STUDIES ON THE GENERATION AND REACTIVITY OF METAL CARBENOIDS

A Thesis Presented by

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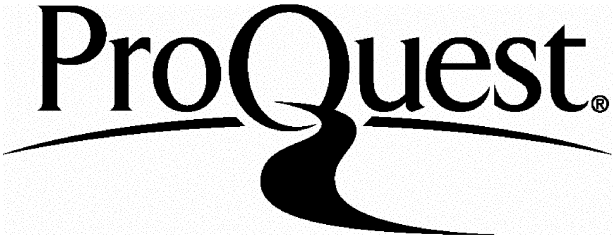

ABSTRACT

This thesis concerns the generation of metal carbenoids, in particular organozinc carbenoids, and their subsequent reactions, such as C-H insertion reactions or cyclopropanation with alkenes. The thesis is divided into three major sections.

The introductory chapter presents a comparative review covering metal carbenoid species. The review focuses on how their reactivity is controlled by the metal, the leaving group and by the nature of electron-donating and –withdrawing groups on the carbenoid and finally which type of alkenes give the highest reactivity and yields as a function of these parameters.

The results and discussion chapter opens with a brief overview of the organozinc carbenoid chemistry which has been developed within our group. Subsequent sections then describe a range of reactions which were investigated. Thus, studies on both the acid catalysed chlorotrimethylsilane-zinc deoxygenation of ketones and the use of iodotrimethylsilane-zinc for reactive carbenoid generation are presented and used in an investigation of transannular insertion in small, medium and large ring sized ketones. The first efforts towards electrochemical generation of organozinc carbenoids for dicarbonyl coupling are then described. This is followed by a detailed study of the regio- and stereoselective behaviour of electron rich dienes with a range of organozinc carbenoids generated from appropriate aldehydes and ketones.

An investigation of both zinc and copper carbenoids in carboalkoxy-cyclopropanations is then presented. In addition, the generation of a novel geminally substituted alkoxy-carboalkoxy copper carbenoid was also examined and used for cyclopropanation. Attempts to generate metal carbenoids from halo iminium salts for aminocylopropanation are also discussed. This is followed by a chapter summarising the results achieved and perspectives for future work.

A concluding chapter provides a formal description of the experimental results and procedures together with appropriate references.

CONTENTS

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ABBREVIATIONS

Ac	acetyl
AIBN	Azo bis-isobutyronitrile
Ar	Unspecified aromatic group
Bn	Benzyl
b.p.	Boiling point
br	Broad
i-Bu	*i*-Butyl
n-Bu	*n*-Butyl
t-Bu	*t*-Butyl
Δ	Heat
d	Doublet
DC	Direct current
DCE	Dichloroethane
DCM	Dichloromethane
dd	double doublet
ddd	double double doublet
ddt	double double triplet
de	Diastereomeric excess
decomp.	Decomposition
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone
dr	Diastereomeric ratio
dt	double triplet
E^+	Unspecified electrophile
ee	Enantiomeric excess
EI	Electron impact
equiv.	Molar equivalent(s)
Et	Ethyl
Et_2O	Diethyl Ether
EtOAc	Ethyl Acetate
EtOH	Ethanol

FAB	Fast atom bombardment
g	Gram(s)
GC	Gas chromatography
h	Hour(s)
hυ	Light
Hz	Hertz
i	Iso
J	Coupling constant
L	Unspecified Ligand
LA	Lewis acid
lit.	Literature value
M	Unspecified metal
m	Multiplet or medium as appropriate
mA	MilliAmp(s)
Me	Methyl
MeO	Methoxy
MeOH	Methanol
mg	Milligram(s)
min	Minutes
ml	Millilitres(s)
mm Hg	Millimetres of mercury
m.p.	Melting point
ms	Molecular sieves
n	Neo
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhäuser effect
Nu	Unspecified nucleophile
o	Ortho
p	Para
Ph	Phenyl
ppm	Parts per million
i-Pr	*i*-Propyl
n-Pr	*n*-Propyl
q	Quartet

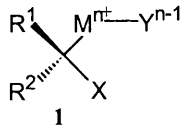
R	Unspecified carbon substituent
R_f	Retention factor
r.t.	Room temperature
s	Singlet or strong as appropriate
sec	Second(s)
t	Triplet
t	Tertiary
TBDMS	*t*-Butyldimethylsilyl
Tf	Trifluoromethylsulfonyl
THF	Tetrahydrofuran
tlc	Thin layer chromatography
TMEDA	*N,N,N,N*-Tetramethylethylenediamine
TMS	Trimethylsilyl
Ts	*para*-Toluenesulfonyl
UV	Ultraviolet
V	Volt(s)
w	weak
X	Leaving group
Y	Functionalised group

1

Introduction
The Generation and Reactivity of Metal Carbenoids

1. The Generation and Reactivity of Metal Carbenoids

The present thesis focuses on the generation and reactivity of organozinc carbenoids,[1] which can be considered as a subset of the more general class of metallocarbenoids of general structure **1**, wherein the central tetrahedral carbon atom is covalently bonded both to a metal and to a leaving group (Figure 1).



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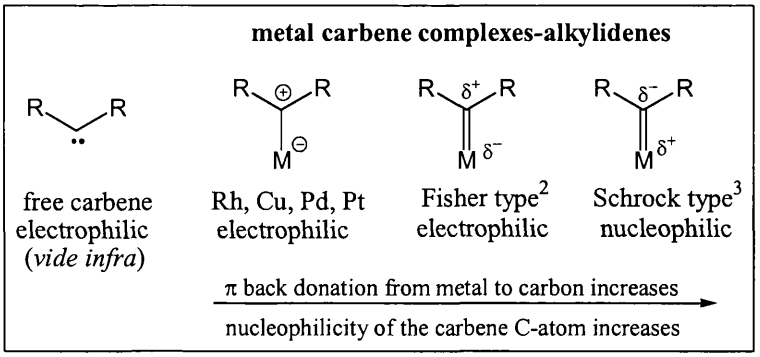
M=metal
X=leaving group
R^1, R^2=H, alkyl, aryl

Reactivity as a funtion of:
M=Al, Cd, Cr, Cu, Hg, In, Li, Mg, Sm, Zn;
X= Cl, Br, I, OMe, OCOPh, OCO(*n*-C_4F_9), $OCOCF_3$;
Y=Cl, Br, I, CH_2Cl, CH_2Br, CH_2I, Et, Me_2, Et_2, $(n\text{-}Pr)_2$, $(i\text{-}Bu)_2$, $OCOCF_3$, OAr, $(CH_2)_2CO_2Et$, $(CH_2)_3OBn$, CH_2TMS, Ph, Ligand.

Figure 1

In order to place this area of chemistry in perspective, the present introductory review will therefore concentrate on highlighting the rich patterns of reactivity exhibited by this general class of reagent, and also attempt to formulate patterns of reactivity as a function of the metal M, the leaving group X, and the nature of the substituents, R^1, R^2 which can be either electron donating or electron withdrawing (Figure 1). To the best of our knowledge, no extensive comparative study of this class of reagents has been made.

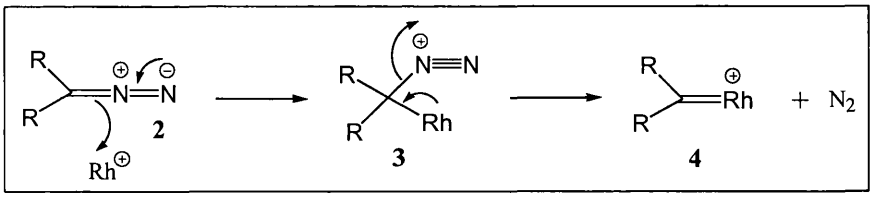
From the outset, it is important to recognise that the nomenclature surrounding "carbene-metal complex" chemistry is currently in a state of evolution and that it is at times loosely employed. For the purpose of clarity, we therefore show some of the other terms used in this general area together with their essential electronic character (Scheme 1).



Scheme 1

As implied in Scheme 1, the reactivity of alkylidene complexes featuring the metal carbon double bond is relatively well understood, has been extensively reviewed,[4] and is the sole subject of a recent book, "Metal Carbenes in Organic Synthesis."[5] Consequently, it is not our intention to discuss such complexes in the present overview, but instead to concentrate on reagents of general structure **1**.

We note parenthetically however that a formal mechanistic link may exist between the carbenoids of structure **1** (Figure 1) and the "carbene-complexes" or alkylidenes of Scheme 1. Thus, one of the traditional routes for generation of alkylidenes **4** involves reaction of a diazo compound **2** with a metal catalyst. Interestingly the penultimate intermediate **3** in the formation of the metal carbene complex can also be classified as a carbenoid in which the leaving group is the most powerful in organic chemistry *viz.* nitrogen (Scheme 2).



Scheme 2

In terms of organisation, following a brief commentary on free carbenes and the use of diazo precursors, the reactivity profiles have been classified in the first instance as a function of the nature of the substituents R^1, R^2 around the carbon atom, and then contrasted therein in terms of reactivity as a function of the metal. Emphasis has been given in particular to those reactions leading to cyclopropanes, not only for comparative purposes, but also in terms of synthetic utility.

1.1 Carbenes and Carbenoids

A carbene, by definition, possesses a divalent carbon atom and is therefore automatically an electron deficient intermediate. Nevertheless, as exemplified in Figure 2, two distinct electronic states can be recognised for the simplest methylene carbene "CH_2". In the triplet state **5**, where each unpaired electron occupies a different energetically equivalent sp^3 orbital, diradical behaviour predominates, and this leads to loss of stereoselectivity in alkene cyclopropanation. The more bent singlet state **6**, with one filled sp^2 orbital and one empty p orbital, is of course generated in thermal reactions, and of greater synthetic utility.[4a]

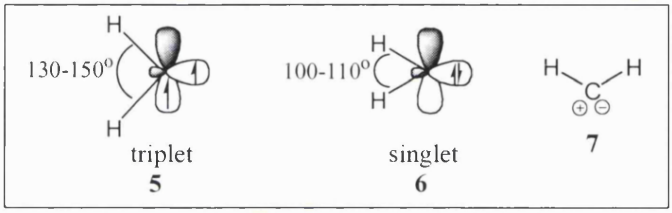
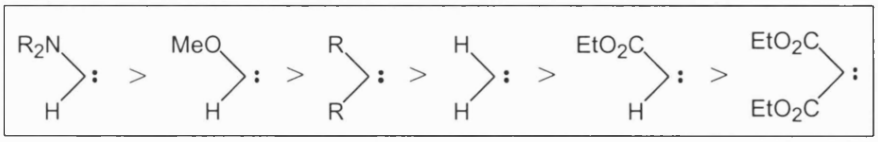


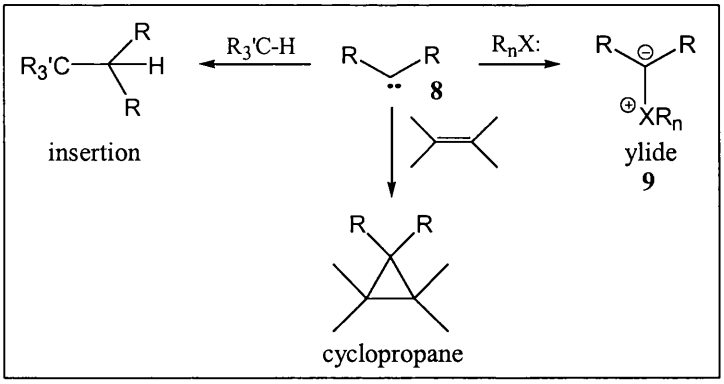
Figure 2

On occasion, the central carbon atom is represented as possessing both a positive and a negative charge (as in **7**, Figure 2) and this convention can prove useful in terms of discussing the relative nucleophilic or electrophilic behaviour of singlet carbenes as a function of the electron withdrawing or electron donating character of functional groups other than hydrogen which are also attracted to the central carbon atom. Thus, as shown in Scheme 3, aminocarbenes can be said to be more nucleophilic in character than carboethoxy carbenes.



Scheme 3

In general terms the typical reactions of these uncomplexed electron deficient intermediates **8** include cyclopropanation, C-H insertion, and reaction with neutral nucleophiles to give ylides **9** (Scheme 4).



Scheme 4

Carbene and carbenoid species are therefore paramount intermediates in organic synthesis mainly due to numerous possibilities of forming several useful cyclopropane intermediates, all of which are widely found in many natural products and biologically active molecules.[6] For example, cyclopropane derivatives such as *gem*-dimethyl-, 1,2-3-substituted-, carboalkoxy- and amino-cyclopropanes are all common targets for organic chemists. In addition, cyclopropanes can also be useful synthons for further synthetic transformations due to the high ring-strain.[1d,6b,7]

Although the influence of the functional groups attracted to the central carbene atom plays the dominant role in determining stability and reactivity within "free" carbene chemistry, the binding of a metal centre can exert a strong and even dominant influence on the range of reactivity of the resultant carbenoids, as we will see in the following sections.

1.2 Methylene Carbenoids [$YMCH_2X$]

Methylene carbenoids have been extensively used in organic synthesis, especially for the cyclopropanation of alkenes and there are several metals which carry out this important transformation:

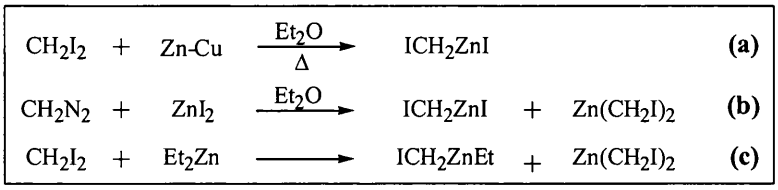
1.2.1 Zinc Carbenoids

By far the most widely used methylene carbenoids are derived from zinc, and these are mainly generated by three classes of reaction:

(i) the oxidative addition of activated zinc metal into a carbon-halogen bond, which was first reported by Simmons and Smith (Scheme 5a);[8,9]

(iii) the insertion of a diazoalkane (usually diazomethane or aryldiazomethane) into a zinc-iodine bond, which was reported by Wittig (Scheme 5b);[10]

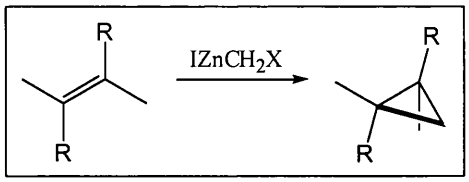
(ii) the alkyl group exchange between an organozinc reagent and a 1,1-dihaloalkane, which is often referred to as the Furukawa procedure (Scheme 5c).[11]



Scheme 5

1.2.1.1 The Evolution of Simmons Smith Carbenoids

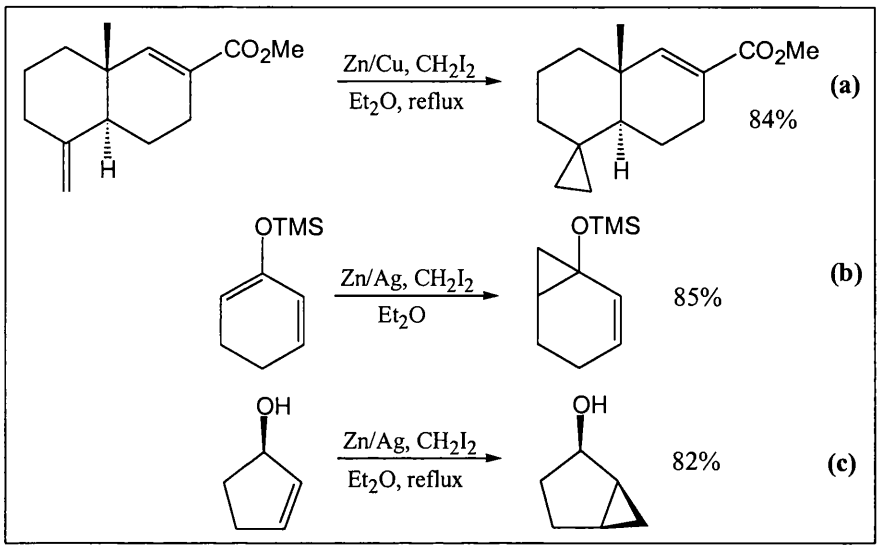
In 1958, Simmons and Smith[8] reported the first metal carbenoid, prepared from an ethereal suspension of zinc/copper couple with diiodomethane, which stereospecifically transforms alkenes to cyclopropanes (Scheme 6).[8] Even now, the Simmons-Smith cyclopropanation is extensively used mainly because of the retention of olefin geometry during the reaction and the wide range of functional groups which may be tolerated.[1]



Scheme 6

The metal carbenoid is essentially electrophilic in nature, and, as a result, electron-rich (i.e. more nucleophilic) alkenes react much faster than electron-poor alkenes (Scheme 7a and b).[1e,12,13] Because of the electrophilic nature of the carbenoids, highly substituted double bonds generally react faster than less substituted ones.[13] Moreover, the presence of a proximal hydroxyl or ether group to direct the stereochemical outcome of C-C bond formation was recognised early[14] and significantly accelerates

the rate of cyclopropanation reactions in comparison to alkenes which lack this moiety (Scheme 7c).[15]



Scheme 7

The cyclopropanation is generally considered to occur through a "butterfly type" transition state **10** as depicted in Figure 3.[8b] Moreover, the directed electrophilic cyclopropanation reactions occur through complexation of the metal carbenoid with the proximal basic group as in **11**.[1,14,16] In the reaction with metal couples, it is likely that the copper and silver activate the zinc surface, rather than play a role in the mechanism for cyclopropanation.

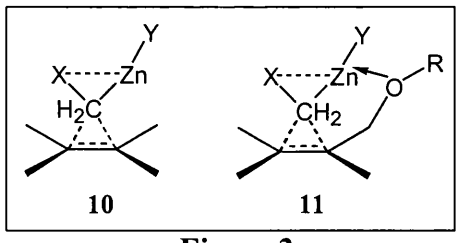
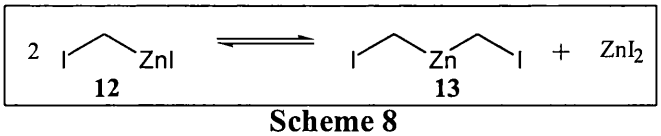


Figure 3

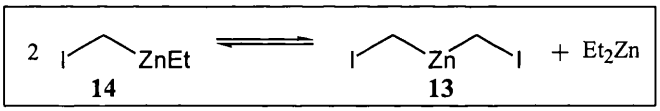
The reactive carbenoid species of iodomethylzinc iodide **12** and bis(iodomethyl)zinc **13**/zinc(II) iodide are believed to be in Schlenck equilibrium[1a,g,17] and recent spectroscopic evidence has revealed that the equilibrium lies heavily on the side of $IZnCH_2I$ **12** (Scheme 8).[18,19] This observation is consistent with several organozinc iodides.[20]



Scheme 8

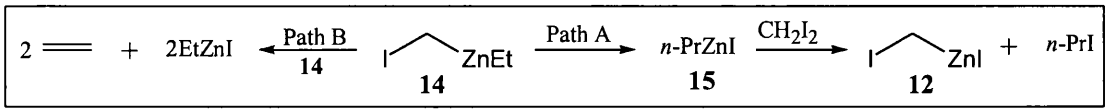
1.2.1.2 The "Furukawa" Modification

Furukawa reported an improved version of the Simmons-Smith cyclopropanation reaction, by generating the zinc carbenoid *via* alkyl-iodine exchange using diethylzinc and diiodomethane.[11,16] Distinct advantages were noted in using the "Furukawa" modification. The homogeneous nature of the reagents led to an increase in the reaction rate and as a result cationically polymerizable alkenes such as vinyl ethers were converted in higher yields and in shorter reaction times.[11b] Furthermore, the absence of a zinc salt avoids further complications of Schlenck-type equilibria. The initial active carbenoid species **14** ($EtZnCH_2I$) is believed to be in equilibrium with the highly reactive bis(iodomethyl)zinc **13** and diethylzinc (Scheme 9).[11,21]



Scheme 9

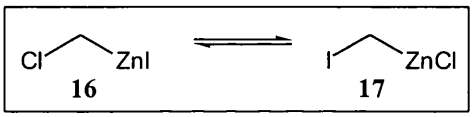
A significant amount of carbenoid decomposition results from homologation to form *n*-propyl zinc iodide **15** *via* facile alkyl-iodo exchange (path A).[18] However, a further carbenoid species **12** ($IZnCH_2I$) can be generated from *n*-PrZnI **15**, if excess diiodomethane is employed.[1g] In addition, a second pathway (path B) involving methyl extrusion can also occur but is less prominent (Scheme 10).[18]



Scheme 10

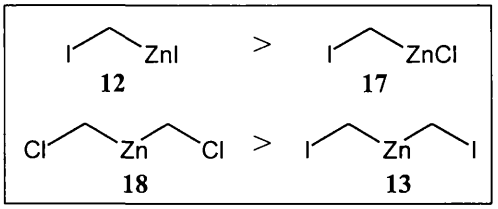
1.2.1.3 (Chloromethyl)zinc v (Iodomethyl)zinc Carbenoid Species

Clearly, the initial carbenoid species generated from activated zinc and chloroiodomethane is **16**, after oxidative addition of zinc into the carbon-iodine bond, since dichloromethane is totally unreactive with the metal.[8b] However, based on the fact that a considerable amount of iodomethane can be detected after quenching of the carbenoid species, it has been suggested that an *in situ* equilibration involving iodo for chloro exchange exists and lies heavily to the right.[17a] Thus as shown in Scheme 11, it is likely that the initially formed chloromethylzinc iodide **16** (or $(ClCH_2)_2Zn/ZnI_2$) is converted to iodomethylzinc chloride **17** (or $(ICH_2)_2Zn/ZnCl_2$) under the refluxing conditions in ether.[17a]



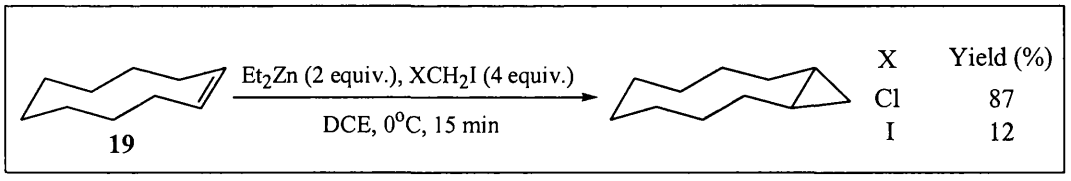
Scheme 11

Simmons and Smith had shown the yield obtained by using chloroiodomethane (8%) was considerably lower than using diiodomethane (48%) in the cyclopropanation of cyclohexene.[8b] On the other hand, Denmark provided substantial spectroscopic evidence for the fact that bis(chloromethyl)zinc reagents **18** prepared from 1 equiv. of diethylzinc with 2 equiv. of chloroiodomethane, were far more reactive than the iodo analogue **13** (Scheme 12).[21] Importantly, the spectroscopic data showed that the diethylzinc/chloroiodomethane system generated a different organometallic species to the diethylzinc/diiodomethane system. For example, the 1,2-dimethoxyethane (DME) complexes of $(ClCH_2)_2Zn$ **18** and $(ICH_2)_2Zn$ **13** in benzene-d_6 displayed resonances for the (halomethyl)zinc moiety at 2.71 and 1.40 ppm, respectively, in the ^1H NMR spectra, and 29.60 and –19.67 ppm, respectively, in the ^{13}C NMR spectra.[22] Solutions of $(ClCH_2)_2Zn$ **18** were found to be generally less stable than solutions of $(ICH_2)_2Zn$ **13**, when analysed spectroscopically.[21]



Scheme 12

The reactivity difference between the iodo and chloro-carbenoids was particularly evident when 1,2-dichloroethane was used as a solvent for the cyclopropanation. For example, the cyclopropanation of a simple aliphatic alkene such as *cis*-cyclodecene **19** in 1,2-dichloroethane, led to a rapid high-yielding reaction by using the bis(chloromethyl)zinc species (Scheme 13).[21] The rate of reaction was significantly reduced by the use of ethereal solvents (Et_2O, THF) and hexane was unsuccessful due to the insolubility of the (halomethyl)zinc reagents in the solvent. Many by-products were obtained when the cyclopropanation was performed in benzene or toluene. However, this was overcome by using chlorobenzene as the solvent, since (halomethyl)zinc reagents are electrophilic and therefore react less readily with electron-poor aromatic compounds.[1,23] As observed with the traditional Simmons-Smith reagents, the cyclopropanation of styrene derivatives such as (*E*)-1-phenylpropene proved to be problematic, presumably due to the possible side reaction of the carbenoid with the aromatic ring as the starting alkene was consumed under the reaction conditions.[21]



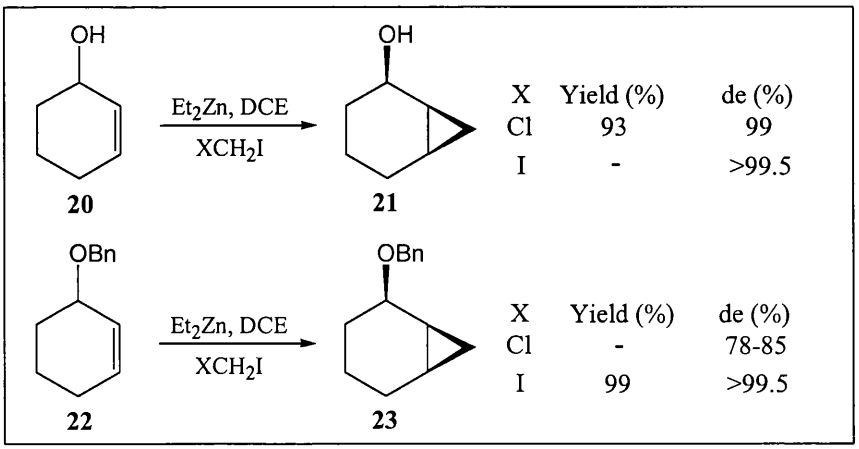
Scheme 13

Thus, the solvent used in zinc-mediated cyclopropanation reactions plays an important role in these reactions, owing to the electrophilic nature of the zinc carbenoid and Lewis acidity of the reagent. The carbenoids prepared from diethylzinc and a dihalocompound, are more reactive in non-complexing solvents such as dichloromethane or 1,2-dichloroethane.[21] Basic solvents decrease the rate of cyclopropanation[24] as they can coordinate to the tetrahedral zinc centre as ligands.

The stability of the carbenoid can be greatly improved by the addition of an equimolar quantity of dimethoxyethane to diethylzinc.[25]

Although the typical procedure for cyclopropanations using diethylzinc/diiodomethane involves treatment of the alkene with diethylzinc followed by addition of diiodomethane, this procedure is inefficient for the cyclopropanation of allylic alcohols as an initial reaction of the alcohol with diethylzinc generates a zinc alkoxide aggregate[1c,26] and this reacts poorly with the dihalomethane to form the (halomethyl)zinc reagent.[21] However, this is overcome by the formation of the reagent prior to addition of the allylic alcohol.[21]

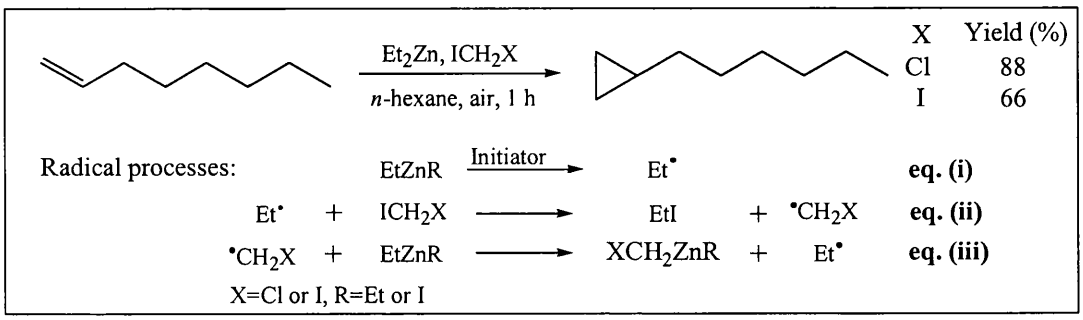
The directing effect of proximal oxygen substituents on the stereochemical outcome of Simmons-Smith cyclopropanations was also exhibited by the (chloromethyl)zinc reagent. Thus, cyclopropanation of 2-cyclohexen-1-ol **20** with $Et_2Zn/ClCH_2I$ afforded the cyclopropane **21** with 99% de. The minor *trans* diastereomer was also not detected in reactions using Et_2Zn/CH_2I_2, but the yields were unstated and lower. On the other hand, cyclopropanation of **22** with $Et_2Zn/ClCH_2I$ afforded the corresponding cyclopropane **23** with only 78-85% de in a lower unstated yield, while the use of Et_2Zn/CH_2I_2 afforded **23** exclusively in quantitative yield (Scheme 14).[21] Moreover, Charette and co-workers have shown that the stoichiometry of the diiodoalkane and diethylzinc is very important for optimising the yields and the diastereomeric ratios for allylic alcohols, when zinc reagents are used.[27]



Scheme 14

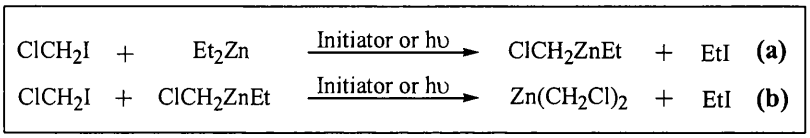
No clear explanations have been proposed for the difference in reactivity, although several factors can be ruled out. From spectroscopic analysis, the rate of formation of both (halomethyl)zinc reagents was extremely rapid using both chloroiodomethane and diiodomethane and furthermore, only trace amounts of dihalomethane were detected from the crude reaction mixture. Hence, the rate of reagent formation does not account for the reactivity difference.[21] The solubility of the reagents also did not seem to be a factor as cyclopropanations involving either the (chloromethyl)zinc or (iodomethyl)zinc reagents, gradually became heterogeneous with the formation of zinc halide salts.[21]

Interestingly, Miyano and co-workers revealed that for a variety of simple olefins, the bis(chloromethyl)zinc reagent affords slightly higher yields than those obtained with the (iodomethyl)zinc analogue in the presence of oxygen (Scheme 15).[28] This was due to the fact that the oxygen promotes radical formation and thus accelerates the rate of reagent formation in diethylzinc/chloroiodomethane reactions. The presence of trace amounts of adventitious oxygen (e.g. from air in syringe needles) was sufficient to catalyse rapid reagent formation in small-scale (0.1-4 mmol) reactions. In addition, the presence of AIBN or UV light were also found to accelerate cyclopropanation. The radical processes are initiated by the formation of the ethyl radical either by the reaction of diethylzinc with oxygen or by the decomposition of AIBN in the presence of diethylzinc (eqs. (i)-(iii), Scheme 15). Addition of dry air to these reactions resulted in the destruction of the reagent and prevented complete consumption of starting material. It is not surprising that adventitious oxygen was not sufficient to promote complete reagent formation in larger scale reactions (10 mmol or greater) as a number of radical-quenching processes are also present (Scheme 15).[28]



Scheme 15

The first equivalent of dihalomethane is consumed rapidly even under a nitrogen atmosphere but cyclopropanation was unsuccessful (Scheme 16a). However, in the presence of oxygen, the accelerated rate of cyclopropanation was attributed to the formation of the more reactive bis(chloromethyl)zinc reagent (Scheme 16b).[28] This is consistent with the general trend observed for the chemistry of dialkylzinc reagents that reaction of the first alkyl group is much more facile than the second.[1c]

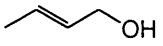


Scheme 16

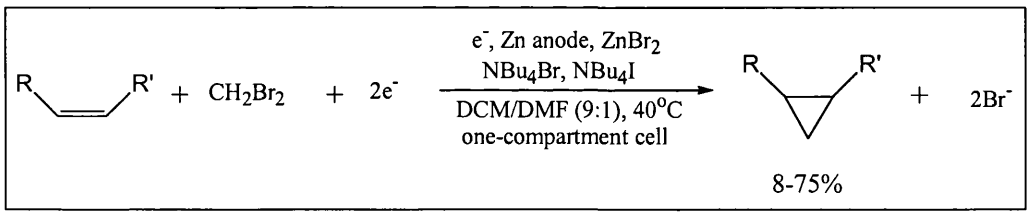
1.2.1.4 The Reactivity of Bromomethylzinc Bromide [$BrZnCH_2Br$]

Although dibromomethane is considerably less expensive and more stable than diiodomethane, only a few papers on the use of this reagent have been reported for the generation of the zinc carbenoids. This is due to the fact that the zinc dust usually needs a special activation procedure involving either sonication[29] or electrochemistry[30] in order to react with the dibromomethane. More recent methods have utilised titanium tetrachloride[31] or acetyl chloride[32] catalysis in order to activate the metal and these protocols afford the cyclopropane in more reproducible yields than using the initial procedure reported by LeGoff.[33] The authors propose that the function of both, acetyl chloride[32] and titanium tetrachloride[31] is the liberation of hydrochloric acid produced from traces of water which then reacts with the oxide layer on the metal surface, rather than the formation of an organotitanium intermediate in the latter case. Moreover, as shown below, the reactivity of the bromomethylzinc carbenoids are generally lower than the corresponding iodo equivalents (Table 1).

Table 1: Cyclopropanation[29-36] of alkenes using $BrZnCH_2Br$ or $IZnCH_2I$

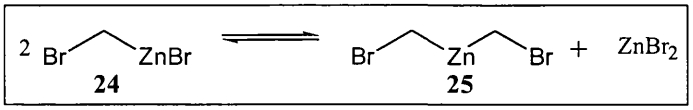
Alkene	Yield of cyclopropane product (%) with activated zinc and CH_2X_2					
	Zn/Cu CH_2I_2[ref.]	Zn/Cu CH_2Br_2[ref.]	Zn/Cu CH_2Br_2 sonication[29]	Zn/Cu CH_2Br_2 $TiCl_4$[31]	Zn/Cu CH_2Br_2 MeCOCl[32]	Zn anode CH_2Br_2 electrolysis[30]
	92[34]	61[33]	60	58	61	-
	94[34]	56[33]	72	73	88	64
	52[35]	68[36]	57	36	58	94

As in the classical zinc-promoted Simmons-Smith reaction,[1a,g] the electrochemical zinc-based system[30] also illustrated that allylic alcohols were more reactive than unfunctionalised alkenes and cyclopropanation occurred with retention of stereochemistry (Table 1). The zinc generated by this method was considerably more reactive due to the high surface area and purity of the metal.[37] In fact, this was the first time that zinc carbenoids were generated by electrochemistry (Scheme 17). As expected, the use of the more reactive diiodomethane, gave slightly higher yields with polymerizable olefins. However, with allylic alcohols, nucleophilic substitution readily occurred. A similar yield with allylic alcohols was observed when bromochloromethane was used to generate the carbenoid.[30]



Scheme 17

Interestingly, in sharp contrast to iodomethylzinc species, spectroscopic evidence showed that the Schlenck equilibrium for bromomethylzinc bromide **24** lies heavily on the side of bis(bromomethyl)zinc species **25** (Scheme 18).[38]

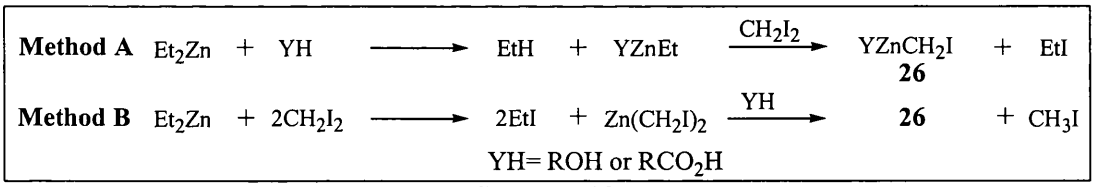


Scheme 18

1.2.1.5 The Effect of the Y Group on the Reactivity in Functionalised Halomethylzinc Carbenoids [$YZnCH_2X$]

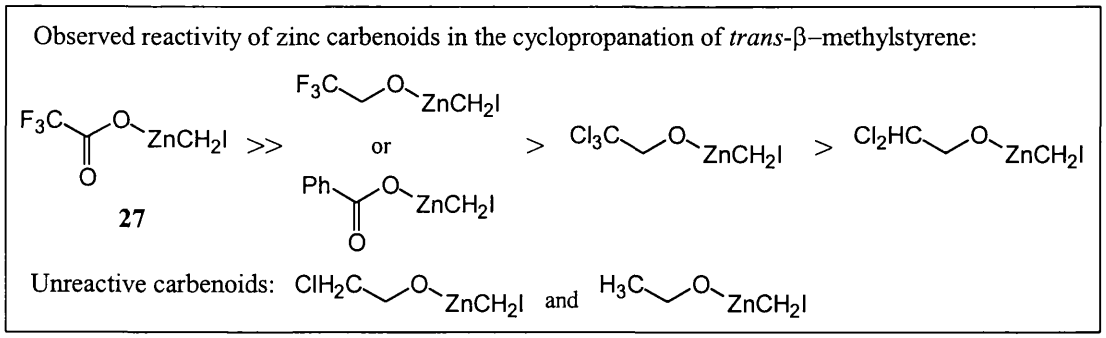
In more recent years, Shi[39] and in particular Charette,[40,41,42] have modified the nature of the Y group on the zinc ($YZnCH_2X$) in order to enhance reactivity and stability of the metal carbenoid in relation to the classical Simmons Smith carbenoids.

Shi and co-workers reported the reactivities of a range of zinc carbenoids derived from a variety of alcohols and acids.[39] The carbenoid species **26** could be generated by two different methods as shown in Scheme 19, differing by the order of reagent addition.[39] In the first instance, the alcohol or acid can be deprotonated using diethylzinc followed by a metal-halogen exchange with diiodomethane to provide the cyclopropanating reagent (Method A). Alternatively, one equivalent of the substrate can be treated with 1 equiv. of $Zn(CH_2I)_2$ (Method B).[11a,b] Both methods of preparation gave similar yields but the first method is more favourable due to the use of only one equivalent of diiodomethane and also avoids the formation of the less stable bis(iodomethyl)zinc species as observed in the latter procedure.



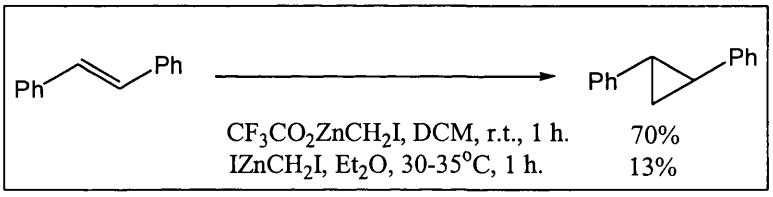
Scheme 19

Interestingly, as illustrated in Scheme 20, a direct link between the acidity and reactivity of the carbenoid species was established.[39] Clearly, the higher the acidity of the Y group on the zinc atom, the higher the reactivity of the carbenoid in the cyclopropanation reaction.



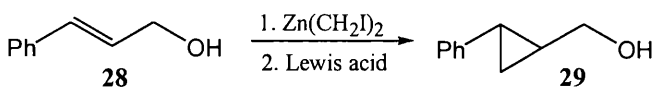
Scheme 20

Thus, the reagent prepared by mixing stoichiometric quantities of diethylzinc, trifluoroacetic acid, and diiodomethane ($CF_3CO_2ZnCH_2I$, **27**)[39] was found to enhance the cyclopropanation of stilbene in comparison to typical cyclopropanation conditions such as the use of "$IZnCH_2I$" (Scheme 21).[43] In similar fashion, a variety of similar unfunctionalised alkenes was successfully cyclopropanated in good yields after short reaction times (typically 20-150 min).[39]



Scheme 21

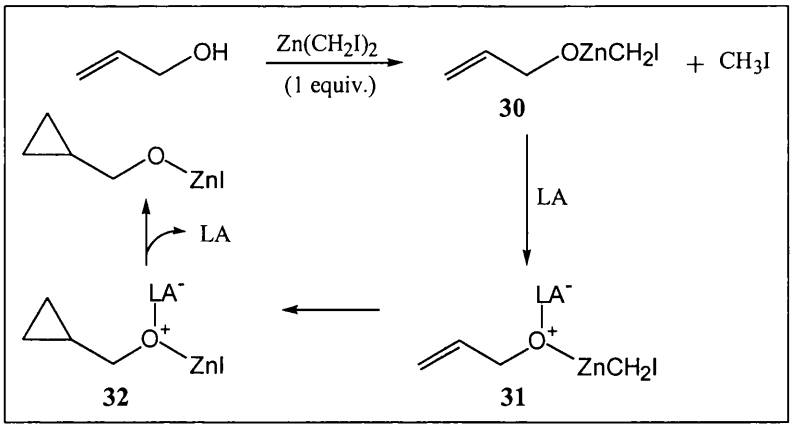
On the other hand, Shi reported that the carbenoids derived from 2-chloroethanol and ethanol were both unreactive in the cyclopropanation of *trans*-β-methylstyrene.[39] In fact, Charette and co-workers reported that the carbenoids of the general form "$ROZnCH_2I$" (R=alkyl or allyl) showed increased reactivity towards alkenes only in the presence of Lewis acids. (Scheme 22).[40a]



	NMR conversion (%)		
Lewis acid	0°C	-20°C	-40°C
none	23	<5	<5
BBr_3	93	90	60
$B(OMe)_3$	50	10	4
$TiCl_4$	94	90	60
$Ti(O\textit{i}\text{-}Pr)_4$	50	45	8
$TiCl_2(O\textit{i}\text{-}Pr)_2$	85	80	45
$SiCl_4$	90	88	58
$SnCl_4$	83	55	55
Et_2AlCl	93	87	70
$Zn(OTf)_2$	45	18	7
ZnI_2	50	14	9

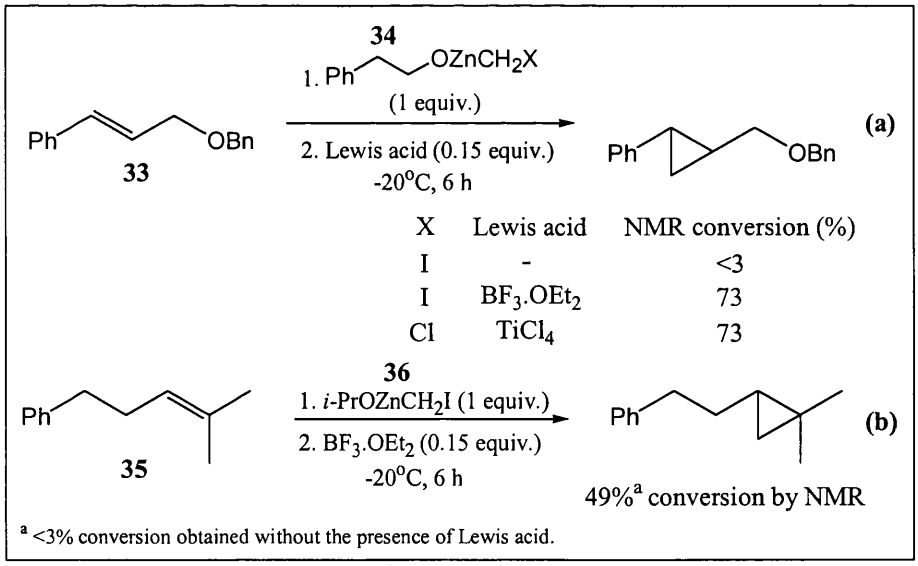
Scheme 22

The carbenoid species **30** were prepared by a similar procedure used by Shi, by treatment of allylic alcohols with 1 equiv. of $Zn(CH_2I)_2$ (method B, Scheme 19).[40a] The rate of the intramolecular cyclopropanation for these alkoxy(iodomethyl)zinc species **31** was significantly accelerated due to the increased electrophilicity of the methylene group upon complexation with the Lewis acid.[40a] Moreover, the Lewis acid was regenerated from the resultant halozinc alkoxide intermediate **32** to complete a catalytic cycle (Scheme 23). Interestingly, in this system, a general trend was formulated between the reactivity of the carbenoid and the strength of the Lewis acid (Scheme 22). Thus, stronger Lewis acids (such as $TiCl_4$, BBr_3, $SiCl_4$, $SnCl_4$, Et_2AlCl) were more effective at catalysing the reaction than weaker Lewis acids ($Ti(O\textit{i}\text{-}Pr)_4$, $B(OMe)_3$, $Zn(OTf)_2$).[40] It is noteworthy to mention that the cyclopropanation of cinnamyl alcohol **28** using $IZnCH_2I$ is competitive with the formation of the zinc alkoxide. For example, the corresponding cyclopropane **29** and iodomethane were formed in a 3:2 mixture.[40a]



Scheme 23

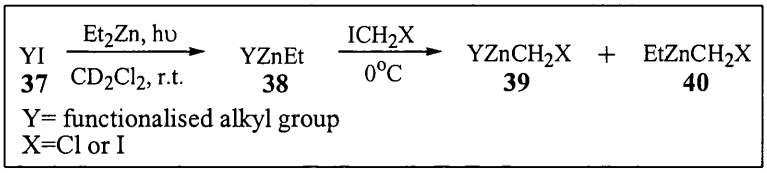
In addition, both iodo- and chloromethylzinc reagents **34** were found to induce intermolecular cyclopropanation of an allylic ether **33** in the presence of Lewis acid (Scheme 24a).[40b] Secondary alcohols were also used to generate efficient halomethylzinc alkoxides **36** as illustrated in the cyclopropanation of the unfunctionalised alkene **35** (Scheme 24b).[40b]



Scheme 24

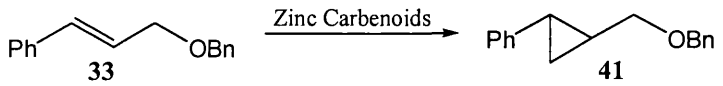
Functionalised halomethylzinc carbenoids **39** were also prepared from several corresponding alkyl iodides **37**.[41] The preparation involved the irradiation of a stoichiometric mixture of diethylzinc and a functionalised alkyl iodide **37** to form a mixed diorganozinc reagent **38**. Subsequent reaction with dihalomethane then results in the formation of a mixture of functionalised zinc carbenoid **39** as well as the achiral Furukawa reagent, $EtZnCH_2X$ **40**, in which the ratio of the carbenoids varied

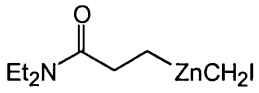
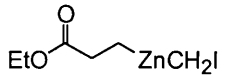
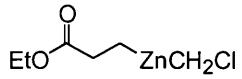
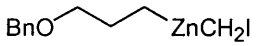
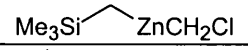
according to the nature of the Y group (Scheme 25).[41] The regioselectivity of the exchange was determined by the relative integration of iodoethane and the starting iodide by ^{1}H NMR. An alternative approach to the carbenoid species, which involves the direct reaction of the diorganozinc reagent, Y_2Zn, with ICH_2X, is undesirable as one equivalent of an alkyl group would be converted into the corresponding alkyl iodide.[41]



Scheme 25

From the study of these functionalised halomethylzinc species, a pattern emerged between basicity of the Y group and reactivity of the carbenoid species.[41] Thus, even though the presence of a basic group led to high regioselectivity in the halogen-metal exchange reaction, the reactivity of the functionalised carbenoid in cyclopropanation of the benzyl ether of cinnamyl alcohol **33**, was higher in the presence of less basic groups. For instance, the presence of an amide group ensured high regioselective exchange of the ethyl group for CH_2I, however, the resulting carbenoid was unsuccessful as a cyclopropanation reagent (entry 1, Scheme 26). Contrastingly, an electron-withdrawing ester group allows the exchange to be partially regioselective, but the carbenoid reacts to afford the cyclopropane **41**, albeit in low yield (entry 2). Interestingly, the addition of ether (2 equiv.) slightly increased regioselectivity but decreased reactivity as the resulting carbenoid was slightly less electrophilic due to the additional complexation. The use of chloroiodomethane in the absence of ether provided high regioselectivity and higher reactivity in the cyclopropanation (entry 3). Although the 3-benzyloxypropyl group led to a relatively efficient zinc carbenoid species, the regioselectivity in the exchange reaction was low (entry 4). By far, the most effective functionalised carbenoid in terms of both, high regioselectivity and excellent reactivity in cyclopropanation, was derived from trimethylsilylmethyl iodide (entry 5).[41] This simple method is compatible with a variety of solvents and also does not lead to any by-products.

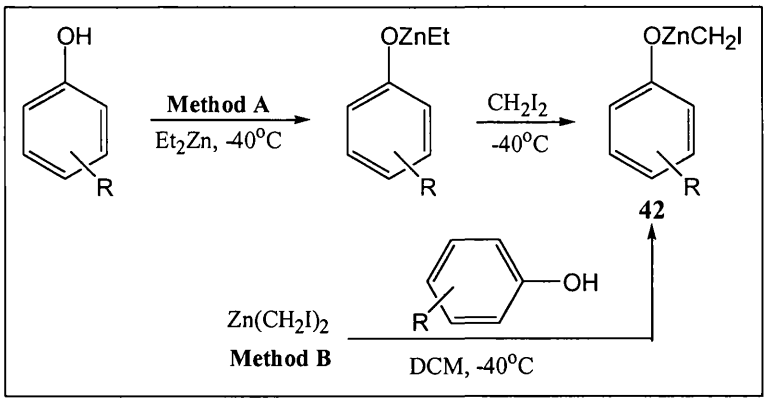


Entry	Zinc Carbenoids			Ratio of Carbenoids	Yield (%)[a]
1		+	$EtZnCH_2I$	(>98:2)	0
2		+	$EtZnCH_2I$	(>97:3)	21
3		+	$EtZnCH_2Cl$	(>98:2)	42
4		+	$EtZnCH_2I$	(72:28)	>90
5		+	$EtZnCH_2Cl$	(94:6)	>95

[a] Determined by ^1H NMR and GC analysis with internal standard.

Scheme 26

Charette has also reported the use of several iodomethylzinc phenoxides **42** ("$ArOZnCH_2I$") as carbenoids for the efficient cyclopropanation of aryl- and alkyl-substituted alkenes.[42] The carbenoids "$ArOZnCH_2I$" **42** were easily prepared by applying the same two methods used in the formation of Shi Carbenoids (Methods A and B, Scheme 27).[42]



Scheme 27

The reactivity of the zinc phenoxide carbenoids **42** was highly dependent upon the position and nature of the substituents on the aromatic ring. For example, carbenoids exhibiting two *ortho* substituents gave high cyclopropane conversions (**43-46**). The substituents are likely to prevent self-destruction of the carbenoid by an intramolecular electrophilic aromatic substitution.[23d] Although a clear trend between

the pK_a of the phenol and the yield of cyclopropanation was not established, several electron-withdrawing groups were also found to be paramount, especially when these were at the *para* position (**43-46**). The highest reactivity was therefore achieved with 2,4,6-trihalophenol precursors **43** (when Z=F, Cl, and Br) as a result of an increase in the electrophilicity of the zinc carbenoid and a decrease in the nucleophilicity of the aromatic ring, thus preventing rapid decomposition of the carbenoid. As little as 1.1 equiv. of the carbenoid prepared from **44** and **45** may be employed to achieve high conversions (Figure 4).[42]

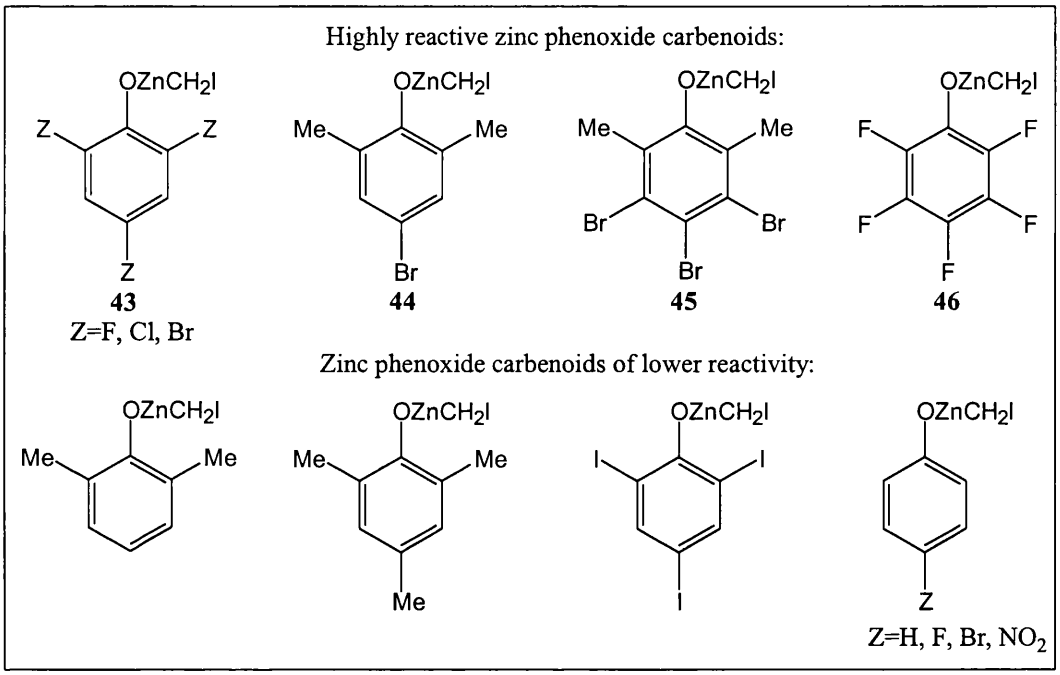
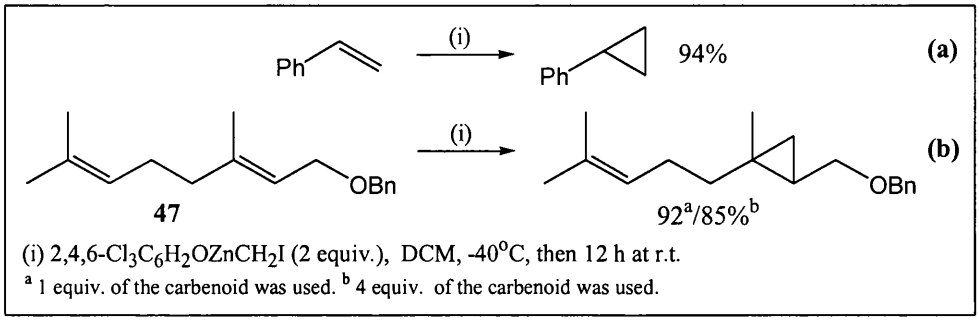


Figure 4

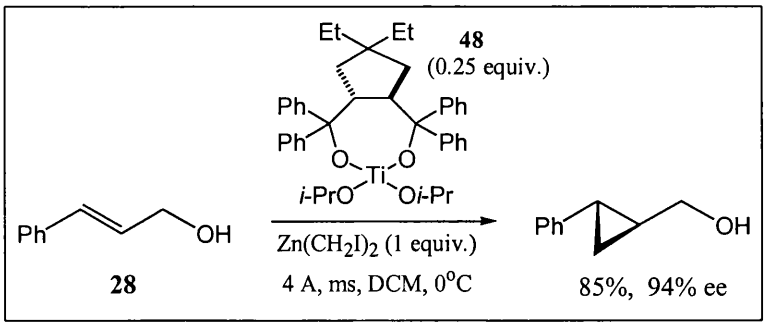
In particular, the carbenoid derived from the cheap and readily available; 2,4,6-trichlorophenol, showed a very high reactivity for the cyclopropanation of aryl- and alkyl-substituted alkenes (Schemes 28a and b).[42] In accord with the traditional chemistry of zinc carbenoids, chemoselective monocyclopropanation of an allylic ether in the presence of a trisubstituted alkene **47** was observed when only one equivalent of the reagent was used, whereas an excess of the reagent, predictably, led to the dicyclopropane derivative (Scheme 28b). Moreover, the carbenoid was relatively stable, as high yields were achieved by using a solution of 2,4,6-$Cl_3C_6H_2OZnCH_2I$ in CH_2Cl_2, which was stored for 1 hour at 0°C. However, a

significant decrease in yields were obtained when a solution of the carbenoid that was four hours old, was used.[42]



Scheme 28

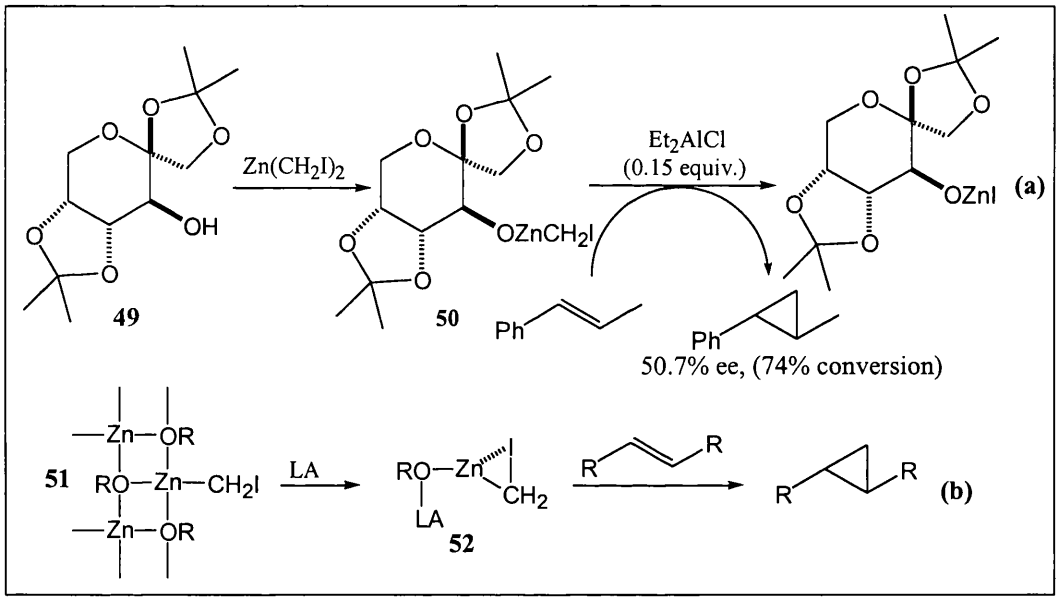
Many of the foregoing studies of Shi[39] and Charette[40,41,42] were carried out in order to explore the possibility of enantioselective cyclopropanation of alkenes. Thus far, these cyclopropanations have relied on the use of stoichiometric[24,25b,27b,44] or catalytic amounts[19,40a,45] of external chiral ligands to direct the stereochemical outcome of the reaction. Furthermore, these are limited to allylic alcohols which usually afford good enantioselectivities since the hydroxy group (or its zinc alkoxide) acts as a linker between the reagent and the chiral additive. For instance, one elegant example has been reported by Charette on the use of the titanium catalyst **48** in the enantioselective cyclopropanation of cinnamyl alcohol **28**. An excellent enantiomeric excess was obtained suggesting that the Lewis acid **48** is involved in the transition state (Scheme 29).[46]



Scheme 29

On the other hand, there are few reports involving the asymmetric cyclopropanation of unfunctionlised alkenes by using chiral (halomethyl)zinc carbenoids. In one case, (-)-menthol was used as the chiral inducer, and >4% ee was obtained.[47] No ee was

reported ($[\alpha]^{25}_D$ of –0.77) in another example involving the use of L-leucine as the chiral inducer.[16a] A much higher enantioselectivity was observed when Shi carbenoids were applied to the asymmetric cyclopropanantion of *trans*-β-methylstyrene in the presence of Lewis acid (50.7% ee).[39] Thus, the chiral (iodomethyl)zinc reagent **50** was prepared from the fructose-derived alcohol **49** (Scheme 30).[48] The Lewis acid was essential for the reaction due to its ability to break down the likely formation of zinc aggregates[49] (ROZnR') or $(ROZnCH_2I)_n$ **51** in the reaction mixture and this results in a vacant zinc orbital for the iodine to coordinate in **52**, thus activating the methylene group for cyclopropanation.[39]



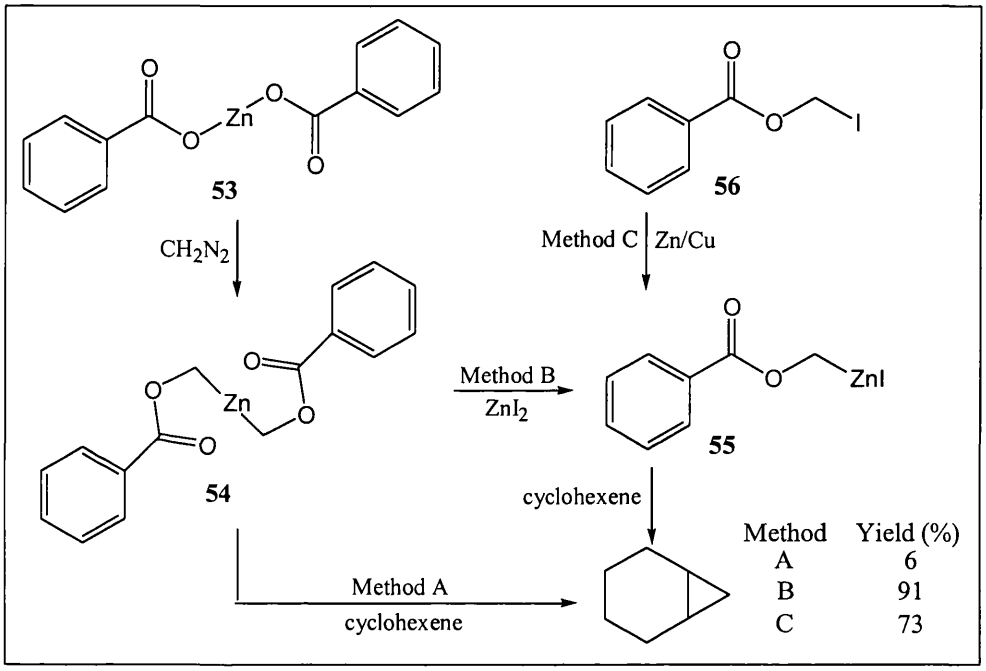
Scheme 30

1.2.1.6 The Effect of the Leaving Group X on the Reactivity in Functionalised Methylene Zinc Carbenoids [$YZnCH_2X$]

Surprisingly, there are few examples to show the variation of the leaving group X in zinc carbenoids, other than the traditional well-known ones which involve the halogen atom (where X=I, Br, Cl).

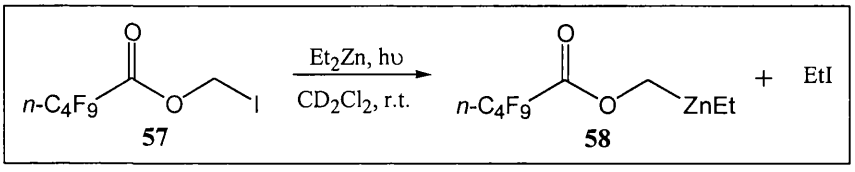
In one case, Wittig[10e] reported the use of bis(benzoyloxymethyl)zinc reagent **54**, prepared easily from zinc benzoate **53** and diazomethane, as a poor cyclopropanating reagent as demonstrated by the reaction of cyclohexene (Method A). However, in the presence of metal halide salts, considerable improvements in the yields were noted

especially in the use of zinc halide (Method B). Thus, in this case the active reagent is likely to be the benzoyloxymethylzinc iodide species **55** generated from the reaction of bis(benzoyloxymethyl)zinc reagent **54** with the metal halide salt. A similar high yield was also obtained when the identical carbenoid species **55** was formed from 1-iodoethyl benzoate **56** and zinc-copper couple (Method C, Scheme 31). Furthermore, the authors provided evidence that the carbenoid species **55** reacted in a concerted fashion with the alkene.[10e]



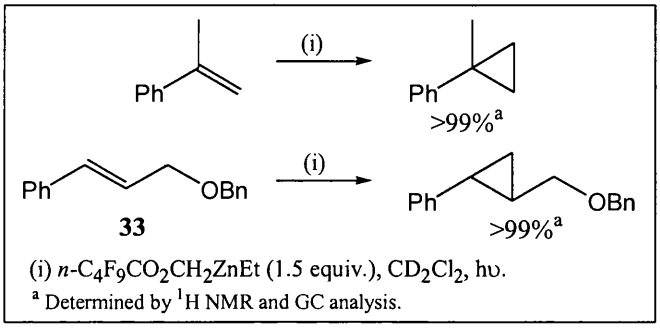
Scheme 31

Charette has recently reported the use of acyloxymethylzinc carbenoids **58** as highly reactive species for cyclopropanation.[50] The carbenoid, ethylzincmethyl perfluoropentanoate **58** was easily prepared from a 1:1 mixture of iodomethyl perfluoropentanoate **57** and diethylzinc by a zinc-iodine exchange and this was indicated by the quantitative formation of iodoethane from ^{1}H NMR analysis.[50] More conveniently, the desired alkylzinc reagent may also be prepared in the presence of the alkene, using photoinduced zinc-iodine exchange (Scheme 32).[51]



Scheme 32

The resulting carbenoid species **58** efficiently cyclopropanated unfunctionalised alkenes such as α-methylstyrene as well as functionalised substrates as illustrated by **33** (Scheme 33).[50] Interestingly, the parent zincmethylbenzoate compounds have been shown to be poorly reactive either as electrophiles[10e] or nucleophiles.[52]



Scheme 33

The enhanced reactivity of this particular type of carbenoid can be explained in terms of an increase in the electrophilicity of the carbenoid as a result of the electron-withdrawing R group which is further enhanced through intramolecular coordination to the zinc atom as illustrated by **59** in Figure 5.[50] This type of carbenoid with internal Lewis Acid activation acting as a methylene transfer reagent is similar to the successful cyclopropanations with Lewis Acid catalysis[40a] in the modification of the Simmons-Smith reaction using Nakamura's reported 5-membered, cyclic transition state.[53]

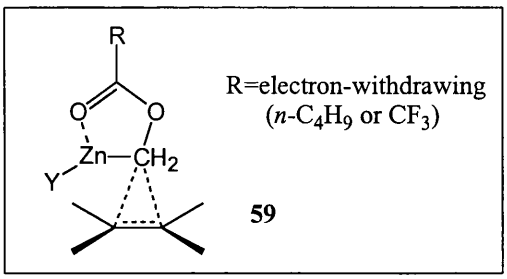
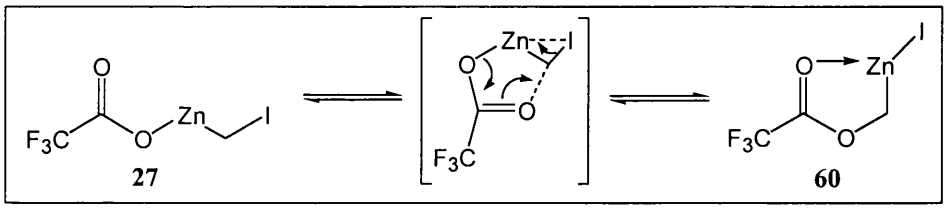


Figure 5

These carbenoids also provide substantial evidence that the enhanced reactivity of Shi's carbenoid[39] might be attributed to the *in situ* equilibration of "$CF_3CO_2ZnCH_2I$" **27** leading to the formation of iodomethylzinc trifluoroacetate **60** under the reaction conditions (Scheme 34).[50] In fact, the ratio of the initial carbenoid species **27** with the acyloxymethylzinc **60**, varied between 2:1 and 4:1 and was determined by NMR and

GC analysis of hydrolysed reaction aliquots, respectively.[50] Hence, a significant amount of the cyclopropane formation can be attributed to the reaction by the zincmethylester **60**, since 2 equiv. of the carbenoid were employed. The proposed equilibrium is precedented and generally applies to several mixed zinc carbenoids as previously discussed ($YZnCH_2X \leftrightarrow YCH_2ZnX$, *vide supra* 1.2.1.2 and 1.2.1.3).[17b,18,54]

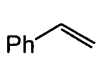
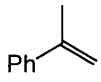
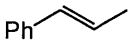
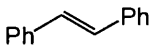
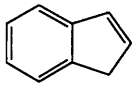
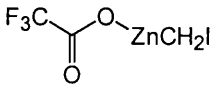
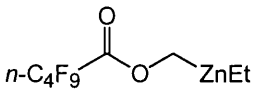
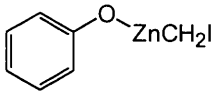
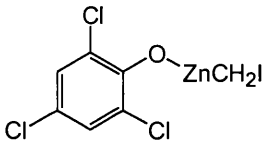


Scheme 34

1.2.1.7 A Direct Comparison of Various Methylene Zinc Carbenoids

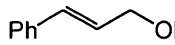
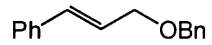
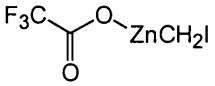
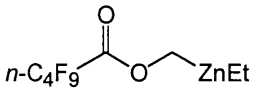
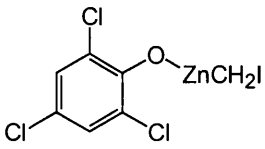
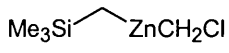
At this stage, it is appropriate to contrast the reactivities of the various methylene zinc carbenoids discussed in the foregoing sections. As shown in Table 2, it is clear that the zinc 2,4,6-trichlorophenoxide[42] **62**, Shi's[39] **27** and acyloxymethylzinc[50] **58** carbenoids are generally more reactive than the Simmons-Smith reagent[8,17] **12**, Furukawa reagent[11a,b] **14** and bis(iodomethyl)zinc[21] **13** for the cyclopropanation of aryl-substituted olefins. Moreover, they show comparable reactivity to Denmark and Edwards' highly reactive bis(chloromethyl)zinc species[21] **18**. The high difference in reactivity between the 2,4,6-trichlorophenoxide **62** and the phenoxide species **61** is particularly noteworthy and illustrates the importance of the effect of the substituents attached to the phenyl ring in determining the reactivity of the resulting carbenoid species.[42] In addition, all of these functionalised methylene carbenoids show an expected high reactivity in the cyclopropanation of allylic alcohols (Table 3).

Table 2: Cyclopropanation of aryl-substituted alkenes using methylene zinc carbenoids

	Zinc Carbenoid	% Yield[ref.] of cyclopropane[a,b]				
						
12	ICH_2ZnI	(69)[34]	(>75)[55]	(41)[56]	(24)[56]	(82)[57]
14	ICH_2ZnEt	(76)[42]	85[42]	-	-	58[42]
13	$Zn(CH_2I)_2$	47[42]	86[42]	88[21]	-	50[42]
18	$Zn(CH_2Cl)_2$	>95[42]	>95[42]	92 (84)[21]	-	93[42]
27		100 (85)[39]	-	100 (77)[39]	>90 (70)[39]	-
58		-	100[50]	78[50]	(35)[50]	88[50]
61		10[42]	22[42]	-	-	<1[42]
62		>95 (94)[42]	>95 (91)[42]	-	-	>95 (94)[42]

[a] Determined by ^1H NMR and GC analysis.[b] Isolated yields are shown in parentheses.

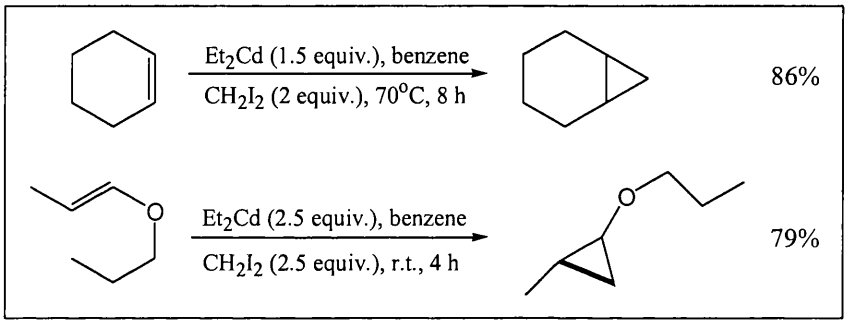
Table 3: Cyclopropanation of allylic alcohols using methylene zinc carbenoids

	Metal Carbenoid (s)	% Yield of cyclopropane[a,b]		Ref.
				
13	$Zn(CH_2I)_2$	(16)	(96)	21
18	$Zn(CH_2Cl)_2$	(96)	(100)	21
27		100 (80)	-	39
58		-	100	50
62		-	>95 (98)	42
63:**64** (94:6)	 + $EtZnCH_2Cl$	-	>95	41

[a] Determined by ^1H NMR and GC analysis.[b] Isolated yields are shown in parentheses.

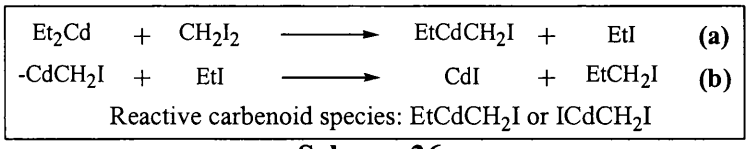
1.2.2 Cadmium Carbenoids

Cadmium carbenoids[58] have also been generated by Furukawa in an analogous manner. Thus, the reaction of diiodomethane with diethylcadmium was found to give an organocadmium reagent which, in contrast to Simmons Smith zinc carbenoids,[1a] could only cyclopropanate electron rich alkenes such as cyclohexene and *cis*- and *trans*-propenyl *n*-propyl ether. As illustrated for these latter alkenes, the reaction was once again stereospecific (Scheme 35).[58]



Scheme 35

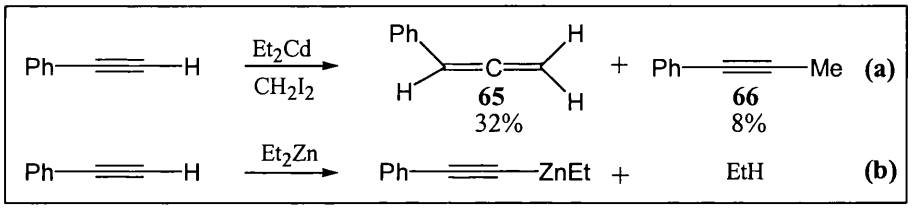
A large amount of iodomethane was detected when a reaction mixture was quenched with water at an early stage of the reaction. This provides evidence for the active species in cyclopropanation containing the -$CdCH_2I$ linkage. The amount of iodoethane formed was nearly equivalent to that of diiodomethane consumed (Scheme 36a). In addition, a small amount of *n*-propyl iodide was observed and considerable amounts of white precipitate, probably cadmium iodide, were formed during the course of the reaction (Scheme 36b).[58] The former salt is likely to be formed by the decomposition of the carbenoid as observed with the corresponding zinc carbenoids.[18]



Scheme 36

Interestingly, the carbenoid generated from diethylcadmium and *gem*-dihaloalkane also reacts with acetylenic compounds to afford allene derivatives. Diethylcadmium and diiodomethane react with phenylacetylene to give phenylpropadiene **65** and

phenylmethylacetylene **66** in the ratio of 4:1 and only 17% of acetylenic hydrogen was consumed to form ethane.[58] A similar type of reaction was reported by Vo-Quang and Cadiot,[59] who obtained a 1:8 mixture of phenylpropadiene **65** and phenylmethylacetylene **66** by the use of zinc-copper couple in ether instead of diethylcadmium. This is in sharp contrast to the corresponding reaction with diethylzinc, in which metallation of acetylenic compound predominated over the formation of allene and 75% of acetylenic hydrogen was converted to ethane (Scheme 37).[59]



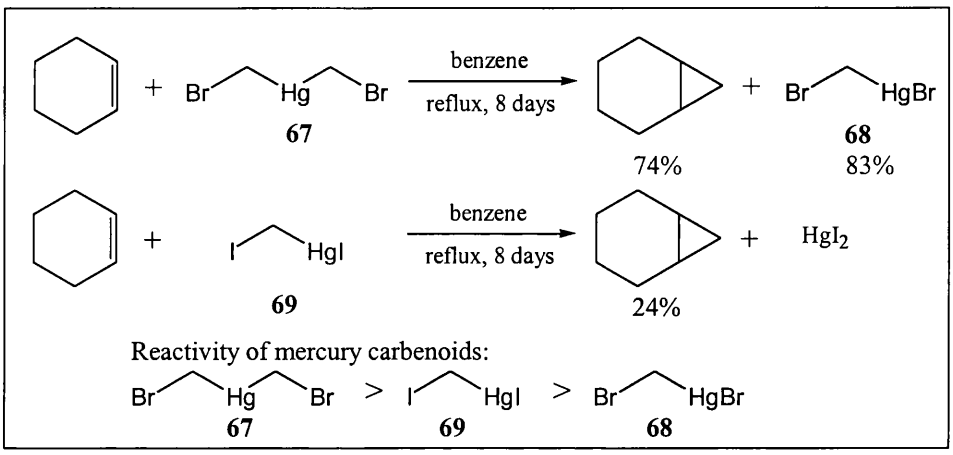
Scheme 37

1.2.3 Mercury Carbenoids

Organomercury compounds such as iodomethylmercury iodide **69** and bis(bromomethyl)mercury **67** are similar to the intermediates which have been considered for the Simmons Smith reaction, and likewise they have been found to cyclopropanate alkenes.[60] Both of the above mercury derivatives were prepared relatively easily in good yield. Thus, a light-induced reaction of diiodomethane with metallic mercury provided the former, while the latter was obtained by the reaction of mercuric bromide with diazomethane.[60]

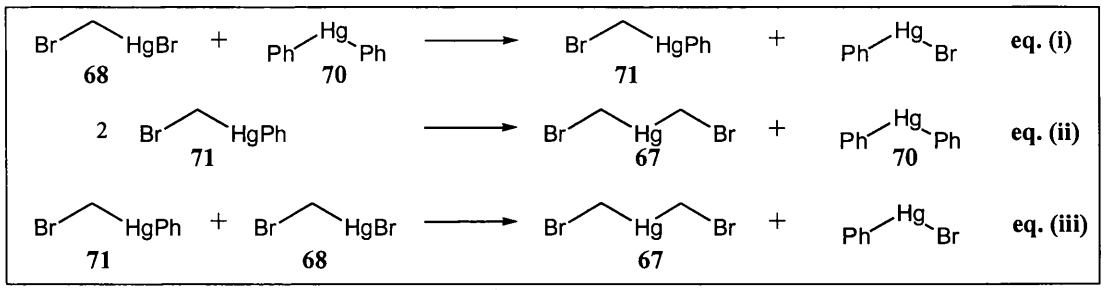
By analogy with zinc carbenoids,[21] bis(halomethyl)mercury reagents are also considerably more reactive than (halomethyl)mercury halide reagents.[60] For example, bis(bromomethyl)mercury **67** reacts with cyclohexene in inert solvents to give the corresponding cyclopropane in good yield after 8 days reflux (80°C or above), whilst bromomethylmercury bromide **68** is totally unreactive towards this alkene. However, in the absence of the alkene, the stability of bis(bromomethyl)mercury **67** in refluxing benzene even after heating times of 20 days is remarkable. Iodomethylmercury iodide **69** was more reactive as a methylene transfer reagent than its bromo analogue **68**. This species **69** reacted with cyclohexene using similar conditions to give the cyclopropane

in 24% yield (Scheme 38).[60] Due to their slow reaction with alkenes and the clearly unattractive nature of large scale preparations, organomercury carbenoids have not been widely used in organic synthesis.



