1360(m), 1261(s), 1218(s), 1148(m), 1106(m), 1054(m), 913(w), 744(s).

^1H NMR (*cis*, $CDCl_3$ / ppm): 7.27-6.86(4H, m, catechol), 5.51(1H, s, O**H** catechol), 3.72(2H, t, J=6.6, C$\mathbf{H}_2$OH), 3.53(1H, dt, J=6.2, 3.5, H1), 1.75-1.72(3H, m, C$\mathbf{H}_2$, O**H**), 1.65-1.22(3H, m, C$\mathbf{H}_2$ and H2), 0.97-0.95(1H, m, H3β), 0.65(1H, q, J=6.2, H3α).

^{13}C NMR (*cis*, $CDCl_3$ / ppm): 145.7, 145.4, 121.7, 120.1, 114.6, 112.5, 62.4, 57.2, 31.7, 27.6, 19.2, 13.2.

Mass Spectrum: calculated for $C_{12}H_{16}O_2$ (M^+) 208.1099; found 208.1080.

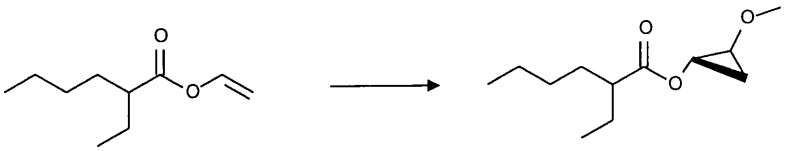
2-(3-oxopropyl)-1,3-benzodioxolane 236



Zn/Hg (1.3g, 50mmol), chlorotrimethylsilane (1.0ml, 8mmol) and isopropenyl acetate (0.77ml, 7mmol), were heated to reflux in ether (10ml). To this mixture, a solution of ethylcatechol orthoformate (0.33g, 2mmol), in ether (2ml) was added *via* syringe pump over 24 hours. The reaction was allowed to cool, and was quenched by the addition of saturated sodium bicarbonate (10ml). After stirring for 10 minutes, the mixture was filtered through celite, and transferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was washed with brine (5ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography to afford (3-oxo)butanal catechol acetal **236** as a buff solid (71mg, 0.20mmol, 20%) mpt 45-46°C.[242]

IR (thin film / cm^{-1}): 2916(m), 2849(m), 1707(m), 1630(s), 1480(m), 1446(m), 1447(s), 1359(m), 1237(m), 1115(s), 1093(s), 1048(s), 913(w), 859(w), 805(w), 787(w), 743(m), 709(w), 651(w).
^1H NMR ($CDCl_3$ / ppm): 6.86-6.73(4H, m, catechol), 6.49(1H, t, J=7.4, $O_2C\mathbf{H}$), 3.10(2H, d, J=7.4, $C\mathbf{H}_2COMe$), 2.26(3H, s, $C\mathbf{H}_3$).
Mass Spectrum: calculated for $C_{10}H_{10}O_3$ (MH^+) 178.0630; found 178.0640.

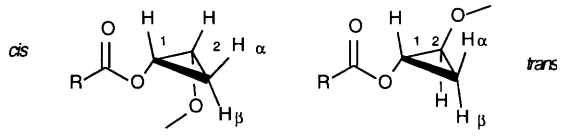
2-Ethyl-(2-methoxycyclopropyl)hexanoate 241



Zn/Hg amalgam (2.5g, 50mmol), chlorotrimethylsilane (1.2ml, 9mmol) and ethylhexanoate vinyl ester (0.35ml, 2mmol) were heated to reflux in ether (10ml). Trimethylorthoformate (1.40ml, 12mmol) was added *via* syringe pump over 48 hours. A further portion of trimethyl orthoformate (1.4ml, 12.0mmol) and chlorotrimethylsilane (1.0ml, 7.9mmol) were added and the mixture was refluxed for a further 2 days. The reaction was allowed to cool, and was quenched by the addition of saturated sodium bicarbonate (10ml). After stirring for 10 minutes, the mixture was filtered through celite, and *t*ransferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography to afford 2-ethyl-(2-methoxycyclopropyl)-hexanoate **241** (198mg. 0.93mmol, 46%, *cis* / *trans* 1:2.6).

***trans*-2-ethyl-(2-methoxycyclopropyl)-hexanoate**

IR (thin film / cm^{-1}): 2964(s), 2995(m), 2875(m), 1742(s), 1459(m), 1431(w), 1382(m), 1339(m), 1235(m), 1200(m), 1168(s), 1147(m), 1096(m), 1073(m), 998(w), 944(w), 813(w).
^1H NMR ($CDCl_3$ / ppm): 3.90(1H,dt, J=7.6, 4.6, H1), 3.36(3H, s, OMe), 3.18(1H, dt, J=7.6, 4.6, H2), 2.27(1H, m, C(O)C**H**), 1.62-1.39(4H, m, alkyl), 1.23(4H, m, alkyl), 0.95(1H, q, J=7.6, H3β), and 0.89-0.77(7H, m, H3α and 2 x Me).
^{13}C NMR ($CDCl_3$ / ppm): 177.3, 58.8, 55.8, 50.8, 47.0, 31.6, 29.5, 25.4, 22.6, 13.9, 11.7, 11.4.



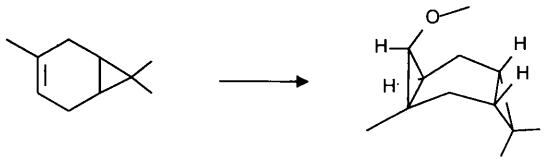
***cis*-2-ethyl-(2-methoxycyclopropyl)-hexanoate**

IR (thin film / cm^{-1}): 3468(w), 2965(s), 2936(s), 2875(s), 1744(s), 1460(s), 1383(m), 1302(w), 1252(m), 1219(s), 1150(s), 1080(m), 1040(w), 997(m), 942(m), 806(w), 749(w).
^1H NMR ($CDCl_3$ / ppm): 4.05(1H, dd, J=8.1, 4.1, H1), 3.39(3H, s, OMe), 3.24(1H, m, H2), 2.18(1H, m, C(O)**H**), 1.58-1.39(4H, m, alkyl), 1.27-1.17(4H, m, alkyl), 1.07and 0.92(1H, td, J=7.9, 4.1, and 1H, m, H3α and H3β), 0.84(6H, m, 2 x Me).

^{13}C NMR ($CDCl_3$ / ppm): 176.7, 58.6, 57.9, 52.3, 47.0, 33.6, 31.7, 29.5, 25.3, 22.6, 14.2, 13.9, 11.8.

Mass Spectrum: (FAB) calculated for $C_{12}H_{23}O_3$ (M^+) 216.1725, found 216.1720.

Methoxy-1,4,4-trimethyl-tricyclo[5,1,0,$0^{3,5}$]octane 238a



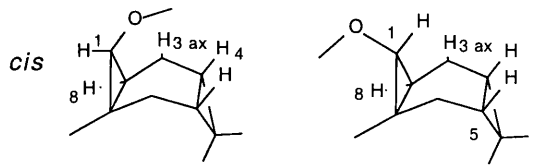
Zn/Hg amalgam (2.5g, 50mmol), chlorotrimethylsilane (1.2ml, 10mmol) and 3-carene (0.32ml, 2mmol) were heated to reflux in ether (10ml). Trimethyorthoformate (1.40ml, 12mmol) was added *via* syringe pump over 48 hours. A further portion of of trimethylorthoformate (1.4ml, 2mmol) and chlorotrimethylsilane (1.0ml, 1mmol) was added. After a further 48 hours at reflux the mixture was allowed to cool, and was quenched by the addition of saturated sodium bicarbonate (10ml). After stirring for 10 minutes, the mixture was filtered through celite and transferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography to afford *cis* and *trans* methoxy-1,4,4-trimethyl-tricyclo[5,1,0,$0^{3,5}$] octane (233mg, 1.29mmol, 65%, *cis* / *trans* 5:2).

IR (mix of *cis* and *trans*, thin film / cm^{-1}): 2988(m), 2932(s), 2862(s), 2818(m), 1450(m), 1375(m), 1333(m), 1221(m), 1184(w), 1134(s), 1080(m), 1034(m), 993(w), 973(w), 757(s).

***cis*-methoxy-1,4,4-trimethyl-tricyclo[5,1,0,$0^{3,5}$]octane**

^1H NMR ($CDCl_3$ / ppm): 3.38(3H, s, OMe), 2.62(1H, d, J=7.8, H1), 1.96(1H, dd, J=14.9, 8.2, H3 axial), 1.69(1H, ddd, J=15.1, 7.9, 1.9, H8), 1.34(1H, dd, J=15.2, 1.7, H3 eq), 0.93(3H, s, Me), 0.86(3H, s, Me), 0.78(3H, s, Me), 0.45-0.38(2H, m, H4,5).

^{13}C NMR ($CDCl_3$ / ppm): 64.9, 58.6, 28.1, 26.0, 23.1, 19.1, 18.0, 16.8, 14.7, 12.2.



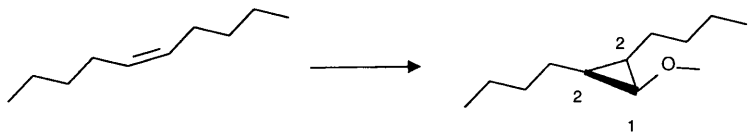
***trans*-methoxy-1,4,4-trimethyl-tricyclo[5,1,0,$0^{3,5}$]octane**

^1H NMR ($CDCl_3$ / ppm): 3.33(3H, s, OMe), 2.61(1H, d, J=6.8,H1), 2.06(1H, dd, H3 axial), 1.38(1H, dt, H8), 1.08(1H, dd), 1.03(3H, s, Me), 0.95(3H, s, Me), 0.73(3H, s, Me), 0.53 and 0.33(2H, 2 x m, H4,5).

^{13}C NMR ($CDCl_3$ / ppm): 64.1, 58.3, 22.1, 19.5, 18.4, 17.0, 15.9, 15.8, 14.9, 14.6.

Mass Spectrum: calculated for $C_{12}H_{20}O$ (M^+)180.1515; found 180.1510.

cis-2,3-Dibutylmethoxycyclopropane 238b



Zn/Hg amalgam (2.5g, 50mmol), chlorotrimethylsilane (1.2ml, 9mmol) and *Z*-dec-4-ene (0.38ml, 2.0mmol) were heated to reflux in ether (10ml). Trimethylorthoformate (1.40ml, 12mmol) was added *via* syringe pump over 48 hours. A further portion of trimethyl orthoformate (1.4ml, 12.0mmol) and chlorotrimethylsilane (1.0ml, 7.9mmol) was added and the mixture was refluxed for a further 2 days. The reaction was allowed to cool and was quenched by the addition of saturated sodium bicarbonate (10ml). After stirring for 10 minutes, the mixture was filtered through celite and transferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography to afford *cis*-dibutylmethoxycyclopropane **238b** (194mg. 1.05mmol, 53%, *cis* / *trans* 6:1).

IR (mix of isomers, thin film / cm^{-1}): 2959(s), 2927(s), 2859(m), 1466(s), 1419(w), 1378(m), 1352(w), 1319(w), 1238(s), 1220(m), 1199(w), 1142(m), 1094(s), 1040(m), 987(w), 930(w), 806(w), 786(w), 764(w), 729(w).

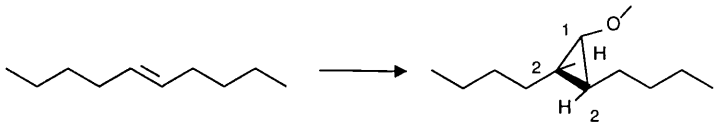
^1H NMR ($CDCl_3$ / ppm): 3.38(3H, s, OMe *cis*), 3.28(3H, s, OMe, *trans*), 3.03(1H, t, J=6.7, H1 *cis*), 2.58(1H, t, J=6.7, H1, *trans*), 1.40-1.30(12H, m, alkyl), 0.88(6H, m, 2 x Me), 0.61(2H, m, H2).

^{13}C NMR (*cis*, $CDCl_3$ / ppm): 59.5, 58.6, 32.5, 22.9, 21.3, 18.8, 14.07.

^{13}C NMR (*trans*, $CDCl_3$ / ppm): 66.9, 57.7, 32.0, 26.0, 24.0, 22.6, 14.0.

Mass Spectrum: (FAB) calculated for $C_{12}H_{24}O$ 184.1827; found 184.1820.

trans-2,3-Dibutyl-1-methoxycyclopropane 238c



Zn/Hg amalgam (2.5g, 50mmol), chlorotrimethylsilane (2.2ml, 9 mmol) and *E*-dec-5-ene (0.38ml, 2mmol) were heated to reflux in ether (10ml). Trimethylorthoformate (1.4ml, 12mmol)l) in ether was added *via* syringe pump over 24 hours. A second portion of trimethylorthoformate (1.4ml, 12mmol) and chlorotrimethylsilane (1.0ml, 8mmol) was added. After a further 2 days at reflux, the reaction was allowed to cool and was quenched by the addition of saturated sodium bicarbonate (10ml). After stirring for 10 minutes, the mixture was filtered through celite, and transferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was

washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography to afford *anti*-2,3-dibutyl-1-methoxycyclopropane **238c** (205mg, 1.11mol, 56%).

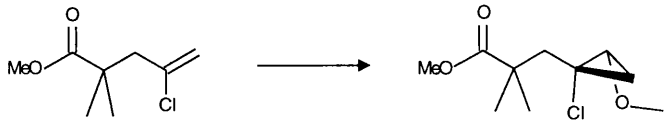
IR (thin film / cm^{-1}): 2957(s), 2928(s), 2859(s), 2821(m), 1731(m), 1581(w), 1467(s), 1378(m), 1288(m), 1219(m), 1123(s), 1086(m), 1040(m), 991(m), 896(w), 833(w), 740(w).

^1H NMR ($CDCl_3$ / ppm): 3.30(3H, s, OMe), 2.83(1H, dd, J=6.5, 2.9, H1), 1.5-1.1(12H, m, alkyl), 0.86(6H, m, 2 x Me), 0.44(2H, m, H2).

^{13}C NMR ($CDCl_3$ / ppm): 65.1, 58.2, 31.2, 26.1, 24.5, 22.6, 14.6.

Mass Spectrum: (FAB) calculated for $C_{12}H_{24}O$ (M^+): 184.1827; found 184.1820.

2,2-Dimethyl-3-(1-chloro-2-methoxycyclopropyl)propanoate methylester 238d



Zn/Hg amalgam (2.5g, 50mmol), chlorotrimethylsilane (2.2ml, 17mmol) and 4-chloro-2,2-dimethylpent-4-enoate methylester (0.34ml, 2mmol) were heated to reflux in ether (10ml). Trimethylorthoformate (1.40ml, 12mmol) was added *via* syringe pump over 48 hours. The mixture was refluxed for a further 2 days, and was then allowed to cool and was quenched by the addition of saturated sodium bicarbonate (10ml). After stirring for 10 minutes, the mixture was filtered through celite, and transferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography to afford *cis* and *trans* 2,2-dimethyl-3-(1-chloro-2-methoxycyclopropyl)propanoate methylester **238d** (205mg, 0.93mmol, 46%, *cis* / *trans* 1:4).

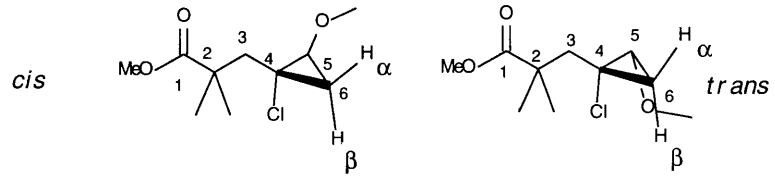
***cis*-2,2-dimethyl-3-(1-chloro-2-methoxycyclopropyl)propanoatemethylester**

IR (thin film / cm^{-1}):2988(m), 2932(s), 2862(s), 2818(m), 1450(m0, 1375(m), 1333(m), 1221(m), 1184(w), 1134(s), 1080)m), 1034(m), 993(w), 973(w), 757(s).

^1H NMR ($CDCl_3$ / ppm): 3.64(3H, s, CO_2Me), 3.36(3H, s, OMe), 3.30(1H, dd, J=7.5, 4.3, H5), 2.43 and 1.42(2H, 2 x d, J=15, $CMe_2C\mathbf{H}_2$), 1.28(3H, s, Me), 1.27(3H, s, Me), 1.18(1H, t, J=7.6, H6), 0.85(1H, dd, J=7.6, 4.4, H6).

^{13}C NMR ($CDCl_3$ / ppm): 178.2(C1), 64.3($\mathbf{C}O_2$), 58.4($O\mathbf{C}H_3$), 51.8(C5), 43.2 (C4), 42.1(C2), 42.0(C3), 26.3(Me), 25.1(Me), 23.0(C6).

Mass Sectrum (FAB 35%), 243 (M+Na).



***trans*-2,2-dimethyl-3-(1-chloro-2-methoxycycloproplyl)propanoatemethylester**

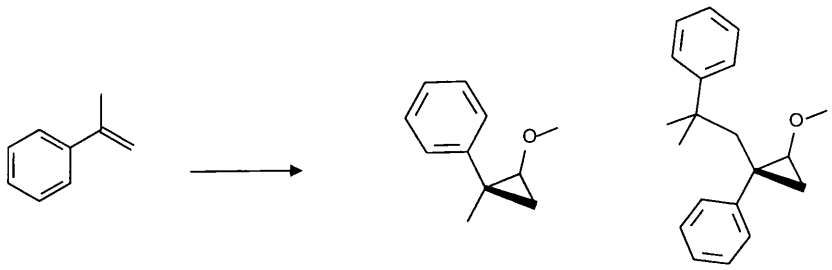
IR (thin film / cm-1): 2977(s), 2950(s), 2835(w), 1736(s), 1474(s), 1451(s), 1434(m), 1390(m), 1304(m), 1321(m), 1266(m), 1227(m), 195(s), 146(s), 1093(s), 1045(w), 1004(m), 943(w), 880(w), 852(w), 823(w), 801(w), 781(w), 768(w).