Scheme 38

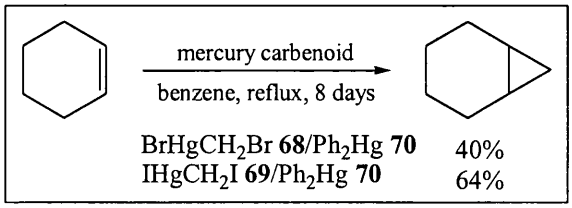
Bromomethylmercury bromide **68**, however, can be activated by the reaction of 1 equiv. of diphenylmercury **70** to generate phenylmethylmercury bromide **71** (eq. (i), Scheme 39), this can then react with itself to give the highly reactive bis(bromomethyl)mercury **67** species [eq. (ii)]. The latter species **67** may also be formed by the reaction of bromo- **68** and phenylmethylmercury bromide **71** [eq. (iii)].[60]



Scheme 39

Thus, under similar reaction conditions, an equimolar mixture of bromomethylmercury bromide **68** and diphenylmercury **70** affords the cyclopropane in moderate yield. In addition, a significant improvement in yield was noted when diphenylmercury **70** was used to activate the iodomethylmercury iodide **69** species

(Scheme 40). Evidence for the intermediacy of bis(iodomethyl)mercury was also obtained in these reactions.[60]



Scheme 40

Once again, electron-deficient alkenes and hindered alkenes were found to react more slowly than simple alkyl-substituted olefins, whereas electron-rich olefins gave higher yields. Thus, the active reagent involved in the methylene transfer from bis(bromomethyl)mercury is an electrophilic species. The carbenoid reaction was also stereospecific as demonstrated by the *cis* methylene addition to *cis*- and *trans* isomers of 3-heptene.[60]

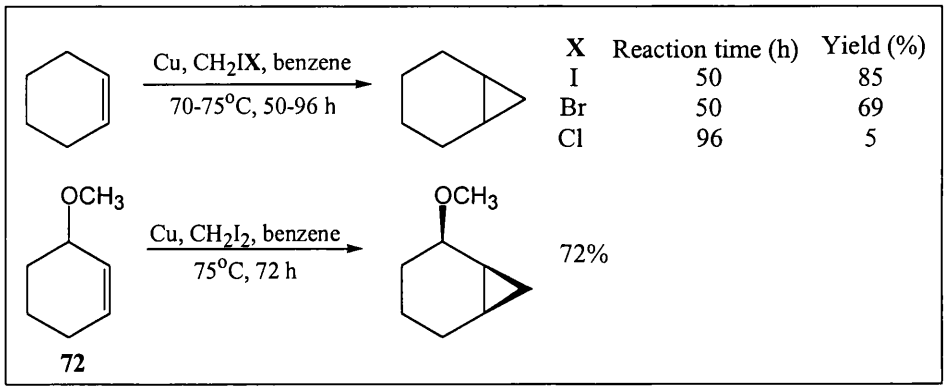
The use of a large amount of benzene as solvent results in a significantly slower reaction. This may be due to a possible side reaction of the carbenoid with the aromatic solvent. Higher temperatures (140°C) usually result in a faster methylene transfer, however, this is impractical for cyclopropane synthesis. Hence, moderate yields of cyclopropane are obtained at higher temperatures in concentrated conditions.[60]

It is of interest to compare the behaviour of organozinc and organomercury carbenoids at this stage. The relative reactivity of olefins in the Simmons-Smith reaction has been extensively studied by Blanchard[17a] and Rickborn[61] and co-workers. According to these groups, the steric effect on the approach of zinc carbenoid to a carbon-carbon double bond is important in the reaction with tetraalkylethylene. On the other hand, Seyferth *et al.*,[60] reported that the steric effect is not significant in the reaction of bis(bromomethyl)mercury with tetraalkylethylene although the reaction proceeds through a transition state similar to that of the Simmons-Smith reaction. They attributed the steric effect of the Simmons-Smith reaction to coordination of ether molecules to the zinc atom of the carbenoid, whereas the mercury carbenoid is not strongly solvated and the olefin reactivities are governed by electronic factors.

Thus, the zinc carbenoid with its associated ether molecules would be more sterically demanding in the determining transition state.

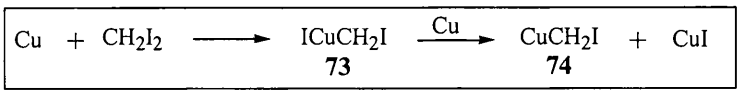
1.2.4 Copper Carbenoids

Copper has also been used for the cyclopropanation of alkenes.[62] High yields were obtained with either diiodomethane or bromoiodomethane by heating a mixture of cyclohexene and copper in benzene (Scheme 41). The reaction was stereospecific and hydroxyl-directed cyclopropanation was evident from the fact that no *trans* isomer was formed by the reaction of 3-methoxycyclohexene **72** with copper and diiodomethane (Scheme 41).[62b]



Scheme 41

However, even although the reaction conditions are similar to those of the Simmons-Smith cyclopropanation, the authors have suggested that the mechanism proceeds through an organocopper(I) intermediate[62b] **74** rather than the carbenoid **73**. However, it is likely that an initial copper carbenoid species **73** is formed by the oxidative addition of the metal into a carbon halogen bond and this is reduced by copper to give the reacting species **74** (Scheme 42). The mechanism of the subsequent cyclopropanation sequence using the organocopper(I) intermediate **74** is then considered to proceed *via* the previously mentioned "butterfly type" transition state (*vide supra* 1.2.1.1, Figure 3).

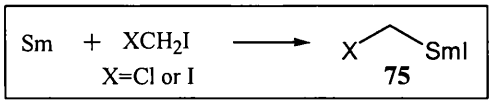


Scheme 42

1.2.5 Samarium Carbenoids

The samarium carbenoids[63] **75** offer several distinct advantages over the other methylene carbenoids (Scheme 43). Their preparation is extremely mild and high reproducible yields are usually obtained in short reaction times (2-3 h). More importantly, they exhibit unique chemoselectivity as they react exclusively with allylic alcohol substrates.[63] Thus, isolated alkenes or homoallylic alcohols are both inert to samarium carbenoids. In accord with normal carbenoid behaviour, the reaction of acyclic allylic alcohols proceeds with retention of alkene geometry.

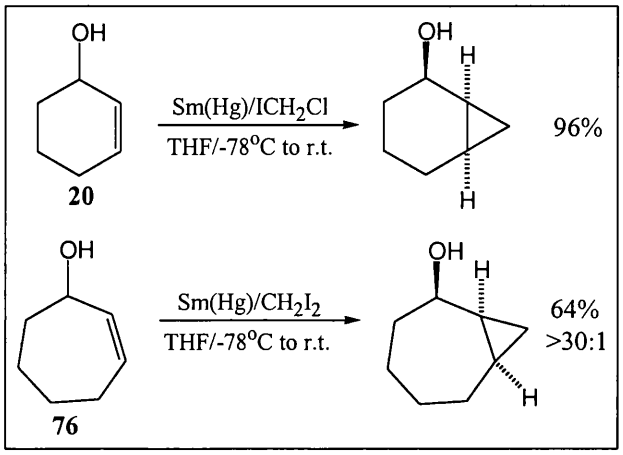
Both (iodomethyl) and (chloromethyl)samarium carbenoid species are easily prepared by the reaction of activated samarium with the corresponding dihalomethane compound (Scheme 43).[63] The metal can either be activated by catalytic amounts of mercury(II) chloride[63] or chlorotrimethylsilane.[64] Molander reported that samarium carbenoids are thermodynamically less stable than zinc carbenoids and decompose exceedingly rapidly *via* α-elimination to give samarium(II) halide and ethylene. Successful cyclopropanations are therefore carried out at –78°C, followed by warming to room temperature.[63]



Scheme 43

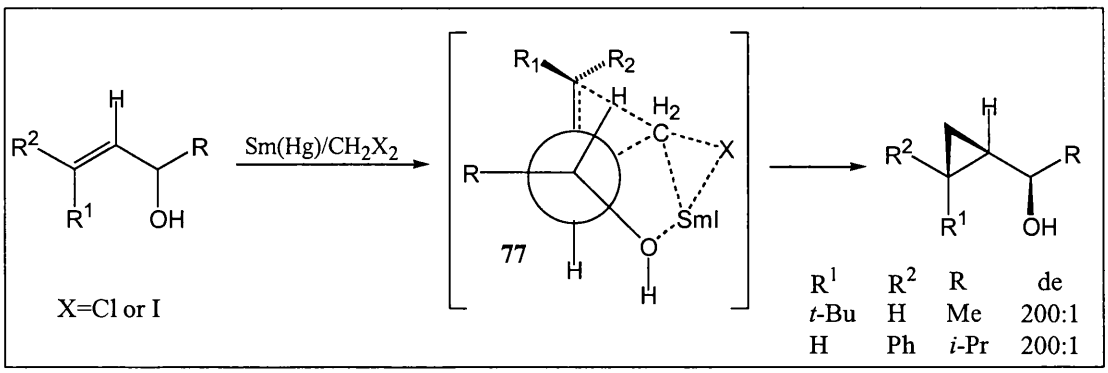
The reactions usually proceed *via* a hydroxyl-directed mechanism, thus, methylenation occurs from "the same side" as the hydroxy group.[63] For example, an excellent yield of "hydroxyl-directed" cyclopropane could be generated upon treatment of 2-cyclohexen-1-ol **20** with iodomethylsamarium iodide (Scheme 44).[63b] As in the case of the Simmons-Smith carbenoid,[65] no traces of the *trans* isomer were observed (Scheme 44). It is notable that in the case of 2-cyclohepten-1-ol **76**, the samarium-based cyclopropanation provides much higher diastereoselectivity (Scheme 44) than that observed under the traditional Simmons-Smith conditions where a 9:1 mixture of diastereomers is obtained.[65] In addition, exposure of the substrate to the samarium(II) iodide reagent for extended periods of time appears to have no effect on either the isolated yield or diastereoselectivity. In comparison, the yields of bicyclic

alcohols produced from cyclopropanation of cyclic allylic alcohols by the Simmons-Smith procedure have decreased over prolonged reactions times in the presence of the zinc carbenoid, no doubt as a consequence of the strongly Lewis acidic character of zinc halides.[65]



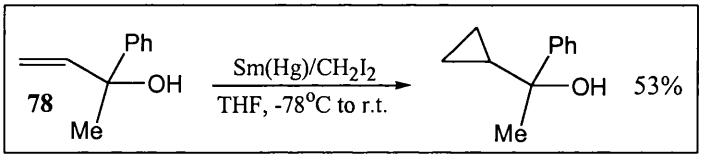
Scheme 44

Molander has proposed a staggered Houk transition structure for the high diastereoselectivity observed in the electrophilic addition to the alkene.[63] Using this model **77**, the favoured transition states for both (*E*)- and (*Z*)-disubstituted allylic alcohols involves R in a position antiperiplanar to the incoming carbenoid so that steric interactions with R^1 are reduced allowing complexation between the hydroxyl group and the carbenoid. Diastereoselectivity therefore increases as the size of R increases and adopts an antiperiplanar position (Scheme 45).



Scheme 45

Unlike zinc carbenoids,[1a] samarium carbenoids gave extremely low yields in more highly hindered allylic alcohols such as tertiary alcohols even those bearing no other substituents around the alkene. For example, 2-phenylbut-3-en-2-ol **78** was cyclopropanated, utilising both chloroiodomethane and diiodomethane in only 14% and 9% yields, respectively, under the standard reaction conditions (4 equiv. of the carbenoid). A higher yield (53%) was obtained by using an excess of the samarium carbenoid (12 equiv.) (Scheme 46).[63] According to the Houk model, tertiary alcohols force the carbenoid to approach the olefin over an alkyl substituent of the fully substituted carbinol carbon and efficient hydroxyl complexation is consequently inhibited. Decomposition of the carbenoid to ethylene is therefore more dominant than cyclopropanation for highly hindered substrates.



Scheme 46

In addition, a number of allylic alcohols **79-81** also gave poor yields of cyclopropane using samarium carbenoids (Figure 6),[63] which is in contrast to using zinc carbenoids.[1a] Once again, steric interactions between R^1 or R^2 with R prevent efficient cyclopropanation.

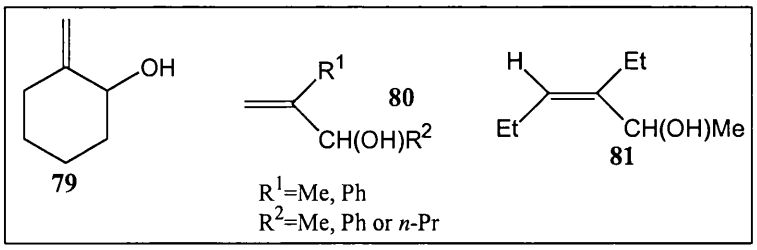
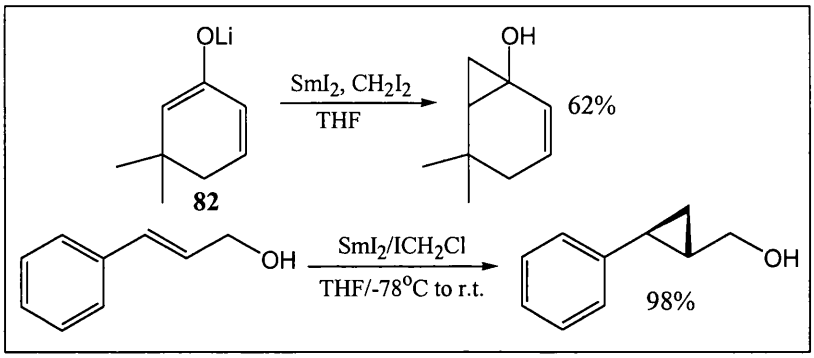


Figure 6

Imamoto and Takiyama generated Sm(III) carbenoids from the reaction of samarium(II) iodide (formed from samarium and diiodomethane) and geminal dihaloalkanes and these cyclopropanated lithium enolates **82** in good yield (Scheme 47).[66] In addition, Molander reported that the reactivity and selectivity of the carbenoids generated from $SmI_2/ClCH_2I$ were similar to those derived from

$Sm(Hg)/CH_2X_2$ and it is possible that the same species may be involved in each case (Scheme 47).[63b] However, from a practical standpoint, the procedure involving samarium(II) iodide is less desirable since more samarium and dihalomethane must be used in order to achieve complete conversion of allylic alcohol to product.

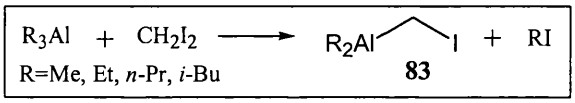


Scheme 47

Molander and Harring[63b] had generally found that the (chloromethyl)samarium species gave higher yields than its iodo analogue especially when steric crowding about the allylic alcohol increases. Two explanations were proposed by Molander for this difference in reactivity. The higher yields were attributed to the greater stability of the chloroiodomethane-derived reagent, which would slow down decomposition of the carbenoid to ethylene. The presumably more stable (chloromethyl)samarium reagent would thus be a longer lived species and have more of an opportunity to interact with an allylic alcohol in solution. However, the lower steric demands of a (chloromethyl)samarium species compared to those of an (iodomethyl)samarium species also seems to be a reasonable rationale for the difference in reactivity and cannot be easily dismissed. Although a similar reactivity was noted by Denmark with (chloromethyl)zinc and (iodomethyl)zinc species, the former was found to be less stable. As we have seen, this reactivity difference is clearly illustrated in the cyclopropanation of cyclodecene and the facile reaction with aromatic solvents (*vide supra* 1.2.1.3, Scheme 13).[21]

1.2.6 Aluminium Carbenoids

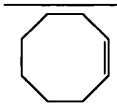
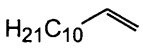
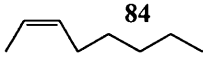
Miller initially reported that the reaction of triethylaluminium with diiodomethane generated a carbenoid species **83**, as illustrated in Scheme 48, which cyclopropanated cyclohexene in 20% yield.[67] The low yield was attributed to the decomposition of the carbenoid in the presence of excess triethylaluminium.[68] Later studies by Yamamoto revealed that the dimethyl(iodomethyl)aluminium species was sufficiently stable in dichloromethane even in the presence of trimethylaluminium and proved to be a far more effective cyclopropantion reagent.[69] Although similar carbenoid species can be generated from a variety of trialkylaluminium reagents with diiodomethane, *i*-Bu_3Al and Et_3Al are normally used for the cyclopropanation (Scheme 48).



Scheme 48

Good yields were obtained in short reaction times (3-8 hours) and the reaction usually occurred readily at low temperatures in the presence of non-polar solvents (Table 4). Moreover, the fact that even 1 equiv. of trialkylaluminium is enough to complete most reactions makes this protocol highly appealing for application to large scale synthesis. The reaction was found to be stereospecific with respect to alkene substituents as illustrated by the alkene **84** shown in Table 4.[69]

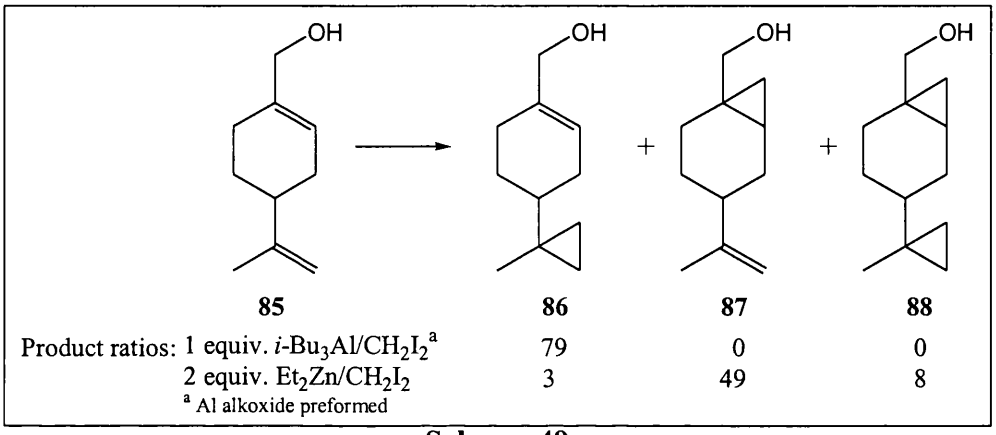
Table 4: Cyclopropanation of alkenes using Al carbenoids[69]

	Yield of cyclopropane (%)[a]		
Alkene	Me_2AlCH_2I	Et_2AlCH_2I	*i*-Bu_2AlCH_2I
	82	75	-
 **84**	98	99	96
	75[b]	66[b]	-

[a] Reaction conditions: aluminium carbenoid (1.2 equiv.), DCM, r.t., 3-8 h. [b] *Cis* cyclopropane only.

Interestingly, the carbenoid generated from triisobutylaluminium and diiodomethane was found to display unique chemoselectivity in the reaction with perillyl alcohol **85**.

Thus, the aluminium carbenoid gave rise to a mono-cyclopropanation product **86** exclusively (64%) with recovery of unreacted allylic alcohol (17%). In contrast the zinc carbenoid generated by the Furukawa procedure, afforded a mixture of cyclopropanated products **86**, **87**, **88**, and perillyl alcohol **85** in a ratio of 3:49:8:40 (81% combined yield), with the preference shown for the double bond of the allylic alcohol (Scheme 49).[69]

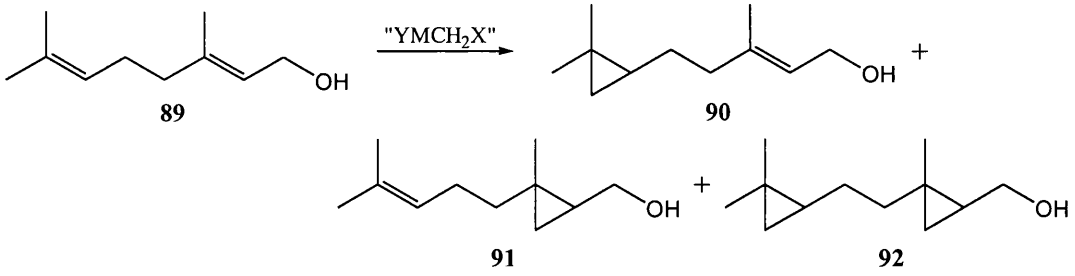


	85	**86**	**87**	**88**
Product ratios: 1 equiv. *i*-Bu_3Al/CH_2I_2[a]		79	0	0
2 equiv. Et_2Zn/CH_2I_2		3	49	8

[a] Al alkoxide preformed

Scheme 49

The contrasting regioselectivities of aluminium, zinc and samarium carbenoids is best illustrated however, in the cyclopropanation of geraniol **89**. By Yamamoto's procedure, aluminium carbenoids react with the distal double bond and a clear explanation for this unique selectivity has not yet been proposed (entry 1).[69] In this case, diiodomethane is added to the aluminium alkoxide species. However, recent studies by Charette have revealed that addition of the alcohol to the preformed aluminium carbenoid species leads to a reversal in selectivity and reaction occurs at the proximal double bond[70] (entry 2) as observed in the reaction of zinc carbenoids[69,70] (entry 3). Samarium carbenoids exclusively react with the proximal double bond site (entry 4).[63b] In addition, both aluminium and zinc carbenoids approximately afford 5% of byproducts as a result of cyclopropanation at the distal or proximal double bonds in geraniol, whereas samarium carbenoids provide one single product (entries 1-4, Scheme 50).

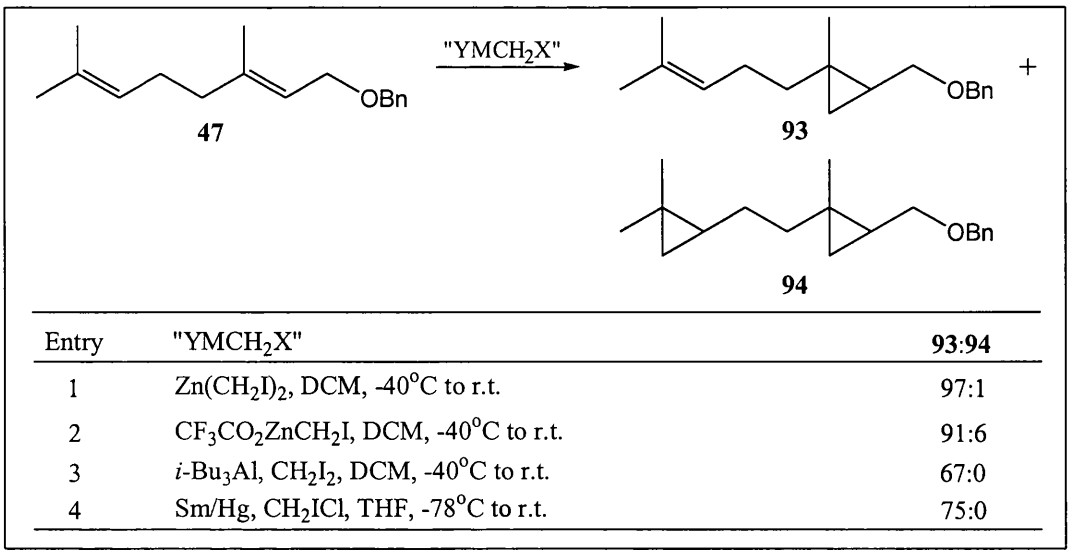


89 90 91 92

Entry	"$YMCH_2X$"	**90:91:92**
1	*i*-Bu_3Al (1.98 equiv.); add **89**; CH_2I_2 (0.98 equiv.), DCM, 0°C to r.t.	73:1:3
2	*i*-Bu_2AlCH_2I (1 equiv.); add **89**, DCM, -40°C to r.t.	1:67:0
3	Et_2Zn (2 equiv.), CH_2I_2 (1 equiv.), Et_2O, r.t.	2:74:3
4	Sm/Hg, CH_2ICl, THF, -78°C to r.t.	0:98:0

Scheme 50

A further example provides an insight into how aluminium carbenoids react. The cyclopropanation of the benzyl ether of geraniol **47** led to a reactivity preference for the proximal double bond site (Scheme 51).[70] In this case, it is reasonable to conclude that a covalent bond between aluminium and the oxygen atom is necessary, since cyclopropanation of the benzyl ether provides complete chemoselectivity at the proximal position.[70] As a result, formation of an aluminium alkoxide is most certainly plausible. In addition, under the reaction conditions (DCM), the aluminium alkoxides are probably forming higher aggregates[71] in which the distal double bond is more exposed than the proximal double bond.



47 93 94

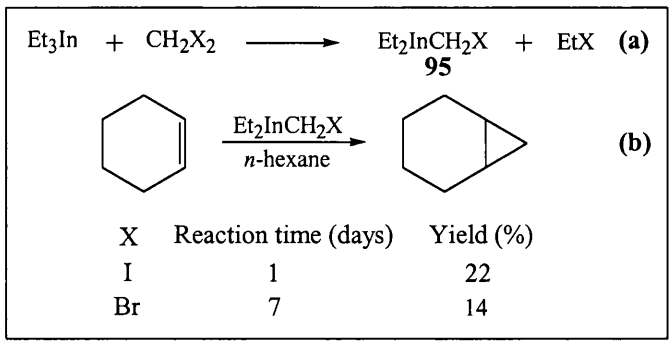
Entry	"$YMCH_2X$"	**93:94**
1	$Zn(CH_2I)_2$, DCM, -40°C to r.t.	97:1
2	$CF_3CO_2ZnCH_2I$, DCM, -40°C to r.t.	91:6
3	*i*-Bu_3Al, CH_2I_2, DCM, -40°C to r.t.	67:0
4	Sm/Hg, CH_2ICl, THF, -78°C to r.t.	75:0

Scheme 51

However, it is still curious that the use of only one equivalent of the preformed aluminium carbenoid in the case of perillyl alcohol **85** demonstrated a chemoselective preference for attack at the isopropenyl group (Scheme 49).

1.2.7 Indium Carbenoids

In similar fashion to aluminium, indium carbenoids **95** may also be prepared by the reaction of triethylindium with dihalomethanes (Scheme 52a).[72] However, as illustrated in the cyclopropanation of cyclohexene, studies of their behaviour are limited because of their low reactivity (Scheme 52b). In line with most methylene carbenoids, diethyl(iodomethyl)indium is more reactive than its bromo equivalent and the difference in reaction time is particularly noteworthy. Expectedly, no cyclopropane was obtained by the reaction of triethylindium with dichloromethane and cyclohexene. Clearly, it would be interesting to investigate the reactivity of the carbenoids in an alternative solvent such as dichloromethane as the improvement in yields for aluminium carbenoids showed.[69] Carbenoids such as tri(iodomethyl)indium species may also be prepared by the reaction of diazomethane with indium trichloride, however, the subsequent cyclopropanation of cyclohexene proceeded in only 1-2% yield.[10b]

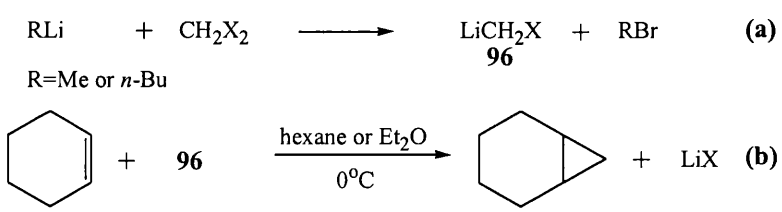


Scheme 52

1.2.8 Lithium Carbenoids

Lithium carbenoids represented as α-halomethyllithium species **96** are also effective cyclopropanation agents. The carbenoid species are prepared from the reaction of geminal dihalides with alkyllithium reagents such as methyllithium[73] or *n*-butyllithium.[74] By way of example, the reagent derived from butyllithium and

dibromomethane reacted with cyclohexene in a 1:2:2 molar ratio (Scheme 53a), to give 13% norcarane and homologous alkyl bromides as the main reaction products (Scheme 53b).[74] Analogously, iodomethyl- and chloromethyllithium were obtained from diiodomethane and bromochloromethane, respectively, by halogen-metal interconversion with butyllithium. The reagent generated from dichloromethane and methyllithium in ether, converts cyclohexene in a significantly higher yield than the use of dibromomethane (entries 3 and 5, Scheme 53).[73,75] Thus, the increase of the norcarane yield in going from iodomethyl- to chloromethyllithium is noteworthy, this trend being completely opposite to the general behaviour exhibited by methylene carbenoid species (Scheme 53). In addition, chloromethyllithium was unsuccessful as a cyclopropanating agent in tetrahydrofuran.[76]



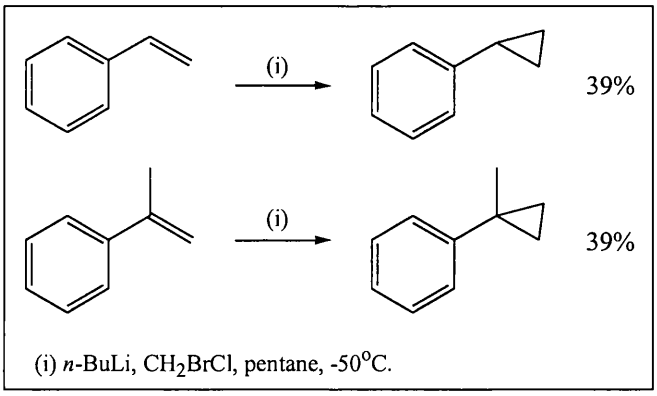
Entry	Li reagent	Dihalomethane	Li Carbenoid	Cyclopropane (%)
1	*n*-BuLi	CH_2I_2	$LiCH_2I$	0.4
2	*n*-BuLi	CH_2Br_2	$LiCH_2Br$	13
3	MeLi	CH_2Br_2	$LiCH_2Br$	14[a]
4	*n*-BuLi	CH_2BrCl	$LiCH_2Cl$	27 (33[b])
5	MeLi	CH_2Cl_2	$LiCH_2Cl$	33

[a] Reaction performed at -20°C. [b] Reaction performed at -50°C.

Carbenoid reactivity: $LiCH_2Cl$ > $LiCH_2Br$ > $LiCH_2I$

Scheme 53

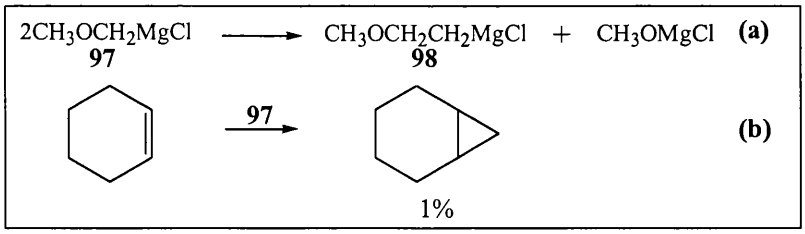
Moreover, the yield was increased to 33% when cyclohexene was reacted with chloromethyllithium *in situ* at –50°C. Under these conditions other electron-rich alkenes gave the corresponding cyclopropane in a similar yield (Scheme 54). In addition, the reactions of chloromethyllithium with *cis*- and *trans*-stilbenes yielded *cis* and *trans*-1,2-diphenylcyclopropane stereospecifically.[74] This provides evidence for the "butterfly structure" as the transition state for methylenation, as discussed previously for zinc carbenoids (*vide supra* 1.2.1.1, Figure 3).



Scheme 54

1.2.9 Magnesium Carbenoids

Methylene carbenoids of magnesium **97** are more likely to undergo homologation by reaction with another carbenoid species **97** as they react readily with external Grignard reagents,[77] rather than cyclopropanate alkenes (Scheme 55a).[78] C-H insertion of the resulting species **98** may lead to the formation of alkene and this may be cyclopropanated. Thus, because of the numerous *in situ* homologation and C-H insertion reactions, only a small amount of cyclopropane was detected when the magnesium carbenoid **97** was employed in the reaction of cyclohexene (Scheme 55b).[78a]



Scheme 55

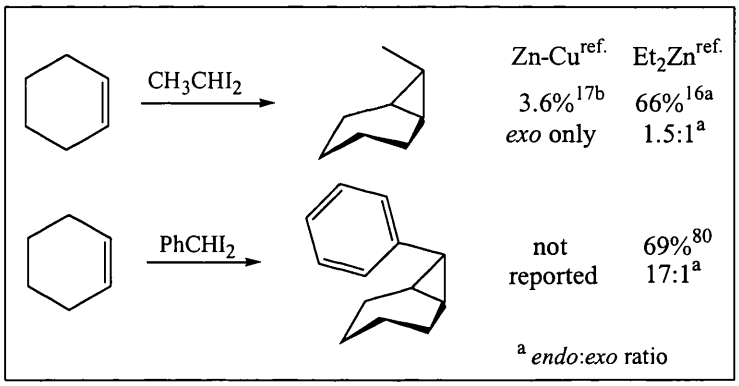
1.3 Alkyl and Aryl Mono- and Di- Substituted Carbenoids

More complex carbenoids may be prepared by reacting the metal source with substituted dihaloalkanes. The reactions are generally successful with diiodo precursors, however, in some cases dibromides may be used. In addition, the generation of a chloro-alkylzinc species[79] may be formed *in situ* from a carbonyl compound and used in the subsequent cyclopropanation.

1.3.1 Methyl- and Phenyl-Substituted Carbenoids [YMCH(R)X]

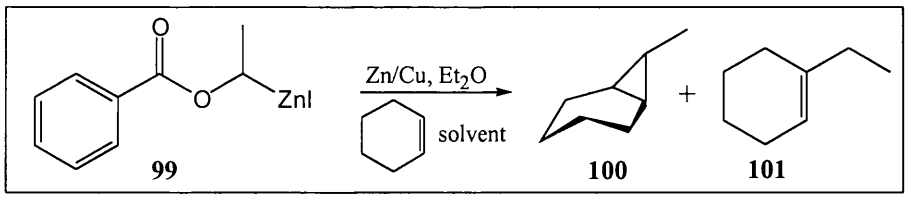
Substituted cyclopropanes may be prepared by using many of the metals discussed in section 1.2.

Successful alkylidenations have been carried out by zinc carbenoids. The use of diethylzinc[16a,80] led to higher yields in the reaction of cyclohexene with both methyl- and phenyl-substituted carbenoids than the use of Simmons Smith zinc carbenoids (Scheme 56).[17b] Although other geminal dihalides such as 1,1-diiodopropane react to form the zinc carbenoid, rearrangement leading to alkene and cyclopropane by-products *via* intramolecular insertion is favoured over the intermolecular cyclopropanation of alkenes.[81]



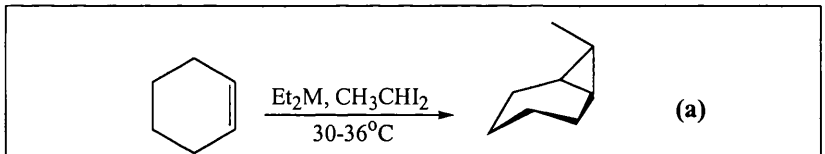
Scheme 56

In addition, Wittig had reported the use of 1-benzoyloxyethylzinc iodide **99**, generated from the corresponding iodoalkyl ester, as an example of an alternative leaving group X to halogen on the carbenoid species (Scheme 57).[10e] Interestingly, the authors discovered that under the reaction conditions, the *cis* methylnorcarane readily isomerised to 2-ethylcyclohexene **101**. In actual fact, the initial product of this cyclopropanation reaction is a 1:1 mixture of *cis* and *trans* methylnorcarane **100** in 37% yield.

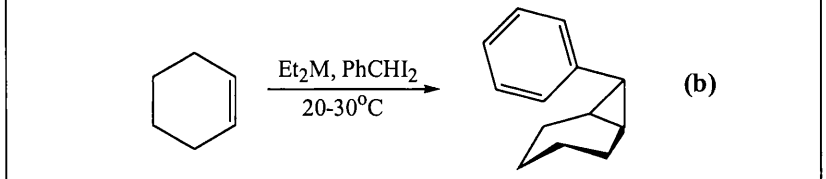


Scheme 57

In similar fashion, methyl- and phenyl-substituted carbenoids may also be prepared by using cadmium.[58] Interestingly, the difference in reactivity between zinc and cadmium is clearly illustrated in the reactions shown in Scheme 58. In the case of zinc, higher yields were obtained in shorter reaction times than employing the corresponding cadmium carbenoids. Moreover, the methyl carbenoid generated by diethylcadmium and 1,1-diiodoethane favours *anti* addition and the nature of the solvent might possibly account for this reversal in stereoselectivity (Scheme 58a).[58] Due to the longer reaction time, a considerable amount of *sec*-butyl iodide was also detected as a result of carbenoid decomposition *via* homologation.



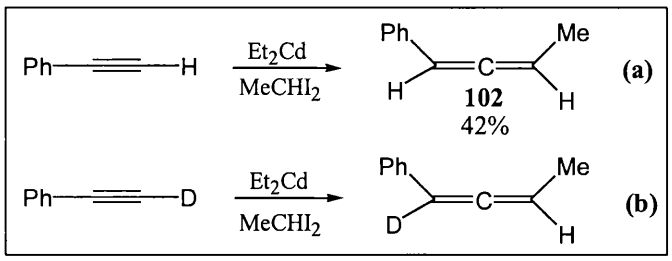
M	solvent	Reaction time (h)	yield (%)	*endo/exo*	Ref.
Cd	cyclohexane	9	19	1:1.1	58
Zn	*n*-pentane	1	66	1.5:1	16a



M	solvent	Reaction time (h)	yield (%)	*endo/exo*	Ref.
Cd	Et_2O	2.5	26	7.5	58
Cd	*n*-pentane	2.5	20	5.5	58
Zn	Et_2O	5	69	17	80
Zn	*n*-pentane	5	68	6.6	80

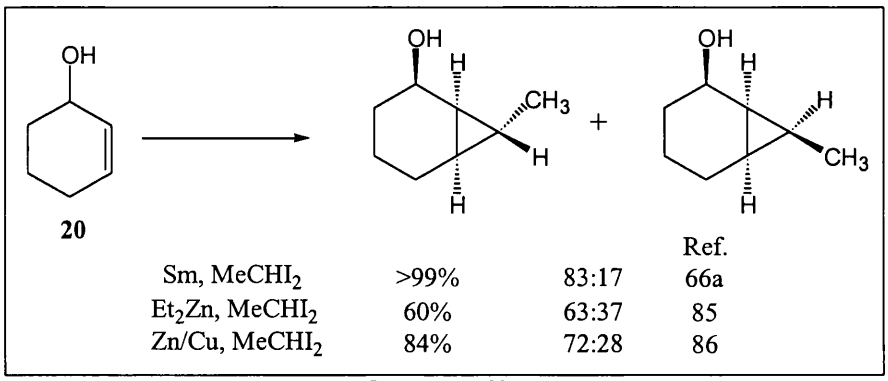
Scheme 58

In the case of cadmium, allene formation results from the reaction of the methyl-substituted carbenoid with phenylacetylene (Scheme 59a). Interestingly, the reaction of deuterated acetylene using these conditions, reveals that migration of acetylenic hydrogen is necessary in order to form the allene derivative **102** (Scheme 59b).[58]



Scheme 59

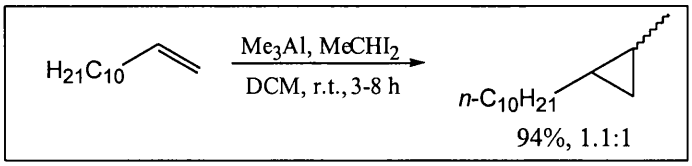
A mixture of samarium amalgam and 1,1-diiodoethane can be used to generate an efficient carbenoid species for the ethylidenation of 2-cyclohexen-1-ol **20**.[63a] In this instance, complete hydroxyl-directed cyclopropanation occurred in quantitative yield, and more importantly, higher *exo*/*endo* diastereoselectivity was achieved with samarium than the use of zinc carbenoids[82,83] (Scheme 60).



			Ref.
Sm, $MeCHI_2$	>99%	83:17	66a
Et_2Zn, $MeCHI_2$	60%	63:37	85
Zn/Cu, $MeCHI_2$	84%	72:28	86

Scheme 60

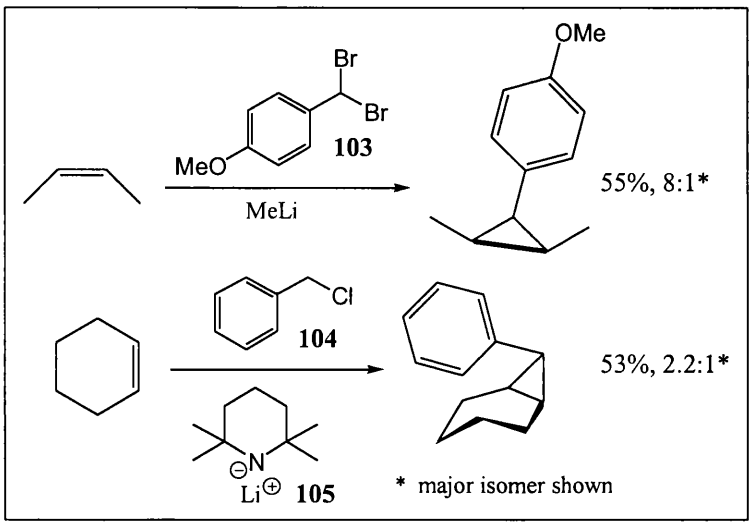
By employing Yamamoto's conditions, the use of a substituted aluminium carbenoid led to a high cyclopropane yield (Scheme 61).[69]



Scheme 61

Finally, the generation of lithium phenyl-substituted carbenoids may be carried out by two procedures. Thus, the active species are generated by either lithium halogen exchange of a geminal dihalide compound[84] **103** or deprotonation of a halo compound

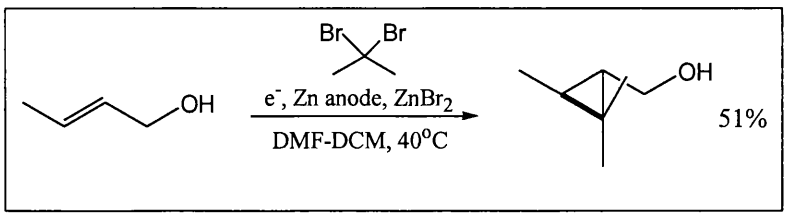
104 using a lithium base such as lithium 2,2,6,6-tetramethylpiperidide[85] **105**. Both of these reactions are illustrated by the two reactions in Scheme 62, respectively.



Scheme 62

1.3.2 Dimethylmethylene Carbenoids [$YMC(CH_3)_2X$]

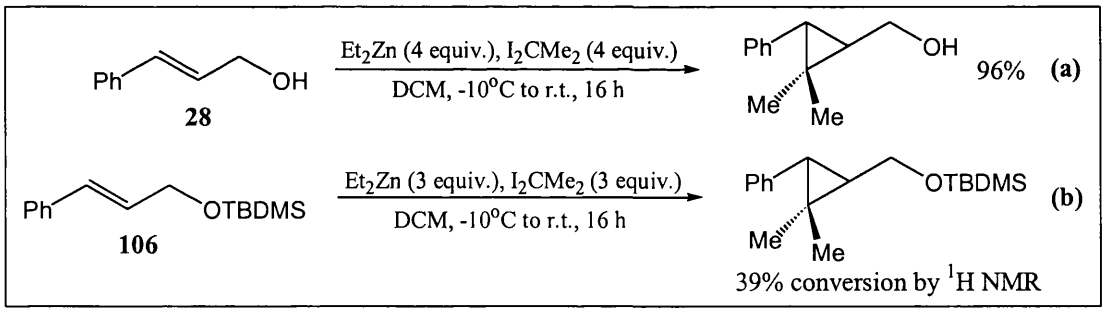
In contrast to mono alkyl- and phenyl-substituted carbenoids, dimethylmethylene carbenoids are rarely used as low yields of the *gem*-dimethylcyclopropane are usually obtained. This is likely due to the obvious high steric hindrance in the cyclopropanation reaction involving the corresponding carbenoid. One successful reaction involves cyclopropanating allylic alcohols using electrosynthesis. However, in this case, an excess of 2,2-dibromopropane and a sacrificial zinc anode are necessary in order to achieve a moderate yield (Scheme 63).[30]



Scheme 63

Using Furukawa's modification,[11,16] zinc carbenoids generated from diethylzinc and 2,2-diiodopropane cyclopropanated cyclopentene and cyclohexene. Moderate yields (45% and 59% respectively) of the corresponding *gem*-dimethylcyclopropane were

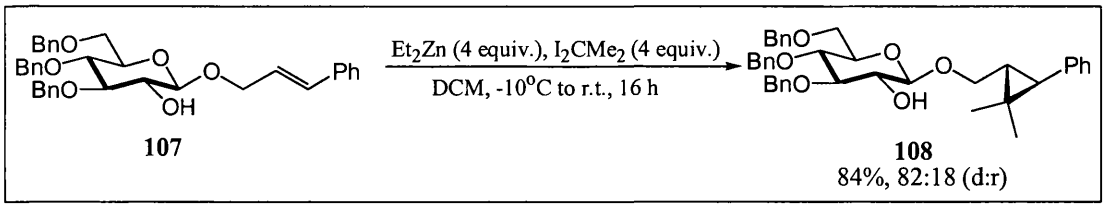
obtained after 5 days.[86] A more efficient synthesis was reported by Charette, who employed equimolar amounts of diethylzinc and 2,2-diiodopropane in the cyclopropanation of allylic alcohols (Scheme 64).[87] Interestingly, spectroscopic analysis revealed that diethylzinc reacted within a few minutes with one equivalent of diiodopropane to generate $EtZnC(Me_2)I$. However, the addition of the second equivalent of 2,2-diiodopropane was unsuccessful due to the bulkiness around the zinc centre. In a series of allylic alcohols including cinnamyl alcohol **28**, the conversions were generally greater than 90% for a variety of alkenes exhibiting a mono-, di- or trisubstitution pattern, independently of the (*Z*)- or (*E*)-configuration (Scheme 64a). Allylic ethers bearing protecting groups were less reactive due to the increased steric hindrance in the cyclopropanation. For example, a low conversion was obtained with the ether **106** bearing a *tert*-butyldimethylsilyl group (Scheme 64b).[87] The addition of DME was found to reduce the conversion to the cyclopropane product. Moreover, the use of carbenoids bearing a trifluoroacetate[39] or a phenolate[42] group instead of the ethyl group resulted in the complete decomposition of the allylic alcohol.



Scheme 64

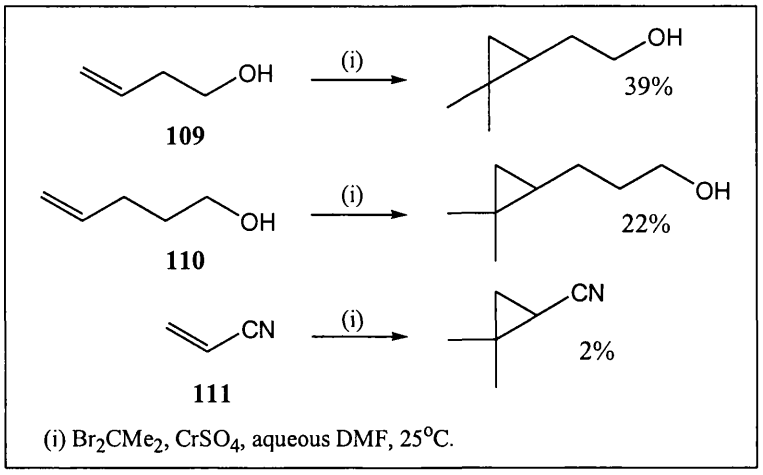
This methodology was successfully applied to an asymmetric version of the reaction using a known glucose derivative as a chiral auxiliary.[24,88] The 1-*O*-cinnamyl-3,4,6-tri-*O*-benzyl-β-D-glucose **107** was prepared using Schmidt's trichloroacetimidate glycosylation method.[89] A high yield of the *gem*-dimethylcyclopropane **108** was obtained with 82:18 dr (Scheme 65).[87] Lower reaction temperatures were found to decrease the conversions of the reaction, and did not significantly increase the diastereomeric ratio. Even though pre-treatment with zinc(II) iodide did slightly increase the conversions, no improvement in diastereomeric ratio was noted. The

chiral auxiliary could be efficiently cleaved,[90] yielding the 3,3-dimethyl-2-phenylcyclopropylmethanol in 65%, without any loss of selectivity.



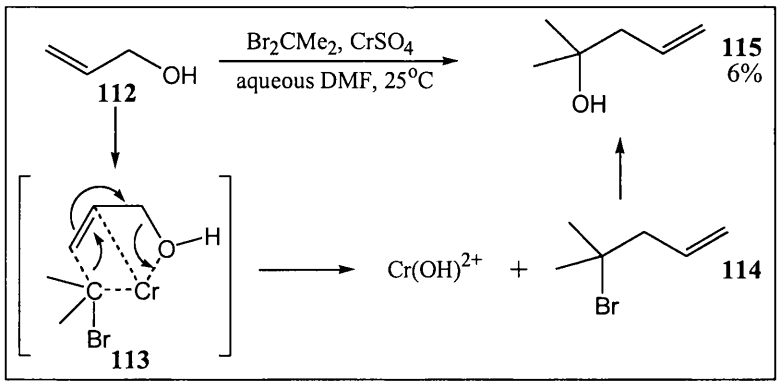
Scheme 65

The generation of chromium carbenoids from chromous sulfate and 2,2-dibromopropane was known to cyclopropanate alkenes in the presence of a hydroxyl group such as **109** and **110** in erratic yields.[91] Moreover, the yield obtained with an electron-deficient alkene **111** was extremely poor and thus the hydroxyl group was essential for coordination to the metal carbenoid in order to achieve efficient formation of the *gem*-dimethylcyclopropane (Scheme 66).[91b]



Scheme 66

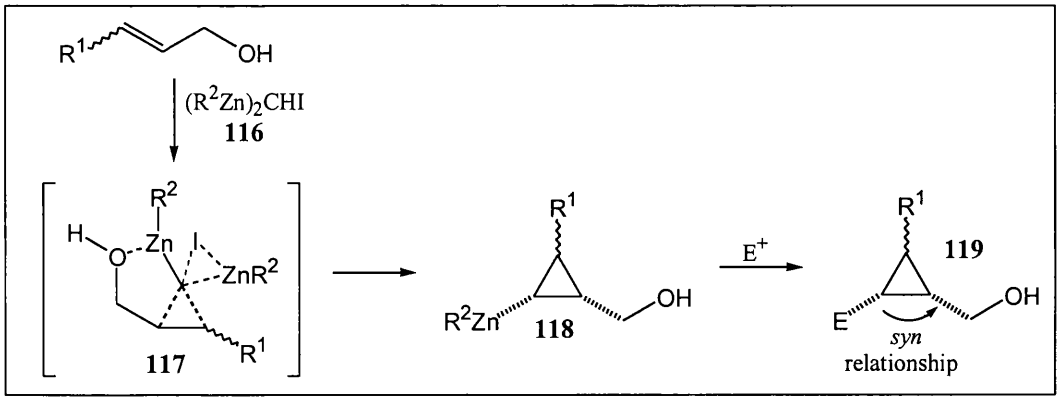
Interestingly, no *gem*-dimethylcyclopropane was isolated when chromium carbenoids were reacted with allylic alcohols **112**. In this case, a postulated intermediate **113** involving coordination of the metal carbenoid to the hydroxyl group followed by rearrangement leads to the formation of the product **115** *via* intermediate **114** (Scheme 67).[91b]



Scheme 67

1.3.3 Geminal Dizinc Carbenoids [(RZn)$_2$CHI]

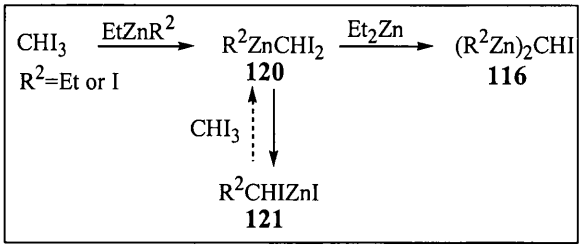
The first generation of a geminal dizinc carbenoid **116** led to a highly stereoselective synthesis of 1,2,3-substituted cyclopropanes from allylic alcohols.[92] In all cases, a *syn* relationship was obtained between the R_2 group and the hydroxymethyl substituent as shown in **119** (Scheme 68). This is because one of the Lewis acidic zinc atoms of the dizinc reagent **116** interacts with the proximal basic group as shown in the transition state intermediate **117**, whilst the stereochemical outcome of the directed reaction is governed by complexation of the zinc centre that is not involved in the electrophilic carbenoid delivery (Scheme 68).[92] The resulting cyclpropylzinc derivative **118** could then be trapped with an electrophile to furnish the tri-substituted cyclopropane **119**.



Scheme 68

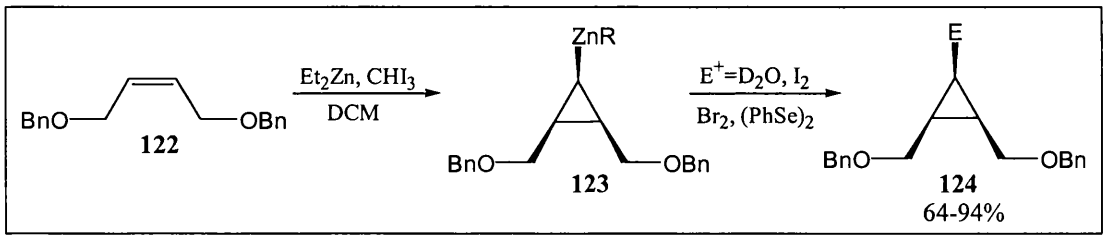
The geminal zinc carbenoids **116** were prepared by mixing iodoform with diethylzinc by two successive alkyl exchanges. A competing pathway involves the decomposition of the species to generate the zinc carbenoid **121**. However, **121** can react further with

iodoform to generate the zinc carbenoid **120** (R^2=I). Alternatively, EtZnI can also be used to generate the geminal zinc carbenoid **116** (R^2=Et) (Scheme 69).[92]



Scheme 69

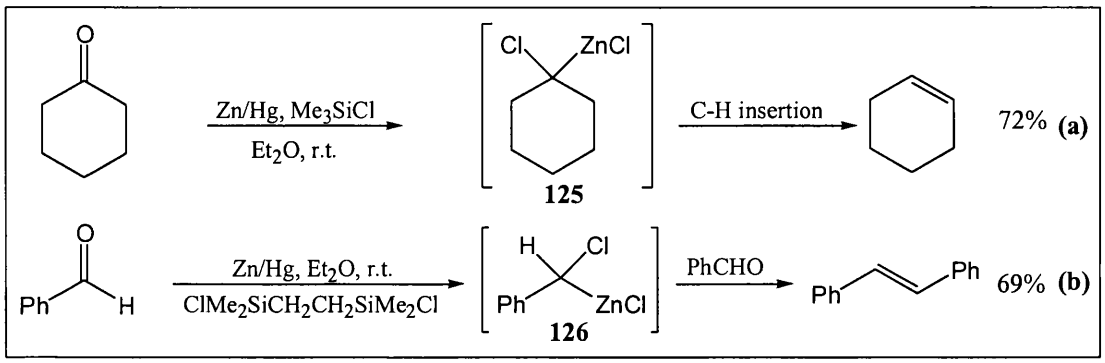
Iodo-, bromo-, and phenylseleno-substituted **124** cyclopropanes were all prepared in good yields by reaction of the *gem*-dizinc carbenoid with the allylic alcohol and subsequent trapping of the resulting cyclopropylzinc derivatives **123** with electrophiles. In all cases the *syn* diastereomer was formed exclusively (>99:1). Interestingly, when D_2O was used as the electrophile, <5% of the iodo-substituted cyclopropane was observed, indicating that the *gem*-dizinc carbenoid **116** is substantially more reactive than the carbenoid **120** (Scheme 70).[92]



Scheme 70

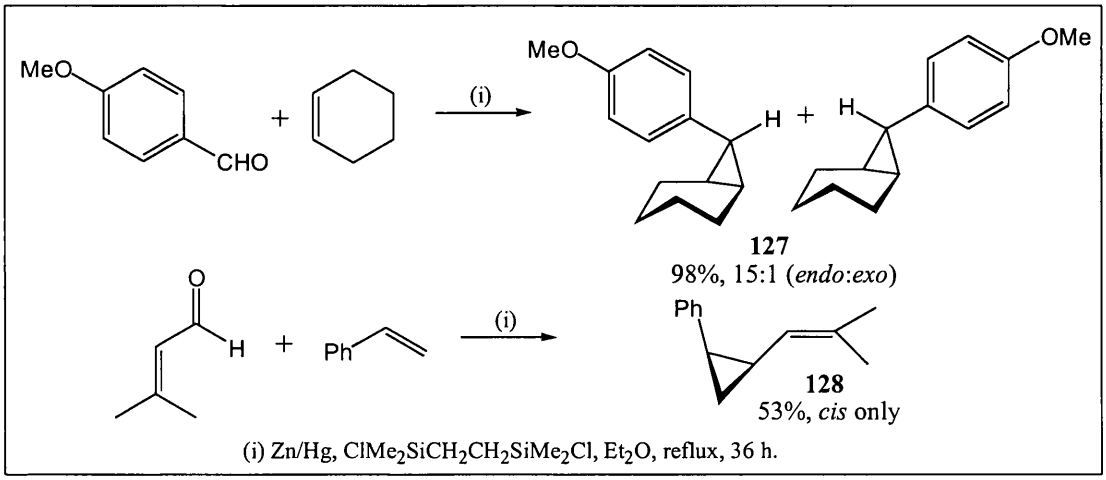
1.3.4 Chloro-Alkyl and –Aryl Zinc Carbenoids

Motherwell reported an excellent method for the generation of chloro-alkyl zinc carbenoids such as **125** and **126** from carbonyl compounds using zinc amalgam and a silicon electrophile; either chlorotrimethylsilane or 1,2-bis(chlorodimethylsilyl)ethane (Scheme 71).[79,93] The mechanism mirrors the Clemmensen reduction, with the exception of silicon acting as the electrophile instead of a proton. C-H insertion reaction were observed in cyclic ketones such as cyclohexanone (Scheme 71a)[93] and in the presence of benzaldehyde, the corresponding zinc carbenoid **126** reacts with benzaldehyde to give the dicarbonyl coupling product (Scheme 71b).[94]



Scheme 71

Moreover, the zinc carbenoid derived from *para*-methoxybenzaldehyde using zinc and bis(chlorodimethylsilyl)ethane could also be trapped with electron-rich alkenes such as cyclohexene to give the corresponding functionalised cyclopropane **127** in excellent yield and stereoselectivity.[79] In similar fashion, unfunctionalised alkenes such as styrene gave good yields of the *cis* cyclopropane **128** with the zinc carbenoid derived from 3-methylbutenal (Scheme 72).[79]



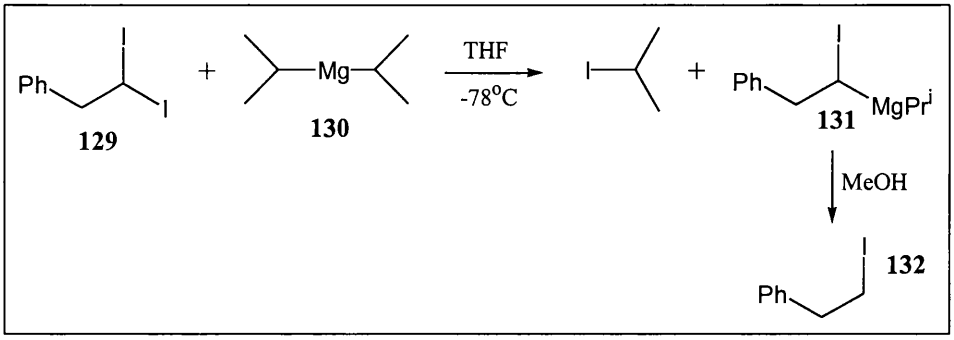
Scheme 72

This chemistry will of course be described in greater detail in the results and discussion section.

1.3.5 Magnesium Carbenoids

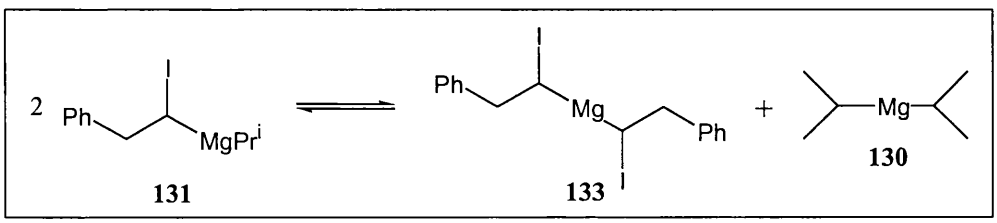
α-Iodoalkylmagnesium compounds **131** are also accessible by an iodine/magnesium exchange reaction.[95] Treatment of the diiodo compound **129** with

diisopropylmagnesium **130** at –78°C for two hours followed by protonation with methanol affords 97% of the iodoalkane **132** (Scheme 73).[95]



Scheme 73

Interestingly, studies showed that the above magnesium carbenoid **131** had no tendency to disproportionate into diisopropylmagenesium **130** and the bis-α-iodoalkylmagnesium **133**. In a separate experiment it could be shown that the bis(iodoalkyl)magnesium **133** is not converted into **131** by addition of diisopropylmagnesium **130** (Scheme 74).[95] This stability of the magnesium carbenoids **131** and **133** at –78°C clearly contrasts with the behaviour of the analogous dialkylzinc reagents, which rapidly comproportionate and disproportionate at –78°C in THF.[18] Likewise, the corresponding alkylzinc iodides also exhibit a rapid Schlenck equilibrium.[18] Interestingly, ^{13}C NMR chemical shifts suggest that α-iodoalkylmagnesium compounds have a carbenoid character in between that of α-haloalkyllithium and the corresponding zinc compounds. This is reflected in a significant downfield shift Δδ of the ^{13}C NMR signal of the carbenoid carbon which may be caused by substantial weakening of the carbon-halogen carbon in the magnesium carbenoids, as supported by *ab initio* calculations and EXAFS studies.[95] Unfortunately however, the reactivity of these species in cyclopropanation studies was not described.

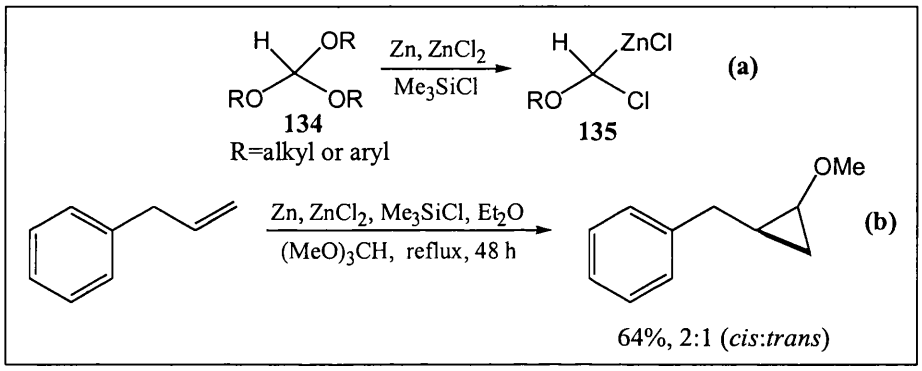


Scheme 74

1.4 Alkoxycarbenoids [YMCH(OR)X]

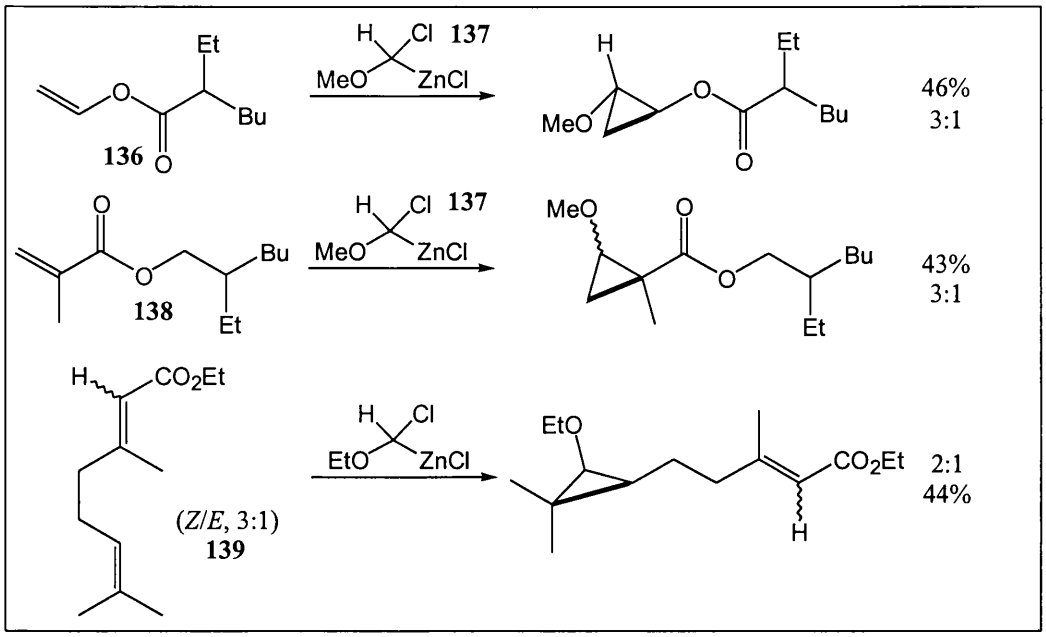
1.4.1 Zinc Carbenoids

Alkoxy zinc carbenoids **135** have been prepared by Motherwell, from orthoformates **134** in the presence of zinc amalgam, zinc chloride and chlorotrimethylsilane (Scheme 75a).[96] The resulting carbenoids **135** reacted with unfunctionalised alkenes to provide the corresponding alkoxycyclopropanes in moderate to good yields (Scheme 75b).[96]



Scheme 75

Interestingly, whilst it could be reasoned that this carbenoid species would exhibit a more nucleophilic character and hence exhibit a chemoselective preference for an electron-deficient alkene, due to the electron-donating nature of the alkoxy group, experiments proved otherwise. Thus, as shown in Scheme 76, both the enol ester **136** and the acrylate **138** gave similar yields of the corresponding cyclopropane in the presence of the methoxy carbenoid **137**. Moreover, the reaction of a direct competition experiment using the monoterpene ester **139** clearly shows that the more electron-rich alkene is favoured over the acrylate.[96] Thus, the alkoxy species like other traditional zinc carbenoids displays essentially electrophilic character.

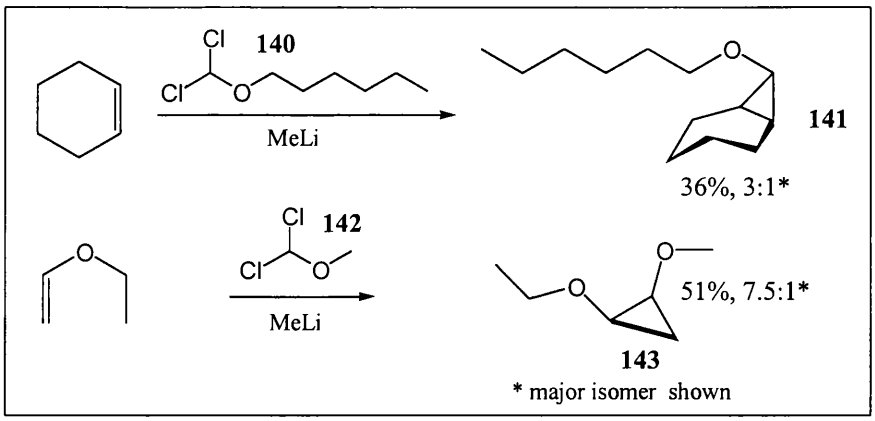


Scheme 76

The chemistry of these alkoxy carbenoids will be discussed in further detail in the results and discussion section.

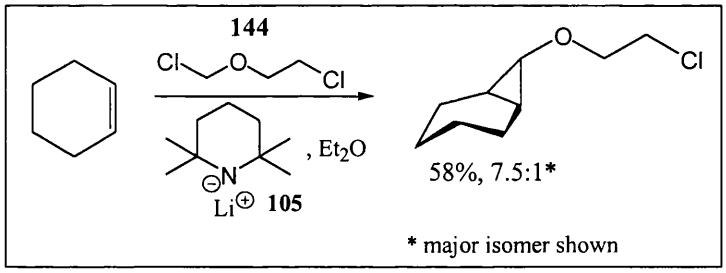
1.4.2 Lithium Carbenoids

A range of alkoxycyclopropanes was also prepared by the use of α-haloalkyllithium carbenoid species generated *via* halogen lithium exchange of α,α-dihalo ethers.[97] For example, Schöllkopf reported that the carbenoid generated from **140** or **142** reacted with a variety of electron rich alkenes to give the corresponding alkoxycyclopropane **141** and **143** in moderate yield with the *cis* cyclopropane favoured (Scheme 77).[97] However, the use of α,α-dihalo ethers as cyclopropanating agents is limited due to their high toxicity.[97,98]



Scheme 77

In addition, lithium alkoxy carbenoids may also be prepared by the deprotonation of α-haloethers and these species are stabilised by the oxygen atom. Thus, the treatment of chloromethyl-β-chloroethyl ether **144** with the previously mentioned lithium 2,2,6,6-tetramethylpiperidide **105** led to the alkoxcyclopropanation of electron-rich alkenes such as cyclohexene (Scheme 78).[99]



Scheme 78

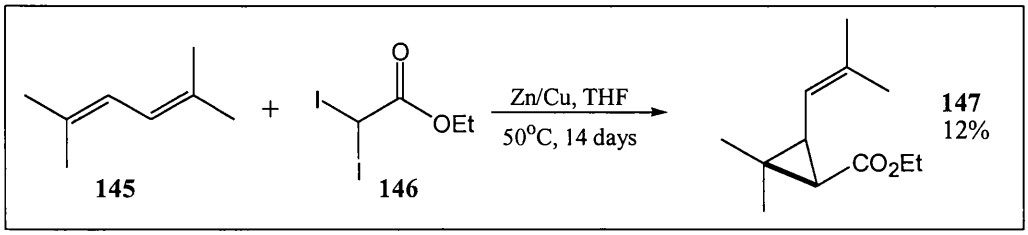
1.5 Carboalkoxy-Carbenoids [YMCR^1(CO$_2$R^2)X]

Although the reaction of ethyl diazoacetate in the presence of rhodium[4b,100] and copper[100,101] salts is of course a very well established reaction, there are few other metals which have been used for the generation of carboalkoxy-carbenoids from other precursors.

1.5.1 Zinc Carbenoids

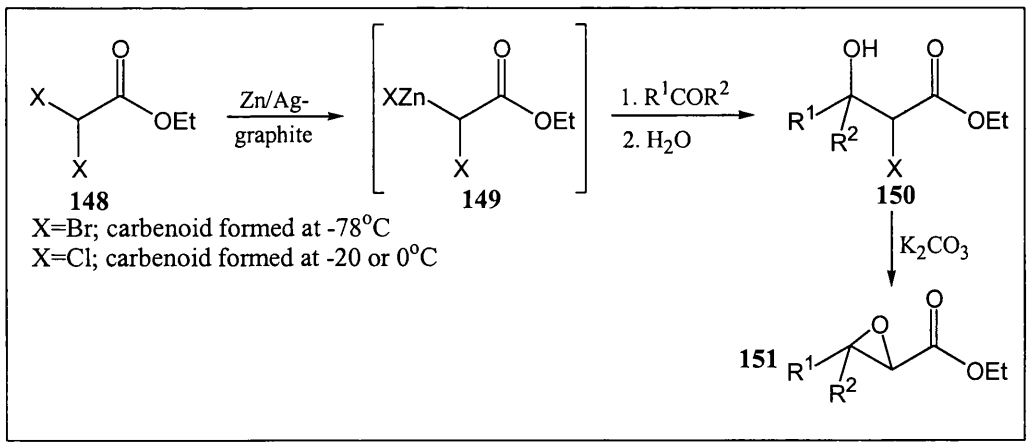
One of these is the Simmons-Smith cyclopropanation of 1,1,4,4-tetramethylbutadiene **145** involving ethyl diiodoacetate **146** and zinc copper couple and this gives a poor

yield of the vinylcyclopropane **147** even after a prolonged reaction time (Scheme 79).[102] No cyclopropanation was observed when employing highly reactive electrogenerated zinc with either methyl dichloro- or dibromoacetate.[30]



Scheme 79

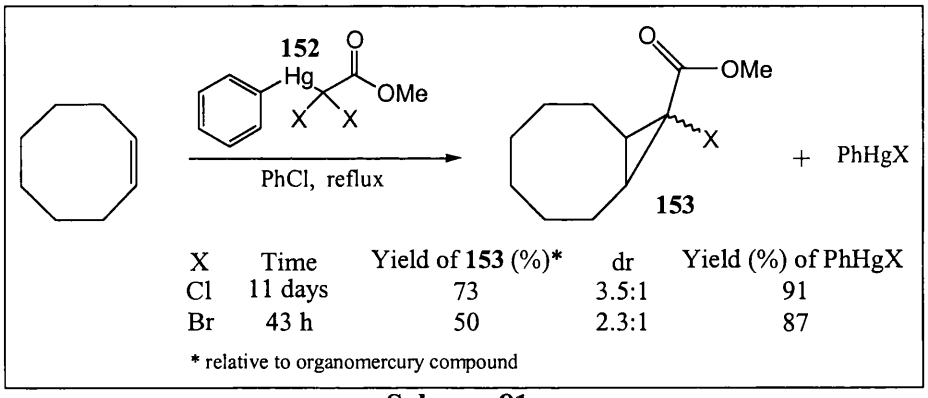
In these cases, it is likely that the zinc carbenoids are formed as the insertion of the metal into the carbon-halogen bond is facile, and the resulting species may undergo rapid decomposition rather than cyclopropanation of the alkene. For example, a Reformatsky-type reaction of ethyl dihaloacetate **148** with carbonyl compounds in the presence of zinc/silver-graphite occurs at temperatures as low as -78°C. The zinc carbenoid species **149** reacts with aldehyde or ketone to form α-halo-β-hydroxyalkanoates **150**, which are then readily converted into glycidates **151** by using a base (Scheme 80).[103] Although the Furukawa modification of the Simmons-Smith reaction using diethylzinc instead of zinc-copper couple is successful with diiodomethane,[11b] 1,1-diiodomethane,[16b] aryldiiodomethane,[80] and trihalomethanes,[104] the reagent is unreactive with alkyl dihaloacetates.



Scheme 80

1.5.2 Mercury Carbenoids

Interesting carbenoid species such as phenyl(dihalocarbomethoxy)mercury **152** can be prepared by the reaction of phenylmercuric halide and methyl dihaloacetate. Cyclopropanation of an excess of cyclooctene with $PhHgCCl_2CO_2Me$ in chlorobenzene gave the halocyclopropane **153** in good yield, however rather severe conditions were necessary for this conversion (Scheme 81).[105] Once again, this is a reflection of the increased stability of organomercury reagents relative to zinc. In similar fashion, the reaction of $PhHgCBr_2CO_2Me$ led to a lower yield with phenylmercury formed in 87% in 43 hours.[105] This suggests that the carbenoid species was less stable thermally.