^{1}H NMR ($CDCl_3$ / ppm): 3.65(3H, s, CO_2Me), 3.44(3H, s, OMe), 2.94(1H, dd, J=7.4, 6.2, H5), 1.93(2H, s, $CMe_2C\mathbf{H}_2$), 1.27(3H, s, Me), 1.24(3H, s, Me), 1.07(1H, dd, J=7.6, 4.6, H6α), 0.98(1H, t, J=7.4, H6β).

^{13}C NMR ($CDCl_3$ / ppm): 177.9(C1), 61.9($\mathbf{C}O_2$), 58.6(O$\mathbf{C}H_3$), 51.0(C5), 48.4(C3), 44.5 (C4), 42.2(C2), 25.9(Me), 25.6(Me), 24.6(C6).

Mass Sectrum: (FAB 42%) 220 (M^+).

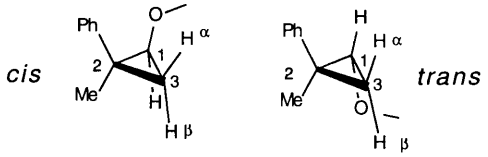
1-Methoxy-2-methyl-2-phenyl-cyclopropane 238e



Zn/Hg amalgam (2.5g, 50mmol), chlorotrimethylsilane (1.2ml, 9mmol) and α-methylstyrene (0.26ml, 2mmol) were heated to reflux in ether (10ml). Trimethylorthoformate (1.40ml, 12mmol) was added *via* syringe pump over 24 hours. After 24 hours at reflux, a further portion of trimethyl orthoformate (1.4ml, 12.0mmol) and chlorotrimethylsilane (1.0ml, 7.9mmol) was added and the mixture was refluxed for another 2 days. The reaction was allowed to cool and was quenched by the addition of saturated sodium bicarbonate (10ml). After stirring for 10 minutes, the mixture was filtered through celite and transferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography to afford 1-methoxy-2-methyl-2-phenylcyclopropane **238e** (182mg, 1.12mmol, 56%, *cis* / *trans* 1.7:1) and 1-methoxy-2-(2,2-dimethyl-2-phenylethyl)-2-phenylcyclopropane **238f** (52mg, 0.18mmol, *cis* / *trans* 3:1 9%).

1-methoxy-2-methyl-2-phenylcyclopropane 238e

IR (mixture of *cis* and *trans*, thin film / cm^{-1}): 3059(s), 3024(s), 2829(m), 1603(m), 1497(s), 1446(s), 1432(m), 1467(m), 1238(w), 1212(m), 1144(s), 1094(m), 1030(m), 996(m), 938(w), 842(w), 764(s), 699(s).



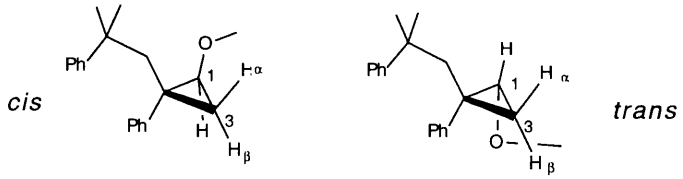
^1H NMR (mix of *cis* and *trans*, $CDCl_3$ / ppm): 7.39-7.19(5H, m, Ph), 3.47(1.2H, s, OMe *trans*), 3.39(0.4H, dd, J=6.4, 3.7, H1 *trans*) 3.23(0.6H, dd, J=6.2, 3.3, H1 *cis*) 3.42(1.8H, s, OMe *cis*),1.51(1.2H, s, Me *trans*), 1.34(1.8 H, s, Me *cis*), 1.15 and 0.84(2H, 2 x m, H3 *cis* and *trans*).

^{13}C NMR ($CDCl_3$ / ppm): (145.8), 141.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 126.8, 125.9, 125.7, (66.0), 65.7, (58.6), 58.0, 26.5, 26.1, 25.3, 20.3, 19.2, 18.6.

Mass Spectrum: (FAB) calculated for $C_{11}H_{13}O$ ($M\text{-}H^+$)161.0966; found 161.0960.

1-methoxy-2-(2,2-dimethyl-2-phenylethyl)-2-phenylcyclopropane 238f

IR (mixture of *cis* and *trans*, 3: 1 thin film / cm^{-1}): 3086(m), 3058(m), 3025(m), 2961(s), 2930(s), 1945(w), 1602(m), 1497(s), 1446(s), 1387(m), 1367(m), 1235(m), 1206(m), 115(s), 1080(s), 1049(w), 1031(m), 1005(m), 917(w), 840(w), 802(w), 763(s), 691(s).



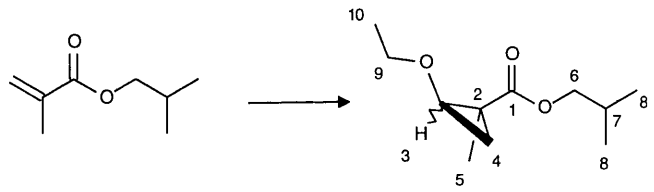
^1H NMR (*cis*, $CDCl_3$ / ppm): 7.4-7.1(10H, m, 2 x Ph), 3.14(3H, s, OMe) 2.98(1H, dd, J=6.4, 3.4, H1), 2.60(1H, dd, J=14.5, 1.5, PhC**H**), 1.36(1H, dd, J=14.5, PhC**H**),1.13(3H, s, Me), 1.11(3H, s, Me), 1.02(1H, dd, J=6.4, 3.4, H3β), 0.58(1H, t, J=6.4, H3α)

^{13}C NMR (*cis*, $CDCl_3$ / ppm): 149.7, 140.4, 130.3, 128.6, 127.8, 125.9,125.8, 125.3, 64.9, 57.9, 52.8, 30.9, 28.2, 17.3.

^1H NMR (*trans*, $CDCl_3$ / ppm): 7.4-7.2(10H, m, 2 x Ph), 3.22(1H, m, H1) 3.20(3H, s, OMe), 1.33(2H, s, PhCH_2), 1.1(6H, 2 x s , 2 x Me obscured by *cis* isomer), 1.10(1H, M, H3β), 0.83(1H, t, J=6.0, H3α)

Mass Spectrum: (FAB) calculated for $C_{20}H_{24}O$ 280.1827; found 280.1820.

1-Isobutoxycarboxy-1-methyl-2-ethoxycyclopropane 243a



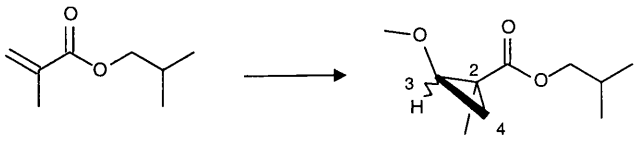
A suspension of Zn/Hg amalgam (1.5g, 22mmol), chlorotrimethylsilane (1.0ml, 8mmol) and *iso*butylmethacrylate (0.32ml, 2mmol) was brought to reflux in ether (8ml). A solution of triethyl orthoformate (0.50ml, 4.6mmol) in ether (1ml) was added *via* syringe pump over 6 hours. After a further 18 hours at reflux, the reaction was allowed to cool, and was quenched by the addition of saturated sodium bicarbonate (10ml). After stirring for 10 minutes, the mixture was filtered through celite, and transferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography to afford 1-Isobutoxycarboxy-1-methyl-2-ethoxycyclopropane **243a** (63mg, 0.31mmol, 16%, 1 isomer only).

IR (thin film / cm^{-1}): 2969(s), 2878(m), 1721(s), 1465(m), 1378(m), 1349(m), 1278(m), 1156(s), 1058(s), 910(w), 829(w), 772(w).

^1H NMR ($CDCl_3$ / ppm): 3.82(2H, d, J=6.6, CO_2CH_2), 3.6-3.5(3H, m, H2 and OCH_2), 1.9(1H, septet, J=6.8, Me_2CH), 1.4(1H, J=7.2, 5.6, H4), 1.33(3H, s, Me), 1.20(3H, t, H10), 0.92(6H, d, J=6.8, $(CH_3)_2CH$), 0.82(1H, dd, J=5.6, 4.2, H4).

^{13}C NMR ($CDCl_3$ / ppm): 174.5(C1), 70.55(C6), 66.8(C9), 63.9(C3), 27.7(C7), 24.5(C2), 21.8(C4), 19.0(C8), 15.0(C10), 12.2(C5).

1-*iso*Butoxycarboxy-1-methyl-2-methoxycyclopropane 243b



To a suspension of Zn/Hg amalgam (0.67gg, 10mmol), chlorotrimethylsilane (0.63ml, 5mmol) and isobutylmethacrylate (0.0.28gl, 2mmol) in ether (8ml) at reflux, a solution of trimethylorthoformate (0.63ml, 4mmol) in ether (1ml) was added *via* syringe pump over 18 hours. After a further 6 hours at reflux, the reaction was allowed to cool, and was quenched by the addition of saturated sodium bicarbonate (10ml). After stirring for 10 minutes, the mixture was filtered through celite, and transferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography to afford1-

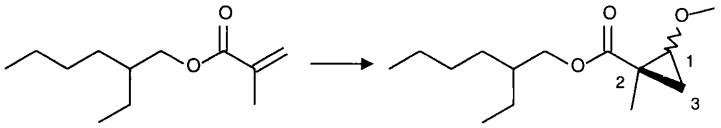
Isobutoxycarboxy-1-methyl-2-methoxycyclopropane **243b** (15mg, 0.081mmol, 4%, 1 isomer only).

IR (thin film / cm^{-1}): 2925(s), 2855(S), 1731(s), 1630(m), 1601(m), 1463(s), 1404(m), 1379(m), 1271(s), 1158(m), 1121(s), 1071(s), 749(w).

^1H NMR ($CDCl_3$ / ppm): 3.80(2H, d, J=6.6, CO_2CH_2), 3.53(1H, dd, J=7.1, 4.4, H2), 3.37(3H, s, OMe), 1.90(1H, septet, J=6.8, Me_2CH), 1.40(1H, dd, J=7.2, 5.6, H4), 1.33(3H, s, Me), 0.91(6H, d, J=6.7, $(CH_3)_2CH$), 0.79(1H, dd, J=5.6, 4.2, H4).

^{13}C NMR ($CDCl_3$ / ppm): 174.4, 70.6, 66.8, 65.5, 58.9, 24.5, 27.7, 24.5, 21.9, 19.1, 12.0.

2-(2-Ethylhexanoxycarbonyloxy)-2-methyl-1-methoxycyclopropane 245



Zn/Hg amalgam (2.5g, 50mmol), chlorotrimethylsilane (1.2ml, 9mmol) and 2-(ethylhexyl)-methacrylate (0.45ml, 2mmol) were heated to reflux in ether (10ml). Trimethylorthoformate (1.40ml, 12mmol) was added *via* syringe pump over 48 hours. A further portion of trimethylorthoformate (1.4ml, 12mmol) and chlorotrimethylsilane (1.0ml, 7.9mmol) was added and the mixture was refluxed for a further 2 days. The reaction was allowed to cool, and was quenched by the addition of saturated sodium bicarbonate (10ml). After stirring for 10 minutes, the mixture was filtered through celite, and transferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was washed with brine (5ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography to afford 2-(2-ethylhexanoxycarbonylxy)-2-methyl-1-methoxycyclopropane **245** as a mixture of diastereoismers (isomer: **A** 155mg, 0.64mmol, 32%; **B** 52mg, 0.21, 11%).

2-(2-ethylhexanoxycarbonyloxy)-2-methyl-1-methoxycyclopropane (Isomer **A**)

IR (thin film / cm^{-1}): 2961(s), 2940(s), 2875(s), 1720(s), 1452(s), 1425(m), 1366(m), 1305(m), 1278(s), 1226(m), 1175(s), 1143(s), 1114(m), 1050(s), 1013(m), 949(w), 861(w), 726(w).

^1H NMR ($CDCl_3$ / ppm): 3.92(2H, d, J=7.7, CH_2OCO), 3.51(1H, dd, J=7.1, 4.4, H1), 3.35(3H, s, OMe), 1.52(1H, m, CH alkyl), 1.4-1.2(13H, m, Me, alkyl and H3), 0.86(6H, t, J=7.2, 2 x CH_2CH_3), 0.79(1H, dd, J=5.5, 4.5, H3).

^{13}C NMR ($CDCl_3$ / ppm): 174.3, 66.9, 65.4, 58.7, 38.7, 30.5, 28.9, 24.5, 23.9, 22.9, 21.8, 13.9, 11.0.

2-(2-ethylhexanoxycarbonyloxy)-2-methyl-1-methoxycyclopropane (Isomer **B**)

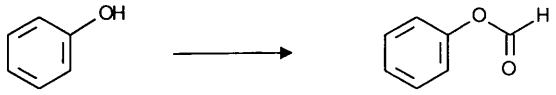
IR (Ithin film / cm^{-1}): 3020(m), 2962(s), 29939(s), 2875(m), 1716(s), 1464(m), 1429(w), 1391(w), 1326(m), 1216(s), 1175(s), 1106(m), 1048(m), 999(m), 945(w), 756(s).

^{1}H NMR ($CDCl_3$ / ppm): 3.98(2H, m, CH_2OCO), 3.28(3H, s, OMe), 3.19(1H, dd, J=6.2, 4.5 H1), 1.69(1H, t, J=6.0, H3), 1.35(1H, m, alkyl), 1.4-1.2(8H, m, alkyl), 1.22(3H, s, Me), 0.87(6H, t, J=7.4, 2 x CH_2CH_3), 0.80(1H, t, J=6.2, H3).

^{13}C NMR ($CDCl_3$ / ppm): 172.0, 67.5, 67.0, 58.4, 38.8, 38.7, 30.5, 28.9, 25.9, 23.8, 22.9, 20.5, 19.0, 14.0, 11.0, 10.9.

Mass Spectrum: calculated for $C_{14}H_{27}O_3$ (M^+) 243.1960; found 243.1950.

Phenylformate



Acetic anhydride (50ml, 0.50mol) and formic acid(19.0ml, 0.50mol) were stirred at 45°C for 1 hour. The solution was allowed to cool and phenol (31.5g, 0.34mol) then pyridine (4.0ml, 0.05mol) were added. After stirring at room temperature for 24 hours the reaction was heated under vacuum (75°C/20mmHg) to remove the anhydride, acetic acid and pyridine to afford the *title compound* as a clear oil (17.1g, 0.14mol, 20%).[241]

IR (thin film / cm^{-1}): 3064(m), 2954(m), 2212(w), 2019(w), 1951(w), 1876(w), 1762(s), 1740(s), 1592(s), 1488(s), 1457(m), 1372(m), 1190(s), 1165(s), 1109(s), 1071(s), 1024(m), 1003(m), 914(m), 893(w0, 872(m), 832(m), 762(m), 733(s), 986(s), 664(w).

^{1}H NMR ($CDCl_3$ / ppm): 8.2(1H, s, OC**H**O), 7.5-7.2(5h, m, Ph).

Phenyldichloromethylether 244

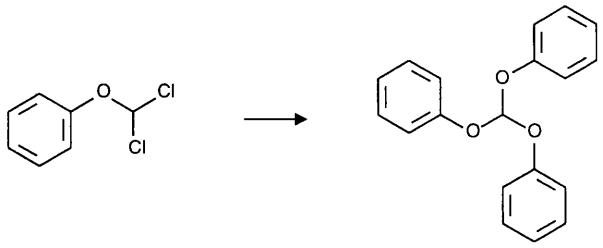
Phenyl formate (1.90g, 15mmol) was added dropwise to a mixture of phosphorus pentachloride (3.2g, 15mmol). After 1 hour, ether was added and the suspension was left overnight. The mixture was filtered, and the solvent removed *in vacuo* to leave a yellow oil. Bulb to bulb distillation of the crude (75°C/2mmHg) afforded **244** as a clear oil (1.82g, 10mmol, 67%).[241]

IR (thin film / cm^{-1}): 3044(w), 2136(w), 1942(w), 1591(s), 1488(s), 1456(m), 1370(m), 1317(m), 1199(s), 1071(s), 1024(w), 1002(m), 926(w), 893(w), 845(s), 816(m), 788(m), 750(s), 688(s), 668(m), 614(w), 585(m).

^{1}H NMR ($CDCl_3$ / ppm): 7.49(1H, s, PhOC**H**Cl_2), 7.41-7.10(5H, m, Ph).

^{13}C (CDCl3 / ppm): 153.4, 129.7, 125.8, 119.1, 96.1.

Triphenylorthoformate 246



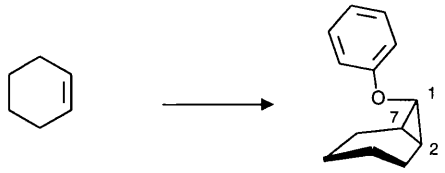
A suspension of sodium phenolate was prepared by adding sodium (0.86g, 37mmol), to a solution of phenol (3.39g, 37mmol) in dimethoxyethane (50ml). The solution was gently warmed to 50°C to aid dissolution of the sodium. To this solution, phenyldichloromethyl ether (3.0g, 17mmol) was added dropwise and the mixture was heated to reflux. After 30 minutes a precipitate had formed. The suspension was allowed to cool and the solvent removed *in vacuo*. Water (20ml) and ether (50ml) were added. the layers were separated and the ethereal layer was washed with water (3 x 15ml).The organic layer was washed with brine (10ml), dried over sodium sulfate and the solvent removed *in vacuo*. The solid was recrystallized from 40-60 petrol to afford the *title compound* **246** as white crystals (3.43g, 12mmol, 71%)mpt 73-75°C.[241]

IR (thin film / cm^{-1}): 2985(m), 2871(m), 1943(w), 1850(w), 1649(w), 1590(s), 1488(s), 1367(w), 1306(w), 1292(w), 1250(w), 1201(s), 1170(m), 1146(m), 10649s), 997(m), 955(m), 891(m), 825(w), 753(s), 687(s).