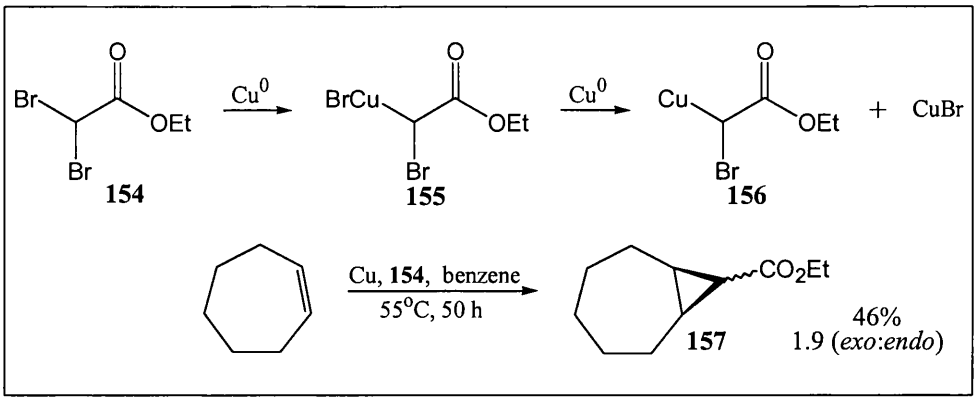
X	Time	Yield of **153** (%)*	dr	Yield (%) of PhHgX
Cl	11 days	73	3.5:1	91
Br	43 h	50	2.3:1	87

* relative to organomercury compound

Scheme 81

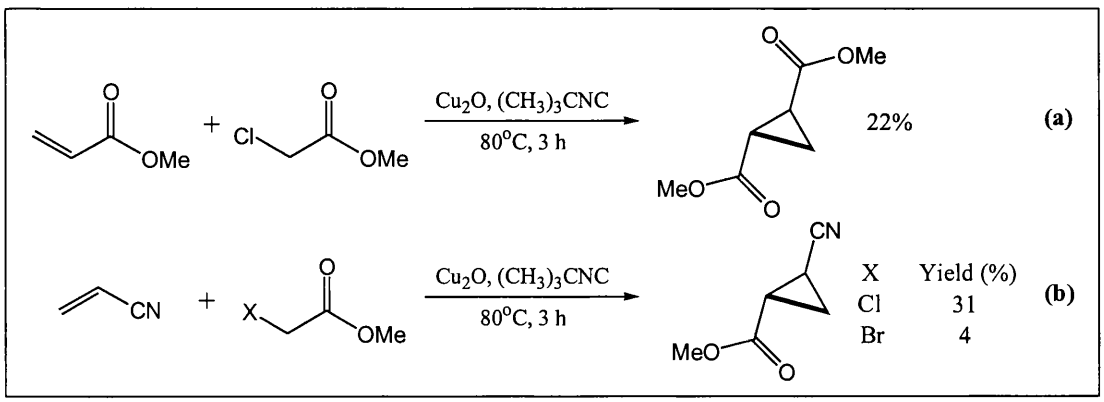
1.5.3 Copper Carbenoids

On the other hand, copper provides higher cyclopropanation yields, although in one case, the authors[62] have suggested that the mechanism proceeds through an organocopper(I) intermediate **156**. However, as previously discussed, the copper carbenoid **155** is initially formed *via* insertion into the carbon-halogen bond, and this is then reduced by copper to give the organocopper intermediate **156** (*vide supra* 1.2.4). In this reaction, a moderate yield of the carboalkoxy-cyclopropane **157** was obtained when copper was heated with an electron-rich alkene (cycloheptene) and ethyl dibromoacetate **154** (Scheme 82).[62]



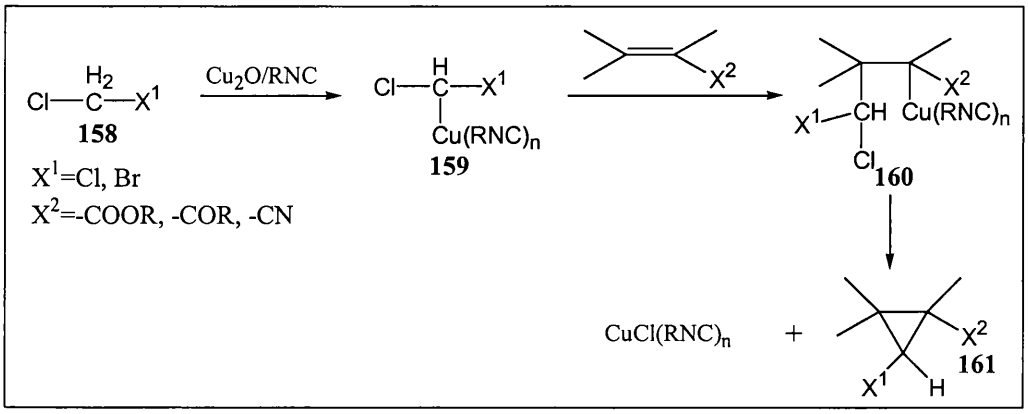
Scheme 82

In a second approach to copper carbenoids using copper oxide as a base to eliminate hydrogen chloride or bromide, copper affords moderate cyclopropanation yields when their carboalkoxy carbenoids react with electron-deficient alkenes (Scheme 83).[106] Interestingly, electron-rich alkenes such as cyclohexene and vinyl ethers are unreactive. Monochloroacetate, monochloroacetonitrile, and monochloroacetone all react with α,β-unsaturated esters and nitriles to afford the corresponding cyclopropanes in a moderate yield. However, monobromoacetate gave a far lower yield than its chloro analogue (Scheme 83b). The cyclopropane synthesis was found to be stereoselective, in which the two polar substituents on the cyclopropane ring were *trans* with respect to each other (Scheme 83).[106] However, a rapid equilibration between the *cis* and *trans* isomers of the products seems to account for the *trans* stereoselectivity. In addition, cyclopropane-1,2-*cis*-dicarboxylates are often found to isomerise rapidly into the *trans* isomer under the same reaction conditions.[106c] Detailed studies using *E* and *Z* alkenes were not reported.



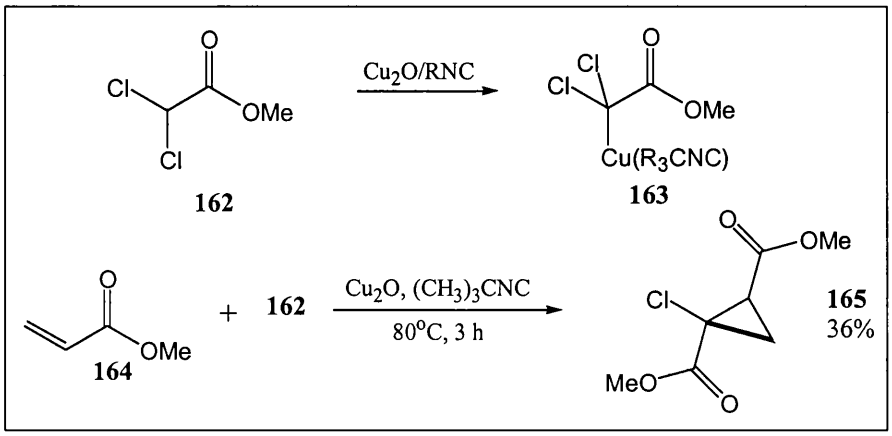
Scheme 83

The copper carbenoids, effectively haloorganocopper-isonitrile complexes **159** are formed by the addition of copper(I) oxide-isonitrile complex to α-halo compound **158**. Unlike many traditional metal carbenoids in cyclopropanation reactions, the copper carbenoids **159** then react in a stepwise manner by the addition of α-halomethylcopper(I) isonitrile intermediate **159** to the alkene which leads to the formation of the corresponding γ-haloorganocopper(I)-isonitrile **160**. The cyclopropane **161** is then formed by intramolecular ring closure (Scheme 84).[106b,c]



Scheme 84

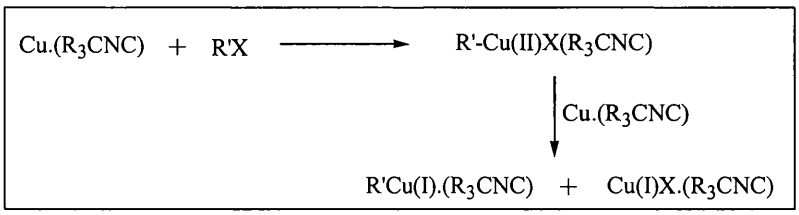
In similar fashion, α,α-dihaloacetate **162** or α,α-dihaloacetonitrile react to form the corresponding copper carbenoids **163** and subsequent addition to an electron-deficient alkene **164** affords the corresponding chlorocyclopropane **165** as shown in Scheme 85.[106b,c]



Scheme 85

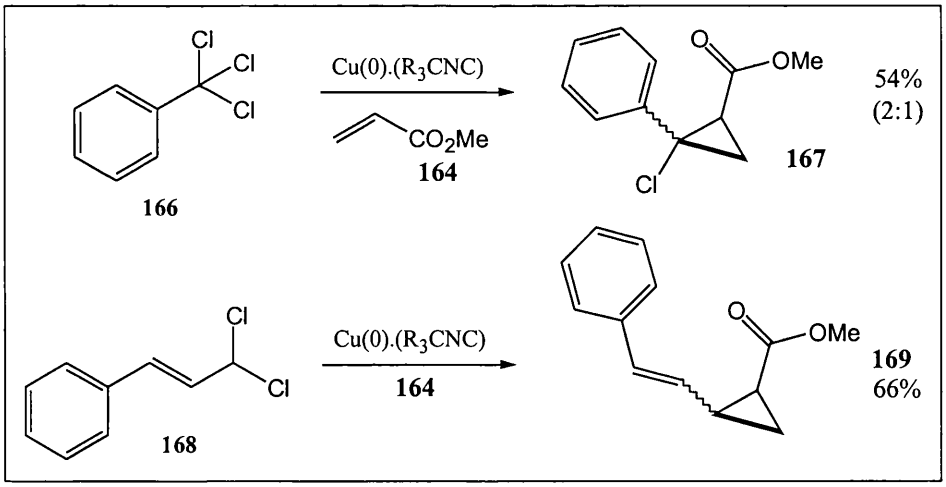
Active copper carbenoids may also be formed by the oxidative addition of the carbon-halogen bond of a trichloromethyl or alkylidene dichloride compound to a copper(0)-

isonitrile complex, followed by reduction of the organocopper(II) to an organocopper(I) carbenoid (Scheme 86). Subsequent intramolecular 1,3-elimination of $CuX(R_3CNC)$ results in the formation of the substituted cyclopropane as in Scheme 84.[106b,c]



Scheme 86

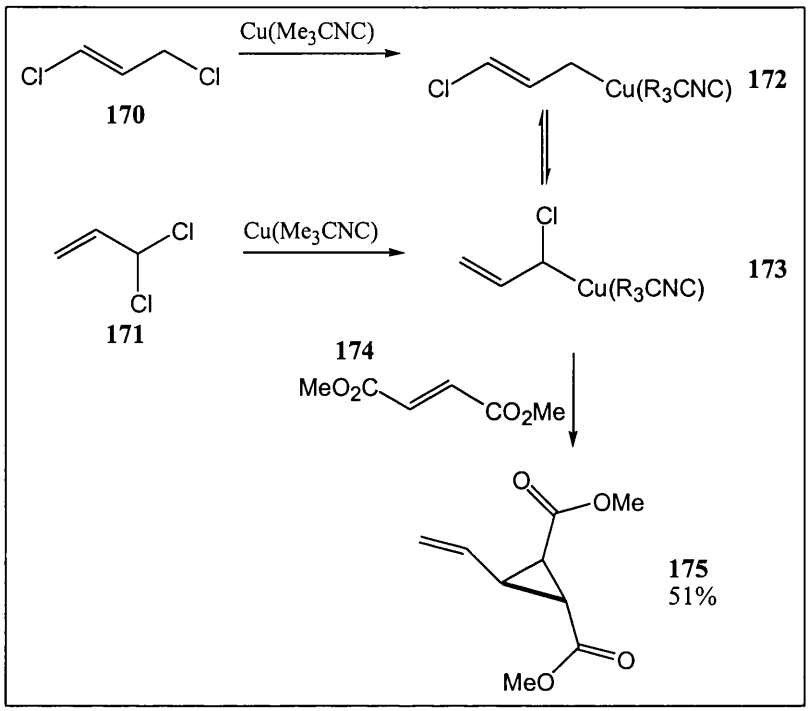
Thus, when a mixture of metallic copper and isonitrile were treated with trichlorotoluene **166** and methyl acrylate **164**, the chloro cyclopropane **167** was formed in a good yield. Similarly, the vinyl cyclopropane **169** was also produced by treating the copper(0)-isonitrile complex with the phenylallylidene dichloride **168** and methyl acrylate **164** (Scheme 87).[106b,c]



Scheme 87

Interestingly, the reaction of either 1,3-dichloropropene **170** or allylidene dichloride **171** with an α,β-unsaturated ester **174** provides an identical product **175** in a similar yield. Both reactions occur through the same proposed intermediate, the 1-chloro-2-propenylcopper-isonitrile complex **173** (Scheme 88).[106c] Thus, the 3-chloro-2-propenylcopper-isonitrile complex **172** is likely formed initially but then isomerises to

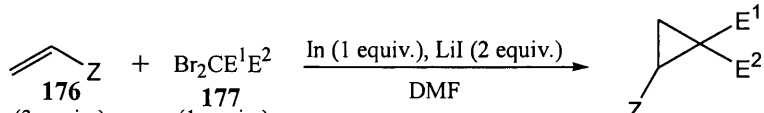
the same copper carbenoid intermediate **173** through 1,3-allyl metal migration as is generated from allylidene dichloride **171**.



Scheme 88

1.5.4 Indium Carbenoids

Carboalkoxy and dicarboalkoxycyclopropanation of electron-deficient alkenes **176** may be achieved by the use of indium in the presence of methylene dibromide **177**, lithium iodide and DMF (Scheme 89).[107] Non-activated and electron-rich alkenes such as cyclohexene and butyl vinyl ether were unreactive and no cyclopropanation occurred in diethyl ether or tetrahydrofuran. Moreover, the yields were lower without the presence of lithium iodide. It is likely that indium carbenoids are formed but no comment was made by the authors on the mechanism of the reaction and in particular, whether loss of alkene stereochemistry occurred during the reaction. Thus, it is probable that the carbenoids react in an analogous stepwise manner to haloorganocopper-isonitrile complexes **159** (*vide supra* 1.5.3, Scheme 84).

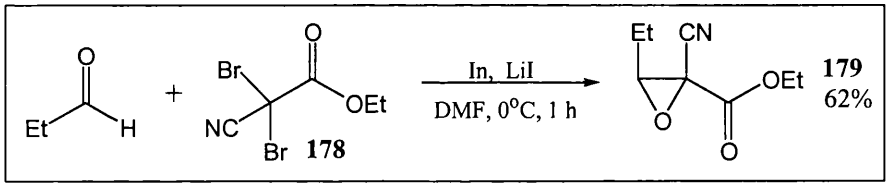


Alkene	$Br_2C(CN)_2$	$Br_2C(CN)CO_2Et_2$	$Br_2C(CO_2Et)_2$
CH_2=CHCOMe	94%	88%	75%
CH_2=$CHCO_2Et$	70%	32%	-
CH_2=CHCN	53%	46%	-
CH_2=CHCHO	-	36%	74%

Observed reactivity of methylene dibromides:
$Br_2C(CN)_2$ > $Br_2C(CN)CO_2Et_2$ > $Br_2C(CO_2Et)_2$

Scheme 89

A similar reaction of aldehydes with dibromomalomalonitrile **178**, lithium iodide, and indium gives the epoxide **179**, and provides evidence for such a two stage mechanism (Scheme 90).[107]



Scheme 90

1.6 Summary and Conclusions

It is hoped that the foregoing review has highlighted several features which are important in determining the reactivity of a metallocarbenoid. For each type of carbenoid species, the patterns of reactivity are formulated in the following tables:

Table 5: Cyclopropanation of alkenes using methylene carbenoids: $YMCH_2X$;

Metal carbenoid	Type of alkene		
	Electron-rich	Electron-deficient	Allylic alcohol
Al	✔	?	✔
Cd	✔	?	?
Cu	✔	?	✔
Hg	✔	✔	?
In	✔	?	?
Li	✔	?	?
Mg	✔	?	?
Sm	✘	✘	✔
Zn	✔	✔	✔

Table 6: Cyclopropanation of alkenes using methyl- or phenyl-substituted carbenoids: YMCH(R)X, R=Me or Ph;

Metal carbenoid	Type of alkene	
	Electron-rich	Allylic alcohol
Al	✔	?
Cd	✔	?
Li	✔	?
Sm	✘	✔
Zn	✔	✔

Table 7: Cyclopropanation of alkenes using dimethylmethylene carbenoids: $YMC(CH_3)_2X$;

Metal carbenoid	Type of alkene	
	Electron-rich	Alkenes with hydroxy moiety
Cr	✘	✔
Zn	✔	✔ [allylic alcohols]

Table 8: Cyclopropanation of alkenes using alkoxycarbenoids: YMCH(OR)X, R=Me, Et, Pr, $(CH_2)_5CH_3$, $(CH_2)_2Cl$;

Metal carbenoid	Type of alkene	
	Electron-rich	Electron-deficient
Li	✔	?
Zn	✔	✔

Table 9: Cyclopropanation of alkenes using carboalkoxy-carbenoids; $YMCR^1(CO_2R^2)X$, R^1=H, Cl, CN, CO_2Et, R^2=Me, Et;

Metal carbenoid	Type of alkene	
	Electron-rich	Electron-deficient
Cu[a]	✔	?
Cu[b]	✘	✔
Hg	✔	?
In	✘	✔
Zn	✔	?

[a] The authors have suggested that the cyclopropanation proceeds through an organocopper(I) intermediate, this is likely to be formed from the initial carbenoid species. [b] The mechanism occurs though a copper carbenoid.

Thus, Tables 5-9 illustrate important differences in reactivity of a metal carbenoid with a particular type of alkene. For example, samarium carbenoids[63] show a chemoselective preference as they exclusively react with allylic alcohol substrates (Table 5) and in similar fashion, chromium carbenoids[91] only react with alkenes with a hydroxy moiety (Table 7). In addition, it is interesting to recall, that by variation of the reaction protocols using aluminium carbenoids,[70] cyclopropanation may favour the proximal or distal double bonds in allylic alcohols. Surprisingly, alkoxycarbenoids of zinc,[96] exhibit a reactivity for both electron-rich and electron-deficient alkenes (Table 8). Finally, in the case of zinc carbenoids,[102] the effect of electron-withdrawing groups leads to low cyclopropanation yields. It may be argued that the initial carbenoid species are too unstable whereas mercury,[105] copper[106] and indium[107] carbenoids offer higher stability in the cyclopropanation reaction. In addition, copper[106] and indium[107] carbenoids react in a stepwise process rather than the usual concerted mechanism, as exhibited for most carbenoid species. By this process, both carbenoids react only with electron-deficient alkenes (Table 9).

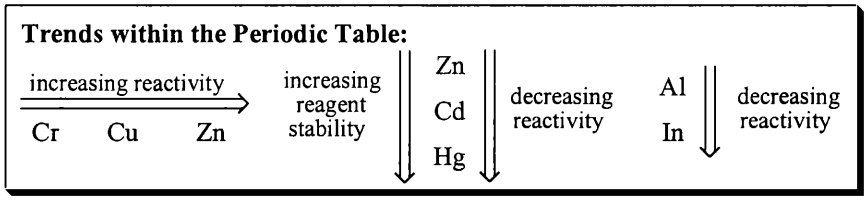
It is interesting to note that the metals discussed in this review, have represented most areas of the Periodic Table; lithium (group I), magnesium (group II), chromium, copper, zinc, cadmium and mercury (transition metals), aluminium and indium (group III), and finally samarium (lanthanide metal). It is clear within these groups, differences between reactivity and stability of the carbenoids may be established. This is illustrated by the last row of the transition metals, where patterns from the reactivity of the metal carbenoids with cyclohexene may be rationalised (Table 10). As shown below, the reaction time and stability from zinc to mercury increases.

Table 10: Cyclopropanation of cyclohexene using methylene carbenoids:

Methylene carbenoid	Reaction time (h)	Yield (%)	Ref.
$ICuCH_2I$[a]	50	85	62
$EtZnCH_2I$	1	91	28b
$EtCdCH_2I$	8	86	58
$Hg(CH_2Br)_2$	192	74	60
$IHgCH_2I$	192	24	60
Et_2AlCH_2I	72	20[b]	67
Et_2InCH_2I	24	22	72

[a] The authors[62] have proposed that the cyclopropanation proceeds through an organocopper(I) reagent, this is likey to be formed from the copper carbenoid shown. [b] Higher yields are obtained using Yamamoto's procedure,[69] but the cyclopropanation of cyclohexene has not been reported.

Thus, it is reasonable to suggest that the metal carbon bond is stronger moving down the group. A similar effect is observed in group III, where aluminium carbenoids show a higher reactivity than indium species. An increase in reactivity may also be noted in moving from chromium to zinc in the first row of the transition metals (Scheme 91). Chromium carbenoids do not react with alkenes whereas copper carbenoids react more slowly than zinc (Table 10).



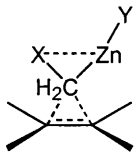
Scheme 91

Most studies on carbenoids have involved the variation of the leaving group X, either as halogen atom or as $-CH_2X$. With the exception of lithium,[73,74] the observed effect of the halogen atom on the reactivity of the metal carbenoid is in the expected order of I > Br > Cl. This is in line with the fact that the carbon-iodine bond would be weaker than the carbon-bromine bond, hence iodide would be a more effective leaving group. Interestingly, in the case of zinc[21] and mercury[60] carbenoids, bis(halomethyl)reagents $[M(CH_2X)_2]$ were found to be more reactive than the corresponding halomethyl reagents ($XMCH_2X$). In addition, (chloromethyl)samarium iodide reagents ($ISmCH_2Cl$) usually exhibit a higher reactivity than (iodomethyl)samarium iodide reagents ($ISmCH_2I$).[63]

The extensive study on methylene zinc carbenoids has revealed the importance of the nature of the leaving group X and the functionalised group Y, in determining the reactivity of such species. In general, high carbenoid reactivity was exhibited when the electrophilicity of the methylene group was increased. In order to achieve this, two main approaches were reported. The first involved the use of electron-withdrawing groups either as the leaving group X or the Y group on the zinc atom as shown in **10a** and this is illustrated by the success of acyloxymethyl zinc reagents[50] or trichlorophenoxide reagent,[42] respectively. Secondly, the use of intermolecular or intramolecular Lewis acid activation also increases electrophilicity, as demonstrated by the dramatic increase in reactivity for alkoxy(iodomethyl)zinc species[40,46] **180** and

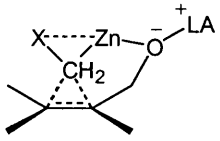
the high reactivity exhibited by acyloxymethyl zinc reagents[50] **59**, respectively. Within these protocols, a pattern between acidity of the Y group and the reactivity of the species may be established. Thus, acidic groups were found to be more beneficial to the reactivity of the carbenoid **10b** (Figure 7). For instance, both trifluoroacetate[39] or trichlorophenoxide[42] groups enhance reactivity in contrast to basic groups such as an amide functionality[41] which led to unsuccessful cyclopropanation reactions. In similar fashion, the use of basic solvents[24] led to a decrease in reactivity of the carbenoid whereas the use of non-complexing solvents such as 1,2-dichloroethane[21] led to high yielding cyclopropanations. The effect of these groups also led to good stability of the resulting carbenoid species, so that the carbenoid was a longer lived species to react with the alkene in solution. However, high stability is of little synthetic importance, as the use of mercury[60] carbenoids has demonstrated with their long reaction times. Thus, a compromise between stability and reactivity is necessary in order to achieve best results. Clearly, there is scope for extending the success of functionalised zinc carbenoids to groups other than methylene. For example, it would be intriguing to see whether any reactivity in carbo-alkoxycyclopropanation could be improved. There is no doubt that applications to other metal functionalised carbenoids will be reported and one appropriate candidate, is cadmium, since diethylcadmium[58] may be used in the preparation of the carbenoids instead of diethylzinc.

Enhanced reactivity of carbenoids as a result of increase in electrophilicity of the methylene group:



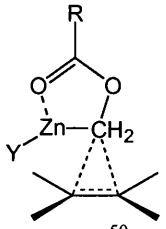
10a[39,42,50]**/b**[39,42]

a, X or Y= electron-withdrawing.
b, Y= acidic group, X=I.



180[40,46]

LA=Lewis acid
X=Cl or I.



59[50]

R=electron-withdrawing
(n-C_4H_9 or CF_3), Y=Et or I.

Figure 7

Clearly, the area of metallocarbenoids remains a subject of great importance due to its synthetic potential. Certainly, chiral metal carbenoids will remain a prime objective in improving the enantioselective cyclopropanation of alkenes, in particular, unfunctionalised alkenes. In order to achieve this, a host of functionalised carbenoids remains to be prepared.

2

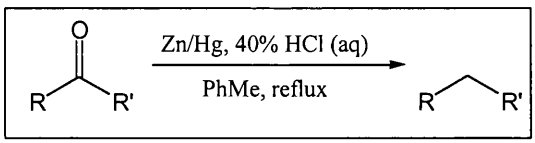
Results and Discussion

2.1 An Insight into The Generation of Organozinc Carbenoids from Carbonyl Compounds

In the first instance, it is appropriate to highlight the evolution of the chemistry of organozinc carbenoids developed within our own group before proceeding to the research carried out in the present thesis. In fact, the origins of this chemistry lie in one of the classical transformations of organic synthesis, the Clemmensen reduction.[108]

2.1.1 The Clemmensen Reduction of Carbonyl Compounds

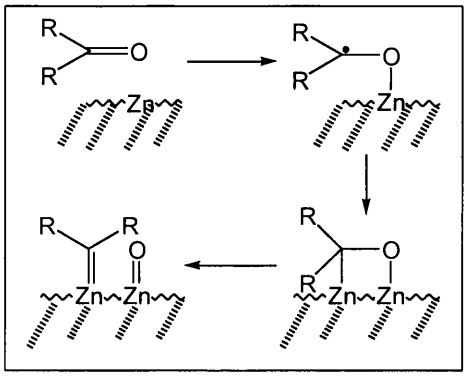
Carbonyl compounds are obviously more attractive starting materials for the generation of carbenoids rather than the handling or preparing of diazo compounds and α,α-dihaloalkanes, reagents which are widely used in metallocarbenoid chemistry. Evidence for an organozinc carbenoid was first shown under Clemmensen reduction conditions,[108] using amalgamated zinc and 40% hydrochloric acid, effectively converting a carbonyl group to a methylene CH_2 (Scheme 92). In addition, the Clemmensen reduction seems to work only with zinc and surprisingly not with other metals of similar redox potential.[109] The reaction has undergone considerable modification since its discovery over 85 years ago and, as a result, the reduction of highly functionalised compounds is much more possible than using the original conditions of Clemmensen's reduction.[110]



Scheme 92

During earlier work Clemmensen observed that the reduction of acetophenone in dilute acid gave styrene rather than ethyl benzene. It was thought that the alkene was formed *via* elimination of the alcohol PhCH(OH)Me in the acidic media rather than by the α-insertion of a carbenoid. Hence, the possible intermediacy of a zinc carbenoid was ignored.[111]

However, a more detailed study directed by Brewster and co-workers[112] suggests that a carbenoid was formed at the surface of the zinc (Scheme 93), in contrast to the homogeneous intermediates identified for the Simmons Smith reaction (*vide supra* 1.2.1.1). Moreover, Brewster also suggested that free alcohols were not in fact intermediates in the Clemmensen reduction due to the fact that alcohols are not generally reduced under Clemmensen conditions.[112]

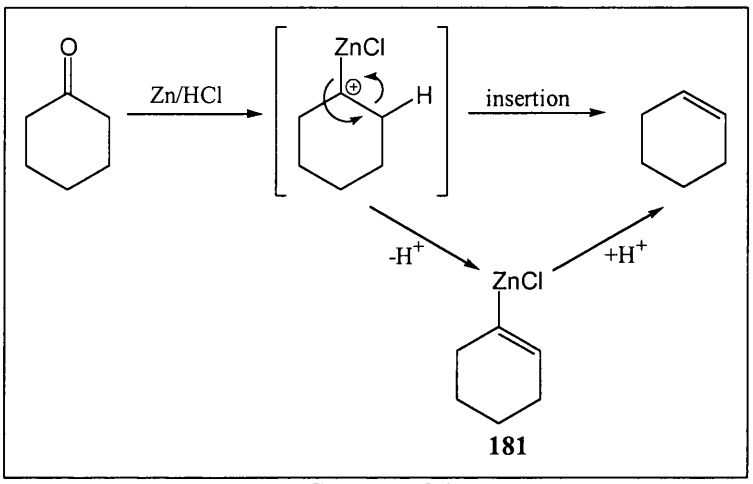


Scheme 93

At a later stage, in a study by Nakabayashi, quenching of the reduction of acetophenone after five minutes generated a complex mixture of saturated, unsaturated and rearranged hydrocarbons, alcohols and pinacol derived products. Experimental and kinetic data suggested that the rate determining step required zinc, a chloride ion and the carbonyl group. Furthermore, Nakabayashi noted that the formation of pinacols, as a result 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 alkenes.[109] Thus, Nakabayashi concluded that the mechanism was a stepwise process, involving the generation of organozinc intermediates.[109]

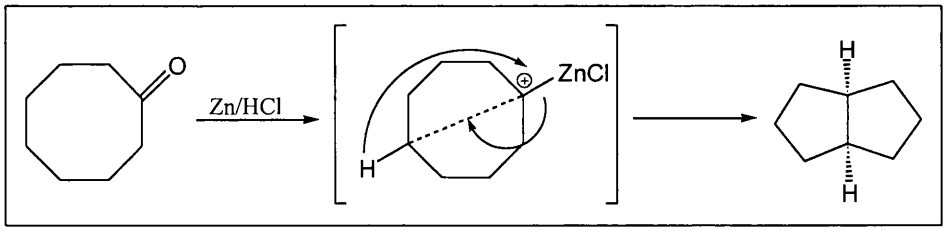
Clear evidence for organozinc carbenoids is provided by the reaction of cyclohexanone with zinc at different concentrations of acid. The relative yield of cyclohexene increases from 6% to 47% as the concentration of hydrogen chloride in the aqueous reduction medium is decreased from 20% to 3%. Thus, the formation of alkene can be regarded as a C-H insertion reaction of an organozinc carbenoid or as a

sequence involving proton loss to give a vinyl zinc intermediate **181** which can then undergo protonolysis (Scheme 94).[113]



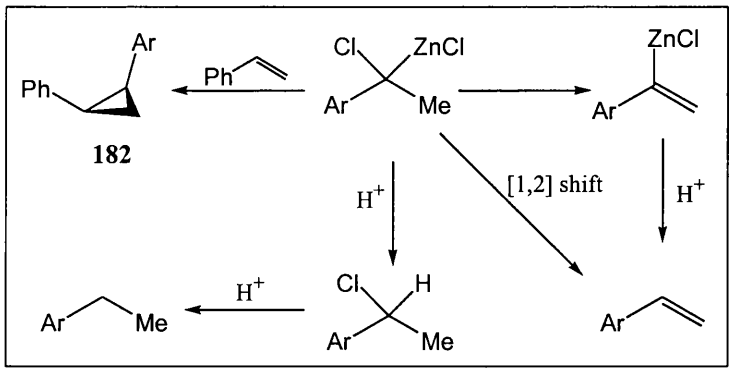
Scheme 94

Additionally, in a classical test, reduction of medium ring cyclic ketones afforded transannular insertion products. Therefore, bicyclo[3.3.0]octane is formed in addition to *cis*-cyclooctene on reduction of cyclooctanone providing clear evidence of carbenoid activity (Scheme 95).[114]



Scheme 95

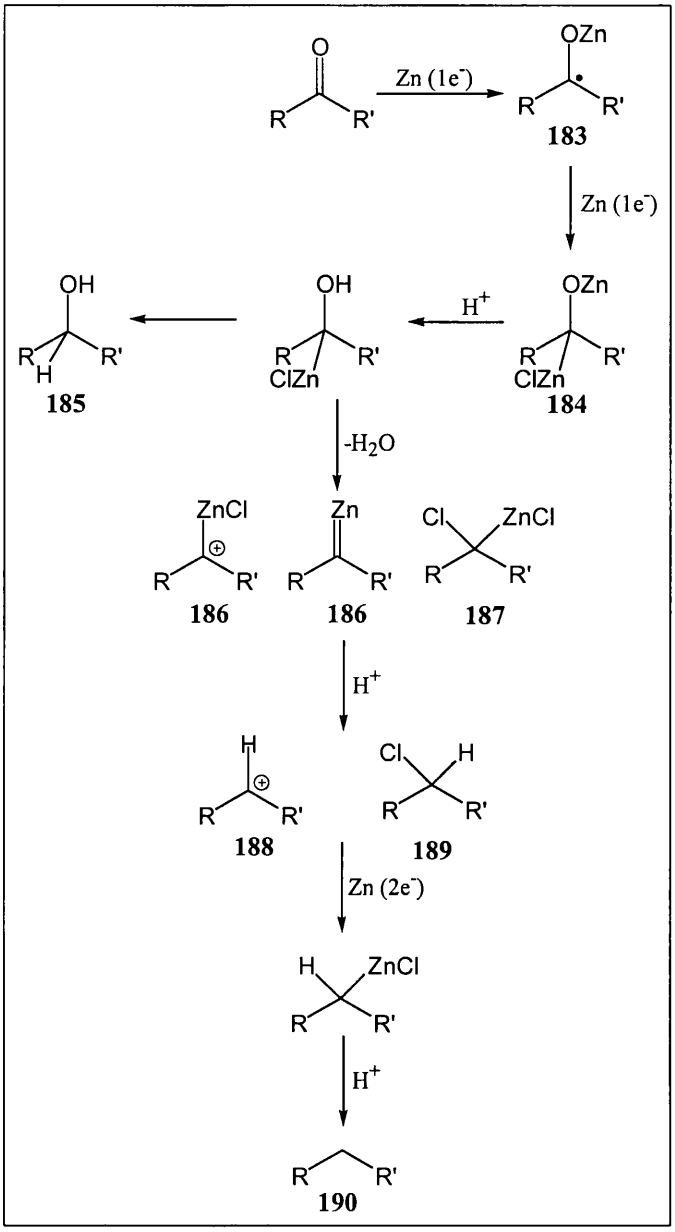
A more recent study by Burden and co-workers[115] also provided further strong evidence for zinc carbenoids. The reaction of 2- and 4-substituted acetophenones in 50% ethanolic hydrochloric acid gave the expected reduced alkanes with styrenes, and the self-coupled cyclopropanes with the *syn* isomers predominating. In the presence of added styrene, *para*-bromoacetophenone gave the cross-coupled cyclopropane **182** with a significant reduction in the yields of other carbenoid or Clemmensen products. Burdon proposed that the products are derived from a zinc carbenoid intermediate (Scheme 96).[115]



Scheme 96

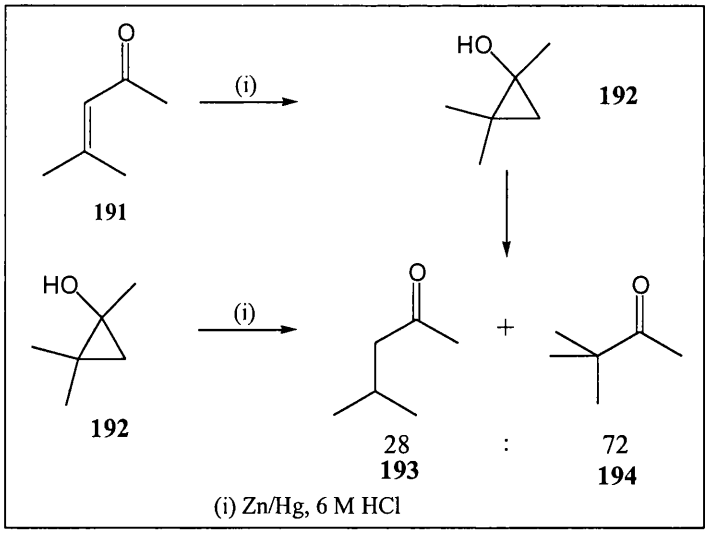
A second mechanism was identified which formed styrenes *via* a proton loss from the zinc carbenoid with subsequent reprotonation of the intermediate vinyl zinc species using deuterated acetophenones. The reduction of 4-$ClC_6H_4COD_3$ gave among other products, $ArCH{=}CD_2$ (30%), and $ArCD{=}CD_2$ (<2%), along with the self-coupled cyclopropane (38%). The longer chain $PhCHCD_2Me$ gives a less stable carbenoid. Rearrangement of PhCD=CDMe (40%) now predominates over the vinyl zinc pathway PhCH=CDMe (17%) with no cyclopropane formed (Scheme 96).[115] The Burdon group also observed that the rate of reduction was independent of the nature of the group in the 4-position. For example, the 4-methoxy derivative gave no styrene or cyclopropane, while the 2-methoxy derivative did.[115]

The proposed mechanism for the reduction of the carbonyl group was based on carbenoid formation and took place *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 **183**. At this stage the intermediate **183** could undergo pinacolic coupling or undergo a further one electron reduction to afford the chloro-zinc alkoxide species **184**. Protonation of the resulting alkoxide **184** and elimination of water generates a zinc-stabilised carbonium ion **186**, an intermediate which may also be represented as an organozinc carbenoid **187**. If the carbenoid is then protonated, the consequence is either the carbonium ion **188** or the chloroalkane **189**. In either case, further two electron reduction by zinc and subsequent protonation will then furnish the methylene compound **190**. Formation of the alcohol **185** was suggested to be the product of a side reaction (Scheme 97).[109,115]



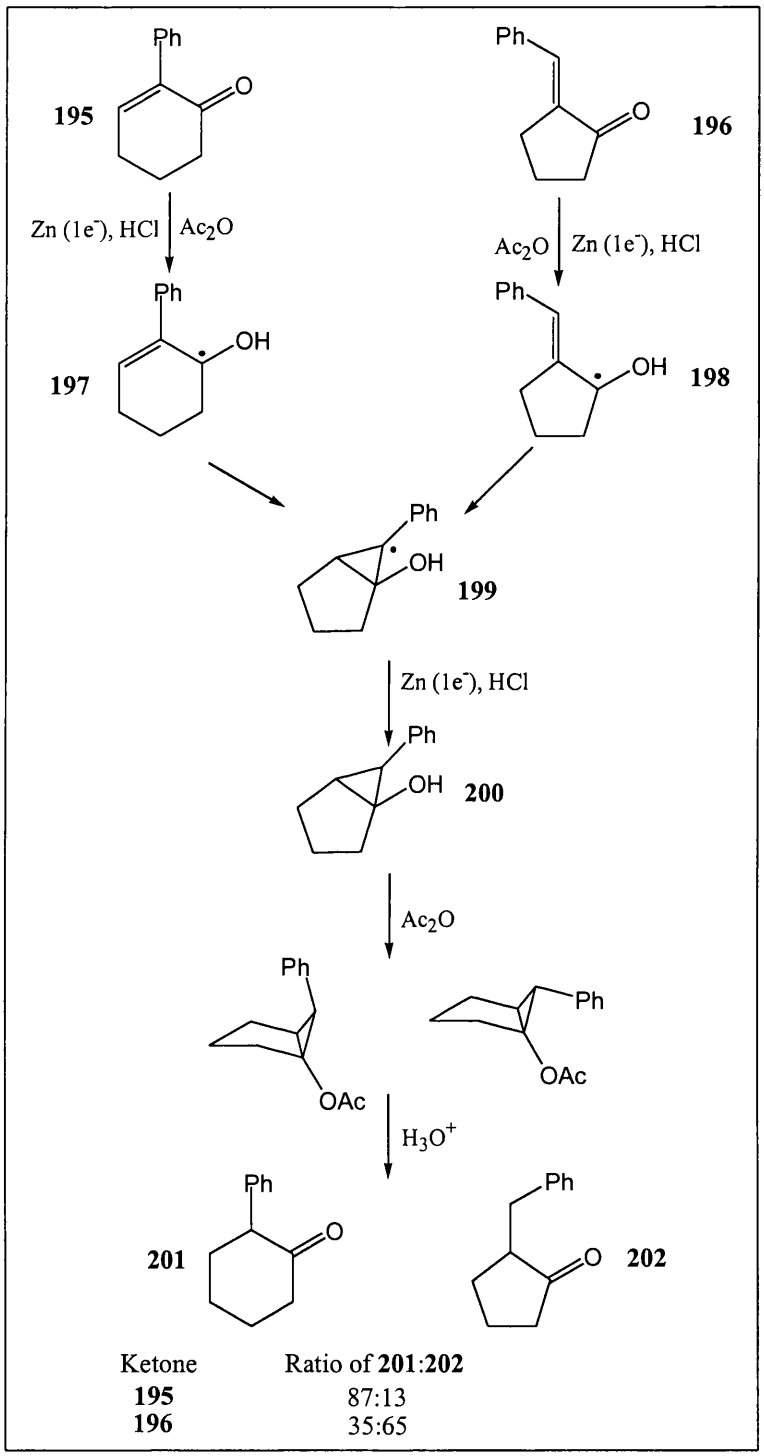
Scheme 97

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 **191** and 1,2,2-trimethylcyclopropanol **192** would generate an identical mixture of 4-methylpentan-2-one **193** and 3,3-dimethylbutan-2-one **194** (Scheme 98).[116]



Scheme 98

Similar evidence of one electron reduction was obtained by Elphimoff-Felkin who examined the behaviour of two α,β-unsaturated ketones **195** and **196** which could be expected to undergo reduction *via* identical cyclopropanal intermediates **200**.[117] The latter could be isolated from the reaction as an acetate derivative by trapping with acetic anhydride, or subjected to solvolytic proton catalysed rearrangement to give the final product ketones **201** and **202** (Scheme 99).[117]



Scheme 99

A more detailed study covering several β-phenyl enones, all of which were subjected to similar reducing conditions was also carried out, and in all cases a cyclopropanol acetate was obtained. Once again, the mechanism involves one electron reduction of the enone to form the radical species **197** and **198**, which with α,β-unsaturated carbonyls will undergo electrolytic ring closure to give the benzylic cyclopropyl

radical **199**. Further reduction of the benzylic radical **199** produced followed by protonation generates the cyclopropanol **200** (Scheme 99).[117]

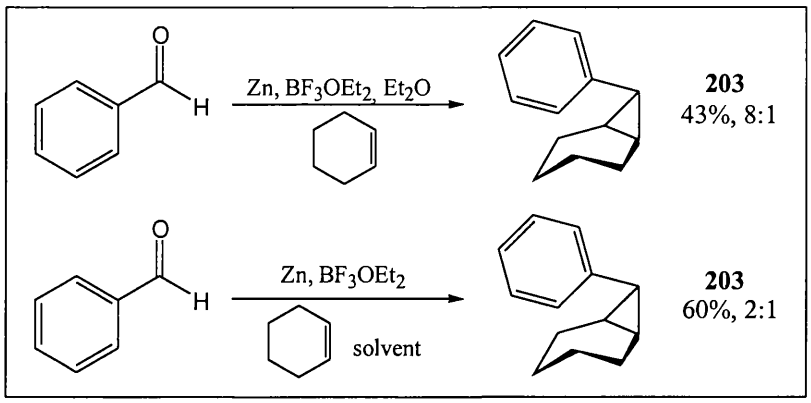
2.1.2 The Controlled Generation of Organozinc Carbenoids from Carbonyl Compounds

Although, sufficient evidence demonstrates that the Clemmensen reduction proceeds *via* an organozinc carbenoid, classical carbenoid behaviour is generally not observed due to the vigorous reaction conditions which favour further electron transfer from zinc and protonation to yield the methylene CH_2 group. In order to utilise the carbenoid synthetically, alternative reactive conditions are therefore required.

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

Two methods both involving replacement of the proton have been developed in order to investigate more synthetically useful reactions.

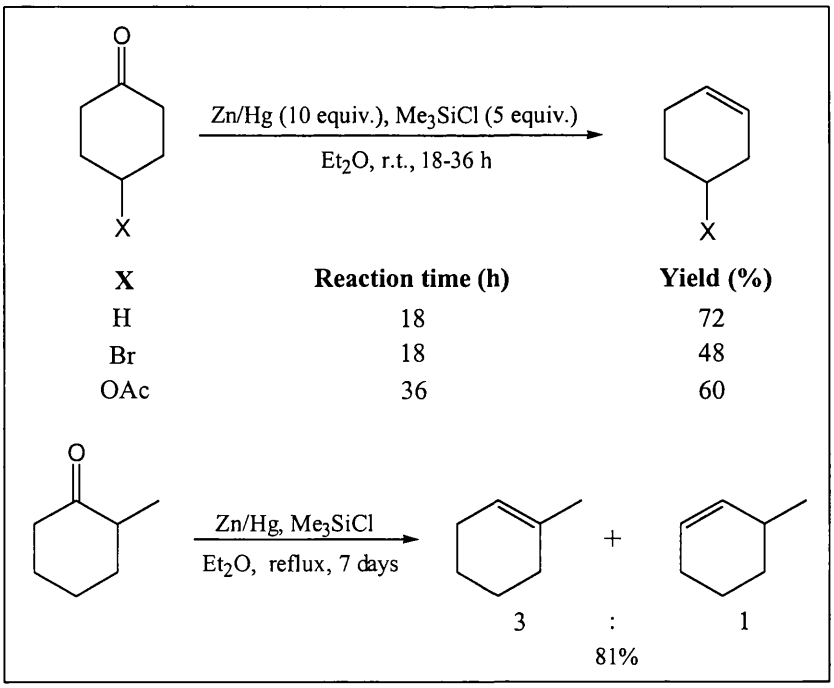
In the first instance, Elphimoff-Felkin reported the use of boron trifluoride diethyletherate as an electrophile in the presence of zinc allowed the carbenoid derived from aromatic aldehydes to be trapped by an alkene to give cyclopropanes. Although the yields were moderate, cyclic alkenes gave the more hindered *cis* isomer preferentially (Scheme 100).[118,119] As we have seen, it was later shown by Burdon[118] that trapping of the carbenoids generated under Clemmensen conditions would similarly afford the *cis* cyclopropane **203** as the major product. Furthermore, the use of cyclohexene as the reaction solvent gave a significant increase in yield but decrease in diastereoselectivity. This is attributed to the fact that the Lewis acidity of boron trifluoride is significantly increased by the loss of the diethyl ether ligand since the boron would be likely to be continually co-ordinated in ethereal solvent.



Scheme 100

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

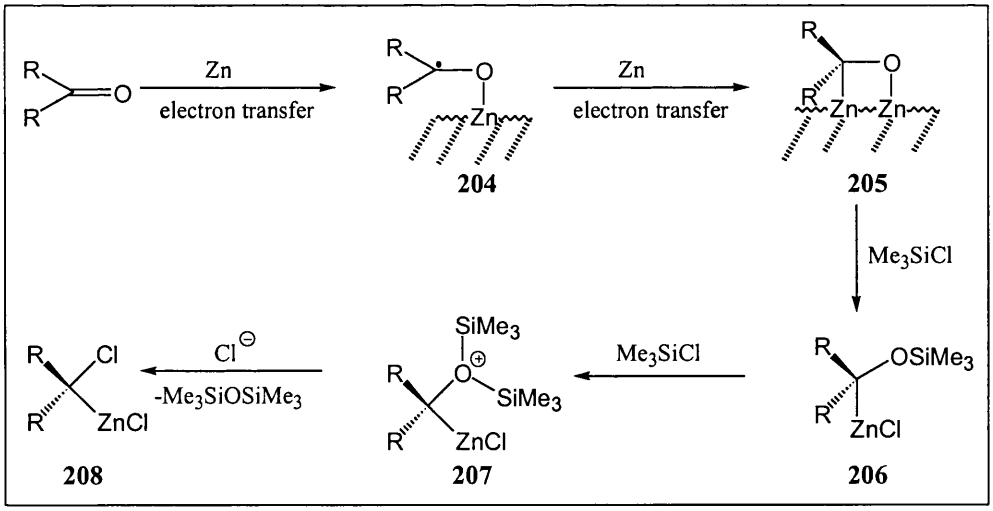
The conversion of carbonyl compounds to alkenes is an important transformation in organic synthesis. A novel method, reported by Motherwell in 1973, introduced a silicon electrophile replacing the proton in HCl, and when used with amalgamated zinc, directed the conversion of cyclic ketones to olefins *via* deoxygenation. As a result of these mild reaction conditions, chemoselective reduction occurred even in the presence of ester and bromide functionality (Scheme 101).[93]



Scheme 101

The deoxygenation reaction can be viewed as a simple variant of the Clemmensen reduction, with the silicon electrophile acting as a direct replacement for the proton and, more importantly, the carbenoid intermediate does not undergo further reaction with silicon electrophiles, but inserts into a neighbouring C-H bond instead.[93] In addition, the possibility of a silyl enol ether intermediate (trimethylcyclohexenyloxysilane) was dismissed as this intermediate gave no cyclohexene when subjected to the reaction conditions.[93]

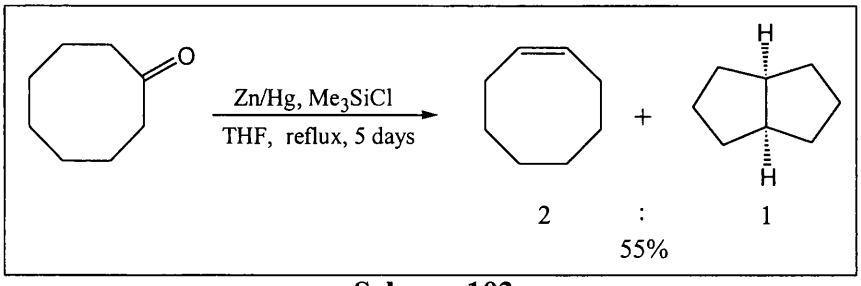
Thus, in analogous fashion to the mechanism proposed by Burdon[115] and Nakabayashi[109] for the Clemmensen reduction, the carbonyl may undergo one electron reduction at the zinc surface to generate the radical species **204** bound *via* the oxygen to zinc. A further electron donation from the zinc generates an intermediate **205**, which in the presence of chlorotrimethylsilane generates an organozinc species **206**, and this is then further silylated. Loss of hexamethyldisiloxane from **207** results in the formation of the tetrahedral zinc carbenoid intermediate **208** (Scheme 102).[120]



Scheme 102

Clear mechanistic support for carbenoid behaviour, was provided when the size of the ring is increased to cyclooctanone, bicyclo[3.3.0]octane (18%) is formed as a result of transannular insertion of the carbenoid as well as the expected *cis*-cyclooctene (36%) product. C-H insertion now occurs at both the 2- and 5- positions due to the ring conformation afforded by the eight-membered ring (Scheme 103).[93] Furthermore,

both deoxygenation reactions were also observed under Clemmensen conditions (*vide supra* 2.1.1, Schemes 94 and 95).[113,114]

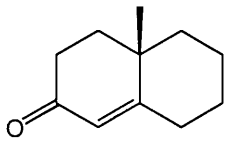
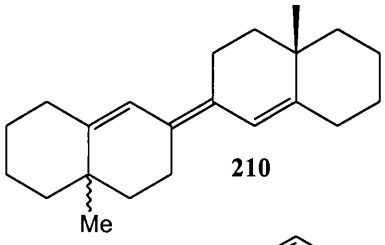
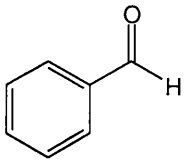
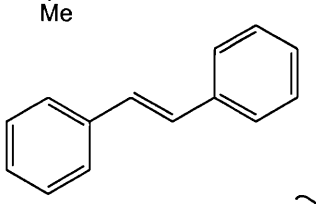
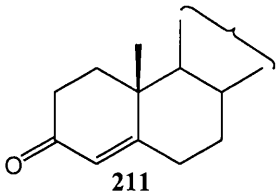
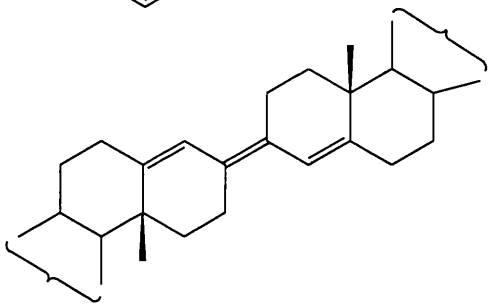
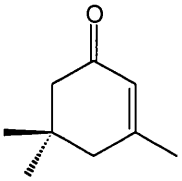
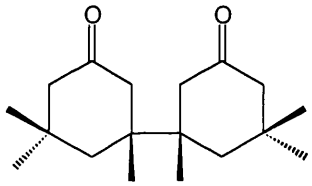


Scheme 103

2.1.2.3 Dicarbonyl Coupling Reactions of Organozinc Carbenoids Generated from Carbonyl Compounds using Zinc and a Silicon Electrophile

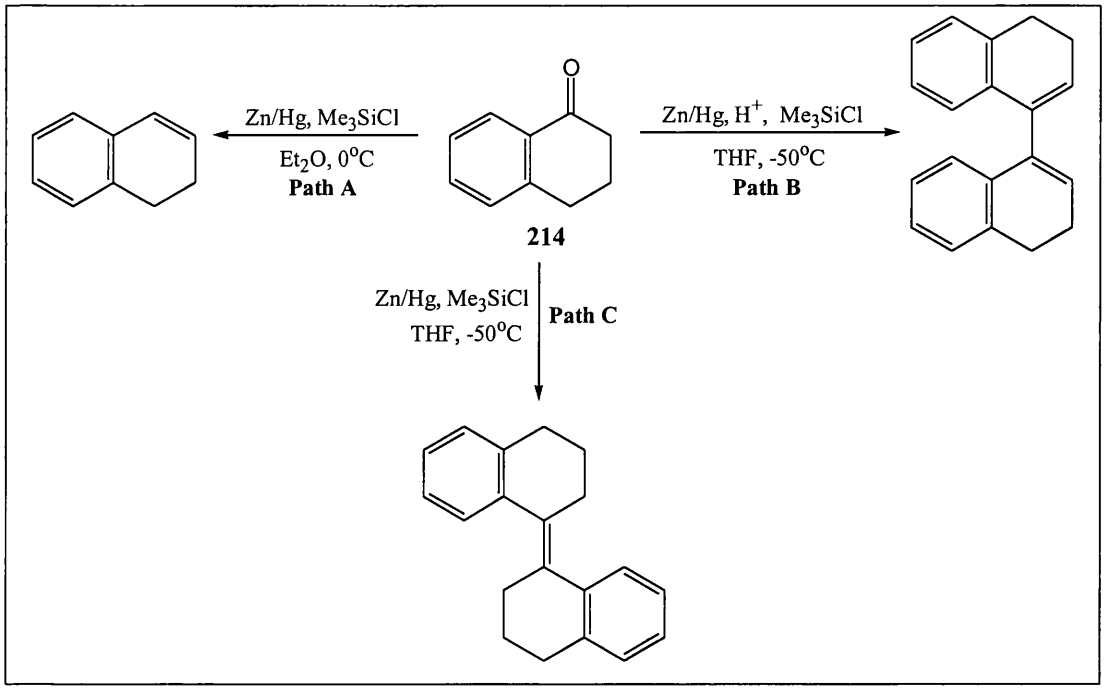
Some years later, Motherwell in collaboration with the group of Banerjee,[121] discovered that certain aryl and α,β-unsaturated carbonyl compounds could be induced to undergo a McMurry-like symmetrical dicarbonyl coupling.[122] Although, octalone **209** coupled to give the triene **210** in excellent yield, aromatic aldehydes and ketones also gave "dimers" in rather lower yields, due to a more dominant process of pinacol coupling, as seen in the examples of benzaldehyde and cholest-4-en-3-one **211** (Table 11). In the case of isophorone **212**, however, radical coupling occurred at the softer β-carbon to give the diketone **213**. The method involves slow addition of the carbonyl compound to zinc and the silicon electrophile in order to reduce the formation of pinacol by-products. It is noteworthy to mention, most of these carbenoids were generated at low temperature.

Table 11: Dicarbonyl coupling using zinc carbenoids generated from carbonyl compounds[121]

Substrate	Product*	Yield (%)
 **209**	 **210**	85
		15
 **211**		43
 **212**	 **213**	15

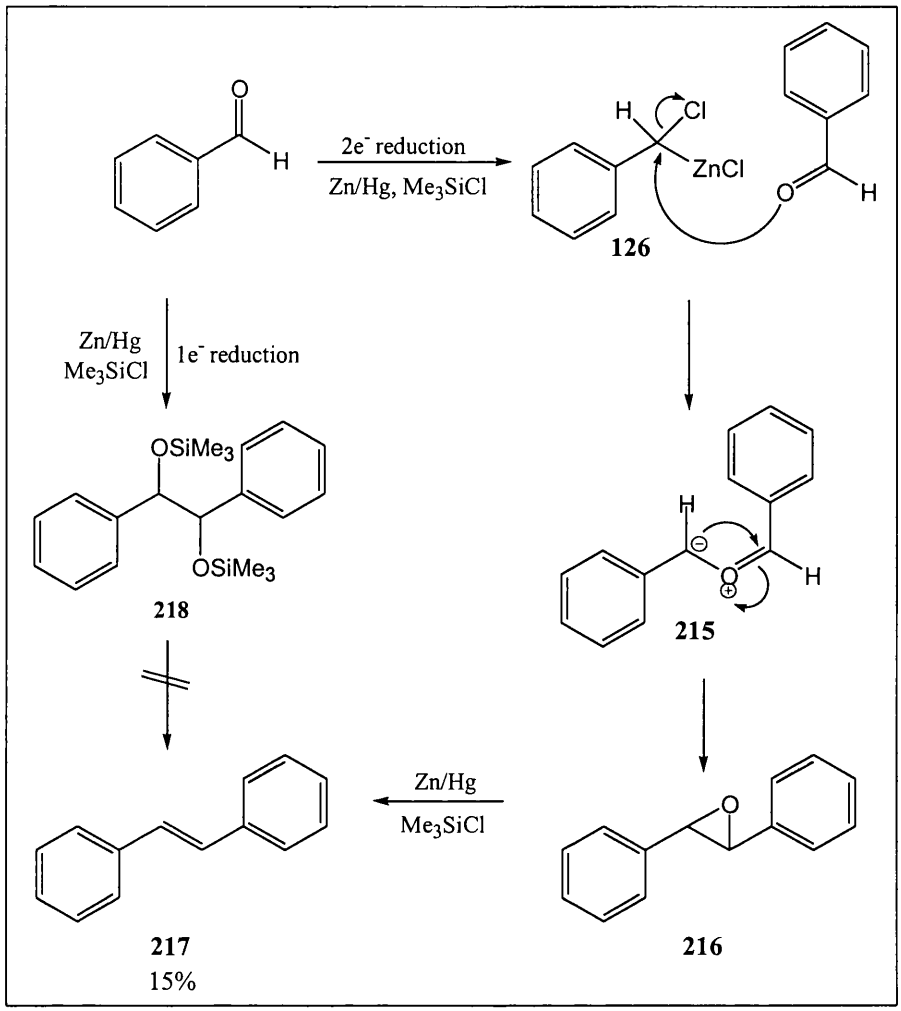
* Reaction conditions: Zn/Hg (10 equiv.), Me_3SiCl (5 equiv.), -30°C, THF.

These results suggest that the coupling reactions were highly substrate specific and in addition influenced by the relative concentrations of substrate, reagents and the presence or absence of small amounts of hydrogen chloride.[121] This is best illustrated by the case of α–tetralone **214**, where the reaction can be controlled to give direct unimolecular C-H insertion (Path A), pinacolic coupling followed by dehydration (Path B), or dicarbonyl coupling (Path C, Scheme 104).



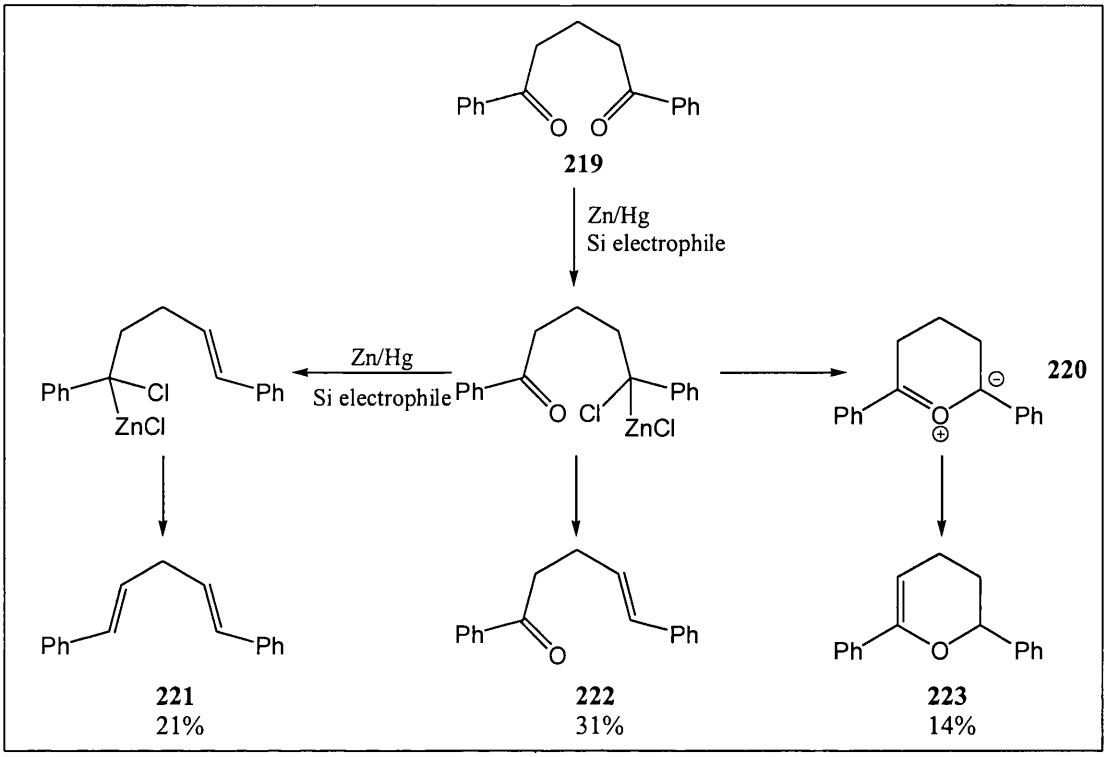
Scheme 104

The mechanism in the case of benzaldehyde occurs *via* the trapping of the zinc carbenoid species **126** by a second molecule of the carbonyl compound to form an oxonium ylide intermediate **215**, which then closes to produce the stilbene oxide **216**. The epoxide **216** is further reduced to furnish the alkene **217** (15%). However, bistrimethylsilyl benzpinacol **218** (50%) had also been isolated (Scheme 105).[121] When *trans*-stilbene oxide **216** was refluxed with zinc and chlorotrimethylsilane, alkene formation was also observed strongly suggesting the epoxide **216** as a suitable intermediate. This was supported by a later study, in which a range of α,β–unsaturated and stilbene epoxides, was shown to deoxygenate to alkenes using zinc and chlorotrimethylsilane *via* siloxychlorohydrin derivatives formed by initial ring opening of the epoxide followed by zinc induced elimination.[123]



Scheme 105

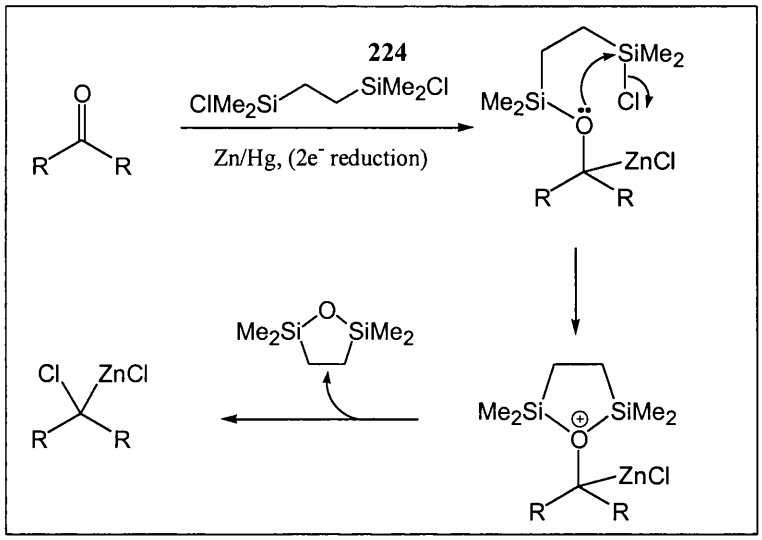
Clear evidence of ylide formation in dicarbonyl coupling reactions was demonstrated by the attempted intramolecular coupling of the symmetrical dicarbonyl precursor **219**. When using zinc/silicon electrophile reduction of the diketone **219**, a mixture of 2,6-diphenyldihydrofuran **223** and the expected products of α-insertion, alkene **222** and diene **221** were isolated. Formation of the dihydropyran **223** was explained as proceeding *via* the ylide **220**, which then fails to close to the epoxide as a consequence of the benzylic nature of the intermediate and the ring strain involved (Scheme 106).[94]



Scheme 106

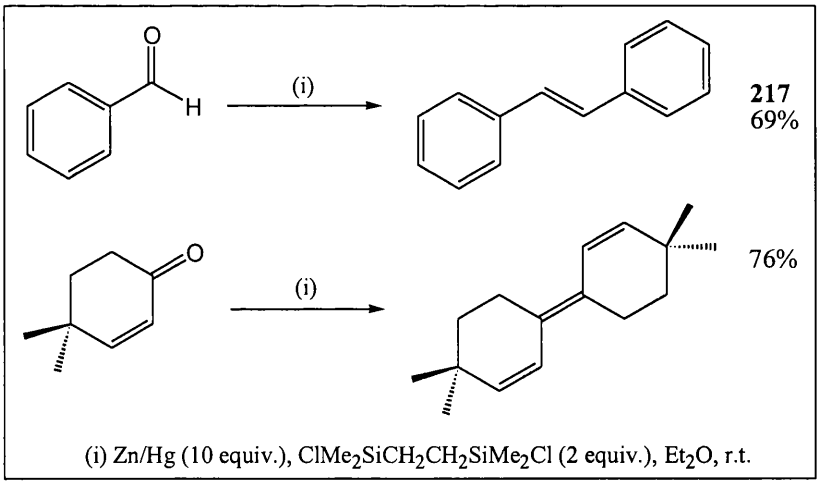
In some cases, however, the pinacol coupling of the carbon centred siloxy radical proved to be problematic and attention was then focused to restrict this pathway. It was clear that this could be retarded if the delivery of the second electron and/or silicon electrophile was more favourable over the pinacol coupling.

Overall, the reduction of a carbonyl compound requires two electrons from zinc and two equivalents of a silicon electrophile. After further investigation, it was found that 1,2-bis(chlorodimethylsilyl)ethane **224** could be used as a bis electrophile to enhance the efficiency of the carbenoid generation, due to the intramolecular delivery of the second electropositive silicon atom (Scheme 107).[94]



Scheme 107

In fact, the use of this reagent had eliminated the formation of pinacol side products in symmetrical dicarbonyl coupling reactions, and as a consequence, significant improvements in yields of alkenes were noted (Scheme 108).[94] This is clearly demonstrated in the coupling of benzaldehyde as the equivalent reaction, in the presence of chlorotrimethylsilane, yielded stilbene **217** in only 15% yield.[121]

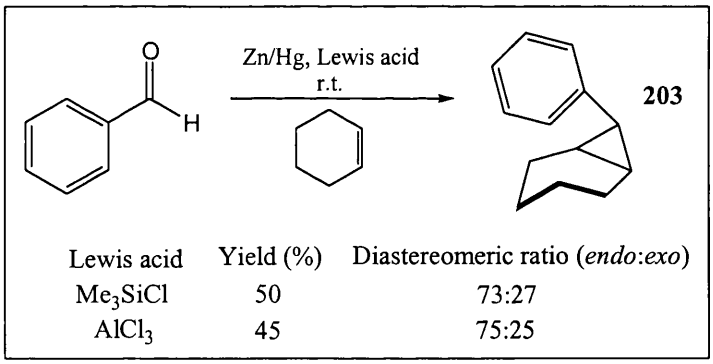


Scheme 108

2.1.2.4 Cyclopropanation with Organozinc Carbenoids Generated from Carbonyl Compounds using Zinc and a Silicon Electrophile

Having achieved significant advances in dicarbonyl coupling yields with the use of the bis silicon electrophile, attention was focused on the very synthetically useful intermolecular cyclopropanation of alkenes with carbenoids derived from carbonyl compounds.

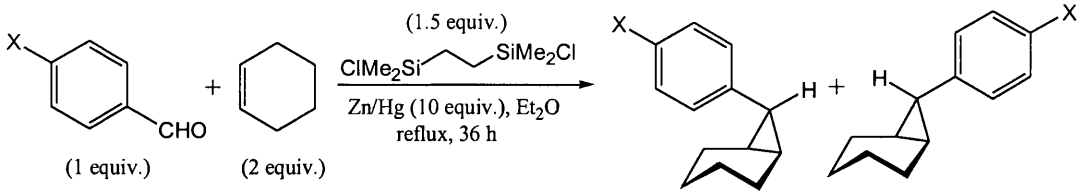
Elphimoff-Felkin and Sarda in 1975 reported the use of zinc and other oxophillic Lewis acids in a series of cyclopropanation reactions of a range of alkenes with various *para*-substituted arylaldehydes. They utilised both chlorotrimethylsilane and aluminium trichloride under the same reaction conditions to afford 7-phenylnorcarane **203** in moderate yields (Scheme 109).[118,119] These reactions illustrated the first controlled attempts at trapping an organozinc carbenoid with an alkene.



Lewis acid	Yield (%)	Diastereomeric ratio (*endo*:*exo*)
Me_3SiCl	50	73:27
$AlCl_3$	45	75:25

Scheme 109

A similar study was carried out by Motherwell who found that simple alkenes could be readily cyclopropanated by the carbenoids efficiently generated from arylaldehydes with zinc and a bis silicon electrophile. As with the chemistry of Elphimoff-Felkin, the more sterically hindered *cis* (or *endo*) cyclopropane is formed preferentially, and the yields and stereoselectivity decrease with decreasing electron donation from the *para*-substituent on the aromatic ring. Interestingly, near quantitative yields are achieved for cyclopropanes generated from *para*-methoxybenzaldehyde (Scheme 110).[79]



X	Yield (%)	Ratio (*endo*:*exo*)
OMe	98	15:1
Me	75	8:1
H	68	4:1
Cl	46	3:1

Scheme 110

Clearly, electron releasing substituents in the 4-position of the arylaldehyde, increase the efficiency of carbenoid generation, possibly by promoting the elimination of the siloxane leaving group, as shown in Figure 8.

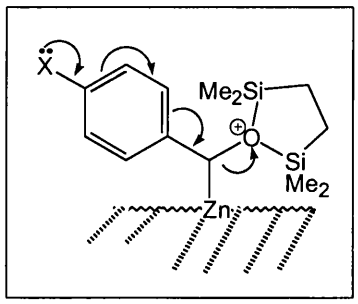
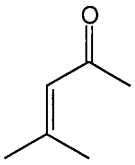
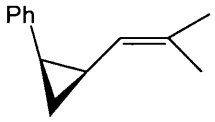
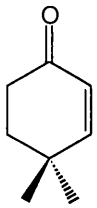
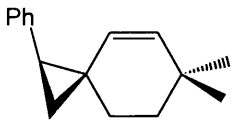
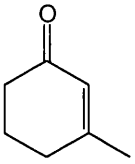
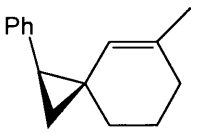
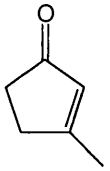
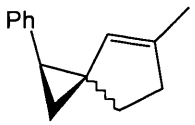
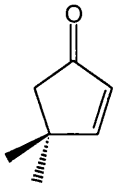
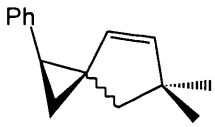


Figure 8

However, no cyclopropanes were obtained from carbenoids derived from arylaldehydes with electron poor alkenes such as acrylonitrile, ethylacrylate, phenylvinylsulfone, maleic anhydride or diethylvinyl phosphate.[124]

The behaviour of non aromatic α,β-unsaturated organozinc carbenoids in cyclopropantion reactions was also investigated in the Motherwell group. A useful range of cyclic and acyclic enones and enals were trapped by alkenes as shown in Table 12.[79] Once again, the *cis* selectivity is maintained in the examples of the isoprenoid enal and cycloalkanone substrates.[79]

Table 12: Cyclopropanation using zinc carbenoids generated from carbonyl compounds[79]

Substrate	Product*	*cis/trans*	Yield (%)
		all *cis*	53
		20:1[a]	55
		11:1[a]	59
		1:1	44
		1:1	19

* Reaction conditions: Zn/Hg (10 equiv.), $ClMe_2SiCH_2CH_2SiMe_2Cl$ (1.5 equiv.), styrene (2 equiv.), Et_2O, reflux, 36 h.

[a] Major isomer shown.

Overall, it was found that a degree of substitution either at or around the β carbon of the unsaturated carbonyl group was beneficial, supported by the fact of the failure of the three α,β-unsaturated ketones and aldehydes shown in Figure 9.[120,124]

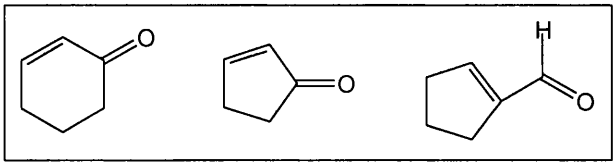
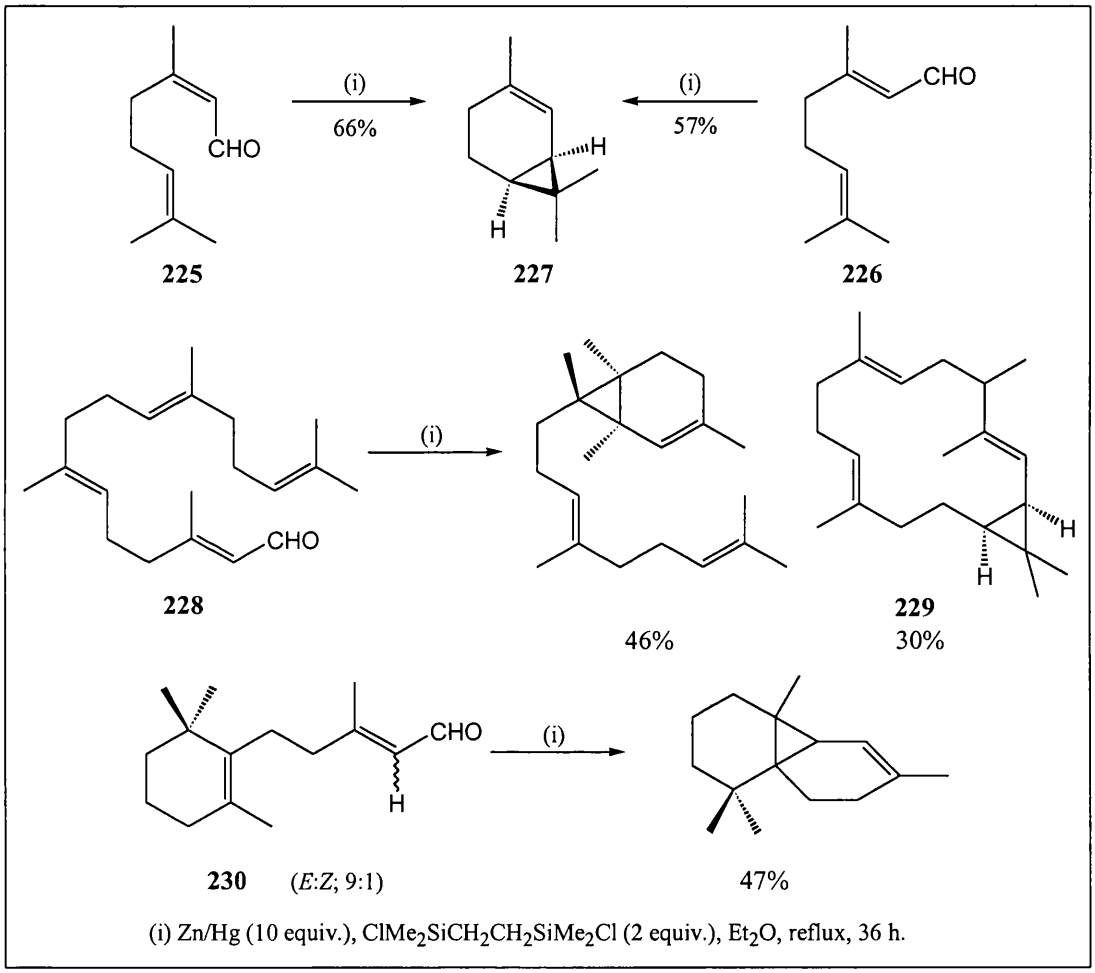


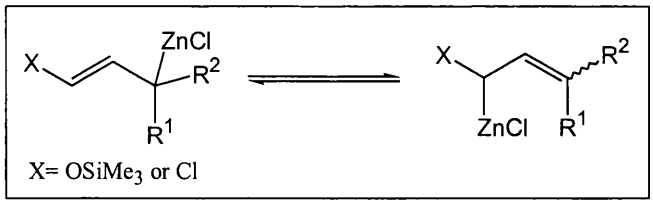
Figure 9

This work was also extended to intramolecular cyclopropanation reactions. By using high dilution conditions, achieved by the slow addition of the terpenoid enals to the other reagents, both geranial **225** and nerol **226** could be cyclised to Δ–2-carene **227** in good yields. However, more impressively geranylgeraniol **228** cyclised to the macrocycle casbene **229** (Scheme 111).[125] The chemistry has proved itself to be applicable to the synthesis of some complex and useful compounds.



Scheme 111

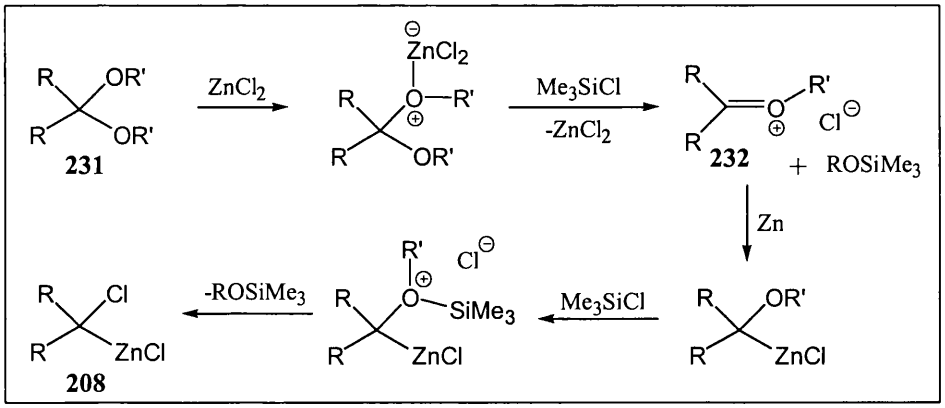
Surprisingly, successful cyclopropanations could occur even when the initial geometry around the enal unit was unfavourable with respect to the alkene trap, as shown in the case of **228** and **230**. These cyclopropanations together with the high degree of steric hindrance around the β-carbon atom of the α,β-unsaturated carbonyl unit suggest that 1,3-allyl migration of the carbon-zinc bond is a likely process, resulting in a loss of alkene geometry, in an attempt to relieve steric congestion (Scheme 112).[120,125]



Scheme 112

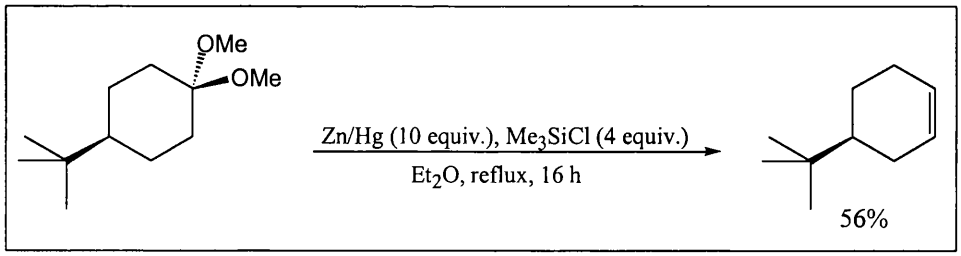
2.1.2.5 Cyclopropanation with Organozinc Carbenoids Generated from Acetals and Ketals

More recently, acetals and ketals were introduced as a new source of carbenoid precursors, thus effectively replacing carbonyl compounds.[126] Hegedus and Hossain had reported muti-step procedures for the preparation of isolable organochromium[127] and organoiron[128] carbenoids prepared by two electron delivery from a metal salt to an oxocarbenium ion derived from an orthocarbonate or acetal. The proposed mechanism was based on the Lewis acid assisted cleavage of an acetal or ketal **231** to give an oxonium ion intermediate **232** which, by virtue of its positive charge, readily accepts two electrons from zinc and in the presence of chlorotrimethylsilane, to afford organozinc carbenoids **208** (Scheme 113).[126] Thus, the formation of carbon centred radicals bound to the zinc surface is avoided.



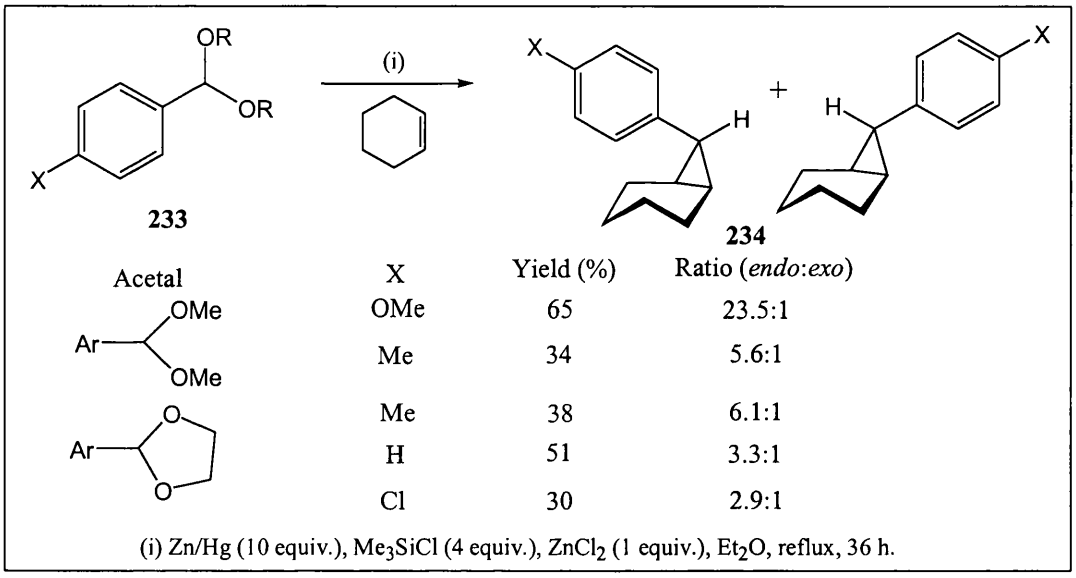
Scheme 113

A useful and direct transformation of an acetal or a ketal to an alkene was observed due to C-H insertion of the resulting carbenoid without the presence of Lewis acid (Scheme 114).[126]



Scheme 114

In addition, the trapping of organozinc carbenoids generated from *para*-substituted aryl acetals **233** with cyclohexene was found to afford the desired cyclopropanes **234** in moderate yields (Scheme 115).[126]



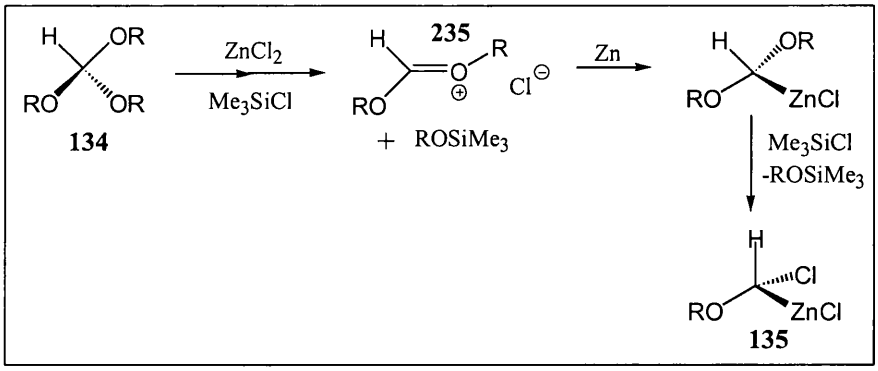
Acetal	X	Yield (%)	Ratio (*endo*:*exo*)
Ar, OMe, OMe	OMe	65	23.5:1
	Me	34	5.6:1
Ar, O, O	Me	38	6.1:1
	H	51	3.3:1
	Cl	30	2.9:1

(i) Zn/Hg (10 equiv.), Me_3SiCl (4 equiv.), $ZnCl_2$ (1 equiv.), Et_2O, reflux, 36 h.

Scheme 115

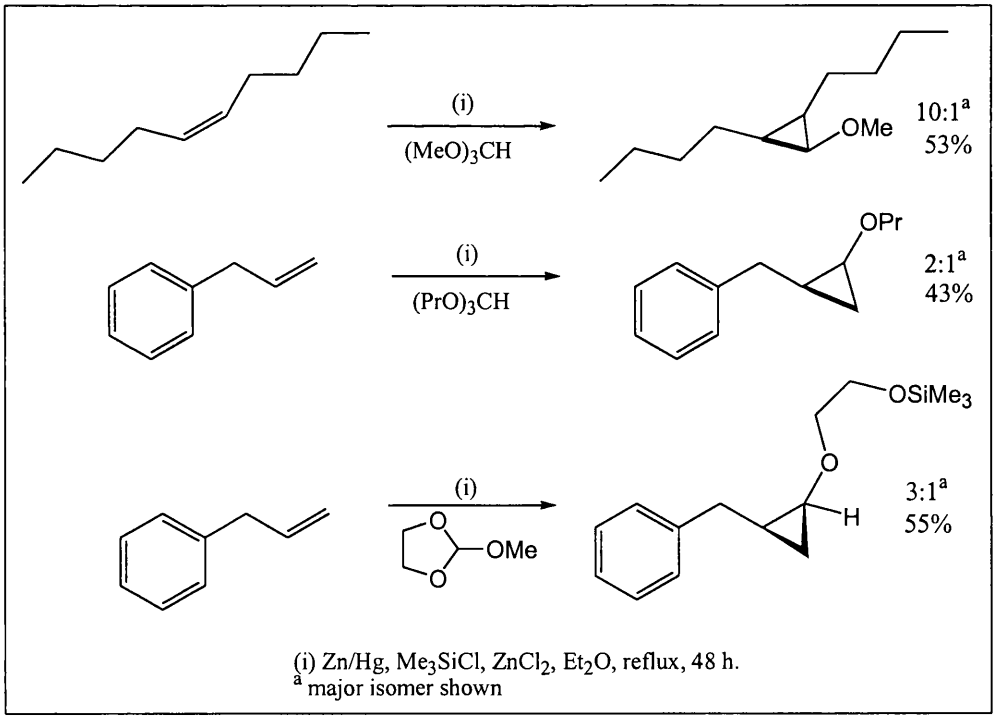
2.1.2.6 Alkoxy- and Aryl-oxycyclopropanation with Organozinc Carbenoids Generated from Orthoformates

As a direct consequence of the work on acetals and ketals, orthoformates **134** were then used to generate a novel class of α-alkoxy and α-aryloxy organozinc carbenoids **135** *via* oxonium ions **235** (Scheme 116).[96] This method was found to provide a simple and inexpensive route to the preparation of alkoxy and aryloxycyclopropanes under mild neutral conditions, thus avoiding the handling of highly carcinogenic α-halo or α,α-dihalo ethers.[97,98]



Scheme 116

Moreover, a range of alkoxy and aryloxycyclopropanes were easily prepared by the selection of the appropriate orthoformate and reaction with an alkene in the presence of zinc, chlorotrimethylsilane and zinc chloride. As in the previous chemistry within the group, there is once again a distinct stereochemical preference for the formation of the more hindered *cis* cyclopropane for the latter (Scheme 117).[96] As discussed earlier, both electron rich and electron poor alkenes react (*vide supra* 1.4.1, Scheme 76).[96]



Scheme 117

From the foregoing overview, we can clearly see that the generation of some simple organozinc carbenoids from carbonyl compounds can be considered as a viable

pathway and that useful reactivity has been demonstrated in three distinct types of reaction *viz.*, deoxygenation to alkenes,[93,123,126] dicarbonyl coupling[94,121] and cyclopropanation.[79,96,125,126] Nevertheless, in terms of our overall understanding of metal carbenoid generation and reactivity, much remains to be achieved.

The following programme of research was initiated with the objectives of developing both new and improved methods for the generation of carbenoids and also extending the range of more highly functionalised carbenoids which can be used in this chemistry. Although the following discussion has of necessity been subdivided into some of the above themes, it should be appreciated that in general several different aspects were always under contemporaneous investigation. The end result, in which some valuable insights into a variety of facets of carbenoid chemistry have been gained, is therefore something of a "pot-porri".

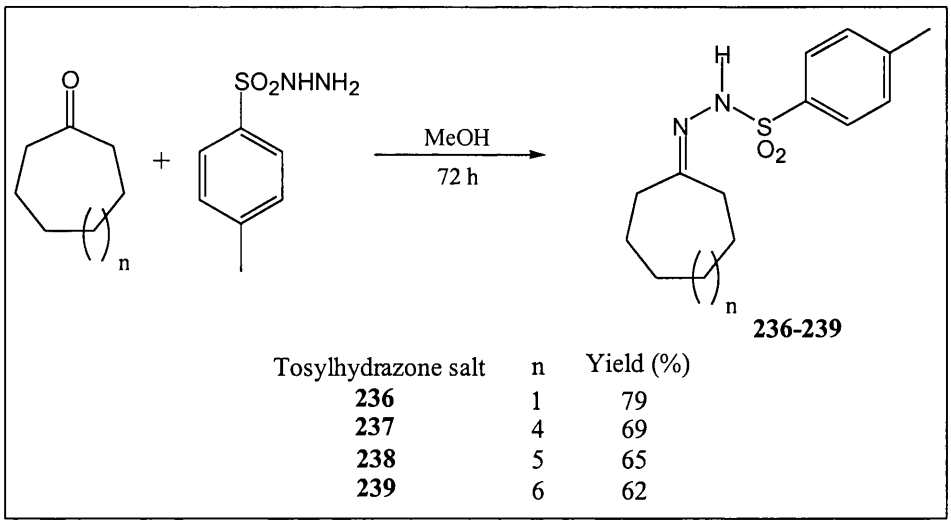
2.2 Deoxygenation of Ketones *via* Formation of Organozinc Carbenoids

Our own work in this area began with an investigation of transannular insertion reactions in small (C-7), medium (C-10) and large (C-11 and C-12) ring sized ketones. This involved the preparation of authentic samples of carbenoid insertion products obtained from pyrolysis of tosylhydrazone salts (the Bamford-Stevens reaction)[129] using a series of cycloalkanones in order to make a comparative study with zinc and chlorotrimethylsilane deoxygenations. Cyclononanone was avoided in this study, due to the difficulty of its preparation and its high cost.

2.2.1 Pyrolysis of Tosylhydrazone Salts

The formation of the desired transannular insertion products *via* thermolysis of the lithium salts of tosylhydrazones was carried out in two steps *viz.*: formation of the lithium salts of tosylhydrazone followed by pyrolysis, in contrast to the use of zinc and a silicon electrophile which provided a one step route to the desired compounds.

The tosylhydrazones **236-239** were easily prepared from the corresponding carbonyl compounds with *p*-toluenesulfonylhydrazide in methanol followed by recrystallisation in good yields (Scheme 118).[130]



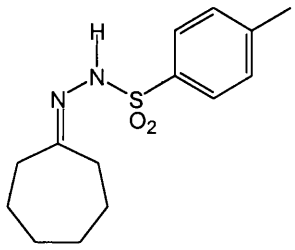
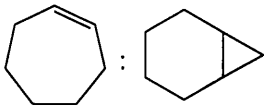
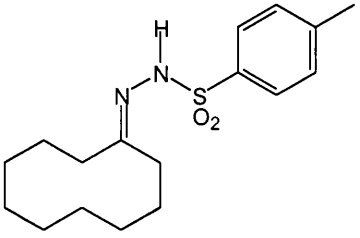
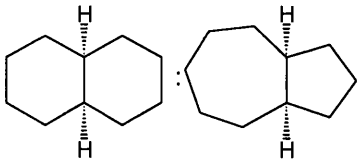
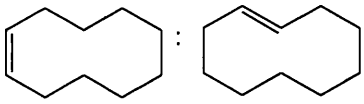
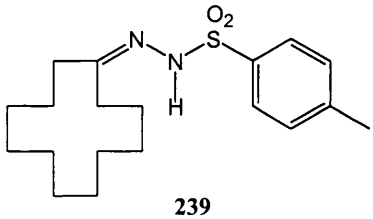
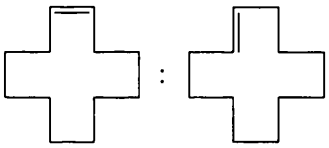
236-239

Tosylhydrazone salt	n	Yield (%)
236	1	79
237	4	69
238	5	65
239	6	62

Scheme 118

There are various methods for the generation of carbenes from tosylhydrazones.[131] C-H transannular insertion reactions have been observed in cycloheptanone, cyclodecanone and cyclododecanone tosylhydrazones, using sodium methoxide in diethyl carbitol, followed by pyrolysis of the resulting dry tosylhydrazone salt (Table 13).[131a]

Table 13: Pyrolysis of sodium salts of tosylhydrazone[131a]

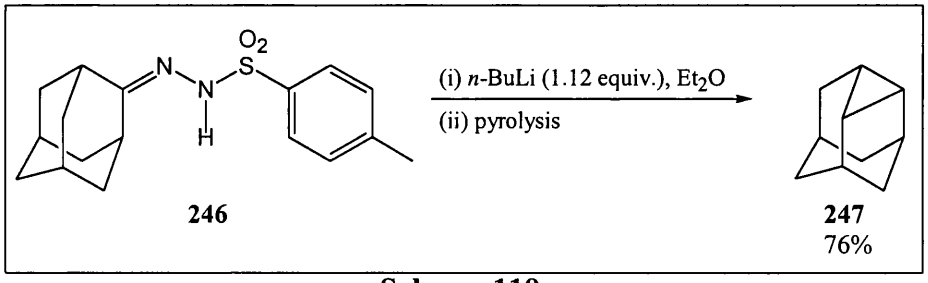
Entry	Tosylhydrazone salt	Products*	Ratio[a]
1	 **236**	 **240** : **241**	**240:241** 82:18
2	 **237**	 **242** : **243**  **244a** : **244b**	**242:243:244a:244b** 18:62:6:14
3	 **239**	 **245a** : **245b**	**245a:245b** 25:75

* Reaction conditions: (i) tosylhydrazone salt (1 equiv.), NaOMe (1.2 equiv.), diethyl carbitol; (ii) pyrolysis.

[a] Mixture of products determined by GC.

Interestingly, the pyrolysis of the cyclodecanone tosylhydrazone salt **237** gave a greater number of products than its lower homologues: *cis*-decalin **242** (18%) and *cis*-bicyclo[5.3.0]decane **243** (62%) result from transannular insertion and *cis*-cyclodecene **244a** (14%) and *trans*-cyclodecene **244b** (6%) are formed by 1,2-insertion (entry 2, Table 13). The absence of 1,4-insertion products is presumably due to the unfavourable geometry in the conformations during decomposition of the tosylhydrazone salt. In addition, the insertion processes are stereoselective as evidenced by the preferential formation of *cis*-fused bicyclic hydrocarbons. This is a consequence of concerted transfer of an axial hydrogen atom in these ring systems, and is consistent with the fact that C-H insertions proceed with retention in configuration.[131a]

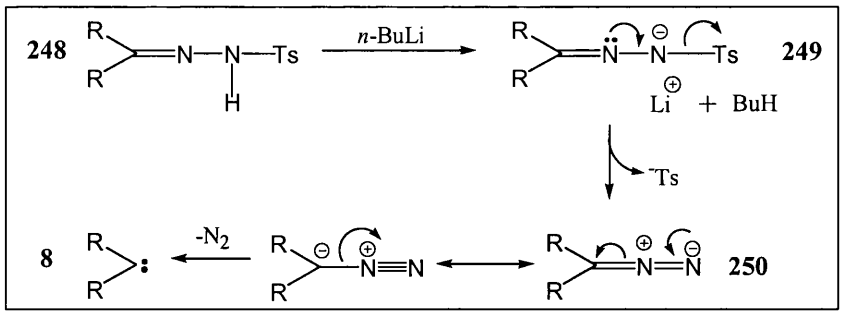
We elected to carry out the reactions on a small scale due to the high cost of cyclodecanone and cycloundecanone. A more suitable method involved the decomposition of 2-adamantanone tosylhydrazone **246** which undergoes 1,3 C-H transannular insertion to give one possible stable compound, 2,4-dehydroadamantane **247** (Scheme 119).[131c] The literature reaction was successfully carried out by reacting 2-adamantanone tosylhydrazone **246** with *n*-butyllithium in a closed one compartment apparatus avoiding any distillations. The reaction flask was connected to a trap in a liquid nitrogen bath, thus after pyrolysis of the lithium tosylhydrazone salt, the transannular insertion product was obtained. Initially, it was found that even after drying the lithium tosylhydrazone salt for 1 hour *in vacuo*, a large quantity of tetrahydrofuran was collected with the product when pyrolysis was performed. It is likely that tetrahydrofuran will be chelating to the lithium salt making it more difficult to remove. The isolation of tetrahydrofuran would make analysis of the products resulting from the pyrolysis of our chosen cycloalkanones, more difficult. However, the use of ether as an alternative solvent gave much better results.



246 **247** 76%

Scheme 119

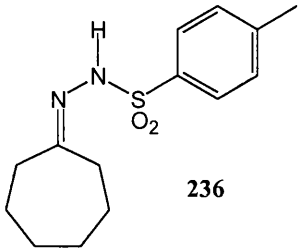
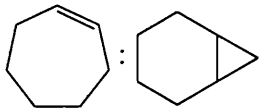
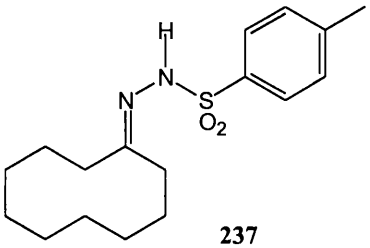
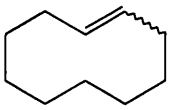
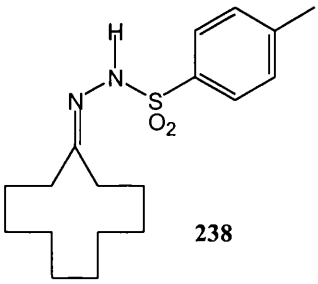
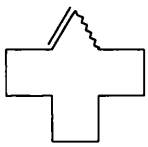
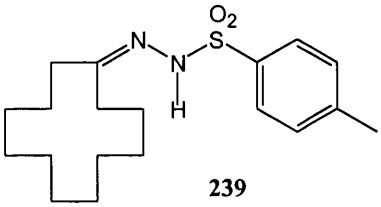
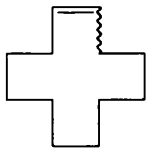
The mechanism involves formation of lithium salt **249** from tosylhydrazone **248** by using *n*-butyllithium followed by the elimination of the tosylate group to give a diazo compound **250**. Loss of nitrogen from **250** generates a "carbene" **8** and this can undergo various transannular insertion reactions depending on the ring size (Scheme 120).[131d]



Scheme 120

Thus, using this modified procedure, the pyrolysis of cycloheptanone tosylhydrazone **236** yielded cycloheptene **240** (87%) as a consequence of 1,2 rearrangement of hydrogen and bicyclo[4.1.0]heptane **241** (13%) due to 1,3-transannular insertion of the resulting carbene. However, the pyrolysis of cyclodecanone tosylhydrazone **237**, cycloundecanone tosylhydrazone **238** and cyclododecanone tosylhydrazone **239** all gave *cis*- and *trans*-cycloalkenes as a result of 1,2-hydrogen insertion with no other transannular insertion products isolated (Table 14).

Table 14: Pyrolysis of lithium salts of tosylhydrazone

Entry	Tosylhydrazone salt	Products*	Yield (%)	Ratio[a]
1	 **236**		61	**240:241** 87:13
2	 **237**		54	**244** 1.1:1[b]
3	 **238**		75	**251** 2.3:1[b]
4	 **239**		81	**245** 2.4:1[b]

* Reaction conditions: (i) tosylhydrazone salt (1 equiv.), *n*-BuLi (1.12 equiv.), Et_2O; (ii) pyrolysis.

[a] Ratio determined by GC and ^{1}H NMR. [b] *E/Z* ratio of cycloalkenes.

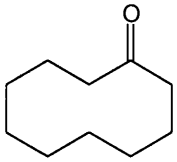
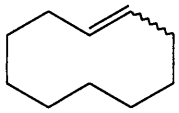
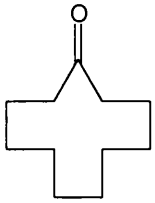
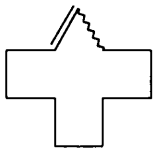
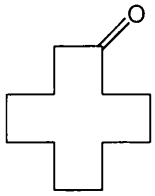
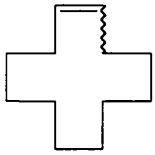
Hence, by changing the metal from sodium to lithium the reactivity of the resulting "carbene" **8**, presumably stabilised by the metal, dramatically changes and favours 1,2-rearrangement of hydrogen in medium and large ring sized ketones. However, normal transannular insertion reactions are observed in small ring sized ketones as supported by the case of the pyrolysis of cycloheptanone tosylhydrazone **236** (Table 14). In addition, later investigations of the base-catalysed decomposition of tosylhydrazones of ketones originally discovered by Bamford and Stevens[129] have shown that the distribution of products is highly dependent on the nature of the

solvent.[132] A good example to illustrate this is the fact that hydrocarbon mixtures isolated from the decomposition of cyclooctanone and cyclodecanone tosylhydrazones in diethyl carbitol were found to contain more bicyclic products than alkenes, while the reverse was true when decompositions were performed in ethylene glycol.[131a,132]

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

With these authentic samples in hand, it was initially envisaged that the zinc and chlorotrimethylsilane reduction could be applied to medium and large ring sized ketones. However, it was found that by increasing the ring size from cyclooctanone under these conditions, unreacted starting ketones (cyclodecanone, cycloundecanone and cyclododecanone) were recovered and only trace amount of cycloalkenes were detected by GC analysis even after long reaction times (Table 15). A closer look at previous results obtained in the deoxygenation of cyclohexanone and cyclooctanone clearly show a difference in reactivity, possibly due to increased congestion around the carbonyl group in the conformations of the larger rings. More harsh conditions and a longer reaction time were required for cyclooctanone in contrast to the shorter reaction time necessary for cyclohexanone which was successfully performed at room temperature (*vide supra* 2.1.2.2, Schemes 101 and 103).[93]

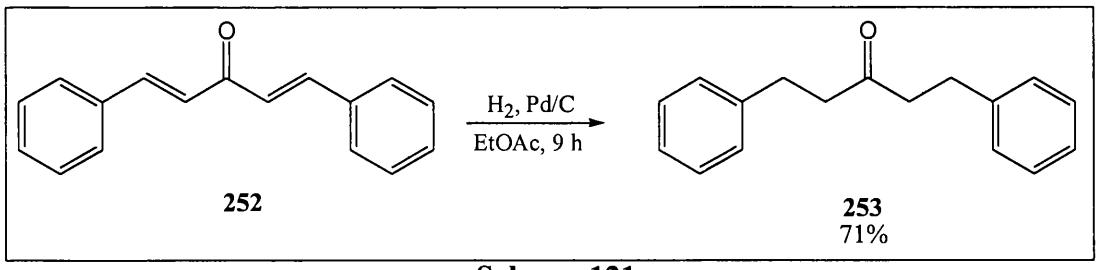
Table 15: Deoxygenation of ketones using zinc and chlorotrimethylsilane

Entry	Ketone	Products*[a,b]
1		
2		
3		

*Reaction conditions (i) Zn/Hg (10 equiv.), TMSCl (5 equiv.), cycloalkanone (1 equiv.), THF, reflux, 120 h.

[a] Only trace amounts of product was detected by GC analysis. [b] Since the conversion was negligible, both yield and *E*/*Z* ratio of cycloalkenes were not determined.

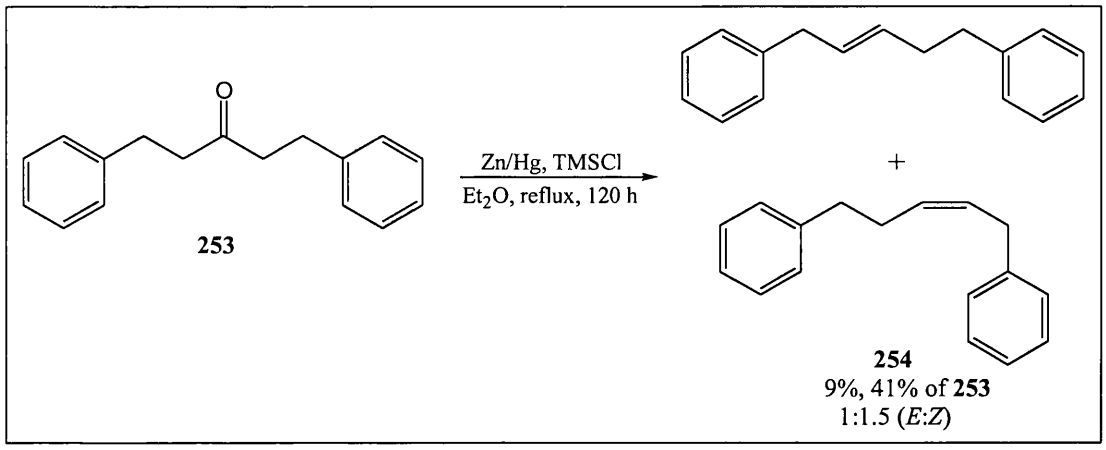
Our attention then focused on the symmetrical open chain non-volatile ketone; 1,5-diphenylpentan-3-one **253**, which was easily prepared in good yield by hydrogenation of the corresponding diene **252** (Scheme 121).[133]



252 **253** 71%

Scheme 121

However, once again, we obtained a low yield of alkenes **254** even after a prolonged reaction time. The *cis* isomer was favoured, in accord to previous organozinc carbenoid chemistry carried out in our group (Scheme 122).[134]

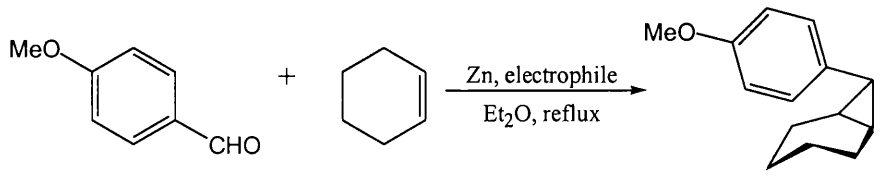


Scheme 122

Throughout these deoxygenation reactions, a common problem experienced was the formation of "zinc balls", as there is a tendency for the finely divided zinc powder to form one or several hard spheres in the reaction flask. This became more noticeable during these long reaction times.

2.2.3 The Generation of Organozinc Carbenoids from Carbonyl Compounds using Zinc and Chlorotrimethylsilane in the Presence of an Additional Proton Source

Since it was possible that the large silicon electrophile could hinder the formation of organozinc carbenoids, our attention was directed towards the use of the smaller proton as an electrophile. Interestingly, previous investigations in the group had shown that the use of a proton electrophile had led to useful cyclopropane yields (Scheme 123).[135]

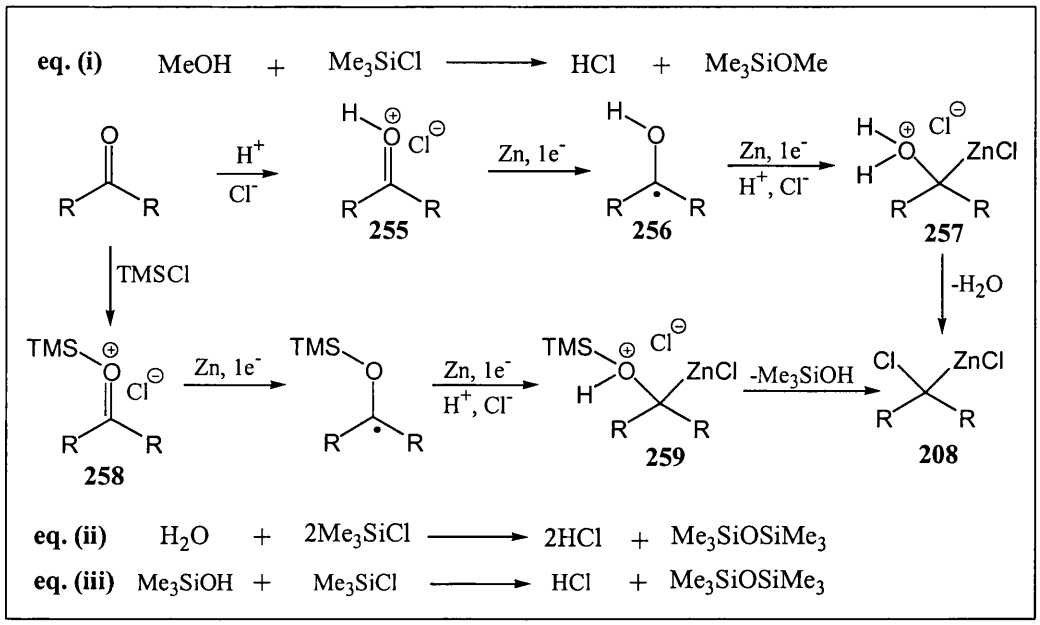


$$H_2O + 2Me_3SiCl \longrightarrow 2HCl + Me_3SiOSiMe_3$$

Entry	Electrophile	Yield (%)	de (*endo*:*exo*)
1	TMSCl (4.75 equiv.) + HCl (0.25 equiv.) (i.e. 5% HCl in TMSCl)	32	93 (27:1)
2	TMSCl (2.5 equiv.) + HCl (2.5 equiv.)	49	93 (28.5:1)
3	HCl (5 equiv.)	43	92 (23:1)
4	HCl (5 equiv.) + H_2O (2.5 equiv.)	66	92 (24:1)
5	HCl (5 equiv.) + H_2O (5 equiv.)	49	93 (29:1)
6	H_2O (5 equiv.)	0	-

Scheme 123

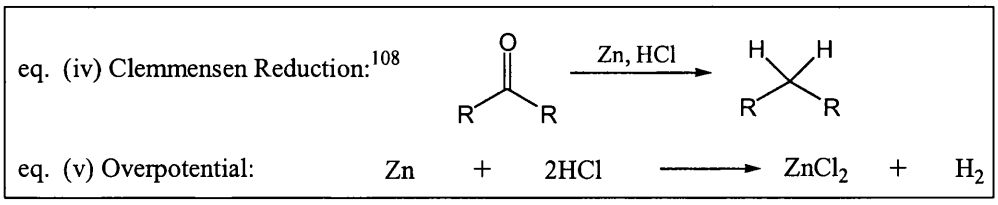
The proposed mechanism, involves the proton initially acting as an electrophile in similar fashion to the Clemmensen reduction[108] instead of a silicon electrophile as widely used in our group. A small quantity of methanol was used to generate the hydrogen chloride *in situ* by its reaction with chlorotrimethylsilane. This was found to be an easy and anhydrous procedure for the formation of low proton concentrations [eq. (i), Scheme 124]. Thus, protonation of the carbonyl compound generates an oxonium ion **255** and the carbonyl group then undergoes one electron reduction to generate the hydroxyallyl radical **256**. This undergoes a further electron donation from zinc in the presence of H^+ to give **257**. Elimination of water then generates our organozinc carbenoid species **208** (Scheme 124) and the proton is then regenerated by the subsequent reaction of the liberated water molecule with chlorotrimethylsilane [eq. (ii), Scheme 124], thereby providing a catalytic cycle for the formation of the proton. In addition, the formation of a silylated intermediate **258** could undergo a similar one electron reduction and protonation, followed by elimination of trimethylsilylalcohol from the penultimate intermediate **259**, to generate the identical organozinc carbenoid species **208**. Once again, the proton may be regenerated by the reaction of liberated trimethylsilylalcohol with chlorotrimethylsilane [eq. (iii), Scheme 124].



Scheme 124

It is noteworthy to mention, that the intermediates, **257** or **259** could also be classed as organozinc carbenoids and the reactivity could be enhanced due to the more potent nature of the leaving groups.

Due to its much lower toxicity, zinc dust was used in this particular study instead of amalgamated zinc, which had been previously widely used in our group. In the event, the reactions were very successful. However, it was necessary to generate a further amount of hydrogen chloride due to the possibility of two possible competing pathways for proton removal through Clemmensen reduction and overpotential [eqs. (iv) and (v), Scheme 125]:

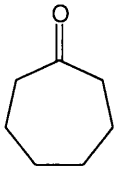
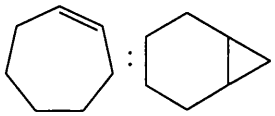
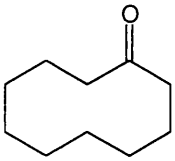
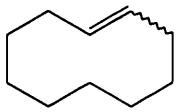
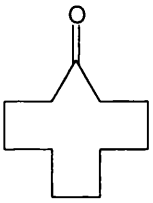
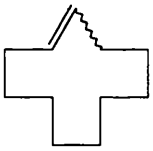
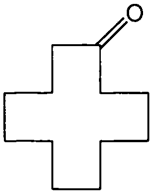
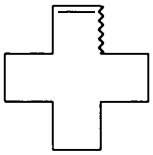


Scheme 125

With this advance, the deoxygenation of cycloheptanone gave similar results to the pyrolysis of the lithium salt of the tosylhydrazone with cycloheptene **240** (93%) and bicyclo[4.1.0]heptane **241** (7%) being obtained (entry 1, Table 16). Similarly, cyclodecanone, cycloundecanone and cyclododecanone all gave a mixture of *cis* and

trans-cycloalkenes, with a preference being shown for the *cis*-isomer and some recovery of the starting unreacted ketone (16-19%) [entries 2-4, table 16]. Low yields were however obtained for the more problematic medium and large ring sized ketones even after prolonged heating (Table 16).

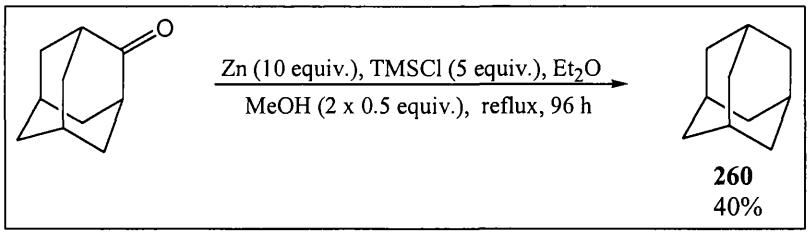
Table 17: Deoxygenation of ketones using zinc and iodotrimethylsilane

Entry	Ketone	Products	Yield (%)	Ratio[a]
1			53	**240:241** 9:1
2			31	**244** 1:3.0[b]
3			29	**251** 1:1.2[b]
4			38	**245** 1:1.1[b]

* Reaction conditions: Zn/Hg (10 equiv.), TMSI (4 equiv.), cycloalkanone (1 equiv.), DCM, 48 h, reflux.

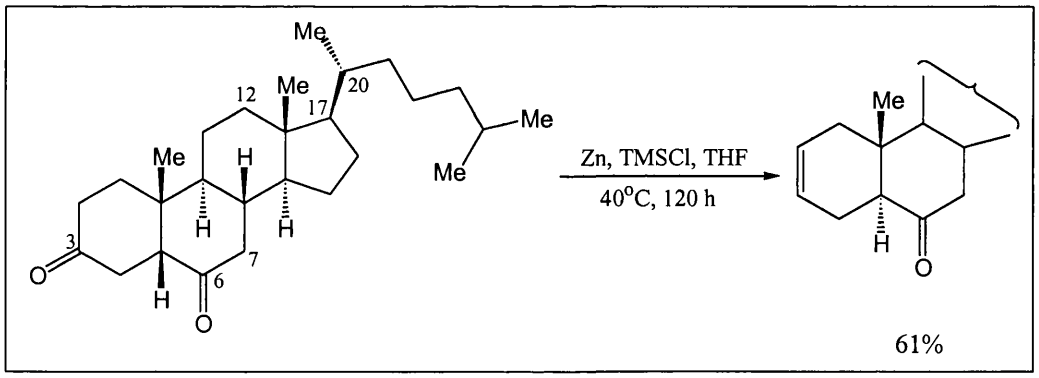
[a] Ratio determined by GC and ^{1}H NMR. [b] *E/Z* ratio of cycloalkenes.

We were also interested in applying these conditions to 2-adamantanone, in order to see whether the resulting carbenoid could undergo C-H insertion. Unfortunately however, only adamantane **260** was obtained from the reaction, formed through Clemmensen reduction with no observations of the cyclopropane product (Scheme 126). In this instance, it may well be that the pathway towards 1,3-insertion product, dehydroadamantane, has a higher activation energy than delivery of further electrons and protons to the organozinc carbenoid.



Scheme 126

A useful study carried out by Hodge and Khan[136] on deoxygenations using zinc and chlorotrimethylsilane in the steroidal series revealed that, as in the Clemmensen reduction, an unhindered 3-oxo steroid can react while carbonyl functionality in 6, 7, 12, 17 and 20 remains intact, likely due to steric constraints (Scheme 127). It would be interesting to investigate whether these hindered oxo positions would undergo deoxygenation using a smaller proton electrophile in the presence of zinc.

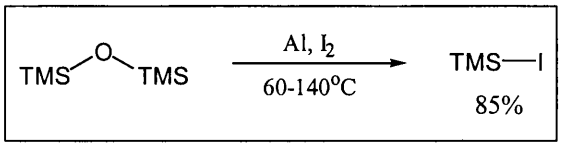


Scheme 127

2.2.4 The Generation of Organozinc Carbenoids from Carbonyl Compounds using Zinc and Iodotrimethylsilane

Although reasonable success was achieved in the proton-catalysed chlorotrimethylsilane-zinc deoxygenation of ketones, the long reaction times remained a major disadvantage. In an attempt to increase the reactivity of the carbenoid, attention was focused on the use of iodotrimethylsilane, which being a more potent silicon electrophile than chlorotrimethylsilane, was appealing. However, iodotrimethylsilane is an unstable reagent which is why there are numerous literature methods employing the *in situ* use of the reagent.[137] The best preparative method involved heating a mixture of aluminium, iodine and hexamethyldisiloxane providing

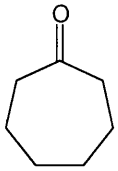
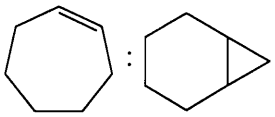
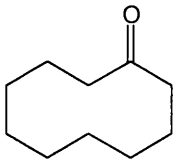
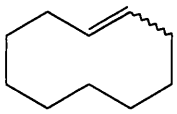
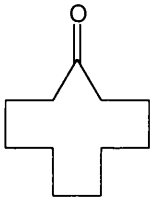
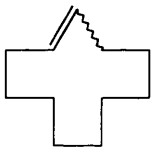
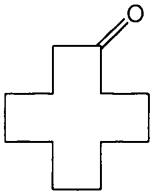
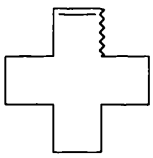
large quantities in high yields (Scheme 128).[138] More consistent results were achieved when the reagent was distilled on a regular basis and stabilised with copper.



Scheme 128

Due to the known reactivity of this silicon electrophile with ethereal solvents,[139] the deoxygenations using zinc amalgam and iodotrimethylsilane were successfully performed in dichloromethane. The results achieved were similar to those performed either with acid catalysed chlorotrimethylsilane-zinc or *via* lithium tosylhydrazone salt pyrolysis. Thus, the deoxygenation of cycloheptanone afforded cycloheptene **240** (90%) and bicyclo[4.1.0]heptane **241** (10%) (entry 1, Table 17) and the deoxygenations of cyclodecanone, cycloundecanone and cyclododecanone all gave *cis*- and *trans*-cycloalkenes with a preference of the *cis* isomer and no recovery of the starting ketone (entries 2-4). It is likely that a side reaction of carbonyl compound with iodotrimethylsilane may lead to the formation of unstable diiodo compounds. Isolation of these likely by-products was unsuccessful. Due to the reaction time being considerably reduced, the formation of "zinc balls" was much less prominent in the reaction flask.

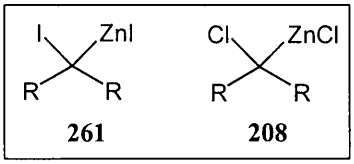
Table 17: Deoxygenation of ketones using zinc and iodotrimethylsilane

Entry	Ketone	Products	Yield (%)	Ratio[a]
1			53	**240:241** 9:1
2			31	**244** 1:3.0[b]
3			29	**251** 1:1.2[b]
4			38	**245** 1:1.1[b]

* Reaction conditions: Zn/Hg (10 equiv.), TMSI (4 equiv.), cycloalkanone (1 equiv.), DCM, 48 h, reflux.

[a] Ratio determined by GC and ^{1}H NMR. [b] *E/Z* ratio of cycloalkenes.

Clearly, the formation of the iodo carbenoid **261** has led to considerably higher efficiency in deoxygenation reactions when compared with its analogous chloro congener **208** but shows similar stereoselectivities in the formation of the alkenes (Figure 10).

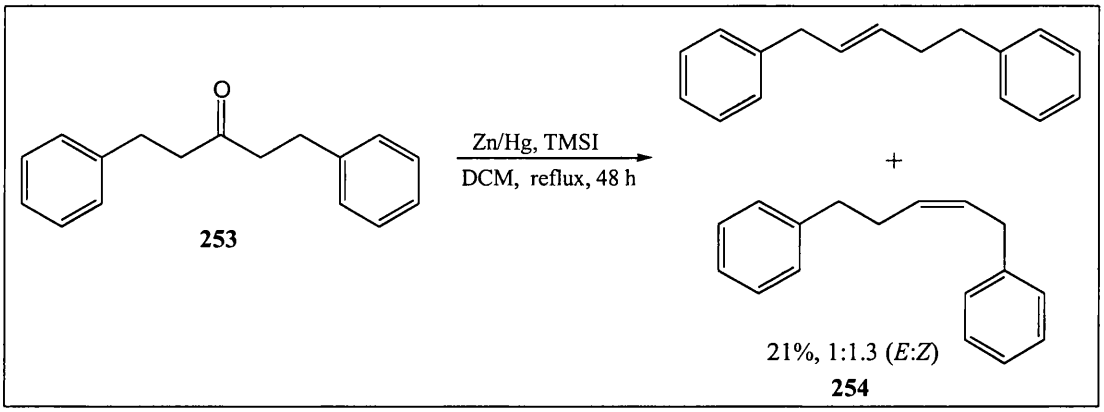


261 **208**

Figure 10

To investigate further the comparison of reactivity between chlorotrimethylsilane and iodotrimethylsilane we then returned to 1,5-diphenylpentan-3-one **253**. As expected,

an improvement in the yield of alkenes **254** was obtained with a reduced reaction time and no recovery of the starting ketone. Once again, the *cis* isomer was favoured (Scheme 129).



Scheme 129

Thus, reasonable yields were obtained and more practical reaction times achieved with the use of this more reactive silicon electrophile and this deoxygenation reaction has also demonstrated that our organozinc carbenoids can also be generated in a chlorinated solvent, as widely used in current Simmons-Smith style reactions (*vide supra* 1.2.1.3).[21]

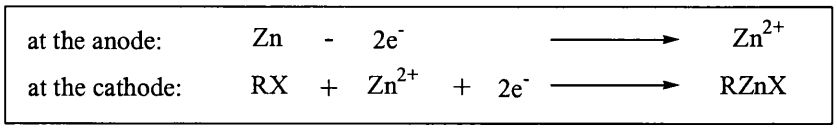
2.3 Electrochemical Generation of Organozinc Carbenoids

The formation of organozinc carbenoids by reaction of zinc metal with dihalo compounds often requires both the activation of zinc metal and the use of relatively unstable and expensive halides (*vide supra* 1.2.1). In addition, these methods usually require high temperatures, long reaction times and vigorous stirring during the reaction.[1a,8] In principle however, the electrochemical approach can act as an useful alternative to the conventional chemical routes, and was accordingly of interest to us in the context of improved efficiency in generation.

2.3.1 Basic Electrochemistry

During electrolysis reactions, the cathodic reduction is combined with the anodic oxidation of an oxidised metal which is therefore used as the anode. Thus, with the

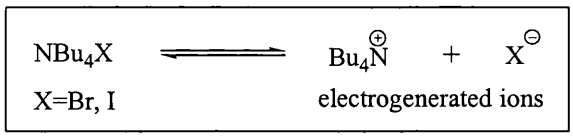
use of a zinc anode the generated Zn^{2+} ions can be used to produce the organozinc intermediate, according to Scheme 130.[140]



Scheme 130

2.3.1.1 Electrochemical Cell and Reaction Conditions

The reactions using a sacrificial anode are usually conducted in a one-compartment cell.[140,141] The anode is usually a rod of magnesium or zinc and the cathode is concentric and made of a grid of stainless steel wires or carbon fibre, or even a foam of nickel. The electrodes are connected by stainless steel wires to the DC power supply. Side-arms equipped with screw caps allow the introduction of solvent and reagents, as well as a permanent supply of an inert gas. Dipolar aprotic solvents are used, with a good dielectric constant to allow better dissociation of salts. DMF, acetonitrile, or their mixtures with DCM are commonly used. A low concentration (0.01-0.02 M) of tetrabutylammonium salt, bromide, iodide or tetrafluoroborate, is necessary to ensure the conductivity of the medium by the electrogenerated ions (Scheme 131). The electrolysis is performed at 0-50°C under an inert gas.



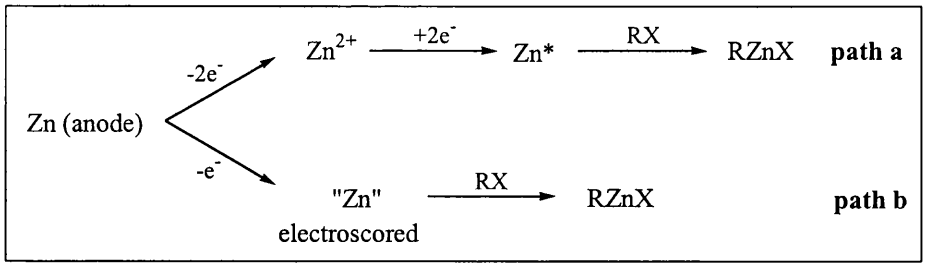
Scheme 131

2.3.1.2 Electrochemical Activation of Zinc

Two processes occur at the anode when reactions are run in the presence of a sacrificial zinc anode (Scheme 132).[140]

(i) The Zn(II) ions produced by electro-oxidation of the anode are reduced at the cathode to produce a reactive zinc species (Zn*) (path a, Scheme 132).

(ii) The electroscoring of the anode makes it reactive towards the alkyl halide (path b, Scheme 132).



Scheme 132

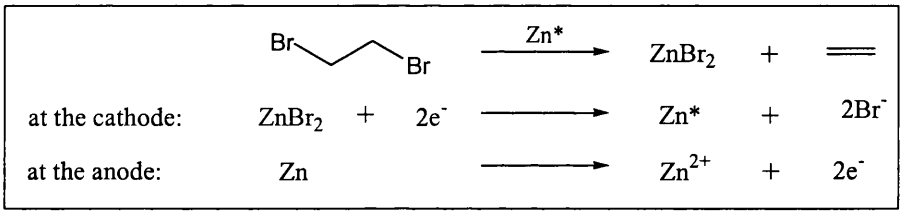
Studies have shown that the electrogenerated zinc (Zn*) is highly reactive due to its high surface area and purity. A group led by Tokuda, characterised the zinc metal prepared by electrolysis of a DMF solution containing Et_4NClO_4 using a platinum cathode and a zinc anode.[37] They found that the electrogenerated zinc is an aggregation of very fine, crystalline particles (less than 0.1 μm) with a specific surface area of 24 m^2/g, which is 100 times larger than that of commercial zinc metal. In comparison, commercially available samples of zinc metal range from 2 to 400 μm in diameter. Moreover, the electrogenerated zinc is a very pure metal, containing no impurities such as lead in contrast to commercial zinc metals which commonly contain 0.01-0.03 mol% of lead. This can be problematic as it was reported by Takai and co-workers that a trace amount of lead in zinc metal retards[142] the Simmons-Smith reaction using diiodomethane or in some cases, promotes Wittig-type olefination.[143]

2.3.2 Electrochemical Cyclopropanation of Alkenes

Whilst there has been a considerable amount of research on organozinc carbenoids carried out within our group (*vide supra* 2.1.2), electrolysis had not been used as an alternative to the conventional chemical reactions. Because there was no previous experience within the group on the use of preparative electrochemical reactions for organic synthesis, it was therefore necessary to construct and test our electrolysis cell and equipment by carrying out a literature reaction. Once a reasonable yield was achieved, we would then apply the technique to carbenoid reactions which had previously been developed within our own group.

Electrosynthesis with sacrificial anodes has been successfully used as a subsititute for many organometallic reactions,[141,144] one of which, is reported by Sibille and co-

workers who investigated an electrochemical version of the Simmons-Smith reaction.[30] This reaction is particularly appropriate for our own electrochemical studies as the cyclopropanation occurs through a carbenoid intermediate. The optimised conditions were found to be a DCM:DMF solvent mixture, using a carbon fibre cathode and a sacrificial zinc anode. A preelectrolysis of 1,2-dibromomethane over 1 hour, generated anhydrous zinc bromide *in situ* and ethylene, which was eliminated by an argon flush. Zinc bromide was then reduced at the cathode to give a reactive zinc deposit (Zn*) (Scheme 133). Tetrabutylammonium bromide and iodide were used as the supporting electrolytes to ensure an initial conductivity (Scheme 131). Under these conditions, alkenes were cyclopropanated using the less reactive dibromomethane (*vide supra* 1.2.1.4).[30]



Scheme 133

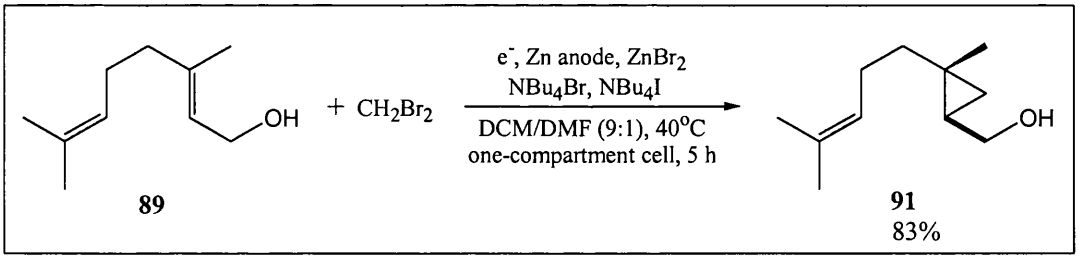
An attempt was made to see whether the electrolysis could be repeated in our one-compartment cell using geraniol **89**.

A considerable amount of time was spent on designing and changing the apparatus and experimental variables in order to determine how to use the electrolysis equipment. Various cells were used including a U-tube, a beaker and a three-neck flask. The main problem was to find an air-tight system.

The following factors were found to be paramount in attempted electrolysis reactions:
(i) With the use of a U-tube, the distance between the electrodes has a direct affect on resistance, thus affecting the current. The resistance of the cell increases as the electrodes move further apart. Hence, the resistance is less in one-compartment cells than in divided cells due to the electrodes being closer together.
(ii) Increasing the temperature decreases the resistance of the cell. Hence, gentle heating is useful in maintaining a good current through the system.

(iii) It is also important to monitor electrolysis reactions carefully in order to determine when the starting material is consumed to prevent the formation of side-products.

In the event, the electrolysis was performed in a 100 ml 3-necked flask using a carbon rod as the cathode and zinc wool as the anode with the latter surrounding the rod avoiding contact, and this protocol proved to be by far the best air-tight system. Both electrodes were fitted tightly through B24 and B14 septa, respectively. Anhydrous zinc bromide was synthesised from 1,2-dibromoethane with 2 hours electrolysis, prior to the addition of the alkene and cyclopropanating agent. The electrolysis cell worked just as well as Sibille's electrochemical cell and afforded the cyclopropane **91** in 83% yield after 5 hours (Scheme 134). Noticeably, the yield obtained was higher than the use of the Furukawa reagent in the same cyclopropanation reaction of geraniol **89** which resulted in 74% yield along with the formation of other minor cyclopropanated compounds (*vide supra* 1.2.6).[30]



89 **91** 83%

Scheme 134

Numerous advantages[145] were observed with the electrochemistry over the conventional chemical routes:

(i) The active species can be formed at the interface which contributes some unique selectivity such as regio-, stereo- and chemo-selectivities to the electroorganic reaction.

(ii) The reactions can be carried out at close to or at room temperature.

(iii) The electroorganic reaction is non-polluting and the energy efficiency is usually high.

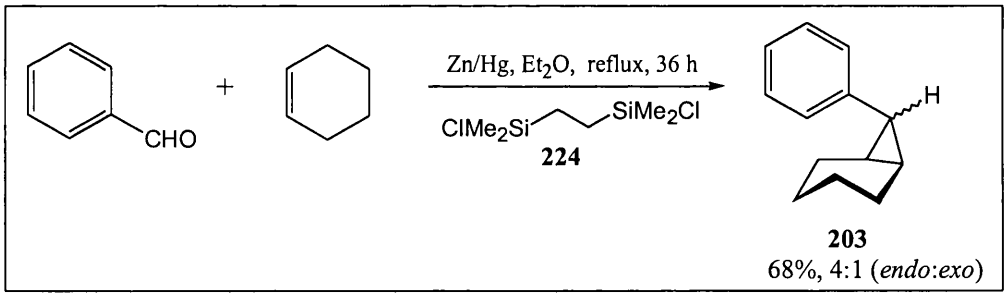
(iv) High yields with shorter reaction times can be achieved.

(v) The biggest advantage is the use of an ordinary solid metal which does not need any other activation other than the electrolysis itself.

2.3.3 Attempted Generation of Organozinc Carbenoids from Carbonyl Compounds using Electrolysis

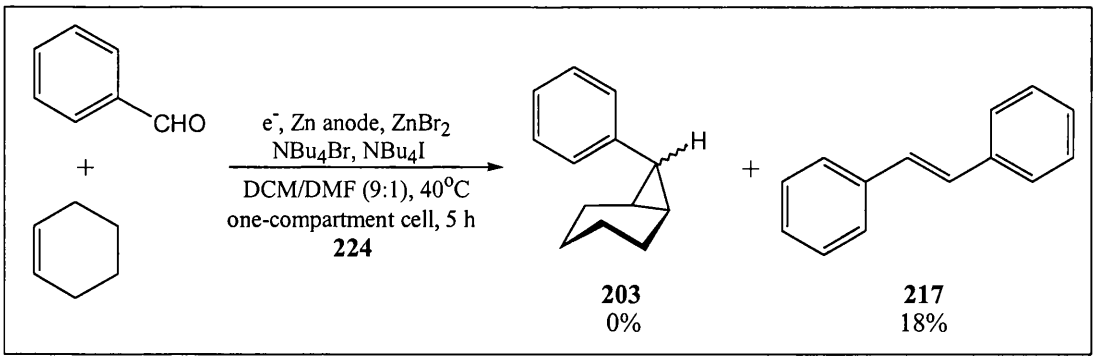
2.3.3.1 Dicarbonyl Coupling Reactions and Intermolecular Cyclopropanation

Having achieved success in reproducing a literature electrolysis reaction, we were then interested in applying electrochemistry to some of our aforementioned intermolecular cyclopropanation work.[79] Previously, within the group, benzaldehyde, which cannot undergo α-C-H insertion, along with cyclohexene as the olefinic acceptor, were used in the presence of zinc and 1,2-bis(chlorodimethylsilyl)ethane **224** to give a diastereomeric mixture of the cyclopropane **203** in moderate yield (*vide supra* 2.1.2.4).[79] The optimised conditions involved slow addition of a solution of benzaldehyde to a mixture of cyclohexene, zinc amalgam and 1,2-bis(chlorodimethylsilyl)ethane in ether at reflux (Scheme 135).



Scheme 135

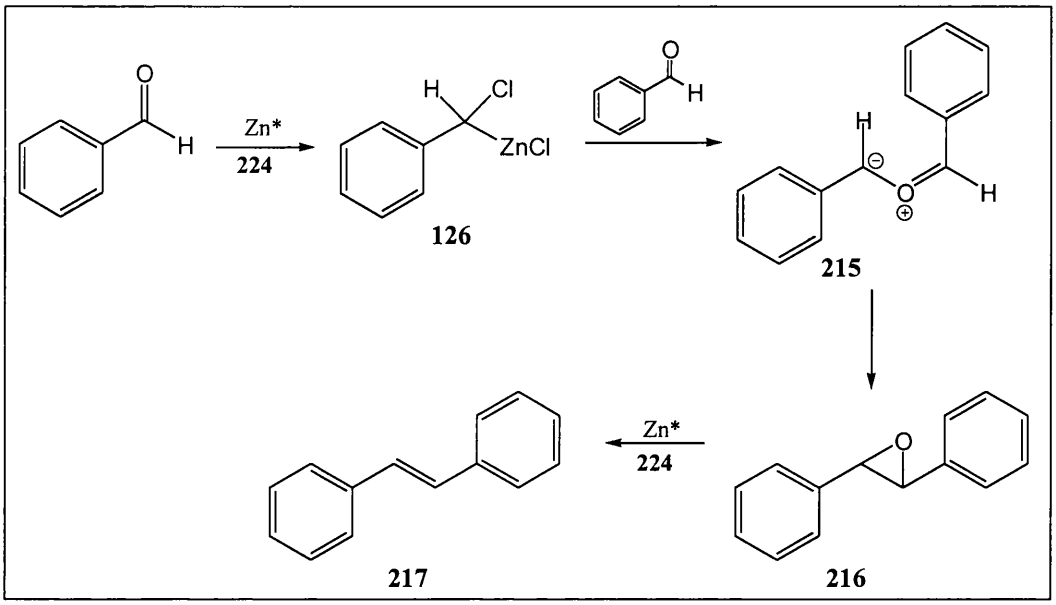
As in the cyclopropanation of geraniol, our electrolysis was set up in the same manner with the formation of zinc bromide *in situ*. In addition, the use of ether as the reaction solvent was avoided due to its low dielectric constant. Cyclohexene and 1,2-bis(chlorodimethylsilyl)ethane **224** were added followed by slow addition of benzaldehyde in DCM over 5 hours with a constant current of 300 mA. To our surprise however, after work-up, only *trans*-stilbene **217** (18%), the product of dicarbonyl coupling could be isolated (Scheme 136).



Scheme 136

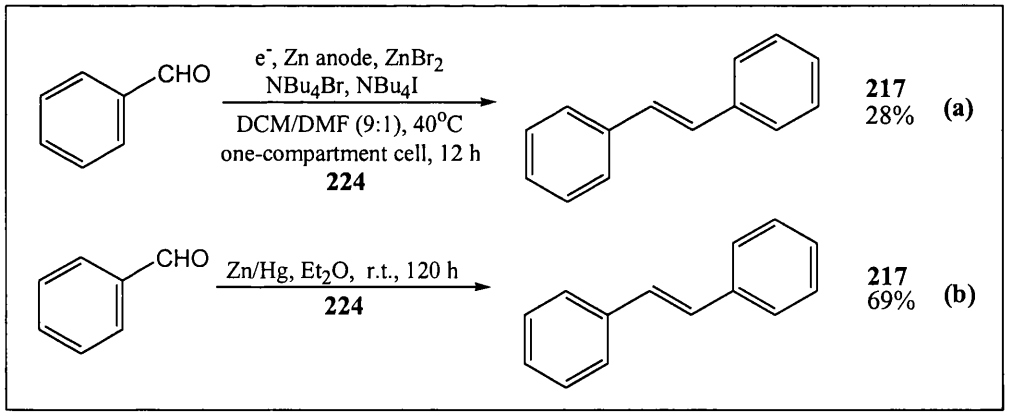
In actual fact, the formation of this cyclopropane is very much dependent on solvent. In previous studies within the group,[124] it was found that diethyl ether was a superior solvent for these reactions, and it may well be that at some stage of the reaction it acts as a ligand for the zinc, occupying the remaining tetrahedral coordination sites. This is supported by an NMR study conducted by Denmark who has shown that highly reactive bis(halomethyl)zinc reagents are stabilised by chelation to ethers.[22,25] The use of THF in the same reaction led to the formation of stilbene **217** (30%).[124] Clearly, in this electrolysis reaction, the DCM/DMF mixture also favours the formation of the alkene.

Although our intention was to achieve cyclopropanation, we were extremely delighted with this result, as it was the first time that electrolysis had been applied to our chemistry. This initial experiment clearly illustrated that the formation of stilbene **217** was through an organozinc intermediate **126** which was generated from benzaldehyde in the presence of electrogenerated zinc (Zn*) and 1,2-bis(chlorodimethylsilyl)ethane. As previously shown, the carbenoid was then trapped by a second molecule of benzaldehyde generating a carbonyl ylide **215**, and subsequent deoxygenation of the resulting epoxide **216** furnished the alkene **217** (Scheme 137, *vide supra* 2.1.2.3).[121]



Scheme 137

This reaction was repeated without the presence of cyclohexene to give the alkene **217** in a slightly higher yield (Scheme 138a). While the yield is low, the reaction time is shorter than in our conventional chemistry route (Scheme 138b, *vide supra* 2.1.2.3).[94]

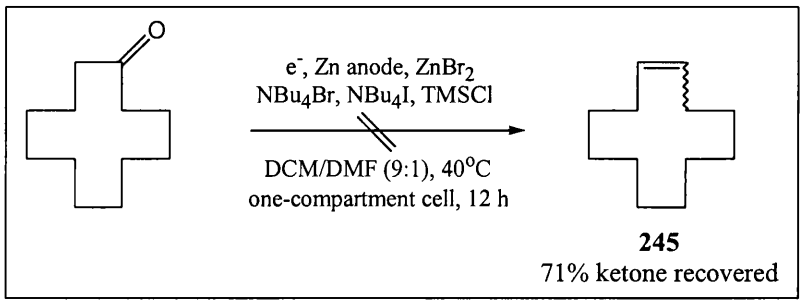


Scheme 138

2.3.3.2 Deoxygenation Reactions

Having achieved some success in the first electrochemical generation of organozinc carbenoids from carbonyl compounds, our attention then focused on deoxygenation of ketones to alkenes using electrogenerated zinc and chlorotrimethylsilane. Small ring sized ketones were avoided as their volatile products would be difficult to obtain from the reaction mixture. Instead, the reaction was attempted with cyclododecanone using

the same set up as in the electrochemical dicarbonyl coupling reaction. Surprisingly, no evidence for alkene **245** was observed during the reaction (Scheme 139).

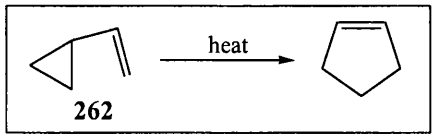


Scheme 139

Thus, the electrochemical reaction of ketone to alkene using a zinc anode and chlorotrimethylsilane to generate the zinc carbenoid has proved unsuccessful. At this stage, it is unclear why the deoxygenation of a ketone to an alkene could not be achieved by electrolysis, considering that the generation of highly reactive zinc (Zn*) occurs during the process. Furthermore, the generation of organozinc carbenoids has been demonstrated both by Sibille[30] and by our own electrochemical dicarbonyl coupling study.

2.4 The Cyclopropanation of Electron Rich Dienes

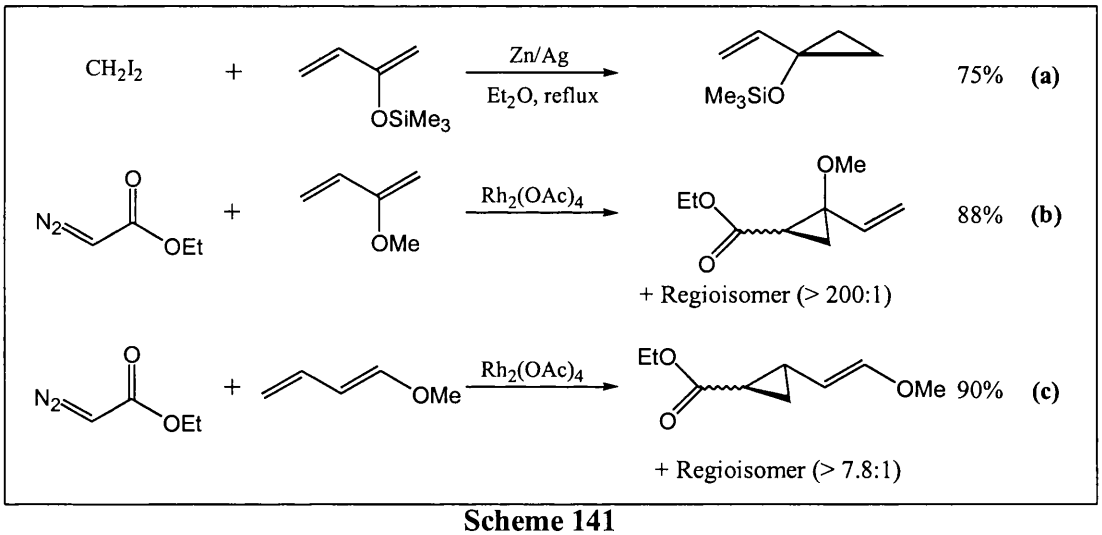
The trapping of an organometallic carbenoid by a diene leads to the formation of vinylcyclopropanes **262**, which are especially useful intermediates for the construction of cyclopentenes either through a concerted [1,3]-sigmatropic rearrangement,[146] or a pathway *via* an intermediate diradical species[147] (Scheme 140).



Scheme 140

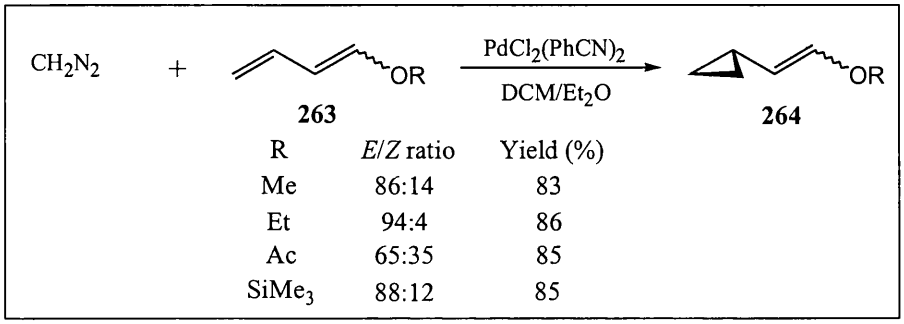
2.4.1 Regioselectivity and Stereoselectivity of Organorhodium and Organozinc Carbenoids

Elegant examples of vinylcyclopropane formation can be found in the work of Conia, who showed that 2-trimethylsiloxybutadiene could undergo monocyclopropanation almost exclusively in the 1,2-position by reaction with 1.1 equiv. of a modified Simmons-Smith reagent (Scheme 141a).[148] Doyle has also illustrated the contrasting regioselectivity in 1- and 2-methoxybutadiene by using rhodium carbenoids (Scheme 141b and c).[149] Thus, regioselective cyclopropanation of (*E*)-1-methoxybutadiene occurred at the least substituted double bond while electronic factors heavily influenced the position of attack in 2-methoxybutadiene.



Scheme 141

Nefedov has recently revealed the regioselective addition of diazomethane to a series of (*E*) and (*Z*) mixtures of 1-oxybutadienes **263** using palladium catalysts. In each case the isomeric ratio was retained in the product **264** (Scheme 142).[150]

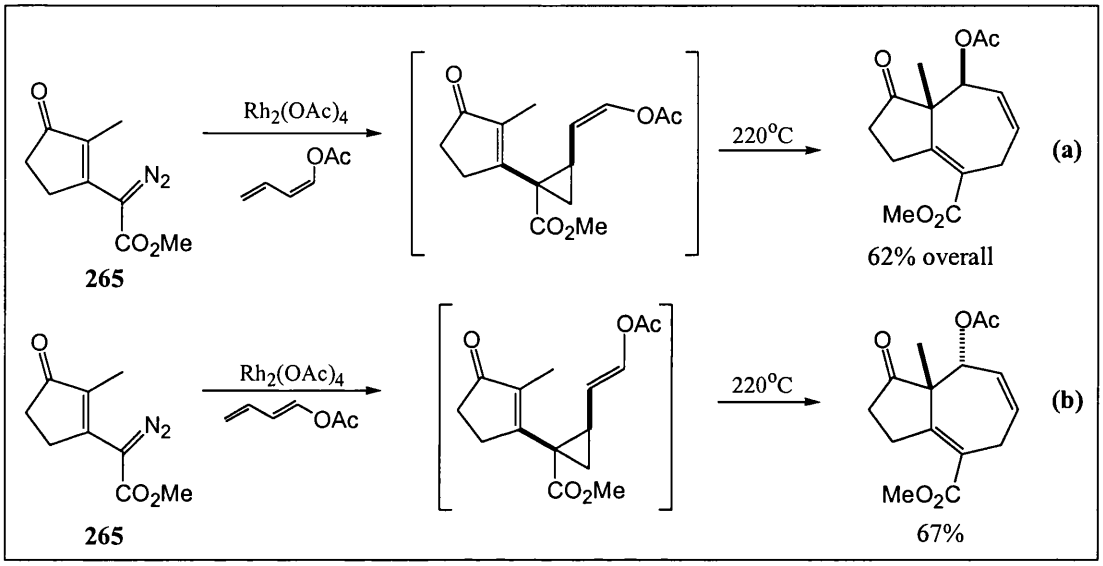


263 **264**

R	*E*/*Z* ratio	Yield (%)
Me	86:14	83
Et	94:4	86
Ac	65:35	85
$SiMe_3$	88:12	85

Scheme 142

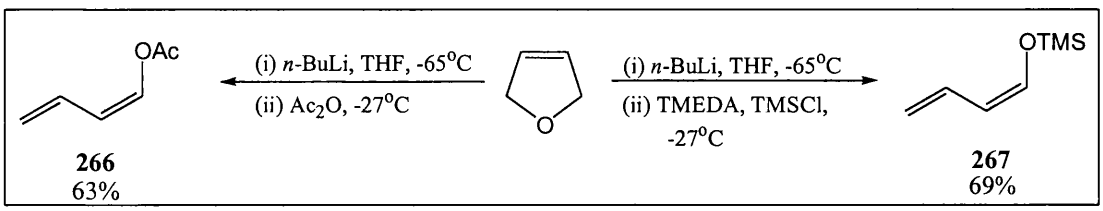
Finally, Davies has reported the reaction of diazocarbonyl **265** with (*E*)- and (*Z*)-1-acetoxybutadiene which led to both regio- and stereoselective addition with no evidence for the formation of the *trans* divinylcyclopropane (Schemes 143a and b).[151] This is in contrast to the low stereoselectivity obtained for both, Fisher carbenes[152] and the parent vinyldiazomethane.[153]



Scheme 143

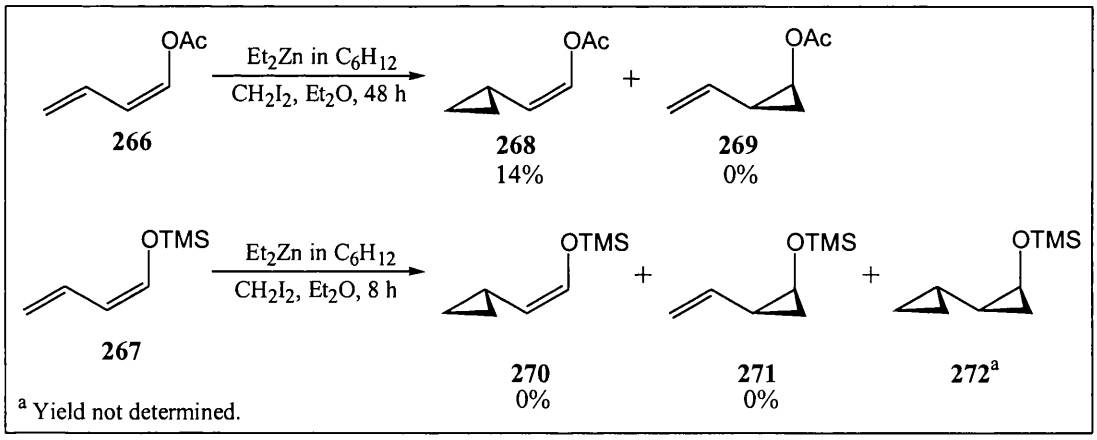
2.4.2 Cyclopropanations of Electron Rich Dienes using Organozinc Carbenoids

Our own work in this area began with a brief investigation of the regio- and stereoselectivity of cyclopropanations of electron rich dienes using organozinc carbenoids. Accordingly, pure samples of the *Z*-isomers of 1-acetoxybutadiene **266** and 1-trimethylsiloxybutadiene **267** were both prepared by a similar literature method involving treatment of 2,5-dihydrofuran with *n*-butyllithium and quenching of the resultant ring-opened dienolate with either acetic anhydride or chlorotrimethysilane, respectively (Scheme 144).[154]



Scheme 144

The reaction of (*Z*)-1-acetoxybutadiene using Furukawa's diethylzinc reagent[11,16] and diiodomethane led to monocyclopropanation occurring at the 3,4-position (**268**) with preservation of the *cis* stereochemistry around the enol acetate. In similar fashion to the rhodium carbenoids[149] and palladium catalysts,[150] there was no evidence for monocyclopropanation occurring at the 1,2-position (**269**). The final yield was low and unreacted starting diene was detected by GC analysis even after a prolonged reaction time (48 hours). When similar cyclopropanation conditions were applied to (*Z*)-1-trimethylsiloxybutadiene **267**, the reaction time was considerably reduced (8 hours) with no detection of the starting diene by GC analysis. However, there was no evidence for any of the monocyclopropanated products **270** and **271** and the NMR spectrum was indicative of the double cyclopropanated product **272**. Unfortunately complete characterisation of this compound was precluded because of contamination with unidentified compounds (Scheme 145).