^1H NMR ($CDCl_3$ / ppm): 7.29-7.34(6H, m, aryl), 7.15-7.12(9H, m, aryl), 6.65(1H, s, $O_3C\mathbf{H}$).

^{13}C NMR ($CDCl_3$ / ppm): 129.7, 129.7, 123.6, 118.1, 110.3.

7-Phenoxynorcarane 255a



A mixture of Zn/Hg amalgam (2.5g, 50mmol), chlorotrimethylsilane (1.2ml, 9mmol) and cyclohexene (0.90ml, 10mmol) were heated to reflux in ether (10ml). Triphenyl-orthoformate **246** (0.50g, 1.7mmol) in ether (2ml) was added *via* syringe pump over 24 hours after which the mixture was refluxed for a further 24 hours. The reaction was allowed to cool, and was quenched by the addition of saturated sodium bicarbonate (10ml). After stirring for 10 minutes, the mixture was filtered through celite, and transferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography to afford 7-phenoxynorcarane **255a** as a clear oil (160mg, 0.85mmol, 50% *cis* / *trans* 1.6 :1).[239]

***cis*-7-phenoxynorcarane**

IR (thin film / cm^{-1}): 3022(m), 2929(s), 2854(s), 2033(w), 1927(w), 1837(w), 1600(s), 1492(s), 1451(s), 1428(s), 1339(m), 1291(m), 1237(s), 1169(s), 1094(s), 1024(w), 988(w), 943(w), 870(m), 833(m), 753(s), 691(s), 636(w), 578(w), 549(w).

^1H NMR ($CDCl_3$ / ppm): 7.30(2H, t, J=6.6, aryl), 7.10(2H, d, J=7.9, aryl), 6.97(1H, t, J=6.4, aryl), 3.61(1H, t, J=6.7, H1), 1.85-1.81(2H, m, alkyl), 1.57(2H, m, alkyl), 1.25(4H, m, alkyl), 1.12(2H, m, H2).

^{13}C NMR ($CDCl_3$ / ppm): 129.2, 126.9,120.5, 114.5, 56.0, 21.9, 20.7, 17.7, 11.6.

***trans*-7-phenoxynorcarane**

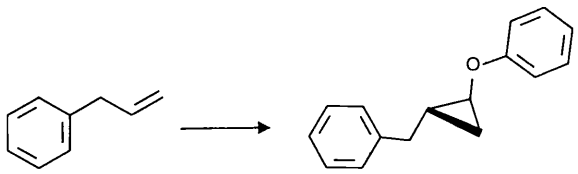
IR (thin film / cm^{-1}): 3009(m), 2934(s), 2862(s), 1932(w), 1839(w), 1763(w), 1595(s), 1492(s), 1447(w), 1410(w), 1342(m), 1245(s), 1167(m), 1105(m), 1048(m), 1017(m), 973(w), 928(m), 886(w), 841(m), 799(w), 752(s), 690(m), 608(w), 508(w).

^1H NMR ($CDCl_3$ / ppm): 7.31(2H, t, J=5.5, aryl), 6.99(3H, m, aryl), 3.38(1H, t, J=2.8, H1), 2.0-1.94(2H, m, alkyl), 1.84-1.79(2H, m, alkyl), 1.35-1.17(6H, m, H2 and alkyl).

^{13}C NMR ($CDCl_3$ / ppm): 129.2, 126.9, 120.5, 114.5, 56.0, 21.9, 20.7, 17.7, 11.6.

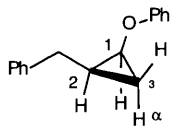
Mass Spectrum: calculated for $C_{13}H_{16}O$ (M+)188.1201; found 188.1210.

2-Benzyl-1-phenoxycyclopropane 255b

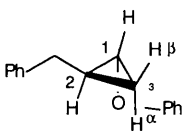


To a suspension of Zn/Hg (1.50g, 30mmol), $ZnCl_2$ (280mg, 1mmol) chlorotrimethylsilane (1.0ml, 7.9mmol) and allylbenzene (0.50ml, 4mmol) in ether (8ml) at reflux, a solution of triphenyl orthoformate **246** (0.50g, 1.64mmol) in ether (5ml) was added dropwise. The mixture was refluxed for 48 hours after which the reaction was allowed to cool, and was quenched by the addition of saturated sodium bicarbonate (5ml). After stirring for 10 minutes, the mixture was filtered through celite, and transferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was washed with brine (5ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography to afford the *title compound* **255b** as a mixture of diastereoisomers (88mg, 0.39mmol, 24%, *cis* / *trans* 1:3).

IR (mix of *cis* and *trans*, thin film / cm^{-1}): 3054(m), 3028(m), 2920(m), 1743(w), 1599(s), 1491(s), 1388(w), 1352(w), 1242(s), 1167(m), 1104(w), 1073(w), 1026(w), 921(w), 845(w), 735(s), 695(s), 590(w), 501(w).



cis

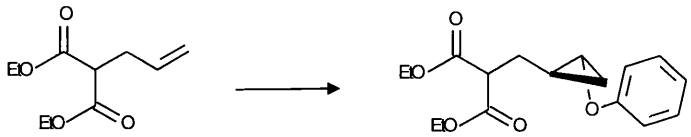


trans

^{1}H NMR ($CDCl_3$ / ppm): 7.4-6.8(10H, m, 2 x Ph), 3.87(0.3H, td, J=6.3, 3.2, H1, *cis*), 3.60(0.7H, dt, J=6.3, 2.7,H1, *trans*), 2.98(0.3H, dd, J=14.8, 6.53, PhC**H**, *cis*), 2.83(0.7H, dd, J=14.7, 6.8, PhC**H**, *trans*), 2.72 and 2.68(1H, 2 xdd, partially overlapping, J=15.5, 8.1, and 14.8, 7.6, PhC**H**, *cis* and *trans*), 1.52-0.94(2H, m, cyclopropyl), 0.80(0.7H, q, J=6.3, *trans,* H3α), 0.63(0.3H, td, J=6.5, 3.3, *cis*, H3α).

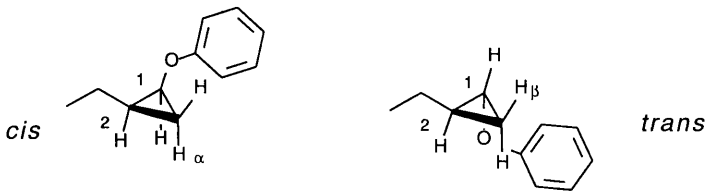
^{13}C NMR (*cis* and *trans,* $CDCl_3$ / ppm): 198.5, 180.1, 169.2, 169.1, 168.3, 168.0, 166.6, 165.7, 160.7, 154.7, (96.0), 94.1, (79.0) , 72.6, 58.7, (53.1), 51.9.

Diethyl (2-phenoxycyclopropyl)methyl malonate 255c



Zn/Hg amalgam (1.3g, 15mmol), chlorotrimethylsilane (1.0ml, 8mmol), diethylallylmalonate (1.6g, 8mmol) and zinc chloride (280mg, 2mmol) were heated to reflux in ether (8ml). Triphenylorthoformate (0.59g, 2mmol) was added *via* syringe pump over 24 hours and the mixture was then refluxed for a further 24 hours. The reaction was allowed to cool, and was quenched by the addition of saturated sodium bicarbonate (10ml). After stirring for 10 minutes, the mixture was filtered through celite, and transferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography to afford (2-phenoxycyclopropyl)methyl diethylmalonate **255c** as a clear oil (184mg, 0.60mmol, 30%, *cis* / *trans* 1 : 1.2)

IR (*cis* / *trans* 1:1.2, thin film / cm^{-1}): 3044(s), 1713(s), 1596(s), 1473(s), 1372(s), 1241(s), 1168(s), 1095(w), 1071(m), 1025(m), 887(m), 858(w), 812(m), 754(s), 692(s).

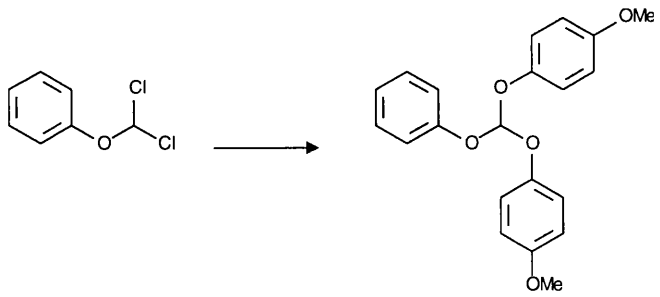


^{1}H NMR (*cis* and *trans*, 1:1.2 $CDCl_3$ / ppm): 7.31-6.80(5H, m, Ph), 4.25-4.17(4H, m, CO_2CH_2), 3.77(0.45H, td, J=6.4, 3.3, H1 *cis*), 3.60-3.51(1.55H, m, H1 *trans*), and $(EtO_2C)_2CH$), 2.26 and 2.22(1.2H, 2 x dd, AB pattern, J=13.8, 7.7 and J=13.8, 7.1, $(EtO_2C)_2CHCH_2$, *trans*), 2.06-1.96 and 1.75(0.8H, 2 x m, $(EtO_2C)_2CHCH_2$, *cis*), 1.28(6H, m, 2 x CH_3), 1.15(1H, m, H2), 1.01-0.92(1H, m, H3), 0.68(0.55H, q, J=6.2, H3β, *trans*), 0.58(0.45H, td, J=6.4, 3.1, H3α, *cis*).

^{13}C NMR (*cis* and *trans,* $CDCl_3$ / ppm): 170, 169, 155.5, 129.4, 121.1, 114.9, 61.8, 61.6, 56.2, 53.8, 52.2, 51.6, 30.6, 29.2, 26.5, 17.4, 15.3, 14.0, 13.2, 11.8.

Mass Spectrum: (FAB) calculated for $C_{17}H_{22}O_5$ (M^+):307.1545, found 307.1560.

Phenyl-di(4-methoxyphenyl)orthoformate 247



Sodium (0.70g, 30mmol) was carefully added to a solution of 4-methoxy phenol (3.70g, 30mmol) in dry dimethoxyethane (40ml). The solution was warmed to 50°C to aid dissolution of the sodium. The mixture was heated to reflux, and phenyldichloromethylether **244** (2.41g, 14mmol) was added dropwise. After 1 hour, the reaction was quenched by the addition of water (20ml). The aqueous layer was extracted with ether (3 x 100ml) and the combined organic extracts were washed with brine. The solution was dried over $MgSO_4$ and the solvent removed *in vacuo* to afford a brown oil, which solidified after 1 hour on a high vacuum line. The oil was recrystallized from ether, to afford the *title compound* **247** as white crystals (3.34g, 9.5mmol, 68%) mpt 94-96°C.

IR (thin film / cm^{-1}): 2889(w), 1591(w), 1504(s), 1455(m), 1376(w), 1303(w), 1246(s), 1203(s), 1084(s), 1028(s), 892(w), 826(m), 756(m), 692(w), 583(w), 518(w).

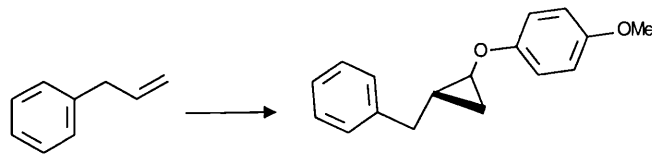
^1H NMR ($CDCl_3$ / ppm): 7.34-7.33(2H, m, Ph), 7.14-7.07(7H, m, aryl), 6.86(4H, d, J=8.1, aryl), 6.43(1H, s, $O_3C\mathbf{H}$), 3.79(6H, s, 2 x OMe).

^{13}C NMR ($CDCl_3$ / ppm): 155.9, 154.0, 129.6, 123.3, 119.9, 118.0,114.6, 112.1, 55.6.

Mass Spectrum: 229 (100%), 259 (40%), 351 (5% $(M-H)^+$).

Microanalysis: calculated for $C_{21}H_{20}O_5$ C71.58 H6.13; found C71.55 H5.73.

1-(4-Methoxyphenoxy)-2-benzylcyclopropane 248



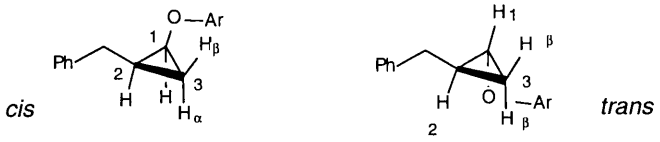
Zn/Hg amalgam (1.30g, 50mmol), chlorotrimethylsilane (1.0ml, 8mmol) and allylbenzene (0.90ml, 7mmol), were heated to reflux in ether (8ml). To this mixture, a solution of phenyl-di-(4-methoxyphenyl)-orthoformate **247** (220mg, 1.28mmol), in benzene (2ml) was added *via* syringe pump over 24 hours. The reaction was allowed to cool, and was quenched by the addition of saturated sodium bicarbonate (5ml). After stirring for 10 minutes, the mixture was filtered through celite, and transferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was washed with brine, dried over $MgSO_4$ and the solvent

removed *in vacuo*. The resulting oil was purified by flash chromatography to afford the *title compound* **248** as a mixture of diastereoisomers (68mg, 0.29mmol, 22%, *cis* / *trans* 1:2).

IR (mix of *cis* and *trans*, 1:2, thin film /cm^{-1}): 3052(s), 3038(s), 2994(s), 2929(s), 2849(m), 2054(w), 1950(w), 1727(w), 1600(m), 1503(s), 1449(s), 1387(w), 1352(w), 1292(w), 1232(s), 1149(m), 1107(m), 1037(s), 826(s), 734(s), 700(s).

***trans*-1-(4-Methoxyphenoxy)-2-benzylcyclopropane**

^1H NMR ($CDCl_3$ / ppm): 7.3-6.8(9H, m, aryl), 3.76(3H, s, OMe), 3.49(1H, m, partially obscured, C**H**OAr), 2.91(1H, dd, J=14.9, 6.6, PhC**H**), 2.77(1H, dd, J=14.9, 7.5, PhC**H**), 1.55 and 0.99(2H, 2 x m, cyclopropyl), 0.73(1H, q, J=6.1, H3β).



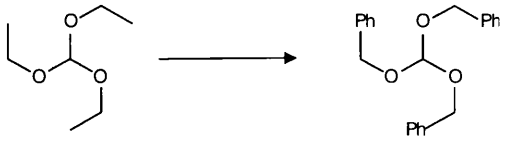
***cis*-1-(4-Methoxyphenoxy)-2-benzylcyclopropane**

^1H NMR ($CDCl_3$ / ppm): 7.3-6.8(9H, m, aryl), 3.82(3H, s, OMe), 3.50(1H, m, partially obscured, H1), 2.96(1H, dd, J=14.9, 6.6, PhC**H**), 2.67(1H, dd, obscured, PhC**H**), 2.0-1.80 and 0.99(2H, 2 x m, 2 x CH cyclopropyl), 0.58(1H, td, J=6.3, 3.3, H3α).

^{13}C NMR (mixture of *cis* and *trans*, $CDCl_3$ / ppm): 140.0, 128.5, 128.3, 126.2, 126.0, 115.6, 114.5, 56.7, 55.7, 44.3, 37.2, 22.8, 29.0, 22.6, 20.1, 13.3, 11.4.

Mass Spectrum: calculated for $C_{17}H_{18}O_2$ (M^+) 238.0994; found 259.0998.

Tribenzyl Orthoformate 249



A mixture of benzylalcohol (10ml, 0.10mol) and triethylorthoformate (16ml, 0.10mol) were heated to reflux for 4 hours, and the ethanol produced collected. ^1H NMR of the residue suggested that reaction with triethyl orthoformate was incomplete. A heat gun was used, in an attempt to drive over the remaining ethanol. Eventually, the crude residue was transferred to a Kugelrohr, where bulb to bulb distillation (100°C/1mmHg) produced the desired tribenzyl orthoformate **249** as a clear oil, which solidified when cooled to -20°C(3.2g, 9.6mmol, 9.6%).[240]

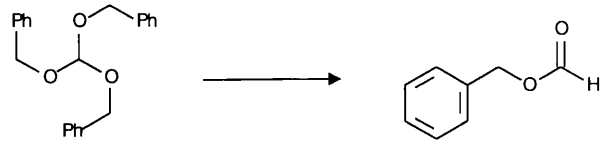
IR (Ithin film / cm^{-1}):3448(s), 3053(s), 3032(s), 2881(s), 1954(w), 1876(w), 1736(m), 1606(m), 1496(s), 1455(s), 1344(s), 1312(m), 1252(s), 1211(s), 1096(s), 907(m), 824(m), 737(s), 698(s), 608(m), 525(w), 462(m).

^1H NMR ($CDCl_3$ / ppm): 7.33(15H, m, aryl), 5.48(1H, s, O_3C**H**), 4.69(6H, s, OCH_2).

^{13}C NMR ($CDCl_3$ / ppm): 137.4, 128.4, 127.9, 127.7, 111.6, 66.3.