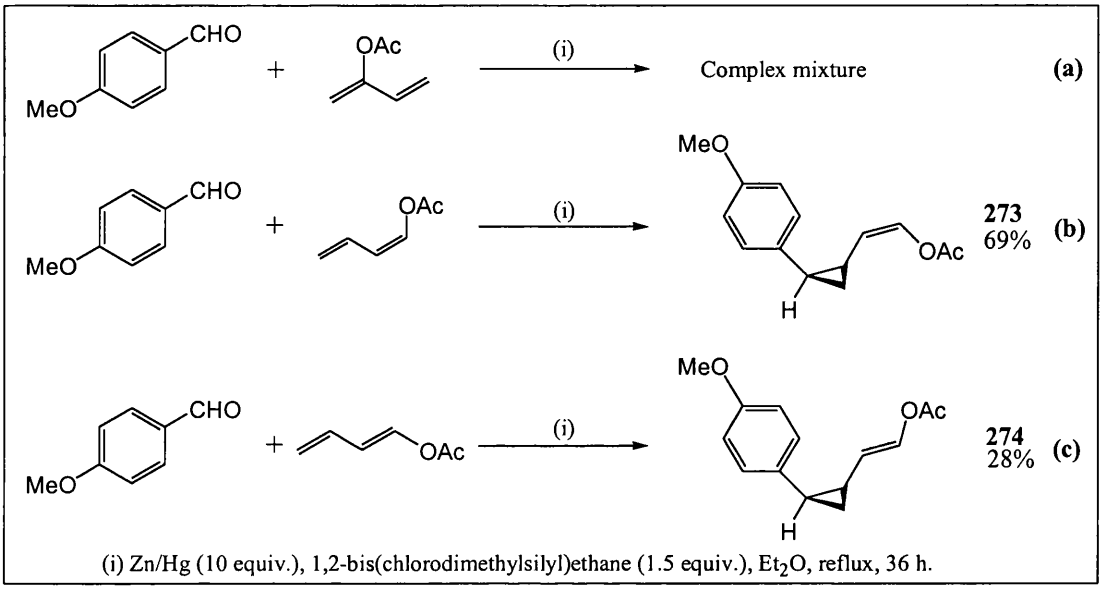


Scheme 145

2.4.3 Trapping of Organozinc Carbenoids using (*Z*)-1-Acetoxy-1,3-butadiene 266

A previous study within our group had examined the trapping of a variety of acetoxybutadienes: 2-acetoxybutadiene, and (*E*)- and (*Z*)-1-acetoxybutadienes with the carbenoid derived from *p*-methoxybenzaldehyde, the aldehyde which had shown highest reactivity in carbenoid reactions.[124] The highest yield was obtained in the reaction of (*Z*)-1-acetoxybutadiene **266** with the aromatic carbenoid (Scheme 146b). Moreover, this cyclopropanation was completely regioselective with only the terminal cyclopropane **273** shown being formed. Contrastingly, selection of the *E*-isomer

although furnishing the same cyclopropane **274** in terms of regio- and stereoselectivity, proceeded in much lower yield (Scheme 146c).[124]



Scheme 146

These observations are indicative of the strongly directing influence of the acetoxy group on the reaction and may be likened to the ability of the hydroxyl groups in an allylic alcohol to control the stereoselectivity of cyclopropanation in the Simmons-Smith (**275** in Figure 11).[16] In addition, the regioselectivity in our work was also observed in 1-acetoxybutadiene using a modified Simmons Smith reagent.[148] It is noteworthy to mention that in the cyclopropanation of acetoxybutadienes using diazo compounds with rhodium or palladium, similar yields were obtained irrespective of whether (*Z*)- or (*E*)-1-acetoxybutadiene was used. In contrast, our zinc carbenoid **276** is strongly influenced by the orientation of the acetoxy group, with the (*Z*) isomer of the alkene showing highest reactivity (Figure 11).[124]

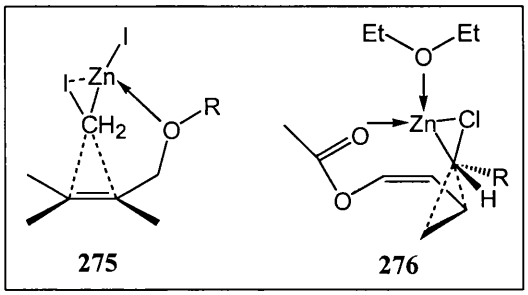
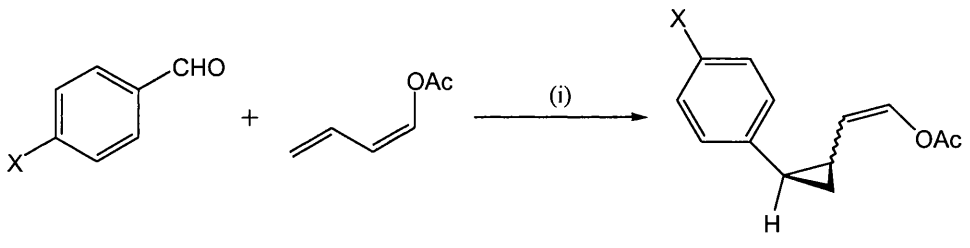


Figure 11

In the first instance, the cyclopropanation reaction from the carbenoid derived from *p*-methoxybenzaldehyde with (*Z*)-1-acetoxybutadiene **266** was repeated and a mixture of *cis* and *trans* diastereomers was obtained (6.4:1). We then decided to examine the behaviour of a series of *para*-substituted aromatic aldehydes in this reaction. Clear trends, in accord with previous cyclopropanation chemistry within our group were observed.[79,96,126] Thus, yields and stereoselectivity both decrease with decreasing electron donation from the *para*-substituent on the aromatic ring. Furthermore, the more sterically hindered *cis* cyclopropane is preferentially formed (Scheme 147).



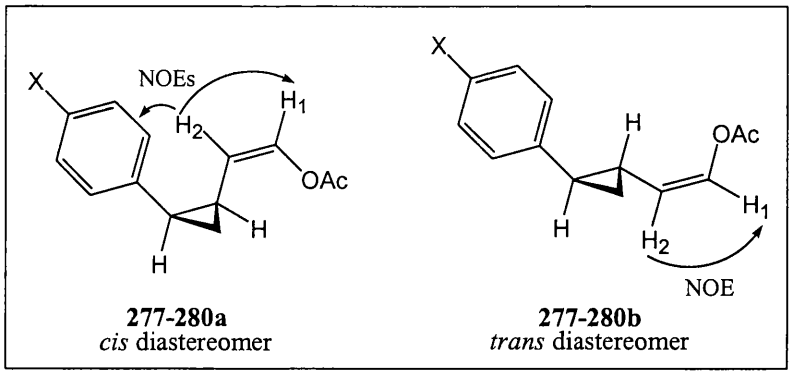
277-280

X	Cyclopropane	Yield (%)	Diastereomeric ratio (*cis*:*trans*)
OMe	**277**	58	6.4:1
Me	**278**	44	4.6:1
H	**279**	35	3.1:1
Cl	**280**	28	2.7:1

(i) Zn/Hg, 1,2-bis(chlorodimethylsilyl)ethane, Et_2O, reflux, 36 h.

Scheme 147

Two methods were used in order to assign the stereochemistry of each isomeric cyclopropane. Firstly, the major and minor isomers were determined by NOEs in which proton H_2 was chosen as a target for both isomers. For the major isomer irradiation of the H_2 proton led to notable NOE enhancements with proton H_1 and the aromatic ring protons (proton H_{ortho}). However, for the minor isomer only NOE enhancements with proton H_1 were observed. These results confirm that the major and minor isomers of the vinylcyclopropanes are in fact diastereomeric; the major diastereomer is the more sterically hindered *cis* isomer, and the minor diastereomer is the *trans* isomer (Figure 12).

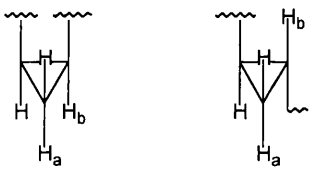


277-280a
cis diastereomer

277-280b
trans diastereomer

Figure 12

Further evidence for the assigned stereochemistry on each cyclopropane was provided by examination of the coupling constants of the cyclopropyl protons. The coupling constants for $J_{a,b}$ *cis* coupling and $J_{a,b}$ *trans* coupling were characteristic values in a *cis* and *trans* cyclopropane, respectively (Table 18).[155]



cis *trans*

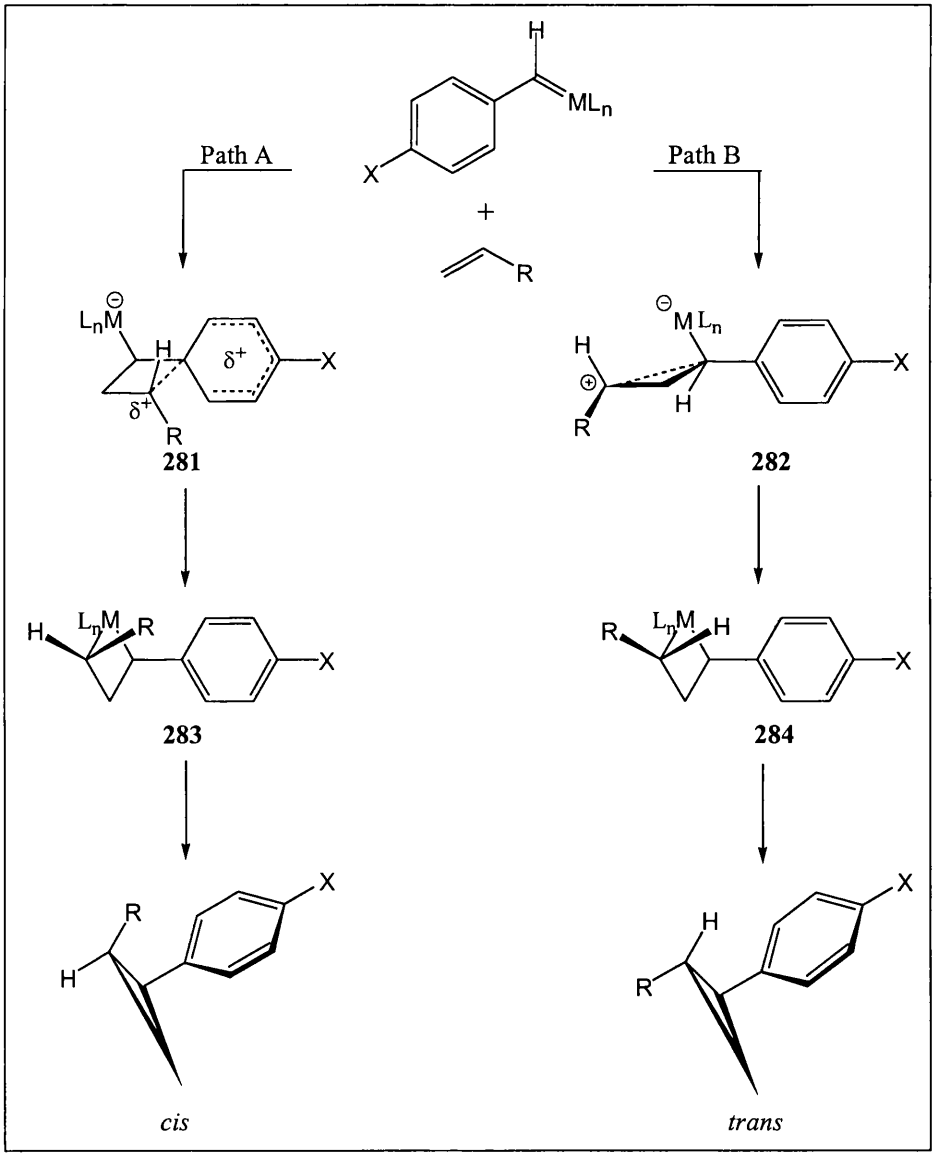
Table 18: Coupling constants in *cis* and *trans* cyclopropane

Cyclopropane	Coupling constant of $H_{a,b}$ (Hz)	
	cis diastereomer/**a**	*trans* diastereomer/**b**
277	8.4	5.6
278	8.5	5.5
279	8.4	5.6
280	8.4	5.4

In terms of stereoselectivity, a similar *cis* preference was also noted in an elegant study by Casey using the reaction of stoichoimetric aromatic tungsten carbenoids with alkenes. The observed stereoselectivity was explained by a mechanistic model involving two competitive pathways in which the relative rates were governed by a combination of steric and electronic effects (Scheme 148).[156]

In both pathways, approach of the alkene to the metal carbenoid occurs in such a way so as to reduce the steric interaction between the alkene substituent R and the transition metal, effectively resulting in two possible polarised intermediates; **281** and **282**. Each intermediate may then undergo closure to afford metallocyclobutanes **283**

and **284** of fixed geometry, which in turn undergo reductive elimination to give the cyclopropanes. As the bulk of the R substituent increases, path B becomes increasingly important resulting in the formation of the *trans* isomer. However, in less sterically demanding cases, as in **281**, the developing positive charge on the alkene is further stabilsed through an *ipso* interaction with the aromatic ring. This pathway becomes more paramount with increasing electron release from the aromatic ring (OMe> Me> H> Cl) and leads to preferential formation of the more hindered *cis* substituted cyclopropane (Scheme 148).[156]

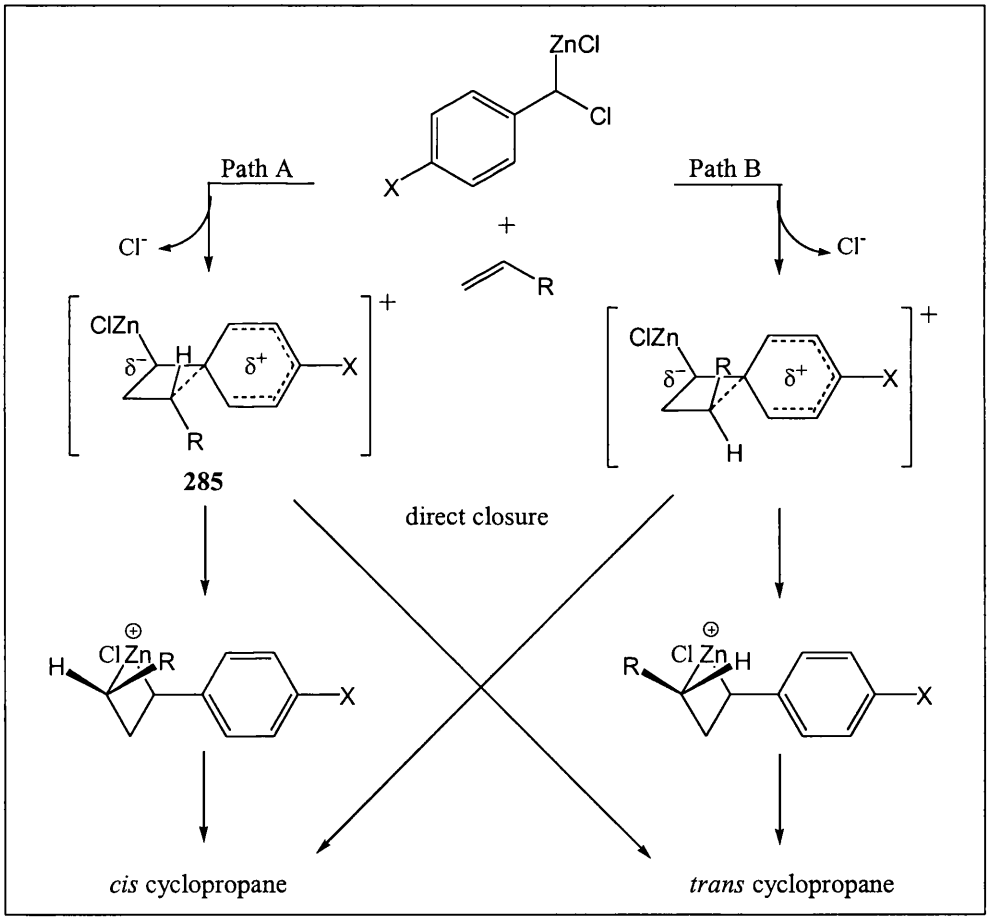


Scheme 148

There is evidence to suggest that for highly substituted alkenes the formation of metallocyclobutanes never occurs and cyclopropanes are formed directly from

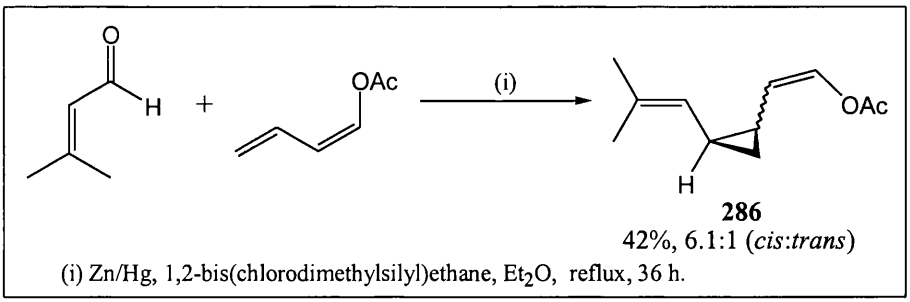
intermediates such as **281** and **282**.[4c] However, for monosubstituted alkenes as shown in Scheme 148 a degree of metallocyclobutane formation is essential for the observed *cis* geometry.[156]

This model can also be applied to organozinc carbenoids and thus provides an excellent explanation for our own results in the observed stereoselectivity pattern as a function of the *para* substituent. In this instance the intermediacy of a metallocyclobutane intermediate is critical, since direct closure of the intermediate **285** would result in the formation of the *trans* cyclopropane (Scheme 149).



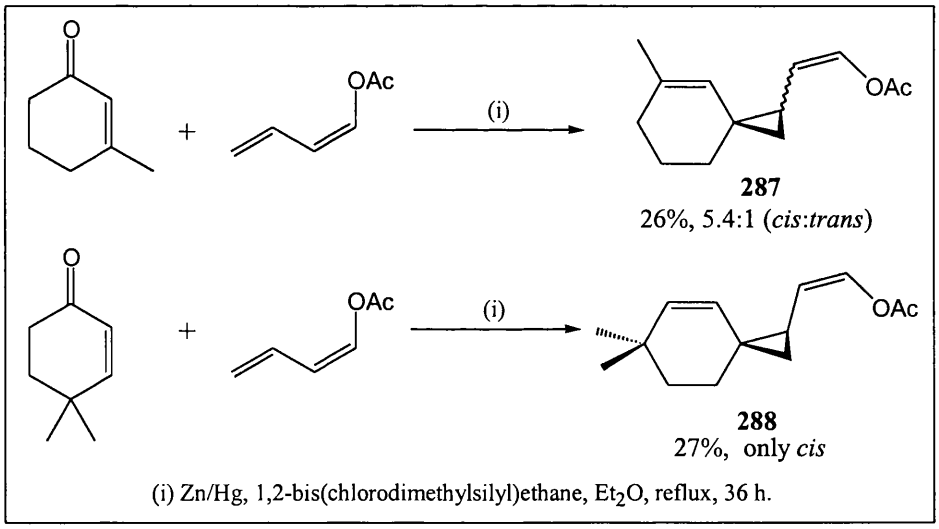
Scheme 149

The high *cis* selectivity and the regioselectivity obtained for *p*-methoxybenzaldehyde was also reproduced in the case of 3-methylbutenal, albeit in moderate yield, to afford the usefully functionalised divinylcyclopropane **286** (Scheme 150).



Scheme 150

Finally, our attention then turned to the cyclic ketones; 3-methylcyclohexanone and 4,4-dimethylcyclohexenone which had also been used as carbenoid precursors in cyclopropanation of simple alkenes. In addition, only *cis* isomer **288** was detected for the latter case (Scheme 151). Polymerisation and/or loss of the acetate group appeared to be occurring from these labile and capricious divinylcyclopropanes and may account for the lower yields observed.



Scheme 151

Once again the major and minor diastereomers of divinylcyclopropanes **286** and **287**, were distinguished by NOEs. For the major isomer, when proton H_2 was irradiated NOE enhancements were observed with protons H_1 and $H_{1''}$, thus providing evidence for *cis* substituents. For the minor isomer, only NOE enhancement was observed with proton H_1, suggesting that the substituents are *trans* with respect to the cyclopropane. For the case of divinylcyclopropane **288**, similar NOEs were observed with protons H_1 and $H_{1''}$ as a result of irradiation of proton H_2, and thus provide evidence for the *cis* isomer (Figure 13).

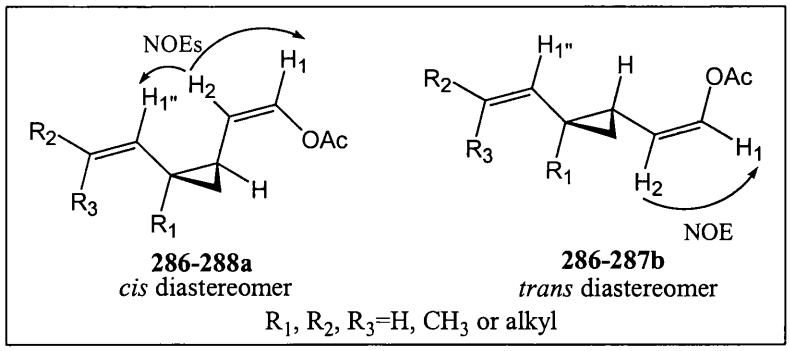
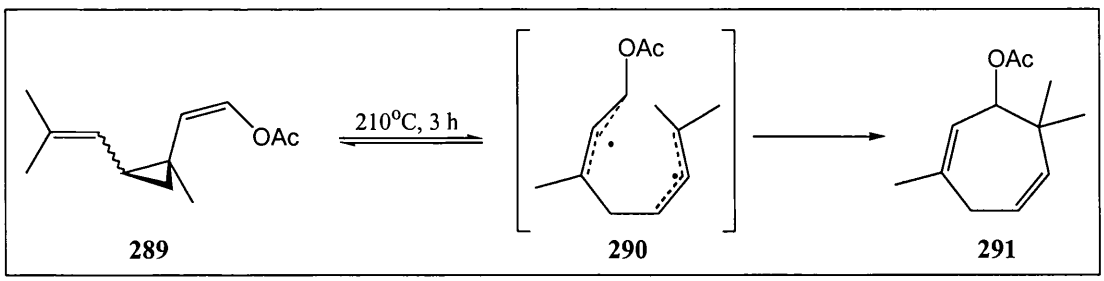


Figure 13

Furthermore, for each *cis* divinylcyclopropane, the coupling constant of the cyclopropyl protons all showed the characteristic value for *cis* coupling ($J_{a,b}$) in a *cis* cyclopropane (J= 8.3-8.5 Hz).[155]

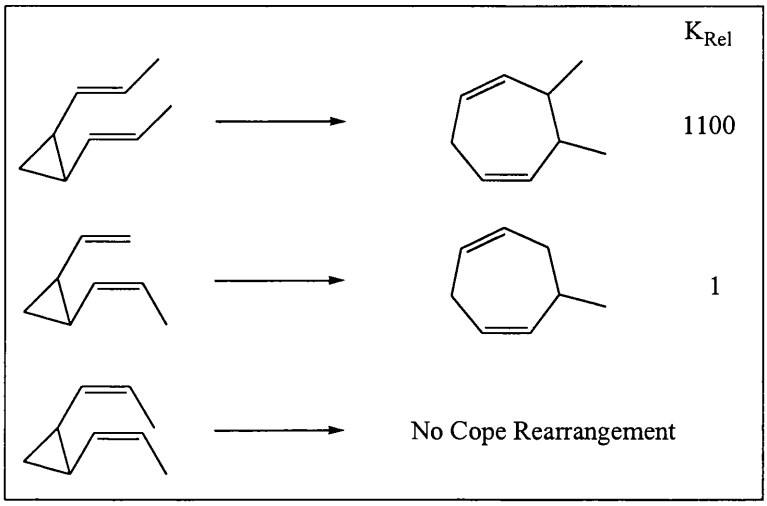
A remarkable feature observed with these products was their stability towards the well known [3,3]-sigmatropic rearrangement to cycloheptadienes, since the parent unsubstituted *cis*-divinylcyclopropane is reported to undergo electrocyclic rearrangements at temperatures as low as –40°C.[157] However, Rautenstrauch found that for more heavily substituted alkenes it was necessary to apply a gas phase temperature in excess of 200°C (sealed glass bulb at 0.1 Torr) in order to convert the isomeric mixture of divinylcyclopropane **289** (3:2; *cis*:*trans*) to the cycloheptadiene **291** in unstated yield (Scheme 152).[154]



Scheme 152

These observations can be explained by the interaction between the open ends of the π-systems of the *cis*-cyclopropane being extremely hindered, as a result *cis-trans* isomerisation through a highly stabilised, diradical intermediate **290**, is favoured due to its faster relative rate over the formation of cycloheptadiene **291**. This is further

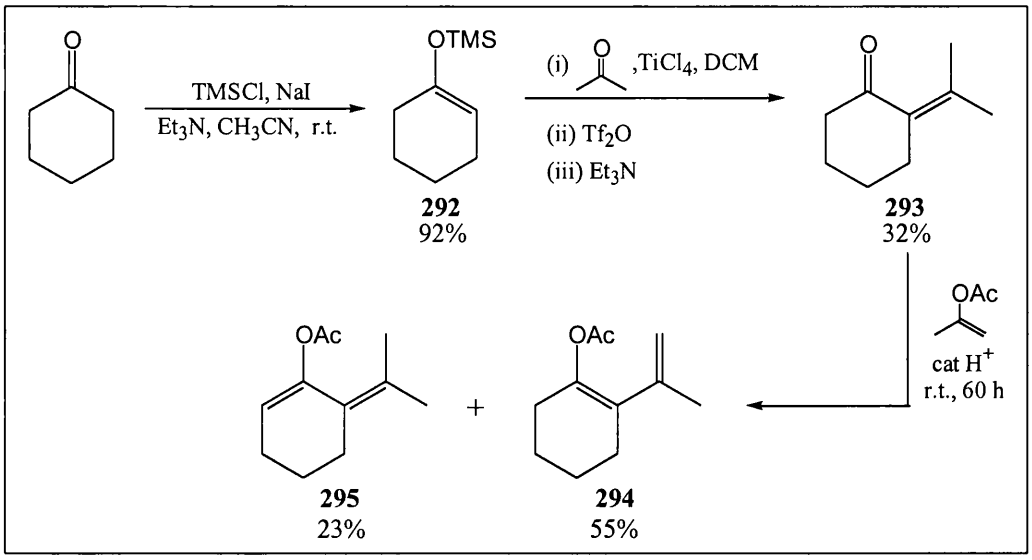
supported by Schneider who studied the geometrical constraints in these reactions, as summarised in Scheme 153.[158]



Scheme 153

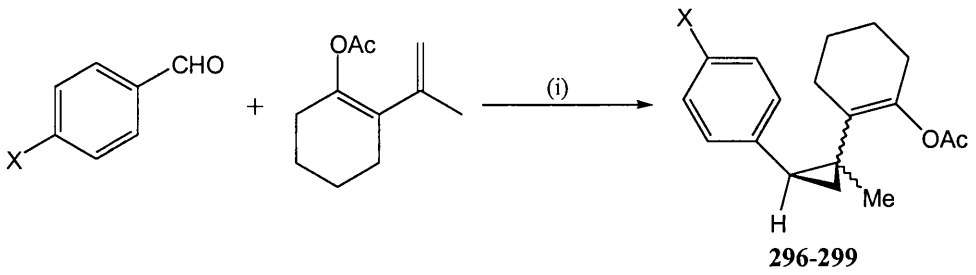
2.4.4 Trapping of Organozinc Carbenoids using 2-(1-Methylethenyl)-1-cyclohexen-1-ol Acetate 294

Other *cisoid* acetoxybutadiene systems of greater complexity were sought, and 2-(1-methylethenyl)-1-cyclohexen-1-ol acetate **294** was selected due to its bulky cycloalkyl group in order to investigate steric effects on the cyclopropanation reaction. Moreover, the *cisoid* acetoxybutadiene **294** was easily accessible from cyclohexanone and synthesised in three steps. Thus, quenching of the intermediate formed by Mukaiyama[159] aldol condensation of acetone with the trimethylsilylenol ether **292**, (prepared from cyclohexanone using triethylamine and *in situ* generation of iodotrimethylsilane[160]) with trifluoroacetic anhydride followed by triethylamine gave α,β-unsaturated ketone **293** in a "one-pot" procedure.[161] This intermediate **293** was then subjected to thermodynamic enolacetylation using isopropenylacetate and a catalytic amount of *p*-toluenesulphonic acid. The mixture of regioisomers **294** and **295** formed in the reaction, could then be separated by column chromatography (Scheme 154).[162]



Scheme 154

In a series of cyclopropanations of 2-(1-methylethenyl)-1-cyclohexen-1-ol acetate **294** with *para*-substituted aromatic aldehydes, a mixture of diastereomers was isolated derived from attack on the isopropenyl group. The expected similar trend in both yield and stereoselectivity was observed as electron donation from the *para*-substitute on the aromatic ring decreases. However, slightly lower yields were obtained and the diastereomeric ratio had decreased relative to the case of 1-acetoxybutadiene **266** (Scheme 155). Hence, if the bulk of the olefin is increased, the yield and stereoselectivity of the cyclopropane is reduced. This is supported by the aforementioned work by Casey on the reaction involving tungsten aryl-carbene complexes.[156] In this case path B is more favoured due to the increase of the R substituent on the alkene, and hence the formation of the *trans* isomer becomes more dominant (Schemes 148 and 149).



296-299

X	Cyclopropane	Yield (%)	Diastereomeric ratio
OMe	**296**	52	2.0:1
Me	**297**	33	1.6:1
H	**298**	19	1.3:1
Cl	**299**	17	1.3:1

(i) Zn/Hg, 1,2-bis(chlorodimethylsilyl)ethane, Et_2O, reflux, 36 h.

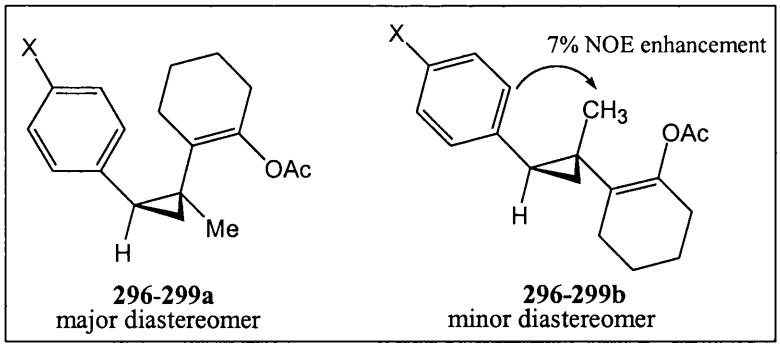
Scheme 155

Interestingly, analysis by proton NMR revealed a significant difference in the chemical shifts for the cyclopropyl methyl groups. For example, for the major isomer in the cyclopropane **296**, the singlet peak due to cyclopropyl methyl occurs at 1.18 ppm, whereas the peak for the minor isomer occurs at the much lower value at 0.79 ppm. A similar effect is repeated throughout the other functionalised cyclopropanes (Table 19).

Table 19: Proton chemical shifts for the cyclopropyl methyl group

Diastereomer	^1H chemical shifts (δ_H) for the cyclopropyl methyl group [ppm]			
	296	**297**	**298**	**299**
major	1.18	1.20	1.20	1.19
minor	0.79	0.81	0.81	0.78

In fact, the low chemical shifts observed for the cyclopropyl methyl protons of the minor isomer is caused by the anistropy of the neighbouring aromatic ring.[163] On this basis, we therefore consider that the major isomer formed in each case exhibits a *cis* configuration **296-299a** (Figure 14). In addition, the configuration of diastereomers **296-299** was firmly established using 1-D selective NOE effect. Thus, selective inversion of peaks corresponding to cyclopropyl methyl protons revealed a 2% and 7% NOE enhancement for *ortho* phenyl protons of the major and minor isomers, respectively. Hence, a greater NOE enhancement in the minor isomer confirms the fact that the configuration is *trans* as depicted as **296-299b** in Figure 14.

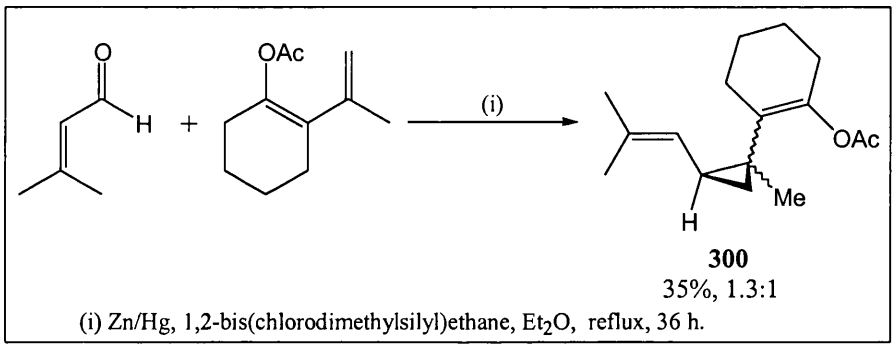


296-299a
major diastereomer

296-299b
minor diastereomer

Figure 14

When this reaction was examined using 3-methylbutenal, a similar decrease in the diastereomeric ratio of the cyclopropane **300** was observed and a slightly lower yield was obtained in comparison with the less bulky 1-acetoxybutadiene (Scheme 156).



300
35%, 1.3:1

(i) Zn/Hg, 1,2-bis(chlorodimethylsilyl)ethane, Et_2O, reflux, 36 h.

Scheme 156

In this instance, it was not possible to distinguish between the two diastereomers. In fact, the chemical shifts for the cyclopropyl methyl group of both the major and minor diastereomers occur very close together at 1.04 and 1.06 ppm, respectively.

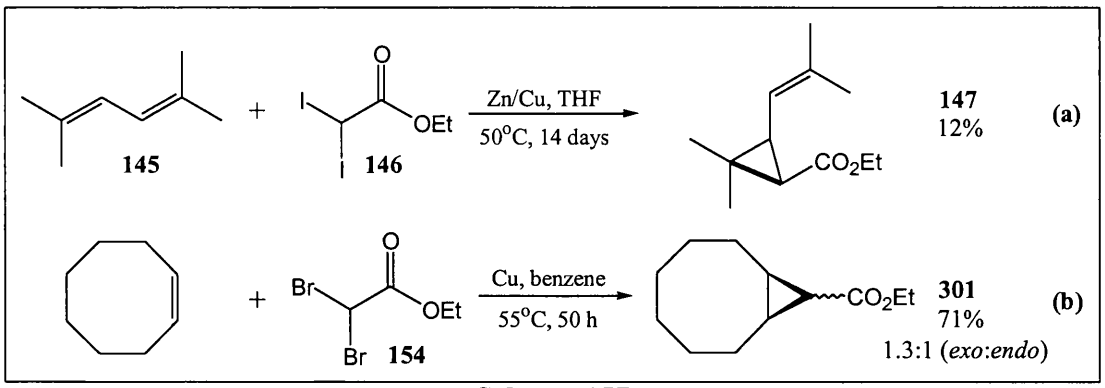
2.5 The Generation and Reactivity of Organometallic Carbenoids from Geminal Dihalo and Novel Haloalkoxy Compounds

This section, which is concerned once again with the generation of carbenoid species and their reactivity in cyclopropanation, includes both an investigation into the patterns of reactivity discussed in the introduction and also our efforts to generate novel functionalised carbenoid precursors.

2.5.1 A Comparison of Organocopper and Organozinc Carbenoids in Carboalkoxycyclopropanations

Carboalkoxycyclopropanes are routinely prepared by thermal, photochemical, and catalytic decomposition of α-diazo esters in the presence of alkenes.[4b,100,101] From a practical standpoint, as with many diazo compounds, this method is not very convenient since alkyl diazoacetates are toxic and potentially explosive. For example, methyl diazoacetate has been reported to explode with extreme intensity on heating.[62]

There have been a few isolated examples of carboalkoxycyclopropanations which do not involve the use of diazo precursors. One of these involves ethyl diiodoacetate **146** and zinc copper couple in a Simmons-Smith type cyclopropanation. Under these conditions 1,1,4,4-tetramethylbutadiene **145** gave the vinylcyclopropane **147**, albeit in low yield after a prolonged reaction time (Scheme 157a, *vide supra* 1.5.1).[102] A more successful cyclopropanation of alkenes was achieved by reacting copper with alkyl dibromoacetates. For example, heating a mixture of copper powder, ethyl dibromoacetate **154** and cyclooctene in a non-polar solvent provided the cyclopropane **301** in a good yield (Scheme 157b, *vide supra* 1.5.3).[62] This is in sharp contrast, to the trend exhibited by the family of organocopper carbenoids, which have shown the ability to cyclopropanate electron deficient alkenes (*vide supra* 1.5.3).[106]



Scheme 157

In the light of the above results, it was therefore of considerable interest to carry out a direct comparison of the various forms of activated zinc, which were widely used in Simmons-Smith cyclopropanation, and also to examine copper as the metal for carboalkoxycyclopropanations of an electron rich alkene. The dihaloacetates (Figure

15) were also chosen to investigate the effect of the halogen atoms on the cyclopropanation. Thus, we were intrigued to see whether ethyl dibromoacetate **154** would react in the same manner as dibromomethane with LeGoff's zinc copper couple,[33] and in similar vein, whether ethyl chloroiodoacetate **302** would react as well as chloroiodomethane in Furukawa's modified Simmons Smith reagent.[21] In addition, we also decided to study 3,3-dibromo-1,1,1-trifluoropropane **303**, because the trifluoromethyl group has proven valuable to the agrochemical industry.[164] Finally, in this series, the α,α-dibromoketone **304** was also selected (Figure 15).

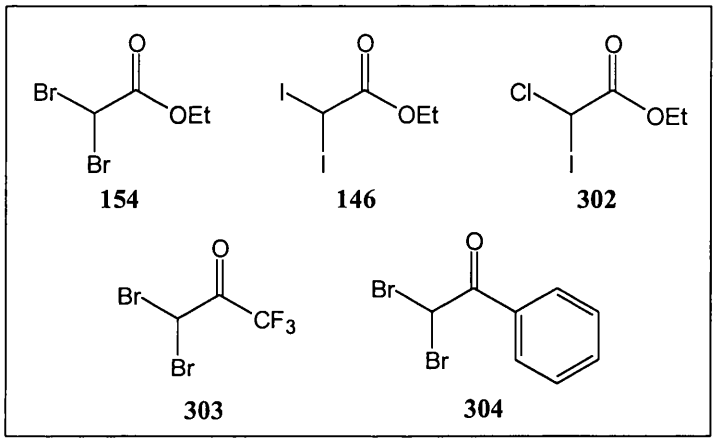
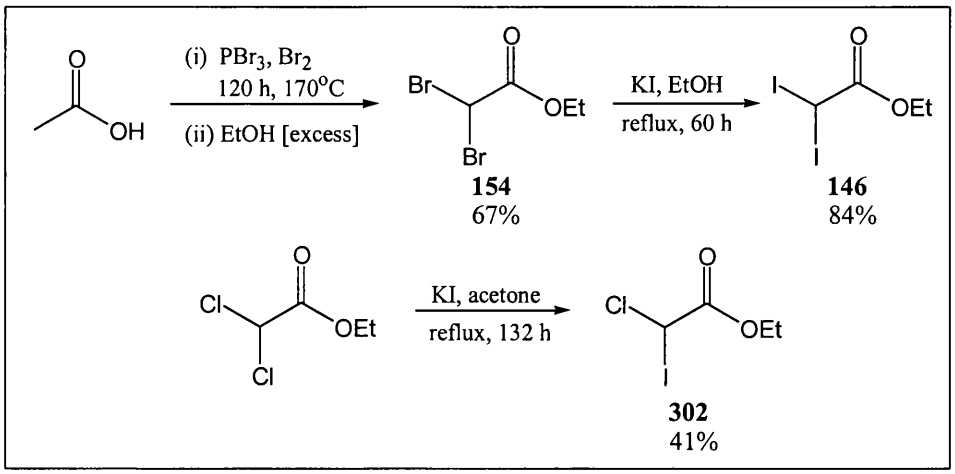


Figure 15

The generation of samarium carbenoids was avoided, due to the fact that they only react with allylic alcohols.[63] In addition, the generation of aluminium carbenoids was also avoided in this study, due to the known literature reactions of trialkylaluminium reagents and esters to give either the corresponding alcohols in high yields[165] or aldehydes and ketones, albeit in lower yields.[166]

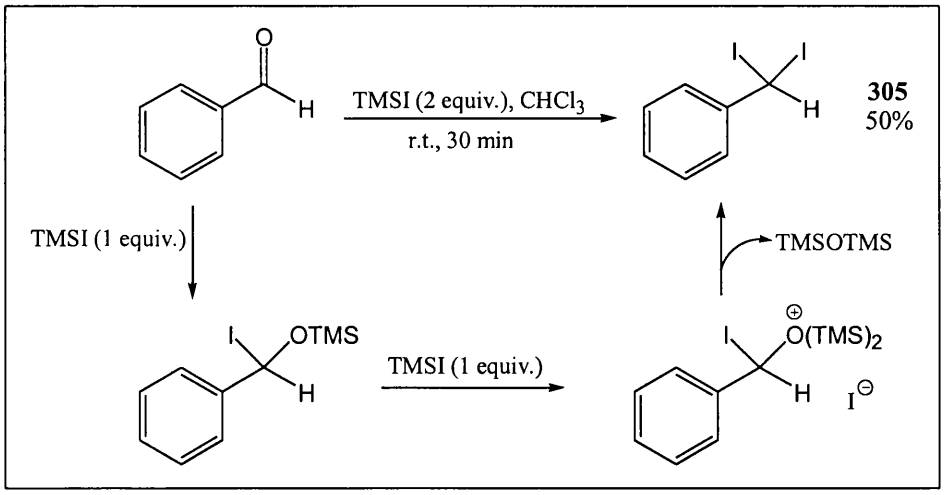
All of the required dihalo compounds were prepared by literature methods. Thus, ethyl dibromoacetate **154** was formed by refluxing phosphorus tribromide and bromine to give first the resulting dibromoacetyl bromide and then subsequent reaction with ethanol.[167] A subsequent Finkelstein reaction with potassium iodide in ethanol provided the corresponding diiodo compound **146**.[168] Similarly, a Finkelstein reaction of ethyl dichloroacetate provided the somewhat unstable chloroiodoacetate **302**,[169] which could however be redistilled prior to use (Scheme 158).



Scheme 158

Having a reference sample of ethyl diiodoacetate **146**, we also attempted an alternative preparation of this unstable compound.

Interestingly, Jung had reported that α,α-diiodotoluene **305** could be prepared from benzaldehyde using 2.2 equiv. of iodotrimethylsilane. The mechanism is shown below (Scheme 159).[170]



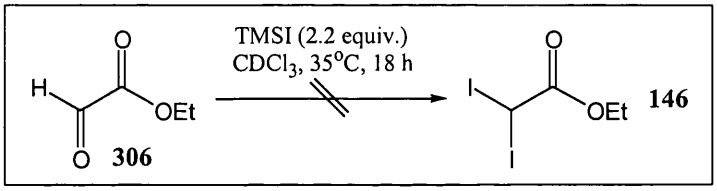
Scheme 159

Thus, by using iodotrimethylsilane, an alternative one step procedure for the synthesis of ethyl diiodoacetate **146** from ethyl glyoxalate was investigated.

Ethyl glyoxalate is in fact a polymeric material at room temperature, and is therefore supplied as a 50:50 mixture by weight in toluene. The compound can be de-

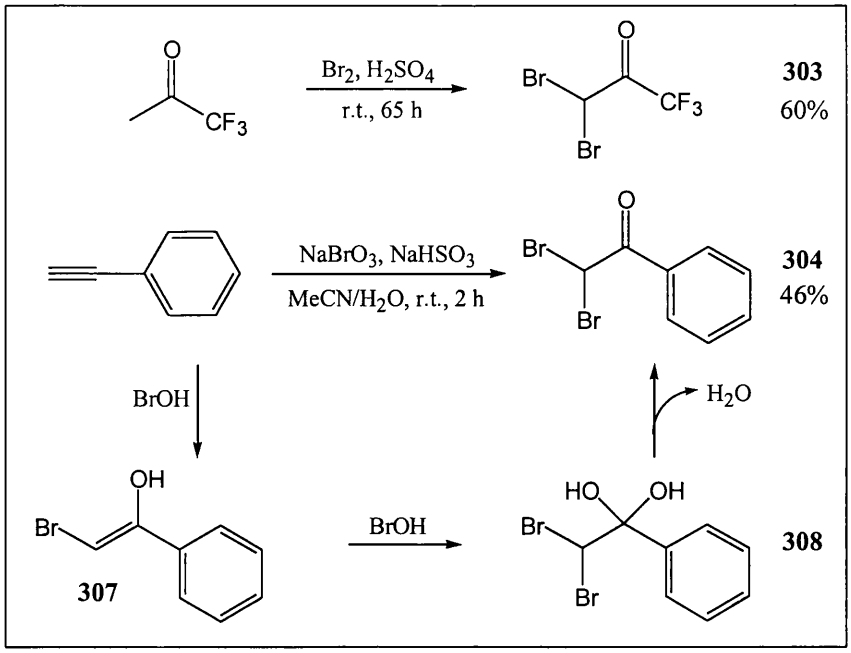
polymerised on heating, and the monomer distilled. However, the compound re-polymerises in a few hours at room temperature. We discovered however that a more effective depolymerisation can be achieved by microwave irradiation. Thus, the polymer-toluene mixture was firstly distilled at 150°C in order to remove the toluene and then subjected to 600 W microwave irradiation for 5 minutes.[171] The resulting oil was then distilled, and the aldehyde was immediately used.

By using similar reaction conditions to those reported by Jung, freshly distilled de-polymerised ethyl glyoxalate **306** was heated at 35°C with 2.2 equiv. of iodotrimethylsilane in deuterated chloroform. Both GC and NMR analysis, however showed no formation of ethyl diiodoacetate **146** over an 18 hour period, during which, polymerisation of the aldehyde **306** occurred (Scheme 160).



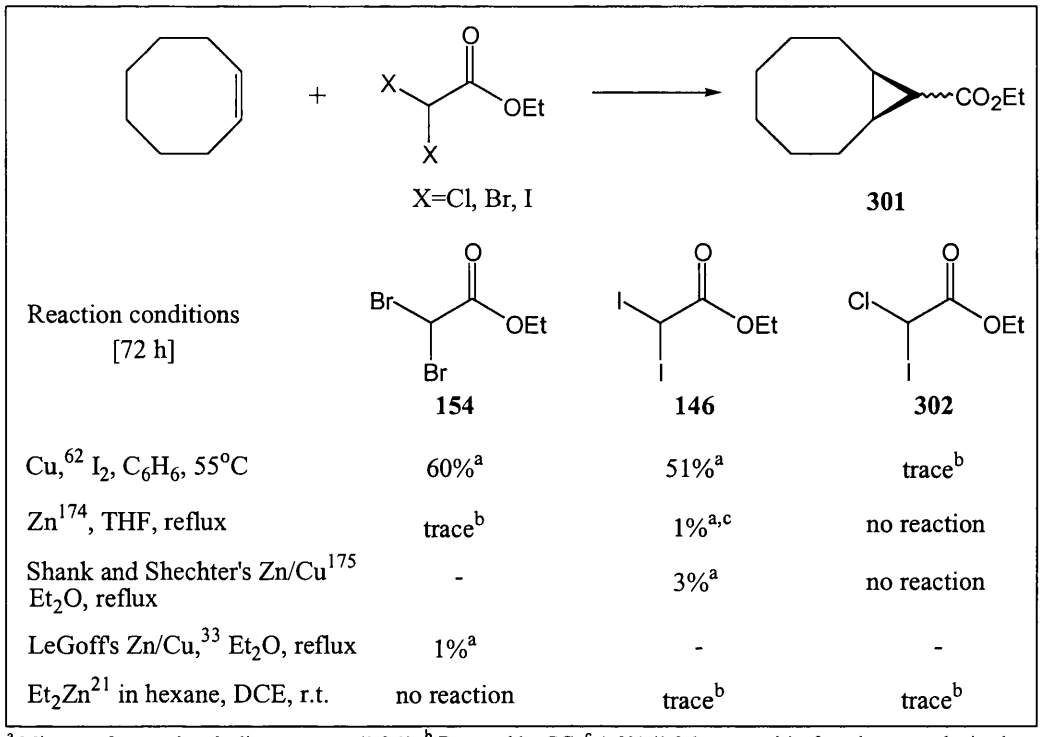
Scheme 160

3,3-Dibromo-1,1,1-trifluoropropane **303** was easily formed by bromination of 1,1,1-trifluoroacetone.[172] Finally, 2,2-dibromo-1-phenylethanone **304** was synthesised by reacting 1-phenylacetylene with hypobromous acid, which was generated *in situ* from sodium bromate and sodium hydrogensulphite. Thus, the reaction is initiated by the addition to the alkyne to form the α-bromoenol **307**. Subsequent addition of a second molecule to the enol **307** then forms the α,α-dibromoketone **304** *via* dehydration of **308** (Scheme 161).[173]



Scheme 161

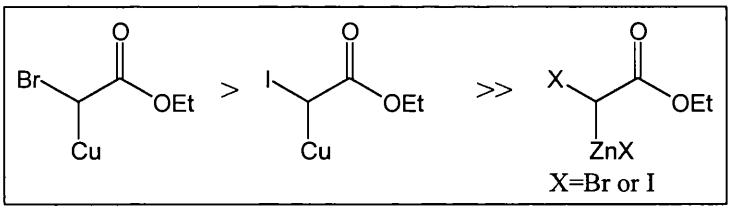
The results of a systematic study for the three ethyl dihaloacetates **154**, **146** and **302** in carboalkoxycyclopropanations of cyclooctene are summarised in Scheme 162. The reaction of ethyl dibromoacetate **154** and ethyl diiodoacetate **146** with copper powder in the presence of cycloctene gave the corresponding carboalkoxycyclopropane **301** in good yield.[62] However, the use of activated zinc dust,[174] Shank-Shechter[175] or LeGoff's[33] zinc copper couple and diethylzinc[21] all gave extremely low yields. Clearly in these reactions, the dihalo reagents **154** and **146** were being readily consumed by the reaction mixture, and no progress was made in identifying the fate of the resulting intermediates. Decomposition of the intermediates appears to take place rapidly, and even when the zinc source is reacted with the dihalo reagent in cyclooctene as the solvent and at low temperature, only a slight improvement in the cyclopropane yield was noted. The observation that the zinc copper couple gives a slightly higher yield than the zinc itself, perhaps suggests that copper can play the vital role in the reaction mechanism. Interestingly, only a trace amount of cyclopropane was observed when copper or diethylzinc was used with the mixed dihalo reagent **302**. This unreactivity could be due to the high instability of the reagent **302** (Scheme 162).



[a] Mixture of *exo* and *endo* diastereomers (1.3:1). [b] Detected by GC. [c] A 3% (1.3:1, *exo:endo*) of product was obtained when the reaction was performed without the presence of ether.

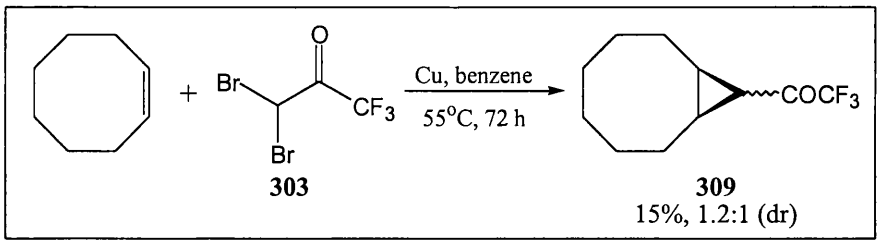
Scheme 162

Thus, the observed reactivity of the species in the carboalkoxy-cyclopropanation of cyclooctene are shown in Scheme 163.



Scheme 163

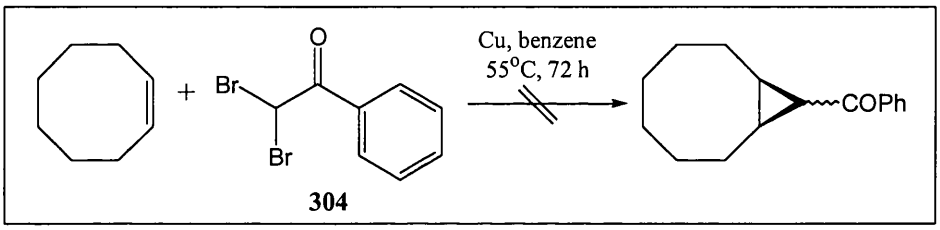
Having observed that copper was clearly the best metal for carboalkoxycyclopropanation, we then focused on applying the copper carbenoid generation method to other dihalo compounds. Thus, heating a mixture of 3,3-dibromo-1,1,1-trifluoropropane **303** with copper powder and cyclooctene in benzene gave the cyclopropane **309** as a mixture of diastereomers. The reaction is similar to using alkyl dihalo acetates in the sense that the trifluoromethyl group is also electron-withdrawing (Scheme 164).



303 **309**
15%, 1.2:1 (dr)

Scheme 164

However, applying this method to the acetophenone derivative **304** was unsuccessful with recovery of the dihalo compound. The failure of this reaction can be attributed to the feeble electron-withdrawing nature of the phenyl group and is illustrative of how the groups attached to the carbenoid can effect its reactivity (Scheme 165).

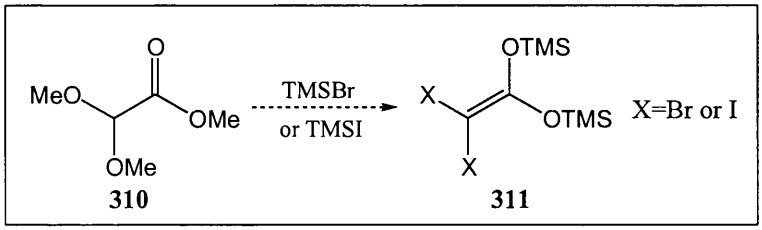


304

Scheme 165

2.5.2 The Generation of a Novel Geminal Alkoxy-Carboalkoxy Organocopper Carbenoid and Reactivity in Cyclopropanation

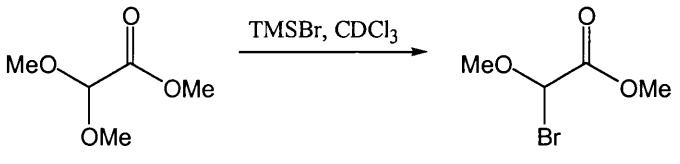
At this stage, we were also interested in expanding the array of carbenoid precursors, through the synthesis of novel dihalo compounds. Our initial study involved an investigation into the cleavage of the acetal[176] and ester[177] groups in methyl dimethoxyacetate **310** by using bromo- or iodotrimethylsilane reagents as this could eventually lead to the formation of novel silylated *gem* dihalo intermediates such as **311**. A series of NMR experiments was performed in order to investigate possible synthesis for these compounds (Scheme 166).



310 **311**

Scheme 166

As expected, a slow conversion to methyl bromomethoxyacetate **312** was observed in a series of NMR experiments involving the reaction of bromotrimethylsilane with methyl dimethoxyacetate **310**. A full conversion could not be achieved even after long reaction times (entries 2 and 4) or on heating over a shorter time (entry 6) (Scheme 167).

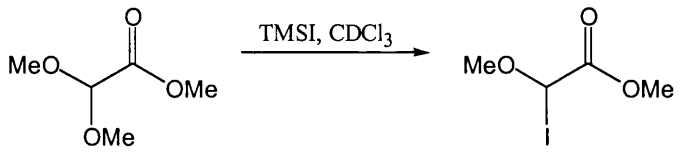


310 **312**

Entry	TMSBr (equiv.)	Reaction temperature (°C)	Reaction time (h)	Yield (% conversion by NMR)
1	1	25	1	19
2	2	25	16	66
3	3	25	3	44
4	3	25	15	60
5	2	40	1	33
6	2	40	2	53

Scheme 167

However, complete conversion to the unknown novel iodo compound **313** was achieved by heating methyl dimethoxyacetate **310** at 40°C with 2 equiv. of the more potent iodotrimethylsilane reagent (entry 5) (Scheme 168).



310 **313**

Entry	TMSI (equiv.)	Reaction temperature (°C)	Reaction time (h)	Yield (% conversion by NMR)
1	1	25	1	71
2	2	25	2	80
3	1.05	40	1	68
4	1.05	40	2	60
5	2	40	1	100

Scheme 168

Due to the instability of both of these α-halo esters, complete characterisation was not possible. Nevertheless, significant differences in the proton and carbon chemical shifts and especially for the α-proton supported the case for each halo compound (Figure 16).

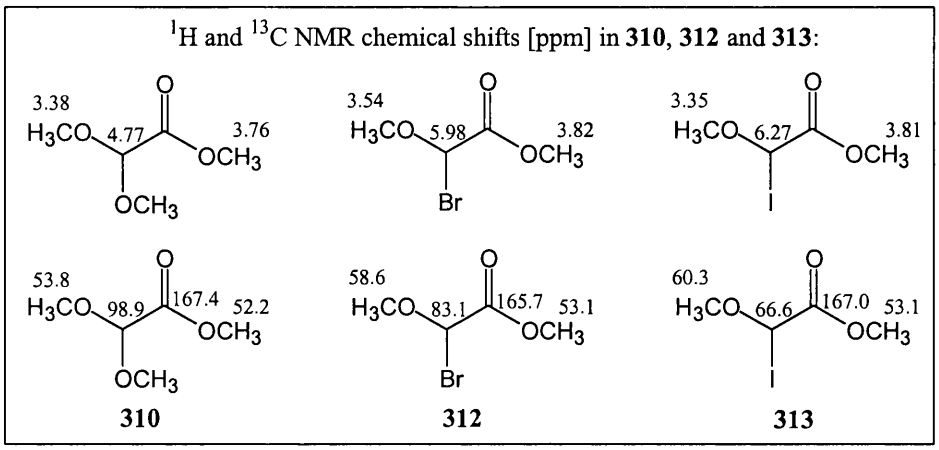
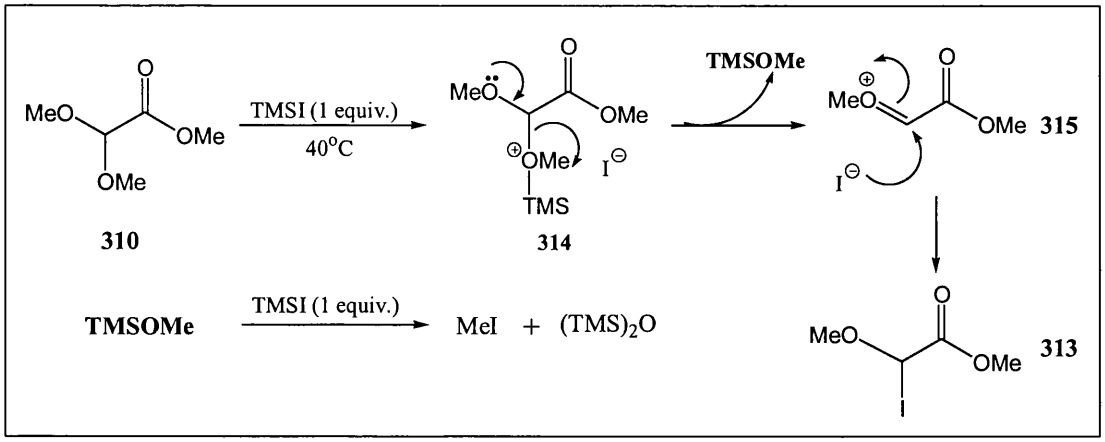


Figure 16

A postulated mechanism involves the formation of a silylated intermediate **314** by reaction of one of the methoxy groups in the acetal **310** with iodotrimethylsilane. This is then followed by expulsion of methyl trimethylsilyl ether promoted by the lone pair on the second oxygen atom of the acetal resulting in the formation of an oxonium intermediate **315**. This then undergoes attack by an iodide ion at the highly electrophilic unhindered carbon atom to give the mono-iodinated product **313**.[176] In other cases in which alkyl groups are at this centre, direct attack of iodine is hindered, thus, dealkylation is favoured over the addition of iodine.[176] It is likely that methyl trimethylsilyl ether also reacts with a further equivalent of iodotrimethylsilane to give iodomethane and hexamethyldisiloxane, both of which were detected by proton and carbon NMR (Scheme 169).



Scheme 169

Further studies showed that the second methoxy group still remained intact even after heating methyl dimethoxyacetate **310** with further equivalents of iodotrimethylsilane (3-5 equiv.) in deuterated chloroform. This observation clearly highlights the importance of the second oxygen atom in its role of displacing the methyl trimethylsilyl ether group (Scheme 169). Contrastingly, the second displacement process is much more difficult in the possible intermediate **316**, and thus, the formation of intermediate **317** is less likely (Figure 17).

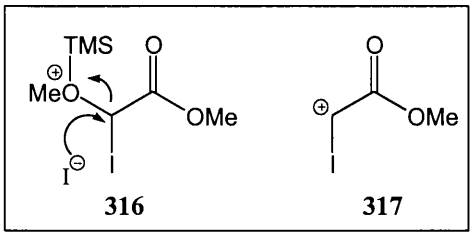
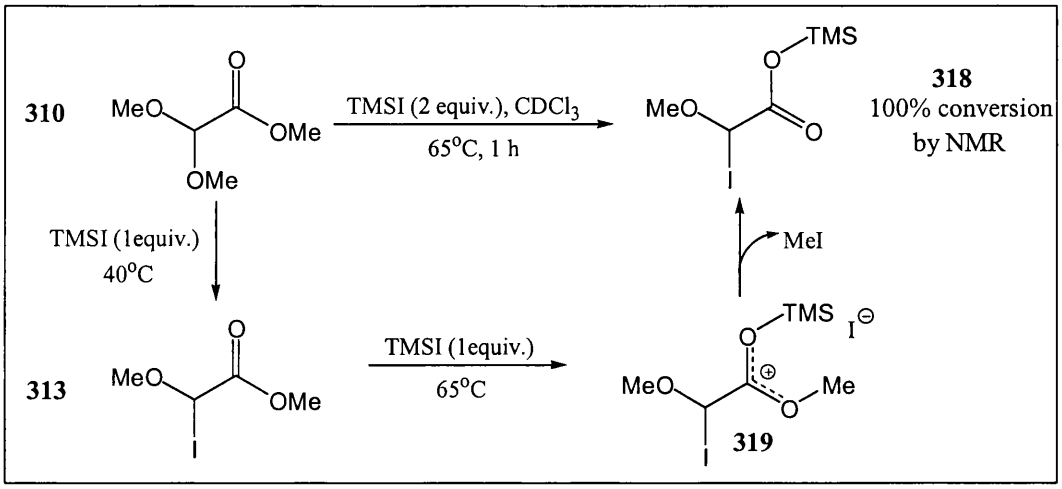


Figure 17

In a final attempt to displace the second methoxy group in the acetal by iodine, methyl dimethoxyacetate **310** and iodotrimethylsilane were refluxed in deuterated chloroform for 1 hour. Instead, these conditions led to the cleavage of the methyl ester group to give the silyl ester **318**. As shown in Scheme 170, the ester intermediate **313** reacts with iodotrimethylsilane to form an initial silylated ester iodide salt **319** which then undergoes S_N2 attack by iodide.[177a,c]



Scheme 170

Although our initial target compound **311** was not achieved, the formation of these α,α-halomethoxy esters **312** and **313**, provided an interesting opportunity to generate a novel class of carbenoid species such as **320** in which the formal positive charge on the carbenoid could be stabilised by the lone pair on the electron-donating methoxy group and the negative charge by the electron-withdrawing nature of the ester group. To the best of our knowledge, these type of "capto-dative" carbenoids have not yet been utilised in cyclopropanation studies (Figure 18).

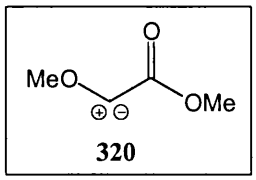
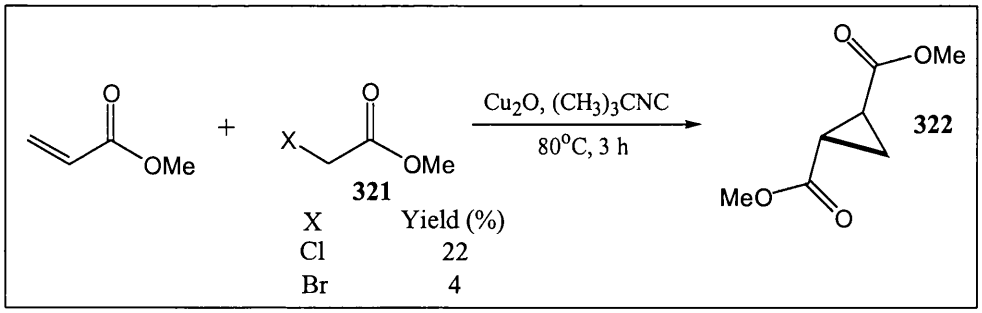


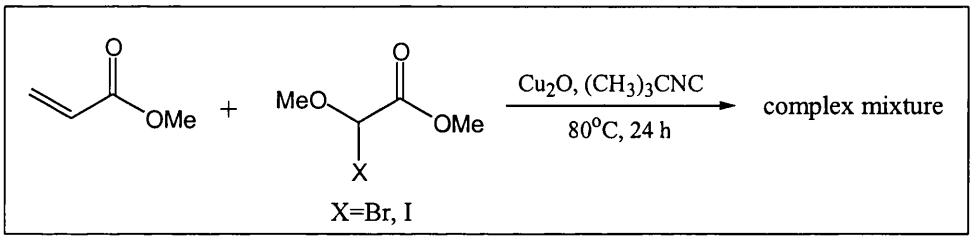
Figure 18

As we have mentioned previously, α-chloroesters **321** have been utilised to form copper carbenoids using a copper(I) oxide-isonitrile complex and then reacted with electron-deficient alkenes to give cyclopropanes (*vide supra* 1.5.3, Scheme 171). In the case of α-bromoester a modest yield was obtained (4%).[106]



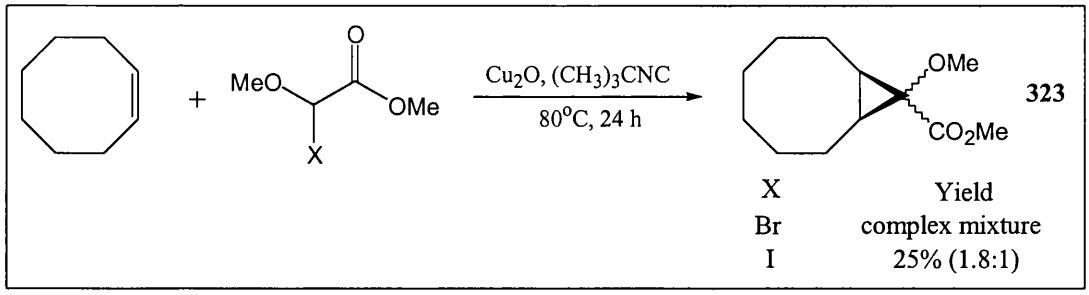
Scheme 171

Thus in order to examine this question, α,α-halomethoxy esters **312** or **313** were formed *in situ* and then reacted in the first instance with a mixture of copper(I) oxide, *t*-butyl isocyanide, and methyl acrylate. However, in both cases a complex mixture was obtained from which no formation of cyclopropane was evident (Scheme 172).



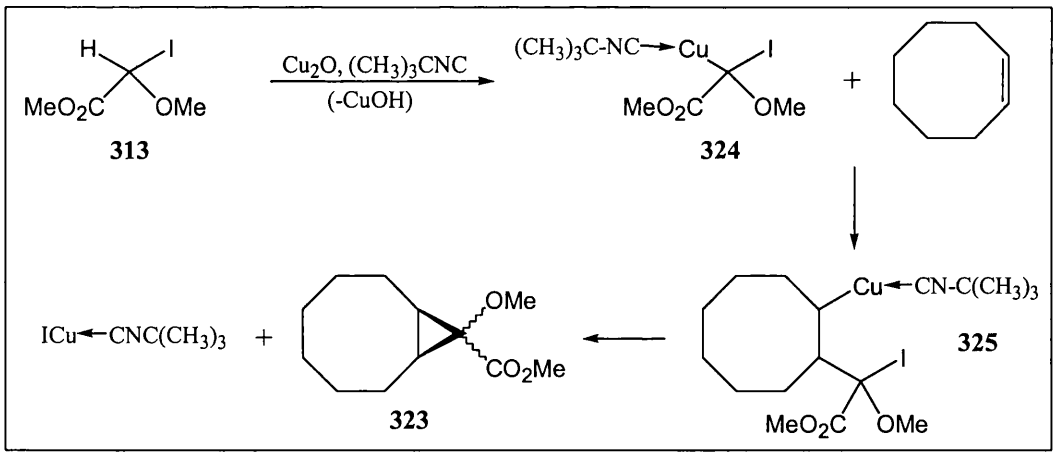
Scheme 172

We then focused on trapping the putative carbenoid intermediates with electron-rich olefins. To our delight, we found that a similar reaction with the formation of the carbenoid from α,α-iodomethoxy ester **313** and *in situ* trapping with cyclooctene gave the corresponding cyclopropane **323** as a mixture of diastereomers. On the other hand, a complex mixture was isolated when the bromo congener **312** was selected (Scheme 173). Hence, a reversal in reactivity is observed (I> Br) with these type of carbenoids in comparison to the literature work on simple α-halo esters where the chloro derivative gave higher yields (Cl> Br).[106] The fact that the iodo intermediate **313** was quantitatively formed whereas the bromo intermediate **312** was formed in a lower conversion must also be taken into account when comparing the use of both halo intermediates.



Scheme 173

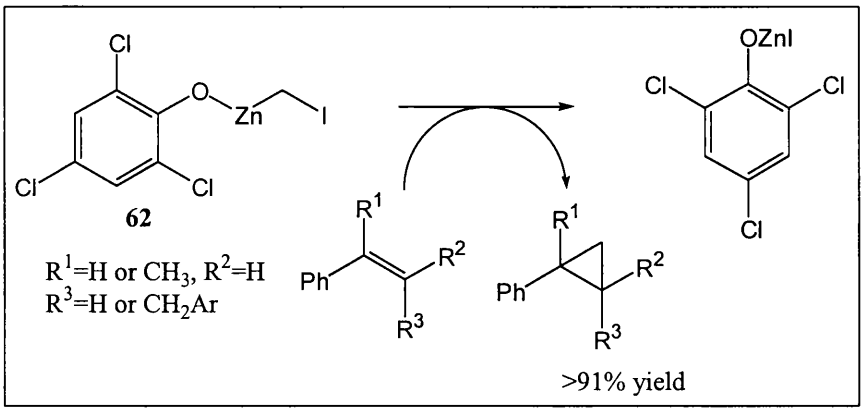
In similar fashion to the mechanism discussed previously (*vide supra* 1.5.3), this cyclopropane synthesis may be explained by a stepwise process involving the addition of α,α-iodomethoxymethylcopper(I)-isonitrile intermediate **324**, copper carbenoid, to cyclooctene. This addition results in the formation of the corresponding γ-iodo-organocopper(I) complex **325**, whose intramolecular ring closure subsequently affords the cyclopropane **323** (Scheme 174).[106b,c]



Scheme 174

This short study has revealed how the reactivity of a carbenoid with a particular type of alkene can be controlled by the nature of the groups attached to the carbenoid, and as discussed in the opening chapter of this thesis will certainly provide opportunities for further research.

When the present work on α,α-halomethoxy esters **312** and **313** was in progress, Charette reported the use of iodomethylzinc phenoxides, such as **62**, as novel carbenoid species (*vide supra* 1.2.1.5). Interestingly, the 2,4,6-trichlorophenyl group in the carbenoid **62** led to high cyclopropanation yields (>95%) (Scheme 175).[42]



Scheme 175

We therefore decided to examine the potential use of ethyl iodo-(2,4,6-trichlorophenoxy)acetate **326** as a carbenoid precursor, which would involve the cleavage of one of the two 2,4,6-trichlorophenyl groups in an acetal by using iodotrimethylsilane, as demonstrated in the cleavage of methyl dimethoxyacetate (Figure 19).

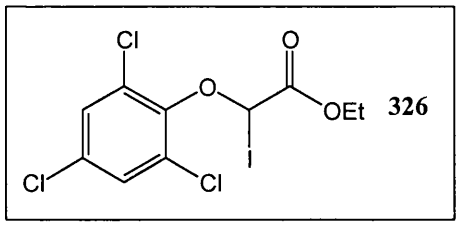
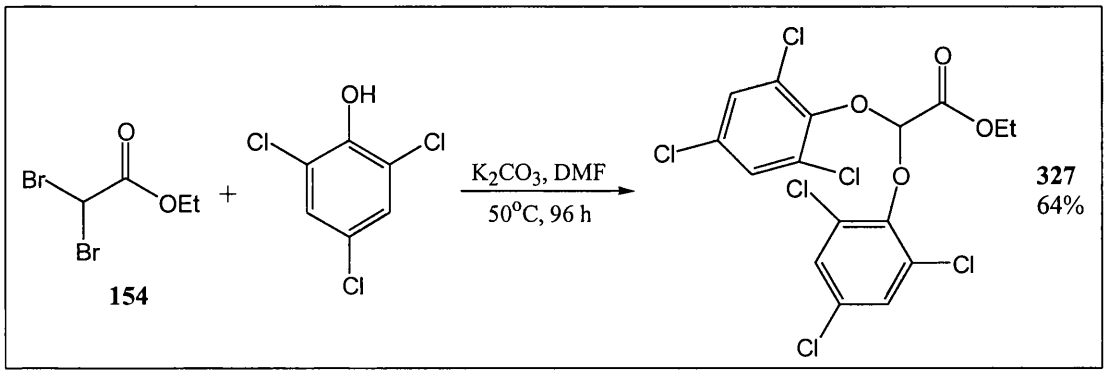


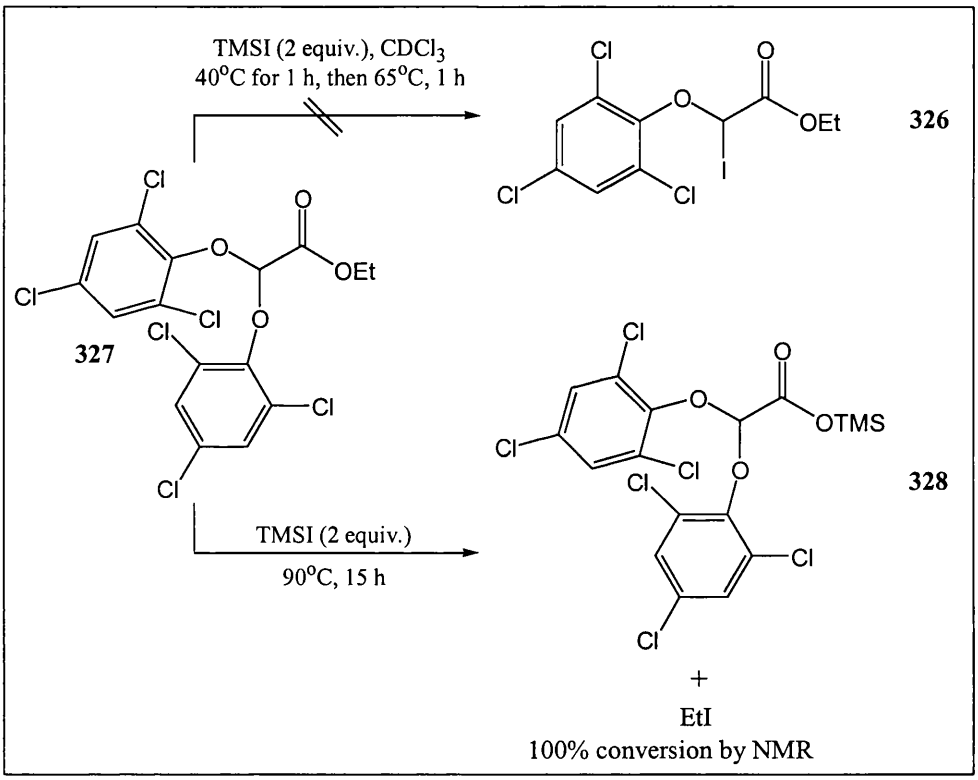
Figure 19

Thus, the acetal **327** was easily prepared from ethyl dibromoacetate **154** and 2 equiv. of deprotonated 2,4,6-trichlorophenol (Scheme 176).