Microanalysis: calculated for $C_{22}H_{22}O_3$ C79.01 H6.63; found C78.78 H 6.68.

Benzylformate 250

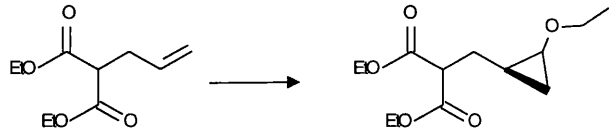


To a suspension of Zn/Hg (1.30g, 20mmol), $ZnCl_2$ (280mg, 1mmol) chlorotrimethylsilane (1.0ml, 7.9mmol) and allylbenzene (0.90ml, 8mmol) in ether (8ml) at reflux, a solution of tribenzylorthoformate **249** (0.67g, 2.0mmol) in ether (5ml) was added via syringe pump over 24 hours. The mixture was refluxed for 48 hours after which the reaction was allowed to cool, and was quenched by the addition of saturated sodium bicarbonate (5ml). After stirring for 10 minutes the mixture was filtered through celite and transferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was washed with brine (5ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography to afford the *title compound* **250** as a clear oil (82mg, 0.6mmol, 30%).[246]

^1H NMR ($CDCl_3$ / ppm): 8.13(1H, s, OC**H**O), 7.38-7.30(5H, m, Ph), 5.20(2H, s, PhC$\mathbf{H}_2$O).

^{13}C NMR ($CDCl_3$ / ppm): 160.7, 135.1, 128.5, 128.4, 128.2, 65.6.

Diethyl 2-((2-ethoxycyclopropyl)methyl) malonate 253



Zn/Hg amalgam (1.3g, 15mmol), chlorotrimethylsilane (1.0ml, 8mmol), diethylallylmalonate (1.6g, 8mmol) and zinc chloride (280mg, 2mmol) were heated to reflux in ether (8ml). Triethylorthoformate (0.34ml, 2mmol) was added *via* syringe pump over 12 hours, after which the mixture was refluxed for a further 8 hours. The reaction was allowed to cool, and was quenched by the addition of saturated sodium bicarbonate (10ml). After stirring for 10 minutes, the mixture was filtered through celite and transferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo.* The resulting oil was purified by flash chromatography to afford 2-((2-ethoxycyclopropyl)methyl)diethylmalonate **253** as a clear oil (116mg, 0.45mmol, 22%, *cis* / *trans* 3.5:1).

diethyl *cis*-2-((2-ethoxycyclopropyl)methyl) malonate

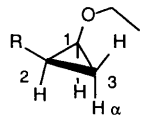
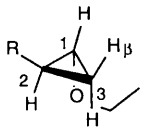
IR (thin film / cm^{-1}): 3076(m), 2979(s), 1734(s), 1447(s), 1371(s), 1336(s), 1278(s), 1237(s), 1158(s), 1064(s), 1028(s), 407(w).

^1H NMR ($CDCl_3$ / ppm): 4.19(4H, m, 2 x overlapping q, 2 x $CO_2C\mathbf{H}_2$), 3.50(2H, q, J=7.1, OC$\mathbf{H}_2$), 3.44(1H, t, J=7.6, (EtO_2C)C**H**),3.25(1H, td, J=6.4, 3.3, H1), 2.14 and 1.87(2H, 2 x m,

(EtO_2C)CH**C**H_2), 1.25(6H, m, 2 x Me), 1.14(3H, t, J=7.1, CH_2C**H**$_3$), 0.77(1H, m, H2), 0.62(1H, m, H3β), 0.22(1H, td, J=6.0, 3.1, H3α).

^{13}C NMR ($CDCl_3$ / ppm): 169.6, 169.4, 66.3, 61.2, 56.1, 52.3, 29.1, 26.4, 15.1, 14.0, 10.9.

Mass Spectrum: (FAB) calculated for $C_{13}H_{23}O_5$ (MH^+) 259.1545; found 259.1536.

cis   *trans*

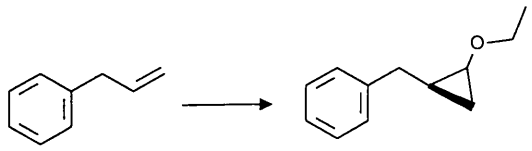
diethyl *trans*-2-((2-ethoxycyclopropyl)methyl) malonate

^{1}H NMR ($CDCl_3$ / ppm, mostly obscured): 4.19(4H, m, 2 x overlapping q, 2 x CO_2C**H**$_2$), 3.44(1H, t, J=7.6, (EtO_2C)C**H**), 3.02(1H, q, J=6.2, H1), 2.14 and 1.87(2H, 2 x m, (EtO_2C)CH**C**H_2), 1.25(6H, m, 2 x Me), 1.14(3H, t, J=7.1, CH_2C**H**$_3$), 0.77(1H, m, H2), 0.35(1H, m, H3α), 0.35(1H, q, J=6.2, H3β).

^{13}C NMR ($CDCl_3$ / ppm): 169.3, 65.8, 61.4,58.7, 51.8, 30.8, 26.4, 16.9, 14.0, 12.5.

Mass Spectrum: (FAB) calculated for $C_{13}H_{23}O_5$ (MH^+) 259.1545; found 259.1536.

2-Benzyl-1-ethoxycyclopropane 219b



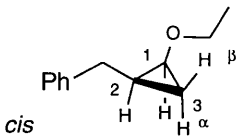
A suspension of Zn/Hg amalgam (1.3g, 19mmol), zinc chloride (560mg, 4mmol), allyl benzene (0.13ml, 1mmol), and chlorotrimethylsilane (2.0ml, 16mmol) were brought to reflux in ether (8ml). Triethyl orthoformate (0.36ml, 3.5mmol) was added dropwise. The mixture was refluxed for 24 hours, and was then allowed to cool. The reaction was quenched by the addition of saturated sodium bicarbonate (10ml). After stirring for 10 minutes, the mixture was filtered through celite and transferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography to afford 2-benzyl-1-ethoxycyclopropane **219b** (122mg, 0.69mmol, 69%, *cis* / *trans* 2:1).

***cis*-2-benzyl-1-ethoxycyclopropane**

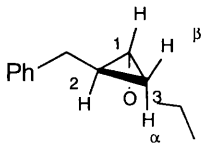
IR (thin film / cm^{-1}): 2967(s), 1726(w), 1660(w), 1603(w), 1447(m), 1379(w), 1344(w), 1280(s), 1100(s), 1022(s), 910(s), 805(s), 734(s), 699(m).

^{1}H NMR ($CDCl_3$ / ppm): 7.4-7.1(5H, m, Aromatic), 3.57(2H, q, J=7.0Hz, OC**H**$_2$CH$_3$), (3.35(1H, td, J=6.4, 3.4, H1), 2.92(1H, dd, J=14.9, 6.5, PhC**H**), and 2.66(1H, dd, J=14.9, 6.5, PhCH), 1.24(1H, dd, J=15.2, 7.9), 1.24(3H, t, J=7.0, CH_2C**H**$_3$), 1.3(1H, m, H2), 0.71(1H, m, H3β), 0.39(1H, td, J=5.9, 3.5, H3α).

^{13}C NMR ($CDCl_3$ / ppm): 142, 128.4, 125.7, 66.3, 56.5, 32.7, 30.3, 18.4, 15.2, 11.3.



cis



trans

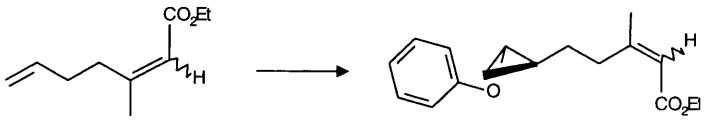
trans-2-benzyl-1-ethoxycyclopropane

IR (thin film / cm^{-1}): 2872(s), 1727(w), 1449(s), 1381(s), 1261(s), 1199(s), 1173(s), 1086(s), 1036(s), 911(s), 801(m), 734(s), 699(m).

^1H NMR ($CDCl_3$ / ppm): 7.3-7.2(5H, m, Aromatic), 3.46(2H, m, $OC\mathbf{H_2}CH_3$), 3.11(1H, dt, J=6.4, 2.5Hz, H1), 2.54(2H, 2xdd, AB system, J=14.7, 7.3 and 16.1, 8.4, $PhC\mathbf{H_2}$), 1.22(1H, m, H2), 1.15(3H, t, J=7.1, $CH_2C\mathbf{H_3}$), 0.81(1H,ddd, J=9.7, 5.7, 2.7, H3β), 0.43(1H, q, J=5.8, H3α).

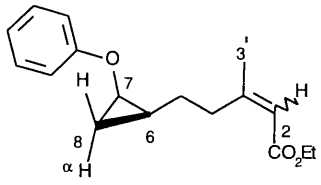
^{13}C NMR ($CDCl_3$ / ppm): 141.1, 128.3, 125.9, 65.8, 58.8, 37.3, 19.8, 15.0, 12.7.

5-(2-Phenoxycyclopropyl)-3-methyl-2-pentenoate Ethyl Ester 257

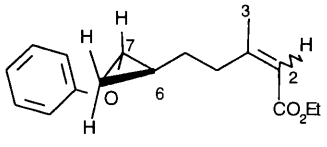


To a suspension of Zn/Hg amalgam (1.0g, 15mmol), chlorotrimethylsilane (0.70ml, 7.5mmol), zinc chloride (210mg, 1.5mmol) and ethyl 3-methyl-2,6-octadienoate (Z/E 2:1) **258** (0.50g, 3mmol) in ether (10ml) at reflux, triphenylorthoformate **246** (0.445g, 1.5mmol) in ether (2ml) was added over *via* syringe pump over 10 hours. The system was maintained at reflux for 18 hours and was then allowed to cool. The reaction was quenched by the addition of saturated sodium bicarbonate (10ml). After stirring for 10 minutes, the mixture was filtered through celite and transferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo.* The resulting oil was purified by flash chromatography to afford the *title compound* **257** as an inseparable mixture of diastereoisomers (140mg, 0.51mmol, 34%, *cis* / *trans* 1:1.2 both as a mixture of Z/E 2:1).

IR (thin film / cm^{-1}): 2982(s), 2934(s), 1713(s), 1649(s), 1597(s), 1491(s), 1450(s), 1375(m), 1242(s), 1159(s), 1041(s), 861(m), 811(w).



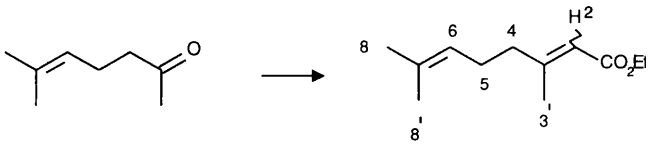
cis



trans

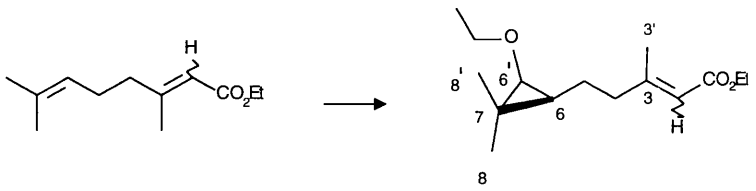
^{1}H NMR ($CDCl_3$ / ppm): 7.34-7.23(2H, m, Ph), 7.09-6.93(3H, m, Ph), 5.70(1H, m, H1), 4.16(2H, q, J=7.1, $CO_2C\mathbf{H}_2$), 3.76(0.45H, td, J=6.5, 3.1, H7 *cis*), 3.52(0.55H, m, H7 *trans*), 2.90-2.60(0.9H, m, H4 *cis*), 2.33-2.19(1.1H, m, H4 *trans*), 2.20, 2.16, 1.93 and 1.85(3H, 4 x d, J=1.3, Me3' *cis* and *trans* E and Z), 1.85-0.87(4H, m, H5 and H6 and H8 *cis* and *trans*), 0.69 and 0.63 (0.55H, 2 x q, 2:1, J=6.2, H8 *trans* Z and E), 0.48 and 0.42(0.45H, 2 x td, 1:2, H8α *cis* Z and E).
^{13}C NMR ($CDCl_3$ / ppm) 167.0, 166.2, 159.6, 159.0, 158.9, 129.3, 121.9, 120.9, 120.8, 116.4, 116.2, 115.9, 115.3, 114.9, 114.9, 114.8, 59.4, 56.5, 56.4, 54.3, 54.2, 40.8, 40.1, 39.9, 33.3, 32.6, 30.2, 29.5, 25.6, 25.4, 25.1, 25.0, 10.5, 19.0, 18.8, 18.7, 17.7, 17.1, 14.3, 13.2, 11.7, 11.6.
Mass Spectrum: (FAB) calculated for $C_{17}H_{23}O_3$ (MH^+) 275.1647; found 275.1660.

Ethyl 3,7-Dimethyl-2,6-octadienoate 258



To a suspension of sodium hydride (2.1g of a 60% dispersion in mineral oil, 53mmol) in tetrahydrofuran (160ml) at 0°C, triethylphosphonoactate (10.5ml, 53mmol) was added dropwise. Still at 0°C, a solution of 6-methylhept-5-ene-2-one (2.2g, 18mmol) in tetrahydrofuran (15ml) was added dropwise. The mixture was allowed to warm to room temperature, and stirring was continued for a further 4 hours, after which time the reaction was quenched by dropwise addition of water (10ml). The mixture was transferred to a separating funnel containing ether (200ml) and water (20ml). The layers were separated and the ethereal layer was washed with water (3 x 20ml), brine (10ml), dried over $MgSO_4$, and the solvent removed *in vacuo* to afford an oil which was purified by flash chromatography to afford the *title compound* **258** as a clear oil (1.01g, 5.1mmol, 29%, E/ Z 3:1).[236]
IR (thin film / cm^{-1}): 2975(s), 2928(s), 1716(s), 1645(s), 1649(s), 1446(s), 1649(s), 1446(s), 1378(s), 1322(m), 1221(s), 1146(s), 1105(m), 1061(s), 1038(s), 989(w), 861(m), 816(w), 735(w), 588(w).
^{1}H NMR ($CDCl_3$ / ppm): 5.67(1H, bs, H2 (E and Z), 5.09(1H, s, H6), 4.16(2H, q, J=7.2, $CO_2C\mathbf{H}_2$), 2.17(7H, m, Me3' and H4 and H5), 1.70 and 1.62(6H, 2 x s, Me8 and 8'), 1.29(3H, d, J=7.2, $CO_2CH_2C\mathbf{H}_3$).
^{13}C NMR ($CDCl_3$ / ppm) (Z isomer only) 166.9, 159.7, 132.5, 115.6, 75.0, 17.6, 14.3.
Mass Spectrum: (FAB): calculated for $C_{12}H_{21}O_2$ (MH^+) 197.1542, found 197.1530.

(2-Ethoxy-3,3-Dimethylcyclopropyl)-3-methyl-2-pentenoate ethyl ester 259a



To a suspension of Zn/Hg amalgam (2g, 30mmol), chlorotrimethylsilane (3.0ml, 23mmol) and ethyl 3,7-dimethyl-2,6-octadienoate (Z/E 3:1) **2** (0.39g, 2mmol) in ether (10ml) at reflux, triethylorthoformate (1.30ml, 8mmol) was added dropwise. The solution became cloudy, and after 5 minutes had turned a deep black colour. 30 minutes later the solution had become clear. The system was maintained at reflux overnight and was then allowed to cool. The reaction was quenched by the addition of saturated sodium bicarbonate (10ml). After stirring for 10 minutes, the mixture was filtered through celite and transferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography to afford E and Z 5-(2-ethoxy-3,3-dimethylcyclopropyl)-3-methyl-2pentenoate ethyl ester **259a** (221mg, 0.87mmol, 44%, *cis* / *trans* 2:1) as a clear oil.

***cis*-(E/Z)-5-(2-ethoxy-3,3-dimethylcyclopropyl)-3-methyl-2-pentenoate ethyl ester**

IR (thin film / cm^{-1}): 2978(s), 2940(s), 1716(s), 1648(s), 1449(m), 1377(m), 1350(m), 1321(m), 1274(m), 1222(s), 1147(s), 1047(m), 916(w), 860(m), 808(w), 734(m).

^1H NMR ($CDCl_3$ / ppm): 5.68 and 5.65(1H, 2 x s, H2 Z and E), 4.14(2H, q, J=7.1, $CO_2C\mathbf{H}_2CH_3$), 3.48(2H, q , J=6.8Hz, $OC\mathbf{H}_2CH_3$), 2.83(1H, d, J=6.9, H6'), 2.17(3H, s, Me3'), 1.8-1.4(4H, m, H4, H5), 1.28(3H, t, J=7.2, $CO_2CH_2C\mathbf{H}_3$), 1.18(3H, t, J=7.1Hz, $OCH_2C\mathbf{H}_3$), 1.02 and 1.04(3H, 2 x s (1:3), Me8, E / Z) 0.97 and 0.98(3H, 2 x s, 3:1, Me8', E / Z), 0.49(0.3H, q, J=6.9, H6 E), 0.39(0.67H, q, J=6.9, H6 Z).

^{13}C NMR ($CDCl_3$ / ppm): 166.90, 160.29, 116.00, (66.41), 64.19, (59.38), (41.23), (33.46), 26.53, 26.34, (21.06), 18.81, 17.93, 15.16, 14.29, 13.37.

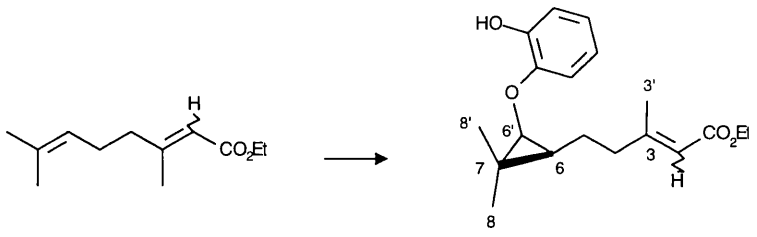
Mass Spectrum: (FAB) calculated for $C_{15}H_{27}O_3$ (MH^+) 255.1960, found 255.1940.

Microanalysis: calculated for $C_{15}H_{26}O_3$ C70.84 H10.31; found C70.85 H10.52.

***trans*-E/Z)-5-(2-ethoxy-3,3-dimethylcyclopropyl)-3-methyl-2-pentenoate ethyl ester** (mostly obscured)

2.68 and 2.64(1H, 2 xd, 1 :3, J=3.2, H6' E / Z), 0.57 and 0.39(1H, 2 x td, 1:3, J=7.4, 3.2, H6 E/Z).

5-((2-Hydroxyphenoxy)-3,3-dimethylcyclopropyl)-3-methyl-2-pentenoate ethyl ester 259b



To a suspension of Zn/Hg amalgam (1.5g, 22mmol), chlorotrimethylsilane (2.0ml, 15mmol) and Z-ethyl 3,7-dimethyl-2,6-octadienoate **258** (0.20g, 1mmol) in ether (10ml) at reflux, ethylcatecholorthoformate (0.50ml, 3.5mmol) was added dropwise. The system was maintained at reflux overnight and was then allowed to cool. The reaction was quenched by the addition of saturated sodium bicarbonate (10ml). After stirring for 10 minutes, the mixture was filtered through celite and transferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo.* The resulting oil was purified by flash chromatography to afford Z 5-(2-((2-hydroxyphenyl)-3,3-dimethylcyclopropyl)-3-methyl-2-pentenoate ethyl ester **259b** (53mg, 0.17mmol, 17%, *cis* / *trans* 4:1) as a clear oil.

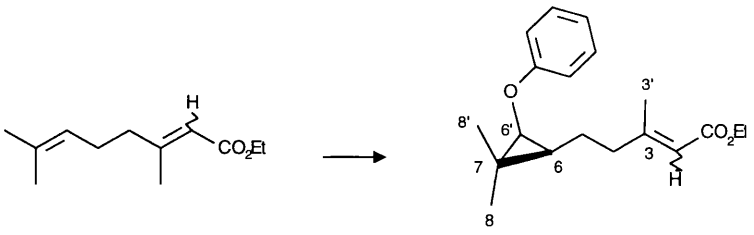
IR (thin film / cm^{-1}): 3436(w), 2945(s), 1712(s), 1647(s), 1599(m), 1499(s), 1372(s), 1259(s), 1220(s), 1149(s), 1036(s), 913(w), 866(m), 791(w), 744(s).

^1H NMR ($CDCl_3$ / ppm): 7.0-6.8(4H, m, aryl), 5.75 (1H, m, H2) 5.60 and 5.50(1H, 2 x bs, 1:4, *trans* and *cis* , O**H**), 4.16(2H, q, J=7.0, $CO_2CH_2CH_3$), 3.4(0.8H, d,J=7.0, H6' *cis),* 3.2(0.2H, d, J=2.7, H6' *trans*), 2.3-2.1(5H, m, Me3' and H4), 1.8-1.4(2H, m, H5), 1.3(3H, t, J=7.2, $CO_2CH_2CH_3$), 1.2 and 1.0(6H, 2 x s, Me8 and 8'), 0.96-0.80 (0.2H, m, H6 *trans*), 0.77(0.8H, q, J=7.0, H6 *cis*).

^{13}C NMR ($CDCl_3$ / ppm): 166.8, 159.4, 145.8, 145.2, 121.6, 120.2, 116.2, 115.9, 114.6, 112.2, 62.5, (59.6), (40.9), 26.4, 25.8, (21.1), 18.8, 14.3, 13.3.

Mass Spectrum: (FAB) calculated for $C_{19}H_{27}O_4$ (MH^+) 319.1909; found 319.1930.

5-(2-phenoxy-3,3-dimethylcyclopropyl)-3-methyl-2-pentenoate ethyl ester 259c



To a suspension of Zn/Hg amalgam (1.5g, 22mmol), chlorotrimethylsilane (2.0ml, 15mmol) and ethyl 3,7-dimethyl-2,6-octadienoate (Z/E 3:1) **258** (0.20g, 0.87mmol) in ether (10ml) at reflux, triphenylorthoformate **246** (0.91g, 3.1mmol) in ether (2ml) was added dropwise. The system was maintained at reflux for 4 days and was then allowed to cool. The reaction was quenched by the addition of saturated sodium bicarbonate (10ml). After stirring for 10 minutes, the mixture was filtered through celite, and transferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was washed with brine, dried over $MgSO_4$ and the slovent removed *in vacuo*. The resulting oil was purified by flash chromatography to afford the *title compound* **259c** as mixture of diastereoismoers (31mg, 0.10mmol, 12% *cis* / *trans* 4:1, E/Z 3:1), plus a number of unidentified other compounds. Repeated flash chromatography afforded a pure fraction of the major product, *cis*-Z-5-(2-phenoxy-3,3-dimethylcyclopropyl)-3-methyl-2-pentenoate ethyl ester (20mg, 0.066mmol, 7.6%).

***cis*-Z-5-(2-phenoxy-3,3-dimethylcyclopropyl)-3-methyl-2-pentenoate ethyl ester**

IR (*cis* / *trans* 3:1, thin film / cm^{-1}): 2942(s), 1926(w), 1713(s), 1648(s), 1596(s), 1491(s), 1376(m), 1226(s), 1147(s), 1095(m), 1033(m), 863(w), 754(s), 691(w).

^1H NMR ($CDCl_3$ / ppm) : 7.30-7.26(2H, m, Ph), 6.47-6.42(3H, m, Ph), 5.67(1H, bs H2), 4.21(2H, q, J= 7.2, $CO_2C\mathbf{H}_2CH_3$), 3.33(1H, d, J=7.0, H6'), 2.3-2.1(2H, m, H4), 2.18(3H, s, Me3'), 1.6(2H, m, H5), (1.29(3H, t, J=7.0, $CO_2CH_2C\mathbf{H}_3$), 1.15 and 0.87(6H, 2 x s, Me8 and 8'), 0.71(1H, q, J=7.08, H6).

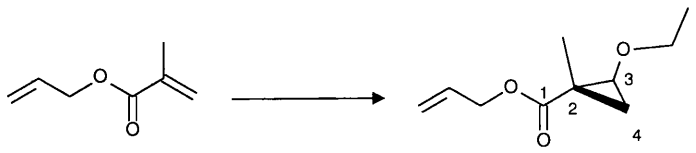
^{13}C NMR ($CDCl_3$ / ppm): 166.9, 160.0, 129.3, 120.7, 115.7, 114.5, 61.6, 59.4, 41.0, 26.4, 25.8, 21.3,18.8, 14.3,13.5.

Mass Spec (FAB): 304(13%, MD^+), 286(13%), 257(30%), 241(52%), 206(63%), 127(100%).

***trans*-(Z/E)-5-(2-phenoxy-3,3-dimethylcyclopropyl)-3-methyl-2-pentenoate ethyl ester (Z/E 3:1):**

^1H NMR ($CDCl_3$ / ppm): 7.30-7.26(2H, m, Ph), 6.47-6.42(3H, m, Phl), 5.67(1H, bs, H2, E/Z), 4.21(2H, q, J= 7.2Hz, $CO_2C\mathbf{H}_2CH_3$), 3.15 and 3.13(1H, 2 x d,1:3, J= 3.1, H6', E/Z), 2.3-2.1(2H, m, H4), 2.19(3H,s, Me3'), 1.6(2H, m, H5), 1.29(3H, t, J=7.0, $CO_2CH_2C\mathbf{H}_3$), 1.19(3H, s, Me8') 1.08 and 1.07(3H, 2 x s, 1:3, Me8 E / Z), 0.8(1H, m, obscured H6).

Allyl (2-ethoxy-1-methylcyclopropyl)carboxylate 261



Zn/Hg (2g, 30mmol), chlorotrimethylsilane (2.0ml, 16mmol) and allyl methacrylate (1.08ml, 8mmol) were heated to reflux in ether (10ml). To this mixture, a solution of triethylorthoformate (0.33g, 3mmol), in ether (2ml) was added *via* syringe pump over 8 hours. After refluxing for a further 24 hours the reaction was allowed to cool and was quenched by the addition of saturated sodium bicarbonate (10ml). After stirring for 10 minutes, the mixture was filtered through celite, and transferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography to afford the *title compound* **261** as a clear oil (42mg, 0.23mmol 12%, one isomer only by GC) and 2,2-dimethyl-4-penteneoic acid (64mg, 0.38mmol, 46% relative to allyl methacrylate).[244]

allyl (2-ethoxy-1-methylcyclopropyl)carboxylate 261

IR (thin film / cm^{-1}): 2978(s), 2938(m), 2879(m), 1721(s), 1648(w), 1457(s), 1378(m), 1349(m), 1349(m), 1305(m), 1277(s), 1155(s), 1056(s), 1024(s), 989(w), 843(m), 806(w), 776(w), 728(w), 631(w).

^1H NMR ($CDCl_3$ / ppm): 5.95-5.85(1H, m, C**H**=CH_2), 5.32-5.20(2H, m, CH=C**H**$_2$), 4.56(2H, d, J=5.5, $CO_2C\mathbf{H}_2$), 3.64-3.49(3H, m, H3), 1.45(1H, td, J=5.5, 1.4, H4), 1.35(3H, s, Me2'), 1.21(3H, t, J=7.0, $OCH_2C\mathbf{H}_3$), 0.85(1H, dd, J=5.5, 4.5, H4).

^{13}C NMR (CDCl3 / ppm): 174.2, 132.3, 117.6, 66.9, 65.1, 24.5, 22.0, 15.0, 12.2.

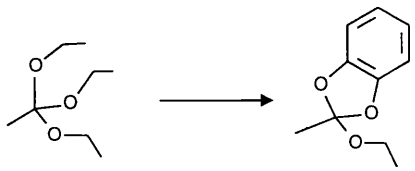
Mass Spectrum: 184 (15% M^+).

2,2-dimethyl-4-penteneoic acid IR (thin film / cm^{-1}): 3074(s), 2979(s), 2921(s), 1780(w), 1700(s), 1643(m), 1474(s), 1409(m), 1367(m), 1318(m), 1237(s), 1180(s), 1041(m), 919(s), 861(m), 789(w), 645(w), 579(w), 543(w).

^1H NMR ($CDCl_3$ / ppm): 5.83-5.72(1H, m, C**H**=CH_2), 5.10(2H, m, CH=C**H**$_2$), 2.30(2H, d, J=7.4, C**H**$_2$), 1.20(6H, s, 2 x Me).

^{13}C NMR (CDCl3 / ppm): 184.4, 133.9, 118.3, 44.4, 42.2, 24.6.

Ethyl(catechol)orthoacetate 265



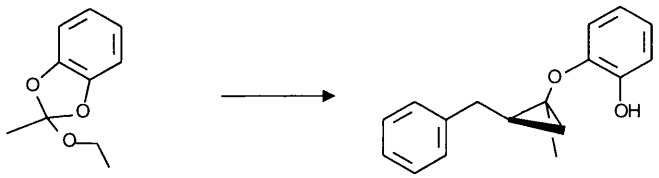
Catechol (5.0g, 45mmol), triethylorthoacetate (22.0ml, 135mmol) and one drop of 1M HCl in dioxane were heated at 110°C for 3 hours. After leaving to stand overnight the mixture was heated to reflux with a heat gun to distill off all the remaining ethanol. The residue from this process was transferrred to a Kugelrohr and bulb to bulb distillation (125°C/0.3mmHg), afforded the *title compound* **265** as a clear oil (4.8g, 0.027mol, 59%).[247]

IR (thin film / cm^{-1}): 2998(m), 2892(s), 2811(m), 1714(s), 1545(w), 1453(s), 1409(s), 1365(s), 1289(s), 1262(s), 1240(s), 1109(s), 1028(s), 908(m), 799(w), 733(s), 701(s).

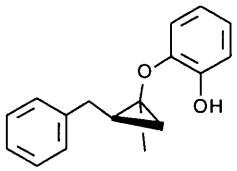
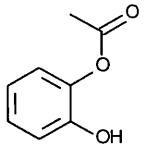
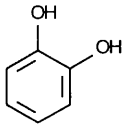
^1H NMR ($CDCl_3$ / ppm): 6.83(4H, m, catechol), 3.59(2H, q, J=7.1, OCH_2), 1.82(3H, s, Me), 1.21(3H, t, J=7.1, OCH_2CH_3).

^{13}C NMR ($CDCl_3$ / ppm): 146.5, 127.4, 121.2, 107.8, 57.9, 24.5, 14.8.

2-Benzyl-1-methyl-1-(2-hydroxyphenoxy)cyclopropane 266



To a suspension of Zn/Hg amalgam (1.3g, 15mmol), trimethylsilane elctrophile (14mmol, 4.7 equivalents) and allylbenzene (0.50ml, 3.7mmol) in diethyl ether (8ml) at reflux, ethyl catecholorthoacetate **265** 0.54g, 3mmol) was added dropwise. After 24 hours at reflux, the reaction was allowed to cool and was quenched by the addition of saturated sodium bicarbonate (10ml). After stirring for 10 minutes, the mixture was filtered through celite, and transferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo.* The resulting oil was purified by flash chromatography to afford 2-benzyl-1-methyl-1-(2-hydroxyphenoxy)-cyclopropane **266** catechol acetate **267** and catechol **268** (see table):

No	electrophile	Products (%)§		
				
1	Me_3SiCl	0	39	16
2	Me_3SiOTf	6 (1 : 2)*	4	49

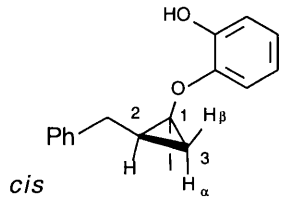
§relative to orthoester
* *cis / trans*

***trans*--2-benzyl-1-methyl-1-(2-hydroxyphenoxy)cyclopropane**

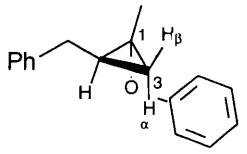
IR (thin film / cm^{-1}): 3543(s), 3064(m), 3028(m), 2975(m), 2931(m), 1599(m), 1494(s), 1452(m), 1416(m), 1376(m), 1257(s), 1218(s), 1142(s), 1104(m), 1033(m), 962(m), 930(m), 853(w), 776(w), 739(s), 695(m), 608(w).

^1H NMR ($CDCl_3$ / ppm): 7.50-7.20(5H, m, Ph), 7.0-6.8(4H, m, catechol), 5.51(1H, s, O**H**), 2.95 and 2.81(2H, 2 x dd, AB pattern, J=15.3, 7.2 and 15.3, 7.4, PhC$\mathbf{H}_2$), 1.60(3H, s, Me), 1.39(1H, dd, J=9.2, 7.0, H2), 1.06(1H, dd, J=9.3, 5.9, H3), 0.87(1H, t, J=6.0, H3).

^{13}C NMR ($CDCl_3$ / ppm): 147, 129.0, 128.5, 128.1, 126.5, 126.0, 121.4, 119.8, 114.7, 114.0, 60.1, 34.3, 25.2, 21.3, 19.4.



cis



trans

***cis*-2-benzyl-1-methyl-1-(2-hydroxyphenoxy)cyclopropane**

IR (thin film / cm^{-1}): 3534(m), 3062(m), 3029(m), 2973(m), 2931(m), 1710(m), 1599(m), 1491(s), 1415(w), 1365(m), 1234(s), 1149(m), 1104(m), 1034(m), 1006(w), 957(w), 910(s), 735(s), 702(m), 648(w), 613(w).

^1H NMR ($CDCl_3$ / ppm): 7.5-7.2(5H, m, Ph), 7.0-6.7(4H, m, catechol), 5.56(1H, s, O**H**), 2.86 and 2.69(2H, 2 x dd, AB pattern, J=15.0, 7.1 and 15.0, 7.8, PhC$\mathbf{H}_2$), 1.62(3H, s, Me), 1.30(2H, m, H2), 1.06(1H, m, H3), 0.59(1H, t, J=6.3, H3).

^{13}C NMR ($CDCl_3$ / ppm): 147, 128.5,128.3, 126.2, 121.2, 119.7, 114.6, 113.7, 60.1, 35.6, 25.1, 19.4, 16.3.

Mass Spectrum: (FAB) calculated for $C_{17}H_{19}O_2$ (MH^+) 255.1385, found 255.1378.

Catechol[249]

^1H NMR ($CDCl_3$ / ppm): 6.9-6.8(4H, m, aryl), 5.25(2H, bs, 2xO**H**).

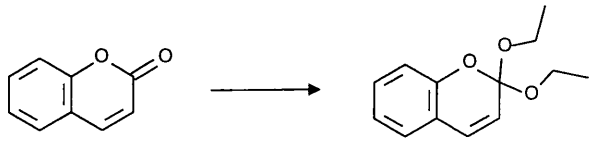
Catechol acetate[248]

^{1}H NMR ($CDCl_3$ / ppm): 7.27-7.11(2H, m, aryl), 7.09-6.88(2H, m, aryl), 5.53(2H, s, OH), 2.36(3H, s, CH3).

^{13}C NMR ($CDCl_3$ / ppm): 127.1, 121.2, 117.7, 20.94.

Mass spectrum: calculated for $C_8H_7O_2$ (M-OH) 135.0446; $C_8H_7O_2$ 135.0455.