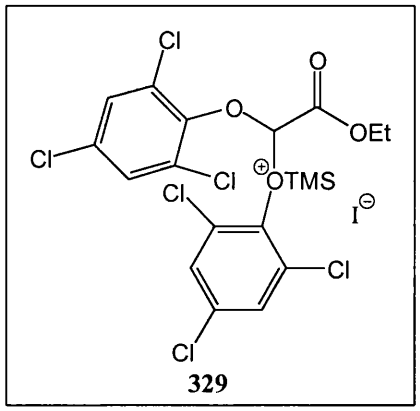
Scheme 176

A series of NMR experiments was then carried out in order to investigate the possibility of selective cleavage of one of the trichlorophenyl groups. Disappointingly, the trichlorophenyl groups in the acetal remained intact when the ester **327** was heated at 40°C, 65°C and finally 90°C. As expected at 90°C, there was cleavage of the ethyl ester group leading to a silylated intermediate **328**, which was clearly evident by the detection of iodoethane from proton and carbon NMR (Scheme 177).



Scheme 177

On closer examination, despite the fact that phenols are good leaving groups, this failure can be attributed to the unlikely formation of the silylated intermediate **329**, due to the obvious steric constraints of the trichlorophenyl and trimethylsilyl groups (Figure 20).



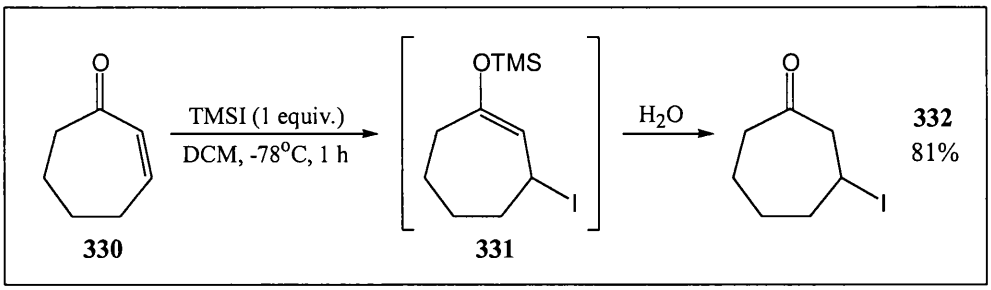
329

Figure 20

2.5.3 Attempted Generation of Organozinc Carbenoids from Novel Geminal Dihalo Intermediates

Thus far, our attempts at generating new functionalised dihalo precursors were unsuccessful (*vide supra* 2.5.2). A different approach was therefore investigated which involved once again, the use of iodotrimethylsilane.

We were particularly attracted to the known[178] reaction involving the addition of iodotrimethylsilane to an α,β-unsaturated compound such as **330** which leads to the iodinated silyl enol ether **331**, and this can then be hydrolysed to the corresponding β-iodocarbonyl compound **332** (Scheme 178).

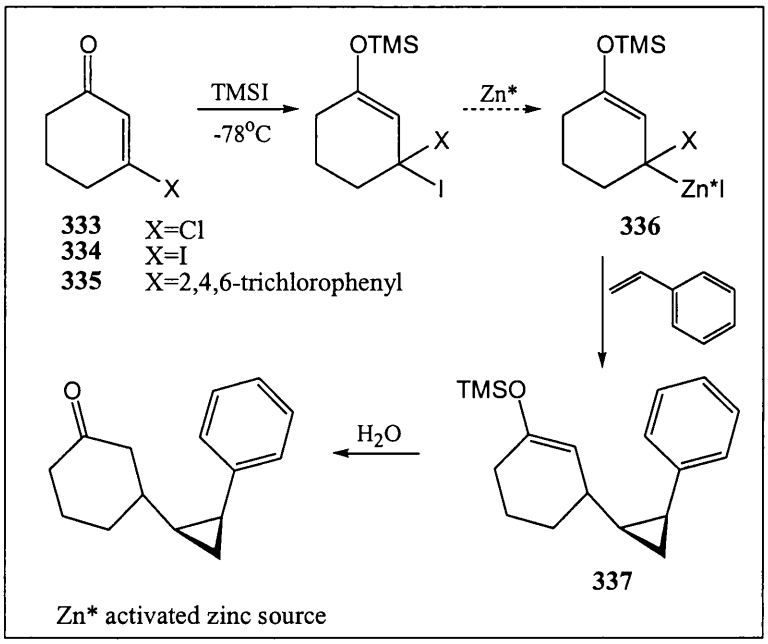


330 **331**

Scheme 178

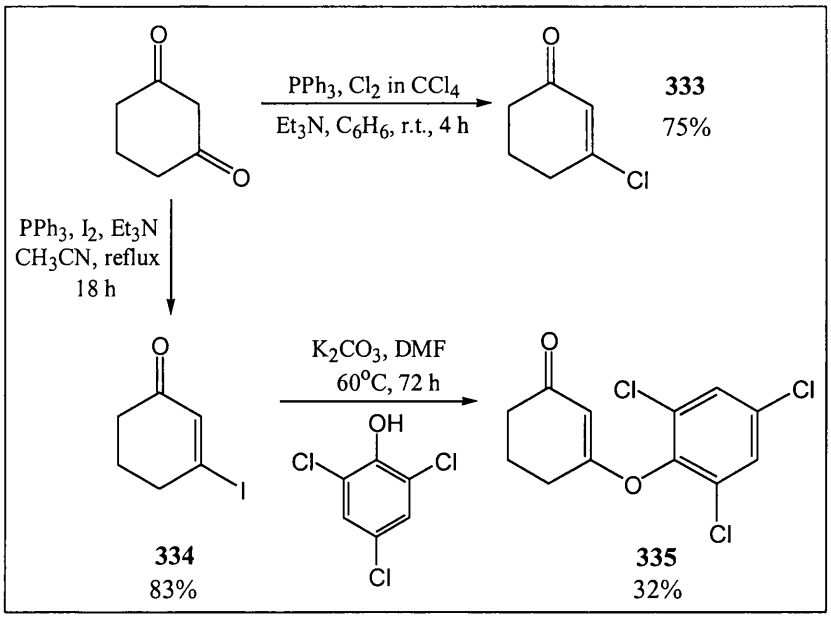
Using this strategy, we envisaged that, in similar fashion, the addition of iodotrimethylsilane to β-halo enones **333** or **334** followed by insertion of zinc would lead us to novel carbenoid species such as **336**. This would be attractive in the case in which the halogens at the β-carbon are chloro and iodo, as Denmark has successfully demonstrated the utility of chloroiodo carbenoids in cyclopropanations (*vide supra*

1.2.1.3).[21] In addition, β-trichlorophenoxy enone **335** would also be useful due to the success of the aforementioned trichlorophenoxy leaving group (*vide supra* 1.2.1.5).[42] After cyclopropanation, the resulting intermediate **337** could then be subjected to reactions such as the Mukaiyama[159] aldol reaction thereby capitalising on the presence of the regiospecific silyl enol ether functionality (Scheme 179).



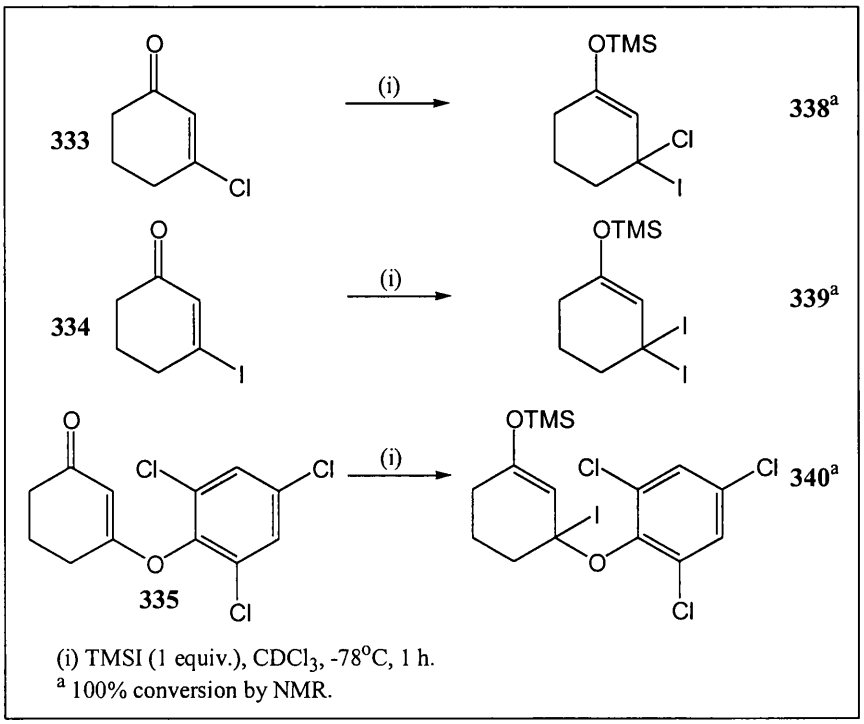
Scheme 179

Thus, β-chloro **333** and β–iodo **334** enones were prepared in good yields using a literature method from the reaction of the symmetrical β–diketone and the appropriate triphenylphosphine dihalide.[179] In addition, β-trichlorophenoxy enone **335** was prepared from the corresponding iodo enone **334** and the potassium salt of 2,4,6-trichlorophenol (Scheme 180).



Scheme 180

For each β-halo enone **333** or **334**, NMR experiments were then performed in deuterated chloroform at –78°C over 1 hour and confirmed that the addition of iodotrimethylsilane to give the corresponding β,β-dihalo silyl enol ether intermediates **338** or **339** had occurred. Similarly, using the same procedure intermediate **340** was also formed (Scheme 181).



Scheme 181

In all cases, the resulting compounds were highly labile and therefore complete characterisation was not possible. However, for two of the intermediates **338** and **340**, clear differences in the chemical shifts in the proton NMR were noted for the α-proton, thereby confirming the addition of the iodide ion to the compound (Figure 21).

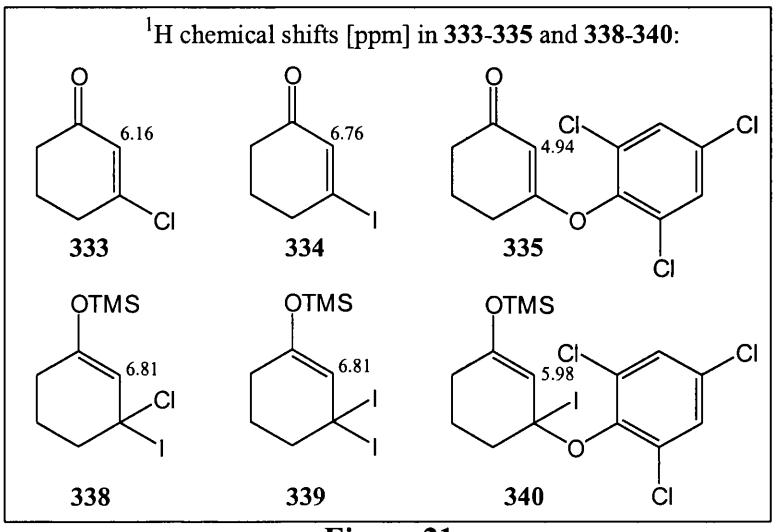
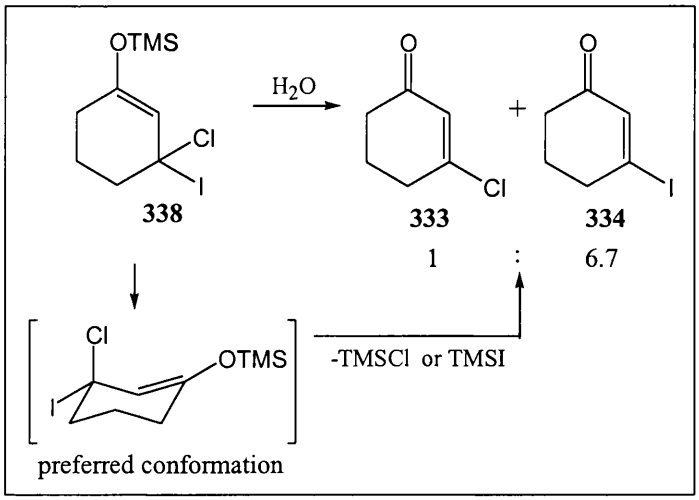


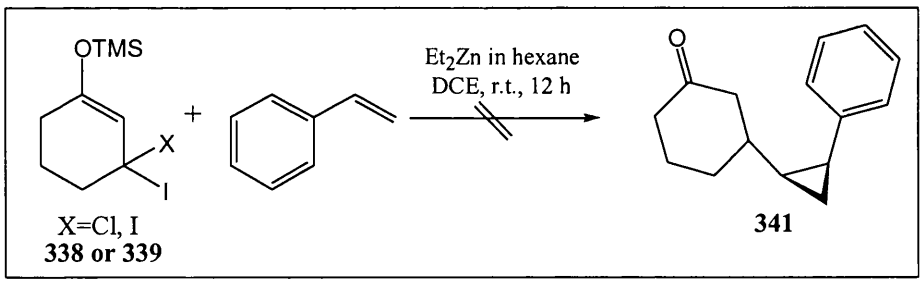
Figure 21

Interestingly, after aqueous work up of the *gem*-chloroiodo intermediate **338**, a mixture of β-iodo and β-chloro enones (**333** and **334**) was recovered in the ratio of 6.7:1. An explanation for this curious observation may be found by consideration of the preferred steric conformation of the cyclohexyl ring based on 1,3-diaxial interactions. Hence, elimination of the axial chlorine is more favourable than iodide. This observation also confirms that the iodide atom from the silicon reagent added to the β-carbon of the enone (Scheme 182).



Scheme 182

A preliminary reaction using diethylzinc and β,β-dihalo silyl enol ether intermediates **338** and **339** in the presence of styrene however produced a highly complex mixture from which no identifiable products such as **341** could be isolated. The major difficulty in this work is based on the fact that there are few examples in the literature which show carbenoid formation from quaternary carbon centers[1] (Scheme 183).



Scheme 183

Unfortunately, due to time constraints, further exciting possibilities such as selective lithiation and transmetallation which could also lead to cyclopropane formation from these carbenoid precursors **338** or **339** could not be investigated.

2.6 Studies on Aminocyclopropanation

One further area of interest to us, was the synthesis of aminocyclopropanes, due to numerous compounds exhibiting agrochemical and pharmological activities.[6] In addition, the incorporation of the amino moiety into the cyclopropane ring can also led to facile nucleophilic substitution of a group X in **342** or a ring-opening

reaction.[1d,7] Intermediates **343** and **344** represent these two types of reaction, respectively (Figure 22).

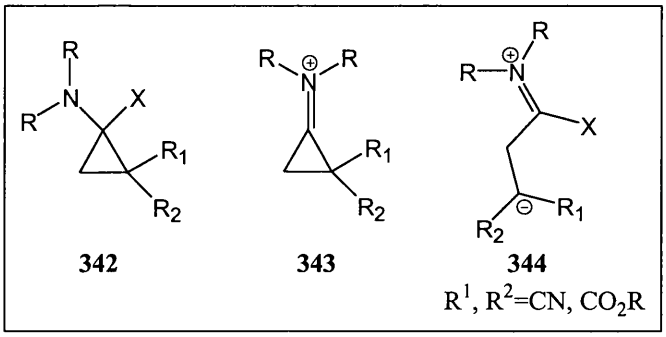
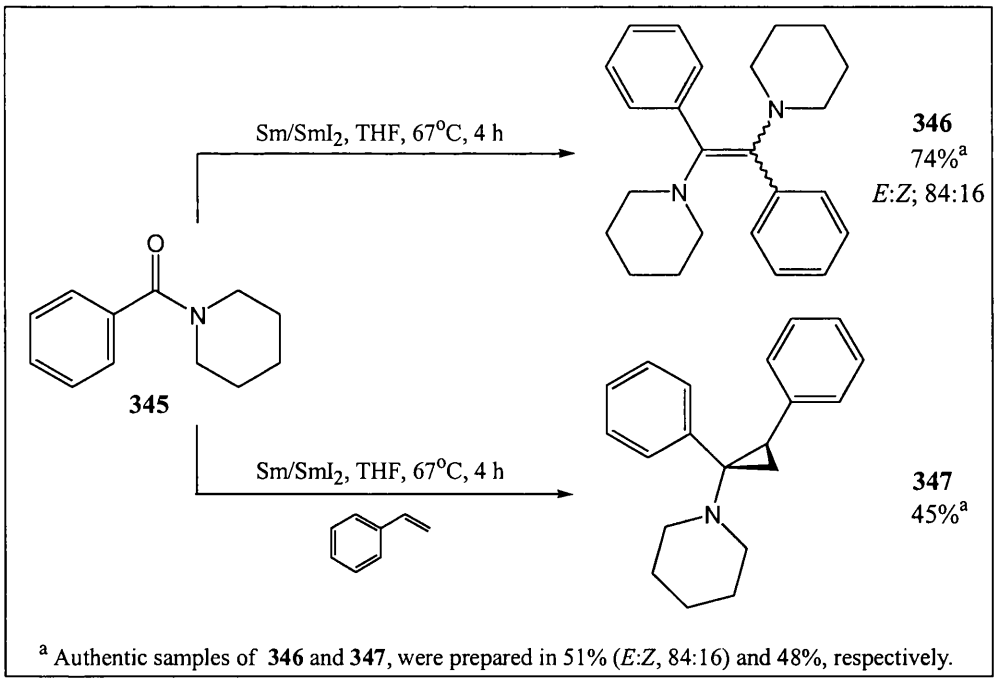


Figure 22

Interestingly, Ogawa has recently shown that aminocyclopropanes **347** can be formed from *N,N*-disubstituted aromatic amides **345** using a samarium/samarium diiodide mixed reagent in the presence of styrene.[180] This was an extension of earlier work, in which using the same conditions and in the absence of alkene, deoxygenative coupling of the amide **345**, to give a *vic*-diaminoalkene **346** was observed (Scheme 184).[181]



[a] Authentic samples of **346** and **347**, were prepared in 51% (*E*:*Z*, 84:16) and 48%, respectively.

Scheme 184

In both cases, the authors suggested that the products are formed through α-aminocarbene species **348**, which can also be represented as samarium carbenoids **349** (Figure 23).[180,181a]

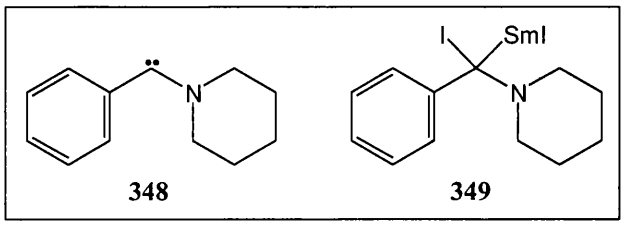
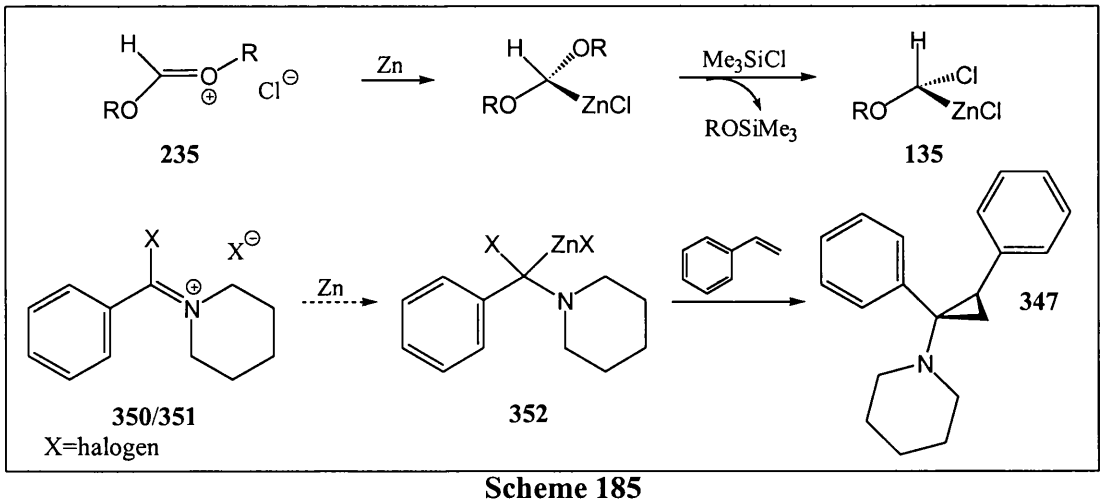


Figure 23

Since previous work within the group had shown that oxonium ions **235** readily accept two electrons from zinc (*vide supra* 2.1.2.5 and 2.1.2.6),[96,126] we envisaged that a similar observation with halo iminium salts **350/351** would lead to organozinc carbenoids of structure **352** which could then undergo aminocyclopropanation of an alkene in similar fashion to the corresponding samarium carbenoids[180,181] (Scheme 185).

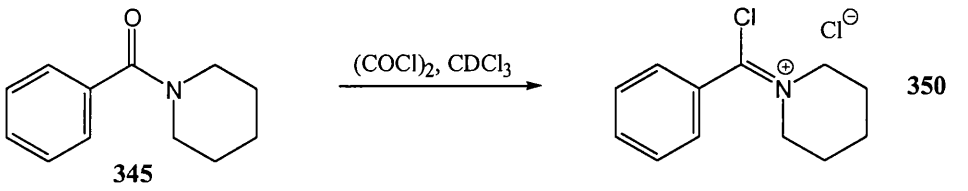


Scheme 185

Authentic samples of the *vic*-diaminoalkene **346** and aminocyclopropane **347** were therefore prepared by the discussed literature methods using the samarium/samarium diiiodide mixed reagent (Scheme 184).[180,181]

2.6.1 Formation of Halo Iminium Salts

Thus, our first task involved the preparation of halo iminium salts. As these compounds are commonly hygroscopic and only soluble in chlorinated solvents,[182] the formation of the chloro iminium salt **350** was investigated in a series of NMR experiments in dry deuterated chloroform and involved the addition of oxalyl chloride to 1-benzoylpiperidine **345**. The reaction time was considerably reduced when the reactants were warmed to 40°C, giving the salt **350** quantitatively after 1 hour (entry 5) (Scheme 186).

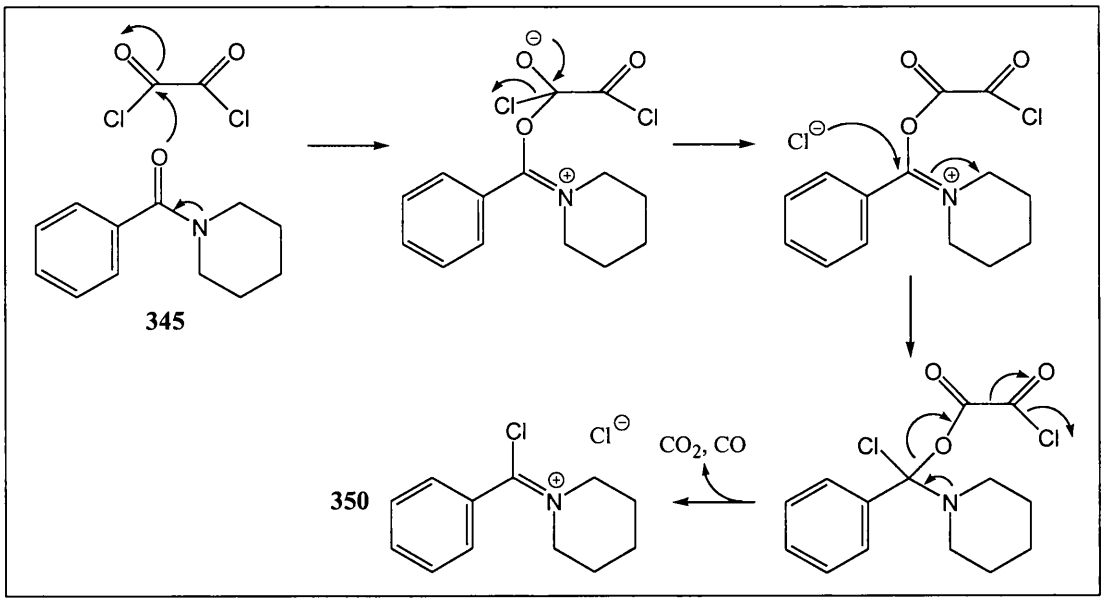


345

Entry	Reaction temperature (°C)	Reaction time (h)	Yield (% conversion by NMR)
1	25	1	64
2	25	4	77
3	25	16	85
4	25	24	100
5	40	1	100

Scheme 186

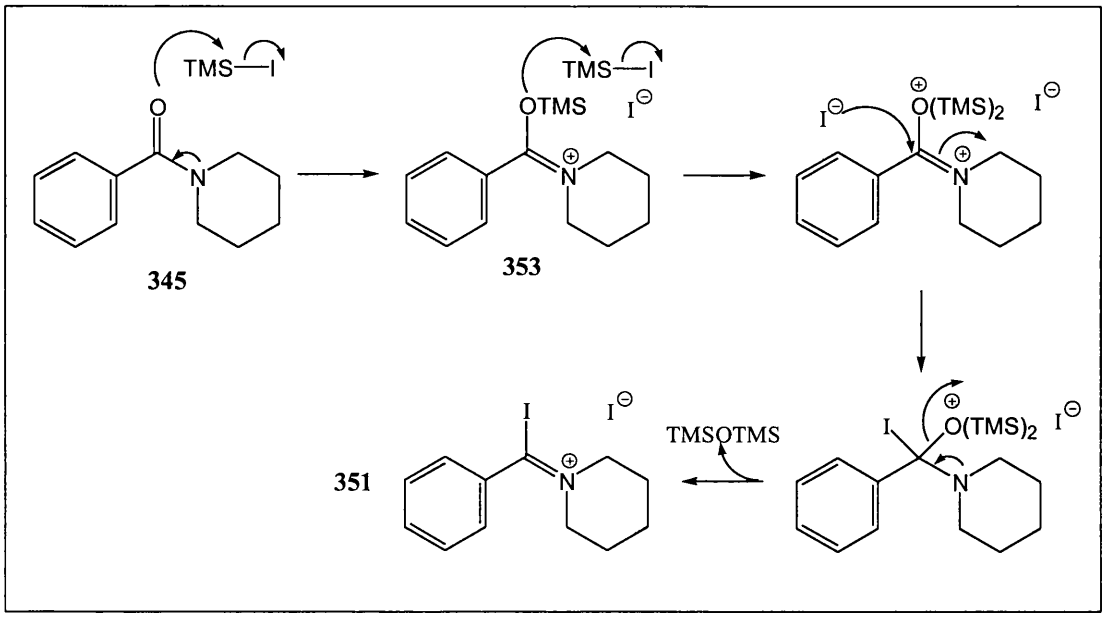
As shown in Scheme 187, the mechanism is similar to the formation of Vilsmeier reagents.[183] Thus, the chloro iminium salt **350** was formed in the final mechanistic step by the loss of carbon monoxide and carbon dioxide, as evidenced by the effervescence observed in the reaction mixture (Scheme 187).



Scheme 187

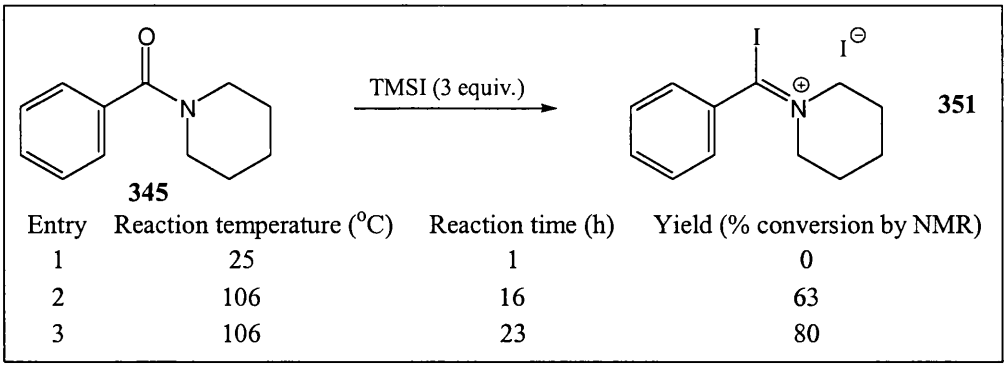
At the same time, we were also interested in synthesising an iodo form of the salt **351** due to its possible higher reactivity. However, since oxalyl iodide was unavailable, studies on an alternative approach involving the possible reaction of iodotrimethylsilane with the amide were sought.

The proposed mechanism first involves *O* silylation of the amide **345** with the silicon electrophile, and further silylation of the resulting iminium intermediate **353**. The iodide, then acting as a strong nucleophile, would displace to form the iodo iminium salt **351** (Scheme 188).



Scheme 188

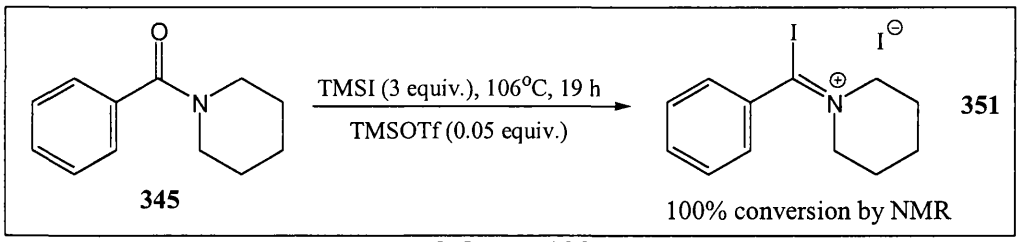
An initial NMR experiment performed at room temperature showed that no reaction had occurred between 1-benzoylpiperidine **345** and the silicon electrophile (entry 1). However, by refluxing the amide **345** in iodotrimethylsilane, high conversions were observed (entries 2 and 3). It is noteworthy that the corresponding reaction with chlorotrimethylsilane was unsuccessful (Scheme 189).



Entry	Reaction temperature (°C)	Reaction time (h)	Yield (% conversion by NMR)
1	25	1	0
2	106	16	63
3	106	23	80

Scheme 189

Moreover, this reaction was successfully catalysed by the addition of trimethylsilyl trifluoromethanesulfonate[184] (5 mol%) which led to quantitative conversion to the iodo iminium salt **351** after 19 hours (Scheme 190). Both of these observations are new reactions of iodotrimethylsilane with amides.

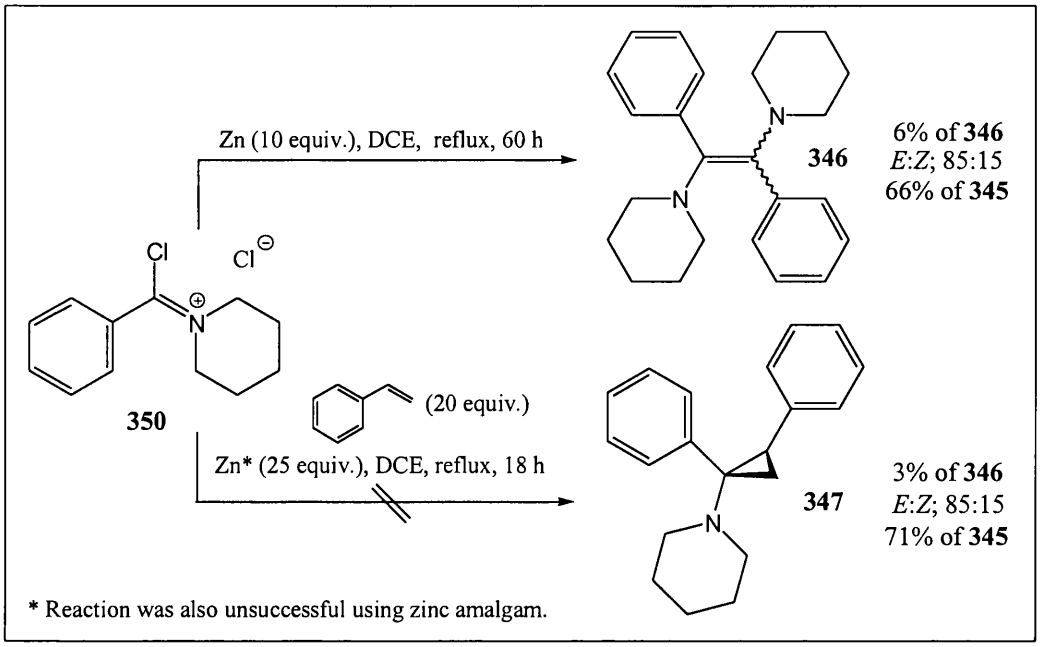


Scheme 190

As both chloro and iodo iminium salts, **350** and **351**, were extremely hygroscopic, complete characterisation was not possible, however, notable proton and carbon chemical shifts supported the case for each iminium ion.

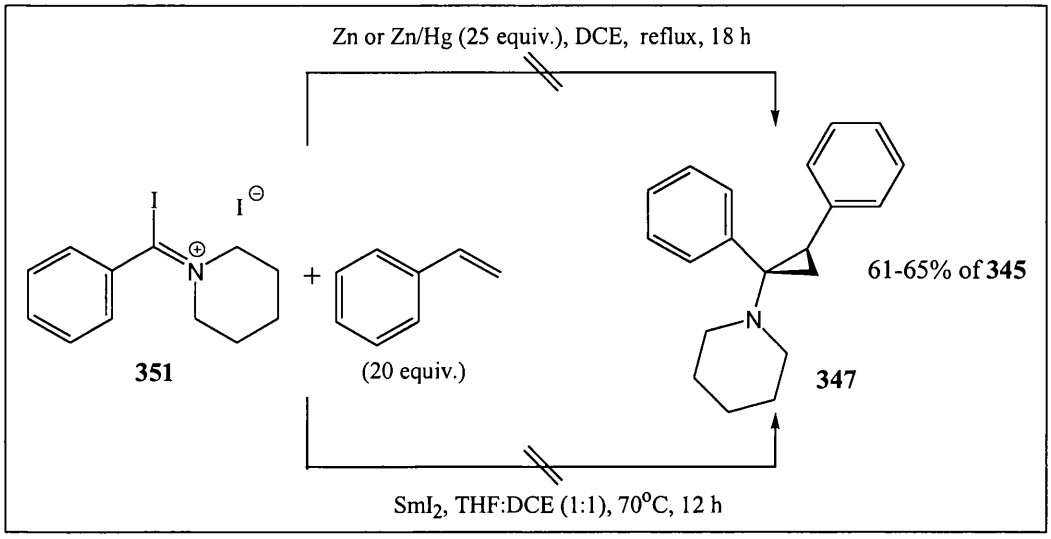
2.6.2 Attempted Generation of Organometallic Carbenoids from Halo Iminium Salts

In our first attempts towards aminocyclopropanation reactions, the chloro iminium salt **350** was quantitatively formed *in situ* due to its senstitive nature and then heated with an activated form of zinc in 1,2-dichloroethane, a solvent which has successfully been used for the generation organozinc carbenoids (*vide supra* 1.2.1.3).[21] Reactions were attempted with and without the presence of styrene but in both cases only a very small amount of *vic*-diaminoalkene **346** (3-6%) was isolated together with recovery of a larger quantity of the amide **345** (65-71%), which is formed by hydrolysis of the iminium salt. At this stage, it was unclear whether this dimer **346** was in fact formed through a zinc carbenoid species or simply *via* a pinacol like coupling of the chloro iminium salt **350** followed by dehalogenation. Even so, our ultimate objective of synthesising aminocyclopropanes **347** was unsuccessful (Scheme 191).



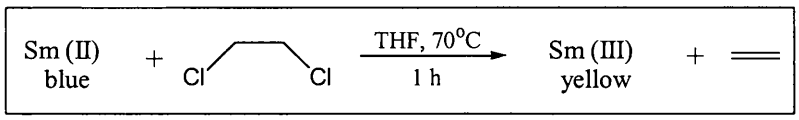
Scheme 191

A similar observation was made when the iodo iminium salt **351**, also formed *in situ*, was heated in the presence of activated form of zinc and styrene, *viz.*, recovery of the amide **345** (61-65%) and no cyclopropane formation. Clearly, iminium ions did not wish to accept electrons from zinc as easily as oxonium ions. We then focused our attention on using other electron-donating reagents, one of which, is samarium(II) iodide, a common one-electron reducing agent.[185] A solution of blue samarium(II) iodide was formed in THF and heated with a mixture of iodo iminium salt **351** in 1,2-dichloroethane. A gradual colour change to yellow, which is characteristic of the samarium(III) species; appeared, and this is likely due to the reaction of samarium(II) species with 1,2-dichloroethane rather than as a result of reducing the iodo iminium salt **351** (Scheme 192).



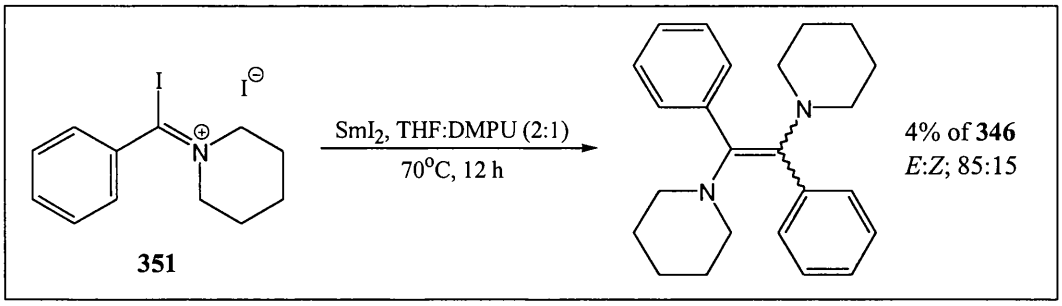
Scheme 192

In fact, a simple experiment which involved the addition of 1,2-dichloroethane to blue samarium(II) iodide, confirmed the problematic nature of this solvent. Thus, reaction occurred on heating (67°C) and the gradual colour change from blue to yellow provides compelling evidence of incompatibility (Scheme 193).



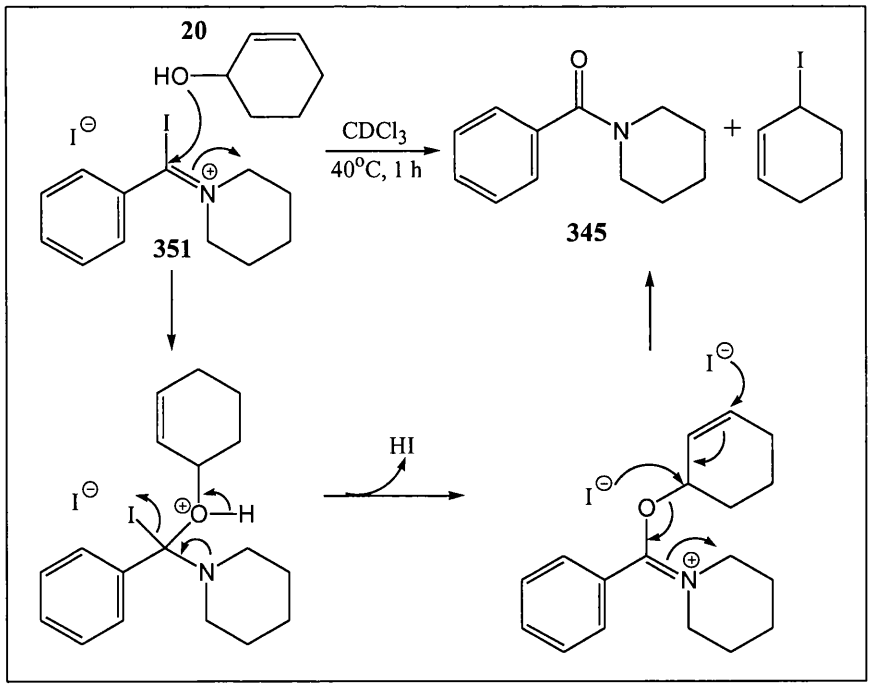
Scheme 193

The use of a chlorinated solvent to solubilise the iminium salt **351** with samarium(II) iodide was proving to be a problem. Due to its high complexing ability, an alternative cosolvent, 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone (DMPU), was investigated. In the event, the iodo iminium salt **351** was soluble in DMPU and then heated with samarium(II) iodide in THF. However, as observed with zinc, dimerisation had occurred in a disappointingly low yield (5%) and once again, it is unclear whether this is through a metal carbenoid species (Scheme 194).



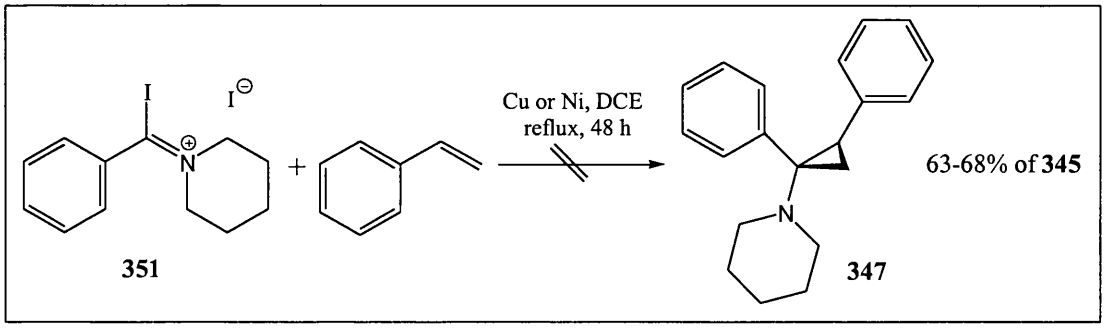
Scheme 194

As Molander had used samarium amalgam with diiodomethane to cyclopropanate allylic alcohols (*vide supra* 1.2.5),[63] we initially considered generating samarium carbenoids from iodo iminium salts **351**, and trapping the species with allylic alcohols. However, as shown in Scheme 195, allylic alcohols can of course react as nucleophiles with iminium salts and this was checked by a simple NMR experiment, in which the iodo iminium salt **351** was heated with 1-cyclohexen-2-ol **20** in dry deuterated chloroform. From ^{1}H NMR, full conversion to 1-benzoylpiperidine **345** after 1 hour was noted. For this reason, using samarium amalgam to generate the carbenoids was not further investigated.



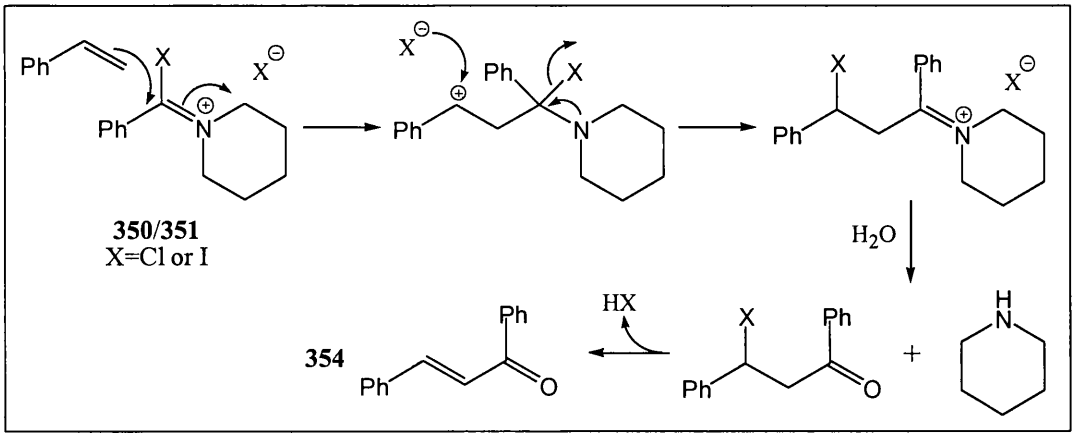
Scheme 195

In our final attempts to reduce the iminium iodide salt **351**, copper[186] and nickel,[186] common reducing metals, were also studied. In both cases, neither the dimer **346** nor the aminocyclopropane **347** were formed (Scheme 196).



Scheme 196

From close examination of literature, one of the problems in these reactions is the known Friedel Crafts reaction of halo iminium salts (Scheme 197),[187] which possibly accounts for, only some of 1-benzoylpiperidine **345** (61-71%) being recovered in all of our attempted aminocyclopropanation reactions. The enone **354** however was not detected as a product.

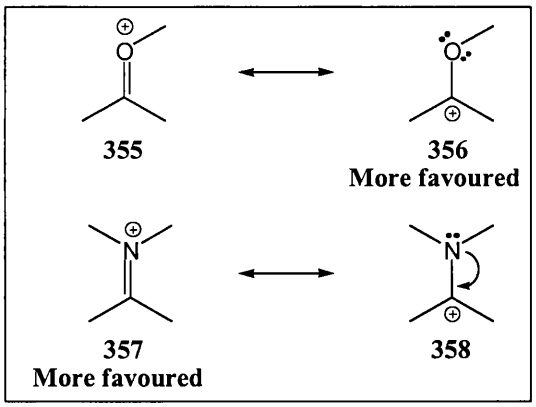


Scheme 197

2.6.3 Iminium and Oxonium Ions

In summary, our aminocyclopropantion studies have shown that neither chloro nor iodo iminium species could be as readily reduced as oxonium ions.

This contrasting behaviour can be attributed to the influence of the relative electronegative nature of the nitrogen and oxygen atoms in the resonance forms (**355-358**) for both species. Thus, due to the higher electronegativity of the oxygen atom, intermediate **356** is "favoured" over the oxonium form **355**, hence electrons can be donated easily to the more electrophilic carbon. In sharp contrast, the iminium form **357** is favoured as the more nucleophilic nitrogen atom easily donates electrons in the resonance intermediate **358** and in this case, the carbon atom is less electrophilic and therefore effectively less likely to accept electrons (Scheme 198).



Scheme 198

3

Conclusions and Perspectives

3. Conclusions and Perspectives

The foregoing discussion of our results has revealed several important findings, and to a certain extent, fulfilled our principal objectives of providing new and improved methods for reactive carbenoid generation together with some initial insights into the formation and reactivity of entirely novel carbenoid precursors. In addition, we have also extended some of the chemistry using organozinc carbenoids generated from carbonyl compounds by the traditional method within our group.

Thus, somewhat surprisingly, when applying the previous work on zinc and chlorotrimethylsilane deoxygenations[93] to medium and large sized ring ketones, extremely low conversions were observed. The failure can be attributed to the steric bulk of the silicon electrophile which effectively hinders the formation of organozinc carbenoids, a problem which was overcome by either using the proton as a potentially catalytic electrophile in the presence of zinc and chlorotrimethylsilane or by using the more potent silicon electrophile; iodotrimethylsilane. In both cases, similar yields were obtained. However, by using the alternative silicon electrophile, the reaction time was considerably reduced. It would therefore be interesting to see whether bromotrimethylsilane may offer a compromise between reactivity and stability in relation to the other aforementioned silicon electrophiles. Figure 24 shows the likely reactive carbenoid species which were generated in this study, expressed either as Simmons Smith[8] like entities **208** and **261** or as penultimate carbenoid intermediates as in **259**, **257** and **359**.

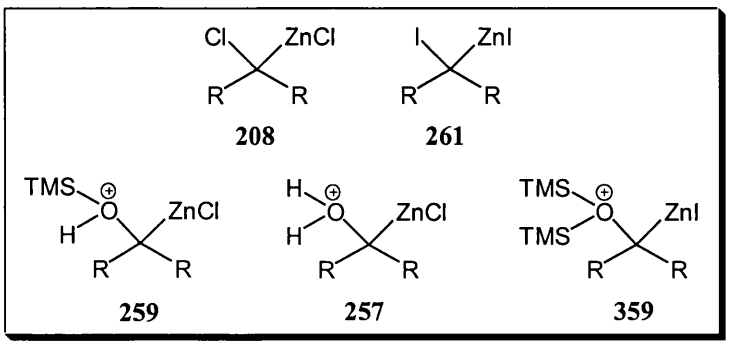
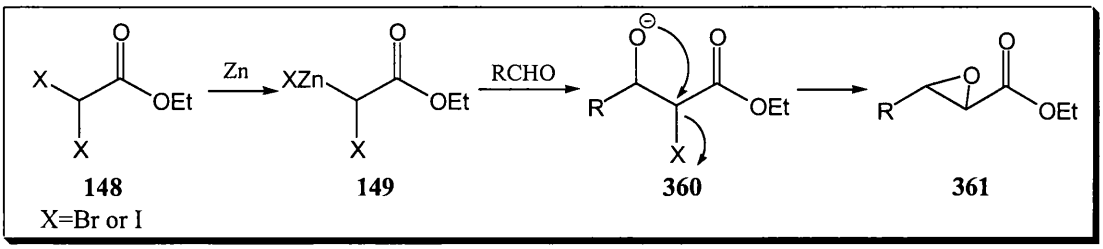


Figure 24

Other techniques to generate organozinc carbenoids have also been explored with some notable successes observed in the preliminary electrochemical version of the dicarbonyl coupling reaction. This was a significant step, as it was the very first time such a technique was applied to chemistry within the group. Clearly, with electrochemical methods becoming more widely used in organic synthesis, this area warrants further investigation as attempting the reactions using such techniques may lead to more efficient reactions.

An extension of previous work within the group[124] led to the synthesis of several vinyl- and divinylcyclopropanes. In all cases the more sterically hindered *cis* cyclopropane is formed preferentially. Furthermore, clear trends were observed in yields and stereoselectivity with variation of electron donation from the *para*-substituent on the aromatic ring. Interestingly, our zinc carbenoids showed the same regioselectivity as has been observed with Simmons Smith and rhodium carbenoids. When the bulk of the olefin was increased, both the yield and diastereoselectivity of the cyclopropane product were reduced. Support for all these observations can be found in the work reported by Casey.[156]

By performing a direct comparison of zinc and copper metals in carboalkoxycyclopropanation, studies showed copper to be a far more effective metal. However, since ethyl dihaloacetates **148** were being readily consumed in the reaction mixture containing zinc, there is no reason why the resulting carbenoid intermediate **149** could react as a Reformatsky-type reagent with an aldehyde. Consequently, epoxides **361** could be formed after intramolecular ring closure of the penultimate intermediate **360**. Even though literature precedent exists to show epoxide formation from ethyl dihaloacetates using zinc/silver on graphite,[103] this reaction could be investigated enantioselectively by adding a chiral catalyst to the reaction mixture (Scheme 199).



Scheme 199

In addition to the generation of reactive carbenoids **261** in deoxygenation reactions, the use of iodotrimethylsilane has also led to the synthesis of three potential types of carbenoid precursors; **313**, **338-340** and **351** as shown in Figure 25. In the case of α–iodomethoxy ester **313**, a novel geminal alkoxy-carboalkoxy organocopper carbenoid **324** was successfully used for cyclopropanation. As yet, further work will be required to determine whether allylic dihalo silyl enol ethers **338-340** are suitable carbenoid precursors and additionally a new reaction of amides with the silicon electrophile led to the formation of iodo iminium salts **351**. Thus, the use of this potent electrophile can lead to several synthetically useful reactions which are not possible with chlorotrimethylsilane (Figure 25).

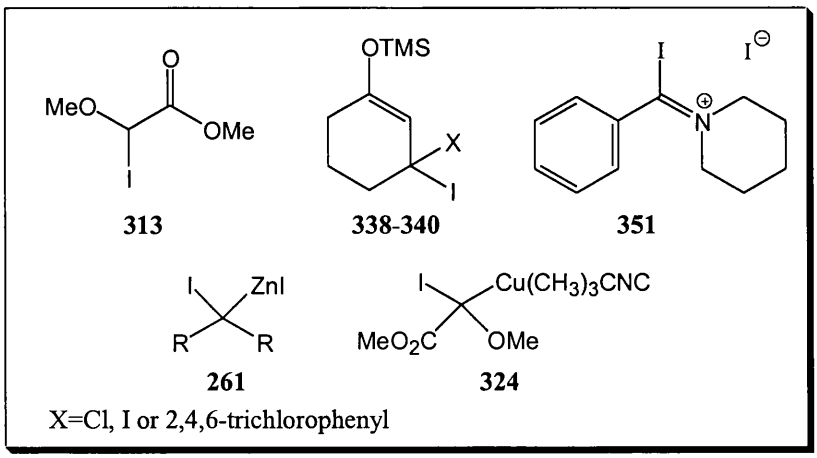


Figure 25

In similar vein, the following compounds **362** and **363** could also be prepared by using iodotrimethylsilane and these would be interesting due to the success of the trifluoromethyl group in reported cyclopropanation studies[39] (Figure 26).

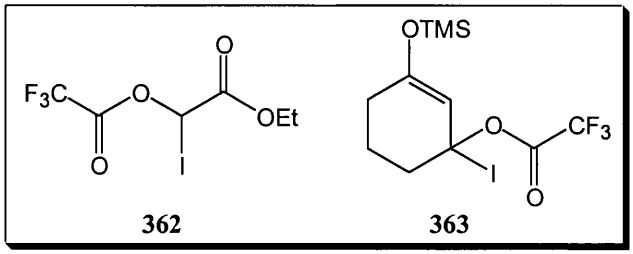
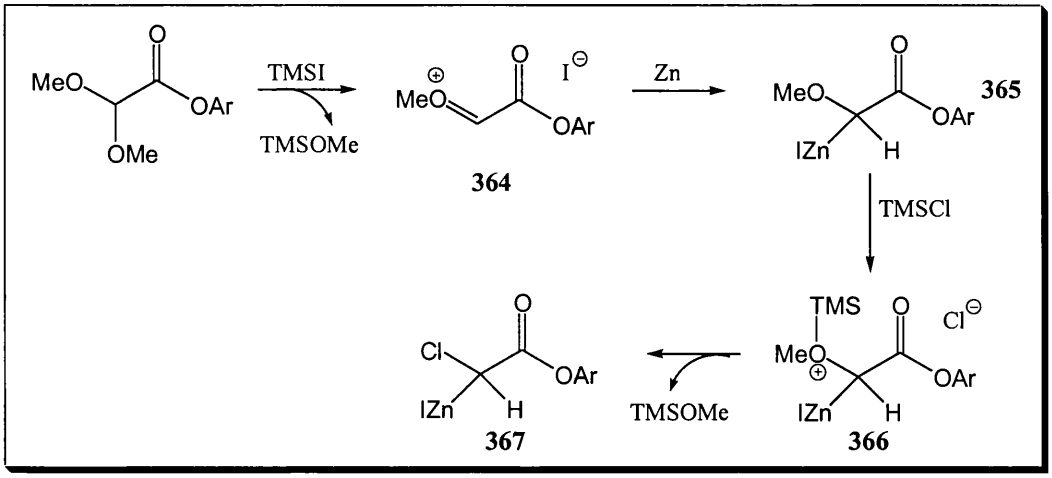


Figure 26

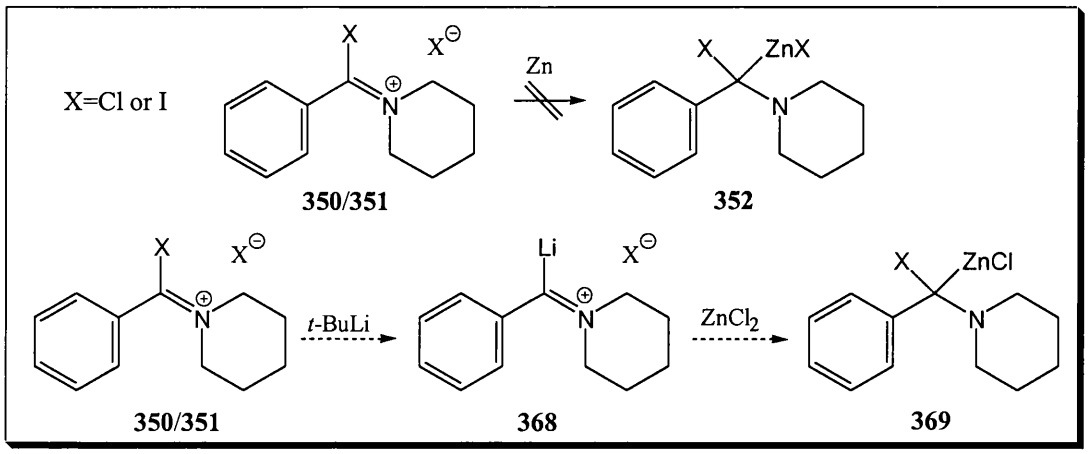
As the mechanism for α–iodomethoxy compounds **313** occurs *via* an oxonium ion such as **364**, zinc can deliver electrons to this species to form an organometallic compound **365**. If the group is large such as an aromatic group then cleavage of the methoxy group may be achieved with chlorotrimethylsilane, as this is favoured over the displacement of the ester group. Elimination of methyl trimethylsilyl ether from the intermediate **366** then results in the formation of a Denmark-type,[21] chloroiodo organozinc carbenoid species **367** (Scheme 200).



Scheme 200

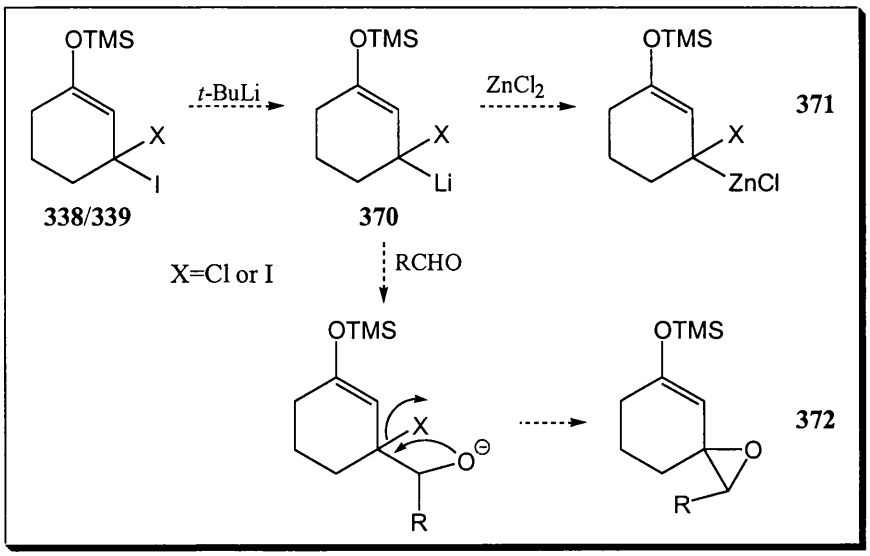
In sharp contrast to oxonium ions,[96,126] our final studies showed electron delivery to iminium salts **350/351** was unsuccessful due to the carbon showing a lower electrophilic character. However, an alternative procedure for organozinc carbenoid generation from these salts can be envisaged. The proposed method involves

treatment of the iminium salt **350/351** with *t*-butyllithium, which can lead to the formation of the lithiated ion **368** *via* lithium-halogen exchange[188] and this may then undergo transmetallation[189] using zinc chloride to form the carbenoid intermediate **369** (Scheme 201).



Scheme 201

The same procedure can also be applied to dihalo silyl enol ether intermediates **338** or **339**, interestingly this time lithium-halogen exchange may result in the generation of organolithium carbenoids **370**. The slightly different behaviour of these carbenoids could allow the possibility of forming epoxides **372** in a stepwise reaction with the aldehyde, as well as the expected cyclopropanes from organozinc carbenoids **371** (Scheme 202).



Scheme 202

Although the foregoing results and discussion section has centred mainly on the generation of organozinc carbenoids, towards the latter parts of the section, increasing emphasis was placed on the generation of other metal carbenoid species which includes copper, samarium and nickel. This coupled with the introductory review, has highlighted the importance of the fact that any metal surface or organometallic anion capable of delivering two electrons to a carbonyl group may, in the presence of two silicon electrophiles, provide a general route to metallocarbenoids. The chemistry of metal carbenoids generated from unusual precursors is therefore at an exciting stage and metals such as aluminium, magnesium, ytterbium and indium would all be viable candidates for the generation of new carbenoid species.

4

Experimental

4.1 General Experimental

Proton NMR spectra were recorded on a Brucker Avance 500, Brucker AMX-400 or a Bruker AMX-300 at 500 MHz, 400 MHz or 300 MHz respectively. Carbon NMR spectra were recorded on the same machines at 126 MHz, 100 MHz and 75 MHz. Further proton NMR spectra were performed at Syngenta Agrochemicals on a Jeol GSX-270 or a Varian VXR-400 at 270 MHz or 400 MHz, respectively. Carbon NMR spectra were carried out on the same machines at 100 MHz and 75 MHz. Assignments were supported by DEPT editing, COSY spectra and ^{1}H-^{13}C COSY spectra. Diastereomers were distinguished by NOESY spectra. Fluorine NMR were recorded on a Bruker AMX-300 at 282 MHz. Proton and carbon NMR chemical shifts are reported as values in ppm from an internal standard (tetramethylsilane) or residual protic solvent. Fluorine NMR shifts are also reported as values in ppm from an external reference (trichlorofluoromethane). The following abbreviations are used to indicate multiplicity: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=double doublet, ddd=double double doublet, dt=double triplet, ddt=double double triplet, br=broad. The coupling constants (*J*) are given in Hertz (Hz). Infrared spectra were recorded as thin films on NaCl plates or as KBr discs on a Perkin-Elmer FT-IR 1605; abbreviations to denote peak intensity are as follows: w=weak, m=medium, s=strong, b=broad. Mass spectra were recorded either under electron impact (EI) at the University College London Chemistry Department or fast atom bombardment (FAB) at the School of Pharmacy. London. Accurate mass measurements were performed either at the University College London Chemistry Department or the School of Pharmacy, London. Gas chromatography was performed on a Hewlett-Packard 5890A machine (flame ionisation detector) with a 25 m x 0.32 mm BPX5 column using helium or hydrogen as a carrier gas. Boiling points for Kugelrohr bulb to bulb distillation refer to uncorrected air temperatures. Pressure was recorded on a standard Gallenkamp manometer. Melting points were taken on a Reichert hot stage and are uncorrected.

All reactions using dry solvents were carried out in flame or oven dried glassware under an inert atmosphere of nitrogen, unless otherwise stated. Solvent transfer was performed by canula or syringe. Molecular sieves were activated by microwave irradiation.

Petroleum ethers (b.p. 30-40°C and 40-60°C) for flash chromatography were distilled prior to use whereas diethyl ether was used as supplied by the manufacturers. Pentane, hexane, ethyl acetate, methanol, absolute ethanol and dry carbon tetrachloride when used experimentally were also used as supplied by the manufacturers. Organic solvents were dried over anhydrous $MgSO_4$ or Na_2SO_4. Diethyl ether and tetrahydrofuran were distilled from sodium and benzophenone. Dichloromethane, 1,2-dichloroethane and acetonitrile were pre-dried with 4Å molecular sieves and distilled over calcium hydride. Dimethylformamide was distilled from calcium hydride at reduced pressure and stored over 4Å molecular sieves under nitrogen. Acetone was pre-dried with $MgSO_4$, distilled and stored under nitrogen. Benzene was distilled from sodium. Triethylamine was pre-dried with anhydrous potassium hydroxide and distilled under nitrogen. Chlorotrimethylsilane was distilled from calcium hydride and iodotrimethylsilane was distilled from copper powder, immediately prior to use. 1,2-bis(chlorodimethylsilyl)ethane (a solution in dry ether) was stored over polyvinyl-4-pyridine to remove any hydrochloric acid. 1,2-diiodoethane was washed with saturated sodium thiosulfate solution and styrene was distilled from hydroquinone at 70°C under reduced pressure, prior to use. For spectroscopic studies, deuterated chloroform was stored with anhydrous potassium carbonate and 4Å molecular sieves. All compounds were used as supplied by the manufacturers unless otherwise stated.

Analytical thin-layer chromatography (tlc) was performed on pre-coated aluminium backed plates (Merck Kieselgel F_{254}). Visualization was afforded either using ultraviolet light (254 nm), iodine, basic potassium permanganate [add 6.25 g of Na_2CO_3 in water (1.25 l) to 12.5 g of $KMnO_4$ in water (1.25 l)], acidic ammonium molybdate (IV) [concentrated H_2SO_4 (250 ml), ammonium molybdate.$4H_2O$ in water (2.25 l)] or anisaldehyde [15 ml anisaldehyde dissolved in EtOH with concentrated H_2SO_4 (25 ml)]. Flash chromatography was performed using BDH flash silica gel (40-60 nm), with a silica to crude mass ratio of 10 to 1 or using Aldrich aluminium oxide (150 mesh) or Acros basic aluminium oxide (50-200 μm). Unless otherwise stated, elution was afforded by a graduated solvent system beginning with 40-60°C or 30-40°C petroleum ether and terminating with diethyl ether.

The following procedures were used to activate zinc:

Acid-washed Zinc dust[190]

Zinc powder (20.0 g, 306 mmol) was stirred vigorously with 5% aqueous hydrochloric acid (24 ml) for 3 min. The zinc was then filtered off then washed successively with water (3 x 24 ml), acetone (2 x 16 ml) and ether (2 x 16 ml), dried *in vacuo* for 3 h at r.t., and stored *in vacuo*.[190]

Activation of Zinc Dust using 1,2-Dibromoethane and Chlorotrimethylsilane[174]

1,2-Dibromoethane (215 µl, 2.50 mmol, 0.05 equiv.) in THF (20 ml) was added to zinc dust (3.27 g, 50.0 mmol, 2.68 equiv.) and the resulting mixture was heated to gentle reflux, then cooled to r.t. This process was repeated a further 4 times. Chlorotrimethylsilane (63.5 µl, 0.50 mmol, 0.01 equiv.) was then added and the solution was stirred for 15 min at r.t. The solvent was removed *in vacuo*, and the zinc dust was further dried *in vacuo*.[174]

Zinc Mercury Amalgam[135]

Zinc powder (10.0 g, 153 mmol) was added to a vigorously stirred solution of mercuric chloride (2.00 g, 7.20 mmol) and hydrochloric acid (0.50 ml, 10 M) in water (30 ml). The mixture was stirred for 10 min, and the zinc filtered off then washed with water (75 ml), acetone (75 ml), ethanol (75 ml) and ether (75 ml). The amalgam was crushed, vacuum dried for 4 h at r.t. and stored under an argon atmosphere.[135]

Zinc Copper Couple (Shank and Shechter)[175]

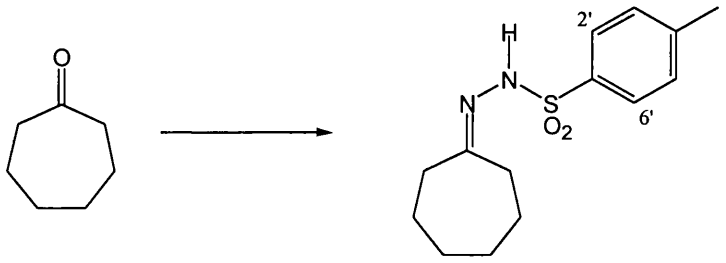
Zinc powder (6.60 g, 101 mmol) was washed successively with 3% aqueous hydrochloric acid (4 x 5 ml), water (4 x 6 ml), 2% copper(II) sulfate (2 x 10 ml), water (4 x 6 ml), ethanol (4 x 6 ml) and ether (5 x 10 ml). The zinc-copper couple was dried *in vacuo* at r.t. for 2 h.[175]

4.2 Experimental Procedures

General Procedure for the Preparation of Tosylhydrazone Salts (236-239 and 246)[130]

The appropriate ketone (1 equiv.) was added to *p*-tolylsulphonylhydrazine (1 equiv.) dissolved in warm (>50°C) methanol (4.7 mlg^{-1} of hydrazine) and the mixture was stirred for 1 h. The flask was stoppered and the mixture was kept first, at r.t. for 24 h, then at 5°C for 48 h. The resultant solid was collected by filtration and washed thoroughly with chilled methanol. Recrystallisation (methanol) provided the required hydrazone **236-239** and **246**.[130]

Preparation of Cycloheptanone-(4-methylbenzenesulfonyl)hydrazone 236[130]

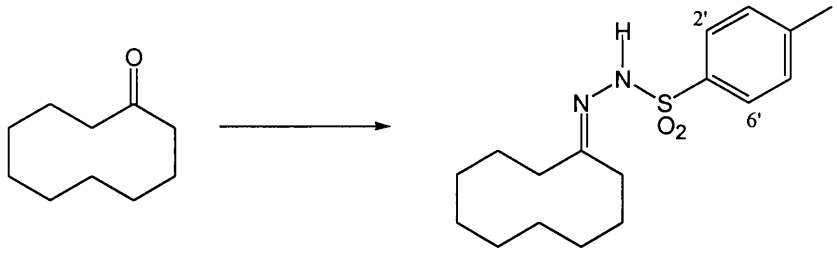


236

Reaction of cycloheptanone (8.41 ml, 71.3 mmol, 1 equiv.) with *p*-tolylsulfonylhydrazine (13.2 g, 71.3 mmol, 1 equiv.) in methanol (62 ml) using the general procedure, afforded the *hydrazone* **236** (15.9 g, 56.7 mmol, 79%) as rods, m.p. 149.5-151°C (decomp.) (from methanol) (lit.,[130] 149.5-151°C).

υ_{max} (KBr disc)/cm^{-1} 3231 (m, N-H), 2916 (m, C-H), 2851 (m, C-H), 1623 (w, C=N), 1591 (m, C=C), 1489 (w, C-H), 1452 (s, C-H), 1382 (s, C-H), 1331 (s, SO_2), 1164 (s, SO_2); δ_H (300 MHz; $CDCl_3$) 7.81 (2H, br d, J_{ortho} 8.3, $H_{2',6'}$), 7.27 (2H, br d, J_{ortho} 8.3, $H_{3',5'}$), 2.39 (3H, s, CH_3), 2.37 (2H, m, CH_2), 2.23 (2H, m, CH_2), 1.63 (2H, m, CH_2), 1.49 (6H, m, CH_2); δ_C (75 MHz; $CDCl_3$) 164.2 (C=N), 143.7 ($C_{1'}$), 135.7 ($C_{4'}$), 129.4, 128.0 ($C_{2',3',5',6'}$), 36.9, 30.3, 30.1, 30.0, 27.2, 24.2 (CH_2), 21.5 (CH_3); *m/z* (EI) 281 (100%, M+1), 157 (10%), 125 (55%, $C_7H_{12}NN^+H$), 95 (21%, $[C_7H_{11}]^+$), 91 (43%, $[C_7H_7]^+$), 81 (30%, $[C_6H_9]^+$), 65 (19%, $[C_5H_5]^+$), 55 (24%, $[C_4H_7]^+$).

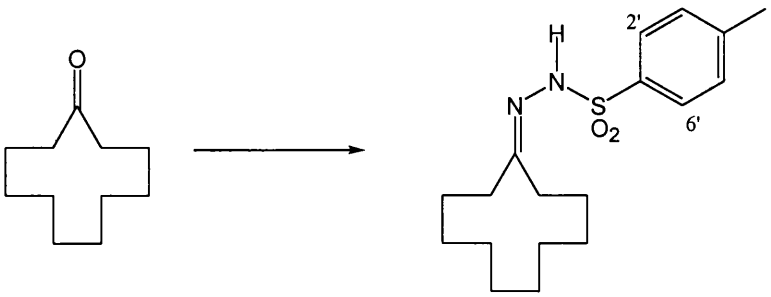
Preparation of Cyclodecanone-(4-methylbenzenesulfonyl)hydrazone 237[130]



237

Reaction of cyclodecanone (938 µl, 5.83 mmol, 1 equiv.) with *p*-tolylsulfonylhydrazine (1.09 g, 5.83 mmol, 1 equiv.) in methanol (5 ml) using the general procedure, afforded the *hydrazone* **237** (1.30 g, 4.03 mmol, 69%) as a white crystalline solid, m.p. 137-139°C (decomp.) (from methanol) (lit.,[131a] 137-138°C). υ_{max} (KBr disc)/cm^{-1} 3199 (m, N-H), 2914 (m, C-H), 2859 (m, C-H), 1622 (w, C=N), 1594 (m, C=C), 1475 (s, C-H), 1443 (s, C-H), 1415 (s, C-H), 1392 (s, C-H), 1328 (s, SO_2), 1158 (s, SO_2); δ_H (300 MHz; $CDCl_3$) 7.83 (2H, br d, J_{ortho} 8.2, $H_{2',6'}$), 7.51 (1H, br s, NH), 7.26 (2H, br d, J_{ortho} 8.2, $H_{3',5'}$), 2.39 (3H, s, CH_3), 2.32 (2H, m, CH_2), 2.18 (2H, m, CH_2), 1.62 (4H, m, CH_2), 1.26-0.94 (10H, br m, CH_2); δ_C (75 MHz; $CDCl_3$) 161.0 (C=N), 143.8 ($C_{1'}$), 135.6 ($C_{4'}$), 129.4, 128.2 ($C_{2',3',5',6'}$), 35.1, 30.1, 25.5, 25.1, 24.0, 23.8, 23.2, 22.8, 22.5 (CH_2), 21.5 (CH_3); *m/z* (EI) 323 (61%, M+1), 167 (99%, $C_{10}H_{18}NN^+H$), 157 (26%), 137 (26%, $[C_{10}H_{17}]^+$), 91 (100%, $[C_7H_7]^+$), 81 (36%, $[C_6H_9]^+$), 65 (42%, $[C_5H_5]^+$), 55 (52%, $[C_4H_7]^+$).

Preparation of Cycloundecanone-(4-methylbenzenesulfonyl)hydrazone 238[130]



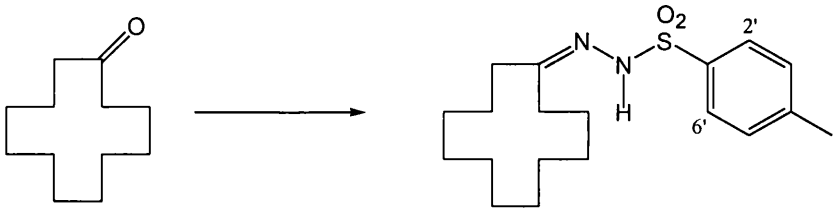
238

Reaction of cycloundecanone (1.06 ml, 5.65 mmol, 1 equiv.) with *p*-tolylsulfonylhydrazine (1.05 g, 5.65 mmol, 1 equiv.) in methanol (5 ml) using the

general procedure, afforded the *hydrazone* **238** (1.23 g, 3.66 mmol, 65%) as a white crystalline solid, m.p. 133.5-135°C (decomp.) (from methanol) (lit.,[131d] 135°C).

υ_{max} (KBr disc)/cm^{-1} 3209 (s, N-H), 2915 (s, C-H), 2855 (s, C-H), 1623 (w, C=N), 1597 (m, C=C), 1491 (m, C-H), 1470 (m, C-H), 1456 (m, C-H), 1385 (m, C-H), 1334 (s, SO_2), 1157 (s, SO_2); δ_H (300 MHz; $CDCl_3$) 7.81 (2H, br d, J_{ortho} 8.3, $H_{2',6'}$), 7.45 (1H, br s, NH), 7.27 (2H, br d, J_{ortho} 8.3, $H_{3',5'}$), 2.39 (3H, s, CH_3), 2.29 (2H, m, CH_2), 2.14 (2H, m, CH_2), 1.55 (4H, br m, CH_2), 1.43-1.09 (12H, m, CH_2); δ_C (75 MHz; $CDCl_3$) 161.5 (C=N), 143.8 ($C_{1'}$), 135.5 ($C_{4'}$), 129.4, 128.1 ($C_{2',3',5',6'}$), 36.0, 30.2, 27.1, 25.5, 25.3, 24.8, 24.1, 23.5, 23.3, 22.4 (CH_2), 21.5 (CH_3); *m/z* (EI) 337 (79%, M+1), 181 (100%, $C_{11}H_{20}NN^+H$), 157 (11%), 151 (37%, $[C_{11}H_{19}]^+$), 91 (70%, $[C_7H_7]^+$), 81 (30%, $[C_6H_9]^+$), 65 (26%, $[C_5H_5]^+$), 55 (46%, $[C_4H_7]^+$).

Preparation of Cyclododecanone-(4-methylbenzenesulfonyl)hydrazone 239[130]

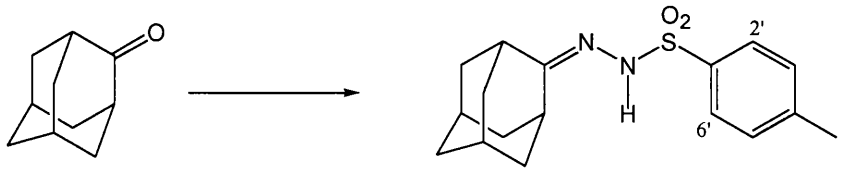


239

Reaction of cyclododecanone (1.50 g, 8.23 mmol, 1 equiv.) with *p*-tolylsulfonylhydrazine (1.53 g, 8.23 mmol, 1 equiv.) in methanol (7 ml) using the general procedure, afforded the *hydrazone* **239** (1.78 g, 5.08 mmol, 62%) as rods, m.p. 156.5-158°C (decomp.) (from methanol) (lit.,[191] 157-158°C).