Coumarin Diethylacetal 273



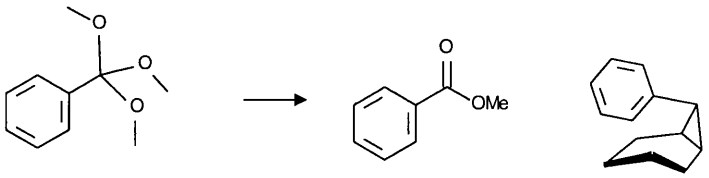
Coumarin (1.46g, 10mmol) was dissolved in dichloromethane (20ml). Triethyloxonium tetrafluoroborate (Meerwein's salt, 1.90g, 10mmol) was added and the mixture was stirred at room temperature for 24 hours. Addition of diethyl ether caused the salt to precipitate out. The solvent was removed using a filter tipped canula, and the salt was washed with dry diethyl ether (3 x 10ml) still under an atmosphere of nitrogen. The residue was dried with a stream of nitrogen, and then dissolved in a minimum of dichloromethane (15ml). The solution was added *via* canula to a solution of sodium ethoxide (0.25g of sodium) in freshly dried ethanol (10ml) at 0°C. The reaction was allowed to warm to room temperature and was stirred for 3 hours. After this time it was quenched by the addition of water (1ml), dried over potassium carbonate and the solvent removed *in vacuo* to afford the *title compound* **273** as a clear oil (0.62g, 3mmol, 30%).[245]

IR (thin film / cm^{-1}): 2979(s), 2932(s), 1647(s), 1607(m), 1489(m), 1458(m), 1397(w), 1257(s), 1204(s), 1168(s), 1121(s), 1083(s), 1035(s), 996(s), 840(m), 779(w), 750(m).

^{1}H NMR ($CDCl_3$ / ppm): 7.20-7.16(3H, m, aryl), 7.02-6.97(1H, m, aryl), 6.85(1H, d, J=9.8, C**H**=CH), 5.74(1H, d, J=9.6, CH=C**H**), 3.70(2H, q, O**CH$_2$**), 1.23(6H, t, J=7.0, **CH$_3$**).

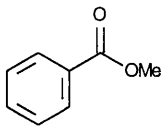
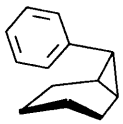
^{13}C NMR ($CDCl_3$ / ppm): 152.6, 129.5, 129.1, 121.3, 120.4, 118.9, 115.7, 112.6, 58.6, 15.2.

Attempted alkoxycyclopropanation with trimethyl orthobenzoate

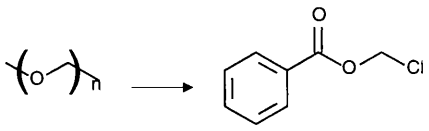


Trimethyl orthobenzoate (0.36g, 2mmol) in ether (2ml) was added *via* syringe pump over 18 hours to a mixture of Zn/Hg amalgam (1.3g, 15mmol), trimethylsilyl electrophile (10mmol, 5 equivalents) and cyclohexene (0.90ml, 8mmol) in ether (6ml). After an additional 6 hours at reflux the reaction was allowed to cool and was quenched by the addition of saturated sodium

bicarbonate (10ml). After stirring for 10 minutes, the mixture was filtered through celite and transferred to a separating funnel containing ether (50ml). The layers were separated and the ethereal layer was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting oil was purified by flash chromatography to afford 7-phenylnorcarane **189** and methyl benzoate **275** (see table), spectroscopically identical to material already prepared.

No.	Lewis ac. (equiv)	Electrophile	Solvent (temp)		
1	$ZnCl_2$ (1)	Me_3SiCl	Et_2O (r.t.)	45	6
2	$ZnCl_2$ (1)	Me_3SiCl	Et_2O (reflux)	63	8
3	-	Me_3SiOTf	Et_2O (reflux)	56	5
4	-	Me_3SiCl	EtOAc (r.t.)	48	6

Synthesis of Chloromethylbenzoate 301



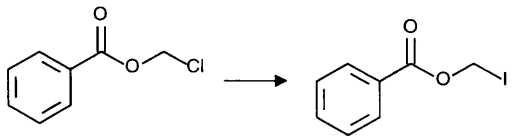
To a flame dried flask containing a few millligrams of fused zinc chloride, benzoyl chloride (24.9ml, 0.21mol) and paraformaldehyde (6.42g, 0.21mol) were added. Heat was evolved and the temperature was maintained at 100°C for 2 hours during which time the suspension cleared. The compound was purified by bulb to bulb distillation (59-60°C, 0.4mmHg) to afford the *title compound* as a clear oil (14.10g, 0.083mol, 39%).[228]

IR (thin / film cm^{-1}): 3471, 3067, 2987, 2069, 1973, 1914, 1741, 1596, 1489, 1446, 1342, 1315, 1257, 1204, 1176, 1086, 1027, 990, 936, 873, 776, 721, 675;

^1H NMR, ($CDCl_3$ / ppm): 8.14-8.06(2H, m, Ph), 7.62-7.47(3H, m, Ph), 5.96(2H, s, OC**H**$_2$Cl).

Microanalysis: calculated for $C_8H_7ClO_2$ C56.34 H 4.10; found C56.43 H 3.83.

Synthesis of Iodomethyl benzoate 295



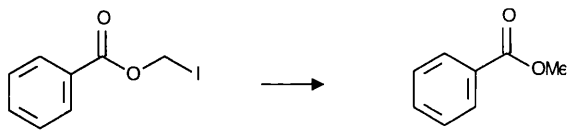
Sodium iodide (7.4g, 0.049mol) and chloromethylbenzoate **301** (7g, 0.04mol) were stirred at room temperature in acetone (40ml) for 4.5 hours. The precipitate was filtered and the acetone removed *in vacuo*. The oily residue was taken up in ether (30ml) and transferred to a separating funnel. On shaking with 1M sodium thiosulfate (20ml), the deep orange colour disappeared. After a second thiosulfate wash (10ml), the ether was washed with brine (10ml). The solution was dried over $MgSO_4$, and the solvent removed *in vacuo* to afford a clear oil. On addition of petrol, crystallization occured. After cooling for several days at -20°C, the petrol was decanted, and the solid washed with 2 further portions of petrol. The compound was dried under vacuum at -20°C to afford the *title compound* **295** as pale yellow crystals (4.40g, 0.017mol, 43%), mpt 30°C.[228]

IR (thin film / cm^{-1}); 3067, 3015, 1691, 1604, 1454, 1425, 1327, 1294, 1182, 1126, 1077, 935, 807, 708, 667.

^1H NMR ($CDCl_3$ / ppm). 8.15-8.04(2H, m, Ph), 7.63-7.44(3H, m, Ph), 76.18(s, 2H, OC**H**$_2$I).

Mass Spectrum (FAB): calculated for $C_8H_8IO_2$ (M+H) 262.9569; found 262.9560.

Synthesis of Methylbenzoate 275 from Iodomethylbenzoate 295

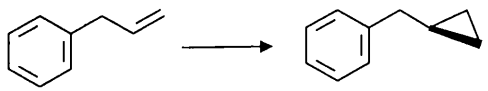


Zn-Cu couple (1.1g, 18mmol), and iodomethyl benzoate (140mg, 0.53mmol) were stirred at reflux in ether. A single crystal of iodine was added and the mixture was refluxed for 3 hours. After this time, the reaction was quenched by addition of saturated ammonium chloride solution (2ml). The mixture was filtered through celite and transferred to a separating funnel containing ether (50ml). The layers were separated, and the ether layer was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo* to afford a clear oil (60mg), which proved to be pure methylbenzoate **275** (50mg, 0.36mmol, 83%).[221]

IR (thin film / cm^{-1}): 2953(w), 2255(w), 1723(s), 1430(m), 1316(m), 1280(s), 1177(m), 1111(s), 1071(w), 1027(w), 967(w), 912(m), 823(w), 736(s), 711(s).

^1H NMR ($CDCl_3$ / ppm). 8.07(2H, d, J=7.6, H2,6), 7.56(1H, t, J=7.6, H4), 7.45(2H, t, J=7.6, H3,5), 6.68(3H, s, OMe).

Benzyl Cyclopropane 303



To freshly prepared Zn-Cu couple (1.04g, 16mmol), dry dichloroethane (8ml), allyl benzene (0.53ml, 4mmol) and methylene iodide (1.3ml, 16mmol) were added. The mixture was sonicated for 6 hours before pouring into a separating funnel containing ether (100ml) and saturated sodium bicarbonate. After separating, the ethereal layer was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo* to afford a brown oil. This was partially purified by flash chromatography to afford the *title compound* **303** mixed with allylbenzene (326mg, approximately 1:2.4 by NMR, 1:2.1 by GC). Yield based on ^1H NMR (1.07mmol, 27%).

^1HNMR ($CDCl_3$ / ppm): 7.23-7.17(5H, m, Ph), 2.53(2H, d, J=7.0, CH_2Ph), 1.01-0.91(1H, m, $PhCH_2CH$), 0.50 and 0.19(2H, 2 x m, cyclopropyl CH_2).[230]

^{13}C NMR ($CDCl_3$ / ppm): 142.1, 125.8, 128.3, 40.4, 11.9, 4.7.[231]

Cyclopropanation of Allylbenzene using Iodomethylbenzoate 295

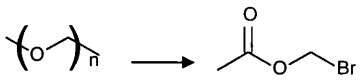
Standard procedure: To a refluxing suspension of activated zinc (1g, 13mmol) and allylbenzene (0.50ml, 5mmol) in ether (5ml), a solution of iodomethylbenzoate **295** (262mg, 1mmol) in ether (1ml) was added, quickly followed by the appropriate additive§ (see table **x**). The reaction was refluxed for 24 hours, and the results examined by GC analysis. The reaction was then quenched by the addition of saturated sodium bicarbonate (5ml) and after 5 minutes, the mixture was filtered through celite, washing with ether (20ml). The layers were separated and the ethereal layer was washed with water (5ml), dried over $MgSO_4$ and the solvent removed *in vacuo* (bath temperature 0°C).

No.	Zinc source	Equiv **295**	Solvent (reflux)	Additives (equiv)	Yield* (%)
1	Zn (on TiO_2)	0.2	Et_2O	Me_3SiCl (4)	15
2	Zn-Cu	0.2	Et_2O (((((	Me_3SiCl (3)	6
3	Zn-Cu	0.2	Et_2O	Me_3SiCl (3)	10
4	Zn/Hg	0.2	Et_2O	Me_3SiCl (3)	7
5	Zn/Cu	0.2	Et_2O	ZnI_2 (1)	1
6	Zn-Cu	0.2	Et_2O	$ZnBr_2$ (1)	0
7	Zn-Cu	0.2	Et_2O	$ZnCl_2$ (1)	2
8	Zn-Cu	0.2	Et_2O	CuI (1)	1
9	Zn-Cu	0.2	Et_2O	I_2 (0.1)	3

* by comparison with GC standard, relative to **295**

§ halide salts were added with the zinc and flame dried

Bromomethylacetate 304



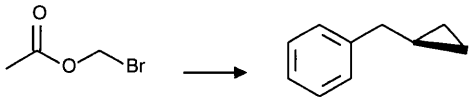
To a flame dried flask containing a few millligrams of fused zinc chloride, acetyl bromide (6.0ml, 80mmol) and paraformaldehyde (2.4g, 80mmol) were added. Heat was evolved and the temperature was maintained at 50°C for 2.5 hours during which time the suspension cleared.

The compound was purified by bulb to bulb distillation (70°C, 1mmHg) to afford the *title compound* **304** as a clear oil (7.9g, 52mmol, 65%).[229]

^{1}H NMR ($CDCl_3$ / ppm): 5.75(2H, s, $OC\mathbf{H}_2Br$), 2.09(3H, s, $C\mathbf{H}_3$).

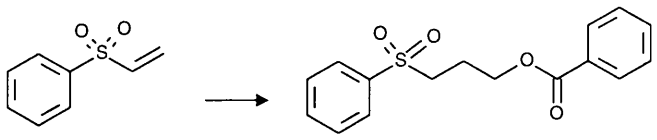
^{13}C NMR ($CDCl_3$ / ppm): 168.0, 59.6, 20.0.

Cyclopropanation of Allylbenzene using Bromomethylacetate 303



To a refluxing suspension of zinc-copper couple (12g, 26mmol) chlorotrimethylsilane (1.0ml,10mmol) and allylbenzene (0.90ml, 8mmol) in ether (5ml), a solution of bromomethylacetate **304**(0.50ml, 5.1mmol) was added. The reaction was refluxed for 24 hours, and the results examined by GC analysis. After 2 hours, GC showed formation of the cyclopropane **303** in approximately 4% relative to the alkene. After a further 48 hours, the yield had risen to about 5%.

Phenyl-(3-benzoyloxypropyl) sulfone 305



Standard procedure: Freshly prepared Zn-Cu couple (1g, 13mmol) phenyl vinylsulfone (0.55g, 3.3mmol) and allylbenzene (1.0g, 16mmol) were heated to reflux in ether (5ml). To this mixture, a solution of iodomethylbenzoate **305** in ether (1ml), was added in one portion. The mixture was refluxed for 24 hours, before allowing to cool. The products were filtered through celite, and transferred to a separating funnel containing brine (5ml) and ether (50ml). The layers were separated the ether layer was dried over $MgSO_4$, and the solvent removed *in vacuo* to afford an oil. The oil was purified by flash chromatography to afford the *title compound* **305** as a clear oil.

IR (thin film / cm^{-1}): 3063(s), 2924(m), 2853(m), 1718(s), 1692(m), 1585(m), 1448(s), 1404(w), 1382(w), 1316(s), 1375(s), 1175(m), 1149(s), 1115(s), 1087(s), 1071(s), 1026(m), 995(w), 891(w), 788(w), 712 (w), 688(s).

^{1}H NMR ($CDCl_3$ / ppm): 7.96-7.90(5H, m, aryl), 7.65(1H, t, J=7.7, aryl), 7.58(2H, m, aryl), 7.42(2H, t, J=7.7, aryl), 4.36(2H, t, J=6.3, $C\mathbf{H}_2OCO$), 3.24(2H, m, $S(O)_2C\mathbf{H}_2$), 2.23-3.16(2H, m, $CH_2C\mathbf{H}_2CH_2$).

^{13}C NMR ($CDCl_3$ / ppm): 166.2, 138.8, 133.9, 129.6, 129.4, 128.4, 128.1, 62.5, 53.2, 29.7.

Mass spectrum: (FAB) calculated for $C_{16}H_{17}O_4S$ (M^+) 305.0848; found 305.0840.

No.	Equiv **295**‡	Solvent (reflux)	Additives (equiv)	Yield* **305**
1	0.3	Et_2O	ZnI_2 (1)	18§
2	0.3	Et_2O	I_2 (0.1)	4
3	0.2	Et_2O	Me_3SiCl (4)	0
4	0.8	Et_2O	$ZnCl_2$ (1)	4

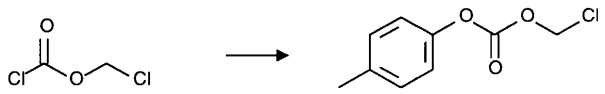
‡ relative to phenylvinyl sulfone

* relative to iodomethyl benzoate

§ 62% of methylbenzoate isolated

table 23

Chloromethyltolylcarbonate 314

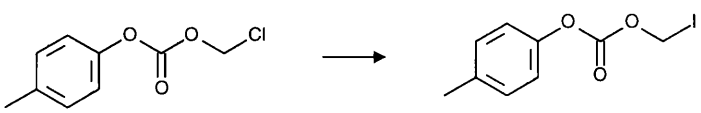


A solution of p-cresol (2.9g, 26mmol) and pyridine (3.4ml) in dichloromethane (45ml) was cooled to 0°C. To this, a solution of chloromethyl chloroformate (3.45g, 15mmol) in dichloromethane (7ml) was added dropwise. After 2 hours, the reaction was transferred to a separating funnel containing dichloromethane (100ml). The solution was washed with 1M HCl (10ml), water (10ml), 1M NaOH (10ml) and brine (10ml). After drying over $MgSO_4$, the solvent was removed *in vacuo* to afford a clear oil which crystallized on standing to afford the *title compound* **315** as large crystals (3.9g, 0.019mmol, 75%) mpt 39-41°C.[232]

IR (thin film / cm^{-1}): 1508(s), 1443(s), 1345(s), 1236(s), 1207(s), 1072(s).

^1H NMR ($CDCl_3$ / ppm): 7.18(2H, d, J=8.5, aryl), 7.06(2H, d, J=8.5, aryl), 5.80(2H, s, CH_2), 2.34(3H, s, $ArCH_3$).

Iodomethyltolyl carbonate 315



Sodium iodide (4.0g, 38 mol) and chloromethyltolyl carbonate **314** (3.90g, 25mmol) were stirred for 24 hours in freshly dried acetone (50ml). The mixture was filtered and most of the acetone was removed *in vacuo.* The resulting brown oil was transferred to a separating funnel with ether (150ml). The ether was washed with 1M sodium thiosulfate (2 x 30ml), water (30ml)

and brine (20ml) before drying over $MgSO_4$. The solvent was removed *in vacuo* to leave a pale yellow oil, which solidified in the freezer to afford **315** as a buff solid (3.88g, 15.7mmol, 61%). On warming to room temperature, the solid melted, and rapidly turned a yellow brown. The compound was stable if stored in the freezer.

IR (thin film / cm^{-1}):1597(s), 1506(s), 1426(s), 1281(s), 1202(s), 1058(s), 1018(s), 960(s), 812(s).