υ_{max} (KBr disc)/cm^{-1} 3219 (s, N-H), 2941 (s, C-H), 2867 (s, C-H), 1645 (w, C=N), 1594 (m, C=C), 1492 (w, C-H), 1469 (s, C-H), 1437 (m, C-H), 1409 (s, C-H), 1376 (m, C-H), 1339 (s, SO_2), 1163 (s, SO_2); δ_H (300 MHz; $CDCl_3$) 7.80 (2H, d, J_{ortho} 8.3, $H_{2',6'}$), 7.26 (2H, d, J_{ortho} 8.3, $H_{3',5'}$), 2.43 (2H, m, CH_2), 2.38 (3H, s, CH_3), 2.15 (4H, m, CH_2), 1.77-0.81 (16H, m, CH_2); δ_C (75 MHz; $CDCl_3$) 159.4 (C=N), 143.9 ($C_{1'}$), 135.4 ($C_{4'}$), 129.5, 128.2 ($C_{2',3',5',6'}$), 31.4, 28.8, 26.0, 25.9, 24.7, 24.2, 23.8, 23.2, 22.9, 22.7, 21.7 (CH_2), 21.5 (CH_3); *m/z* (EI) 351 (100%, M+1), 195 (90%, $C_{12}H_{22}NN^+H$), 165 (11%, $[C_{12}H_{21}]^+$), 157 (5%), 91 (39%, $[C_7H_7]^+$), 81 (11%, $[C_6H_9]^+$), 65 (10%, $[C_5H_5]^+$), 55 (16%, $[C_4H_7]^+$).

Preparation of 2-Adamantanone-(4-methylbenzenesulfonyl)hydrazone 246[130]



246

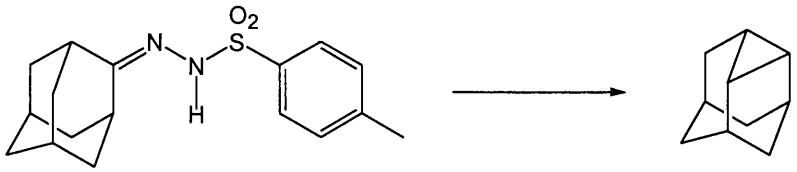
Reaction of 2-adamantanone (5.00 g, 33.3 mmol, 1 equiv.) with *p*-tolylsulfonylhydrazine (6.20 g, 33.3 mmol, 1 equiv.) in methanol (29 ml) using the general procedure, afforded the *hydrazone* **246** (7.36 g, 23.1 mmol, 69%) as rods, m.p. 174.5-176°C (decomp.) (from methanol) (lit.,[192] 174-175.5°C).

υ_{max} (KBr disc)/cm^{-1} 3221 (s, N-H), 2921 (s, C-H), 2845 (s, C-H), 1636 (s, C=N), 1594 (s, C=C), 1491 (m, C-H), 1444 (s, C-H), 1402 (s, C-H), 1318 (s, SO_2), 1159 (s, SO_2); δ_H (300 MHz; $CDCl_3$) 7.80 (2H, br d, J_{ortho} 8.2, $H_{2',6'}$), 7.26 (2H, br d, J_{ortho} 8.2, $H_{3',5'}$), 3.04 (1H, br s, CH), 2.59 (1H, br s, CH), 2.38 (3H, s, CH_3), 1.91-1.66 (12H, m, CH and CH_2); δ_C (75 MHz; $CDCl_3$) 172.2 (C=N), 143.8 ($C_{1'}$), 135.4 ($C_{4'}$), 129.5, 128.0 ($C_{2',3',5',6'}$), 39.4 (2 x CH), 39.0, 37.8, 36.1 (5 x CH_2), 31.7, 27.5 (CH), 21.5 (CH_3); *m/z* (EI) 319 (19%, M+1), 163 (100%, $C_{10}H_{14}NN^+H$), 157 (1%), 134 (15%, $C_{10}H_{14}$), 133 (1%, $[C_{10}H_{13}]^+$), 91 (70%, $[C_7H_7]^+$), 79 (25%, $[C_6H_7]^+$), 65 (24%, $[C_5H_5]^+$), 55 (6%, $[C_4H_7]^+$).

General Procedure for the Pyrolysis of Tosylhydrazones 236-239 and 247

n-Butyllithium (2.4 M solution in hexane, 1.12 equiv.) was added dropwise to a stirred suspension of ketone tosylhydrazone salt (1 equiv.) in dry ether (7 mlg^{-1} of ketone hydrazone salt) under nitrogen at r.t. The solution was stirred for a further 30 min and the flask was connected to the vacuum. The solvents were removed *in vacuo* for 1 h at r.t. to give a white-orange precitipate. The flask was then connected to a pre-weighed trap placed in a liquid nitrogen bath and the reaction flask was heated *in vacuo* using a Bunsen burner for 5 min and the *cycloalkene* **240**, **244**, **251** or **245** and/or *cyclopropane* **241** or **247** was collected as a colourless oil. The whole system was allowed to cool to r.t. under nitrogen, the collection flask was immediately weighed and the products were analysed by GC and NMR.[131c]

Preparation of 2,4-Dehydroadamantane 247

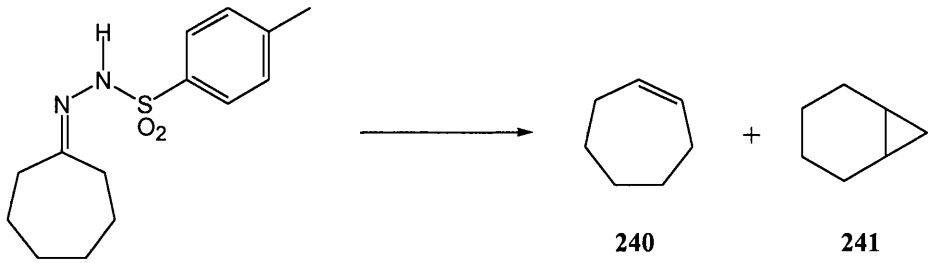


247

The *title compound* was prepared by the modification of the literature method.[131c] Reaction of 2-adamantanone-(4-methylbenzenesulfonyl)hydrazone **246** (2.00 g, 6.28 mmol, 1 equiv.) with *n*-butyllithium (3.12 ml of a 2.25 M solution in hexane, 7.03 mmol, 1.12 equiv.) in dry ether (14 ml) using the general procedure, afforded the *cyclopropane* **247** (637 mg, 4.75 mmol, 76%) as a colourless oil which crystallised on standing and whose spectral properties were in accord with literature,[131c] m.p. 198-200°C (from methanol) (lit.,[193] 198-201°C).

υ_{max} (KBr disc)/cm^{-1} 3029 (s, C-H), 2907 (s, C-H), 2845 (s, C-H), 1442 (s, C-H), 1032 (w, C-H), 830 (w, C-H); δ_H (300 MHz; $CDCl_3$) 2.36-0.83 (14H, m, CH and CH_2); δ_C (75 MHz; $CDCl_3$) 35.1, 33.7, 32.5, 32.0, 29.1, 27.3, 25.7, 24.4, 15.7, 14.5 (CH and CH_2); *m/z* (EI) 135 (100%, M+1), 119 (9%, M-CH_3), 105 (12%, M-C_2H_5), 91 (39%, $[C_7H_7]^+$), 79 (53%, $[C_6H_7]^+$), 67 (28%, $[C_5H_7]^+$), 56 (14%, $[C_4H_8]^+$).

Preparation of Cycloheptene 240 and Bicyclo[4.1.0]heptane 241

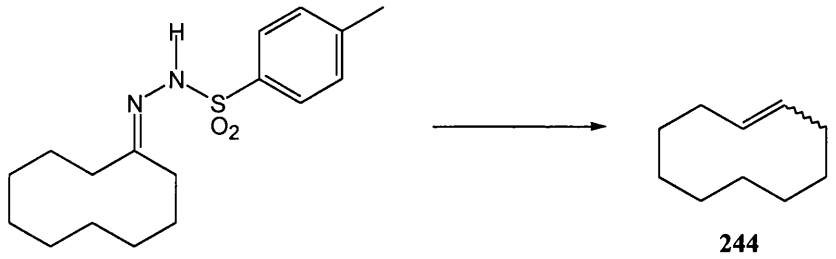


240 **241**

Reaction of cycloheptanone-(4-methylbenzenesulfonyl)hydrazone **236** (1.00 g, 3.57 mmol, 1 equiv.) with *n*-butyllithium (1.67 ml of a 2.4 M solution in hexane, 4.00 mmol, 1.12 equiv.) in dry ether (7 ml) using the general procedure, afforded a mixture of cycloheptene[194] **240** and bicyclo[4.1.0]heptane[195] **241** (208 mg, 2.16 mmol, 61%, 87:13 as determined by GC and NMR) as a colourless oil, whose spectral properties were both in accord with literature.[194,195]

υ_{max} (NaCl; thin film)/cm^{-1} 3009 (m, C-H), 2919 (s, C-H), 2845 (m, C-H), 1652 (w, C=C), 1443 (m, C-H); δ_H (300 MHz; $CDCl_3$) *cycloheptene* **240**: 5.76 (2H, m, 2 x CH), 2.09 (4H, m, CH_2), 1.70 (2H, m, CH_2), 1.48 (4H, m, CH_2); *bicyclo[4.1.0]heptane* **241**: 1.70 (4H, m, CH_2), 1.18 (4H, m, CH_2), 0.82 (2H, m, CH), 0.49 (1H, dt, *J* 4.3 and 8.9, CH_2), -0.03 (1H, q, *J* 5.2, CH_2); δ_C (75 MHz; $CDCl_3$) *cycloheptene* **240**: 132.3 (C=C), 32.0, 29.1, 27.4 (5 x CH_2); *bicyclo[4.1.0]heptane* **241**: 25.6 (2 x CH_2), 21.3 (2 x CH_2), 10.2 (CH_2), 9.3 (2 x CH); *m/z* (EI) 97 (13%, M+1), 96 (18%, M^+), 81 (92%, $[C_6H_9]^+$), 67 (88%, $[C_5H_7]^+$), 55 (33%, $[C_4H_7]^+$).

Preparation of *trans*- and *cis*-Cyclodecene 244

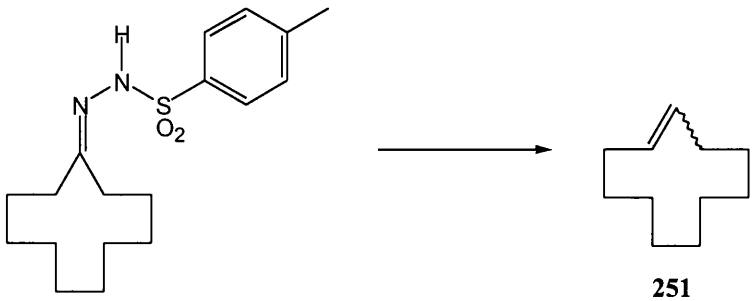


244

Reaction of cyclodecanone-(4-methylbenzenesulfonyl)hydrazone **237** (1.00 g, 3.10 mmol, 1 equiv.) with *n*-butyllithium (1.45 ml of a 2.4 M solution in hexane, 3.48 mmol, 1.12 equiv.) in dry ether (7 ml) using the general procedure, afforded a mixture of *E*- and *Z*-cyclodecene **244** (232 mg, 1.68 mmol, 54%, *E*/*Z*: 1.1:1 as determined by GC and NMR) as a colourless oil, whose spectral properties were in accord with literature.[196]

υ_{max} (NaCl; thin film)/cm^{-1} 2922 (s, C-H), 2855 (s, C-H), 1656 (w, C=C), 1470 (m, C-H), 1452 (m, C-H), 1441 (m, C-H); δ_H (300 MHz; $CDCl_3$) *trans-cyclodecene*: 5.46 (2H, m, 2 x CH), 2.20 (4H, m, CH_2), 1.54-1.23 (12H, m, CH_2); *cis-cyclodecene*: 5.36 (2H, m, CH), 2.20 (4H, m, CH_2), 1.54-1.23 (12H, m, CH_2); δ_C (75 MHz; $CDCl_3$) *trans-cyclodecene*: 129.9 (C=C), 26.9, 26.1, 25.1, 20.9 (8 x CH_2); *cis-cyclodecene*: 131.2 (C=C), 32.0, 26.8, 26.2, 25.0 (8 x CH_2); *m/z* (EI) 138 (84%, M^+), 110 (39%, M-C_2H_4), 95 (99%, $[C_7H_{11}]^+$), 81 (100%, $[C_6H_9]^+$), 67 (100%, $[C_5H_7]^+$), 55 (100%, $[C_4H_7]^+$).

Preparation of *trans*- and *cis*-Cycloundecene 251

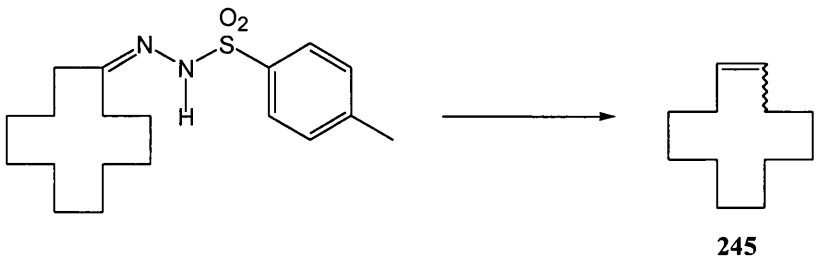


251

Reaction of cycloundecanone-(4-methylbenzenesulfonyl)hydrazone **238** (1.00 g, 2.97 mmol, 1 equiv.) with *n*-butyllithium (1.39 ml of a 2.4 M solution in hexane, 3.34 mmol, 1.12 equiv.) in dry ether (7 ml) using the general procedure, afforded a mixture of *E*- and *Z*-cycloundecene **251** (341 mg, 2.24 mmol, 75%, *E*:*Z*: 2.3:1 as determined by GC and NMR) as a colourless oil, whose spectral properties were in accord with literature.[197]

υ_{max} (NaCl; thin film)/cm^{-1} 2931 (s, C-H), 2846 (s, C-H), 1656 (w, C=C), 1457 (m, C-H), 1436 (m, C-H); δ_H (300 MHz; $CDCl_3$) *trans-cycloundecene*: 5.42 (2H, m, CH), 2.03 (4H, m, CH_2), 1.47-1.24 (14H, m, CH_2); *cis-cycloundecene*: 5.31 (2H, m, CH), 2.18 (4H, m, CH_2), 1.47-1.24 (14H, m, CH_2); δ_C (75 MHz; $CDCl_3$) *trans-cycloundecene*: 131.2 (C=C), 34.1, 26.9, 25.9, 25.8 (9 x CH_2); *cis-cycloundecene*: 130.9 (C=C), 27.5, 26.5, 26.3, 26.0 (9 x CH_2); *m/z* (EI) 152 (6%, M^+), 95 (50%, $[C_7H_{11}]^+$), 81 (50%, $[C_6H_9]^+$), 69 (77%, $[C_5H_9]^+$), 55 (100%, $[C_4H_7]^+$).

Preparation of *trans*- and *cis*-Cyclododecene 245



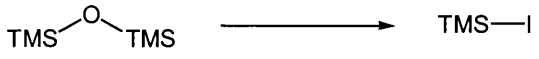
245

Reaction of cyclododecanone-(4-methylbenzenesulfonyl)hydrazone **239** (1.00 g, 2.85 mmol, 1 equiv.) with *n*-butyllithium (1.33 ml of a 2.4 M solution in hexane, 3.19 mmol, 1.12 equiv.) in dry ether (7 ml) using the general procedure, afforded a mixture

of *E*- and *Z*-cyclododecene **245** (385 mg, 2.32 mmol, 81%, *E/Z*: 2.4:1 as determined by GC and NMR) as a colourless oil, whose spectral properties were in accord with literature.[198]

υ_{max} (NaCl; thin film)/cm^{-1} 2924 (s, C-H), 2855 (s, C-H), 1657 (w, C=C), 1464 (m, C-H), 1439 (m, C-H); δ_H (300 MHz; $CDCl_3$) *trans-cyclododecene*: 5.36 (2H, m, CH), 2.08 (4H, m, CH_2), 1.47-1.25 (16H, m, CH_2); *cis-cyclododecene*: 5.30 (2H, m, CH), 2.08 (4H, m, CH_2), 1.47-1.25 (16H, m, CH_2); δ_C (75 MHz; $CDCl_3$) *trans-cyclododecene*: 131.4 (C=C), 32.1, 26.3, 25.6, 25.0, 24.7 (10 x CH_2); *cis-cyclododecene*: 130.4 (C=C), 27.0, 24.4, 24.0, 22.1 (10 x CH_2); *m/z* (EI) 166 (44%, M^+), 109 (24%, $[C_8H_{13}]^+$), 95 (50%, $[C_7H_{11}]^+$), 81 (50%, $[C_6H_9]^+$), 69 (77%, $[C_5H_9]^+$), 67 (54%, $[C_5H_7]^+$), 55 (100%, $[C_4H_7]^+$).

Preparation of Iodotrimethylsilane[138a]



To a dry two-necked flask equipped with a glass addition funnel for solids was added aluminium powder (5.67 g, 210 mmol, 2.1 equiv.), followed by hexamethyldisiloxane (21.3 ml, 100 mmol, 1 equiv.) under nitrogen at r.t. The mixture was stirred, warmed to 60°C and then crushed iodine (50.8 g, 200 mmol, 2 equiv.) powder was added slowly through the addition funnel over 1 h. The resulting mixture was heated at reflux for 3 h and then distilled at atmospheric pressure to afford iodotrimethylsilane (34.0 g, 170 mmol, 85%) as a clear, colourless oil, b.p. 106°C/760 mmHg, lit.,[138a] 106-109°C/760 mmHg. The reagent was stored in a flask containing a small amount of copper wire under nitrogen at 5°C.

υ_{max} (NaCl; thin film)/cm^{-1} 2952 (s, C-H), 2891 (w, C-H), 1447 (w, C-H), 1406 (w, C-H), 1253 (s, Si-C), 1055 (s, Si-C), 841 (s, Si-C); δ_H (300 MHz; $CDCl_3$) 0.77 (3H, s, -$Si(CH_3)_3$); δ_C (75 MHz; $CDCl_3$) 5.6 (-$Si(CH_3)_3$).

General procedures for the Deoxygenation of Ketones using Zinc Carbenoids-Methods A-C

Method A: Deoxygenation of Ketones using Zinc Amalgam[135] and Chlorotrimethylsilane

A solution of chlorotrimethylsilane (1.10 ml, 8.65 mmol, 5 equiv.) in dry THF (12 ml) [ether (12 ml) in the case of 1,5-diphenylpentan-3-one] was added to flame dried zinc amalgam (1.13 g, 17.3 mmol, 10 equiv.) under nitrogen at r.t. The resultant vigorously stirred suspension was heated to reflux and after 5 min a solution of ketone (1.73 mmol, 1 equiv.) in dry THF (8 ml) [ether (8 ml) in the case of 1,5-diphenylpentan-3-one] was added dropwise over a further 5 min. The reaction mixture was stirred at reflux for 120 h and then cooled to ambient temperature. The reaction was quenched by addition of saturated aqueous sodium bicarbonate solution (24 ml), and the mixture was stirred for 5 min. The resultant suspension was filtered through Celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 30 ml) and the combined organic layers washed with brine (15 ml), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to a light yellow oil which was absorbed onto silica. Column chromatography (petrol [40-60°C]) gave an inseparable mixture of *cis* and *trans* alkenes as a colourless oil (Table 20).

Method B: Deoxygenation of Ketones using Zinc Dust[190] and Chlorotrimethylsilane in the Presence of an Additional Proton Source

Methanol (46.2 μl, 1.14 mmol, 0.5 equiv.) was added dropwise to a solution of chlorotrimethylsilane (1.45 ml, 11.4 mmol, 5 equiv.) in dry ether (6 ml). The resultant solution was added to flame dried zinc dust (1.48 g, 22.7 mmol, 10 equiv.) in dry ether (6 ml), under nitrogen at r.t. The vigorously stirred suspension was heated to reflux and after 5 min a solution of ketone (2.27 mmol, 1 equiv.) in dry ether (8 ml) was added dropwise over a further 5 min. Aliquots of methanol (46.2 μl, 1.14 mmol, 0.5 equiv.) were added dropwise after 48 h [in total 4 aliquots (2 aliquots for cycloheptanone)]. The reaction mixture was stirred at reflux for 192 h (96 h for cycloheptanone) and then cooled to ambient temperature. The reaction was quenched by addition of saturated aqueous sodium bicarbonate solution (24 ml), and the mixture

was stirred for 5 min. The resultant suspension was filtered through Celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to a light yellow oil which was absorbed onto silica. Column chromatography (petrol [40-60°C]) gave an inseparable mixture of *cis* and *trans* cycloalkenes as a colourless oil [in the case of cycloheptanone, the products were isolated by distillation] (Table 20).

Method C: Deoxygenation of Ketones using Zinc Amalgam[135] and Iodotrimethylsilane

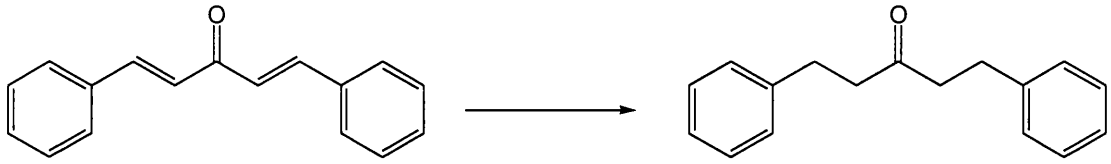
A solution of iodotrimethylsilane (985 μl, 6.92 mmol, 4 equiv.) in dry DCM (12 ml) was added to flame dried zinc dust (1.13 g, 17.3 mmol, 10 equiv.), under nitrogen at r.t. The resultant vigorously stirred suspension was heated to reflux, and after 5 min a solution of ketone (1.73 mmol, 1 equiv.) in dry DCM (8 ml) was added dropwise over a further 5 min. The reaction mixture was stirred at reflux for 48 h and then cooled to ambient temperature. The reaction was then quenched by addition of saturated aqueous sodium bicarbonate solution (24 ml), and the mixture was stirred for 5 min. The resultant suspension was filtered through Celite, and the filter cake washed with DCM (40 ml). The aqueous layer was extracted with DCM (2 x 30 ml), and the combined organic layers were washed with brine (15 ml), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to a dark red oil which was absorbed onto silica gel. Column chromatography (petrol [b.p. 40-60°C]) gave an inseparable mixture of *cis* and *trans* alkenes as a colourless oil [in the case of cycloheptanone, the products were isolated by distillation] (Table 20).

Table 20: Deoxygenation of ketones using Methods A-C:

Ketone	Products	Yield (%) and ratio of products		
		Method A	Method B	Method C
cycloheptanone	**240**:**241**[a]	-	49%, 13.3:1[d]	53%, 9:1[d]
cyclodecanone	**244**[a]	trace[b]	25%, 1:3.2[c]	31%, 1:3.0[c]
cycloundecanone	**251**[a]	trace[b]	22%, 1:1.1[c]	29%, 1:1.2[c]
cyclododecanone	**245**[a]	trace[b]	34%, 1:1.2[c]	38%, 1:1.1[c]
diphenyl ketone	**254**	9%, 1:1.5[c]	-	21%, 1:3.3[c]

[a] Mixture of products spectroscopically identical to material already prepared. [b] Detected by GC and ratio of *E*/*Z* of alkenes not determined. [c] *E*/*Z* ratio of alkenes determined by GC and NMR. [d] Ratio of products determined by GC and NMR.

Preparation of 1,5-Diphenylpentan-3-one 253[133]

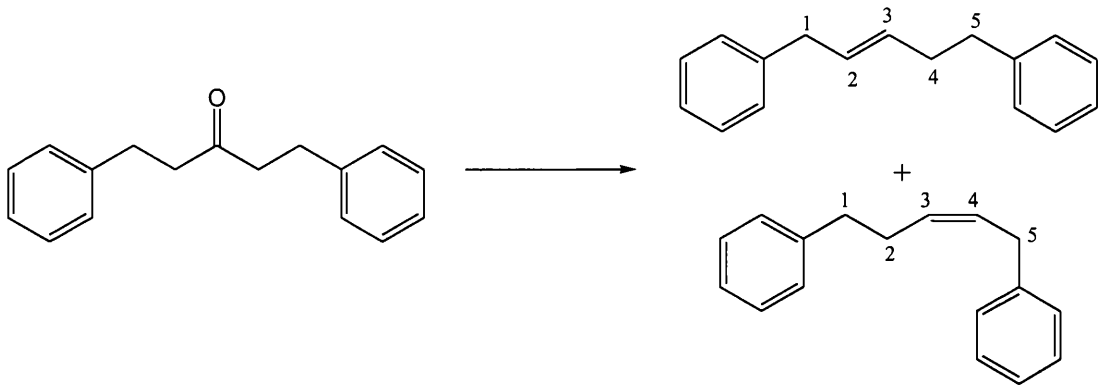


253

Dibenzylidene acetone (15.4 g, 65.9 mmol, 1 equiv.) was dissolved in EtOAc (140 ml), and the flask was flushed with argon. The catalyst 10% palladium on charcoal (2.00 g, 13%wt) was added and the reaction mixture was hydrogenated at slight positive pressure for 9 h with vigorous stirring. The flask was then flushed with argon, the suspension filtered through a pad of Celite, and concentrated *in vacuo* to a light yellow oil. The crude product was purified by column chromatography using 10% ether in light petroleum [40-60°C] which gave the *ketone* **253** (11.1 g, 46.6 mmol, 71%) as a colourless oil, R_f= 0.27 (silica, 10% ether in light petroleum [40-60°C]).

υ_{max} (NaCl; thin film)/cm^{-1} 3081 (w, C-H), 3060 (w, C-H), 3023 (m, C-H), 2929 (m, C-H), 1706 (s, C=O), 1598 (m, C=C), 1496 (m, C-H), 1453 (m, C-H); δ_H (300 MHz; $CDCl_3$) 7.39-7.26 (10H, m, ArH), 2.99 (4H, t, *J* 7.8, 2 x CH_2CO), 2.83 (4H, t, *J* 7.8, 2 x CH_2Ar); δ_C (75 MHz; $CDCl_3$) 209.0 (C=O), 140.9, 128.4, 128.2, 126.0 (12 x $C_{Ar}H$), 44.4, 29.6 (4 x CH_2); *m/z* (EI) 238 (40%, M^+), 91 (100%, $[C_7H_7]^+$).

Preparation of *trans*- and *cis*-1,5-Diphenylpent-2-ene 254

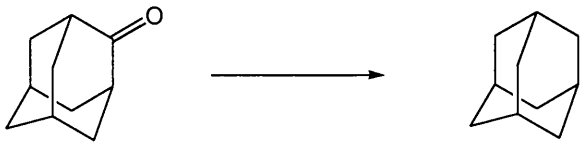


254

The crude product obtained from 1,5-diphenylpentan-3-one **253** (412 mg, 1.73 mmol, 1 equiv.), zinc amalgam, chlorotrimethylsilane in ether [120 h reflux] using method A, was purified by flash column chromatography using light petroleum [40-60°C]) to give in order of elution: an inseparable mixture of *cis* and *trans* 1,5-diphenylpent-2-ene **254** (32.0 mg, 0.15 mmol, 9%, *cis*:*trans*: 1.5:1 as determined by GC and NMR) [Table 20] as a colourless oil, whose spectral properties were in accord with literature,[199] R_f= 0.55 (silica, light petroleum [40-60°C]) and recovered 1,5-diphenylpentan-3-one **253** (170 mg, 0.71 mmol, 41%).

υ_{max} (NaCl; thin film)/cm^{-1} 3080 (w, C-H), 3026 (m, C-H), 2919 (s, C-H), 2829 (s, C-H), 1603 (m, C=C), 1584 (w, C=C), 1495 (m, C-H), 1453 (m, C-H), 1446 (w, C-H); δ_H (300 MHz; $CDCl_3$) *trans 1,5-diphenylpent-2-ene*: 7.29-7.07 (10H, m, ArH), 5.55 (2H, m, $H_{2,3}$), 3.30 (2H, d, *J* 4.6, H_1), 2.68 (2H, t, *J* 8.8, H_5), 2.58 (2H, m, H_4); *cis 1,5-diphenylpent-2-ene*: 7.29-7.07 (10H, m, ArH), 5.55 (2H, m, $H_{3,4}$, masked by other isomer), 3.32 (2H, d, *J* 4.3, H_5), 2.69 (2H, t, *J* 8.8, H_1), 2.33 (2H, m, H_2); *m/z* (EI) 222 (35%, M^+), 131 (58%, M-$PhCH_2$), 91 (100%, $[C_7H_7]^+$).

Preparation of Adamantane 260

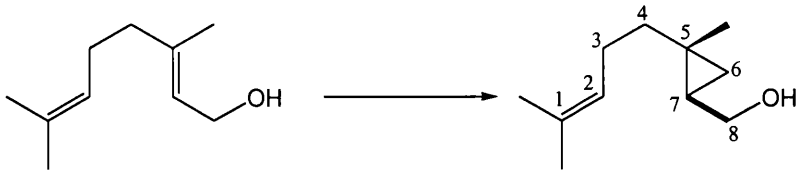


260

The crude product obtained from 2-adamantanone (305 mg, 2.27 mmol, 1 equiv.), zinc amalgam, chlorotrimethylsilane and methanol [2 x (46.2 μl, 1.14 mmol, 0.5 equiv.)] in ether [96 h reflux] using method B, was purified by flash column chromatography using light petroleum [40-60°C]) to afford adamantane **260** (124 mg, 0.91 mmol, 40%) as a white crystalline solid, R_f= 0.30 (silica, light petroleum [40-60°C]), m.p. 209-210°C (subl.) (from methanol) (lit.,[200] 209-213°C).

υ_{max} (KBr disc)/cm^{-1} 2904 (s, C-H), 2838 (s, C-H), 1446 (s, C-H); δ_H (300 MHz; $CDCl_3$) 1.85 (4H, m, CH and CH_2), 1.74 (12H, m, CH and CH_2); δ_C (75 MHz; $CDCl_3$) 37.7, 28.3 (CH and CH_2); *m/z* (EI) 136 (100%, M^+), 121 (8%, M-CH_3), 107 (8%, M-C_2H_5), 93 (45%, $[C_7H_9]^+$), 79 (38%, $[C_6H_7]^+$), 67 (17%, $[C_5H_7]^+$), 56 (8%, $[C_4H_8]^+$).

Preparation of *E*-1-(Hydroxymethyl)-2-methyl-2,4-methyl-3-pentenyl cyclopropane 91[30]



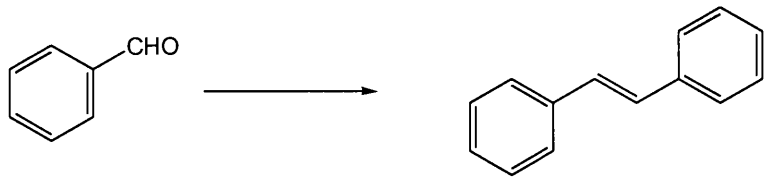
91

To a dry DCM/DMF mixture (45 ml, 9:1) containing tetrabutylammonium bromide (420 mg, 1.30 mmol, 0.19 equiv.) and tetrabutylammonium iodide (180 mg, 0.50 mmol, 0.07 equiv.) in an electrochemical cell, was added 1,2-dibromoethane (1.72 ml, 20.0 mmol, 2.86 equiv.) under a constant flow of nitrogen at r.t. The anode (zinc wool) was connected to the positive pole of the power supply, and the cathode (carbon rod) to the negative pole. The current intensity was set at 300 mA for 2 h. After effervescence had ceased, geraniol (1.21 ml, 7.00 mmol, 1 equiv.) was added to the reaction flask followed by dibromomethane (1.28 ml, 18.2 mmol, 2.6 equiv.). The

electrolysis was performed at 40°C for 5 h with a constant current of 300 mA, and was monitored by GC. The reaction mixture was cooled to ambient temperature, filtered through Celite and washed with ether (3 x 50 ml). This was hydrolysed by saturated aqueous ammonium chloride solution (75 ml) and extracted with ether (3 x 50 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to a light yellow oil. The crude product was purified by flash chromatography using 20% ether in light petroleum [40-60°C] to afford the *cyclopropane* **91** (973 mg, 5.78 mmol, 83%) as a colourless oil, R_f= 0.14 (silica, 20% ether in light petroleum [40-60°C]).

υ_{max} (NaCl; thin film)/cm^{-1} 3356 (b, O-H), 2968 (m, C-H), 2919 (s, C-H), 1652 (w, C=C), 1454 (m, C-H), 1406 (w, C-H), 1088 (w, C-O), 1028 (s, C-O); δ_H (400 MHz; $CDCl_3$) 5.02 (1H, m, H_2), 3.60 (1H, dd, *J* 11.4 and 6.7, H_8), 3.41 (1H, dd, *J* 11.3 and 8.4, H_8), 2.28 (1H, br s, OH), 1.98 (2H, m, H_3), 1.59 (3H, s, CH_3), 1.53 (3H, s, CH_3), 1.30 (1H, m, H_4), 1.06 (1H, m, H_4), 1.01 (3H, s, CH_3), 0.81 (1H, m, H_7), 0.41 (1H, dd, *J* 4.5 and 8.6, $H_{6\alpha}$), 0.03 (1H, t, *J* 4.9, $H_{6\beta}$); δ_C (75 MHz; $CDCl_3$) 130.9 (C_1), 124.5 (C_2), 63.4 (C_8), 41.0 (C_3), 26.0 (CH_3), 25.5 (CH_3), 25.3 (C_4), 19.7 (C_5), 17.5 (C_6), 17.4 (C_7), 16.9 (CH_3); *m/z* (EI) 167 (7%, M^+), 69 (100%).

Preparation of *trans*-Stilbene 217



217

To a dry DCM/DMF mixture (45 ml, 9:1) containing tetrabutylammonium bromide (420 mg, 1.30 mmol, 0.09 equiv.) and tetrabutylammonium iodide (180 mg, 0.50 mmol, 0.04 equiv.) in an electrochemical cell, was added 1,2-dibromoethane (1.72 ml, 20.0 mmol, 1.43 equiv.) under a constant flow of nitrogen at r.t. The anode (zinc wool) was connected to the positive pole of the power supply, and the cathode (carbon rod) to the negative pole. The current intensity was set at 300 mA for 2 h. After effervescence had ceased, 1,2-bis(chlorodimethylsilylethane) (3.32 g, 15.4 mmol, 1.1 equiv.) in dry DCM (5 ml) was then added to the reaction flask followed by the addition of benzaldehyde (1.42 ml, 14.0 mmol, 1 equiv.) over 5 min. The electrolysis

was performed at 40°C for 12 h with a constant current of 300 mA. The reaction mixture was cooled to ambient temperature, filtered through Celite, washed with ether (2 x 25 ml) and the solvent removed *in vacuo*. The residue was dissolved in acetonitrile (20 ml), and stirred with aqueous hydrofluoric acid (6 ml, 48%) for 2 h. The acid was neutralised with saturated aqueous sodium bicarbonate solution (30 ml), extracted with ether (3 x 30 ml), and the organic phase washed with water (2 x 25 ml). The combined ether extracts were dried ($MgSO_4$) and evaporated *in vacuo* to a brown solid. The crude product was chromatographed using light petroleum [40-60°C] to give *trans*-stilbene **217** (351 mg, 1.95 mmol, 28%) as white crystalline plates, R_f= 0.24 (silica, light petroleum [40-60°C]), m.p. 122-124°C (from ethanol) (lit.,[201] 124°C).

υ_{max} (KBr disc)/cm^{-1} 3056 (w, C-H), 3017 (w, C-H), 2924 (w, C-H), 2854 (w, C-H), 1598 (w, C=C), 1491 (m, C-H), 1460 (m, C-H); δ_H (300 MHz; $CDCl_3$) 7.52-7.22 (10H, m, 2 x –Ph), 7.10 (2H, s, 2 x –CH=); δ_C (75 MHz; $CDCl_3$) 137.4 (C), 128.8 (CH), 128.7 (CH), 127.6 (CH), 126.5 (CH); *m/z* (EI) 180 (100%, M^+), 165 (57%, M-CH_3).

Preparation of (*Z*)-1-Acetoxy-1,3-butadiene 266[154]

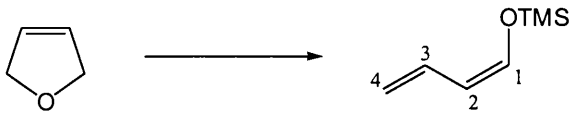
266

n-Butyllithium (34.3 ml of a 2.35 M solution in hexane, 80.6 mmol, 1.13 equiv.) was added to a stirred solution of redistilled 2,5-dihydrofuran (5.39 ml, 71.3 mmol, 1 equiv.) in dry THF (71.3 ml) under nitrogen at –65°C. The resultant yellow solution was warmed to –27°C and stirred for 2.5 h, recooled to –65°C, then quenched with acetic anhydride (61.9 ml, 656 mmol, 9.2 equiv.). This was warmed again to –27°C and stirred for a further 2 h, after which the reaction mixture was allowed to warm to r.t. and then poured into a cooled stirred mixture of pentane (475 ml), saturated aqueous sodium bicarbonate solution (150 ml) and stirred for 45 min. The layers were separated and the aqueous phase extracted with more pentane (2 x 250 ml). The combined organic phases were washed with water (500 ml), dried ($MgSO_4$) and the solvents removed by distillation. The crude product was distilled to give the

acetoxybutadiene **266** (5.05 g, 45.0 mmol, 63%) as a colourless oil, b.p. 53-55°C/32 mmHg (lit.,[154] 50-51°C/30 mmHg).

υ_{max} (NaCl; thin film)/cm^{-1} 3085 (w, C-H), 3053 (w, C-H), 2959 (w, C-H), 1759 (s, C=O), 1654 (m, C=C), 1597 (w, C=C), 1430 (w, C-H), 1372 (m, C-H), 1230 (s, C-O), 1043 (s, C-O); δ_H (300 MHz, $CDCl_3$) 7.02 (1H, d, *J* 6.9, H_1), 6.67 (1H, dt, *J* 17.2 and 10.9, H_3), 5.47 (1H, dd, *J* 10.9 and 6.2, H_2), 5.21 (1H, d, *J* 17.2, $H_{4\alpha}$), 5.07 (1H, d, *J* 10.6, $H_{4\beta}$); 2.14 (3H, s, AcO-); δ_C (75 MHz, $CDCl_3$) 167.3 (C=O), 134.1 (C_1), 128.8 (C_2), 117.6 (C_4), 113.3 (C_3), 20.5 (AcO-); *m/z* (EI) 112 (12%, M^+), 101 (100%), 83 (18%, M-CHO), 70 (14%), 57 (17%), 55 (21%, $[C_4H_7]^+$).

Preparation of (*Z*)-1-Trimethylsilyloxybuta-1,3-diene 267[154]



267

n-Butyllithium (36.8 ml of a 2.15 M solution in hexane, 79.2 mmol, 1.1 equiv.) was added to a stirred solution of redistilled 2,5-dihydrofuran (5.44 ml, 72.0 mmol, 1 equiv.) and tetramethylethylenediamine (12.0 ml, 79.2 mmol, 1.1 equiv.) in dry ether (60 ml) under nitrogen at –65°C. The solution was warmed to –27°C and stirred for 2.5 h, recooled to –65°C, then quenched with chlorotrimethylsilane (18.3 ml, 144 mmol, 2 equiv.). The resultant solution was stirred for 15 min at -65°C and then for 1 h at 5°C, after which, the solution was poured into pentane (475 ml). The organic layer was washed with aqueous sulfuric acid (2 x 500 ml, 2%) and then with aqueous sodium bicarbonate solution (2 x 500 ml, 3%), dried over 4Å molecular sieves, filtered and the solvents were removed by distillation. The crude product was fractionally distilled to give the *title compound* **267** (7.04 g, 49.5 mmol, 69%) as a colourless oil, b.p. 65-67°C/60 mmHg (lit.,[202] 71-73°C/65 mmHg).

υ_{max} (NaCl; thin film)/cm^{-1} 3082 (w, C-H), 3039 (w, C-H), 3014 (w, C-H), 2992 (w, C-H), 2953 (m, C-H), 2893 (w, C-H), 1644 (s, C=C), 1596 (m, C=C), 1438 (m, C-H), 1253 (s, Si-C), 1171 (m, C-O), 1077 (s, C-O), 866 (s, Si-O), 845 (s, Si-C); δ_H (300 MHz; $CDCl_3$) 6.72 (1H, dt, *J* 17.0 and 10.6, H_3), 6.15 (1H, d, *J* 5.7, H_1), 5.22 (1H, dd, *J* 10.9 and 5.8, H_2), 5.06 (1H, d, *J* 17.2, $H_{4\alpha}$), 4.88 (1H, d, *J* 10.4, $H_{4\beta}$), 0.20 (9H, s, $Si(CH_3)_3$); δ_C (75 MHz; $CDCl_3$) 139.7 (C_1), 129.8 (C_2), 113.2 (C_4), 111.9 (C_3), –0.6

($Si(CH_3)_3$); *m/z* (EI) 142 (1%, M^+), 129 (17%), 115 (5%, $M-C_2H_3$), 103 (19%), 75 (100%), 73 (96%), 55 (10%, $[C_4H_7]^+$).

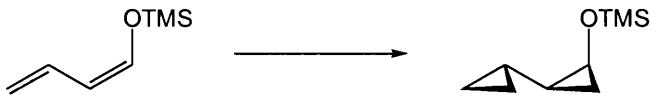
Preparation of 2-Cyclopropylethen-1-ol Acetate 268

268

To a cooled solution of diethylzinc (30.4 ml of a solution of 15%wt in hexane, 26.8 mmol, 2 equiv.) in dry ether (10 ml), was added diiodomethane (4.32 ml, 53.6 mmol, 4 equiv.) dropwise at 0°C. The mixture was stirred for a further 5 min at 0°C, and a solution of (*Z*)-1-acetoxy-1,3-butadiene **266** (1.50 g, 13.4 mmol, 1 equiv.) in dry ether (40 ml) was then added slowly over 5 min. The reaction mixture was allowed to warm to r.t. and then stirred for 48 h after which the reaction was quenched with saturated aqueous ammonium chloride solution (20 ml). The organic layer was separated, washed with ammonium chloride solution (20 ml), water (20 ml) and brine (20 ml). The organic layer was dried ($NaSO_4$), filtered and the solvents were removed by distillation. The product was then distilled twice to give the *cyclopropane* **268** (242 mg, 1.92 mmol, 14%) as a colourless oil, b.p. 63-65°C/50 mmHg (lit.,[150] 71-73°C/53 mmHg).

υ_{max} (NaCl; thin film)/cm^{-1} 3016 (m, C-H), 1752 (s, C=O), 1553 (m, C=C), 1435 (w, C-H), 1396 (m, C-H), 1200 (w, C-O), 1072 (m, C-O); δ_H (300 MHz; $CDCl_3$) 6.99 (1H, d, *J* 6.4, H_1), 4.29 (1H, dd, *J* 9.9 and 6.4, H_2), 2.14 (3H, s, AcO-), 1.79 (1H, m, $H_{1'}$), 0.70 (2H, m, $H_{2'\alpha,3'\alpha}$), 0.36 (2H, m, $H_{2'\beta,3'\beta}$); δ_C (75 MHz; $CDCl_3$) 169.0 (C=O), 133.7 (C_1), 118.3 (C_2), 20.5 (AcO-), 12.9 ($C_{1'}$), 6.9, 6.8 ($C_{2',3'}$); *m/z* (EI) 126 (22%, M^+), 125 (30%, M-1), 111 (19%, $M-CH_2$), 83 (17%, $M-CH_3O$).

Attempted Cyclopropanation of (*Z*)-1-Trimethylsilyloxybuta-1,3-diene 272



272

To a cooled solution of diethylzinc (30.4 ml of a solution of 15%wt in hexane, 26.8 mmol, 2 equiv.) in dry ether (10 ml), was added diiodomethane (4.32 ml, 53.6 mmol, 4 equiv.) dropwise under nitrogen at 0°C. The mixture was stirred for a further 5 min at 0°C, and a solution of (*Z*)-1-trimethylsilyloxybuta-1,3-diene **267** (1.91 g, 13.4 mmol, 1 equiv.) in dry ether (40 ml) was then added slowly over 5 min. The reaction mixture was allowed to warm to r.t. and stirred for 12 h after which the reaction was quenched with saturated aqueous ammonium chloride solution (20 ml). The organic layer was separated, washed with ammonium chloride solution (20 ml), water (20 ml) and brine (20 ml). The organic layer was dried ($NaSO_4$), filtered and the solvents were removed by distillation. The crude product was then distilled twice to give a complex mixture of compounds (560 mg) with no evidence for mono-cyclopropanated products. However, incomplete characterisation for the major product, a double cyclopropanated product **272** is shown below, b.p. 50-52°C/40 mmHg.

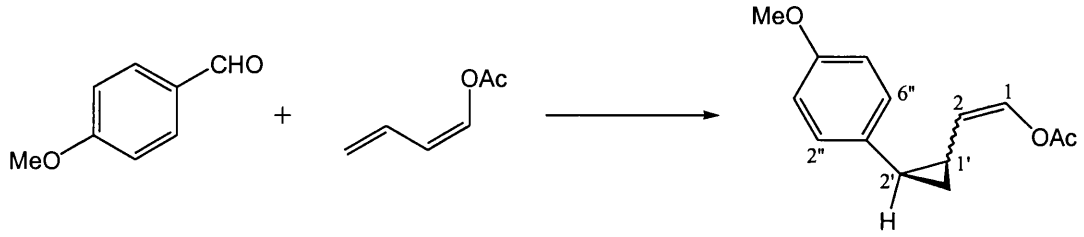
υ_{max} (NaCl; thin film)/cm^{-1} 3085 (w, C-H), 1641 (m, C=C), 1552 (m, C=C), 1412 (w, C-H), 1240 (m, Si-C), 1173 (m, C-O); δ_H (300 MHz; $CDCl_3$) 3.37 (1H, m, CH), 1.87-0.19 (8H, m, CH and CH_2), 0.14 ($Si(CH_3)_3$); δ_C (75 MHz; $CDCl_3$) 50.6 (CO), 20.8 (CH), 11.3 (CH_2), 8.1 (CH), 5.0 (CH_2), 3.6 (CH_2), -0.1 ($Si(CH_3)_3$).

General Method for the Cyclopropanation of Aldehydes and Ketones using (*Z*)-1-Acetoxy-1,3-butadiene 266

A solution of freshly distilled aldehyde/ketone (1.88 mmol, 1 equiv.) in dry ether (1.8 ml) was added slowly *via* a motorized syringe pump over 36 h to a vigorously stirred mixture of flame dried zinc amalgam (1.23 g, 18.8 mmol, 10 equiv.), dry ether (2 ml), (*Z*)-1-acetoxy-1,3-butadiene **266** (422 mg, 3.76 mmol, 2 equiv.) and 1,2-bis(chlorodimethylsilyl)ethane (2.20 ml of a 1.28 M solution in ether, 2.82 mmol, 1.5 equiv.) under nitrogen at reflux. The cooled mixture was filtered through Celite and the separated zinc was washed with ether (50 ml). The ethereal solution was washed

with saturated aqueous sodium bicarbonate solution (2 x 40 ml) and the aqueous layer extracted with ether (2 x 40 ml). The combined organic phase was washed with brine (30 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified twice by flash chromatography (silica, ether (0-2/5/10%)-light petroleum [40-60°C] to give the *cyclopropanes* **277-280** and **286-288**.

Preparation of *cis* and *trans* (*Z*)-2-[2-(4-Methoxyphenyl)cyclopropyl]ethen-1-ol Acetate 277



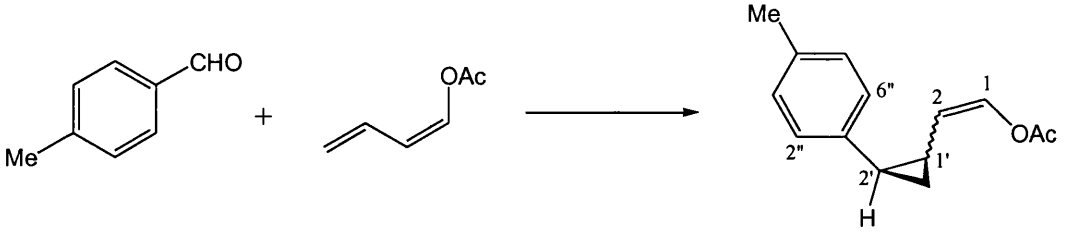
277

Using the general procedure, the crude product obtained from *p*-methoxybenzaldehyde (229 μl, 1.88 mmol, 1 equiv.), *Z*-acetoxybutadiene **266**, zinc amalgam and 1,2-bis(chlorodimethylsilyl)ethane was purified twice by flash column chromatography (silica, ether (0-10%)-light petroleum [40-60°C]) to give an inseparable diastereomeric mixture of *cis* and *trans* *Z*-2-[2-(4-methoxyphenyl)cyclopropyl]ethen-1-ol acetate **277** (252 mg, 1.08 mmol, 58%, *cis/trans*: 6.4:1 as determined by NMR) as a colourless oil, R_f= 0.22 (silica, 10% ether in light petroleum [40-60°C]).

υ_{max} (NaCl; thin film)/cm^{-1} 2989 (m, C-H), 2946 (m, C-H), 2837 (m, C-H), 1749 (s, C=O), 1608 (m, C=C), 1510 (s, C-H), 1365 (m, C-H), 1247 (s, C-O), 1229 (s, C-O); δ_H (500 MHz, $CDCl_3$) *cis* isomer: 7.11 (2H, d, J_{ortho} 8.5, $H_{2",6"}$), 6.96 (1H, d, *J* 6.5, H_1), 6.81 (2H, d, J_{ortho} 8.5, $H_{3",5"}$), 4.13 (1H, dd, *J* 10.1 and 6.5, H_2), 3.77 (3H, s, -OCH_3), 2.34 (1H, dt, *J* 6.5 and 8.4, $H_{2'}$), 2.16 (3H, s, AcO-), 2.14 (1H, m, $H_{1'}$), 1.28 (1H, dt, *J* 5.1 and 8.4, $H_{3'\alpha}$), 0.91 (1H, dt, *J* 5.3 and 6.5 $H_{3'\beta}$); *trans* isomer: 7.06 (1H, d, *J* 6.4, H_1), 7.02 (2H, d, J_{ortho} 8.8, $H_{2",6"}$), 6.81 (2H, d, J_{ortho} 8.8, $H_{3",5"}$), 4.46 (1H, dd, *J* 9.4 and 6.4, H_2), 3.78 (3H, s, -OCH_3), 2.12 (3H, s, AcO-), 1.93 (1H, m, $H_{1'}$), 1.91 (1H, dt, *J* 6.0 and 8.8, $H_{2'}$), 1.19 (1H, ddd, *J* 5.0, 6.0 and 8.6, $H_{3'\alpha}$), 1.00 (1H, ddd, *J* 5.0, 5.6 and 8.8, $H_{3'\beta}$); δ_C (126 MHz; $CDCl_3$) *cis* isomer: 168.0 (C=O), 158.0 ($C_{4"}$), 134.5 (C_1), 130.4 ($C_{1"}$), 130.1 ($C_{2",6"}$), 113.8 (C_2), 113.5 ($C_{3",5"}$), 55.2 (-OCH_3), 22.2

($C_{2'}$), 20.7 (AcO-), 14.8 ($C_{1'}$), 12.2 ($C_{3'}$); *trans* isomer: 168.0 (C=O), 157.8 ($C_{4''}$), 133.9 ($C_{1''}$), 133.7 (C_1), 126.7 ($C_{2'',6''}$), 116.8 (C_2), 113.8 ($C_{3'',5''}$), 55.3 (-OCH_3), 24.3 ($C_{2'}$), 20.7 (AcO-), 19.5 ($C_{1'}$), 16.4 ($C_{3'}$); *m/z* (EI) 232 (40%, M^+), 190 (56%, M-CH_2CO), 172 (100%, M-CH_3CO_2H), 159 (47%, M-$C_3H_5O_2$), 147 (51%, M-$C_4H_5O_2$), 134 (76%), 128 (35%), 121 (100%, $[C_8H_9O]^+$), 115 (44%), 108 (49%, $[C_6H_5]^+OCH_3$), 103 (15%), 91 (62%, $[C_7H_7]^+$), 77 (53%, $[C_6H_5]^+$), 65 (28%, $[C_5H_5]^+$), 57 (26%); (Found: M^+, 232.1099. $C_{14}H_{16}O_3$ requires *M*, 232.1099).

Preparation of *cis* and *trans* (*Z*)-2-[2-(4-Methylphenyl)cyclopropyl]ethen-1-ol Acetate 278



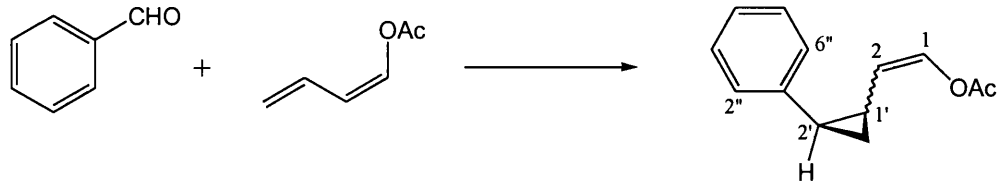
278

Using the general procedure, the crude product obtained from *p*-methylbenzaldehyde (222 µl, 1.88 mmol, 1 equiv.), *Z*-acetoxybutadiene **266**, zinc amalgam and 1,2-bis(chlorodimethylsilyl)ethane was purified twice by flash column chromatography (silica, ether (0-5%)-light petroleum [40-60°C]) to give an inseparable diastereomeric mixture of *cis* and *trans Z*-2-[2-(4-methylphenyl)cyclopropyl]ethen-1-ol acetate **278** (177 mg, 0.82 mmol, 44%, *cis/trans*: 4.6:1 as determined by NMR) as a colourless oil, R_f= 0.21 (silica, 5% ether in light petroleum [40-60°C]).

υ_{max} (NaCl; thin film)/cm^{-1} 3017 (m, C-H), 2959 (m, C-H), 2910 (m, C-H), 1748 (s, C=O), 1607 (w, C=C), 1515 (m, C-H), 1368 (m, C-H), 1217 (s, C-O), 1159 (m, C-O); δ_H (500 MHz; $CDCl_3$) *cis* isomer: 7.08 (4H, s, $H_{2'',3'',5'',6''}$), 6.97 (1H, d, *J* 6.5, H_1), 4.16 (1H, dd, *J* 10.2 and 6.5, H_2), 2.37 (1H, dt, *J* 6.4 and 8.5, $H_{2'}$), 2.31 (3H, s, -CH_3), 2.17 (1H, m, $H_{1'}$), 2.16 (3H, s, AcO-), 1.29 (1H, dt, *J* 5.1 and 8.5, $H_{3'\alpha}$), 0.92 (1H, dt, *J* 5.3 and 6.4, $H_{3'\beta}$); *trans* isomer: 7.08 (4H, s, $H_{2'',3'',5'',6''}$), 7.07 (1H, d, *J* 6.5, H_1), 4.46 (1H, dd, *J* 9.8 and 6.5, H_2), 2.31 (3H, s, -CH_3), 2.12 (3H, s, AcO-), 1.98 (1H, m, $H_{1'}$), 1.92 (1H, dt, *J* 5.8 and 8.8, $H_{2'}$), 1.24 (1H, ddd, *J* 5.0, 5.8 and 8.6, $H_{3'\alpha}$), 1.03 (1H, ddd, *J* 5.1, 5.5 and 8.8, $H_{3'\beta}$); δ_C (126 MHz; $CDCl_3$) *cis* isomer: 168.0 (C=O), 135.6, 135.2 ($C_{1'',4''}$), 134.6 (C_1), 128.9 ($C_{2'',6''}$), 128.8 ($C_{3'',5''}$), 113.6 (C_2), 22.6 ($C_{2'}$), 21.1 (-CH_3),

20.8 (AcO-), 15.0 ($C_{1'}$), 12.1 ($C_{3'}$); *trans* isomer: 168.0 (C=O), 136.1, 135.3 ($C_{1'',4''}$), 133.7 (C_1), 129.0, 128.7 ($C_{2'',3'',5'',6''}$) 116.8 (C_2), 24.7 ($C_{2'}$), 20.9 (-CH_3), 20.7 (AcO-), 19.7 ($C_{1'}$), 16.6 ($C_{3'}$); *m/z* (EI) 216 (58%, M^+), 174 (85%, M-CH_2CO), 156 (92%, M-CH_3CO_2H), 145 (71%, M-C_4H_7O), 143 (70%), 141 (46%), 128 (71%, M-$C_5H_{10}O$), 118 (90%), 105 (100%), 103 (29%), 91 (72%, $[C_7H_7]^+$), 81 (18%), 77 (54%, $[C_6H_5]^+$), 65 (41%, $[C_5H_5]^+$); (Found: M^+, 216.1149. $C_{14}H_{16}O_2$ requires *M*, 216.1150).

Preparation of *cis* and *trans* (*Z*)-2-[2-Phenylcyclopropyl]ethen-1-ol Acetate 279



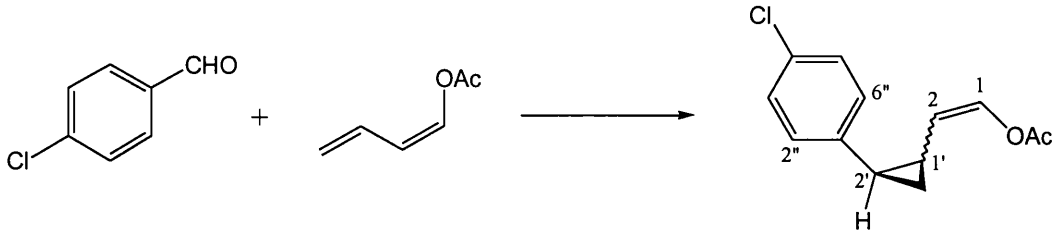
279

Using the general procedure, the crude product obtained from benzaldehyde (191 µl, 1.88 mmol, 1 equiv.), *Z*-acetoxybutadiene **266**, zinc amalgam and 1,2-bis(chlorodimethylsilyl)ethane was purified twice by flash column chromatography (silica, ether (0-5%)-light petroleum [40-60°C]) to give an inseparable diastereomeric mixture of *cis* and *trans* *Z*-2-[2-phenylcyclopropyl]ethen-1-ol acetate **279** (132 mg, 0.65 mmol, 35%, *cis/trans*: 3.1:1 as determined by NMR) as a colourless oil, R_f= 0.20 (silica, 5% ether in light petroleum [40-60°C]).

υ_{max} (NaCl; thin film)/cm^{-1} 3028 (m, C-H), 2952 (m, C-H), 2909 (m, C-H), 1756 (s, C=O), 1603 (w, C=C), 1497 (w, C-H); 1453 (w, C-H), 1369 (m, C-H), 1253 (s, C-O), 1221 (s, C-O); δ_H (500 MHz; $CDCl_3$) *cis* isomer: 7.28-7.09 (5H, m, $H_{2'',3'',4'',5'',6''}$), 6.96 (1H, d, *J* 6.5, H_1), 4.16 (1H, dd, *J* 10.0 and 6.5, H_2), 2.40 (1H, dt, *J* 6.6 and 8.4, $H_{2'}$), 2.20 (1H, m, $H_{1'}$), 2.16 (3H, s, AcO-), 1.31 (1H, dt, *J* 5.1 and 8.4, $H_{3'\alpha}$), 0.99 (1H, dt, *J* 5.3 and 6.5, $H_{3'\beta}$); *trans* isomer: 7.28-7.09 (5H, m, $H_{2'',3'',4'',5'',6''}$), 7.06 (1H, d, *J* 6.4, H_1), 4.47 (1H, dd, *J* 9.7 and 6.4, H_2), 2.12 (3H, s, AcO-), 2.01 (1H, m, $H_{1'}$), 1.92 (1H, dt, *J* 5.7 and 9.0, $H_{2'}$), 1.25 (1H, ddd, *J* 5.1, 5.8 and 8.7, $H_{3'\alpha}$), 1.05 (1H, ddd, *J* 5.0, 5.6 and 8.8, $H_{3'\beta}$); δ_C (126 MHz; $CDCl_3$) *cis* isomer: 168.0 (C=O), 138.4 ($C_{1''}$), 134.8 (C_1), 2 x 129.1, 2 x 128.1, 126.1 ($C_{2'',3'',4'',5'',6''}$), 113.4 (C_2), 23.0 ($C_{2'}$), 20.8 (AcO-), 15.1 ($C_{1'}$), 12.2 ($C_{3'}$); *trans* isomer: 168.0 (C=O), 142.0 ($C_{1''}$), 133.9 (C_1), 128.4, 125.8, 125.5, ($C_{2'',3'',4'',5'',6''}$), 116.6 (C_2), 25.1 ($C_{2'}$), 20.8 (AcO-), 19.9 ($C_{1'}$), 16.9 ($C_{3'}$); *m/z* (EI) 202 (32%, M^+), 172 (28%), 160 (88%, M-CH_2CO), 142 (83%, M-CH_3CO_2H), 129 (74%),

115 (70%), 104 (90%), 91 (92%, $[C_7H_7]^+$), 77 (75%, $[C_6H_5]^+$), 65 (29%, $[C_5H_5]^+$); (Found: M^+, 202.0994. $C_{13}H_{14}O_2$ requires *M*, 202.0994).

Preparation of *cis* and *trans* (*Z*)-2-[2-(4-Chlorophenyl)cyclopropyl]ethen-1-ol Acetate 280



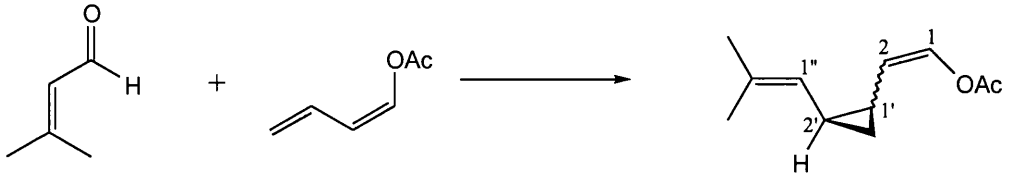
280

Using the general procedure, the crude product obtained from *p*-chlorobenzaldehyde (264 mg, 1.88 mmol, 1 equiv.), *Z*-acetoxybutadiene **266**, zinc amalgam and 1,2-bis(chlorodimethylsilyl)ethane was purified twice by flash column chromatography (silica, ether (0-5%)-light petroleum [40-60°C]) to give an inseparable diastereomeric mixture of *cis* and *trans* *Z*-2-[2-(4-chlorophenyl)cyclopropyl]ethen-1-ol acetate **280** (123 mg, 0.52 mmol, 28%, *cis*/*trans*: 2.7:1 as determined by NMR) as a colourless oil, R_f= 0.19 (silica, 5% ether in light petroleum [40-60°C]).

υ_{max} (NaCl; thin film)/cm^{-1} 3002 (m, C-H), 2942 (m, C-H), 2908 (m, C-H), 1755 (s, C=O), 1596 (w, C=C), 1490 (m, C-H), 1361 (m, C-H), 1214 (s, C-O), 1161 (m, C-O), 756 (m, C-Cl); δ_H (500 MHz; $CDCl_3$) *cis* isomer: 7.23 (2H, d, J_{ortho} 8.6, $H_{3",5"}$), 7.09 (2H, d, J_{ortho} 8.6, $H_{2",6"}$), 6.95 (1H, d, *J* 6.5, H_1), 4.08 (1H, dd, *J* 10.0 and 6.5, H_2), 2.33 (1H, dt, *J* 6.5 and 8.4, $H_{2'}$), 2.17 (1H, m, $H_{1'}$), 2.14 (3H, s, AcO-), 1.30 (1H, dt, *J* 5.2 and 8.4, $H_{3'\alpha}$), 0.92 (1H, dt, *J* 5.4 and 6.5, $H_{3'\beta}$); *trans* isomer: 7.22 (2H, d, J_{ortho} 8.6, $H_{3",5"}$), 7.09 (2H, d, J_{ortho} 8.6, $H_{2",6"}$), 7.05 (1H, d, *J* 6.4, H_1), 4.44 (1H, dd, *J* 9.6 and 6.4, H_2), 2.10 (3H, s, AcO-), 1.94 (1H, m, $H_{1'}$), 1.89 (1H, dt, *J* 5.8 and 8.8, $H_{2'}$), 1.21 (1H, ddd, *J* 5.1, 5.8 and 8.7, $H_{3'\alpha}$), 1.04 (1H, ddd, *J* 5.1, 5.4 and 8.8, $H_{3'\beta}$); δ_C (126 MHz; $CDCl_3$) *cis* isomer: 167.9 (C=O), 137.0 ($C_{4"}$), 135.0 (C_1), 131.4 ($C_{1"}$), 130.4, 128.2 ($C_{2",3",5",6"}$), 113.0 (C_2), 22.4 ($C_{2'}$), 20.8 (AcO-), 16.9 ($C_{1'}$), 12.3 ($C_{3'}$); *trans* isomer: 167.9 (C=O), 140.5 ($C_{4"}$), 134.2 (C_1), 128.4, 127.1 ($C_{2",3",5",6"}$), 125.5 ($C_{1"}$), 116.2 (C_2), 24.5 ($C_{2'}$), 20.8 (AcO-), 20.1 ($C_{1'}$), 15.2 ($C_{3'}$); *m/z* (EI) 236 (12%, M^+), 194 (48%, M-CH_2CO), 176 (65%, M-CH_3CO_2H), 165 (9%, M-C_4H_7O), 159 (6%, M-CH_2OCl), 151 (9%, M-C_5H_9O), 138 (60%, M-$C_2H_5O_2Cl$), 125 (91%), 115 (15%), 103

(6%), 89 (7%), 77 (7%, $[C_6H_5]^+$); (Found: M^+, 236.0601. $C_{13}H_{13}O_2Cl$ requires *M*, 236.0604).

Preparation of *cis* and *trans* (*Z*)-2-[2-(2-Methyl-1-propenyl)cyclopropyl]ethen-1-ol Acetate 286

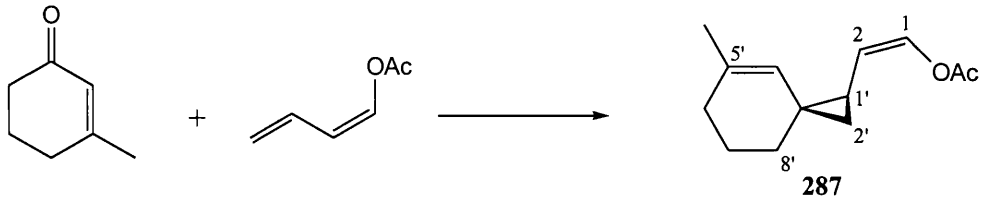


286

Using the general procedure, the crude product obtained from 3-methylbutenal (181 µl, 1.88 mmol, 1 equiv.), *Z*-acetoxybutadiene **266**, zinc amalgam and 1,2-bis(chlorodimethylsilyl)ethane was purified twice by flash column chromatography (silica, ether (0-2%)-light petroleum [40-60°C]) to give an inseparable diastereomeric mixture of *cis* and *trans* *Z*-2-[2-(2-methyl-1-propenyl)cyclopropyl]ethen-1-ol acetate **286** (142 mg, 0.79 mmol, 42%, *cis/trans*: 6.1:1 as determined by NMR) as a colourless oil, R_f= 0.20 (silica, 2% ether in light petroleum [40-60°C]).

υ_{max} (NaCl; thin film)/cm^{-1} 2960 (m, C-H), 2935 (m, C-H), 2870 (w, C-H), 1754 (s, C=O), 1665 (m, C=C), 1443 (m, C-H), 1369 (s, C-H), 1217 (s, C-O), 1158 (m, C-O), 1046 (m, C-O); δ_H (500 MHz; $CDCl_3$) *cis* isomer: 7.07 (1H, d, *J* 6.4, H_1), 4.82 (1H, dt, *J* 8.4 and 1.3, $H_{1''}$), 4.55 (1H, dd, *J* 10.0 and 6.4, H_2), 2.13 (3H, s, AcO-), 1.96 (1H, ddt, *J* 10.0, 5.7 and 8.4, $H_{1'}$), 1.77 (1H, dq, *J* 6.2 and 8.4, $H_{2'}$), 1.68 (6H, s, 2 x -CH_3) 1.15 (1H, dt, *J* 4.5 and 8.4, $H_{3'\alpha}$), 0.40 (1H, ddd, *J* 4.5, 5.7 and 6.2, $H_{3'\beta}$); *trans* isomer: 7.00 (1H, d, *J* 6.4, H_1), 4.61 (1H, dt, *J* 8.6 and 1.3, $H_{1''}$), 4.35 (1H, dd, *J* 9.9 and 6.4, H_2), 2.13 (3H, s, AcO-), 1.68 (1H, m, $H_{1'}$), 1.68 (6H, s, 2 x -CH_3), 1.48 (1H, m, $H_{2'}$), 0.77 (1H, m, $H_{3'\alpha}$), 0.76 (1H, m, $H_{3'\beta}$); δ_C (126 MHz; $CDCl_3$) *cis* isomer: 168.0 (C=O), 135.9 (C_1), 134.1 ($C_{2''}$), 122.8 ($C_{1''}$), 114.1 (C_2), 25.6 (-CH_3), 20.7 (AcO-), 18.2 (-CH_3), 17.4 ($C_{2'}$), 15.4 ($C_{3'}$), 14.2 ($C_{1'}$); *trans* isomer: 168.1 (C=O), 133.3 (C_1), 131.6 ($C_{2''}$), 126.3 ($C_{1''}$), 117.0 (C_2), 25.5 (-CH_3), 20.7 (AcO-), 20.1 (-CH_3), 16.8 ($C_{2'}$), 15.4 ($C_{3'}$), 14.2 ($C_{1'}$); *m/z* (EI) 180 (2%, M^+), 179 (21%, M-1), 166 (12%), 149 (6%, M-CH_3O), 136 (29%), 121 (45%, $[C_8H_9O]^+$), 107 (30%, $[C_7H_7O]^+$), 95 (28%, $[C_6H_7O]^+$), 83 (30%), 79 (18%, $[C_6H_7]^+$); (Found: M^+, 180.1145. $C_{11}H_{16}O_2$ requires *M*, 180.1150).

Preparation of *cis* and *trans* (*Z*)-2-[4-Methylspiro[2.5]oct-4-en-1-yl]ethen-1-ol Acetate 287

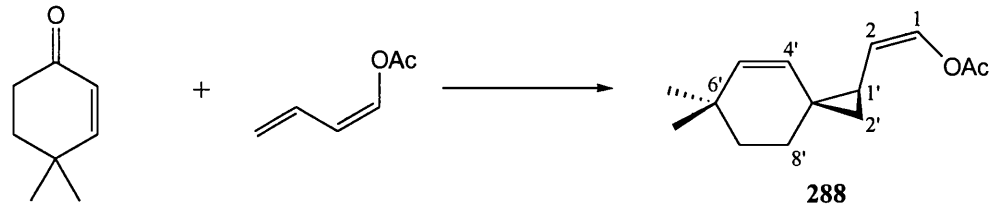


287

Using the general procedure, the crude product obtained from 3-methylcyclohexenone (213 μl, 1.88 mmol, 1 equiv.), *Z*-acetoxybutadiene **266**, zinc amalgam and 1,2-bis(chlorodimethylsilyl)ethane was purified twice by flash column chromatography (silica, ether (0-2%)-light petroleum [40-60°C]) to give an inseparable diastereomeric mixture of *cis* and *trans* *Z*-2-[4-methylspiro[2.5]oct-4-en-1-yl]ethen-1-ol acetate **287** (99.0 mg, 0.48 mmol, 26%, *cis*/*trans*: 5.4:1 as determined by NMR) as a colourless oil, R_f= 0.20 (silica, 2% ether in light petroleum [40-60°C]).

υ_{max} (NaCl; thin film)/cm^{-1} 3064 (w, C-H), 2954 (s, C-H), 2917 (m, C-H), 2831 (w, C-H), 1757 (s, C=O), 1670 (w, C=C), 1440 (w, C-H), 1367 (m, C-H), 1252 (s, C-O), 1216 (s, C-O); δ_H (500 MHz; $CDCl_3$) *cis* isomer: 7.06 (1H, d, *J* 6.5, H_1), 4.97 (1H, m, $H_{4'}$), 4.62 (1H, dd, *J* 9.9 and 6.5, H_2), 2.14 (3H, s, AcO-), 1.98-1.20 (6H, m, $H_{6',7',8'}$), 1.70 (1H, m, $H_{1'}$), 1.66 (3H, s, -CH_3), 0.98 (1H, dd, *J* 8.5 and 4.6, $H_{2'\alpha}$), 0.59 (1H, dd, *J* 5.2 and 5.0, $H_{2'\beta}$); *trans* isomer: 7.08 (1H, d, *J* 6.5, H_1), 4.76 (1H, m, $H_{4'}$), 4.56 (1H, dd, *J* 10.0 and 6.5, H_2), 2.15 (3H, s, AcO-), 1.98-1.20 (6H, m, $H_{6',7',8'}$), 1.70 (1H, m, $H_{1'}$), 1.65 (3H, s, -CH_3), 0.93 (1H, dd, *J* 8.7 and 4.9, $H_{2'\alpha}$), 0.56 (1H, dd, *J* 5.4 and 4.8, $H_{2'\beta}$); δ_C (126 MHz; $CDCl_3$) *cis* isomer: 168.0 (C=O), 135.8 ($C_{5'}$), 134.3 (C_1), 124.2 ($C_{4'}$), 114.5 (C_2), 34.5 (CH_2), 30.4 ($C_{1'}$), 30.3 (CH_2), 23.8 (-CH_3), 23.2 (CH_2), 23.0 ($C_{3'}$), 22.4 ($C_{2'}$), 20.7 (AcO-); *trans* isomer: 168.0 (C=O), 135.8 ($C_{5'}$), 134.7 (C_1), 125.5 ($C_{4'}$), 113.4 (C_2), 35.6 (CH_2), 28.6 (CH_2), 28.4 ($C_{3'}$), 25.8 ($C_{1'}$), 23.6 (-CH_3), 22.6 (CH_2), 22.3 ($C_{2'}$), 20.8 (AcO-); *m/z* (EI) 206 (21%, M^+), 205 (39%, M-1), 163 (35%, M-CH_3CO), 146 (32%, M-CH_3CO_2H), 131 (32%, M-$C_3H_7O_2$), 108 (100%, C_7H_7OH), 105 (21%), 95 (70%, $[C_6H_7O]^+$), 93 (59%), 91 (43%, $[C_7H_7]^+$), 79 (39%, $[C_6H_7]^+$), 67 (19%, $[C_5H_5]^+$), 55 (25%); (Found: M^+, 206.1305. $C_{13}H_{18}O_2$ requires *M*, 206.1307).

Preparation of *cis* (*Z*)-2-[6,6-Dimethylspiro[2.5]oct-4-en-1-yl]ethen-1-ol Acetate 288

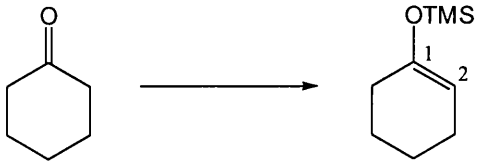


288

Using the general procedure, the crude product obtained from 4,4-dimethylcyclohexenone (247 μl, 1.88 mmol, 1 equiv.), *Z*-acetoxybutadiene **266**, zinc amalgam and 1,2-bis(chlorodimethylsilyl)ethane was purified twice by flash column chromatography (silica, ether (0-2%)-light petroleum [40-60°C]) to give *cis* (*Z*)-2-[6,6-dimethylspiro[2.5]oct-4-en-1-yl]ethen-1-ol acetate **288** (111 mg, 0.50 mmol, 27%) as a colourless oil, R_f= 0.22 (silica, 2% ether in light petroleum [40-60°C]).