^1H NMR, ($CDCl_3$ / ppm): 7.19(2H, d, J=8.5, aryl), 7.08(2H, d, J=8.5, aryl), 6.04(2H, s, CH_2), 2.364(3H, s, $ArCH_3$).

^{13}C NMR (ppm / $CDCl_3$): 151.9, 148.6, 136.2, 130.0, 20.6, 120.4, 33.78, 20.5.

Mass spectrum: (FAB) calculated for $C_9H_9O_3I$ (M+) 292.9675; found 292.9690.

Synthesis of Benzylcyclopropane 303 from iodomethyl tolylcarbonate 315

A suspension of flame dried zinc (1g, 15mmol), and allyl benzene (0.90ml, 8mmol) in the appropriate solvent (5ml) were heated to reflux. A solution of iodomethyltolyl carbonate **315** in the same solvent (1ml), was added dropwise. The reaction was refluxed overnight, and the generation of benzylcyclopropane was monitored by GC. After 24 hours, the reaction was quenched by the addition of water (0.5ml). The system was filtered through celite, washing with ether (20ml), and the resulting solution was dried over $MgSO_4$. The solvent was removed *in vacuo* (water bath temperure 0^oC) to afford an oil which was studied by ^1H NMR. Flash chromatography (entry 2) afforded allylbenzene and benzyl cyclopropane **303,** spectroscopically identical to material already prepared.

No.	Zinc source	Equiv 315‡	Solvent (reflux)	Additives (equiv)	Yield* (%)
1	Zn-Cu	0.5	Et_2O	I_2 (0.2)	4
2	Zn-Cu	0.5	Et_2O	Me_3SiCl (1.1)	17†
3	Zn-Cu	0.2	Et_2O	I_2 (0.2)	20
4	Zn/Hg	0.2	Et_2O	-	0
5	Zn/Hg	0.5	Et_2O	$ZnCl_2$ (1)	3
6	Zn/Hg	0.5	PhMe	-	5
7	Zn/Hg	0.5	PhMe	I_2 (0.2)	5

* by comparison with GC standard

† confirmed by ^1H NMR of the crude

‡ relative to allylbenzene

table 24

Control reactions of Iodomethyltolylcarbonate 315

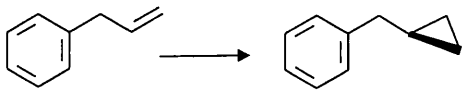
In order to ascertain whether or not methylene iodide or chloroiodomethane were being produced under the reaction conditions, iodomethyltolylcarbonate (60mg, 0.20mmol) was stirred in a flame dried flask in 2ml of $CDCl_3$, under the conditions shown below (see table). The brown solution was then transferred *via* syringe to an NMR tube. In every case only the starting material was present.

No.	Time	Solvent (temp)	Additives (eq)*
1	3 days	$CDCl_3$ (r.t.)	Me_3SiCl (1.7)
2	5 hours	$CDCl_3$ (50°C)	Me_3SiCl (2)
3	2 hours	$CDCl_3$ (50°C)	I_2 (1)
4	6 hours	$CDCl_3$ (50°C)	ZnI_2 (2)

* relative to iodomethyltolyl carbonate

table 23

Benzylcyclopropane 303



A suspension of Zn-Cu couple (1.0g, 15mmol) and allylbenzene (0.50ml, 4.5mmol) in ether (5ml) was heated to reflux. A solution of iodomethyltolyl carbonate **315** (280mg, 0.96mmol) in ether (1ml) was added dropwise. Chlorotrimethylsilane (0.20ml, 1.6mmol) was added, and the mixture was refluxed for 24 hours. After allowing the system to cool, the reaction was quenched by addition of saturated bicarbonate (2ml). The mixture was filtered through celite, and transferred to a separating funnel containing ether (50ml). The layers were separated, and the ethereal layer was washed with brine (5ml), dried over $MgSO_4$, and the solvent removed *in vacuo* to afford an oil which was purified by flash chromatography to afford (in order of elution) benzylcyclopropane **303** (276mg, as a mixture with allyl benzene, 15:1 b y ^1H NMR, 0.15mmol, 16%),[233] (4-phenylbutyl)tolyl carbonate (18mg, 0.07mmol, 7%) methyltolyl carbonate **319** (30mg, 0.19mmol, 20%)[e36] and p-cresol **318** (30mg, 0.28mmol, 29%).[234]

(4-Phenylbutyl)tolylcarbonate

^1H NMR ($CDCl_3$ / ppm): 7.32-7.00(9H, m, aryl), 4.27(2H, t, J=6.2, CH_2OCO_2), 2.69(2H, t, J=6.1, $PhCH_2$), 2.36(3H, s, $ArCH_3$), 1.78(4H, m, $PhCH_2CH_2$),

^{13}C ($CDCl_3$ / ppm): 153.9. 148.8. 135.9. 133.3, 120.4, 117.8, 72.4, 68.6, 35.4, 28.1, 27.5.

tolylmethylcarbonate 319

^1H NMR ($CDCl_3$ / ppm): 7.20(2H, d, J=8.7, aryl), 7.06(2H, d, J=8.5, aryl), 3.90(3H, s, OMe), 2.36(3H, s, $ArCH_3$).

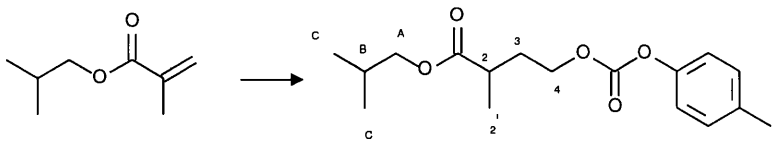
^{13}C ($CDCl_3$ / ppm): 148.9, 135,7, 130.0, 129.9, 120.7, 67.6.

p-cresol 318

^1H NMR, ($CDCl_3$ / ppm); 7.04(2H, d, J=8.7, aryl), 6.74(2H, d, J=8.5, aryl), 5.21(1H, bs, OH), 2.29(3H, s, $ArCH_3$).

13C ($CDCl_3$ / ppm): 153.2, 130.0, 15.0, 66.0, 20.4, 15.1.

(3-Methyl-*iso*butylbutan-4-oate) tolylcarbonate 320



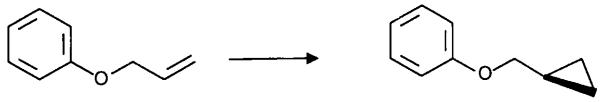
To a suspension of Zn/Hg amalgam (0.5g, 8mmol), isobutyl methacrylate (0.25g, 1.1mmol) and chlorotrimethylsilane (0.10ml) in ether (5ml) at reflux, a solution of iodomethyltolylcarbonate **315** (262mg, 0.90mmol) in ether (1ml) was added. The mixture was refluxed for 24 hours, and was then allowed to cool before being quenched by the addition of saturated sodium bicarbonate (1ml). The solution was filtered through celite and transferred to a separating funnel containing

ether (30ml). The ethereal solution was washed with brine (5ml), dried over $MgSO_4$ and the solvent removed *in vacuo* to leave a yellow oil. The oil was purified by flash chromatograhy to afford methyl tolylcarbonate **319** (74mg, 0.45mmol, 49%),[233] p-cresol **318** (5mg, 0.05mmol, 6%)[234] and the *title compound* **320** (9mg, 0.03mmol, 3%).

^1H NMR, ($CDCl_3$ / ppm): 7.17(2H, d, J=8.6, aryl), 7.05(2H, d, J=8.4, aryl), 4.30(2H, t, J=6.4, CH_2OCO_2), 3.91(2H, d, J=6.3, HA), 2.67(1H, sext, J=6.4, HB), 2.35(3H, s, $ArCH_3$), 2.22-2.14(1H, m, H2), 2.03-1.83(2H, m, 2 x H3), 1.25(3H, d, J=7.1, Me2'), 0.94(6H, d, J=6.7, Me C and C').

Mass spectrum: calculated for $C_{19}H_{24}O_7$ (M^+) 365.1600; found 365.1620.

Phenoxymethylcyclopropane 321



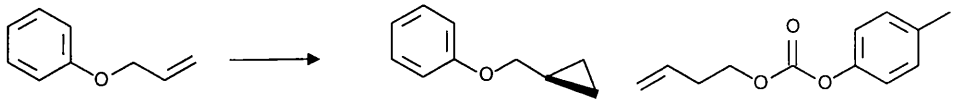
To a solution of allylphenyl ether (0.50g, 3.7mmol) and methylene iodide (2.0g, 7.5mmol) in ether (10.0ml) at 0°C, a 1M solution of diethyl zinc (7.5ml, 7.5mmol) in hexane was added dropwise. The reaction was stirred for 5 hours at 0°C, before quenching with water (5ml). The system was filtered and transferred to a separating funnel containing ether (50ml). The layers were separated, and the ether layer was washed with brine (5ml), dried over $MgSO_4$ and the solvent removed *in vacuo* to afford an oil. The oil was purified by flash chromatography to afford the *title compound* as a clear oil (66mg, 0.67mmol, 18%).[235]

IR (thin film / cm^{-1}): 3080(s), 3009(s), 2920(s), 1600(s), 1495(s), 1406(m), 1337(w), 1298(m), 1243(s), 1172(m), 1079(m), 1013(s), 753(s) 691(s).

^1H NMR, ($CDCl_3$ / ppm): 7.30-6.75(5H, m, Ph), 3.38(2H, d, J=6.9, $PhOCH_2$), 1.3-1.2(1H, m, $PhOCH_2CH$), 0.66-0.52 and 0.36-0.27(4H, 2 x m, 2 x cyclopropyl CH_2).

^{13}C ($CDCl_3$ / ppm): 159.0, 129.4, 120.6, 114.5, 72.6, 10.3, 3.1.

Attempted Cyclopropanation of Allylphenylether 321 using Iodomethyltolyl carbonate 315



To a suspension of Zn-Cu couple (0.50g) and allylphenyl ether (260mg, 1.94mmol) in ether (5ml) at reflux, was added iodomethyl tolylcarbonate **315** (216mg, 0.74mmol) in ether (1ml). Chlorotrimethylsilane (0.14ml, 1.1mmol) was added. After 24 hours at reflux, the reaction was allowed to cool and then quenched by the addition of saturated sodium bicarbonate (2ml). The

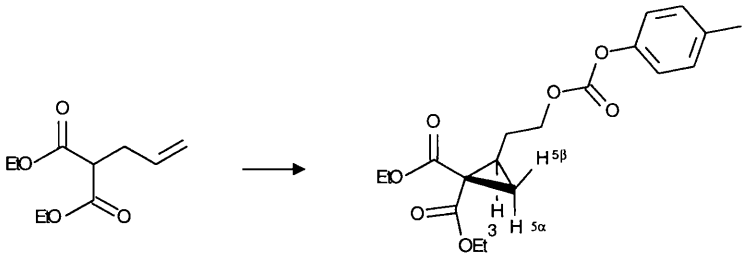
mixture was filtered and transferred to a dropping funnel containing ether (50ml). The layers were separated, and the ethereal layer was washed with brine (5 ml), dried over $MgSO_4$ and the solvent removed *in vacuo* to afford an oil, which was purified by flash chromatography to afford phenoxymethylcyclopropane **321** (10mg, 9%) and methyl tolylcarbonate **319** (4mg, 0.04mmol 3%), both spectroscopically identical to material already prepared, and 3-butenoxytolyl carbonate **322** (23mg, 0.11mmol, 15%).

IR (thin film/ cm^{-1}): 3037(m), 2960(s), 2936(s), 2279(w), 1765(s), 1643(w), 1598(w), 1509(s), 1442(m), 1385(w), 1259(s), 1100(w), 1069(s), 1017(m), 948(m), 926(m), 885(w), 819(s), 780(m), 725(m), 638(w), 560(w).

^1H NMR, ($CDCl_3$ / ppm); 7.22(2H, d, J=8.7, aryl), 7.05(2H, d, J=8.4, aryl), 5.83(1H, m, C**H**=CH_2), 5.21(2H, m, CH=C**H**$_2$), 4.30(2H, t, J=6.7, OCO_2CH_2), 2.51(2H, q, J=9.8, OCH_2CH_2), 2.18(3H, s, Ar**CH**$_3$).

^{13}C ($CDCl_3$ / ppm): 129.9, 120.7, 120.6, 117.8, 67.6, 33.0, 28.3.

(2-((4-Methylphenoxy)carbonyloxy)ethyl)-1,1-(diethoxycarboxy)cyclopropane 325



To a suspension of Zn/Hg amalgam (1.0g, 15mmol) diethylallylmalonate (0.20g, 1mmol) and chlorotrimethylsilane (0.10ml, 0.8mmol) in ether (5ml), at reflux a solution of iodomethyl-tolylcarbonate **315** (0.33g, 1.1mmol) in ether (1ml) was added. After 48 hours at reflux, the reaction cooled, and was then quenched by addition of saturated sodium bicarbonate (2ml). The mixture was filtered through celite and transferred to a dropping funnel containing ether (50ml). The layers were separated, and the ethereal layer was washed with brine (5ml), dried over $MgSO_4$, and the solvent removed *in vacuo* to leave an oil which was purified by flash chromatography to afford the *title compound* **325** as a clear oil (50mg, 0.15mmol, 15%).

IR (thin film / cm^{-1}); 2983(s), 1763(s), 1728(s), 1510(m), 1451(m), 1372(m), 1256(s), 1206(s), 1133(m), 1020(m), 823(w), 780(w), 734(w).

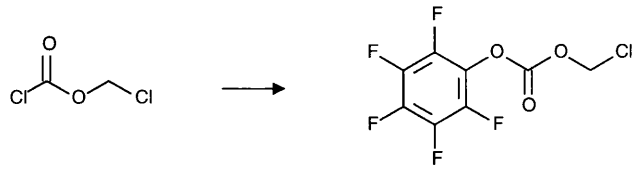
^1H NMR, ($CDCl_3$ / ppm): 7.17(2H, d, J=8.4, aryl), 7.05(2H, d, J=8.4,aryl), 4.35(2H, t, J=6.4, CH_2OCO_2), 4.3-4.12(4H, m, 2 x CO_2CH_2), 2.35(3H, s, PhMe), 2.06-1.88(2H, m, $CH_2CH_2OCO_2$), 1.75-1.66(2H, m, 2 x H3, H5β), 1.43(1H, dd, J=10.7, 9.2, H5α), 1.27(3H, t, J=7.0, C**H**$_3$), 1.16(3H, t, J=7.2, C**H**$_3$).

^{13}C ($CDCl_3$ / ppm): 170.0, 168.0, 167.4, 158.8, 148.9, 135.7, 129.9, 120.7, 67.4, 61.6, 33.8, 28.0, 24.3, 20.8, 20.3,15.2, 14.1, 14.0.

Mass spectrum: calculated for $C_{19}H_{24}O_7$ (M^+) 365.1600; found 365.1620.

Microanalysis: calculated for $C_{19}H_{24}O_7$ C62.62 H6.64; found C62.48, H 6.78.

Chloromethyl-pentafluorophenylcarbonate 337



To a solution of pentafluorophenol (2.76g, 15mmol) and pyridine (1.2ml, 15mmol) in dichloromethane (30ml), a solution of chloromethylchloroformate (2.0g, 15mmol) in dichloromethane (7ml) was added over 15 minutes. The reaction was stirred for 2.5 hours, before quenching with 3% HCl (5ml). The layers were separated and the organic layer was washed with 1M NaOH (5ml) and brine (5ml), dried over $MgSO_4$ and the solvent removed *in vacuo* to afford a pale solid which was recrystallized from petrol to afford the *title compound* **337** as white crystals (1.80g, 6.1mmol, 41%), mpt 34-36°C.

IR (thin film / cm^{-1}); 3108(m), 2977(w), 2974(w), 2342(w), 2139(w), 1896(w), 1656(m), 1479(m), 1447(s), 1352(s), 1329(m), 1276(s), 1214(s), 1071(m), 978(s), 920(s), 790(m), 7773(s), 723(s), 675(m), 622(w), 504(s).

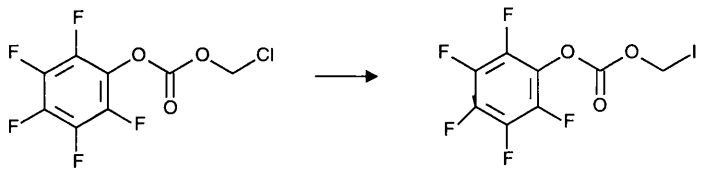
^1H NMR ($CDCl_3$ / ppm): 7.27(2H, s, OCH_2Cl).

^{13}C NMR ($CDCl_3$ / ppm): 150.0, 142.3(m), 141.4(m), 139.9(m), 139.8(m), 139.1(m), 125.5(m), 73.3.

^{19}F NMR ($CDCl_3$ / ppm): -153.2(d), -156.7(t), -161.8(t).

Microanalysis: calculated for $C_8H_2IF_6O_3$: C34.75 H0.73 CI12.82; found C34.62 H0.63 CI12.61.

Iodomethyl-(pentafluorophenyl) carbonate 328



A mixture of chloromethyl(pentafluorophenyl) carbonate (1.80g, 6.6mmol) and sodium iodide (1.30g, 8.5mmol) in freshly dried acetone (15ml) were stirred at room temperature for 30 hours. The acetone was removed *in vacuo* and to the residue 1M sodium thiosulfate (10ml) and ether (30ml) were added. The layers were separated, and the ethereal layer was washed with brine,

dried over $MgSO_4$ and the solvent removed *in vacuo* to afford a pale yellow oil. This was recrystallized from petrol, to afford a buff solid **328** (0.81g, 2.2mmol, 34%) mpt 45-48°C.

IR (thin film / cm^{-1}); 3082(w), 2917(w), 2229(w), 1787(s), 1652(m), 1522(s), 1428(m), 1285(s), 1201(s), 1062(w), 1008(s), 973(s), 768(w), 724(w), 562(m).

^1H NMR, ($CDCl_3$ / ppm); 7.86(2H, s, OCH_2Cl).

^{13}C ($CDCl_3$ / ppm) 149.7, 142.3(m), 141.4(m), 139.8(m), 139.0(m), 136.7(m), 73.3.

^{19}F NMR ($CDCl_3$ / ppm): -151.9(d, J=17.4), 1-55.5(t, J=21.7), -160.5(t, J=21.4).

Attempted Cyclopropanation of allyl benzene using Iodomethyl-(pentafluorophenyl) carbonate 328

A suspension of flame dried zinc (1g, 15mmol), and allyl benzene (0.90ml, 8mmol) in the appropriate solvent (5ml) were heated to reflux. A solution of Iodomethyl-(pentafluorophenyl) carbonate **28** in the same solvent (1ml), was added dropwise. The reaction was refluxed overnight, and the generation of benzylcyclopropane was monitored by GC.

No.	Zinc	Allylbenzene (equiv)	Solvent (temp)	Additives (eq)*	Yield of benzylcylopropane
1	Zn-Cu	6	Et_2O (reflux)	Me_3SiCl (2)	0
2	Zn/Hg	6	Et_2O (reflux)	Me_3SiCl (2)	trace
3	Zn-Cu	6	Et_2O (reflux)	I_2 (0.5)	0
4	Zn/Hg	6	PhMe (reflux)	I_2 (0.5)	0

* relative to iodomethyl tolylcarbonate

Methyl (dimethoxyacetate) 347

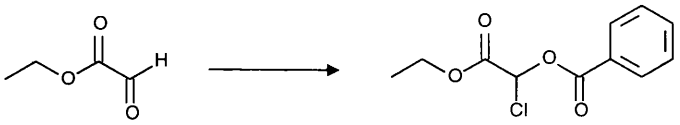
Glyoxylic acid monohydrate (5.0g, 54mmol) anhydrous copper sulfate (8.61g, 54mmol), concentrated H_2SO_4 (1.0ml) and dry methanol (20ml) were stirred at reflux for 12 days. The reaction was poured into saturated sodium bicarbonate (30ml) and extracted with dichloromethane (3 x 80ml). The combined extracts were washed with brine (20ml) dried over $MgSO_4$ and the solvent removed *in vacuo* to afford a yellow oil which was purified bulb to bulb distillation (125°C/20mmHg) to afford the *title compound* **347** (4.96g, 35mmol, 65%) as a clear oil.[219]

IR (thin film / cm^{-1}): 2948(s), 2844)m), 1748(s), 1637(m), 1448(m), 1382(w), 1351(w), 1245(s), 1200(s).

^1H NMR ($CDCl_3$ / ppm): 4.97(1H, s, C**H**), 3.93(3H, s, CO_2Me), 3.54(6H, s, 2 x OMe)

^{13}C NMR ($CDCl_3$ / ppm): 170.0, 98.4, 53.9.

Ethyl(1-benzoyloxy-1-chloroacetate) 352



Benzoyl chloride (2.30ml, 0.020mol) and a mixture of toluene and ethyl glyoxylate (1:1 mixture, 4.0g, 22mmol of ethyl glyoxolate) were heated in a microwave for 15 minutes. The resulting clear oil was transferred to a Kugelrohr, and bulb to bulb distillation (100°C, 40mm/Hg) afforded toluene and a mixture of benzoyl chloride and ethylglyoxylate. Zinc chloride (20mg) was addded, and the mixture was stirred at room temperature overnight. Flash chromatography of the product afforded the *title compound* **352** as a clear oil (400mg, 1.6mmol, 7%).

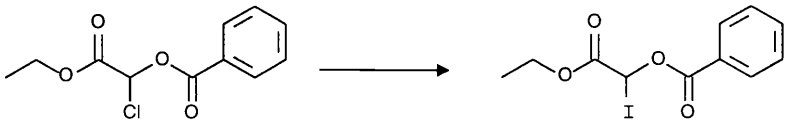
IR (thin film / cm^{-1}): 3069(m), 2987(s), 1746(s), 1602(m), 1452(m), 1374(m), 1346(m), 1284(s), 1245(s), 1185(s), 1091(s), 1017(s), 943(w), 856(s), 709(s), 558(w).

^1H NMR ($CDCl_3$ / ppm): 8.14(2H, d, J=8.5, aryl), 7.66-7.27(3H, m, aryl), 6.85(1H, s, C**H**Cl), 4.38(2H, q, J=7.2, $CO_2C\mathbf{H}_2$), 1.39(3H, t, J=7.2, $C\mathbf{H}_3$).

^{13}C NMR ($CDCl_3$ / ppm): 167.4, 163.8, 134.3, 130.5, 130.3, 128.8, 128.6, 127.9, 76.4, 63.0, 13.9.

Microanalysis: calculated for $C_{11}H_{11}ClO_4$ C54.41 H4.57 Cl14.96; found C54.63 H4.56 Cl14.36.

Ethyl(benzoyloxyiodoacetate) 353



Ethyl(benzoyloxychloroacetate) (400mg, 1.8mmol) was stirred with sodium iodide (2mmol, 320mg), in acetone (5.0ml) for 3 days. The reaction was filtered and the acetone removed *in vacuo*. Ether (50ml) was added, and the solution washed with 1M sodium thiuosulphate (5ml), brine (5ml) and dried over $MgSO_4$. The solvent was removed *in vacuo* to afford the *title compound* **353** as a clear oil (409mg, 1.2mmol, 68%).

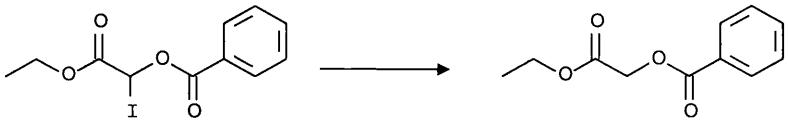
IR (thin film / cm^{-1}): 3067(w), 2985(m), 2092(w), 1976(w), 1921(w), 1739(s), 1601(m), 1452(m), 1373(m), 1342(s), 1221(s), 1177(s), 1064(s), 940(w), 852(m), 800(w), 764(w), 709(s), 616(w), 530(m).

^1H NMR ($CDCl_3$ / ppm): 8.11(2H, d, J=7.6, aryl), 7.64-7.47(3H, m, aryl), 7.38(1H, s, C**H**I), 4.36(2H, q, J=7.3, $CO_2C\mathbf{H}_2$), 1.36(3H, t, J=7.3, $C\mathbf{H}_3$).

^{13}C NMR ($CDCl_3$ / ppm): 168.0, 164.0, 134.0, 133.4, 130.2, 129.9, 128.5, 128.4, 85.2, 61.2, 14.1.

Mass Spectrum: (FAB 63%) 335 (MH^+).

Ethyl(benzoyloxyacetate) 354



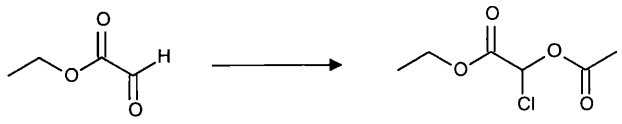
To a mixture of Zn/Hg (1.0g, 15mmol), chlorotrimethylsilane (1.0ml, 8mmol), allylbenzene (0.90ml, 8mmol) in ether (8ml) at reflux, a solution of ethyl (benzoyloxyiodo)acetate (200mg, 0.60mmol) in ether (1ml) was added, and the mixture was refluxed over night. After quenching with saturated sodium bicarbonate (5ml), the reaction was filtered and transferred to a separating funnel containing ether (30ml). The layers were separated, and the ether layer was washed with brine (5ml) dried over $MgSO_4$ and the solvent removed *in vacuo* to afford a yellow oil, which was purified by flash chromatography, to afford the *title compound* **353**(29mg, 0.14 mmol, 24%).[226]

IR (thin film / cm^{-1}): 3067(m). 2984(s), 2103(w), 1977(w), 1918(w), 1746(s), 1602(m), 1451(s), 1345(m), 1245(s), 1213(s), 1178(s), 1120(s), 1061(s), 856(w) 802(w), 712(s), 526(w.

^1H NMR ($CDCl_3$ / ppm): 8.11(2H, d, J=6.9, aryl), 7.60(1H, t, J=7.5, aryl), 7.49(1H, t, J=7.66, aryl), 4.86(2H, s, $C\mathbf{H}_2OCOPh$), 4.27(2H, q, J=7.2, $CO_2C\mathbf{H}_2$), 1.31(3H, t, J=7.1, $C\mathbf{H}_3$).

^{13}C NMR ($CDCl_3$ / ppm): 168.0, 167.2, 134.3, 130.3, 1287, 62.7, 40.7, 13.7.

Ethyl (acetoxychloro)acetate 355



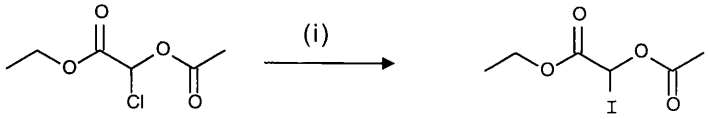
A mixture of ethylglyoxylate polymer and toluene (12g, approximately 6g of ethylglyoxylate by weight, 58.8mmol) was distilled in a Kugelrohr to remove the toluene (150°C, atmospheric pressure). The residue was subjected to microwave irradiation for five minutes, and then distilled (100°C/35mmHg), to afford depolymerized ethyl glyoxolate (5.4g, 52.9mol). The oil was transferred to a flask containing fused zinc chloride (20mg), and acetyl chloride (4.0ml, 0.53mmol), and an increase in temperature was observed. After stirring overnight, the reaction mixture was distilled to remove unreacted acetyl chloride (75°C/30mmHg) and the residue itself distilled (180°C/30mmHg) to afford the *title compound* **355** as a clear oil (1.74g, 9.6mmol, 16%).

^{1}H NMR ($CDCl_3$ / ppm): 6.53(1H, s, C**H**Cl), 4.29(2H, q, J=7.2, $CO_2C\mathbf{H}_2$), 2.19(3H, s, OAc), 1.31(3H, t, J=7.2, Me).

^{13}C NMR ($CDCl_3$ / ppm): 168.4, 166.4, 68.2, 39.9, 20.2, 13.9.

Microanalysis: calculated for $C_6H_9ClO_4$ C39.90 H 5.05; found C41.08, H5.15.

Ethyl (acetoxyiodoacetate) 356



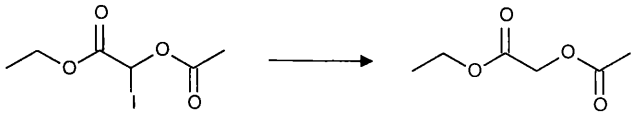
Ethyl (2-iodoacetoxy)acetate (1.30g, 7.2mmol) and sodium iodode (1.20g, 7.4mmol) were stirred in acetone (10ml, freshly dried) at room temperature for 16 hours. ^{1}H NMR of the cude showed complete formation of the *title compound*. The mixture was filtered, and the acetone removed *in vacuo*. The residue was transferred to a separating funnel containg ether (50ml), and the ethereal solution was washed with 1M sodium thiosulfate (5ml), and brine (5ml). The solution was dried over $MgSO_4$ and the solvent removed *in vacuo* to afford ethyl(acetoxyiodo)acetate **356** as a clear oil, which yellowed slowly above -20°C (1.32g, 4.85mmol, 67%).

IR (thin film / cm^{-1}): 2986(s), 2090(w), 1450(s), 1637(w), 1445(m), 1374(s), 1338(s), 1200(s), 1136(s), 1056(s), 955(w), 895(w), 853(w), 804(w), 729(w0, 604(w), 540(w), 497(w).

^{1}H NMR ($CDCl_3$ / ppm): 7.13(1H, s, CHI), 4.32(2H, q, J=7.1, CO_2CH_2), 2.19(3H, s, OAc), 1.34(3H, t, J=7.1, Me).

^{13}C NMR ($CDCl_3$ / ppm): 168.1, 166.6, 62.6, 39.9, 20.9, 13.6

Ethyl(acetoxyacetate) 357

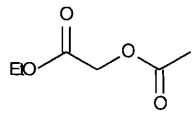


Typical procedure: To a suspension of Zn/Hg amalgam (20mmol, 1.50g), the electrophile and Lewis acid at reflux (see table), a solution of ethyl(acetoxyiodoacetate) (x) (1mmol, 272mg) in ether (1ml) was added. After stirring at reflux for 24 hours, the reaction was quenched by the addition of saturated sodium bicarbonate (5ml), filtered, and transferred to a separating funnel containing ether (30ml). The layers were separated, and the ethereal layer was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The product was then purified by flash chromatography.[227]

IR (thin film / cm^{-1}): 3063(s), 3028(s), 2920(s), 1948(w), 1861(w), 1801(w), 1637(m), 1605(m), 1495(s), 1454(s), 1076(s), 1027(s), 989(s), 912(s), 809(w), 727(s), 695(s), 651(w).

^1H NMR ($CDCl_3$ / ppm): 4.55(2H, s, CH_2OAc), 4.18(2H, q, J=5.3, CO_2CH_2), 2.12(3H, s, OAc), 1.24(3H, t, J=5.3, CH_3).

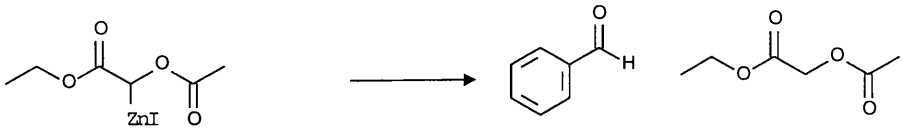
^{13}C NMR ($CDCl_3$ / ppm): 171, 169.8, 61.4, 60.7, 20.4, 14.0.

No.	Solv	Elec. (eq)	Add^n (hrs)	L.A. (eq)	Alkene (eq)	
1	Et_2O	Me_3SiCl (2)	0	-	 2	48
2	Et_2O	-	6	$ZnCl_2$	 2.5	30
3	Et_2O	Me_3SiCl (1.5)	6	-	 2	12
4	PhMe	-	0	-	 6	22
5	Et_2O	Me_3SiCl (3)	6	$ZnCl_2$	 5	32
6	Et_2O	BF_3OEt_2 (1)	6	-	 4.5	39
7	Et_2O	-	0	$MeAlCl_4$	 4.5	43
8	Et_2O	-	0	$TiCl_4$	 4.5	0*
9	Et_2O	-	0	$Pd(Ph_3)_4$	 4.5	0‡

* onyl identifiable product was 2-chloro-3-phenyl propane[220]

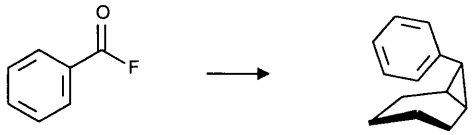
‡ no identifiable products

Attempted Reformatsky reaction using ethyl(acetoxyiodoacetate) 356



To a suspension of Zn/Hg amalgam (1.0g, 15mmol) in ether (5ml) at reflux a solution of ethyl(acetoxyiodoacetate) (167mg, 0.61mmol) in ether (1ml) was added. After stirring at reflux for 2 hours the reaction was cooled and the mixture transferred by filter tipped canula to a flask containg benzaldehyde (0.06ml, 0.6mmol). After stirring at room temperature overnight, the reaction was quenched by the addition of saturated sodium bicarbonate (5ml), filtered, and transferred to a separating funnel containing ether (30ml). The layers were separated, and the ethereal layer was washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude product was examined by NMR, and contained only a 1:1 mixture of ethyl acetoxyacetate and benzaldehyde, 180mg, 79% recovery.

Attempted cyclopropanation using Benzoyl Fluoride365



method A

To a suspension of zinc (1.0g, 15mmol), cyclohexene (1ml, 10mmol) and chlorotrimethylsilane (2.0ml, 16mmol) in ether (10ml), a 13% solution of titanium trichloride in 20% aqueous HCl (0.10ml, equivalent to 0.013g $TiCl_3$, 0.08mmol) was added. To this refluxing mixture, benzoyl fluoride (0.50g, 4mmol) in ether (2ml) was added over 16 hours. After a further 8 hours at reflux, the reaction was quenched by stirring with saturated sodium bicarbonate solution (10ml) for 15 minutes. The solids were removed by filtration through celite, and the aqueous solution was extracted with ether (2 x 20ml). The combined extracts were washed with brine (10ml), dried over $MgSO_4$, and the solvent removed *in vacuo* to afford a viscous yellow oil. The oil was purified by flash chromatography (petrol) to afford 7-phenylnorcarane **189** as a clear oil (9mg, 0.05mmol,1%) spectroscopically dentical to material already prepared.

method B

To a suspension of zinc (1.5g, 22mmol), cyclohexene (1ml, 10mmol) and chlorotrimethylsilane (2.0ml, 16mmol) in ether (10ml), anhydrous titanium trichloride (115mg, 0.75mmol) was added. To this refluxing mixture, benzoyl fluoride (0.50g, 4mmol) in ether (2ml) was added over 10

hours. After a further 2 days at reflux, the reaction was quenched by stirring with saturated sodium bicarbonate solution (10ml) for 15 minutes. The solids were removed by filtration through celite, and the aqueous solution was extracted with ether (2 x 20ml). The combined extracts were washed with brine (10ml), dried over $MgSO_4$, and the solvent removed *in vacuo* to afford a viscous yellow oil. The oil was purified by flash chromatography (petrol) to afford 7-phenylnorcarane **189** as a clear oil (32mg, 0.12mmol,3%) spectroscopically identical to material already prepared.

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