υ_{max} (NaCl; thin film)/cm^{-1} 2954 (s, C-H), 2927 (w, C-H), 2863 (w, C-H), 1767 (s, C=O), 1651 (w, C=C), 1458 (w, C-H), 1351 (w, C-H), 1250 (s, C-O), 1214 (m, C-O), 1126 (m, C-O); δ_H (300 MHz; $CDCl_3$) 7.06 (1H, d, *J* 6.4, H_1), 5.48 (1H, d, *J* 10.0, $H_{5'}$), 5.08 (1H, d, *J* 10.0, $H_{4'}$), 4.60 (1H, dd, *J* 9.6 and 6.4, H_2), 2.15 (3H, s, AcO-), 1.78 (1H, dt, *J* 5.7 and 8.9, $H_{1'}$), 1.72-1.30 (4H, m, $H_{7',8'}$), 1.06 (1H, dd, *J* 8.3 and 4.6, $H_{2'\alpha}$), 0.99 (6H, s, 2 x $-CH_3$), 0.51 (1H, dd, *J* 5.7 and 4.4, $H_{2'\beta}$); δ_C (75 MHz; $CDCl_3$) 167.4 (C=O), 138.6 (C_1), 134.1, 128.8 ($C_{4',5'}$), 113.3 (C_2), 38.0 (C), 35.5 (CH_2), 34.9 ($C_{1'}$), 33.0 (CH_2), 29.0 (C), 28.4, 25.9 (2 x $-CH_3$), 20.6 (AcO-), 14.3 ($C_{2'}$); *m/z* (EI) 220 (69%, M^+), 205 (95%, M-CH_3), 177 (19%, M-CH_3CO), 160 (22%, M-CH_3CO_2H), 145 (36%, M-$C_3H_7O_2$), 122 (38%), 107 (36%, $[C_7H_7O]^+$), 91 (41%, $[C_7H_7]^+$), 79 (24%), 77 (22%, $[C_6H_5]^+$), 67 (19%, $[C_5H_5]^+$), 57 (52%), 55 (26%, $[C_4H_7]^+$); (Found: M^+, 220.1462. $C_{14}H_{20}O_2$ requires *M*, 220.1463).

Preparation of 1-Trimethylsilyloxycyclohexene 292[160]

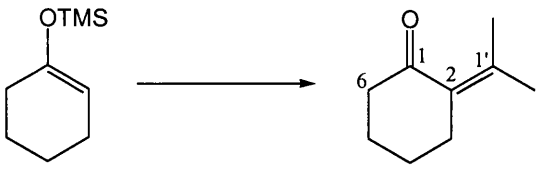


292

A solution of oven-dried sodium iodide (56.2 g, 375 mmol, 1.25 equiv.) in dry acetonitrile (372 ml) was added to a stirred solution of cyclohexanone (31.1 ml, 300 mmol, 1 equiv.), triethylamine (52.5 ml, 375 mmol, 1.25 equiv.) and chlorotrimethylsilane (47.6 ml, 375 mmol, 1.25 equiv.) over 10 min, and the resultant suspension was stirred for a further 20 min at ambient temperature. The reaction mixture was then poured into ice-water (1200 ml), and extracted with pentane (3 x 400 ml). The combined organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* at 0°C to a light yellow oil. The crude product was fractionally distilled to give the *silyl enol ether* **292** (46.8 g, 275 mmol, 92%) as a clear colourless oil, b.p. 100-104°C/70 mmHg (lit.,[203] 97-99°C/65 mmHg).

υ_{max} (NaCl; thin film)/cm^{-1} 3046 (w, C-H), 3015 (w, C-H), 2936 (s, C-H), 2864 (w, C-H), 2846 (s, C-H), 1661 (s, C=C), 1441 (m, C-H), 1361 (s, C-H), 1265 (s, C-O), 1251 (s, C-O), 1195 (s, Si-C), 1080 (w, Si-C), 1045 (w, Si-C), 985 (s, Si-C), 900 (s, Si-C), 839 (s, Si-O); δ_H (300 MHz; $CDCl_3$) 4.83 (1H, m, H_2), 1.98 (4H, m, $H_{3,6}$), 1.63 (2H, m, H_4), 1.48 (2H, m, H_5), 0.15 (9H, s, $Si(CH_3)_3$); δ_C (75 MHz; $CDCl_3$) 150.3 (C_1), 104.2 (C_2), 29.9, 23.8, 23.2, 22.4 ($C_{3,4,5,6}$), 0.3 ($Si(CH_3)_3$); *m/z* (EI) 170 (62%, M^+), 143 (25%), 129 (36%), 113 (79%), 103 (22%), 97 (31%, M-TMS), 85 (34%), 81 (9%, M-OTMS), 75 (90%), 73 (100%), 67 (70%), 61 (15%), 59 (18%), 55 (59%, $[C_4H_7]^+$).

Preparation of 2-Isopropylidenecyclohexanone 293

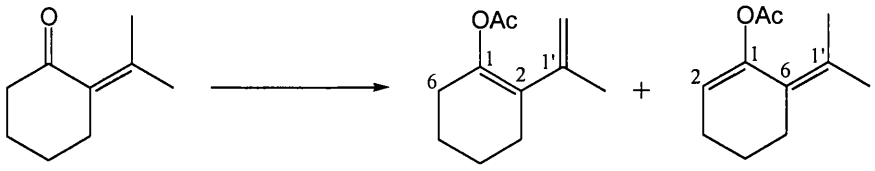


293

The *title compound* was prepared by the modification of the literature method.[163] A solution of 1-trimethylsilyoxycyclohexene **292** (18.3 g, 107 mmol, 1 equiv.) in dry dichloromethane (215 ml) was added dropwise to a stirred mixture of dry acetone (7.86 ml, 107 mmol, 1 equiv.) and titanium tetrachloride (11.7 ml, 107 mmol, 1 equiv.) in dry dichloromethane (96 ml) at 0°C. The resultant solution was stirred for 1 h at r.t., after which, distilled trifluoroacetic anhydride (15.1 ml, 107 mmol, 1 equiv.) was added. The reaction mixture was stirred for 15 min at r.t., recooled to 0°C and dry triethylamine (21.7 g, 214 mmol, 2 equiv.) was then carefully added dropwise over 15 min. The final reaction mixture was warmed to r.t., stirred for an additional 1 h and quenched with saturated aqueous ammonium chloride solution (200 ml). The organic layer was extracted with ether (3 x 100 ml) and the separated aqueous layer was further extracted with ether (2 x 100 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residual liquid was filtered through a short column of silica gel and eluted with 10% ether in light petroleum [40-60°C] after which the liquid was fractionally distilled to give a pale yellow oil, b.p. 80-83°C/10 mmHg (lit.,[204] 94-98°C/14 mmHg). Finally, the crude oil was chromatographed [silica, ether (0-5%)-light petroleum (b.p. 40-60°C)] to give the *title compound* **293** (4.76 g, 34.4 mmol, 32%) as a colourless oil, R_f= 0.15 (silica, 5% ether in light petroleum [40-60°C]).

υ_{max} (NaCl; thin film)/cm^{-1} 2931 (s, C-H), 2861 (m, C-H), 1678 (s, C=O), 1614 (w, C=C), 1449 (m, C-H), 1373 (w, C-H); δ_H (500 MHz; $CDCl_3$) 2.42 (2H, t, *J* 6.3, H_3), 2.33 (2H, t, *J* 6.8, H_6), 1.92 (3H, t, *J* 1.5, $-CH_3$), 1.79 (2H, m, H_5), 1.71 (3H, s, $-CH_3$), 1.66 (2H, m, H_4); δ_C (126 MHz; $CDCl_3$) 204.5 (C=O), 141.9 (C_2), 132.5 ($C_{1'}$), 42.5 (C_6), 29.8 (C_3), 24.5 x 2 ($C_{5,4}$), 22.9, 21.9 (2 x $-CH_3$); *m/z* (EI) 138 (81%, M^+), 123 (36%, M-CH_3), 111 (29%, M-C_2H_3), 95 (72%, M-C_3H_2O), 83 (38%, M-C_4H_2O), 67 (85%, M-C_4H_7O), 59 (100%).

Preparation of 2-(1-Methylethenyl)-1-cyclohexen-1-ol Acetate 294 and 6-(1-Methylethylidene)-1-cyclohexen-1-ol Acetate 295



294 **295**

A mixture of 2-isopropylidenecyclohexanone **293** (3.20 g, 23.2 mmol, 1 equiv.), isopropenyl acetate (4.53 ml, 41.1 mmol, 1.77 equiv.) and anhydrous *p*-toluenesulfonic acid (0.44 g, 2.55 mmol, 0.11 equiv.) was stirred under nitrogen at r.t. for 60 h. The reaction mixture was chromatographed [silica, ether (0-2%)-light petroleum (b.p. 30-40°C)] to give first, the excess isopropenyl acetate, secondly, *enol acetate* **294** (2.30 g, 12.8 mmol, 55%), R_f= 0.14 (silica, 2% ether in light petroleum [30-40°C]), thirdly, a mixture of the *enol acetates* **294** and **295** (0.50 g, 2.77 mmol, 12%, 1:4.7 as determined by NMR) and finally *enol acetate* **295** (0.96 g, 5.33 mmol, 23%), R_f= 0.10 (silica, 2% ether in light petroleum [30-40°C]), all as colourless oils.

2-(1-Methylethenyl)-1-cyclohexen-1-ol Acetate 294: υ_{max} (NaCl; thin film)/cm^{-1} 3083 (w, C-H), 2934 (m, C-H), 2854 (w, C-H), 1750 (s, C=O), 1681 (w, C=C), 1646 (w, C=C), 1636 (w, C=C), 1457 (m, C-H), 1437 (m, C-H), 1367 (m, C-H), 1218 (s, C-O), 1173 (m, C-O); δ_H (400 MHz; $CDCl_3$) 4.84 (1H, m, $H_{2'\alpha}$), 4.75 (1H, m, $H_{2'\beta}$), 2.13 (4H, m, $H_{3,6}$), 2.03 (3H, s, AcO-), 1.77 (3H, dd, *J* 1.3 and 1.0, -CH_3), 1.77-1.58 (4H, m, $H_{4,5}$); δ_C (75 MHz; $CDCl_3$) 169.3 (C=O), 142.6 (C_1), 142.0 (C_2), 126.5 ($C_{1'}$), 113.0 ($C_{2'}$), 28.1, 27.4, 22.7, 22.3 ($C_{3,4,5,6}$), 21.8 (-CH_3), 21.0 (AcO-); *m/z* (EI) 180 (1%, M^+), 163 (3%), 149 (31%, M-CH_3O), 138 (22%, M-C_2H_2O), 123 (12%, C_3H_5O), 111 (13%, M-C_2H_3), 95 (27%, M-CO), 81 (24%, M-CH_2), 69 (40%), 57 (53%); (Found: M^+, 180.1149. $C_{11}H_{16}O_2$ requires *M*, 180.1150).

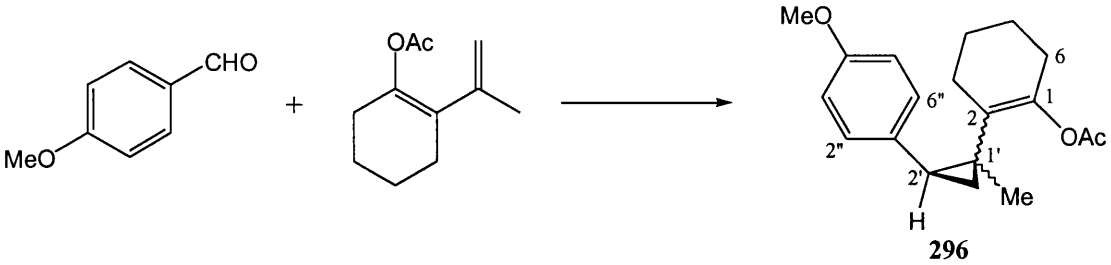
6-(1-Methylethylidene)-1-cyclohexen-1-ol Acetate 295: υ_{max} (NaCl; thin film)/cm^{-1} 2918 (m, C-H), 2859 (w, C-H), 1754 (s, C=O), 1661 (w, C=C), 1641 (w, C=C), 1441 (w, C-H), 1367 (m, C-H), 1216 (s, C-O), 1142 (m, C-O); δ_H (300 MHz; $CDCl_3$) 5.27 (1H, t, *J* 4.2, H_2), 2.35 (2H, t, *J* 5.9, H_5), 2.20 (2H, m, H_3), 2.11 (3H, s, AcO-), 1.81 (3H, s, -CH_3), 1.74 (3H, br s, -CH_3), 1.65 (2H, m, H_4); δ_C (75 MHz; $CDCl_3$) 169.3

(C=O), 147.1 (C_1), 127.1 (C_6), 124.3 ($C_{1'}$), 117.4 (C_2), 28.3, 24.7, 22.7 ($C_{3,4,5}$), 22.5, 22.0, 21.0 (AcO-, 2 x -CH_3); *m/z* (EI) 180 (17%, M^+), 163 (7%), 153 (21%, M-C_3H_3), 138 (74%, M-C_2H_2O), 123 (34%, C_3H_5O), 112 (23%, M-C_4H_4O), 95 (21%), 81 (19%), 67 (36%), 55 (40%, $[C_4H_7]^+$); (Found: M^+, 180.1147. $C_{11}H_{16}O_2$ requires *M*, 180.1150).

General Method for the Cyclopropanation of Aldehydes using 2-(1-Methylethenyl)-1-cyclohexen-1-ol Acetate 294

A solution of freshly distilled aldehyde (0.94 mmol, 1 equiv.) in dry ether (0.9 ml) was added slowly *via* a motorized syringe pump over 36 h to a vigorously stirred mixture of flame dried zinc amalgam (614 mg, 9.40 mmol, 10 equiv.), dry ether (1 ml), 2-(1-methylethenyl)-1-cyclohexen-1-ol acetate **294** (339 mg, 1.88 mmol, 2 equiv.) and 1,2-bis(chlorodimethylsilyl)ethane (1.41 ml of a 1.0 M solution in ether, 1.41 mmol, 1.5 equiv.) under nitrogen at reflux. The cooled mixture was filtered through Celite and the separated zinc was washed with ether (50 ml). The ethereal solution was washed with saturated aqueous sodium bicarbonate solution (2 x 40 ml) and the aqueous layer extracted with ether (2 x 25 ml) The combined organic phase was washed with brine (15 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified twice by flash chromatography (silica, ether (0-2/5%)-light petroleum [40-60°C] to give the cyclopropanes **296-300**.

Preparation of 2-[2-(4-Methoxyphenyl)-1-methylcyclopropyl]cyclohexen-1-ol Acetate 296



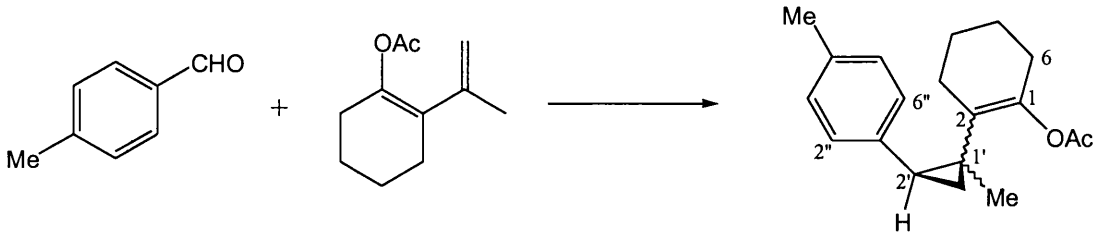
296

Using the general procedure, the crude product obtained from *p*-methoxybenzaldehyde (114 μl, 0.94 mmol, 1 equiv.), 2-(1-methylethenyl)-1-cyclohexen-1-ol acetate **294**, zinc amalgam and 1,2-bis(chlorodimethylsilyl)ethane was purified twice by flash column chromatography (silica, ether (0-5%)-light petroleum [40-60°C]) to give an inseparable diastereomeric mixture of 2-[2-(4-methoxyphenyl)-1-methylcyclopropyl]cyclohexen-1-ol acetate **296** (146 mg, 0.49 mmol, 52%, 2.0:1 as determined by NMR) as a colourless oil, R_f= 0.12 (silica, 5% ether in light petroleum [40-60°C]).

υ_{max} (NaCl; thin film)/cm^{-1} 3002 (m, C-H), 2929 (s, C-H), 2866 (m, C-H), 2839 (m, C-H), 1752 (s, C=O), 1689 (w, C=C), 1579 (w, C=C), 1516 (s, C-H), 1443 (m, C-H), 1369 (m, C-H), 1296 (w, C-H), 1249 (s, C-O), 1222 (s, C-O), 1175 (s, C-O), 1107 (m, C-O), 1071 (m, C-O), 1039 (m, C-O); δ_H (500 MHz; $CDCl_3$) major diastereomer: 6.94 (2H, d, J_{ortho} 8.8, $H_{2",6"}$), 6.75 (2H, d, J_{ortho} 8.8, $H_{3",5"}$), 3.75 (3H, s, -OCH_3), 2.21-1.15 (8H, m, $H_{3,4,5,6}$), 2.14 (3H, s, AcO-), 1.77 (1H, dd, *J* 8.9 and 5.9, $H_{2'}$), 1.22 (1H, dd, *J* 5.1 and 5.9, $H_{3'\alpha}$), 1.18 (3H, s, -CH_3), 0.99 (1H, dd, *J* 8.9 and 5.1, $H_{3'\beta}$); minor diastereomer: 7.09 (2H, d, J_{ortho} 8.5, $H_{2",6"}$), 6.80 (2H, d, J_{ortho} 8.5, $H_{3",5"}$), 3.76 (3H, s, OCH_3), 2.14 (3H, s, AcO-), 1.99 (1H, dd, *J* 9.0 and 6.2, $H_{2'}$), 1.70-1.15 (8H, m, $H_{3,4,5,6}$), 1.04 (1H, dd, *J* 4.9 and 9.0, $H_{3'\alpha}$), 0.79 (3H, s, -CH_3), 0.79 (1H, dd, *J* 6.2 and 4.9, $H_{3'\beta}$); δ_C (126 MHz; $CDCl_3$) major diastereomer: 169.3 (C=O), 157.4 ($C_{4"}$), 145.9 (C_1), 132.6 ($C_{1'}$), 131.4 ($C_{1"}$), 127.4 ($C_{2",6"}$), 113.1 ($C_{3",5"}$), 55.1 (-OCH_3), 29.4 ($C_{2'}$), 27.0 ($C_{1'}$), 27.6, 27.4, 26.8, 26.5 ($C_{3,4,5,6}$), 24.6 (-CH_3), 21.0 (AcO-), 20.4 ($C_{3'}$); minor diastereomer: 169.4 (C=O), 157.7 ($C_{4"}$), 144.1 (C_1), 129.9 ($C_{2",6"}$), 128.6 ($C_{1"}$), 124.2 (C_2), 113.3 ($C_{3",5"}$), 55.1 (-OCH_3), 27.6 ($C_{2'}$), 24.1 ($C_{1'}$), 22.8, 22.6, 22.5, 22.2 ($C_{3,4,5,6}$), 21.2 (AcO-), 18.0 (-CH_3), 17.7 ($C_{3'}$); *m/z* (EI) 300 (1%, M^+), 282 (6%, M-H_2O), 257

(15%, M-CH_3CO), 240 (64%, M-CH_3CO_2H), 225 (8%), 134 (24%), 121 (100%), 115 (2%), 91 (9%, $[C_7H_7]^+$), 77 (6%, $[C_6H_5]^+$), 65 (2%, $[C_5H_5]^+$); (Found: M^+, 300.1723. $C_{19}H_{24}O_3$ requires *M*, 300.1725).

Preparation of 2-[2-(4-Methylphenyl)-1-methylcyclopropyl]cyclohexen-1-ol Acetate 297



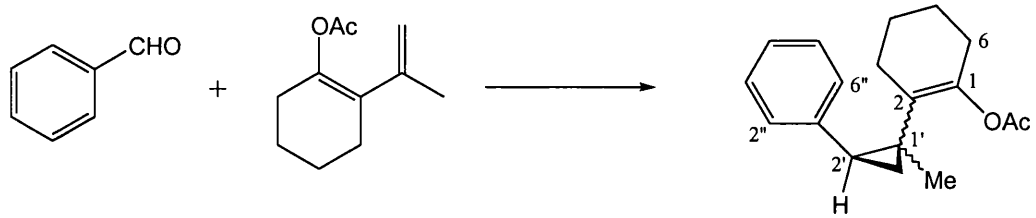
297

Using the general procedure, the crude product obtained from *p*-methylbenzaldehyde (111 μl, 0.94 mmol, 1 equiv.), 2-(1-methylethenyl)-1-cyclohexen-1-ol acetate **294**, zinc amalgam and 1,2-bis(chlorodimethylsilyl)ethane was purified twice by flash column chromatography (silica, ether (0-2%)-light petroleum [40-60°C]) to give an inseparable diastereomeric mixture of 2-[2-(4-methylphenyl)-1-methylcyclopropyl]cyclohexen-1-ol acetate **297** (88.3 mg, 0.31 mmol, 33%, 1.6:1 as determined by NMR) as a colourless oil, R_f= 0.17 (silica, 2% ether in light petroleum [40-60°C]).

υ_{max} (NaCl; thin film)/cm^{-1} 3045 (m, C-H), 3001 (m, C-H), 2930 (s, C-H), 2859 (m, C-H), 1749 (s, C=O), 1687 (m, C=C), 1576 (w, C=C), 1515 (m, C-H), 1448 (m, C-H), 1364 (m, C-H), 1316 (w, C-H), 1254 (m, C-O), 1223 (s, C-O), 1174 (m, C-O), 1108 (m, C-O), 1068 (m, C-O), 1042 (m, C-O); δ_H (500 MHz; $CDCl_3$) major diastereomer: 7.00 (2H, d, J_{ortho} 8.2, $H_{2",6"}$), 6.91 (2H, d, J_{ortho} 8.2, $H_{3",5"}$), 2.28 (3H, s, -CH_3), 2.23-1.12 (8H, m, $H_{3,4,5,6}$), 2.15 (3H, s, AcO-), 1.79 (1H, dd, *J* 8.9 and 5.8, $H_{2'}$), 1.26 (1H, dd, *J* 5.2 and 5.8, $H_{3'\alpha}$), 1.20 (3H, s, -CH_3), 1.02 (1H, dd, *J* 8.9 and 5.2, $H_{3'\beta}$); minor diastereomer: 7.07 (4H, s, $H_{2",3",5",6"}$), 2.31 (3H, s, -CH_3), 2.15 (3H, s, AcO-), 2.02 (1H, dd, *J* 9.0 and 6.3, $H_{2'}$), 1.76-1.12 (8H, m, $H_{3,4,5,6}$), 1.06 (1H, dd, *J* 4.8 and 9.0, $H_{3'\beta}$), 0.85 (1H, dd, *J* 6.3 and 4.8, $H_{3'\alpha}$) 0.81 (3H, s, -CH_3); δ_C (126 MHz; $CDCl_3$) major diastereomer: 169.3 (C=O), 145.9 (C_1), 137.4 ($C_{1"}$), 134.5 ($C_{4"}$), 128.4 (C_2), 128.3, 128.2 ($C_{2",6"}$), 126.6, 126.4 ($C_{3",5"}$), 29.9 ($C_{2'}$), 27.6, 27.4 ($C_{3,6}$), 27.3 ($C_{1'}$), 26.9, 26.6 ($C_{4,5}$), 24.7 ($C_{1'}CH_3$), 21.1 (AcO-), 20.9 ($C_{4"}CH_3$), 20.8 ($C_{3'}$); minor diastereomer:

169.4 (C=O), 144.1 (C_1), 136.3 ($C_{1''}$), 135.1 ($C_{4''}$), 128.9, 128.7, 128.6, ($C_{2'',3'',5'',6''}$), 124.1 (C_2), 28.1 ($C_{2'}$), 24.3 ($C_{1'}$), 22.9, 22.7, 22.6, 22.3 ($C_{3,4,5,6}$), 21.3 (AcO-), 21.0 ($C_{4''}CH_3$), 18.0 ($C_{1'}CH_3$), 17.6 ($C_{3'}$); *m/z* (EI) 284 (0.1%, M^+), 266 (5%, M-H_2O), 241 (23%), 224 (46%, M-CH_3CO_2H), 209 (9%), 195 (5%), 145 (17%), 128 (3%), 118 (24%), 105 (100%), 91 (9%, $[C_7H_7]^+$), 77 (6%, $[C_6H_5]^+$), 65 (2%, $[C_5H_5]^+$); (Found: M^+-H_2O, 266.1668. $C_{19}H_{22}O$ requires *M*, 266.1670).

Preparation of 2-[2-Phenyl-1-methylcyclopropyl]cyclohexen-1-ol Acetate 298



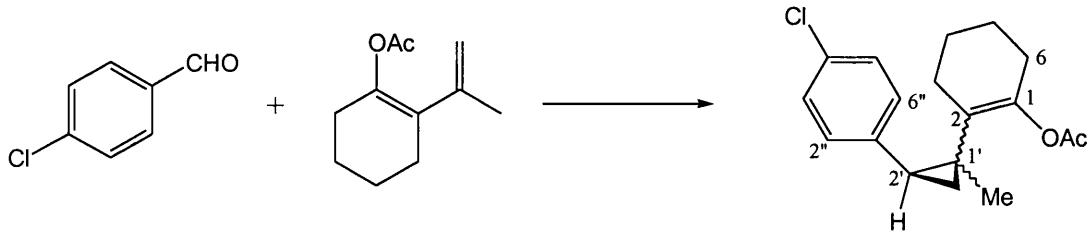
298

Using the general procedure, the crude product obtained from benzaldehyde (95.5 µl, 0.94 mmol, 1 equiv.), 2-(1-methylethenyl)-1-cyclohexen-1-ol acetate **294**, zinc amalgam and 1,2-bis(chlorodimethylsilyl)ethane was purified twice by flash column chromatography (silica, ether (0-2%)-light petroleum [40-60°C]) to give an inseparable diastereomeric mixture of 2-[2-phenyl-1-methylcyclopropyl]cyclohexen-1-ol acetate **298** (47.9 mg, 0.18 mmol, 19%, 1.3:1 as determined by NMR) as a colourless oil, R_f= 0.16 (silica, 2% ether in light petroleum [40-60°C]).

υ_{max} (NaCl; thin film)/cm^{-1} 3056 (w, C-H), 3015 (w, C-H), 2924 (s, C-H), 2863 (m, C-H), 1747 (s, C=O), 1681 (m, C=C), 1600 (w, C=C), 1493 (m, C-H), 1448 (m, C-H), 1367 (m, C-H), 1316 (w, C-H), 1219 (s, C-O), 1174 (m, C-O), 1108 (m, C-O), 1067 (m, C-O), 1042 (m, C-O); δ_H (500 MHz; $CDCl_3$) major diastereomer: 7.27-7.07 (5H, m, $H_{2'',3'',4'',5'',6''}$), 2.22-1.11 (8H, m, $H_{3,4,5,6}$), 2.14 (3H, s, AcO-), 1.83 (1H, dd, *J* 8.7 and 6.0, $H_{2'}$) 1.30 (1H, dd, *J* 5.1 and 6.0, $H_{3'\alpha}$), 1.20 (3H, s, -CH_3), 1.04 (1H, dd, *J* 8.7 and 5.1, $H_{3'\beta}$); minor diastereomer: 7.19-7.00 (5H, m, $H_{2'',3'',4'',5'',6''}$), 2.14 (3H, s, AcO-), 2.06 (1H, dd, *J* 8.9 and 6.3, $H_{2'}$), 1.73-1.11 (8H, m, $H_{3,4,5,6}$), 1.08 (1H, dd, *J* 4.9 and 8.9, $H_{3'\alpha}$), 0.88 (1H, dd, *J* 6.3 and 4.9, $H_{3'\beta}$), 0.81 (3H, s, -CH_3); δ_C (126 MHz; $CDCl_3$) major diastereomer: 169.3 (C=O), 146.0 (C_1), 140.6 ($C_{1''}$), 127.9, 127.6, 125.2 ($C_{2'',3'',4'',5'',6''}$), 123.9 (C_2), 30.3 ($C_{2'}$), 27.7 ($C_{1'}$), 27.6, 27.4, 26.9, 26.7 ($C_{3,4,5,6}$), 24.8 (-CH_3), 21.1 (AcO-), 20.9 ($C_{3'}$); minor diastereomer: 169.4 (C=O), 144.2 (C_1), 139.4

($C_{1''}$), 129.0, 126.6, 125.7 ($C_{2'',3'',4'',5'',6''}$), 128.3 (C_2), 28.5 ($C_{1'}$), 24.5 ($C_{2'}$), 22.9, 22.6, 22.2 ($C_{3,4,5,6}$), 21.3 (AcO-), 18.0 (-CH_3), 17.7 ($C_{3'}$); *m/z* (EI) 252 (5%, M-H_2O), 227 (39%), 210 (54%, M-CH_3CO_2H), 195 (6%), 181 (5%), 91 (100%, $[C_7H_7]^+$), 77 (35%, $[C_6H_5]^+$), 65 (5%, $[C_5H_5]^+$); (Found: M^+-H_2O, 252.1512. $C_{18}H_{20}O$ requires *M*, 252.1514).

Preparation of 2-[2-(4-Chlorophenyl)-1-methylcyclopropyl]cyclohexen-1-ol Acetate 299



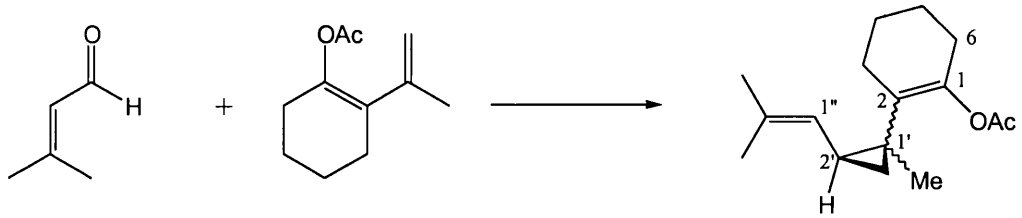
299

Using the general procedure, the crude product obtained from *p*-chlorobenzaldehyde (132 mg, 0.94 mmol, 1 equiv.), 2-(1-methylethenyl)-1-cyclohexen-1-ol acetate **294**, zinc amalgam and 1,2-bis(chlorodimethylsilyl)ethane was purified by twice flash column chromatography (silica, ether (0-2%)-light petroleum [40-60°C]) to give an inseparable diastereomeric mixture of 2-[2-(4-chlorophenyl)-1-methylcyclopropyl]cyclohexen-1-ol acetate **299** (48.8 mg, 0.16 mmol, 17%, 1.3:1 as determined by NMR) as a colourless oil, R_f= 0.12 (silica, 2% ether in light petroleum [40-60°C]).

υ_{max} (NaCl; thin film)/cm^{-1} 3082 (w, C-H), 2928 (s, C-H), 2860 (m, C-H), 1746 (s, C=O), 1688 (w, C=C), 1596 (w, C=C), 1495 (m, C-H), 1447 (m, C-H), 1370 (m, C-H), 1298 (w, C-H), 1225 (s, C-O), 1172 (m, C-O), 1109 (m, C-O), 1071 (m, C-O), 1042 (m, C-O), 786 (m, C-Cl); δ_H (500 MHz; $CDCl_3$) major diastereomer: 7.14 (2H, d, J_{ortho} 8.5, $H_{3'',5''}$), 6.94 (2H, d, J_{ortho} 8.5, $H_{2'',6''}$), 2.19-1.14 (8H, m, $H_{3,4,5,6}$), 2.13 (3H, s, AcO-), 1.78 (1H, dd, *J* 8.6 and 5.9, $H_{2'}$), 1.23 (1H, dd, *J* 5.2 and 5.9, $H_{3'\alpha}$), 1.19 (3H, s, -CH_3), 1.05 (1H, dd, *J* 8.6 and 5.2, $H_{3'\beta}$); minor diastereomer: 7.21 (2H, d, J_{ortho} 8.4, $H_{3'',5''}$), 7.09 (2H, d, J_{ortho} 8.4, $H_{2'',6''}$), 2.13 (3H, s, AcO-), 2.00 (1H, dd, *J* 9.1 and 6.4, $H_{2'}$), 1.71-1.14 (8H, m, $H_{3,4,5,6}$), 1.09 (1H, dd, *J* 5.1 and 9.1, $H_{3'\beta}$), 0.83 (1H, dd, *J* 6.4 and 5.1, $H_{3'\alpha}$), 0.78 (3H, s, -CH_3); δ_C (126 MHz; $CDCl_3$) major diastereomer: 169.3 (C=O), 146.3 (C_1), 139.3 ($C_{4''}$), 131.4 ($C_{1''}$), 130.8 (C_2), 127.8, 127.7 ($C_{2'',3'',5'',6''}$), 29.7

($C_{2'}$), 27.9 ($C_{1'}$), 27.6, 27.4, 26.9, 26.7 ($C_{3,4,5,6}$), 24.7 (-CH_3), 2 x 21.1 ($C_{3'}$, AcO-); minor diastereomer: 169.3 (C=O), 144.4 (C_1), 138.0 ($C_{4''}$), 131.5 ($C_{1''}$), 130.3, 128.0 ($C_{2'',3'',5'',6''}$), 123.6 (C_2), 27.9 ($C_{2'}$), 24.6 ($C_{1'}$), 22.8, 22.6, 22.5, 22.2 ($C_{3,4,5,6}$), 21.2 (AcO-), 18.0 (-CH_3), 17.9 ($C_{3'}$); *m/z* (EI) 304 (6%, M^+), 286 (32%, M-H_2O), 261 (34%), 244 (100%, M-CH_3CO_2H), 229 (12%), 193 (3%), 138 (52%), 125 (82%), 115 (6%), 103 (8%), 91 (9%, $[C_7H_7]^+$), 77 (9%, $[C_6H_5]^+$), 65 (3%, $[C_5H_5]^+$); (Found: M^+, 304.1229. $C_{18}H_{21}O_2Cl$ requires *M*, 304.1230).

Preparation of 2-[1-Methyl-2-(2-methylpropenyl)cyclopropyl]cyclohexen-1-ol Acetate 300



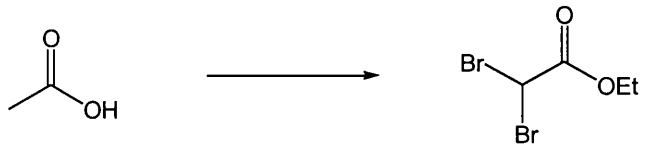
300

Using the general procedure, the crude product obtained from 3-methylbutenal (90.7 µl, 0.94 mmol, 1 equiv.), 2-(1-methylethenyl)-1-cyclohexen-1-ol acetate **294**, zinc amalgam and 1,2-bis(chlorodimethylsilyl)ethane was purified twice by flash column chromatography (silica, ether (0-2%)-light petroleum [40-60°C]) to give an inseparable diastereomeric mixture of 2-[1-methyl-2-(2-methylpropenyl)cyclopropyl]cyclohexen-1-ol acetate **300** (82.1 mg, 0.33 mmol, 35%, 1.3:1 as determined by NMR) as a colourless oil, R_f= 0.16 (silica, 2% ether in light petroleum [40-60°C]).

υ_{max} (NaCl; thin film)/cm^{-1} 2924 (s, C-H), 2863 (m, C-H), 1752 (s, C=O), 1681 (w, C=C), 1443 (m, C-H), 1367 (m, C-H), 1250 (m, C-O), 1219 (s, C-O), 1174 (m, C-O), 1108 (m, C-O), 1067 (m, C-O), 1042 (m, C-O); δ_H (500 MHz; $CDCl_3$) major diastereomer: 4.85 (1H, dt, *J* 9.1 and 1.2, $H_{1''}$), 2.12-1.65 (8H, m, $H_{3,4,5,6}$), 2.07 (3H, s, AcO-), 1.69 (3H, s, -CH_3), 1.64 (3H, s, -CH_3), 1.46 (1H, dt, *J* 5.8 and 9.1, $H_{2'}$), 1.04 (3H, s, -CH_3), 0.90 (1H, dd, *J* 9.1 and 4.3, $H_{3'\alpha}$), 0.24 (1H, dd, *J* 4.3 and 5.8, $H_{3'\beta}$); minor diastereomer: 4.51 (1H, dt, *J* 8.4 and 1.2, $H_{1''}$), 2.08 (3H, s, AcO-), 1.70 (3H, s, -CH_3), 1.68 (3H, s, -CH_3), 1.63-0.97 (8H, m, $H_{3,4,5,6}$), 1.58 (1H, dt, *J* 5.0 and 8.4, $H_{2'}$), 1.06 (3H, s, -CH_3), 0.76 (1H, dd, *J* 8.4 and 4.3, $H_{3'\alpha}$), 0.62 (1H, dd, *J* 4.3 and 5.0,

$H_{3'\beta}$); δ_C (126 MHz; $CDCl_3$) major diastereomer: 169.5 (C=O), 144.1 (C_1), 132.4 (C_2), 128.7 ($C_{2''}$), 124.0 ($C_{1''}$), 27.6, 27.4, 26.9, 26.5 ($C_{3,4,5,6}$), 25.9, 25.7 (2 x -CH_3), 23.4 ($C_{1'}$), 22.9 ($C_{2'}$), 20.9 (AcO-), 20.8 ($C_{3'}$), 18.4 (-CH_3); minor diastereomer: 169.2 (C=O), 144.6 (C_1), 130.0 (C_2), 126.2 ($C_{1''}$), 125.3 ($C_{2''}$), 24.6 ($C_{2'}$), 24.1 ($C_{1'}$), 24.1 (-CH_3), 22.9, 22.8, 22.5, 22.5 ($C_{3,4,5,6}$), 21.5 ($C_{3'}$), 21.0 (AcO-), 18.2, 18.1 (2 x -CH_3); *m/z* (EI) 248 (13%, M^+), 230 (16%, M-H_2O), 220 (28%, M-C_2H_4), 205 (77%, M-CH_3CO), 188 (72%, M-CH_3CO_2H), 178 (68%), 149 (92%), 135 (93%), 125 (79%), 121 (57%, $[C_8H_9O]^+$), 107 (69%, $[C_7H_7O]^+$), 95 (76%, $[C_6H_7O]^+$), 81 (77%, $[C_5H_5O]^+$), 79 (73%, $[C_6H_7]^+$), 69 (98%), 65 (20%, $[C_5H_5]^+$), 55 (88%, $[C_4H_7]^+$); (Found: M^+, 248.1770. $C_{16}H_{24}O_2$ requires *M*, 248.1776).

Preparation of Ethyl Dibromoacetate 154[167]

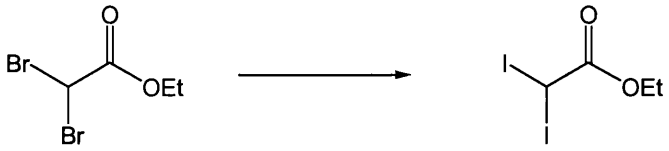


154

Phosphorus tribromide (13.3 ml, 140 mmol, 4 equiv.) was added to acetic acid (2.00 ml, 35.0 mmol, 1 equiv.) in a flask fitted with a condenser, a dropping funnel and a trap for the hydrogen bromide evolved. The mixture was cooled to 0°C, whereupon bromine (18.0 ml, 349 mmol, 10 equiv.) was added dropwise over 30 min. The reaction mixture was then refluxed at 170°C for 120 h. After cooling to 0°C, absolute ethanol (60.0 ml, 1.03 mol, 29.4 equiv.) was carefully added over 15 min and the resulting solution was stirred at r.t. for 1 h. The reaction mixture was quenched with water (80 ml) at 0°C and the aqueous layer was extracted with ether (3 x 100 ml). The combined organic layers were adjusted to pH4 with solid sodium bicarbonate and then washed successively with saturated aqueous sodium bicarbonate solution (2 x 60 ml), saturated aqueous sodium thiosulfate solution (2 x 60 ml), water (2 x 60 ml), brine (50 ml), and finally dried ($MgSO_4$). Filtration and concentration *in vacuo* gave a red oil which was purified by column chromatography (ether (0-10%)-hexane) to afford the *title compound* **154** (5.72 g, 23.3 mmol, 67%) as a yellow oil, R_f= 0.46 (silica, 10% ether in hexane).

υ_{max} (NaCl; thin film)/cm^{-1} 2983 (m, C-H), 2936 (w, C-H), 2889 (w, C-H), 1756 (s, C=O), 1734 (s, C=O), 1464 (w, C-H), 1394 (w, C-H), 1370 (w, C-H), 1276 (s, C-O), 1144 (s, C-O); δ_H (400 MHz; $CDCl_3$) 5.82 (1H, s, CH), 4.33 (2H, q, *J* 7.0, CH_2), 1.34 (3H, t, *J* 7.0, CH_3); δ_C (100 MHz; $CDCl_3$) 164.7 (C=O), 63.7 (CH), 32.5 (CH_2), 13.7 (CH_3); *m/z* (EI) 182 (46%), 174 (15%), 149 (42%), 105 (33%), 83 (24%), 69 (33%), 55 (78%).

Preparation of Ethyl Diiodoacetate 146

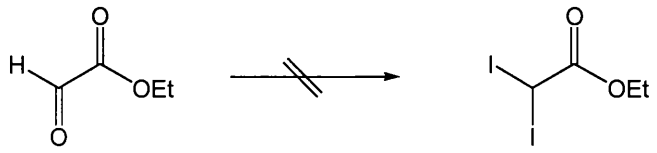


146

The *title compound* was prepared by the modification of the literature method.[168] Ethyl dibromoacetate **154** (2.63 ml, 20.3 mmol, 1 equiv.) was added to a solution of potassium iodide (10.1 g, 60.9 mmol, 3 equiv.) in absolute ethanol (8 ml). The reaction mixture was refluxed for 60 h, then cooled to r.t. and ethanol was removed *in vacuo*. The residue was taken up in ether (30 ml), washed with water (30 ml) and the aqueous layer was extracted with ether (2 x 20 ml). The combined organic layers were further washed with sodium thiosulfate solution (3 x 30 ml), water (20 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a dark red oil. Bulb to bulb distillation gave the *title compound* **146** (5.79 g, 17.0 mmol, 84%) as an orange oil, b.p. 122-125°C/1 mmHg.

υ_{max} (NaCl; thin film)/cm^{-1} 2980 (m, C-H), 1725 (s, C=O), 1465 (w, C-H), 1443 (w, C-H), 1259 (s, C-O), 1118 (s, C-O), 1020 (s, C-O); δ_H (300 MHz; $CDCl_3$) 5.34 (1H, s, CH), 4.28 (2H, q, *J* 7.0, CH_2), 1.28 (3H, t, *J* 7.0, CH_3); δ_C (75 MHz; $CDCl_3$) 209.6 (CH), 166.2 (C=O), 63.5 (CH_2), 13.6 (CH_3); *m/z* (EI) 340 (45%, M^+), 312 (100%, M-C_2H_4), 267 (17%, $[CHI_2]^+$), 254 (10%, I_2), 213 (26%), 185 (56%), 168 (16%), 157 (20%), 140 (14%, $[ICH]^+$), 127 (24%, I^+).

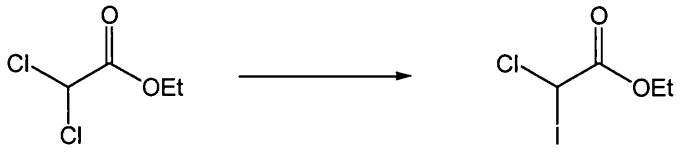
Attempted Reaction of Ethylglyoxalate with Iodotrimethylsilane



146

A mixture of ethylglyoxalate polymer and toluene (6.00 g, approximately 3.00 g of ethylglyoxalate by weight, 29.4 mmol) was distilled in a Kugelrohr to remove the toluene (150°C, atmospheric pressure). The residue was subjected to microwave irradiation for 5 min, and then distilled (100°C, 35 mmHg), to afford depolymerised ethyl glyoxalate[171] (1.50 g, 14.7 mmol). Iodotrimethylsilane (398 µl, 2.79 mmol, 2.2 equiv.) was then added to freshly depolymerised distilled ethyl glyoxalate (130 mg, 1.27 mmol, 1 equiv.) in DCM (1 ml) under nitrogen. The reaction mixture was heated at 35°C for 18 h, then cooled to r.t. and the viscous solution was dissolved in DCM (20 ml). The organic layer was washed with sodium thiosulfate solution (3 x 20 ml), brine (20 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. GC and NMR analysis showed no formation of ethyl diiodoacetate **146**.

Preparation of Ethyl Iodochloroacetate 302[169]

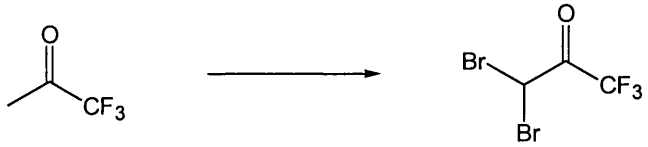


302

A mixture of ethyl dichloroacetate (12.3 ml, 100 mmol, 1 equiv.) and potassium iodide (33.2 g, 200 mmol, 2 equiv.) in dry acetone (85 ml) was heated to reflux and stirred for 132 h. The reaction mixture was cooled to ambient temperature, and the acetone solution was washed with water (40 ml) which was then extracted with carbon tetrachloride (5 x 40 ml). The combined organic phase was washed with sodium thiosulfate solution (2 x 40 ml), dried ($NaSO_4$), filtered and concentrated *in vacuo*. The crude oil was distilled twice to give the *title compound* **302** (10.2 g, 41.1 mmol, 41%) as a yellow oil, b.p. 54-56°C/0.7 mmHg (lit.,[169] 65°C/0.4 mmHg).

υ_{max} (NaCl; thin film)/cm^{-1} 2987 (s, C-H), 2928 (w, C-H), 2815 (w, C-H), 1753 (s, C=O), 1464 (m, C-H), 1444 (m, C-H), 1394 (m, C-H), 1364 (m, C-H), 1281 (s, C-O), 1180 (s, C-O), 1109 (s, C-O); δ_H (270 MHz; $CDCl_3$) 6.04 (1H, s, CH), 4.32 (2H, q, *J* 7.2, CH_2), 1.34 (3H, t, *J* 7.2, CH_3); δ_C (75 MHz; $CDCl_3$) 166.3 (C=O), 63.5 (CH), 15.4 (CH_2), 13.6 (CH_3); *m/z* (EI) 248 (14%, M^+), 220 (86%, M-C_2H_4), 213 (36%, M-Cl), 185 (25%, M-C_2H_4Cl), 175 (36%, CHClI), 168 (21%, $[ICHCO]^+$), 157 (21%, M-C_3H_4ClO), 140 (45%, $[ICH]^+$), 127 (80%, I^+), 121 (11%, M-I), 105 (85%, $ClCHCO_2H$), 93 (85%, M-C_2H_4I), 77 (20%, M-C_2H_4IO), 65 (42%, M-C_3H_4IO).

Preparation of 3,3-Dibromo-1,1,1-trifluoropropanone 303[172]

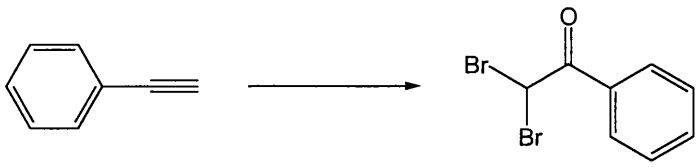


303

1,1,1-trifluoroacetone (4.47 ml, 50.0 mmol, 1 equiv.) was added to cooled (5°C) concentrated sulfuric acid (35.0 ml, 657 mmol, 13.1 equiv.) with stirring. Bromine (3.68 ml, 71.5 mmol, 1.43 equiv.) was added dropwise over 45 min whilst maintaining the temperature of the reaction mixture below 5°C. The solution was stirred at ambient temperature for 65 h and the more dense layer was collected and distilled. Excess bromine was removed at 59°C, and the temperature of the bath was further increased to give the *title compound* **303** (8.16 g, 30.2 mmol, 60%) as a straw coloured liquid, b.p. 111-112°C/760 mmHg (lit.,[205] 110-112°C/760 mmHg).

υ_{max} (NaCl; thin film)/cm^{-1} 3012 (w, C-H), 1774 (s, C=O), 1456 (w, C-H), 1206 (s, C-F), 1172 (s, C-F); δ_H (300 MHz; $CDCl_3$) 6.22 (1H, s, CH); δ_C (75 MHz; $CDCl_3$) 178.2 (q, $^2J_{F\text{-}C}$ 37.0, CF_3CO), 114.3 (q, $^1J_{F\text{-}C}$ 292.3, CF_3CO), 32.0 (CH); δ_F (282 MHz; $CDCl_3$) –72.7; *m/z* (EI) 201 (10%, M-CF_3), 174 (84%, CH_2Br_2), 173 (59%, $CHBr_2$), 172 (75%, CBr_2), 120 (69%, M-CF_3Br), 115 (100%), 105 (93%, $[C_2HBr]^+$), 92 (53%, $[CBr]^+$), 69 (93%, CF_3).

Preparation of 2,2-Dibromo-1-phenylethanone 304[172]



304

Sodium borate (10.9 g, 72.0 mmol, 2.4 equiv.) was dissolved in water (18 ml) by gentle warming and the solution was adjusted to pH1 with sulfuric acid (2 M). To the resulting solution was added 1-phenylacetylene (3.29 ml, 30.0 mmol, 1 equiv.) in acetonitrile (60 ml). Sodium hydrogen sulfite (72 ml of a 2 M solution in water, 144 mmol, 4.8 equiv.) was then added dropwise over a period of approximately 1 h at 0°C, and the reaction mixture was warmed to r.t. and stirred for 2 h. The reaction mixture was extracted with ether (5 x 100 ml), and the combined organic layers were washed with aqueous sodium bisulfite (2 x 100 ml) and dried ($MgSO_4$). After filtration, the solvent was removed *in vacuo* to give a dark red oil which was purified by column chromatography (ether (0-10%)-hexane) to give the *title compound* **304** (3.80 g, 13.7 mmol, 46%) as an orange oil, R_f= 0.33 (silica, 10% ether in hexane).

υ_{max} (NaCl; thin film)/cm^{-1} 3058 (m, C-H), 3002 (m, C-H), 1695 (s, C=O), 1596 (m, C=C), 1441 (s, C-H); δ_H (400 MHz; $CDCl_3$) 8.09 (2H, d, *J* 8.6, ArH), 7.65 (1H, t, *J* 7.2, ArH), 7.52 (2H, dd, *J* 7.2 and 8.3, ArH), 6.72 (1H, s, CH); δ_C (100 MHz; $CDCl_3$) 185.9 (C=O), 134.4, 130.8, 129.7, 128.9 (C_{Ar}), 39.7 (CH); *m/z* (EI) 278 (4%, M^+), 277 (2%, M-1), 105 (100%, $[C_6H_5CO]^+$), 90 (40%), 89 (24%, $[C_7H_5]^+$), 77 (60%, $[C_6H_5]^+$).

General Procedures for Carboethoxycyclopropanation of Cyclooctene-Methods A-D

X=Cl, Br, I **301**

Method A: Carboethoxycyclopropanations using Copper[62] and Ethyl Dihaloacetates 154, 146 or 302

Copper powder (429 mg, 6.75 mmol, 4.5 equiv.) was stirred with a small amount of iodine (19.0 mg, 0.075 mmol, 0.05 equiv.) in dry benzene (1 ml) at r.t. After the brown colour of iodine disappeared (1 min), cyclooctene (195 µl, 1.50 mmol, 1 equiv.) and ethyl dihaloacetate **154**, **146** or **302** (3.00 mmol, 2 equiv.) were added, and the mixture was heated at 55°C and stirred for 72 h. The reaction mixture was cooled to ambient temperature and filtered through a short column of Celite and the suspension was washed with ether (3 x 5 ml). The organic layer was washed with water (10 ml), dried ($MgSO_4$) and filtered. The solvent was removed *in vacuo* and the crude product was chromatographed on neutral alumina using light petroleum [40-60°C] to give a diastereomeric mixture of *exo-/endo*-9-ethoxycarbonyl-*cis*-bicyclo[6.1.0]nonane **301** as a colourless oil, whose spectral properties were in accord with literature[62] (Table 21), R_f= 0.22 (neutral alumina, light petroleum [40-60°C]).
υ_{max} (NaCl; thin film)/cm^{-1} 2981 (m, C-H), 2933 (s, C-H), 2852 (m, C-H), 1720 (s, C=O), 1488 (m, C-H), 1443 (m, C-H), 1174 (s, C-O), 1144 (s, C-O); δ_H (300 MHz, $CDCl_3$) 4.07 (2H, q, *J* 7.1, *exo* OCH_2-), 4.06 (2H, q, *J* 7.1, *endo* OCH_2-), 2.04-1.01 (30H, m, CH_2 and CH), 1.22 (6H, t, *J* 7.1, 2 x $-CH_3$); δ_C (75 MHz, $CDCl_3$) 174.4, 172.4 (C=O), 60.2, 59.7 (CH_2), 29.2, 29.1 (CH_2), 27.3 (CH), 26.4 x 2, 25.9 (CH_2), 25.9, 24.6, 21.0 (CH), 20.8 (CH_2), 14.4, 14.3 (CH_3); *m/z* (EI) 197 (91%, M+1), 168 (56%, M-C_2H_4), 151 (100%, M-C_2H_4OH), 139 (30%), 121 (77%, M-$C_3H_7O_2$), 108 (92%, M-$C_4H_8O_2$), 95 (63%, M-$C_5H_9O_2$), 88 (72%), 81 (82%, $[C_5H_5O]^+$), 73 (42%, $[CO_2C_2H_5]^+$), 67 (71%, $C_5H_7]^+$), 55 (67%, $[C_4H_7]^+$).

Method B: Carboethoxycyclopropanations using Zinc Dust[190] and Ethyl Dihaloacetates 154, 146 or 302

Ethyl dihaloacetate **154**, **146** or **302** (5.40 mmol, 1.35 equiv.) was added to a stirred mixture of acid-washed zinc dust[190] (699 mg, 10.7 mmol, 2.68 equiv.) and cyclooctene (0.52 µl, 4 mmol, 1 equiv.) in dry THF (10 ml). The reaction mixture was heated at 80°C for 72 h, then cooled to ambient temperature and the THF removed *in vacuo*. The crude mixture was filtered through a short column of Celite and the suspension was washed with ether (3 x 10 ml). The organic layer was washed with water (10 ml), dried ($MgSO_4$) and filtered and the solvent was removed *in vacuo*. The crude product was chromatographed on neutral alumina using light petroleum [40-60°C] to give a diastereomeric mixture of *exo-/endo*-9-ethoxycarbonyl-*cis*-bicyclo[6.1.0]nonane **301** as a colourless oil. The mixture of products were spectroscopically identical to material already prepared (Table 21).

Method C: Carboethoxycyclopropanations using Shank and Shechter Zinc Copper Couple[175] and Ethyl Dihaloacetates 146 or 302

Ethyl dihaloacetate **146** or **302** (5.40 mmol, 1.35 equiv.) was added over 5 min to a stirred mixture of Shank and Shechter's zinc-copper couple[175] (1.31 g, 20.0 mmol, 5 equiv.) and cyclooctene (0.52 µl, 4.00 mmol, 1 equiv.) in dry ether (5 ml). The resultant solution was refluxed for 72 h and then cooled to ambient temperature. The reaction mixture was filtered through a short column of Celite and the suspension was washed with ether (3 x 5 ml). The organic layer was washed with water (20 ml), dried ($MgSO_4$) and filtered. The solvent was removed *in vacuo*. The crude product was chromatographed on neutral alumina using light petroleum [40-60°C] to give a diastereomeric mixture of *exo-/endo*-9-ethoxycarbonyl-*cis*-bicyclo[6.1.0]nonane **301** as a colourless oil. The mixture of products were spectroscopically identical to material already prepared (Table 21).

Method D: Carboethoxycyclopropanations using Diethylzinc[21] and Ethyl Dihaloacetates 154, 146 or 302

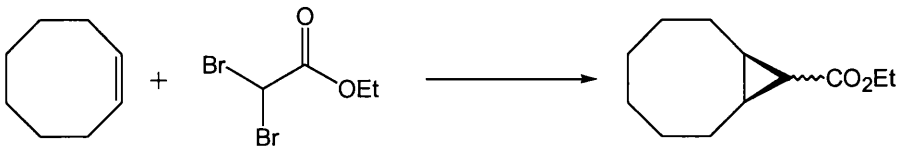
Ethyl dihaloacetate **154, 146** or **302** (4.00 mmol, 4 equiv.) was added to a stirred solution mixture of diethylzinc (2.83 ml of a 12% solution in hexane, 2.00 mmol, 2 equiv.) and cyclooctene (130 µl, 1.00 mmol, 1 equiv.) in dry DCE (5 ml) over 10 min under nitrogen at 0°C. The reaction mixture was stirred for a further 72 h at r.t., and then quenched with ammonium chloride (20 ml). The resulting solution was vigorously stirred for 10 min. The organic layer was separated, washed with water (10 ml) and brine (20 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. No products could be isolated after attempted purification using neutral alumina and light petroleum [40-60°C] as eluent (Table 21).

Table 21: Carboethoxycyclopropanations of Cyclooctene [Methods A-D]

Method	Br_2CHCO_2Et **154**	I_2CHCO_2Et **146**	$IClCHCO_2Et$ **302**
A	60%[a]	51%[a]	trace[b]
B	trace[b]	1%[a,c]	no reaction
C	-	3%[a]	no reaction
D	no reaction	trace[b]	trace[b]

[a] Isolated as a diastereomeric mixture of *exo* and *endo* in the ratio of 1.3:1 as determined by GC. [b] Detected by GC. [c] Reaction also attempted neat with zinc dust (699 mg, 10.7 mmol, 2.68 equiv.) and ethyl diiodoacetate (1.84 g, 5.40 mmol, 1.35 equiv.) in cyclooctene (0.52 µl, 4.00 mmol, 1 equiv.) at -40°C for 8 h. After the standard work-up procedure and purification this gave an inseparable mixture of diastereomers of *exo-/endo*-9-ethoxycarbonyl-*cis*-bicyclo[6.1.0]nonane **301** (23.5 mg, 0.12 mmol, 3%, 1.3:1) as a colourless oil.

Carboethoxycyclopropanation of Cyclooctene using LeGoff's Zinc Copper Couple[33] and Ethyl Dibromoacetate 154

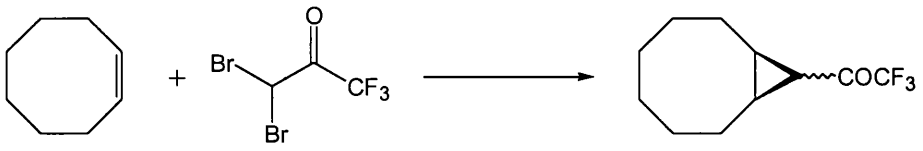


301

To a hot, rapidly solution of cupric acetate monohydrate (39.9 mg, 0.20 mmol, 0.05 equiv.) in glacial acetic acid (2 ml) was added zinc dust (699 mg, 10.7 mmol, 2.68 equiv.). After approximately 30 sec all of the copper had deposited on the zinc. The couple was allowed to settle for 1 min, after which the acetic acid was decanted away

from the Zn-Cu couple. The dark, red gray couple was washed with acetic acid (2 ml), followed by dry ether (3 x 2 ml) and then dried *in vacuo* for 3 h. To the couple, was added dry ether (5 ml) followed by 3 drops of ethyl dibromoacetate **154** (699 µl, 5.40 mmol, 1.35 equiv.). A mixture of cyclooctene (0.52 µl, 4.00 mmol, 1 equiv.) in dry ether (2 ml) with the remainder of the dibromomethane was added dropwise over 5 min. The resulting mixture was refluxed for 72 h, then cooled to ambient temperature and filtered through a short column of Celite with the suspension washed with ether (3 x 5 ml). The organic layer was washed with water (20 ml), dried ($MgSO_4$) and filtered. The solvent was removed *in vacuo*. The crude product was chromatographed on neutral alumina using light petroleum [40-60°C] to give a diastereomeric mixture of *exo-/endo*-9-ethoxycarbonyl-*cis*-bicyclo[6.1.0]nonane **301** (5.00 mg, 0.025 mmol, 1%, *exo/endo*, 1.3:1) as a colourless oil. The mixture of products were spectroscopically identical to material already prepared.

Preparation of *exo-/endo*-9-Trifluoroacetyl-*cis*-bicyclo[6.1.0]nonane 309

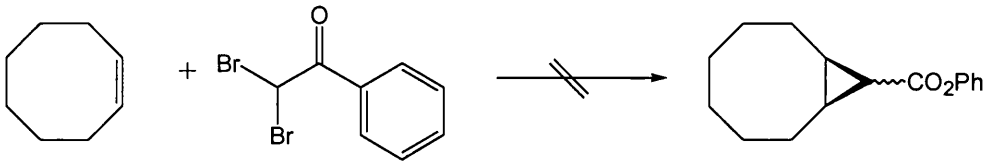


309

Copper powder (1.14 g, 18.0 mmol, 4.5 equiv.) was stirred with a small amount of iodine (50.8 mg, 0.20 mmol, 0.05 equiv.) in dry benzene (1.5 ml) at r.t. After the brown colour of iodine disappeared (1 min), cyclooctene (0.52 µl, 4.00 mmol, 1 equiv.) and 3,3-dibromo-1,1,1-trifluoropropanone **303** (1.08 g, 4.00 mmol, 1 equiv.) were added, and the mixture was heated at 55°C and stirred for 72 h. The reaction mixture was cooled to ambient temperature and filtered through a short column of Celite and the suspension washed with ether (3 x 5 ml). The organic layer was washed with water, dried ($MgSO_4$) and filtered. The solvent was removed *in vacuo* and the crude product was chromatographed on neutral alumina using light petroleum [40-60°C] to give a diastereomeric mixture of the *exo-/endo*-9-trifluorocarbonyl-*cis*-bicyclo[6.1.0]nonane **309** (134 mg, 0.61 mmol, 15%, 1.2:1 as determined by GC) as a colourless oil, R_f= 0.54 (neutral alumina, light petroleum [40-60°C]).

υ_{max} (NaCl; thin film)/cm^{-1} 2925 (s, C-H), 2861 (s, C-H), 1735 (s, C=O), 1466 (m, C-H), 1446 (m, C-H), 1197 (s, C-F), 1140 (s, C-F); δ_H (500 MHz; $CDCl_3$) 2.22-1.15 (30H, m, CH and CH_2); δ_C (126 MHz; $CDCl_3$) 189.8 (q, $^2J_{F\text{-}C}$ 33.8, 2 x CF_3CO), 140.4 (q, $^1J_{F\text{-}C}$ 37.0, CF_3CO), 140.3 (q, $^1J_{F\text{-}C}$ 37.1, CF_3CO), 32.1 (CH), 29.6, 27.1, 26.8, 26.7, 25.7, 25.5 (12 x CH_2), 23.9 (2 x CH); δ_F (282 MHz; $CDCl_3$) –66.9, -67.0; *m/z* (FAB) 219 (57%, M-1), 149 (40%, M-CF_3H_2), 133 (16%, M-CF_3H_2O), 109 (64%, M-$C_3F_3H_2O$), 105 (58%); (Found: M-1, 219.0990. $C_{11}H_{14}OF_3$ requires *M*-1, 219.0997).

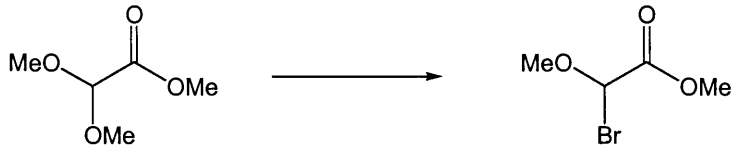
Attempted Reaction of Cyclooctene with 2,2-Dibromo-1-phenylethanone 304



373

Copper powder (858 mg, 13.5 mmol, 4.5 equiv.) was stirred with a small amount of iodine (38.1 mg, 0.15 mmol, 0.05 equiv.) in dry benzene (1 ml) at r.t. After the brown colour of iodine disappeared (1 min), cyclooctene (391 µl, 3.00 mmol, 1 equiv.) and 2,2-dibromo-1-phenylethanone **304** (834 mg, 3.00 mmol, 1 equiv.) were added, and the mixture was heated at 55°C and stirred for 72 h. The reaction mixture was cooled to ambient temperature and filtered through a short column of Celite and the suspension washed with ether (3 x 5 ml). The organic layer was washed with water, dried ($MgSO_4$) and filtered. The solvent was removed *in vacuo* and the crude product was chromatographed on neutral alumina using 5% ethyl acetate in light petroleum [40-60°C] to give recovered 2,2-dibromo-1-phenylethanone **304** (0.72 g, 2.59 mmol, 86%) as a colourless oil which was spectroscopically identical to material prepared before.

Formation of Methyl Bromomethoxyacetate 312- A Spectroscopic Study



312

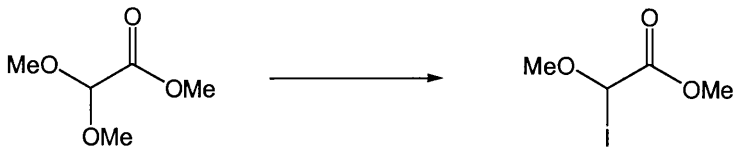
Freshly distilled bromotrimethylsilane was added dropwise to a stirred solution of methyl dimethoxyacetate (123 μl, 1.00 mmol, 1 equiv.) in dry deuterated chloroform (1 ml) under nitrogen at r.t. The reaction mixture was stirred at the stated temperature (°C) and time (h). Small aliquots were removed for spectroscopic analysis. However, the instability of the *title compound* **312** precluded complete characterisation (Table 22).

υ_{max} (NaCl; thin film)/cm^{-1} 2947 (w, C-H), 2837 (w, C-H), 1746 (s, C=O), 1456 (w, C-H), 1215 (m, C-O), 1105 (m, C-O); δ_H (300 MHz, $CDCl_3$) 5.98 (1H, s, CH), 3.82 (3H, s, CO_2CH_3), 3.54 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 165.7 (C=O), 83.1 (CH), 58.6 (OCH_3), 53.1 (CO_2CH_3); *m/z* (EI) 169 (7%, M-CH_2), 147 (100%), 125 (33%), 123 (34%), 103 (100%, M-Br), 81 (18%, BrH), 80 (51%, Br^+), 75 (97%, M-C_2H_4Br).

Table 22: Formation of Methyl Bromomethoxyacetate 312

TMSBr (equiv.)	Reaction temperature (°C)	Reaction time (h)	Yield (% conversion by NMR)
1	25	1	19
2	25	16	66
3	25	3	44
3	25	15	60
2	40	1	33
2	40	2	53

Formation of Methyl Iodomethoxyacetate 313-A Spectroscopic Study



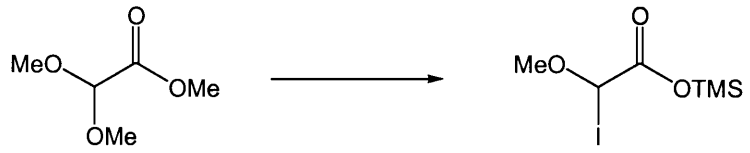
313

Iodotrimethylsilane was added dropwise to a stirred solution of methyl dimethoxyacetate (123 µl, 1.00 mmol, 1 equiv.) in dry deuterated chloroform (1 ml) under nitrogen at r.t. The reaction mixture was stirred at the stated temperature (°C) and time (h). Small aliquots were removed for spectroscopic analysis. However, the instability of the *title compound* **313** precluded complete characterisation (Table 23). υ_{max} (NaCl; thin film)/cm^{-1} 2957 (w, C-H), 2837 (w, C-H), 1736 (s, C=O), 1456 (w, C-H), 1245 (m, C-O), 1210 (w, C-O), 1109 (m, C-O), 1069 (m, C-O); δ_H (300 MHz, $CDCl_3$) 6.31 (1H, s, CH), 3.81 (3H, s, CO_2CH_3), 3.35 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 167.0 (C=O), 66.6 (CH), 60.3 (OCH_3), 53.1 (CO_2CH_3); *m/z* (EI) 254 (32%, I_2), 147 (23%), 128 (27%, IH), 127 (21%, I^+), 103 (100%, M-I), 75 (28%, M-C_2H_4I).

Table 23: Formation of Methyl Iodomethoxyacetate 313

TMSI (equiv.)	Reaction temperature (°C)	Reaction time (h)	Yield (% conversion by NMR)
1	25	1	71
2	25	2	80
1.05	40	1	68
1.05	40	2	60
2	40	1	100

Formation of Trimethylsilyloxy iodomethoxyacetate 318- A Spectroscopic Study



318

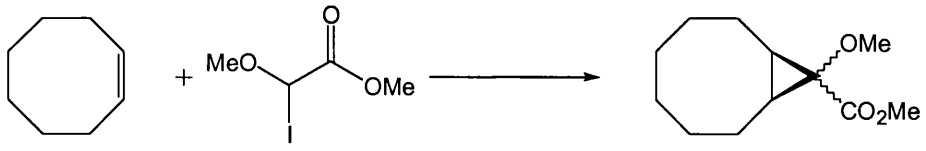
Iodotrimethylsilane (285 µl, 2.00 mmol, 2 equiv.) was added dropwise to a stirred solution of methyl dimethoxyacetate (123 µl, 1.00 mmol, 1 equiv.) in dry deuterated chloroform (1 ml) under nitrogen at r.t. The reaction mixture was warmed to 65°C and stirred for 1 h after which a small aliquot was removed for spectroscopic analysis (100% conversion by NMR). However, the instability of the *title compound* **318** precluded complete characterisation.

δ_H (300 MHz, $CDCl_3$) 6.27 (1H, s, CH), 3.34 (3H, s, OCH_3), 0.32 (9H, s, $Si(CH_3)_3$);

δ_C (75 MHz, $CDCl_3$) 166.1 (C=O), 69.4 ($CHIOCH_3$), 60.2 (OCH_3), 1.9 (O $Si(CH_3)_3$);

m/z (EI) 257 (4%, M-CH_3O), 140 (15%, $[CHI]^+$), 117 (38%, CO_2TMS).

Preparation of *exo-/endo*-9-Methoxy-9-methoxycarbonyl-*cis*-bicyclo[6.1.0]nonane 323



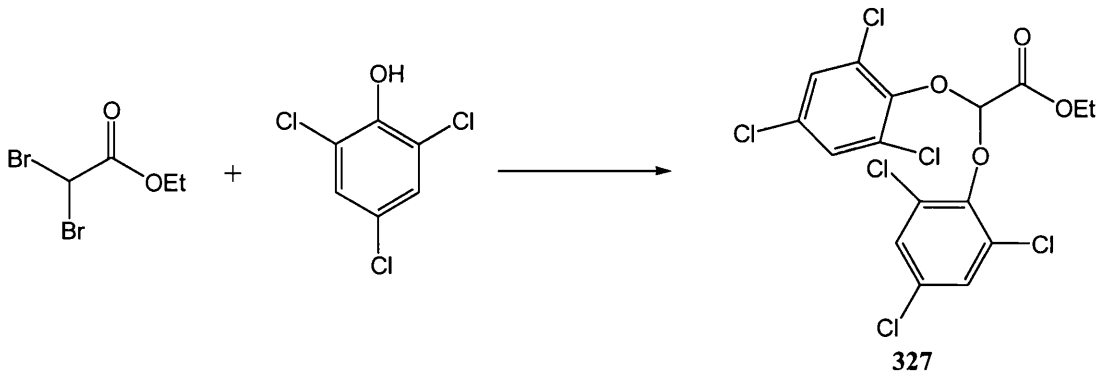
323

Iodotrimethylsilane (712 µl, 5.00 mmol, 2 equiv.) was added to a stirred solution of methyl dimethoxyacetate (308 µl, 2.50 mmol, 1 equiv.) at r.t. and the resulting solution was then stirred at 40°C for 1 h to form methyl iodomethoxyacetate **313**, which was used without complete characterisation. To the reaction mixture, copper(I) oxide (179 mg, 1.25 mmol, 0.5 equiv.), *t*-butyl isocyanide (848 µl, 7.50 mmol, 3 equiv.) and cyclooctene (651 µl, 5.00 mmol, 2 equiv.) were added. The resulting mixture was heated to 80°C and stirred for 24 h. The reaction mixture was cooled to ambient temperature, filtered through Celite and the filter cake was washed with ether (2 x 20 ml). The organic layer was washed with sodium thiosulfate solution (2 x 20

ml), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude oil was chromatographed on neutral alumina using ether (0-10%)-light petroleum [40-60°C]) to give a diastereomeric mixture of *exo-/endo*-9-methoxy-9-methoxycarbonyl-*cis*-bicyclo[6.1.0]nonane **323** (132 mg, 0.62 mmol, 25%, 1.8:1 as determined by GC) as a red oil, R_f= 0.25 (neutral alumina, 10% ether in light petroleum [40-60°C]).

υ_{max} (NaCl; thin film)/cm^{-1} 2927 (s, C-H), 2854 (m, C-O), 1750 (s, C=O), 1734 (m, C=O), 1459 (m, C-H), 1439 (m, C-H), 1357 (w, C-H), 1193 (m, C-O), 1123 (m, C-O); δ_H (500 MHz; $CDCl_3$) 3.74 (3H, s, CO_2CH_3), 3.73 (3H, s, CO_2CH_3), 3.34 (3H, s, OCH_3), 3.33 (3H, s, OCH_3), 2.24-1.30 (28H, m, CH and CH_2); δ_C (126 MHz; $CDCl_3$) 173.1, 172.9 (2 x C=O), 172.7, 172.5 (2 x C), 58.5 (2 x OCH_3), 51.8, 51.7 (2 x CO_2CH_3), 42.8 (4 x CH), 29.1, 28.9, 28.6, 27.8, 27.1, 26.4 (12 x CH_2); *m/z* (EI) 213 (16%, M+1), 181 (62%, M-C_2H_5), 153 (36%, M-$C_2H_3O_2$), 121 (100%, M-$C_3H_6O_3$), 104 (78%, M-$C_4H_{11}O_3$), 93 (38%, M-$C_5H_{10}O_3$), 79 (51%, M-$C_6H_{12}O_3$), 75 (20%, $C_2H_5CO(OH_2)^+$), 71 (37%, $[C_5H_{11}]^+$), 67 (44%, $[C_5H_7]^+$), 55 (25%, $[C_4H_7]^+$); (Found: M+1, 213.1489. $C_{12}H_{20}O_3$ requires *M*+1, 213.1490).

Preparation of Ethyl bis(2,4,6-trichlorophenoxy)acetate 327



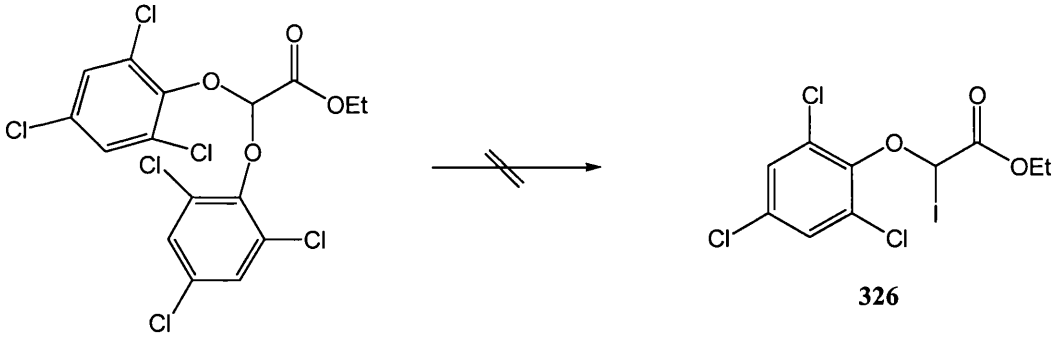
327

Anhydrous potassium carbonate (580 mg, 4.20 mmol, 2.1 equiv.) was added to 2,4,6-trichlorophenol (828 mg, 4.20 mmol, 2.1 equiv.) in dry DMF (5 ml). The resulting solution was stirred at r.t. for 30 min and ethyl dibromoacetate **154** (259 µl, 2.00 mmol, 1 equiv.) was added. The reaction mixture was then stirred at 50°C for 96 h. Water was then added (30 ml) and this was extracted with ether (5 x 30 ml). The organic layer was further washed with water (60 ml) and then brine (60 ml). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow-white crystalline solid which was crystallised from 10% ether in light petroleum [40-

60°C] to give the *title compound* **327** (612 mg, 1.28 mmol, 64%) as a white crystalline solid. m.p. 104-105°C (from methanol).

υ_{max} (KBr disc)/cm^{-1} 3080 (m, C-H), 2988 (w, C-H), 1762 (s, C=O), 1552 (s, C=C), 1442 (s, C-H), 1236 (s, C-O), 1214 (s, C-O), 1113 (s, C-O); δ_H (300 MHz; $CDCl_3$) 7.30 (4H, s, ArH), 5.96 (1H, s, CH), 4.31 (2H, q, *J* 7.2, CH_2), 1.29 (3H, t, *J* 7.2, CH_3); δ_C (75 MHz; $CDCl_3$) 164.2 (C=O), 146.5 (2 x C_{Ar}-O), 131.1, 130.1 (6 x C_{Ar}-Cl), 128.9 (4 x C_{Ar}-H), 99.2 (CH), 62.7 (CH_2), 13.9 (CH_3); *m/z* (FAB) 477 (2%, M+1), 405 (23%, M-$C_3H_5O_2$), 289 (18%), 281 (100%), 225 (38%, $[C_6H_2Cl_3OCO]^+$) , 209 (53%, $[C_6H_2Cl_3OC]^+$), 197 (35%, $[C_6H_2Cl_3O]^+$), 181 (16%, $[C_6H_2Cl_3]^+$); (Found: M+H, 476.8781. $C_{16}H_{11}O_4Cl_6$ requires *M*+1, 476.8789).

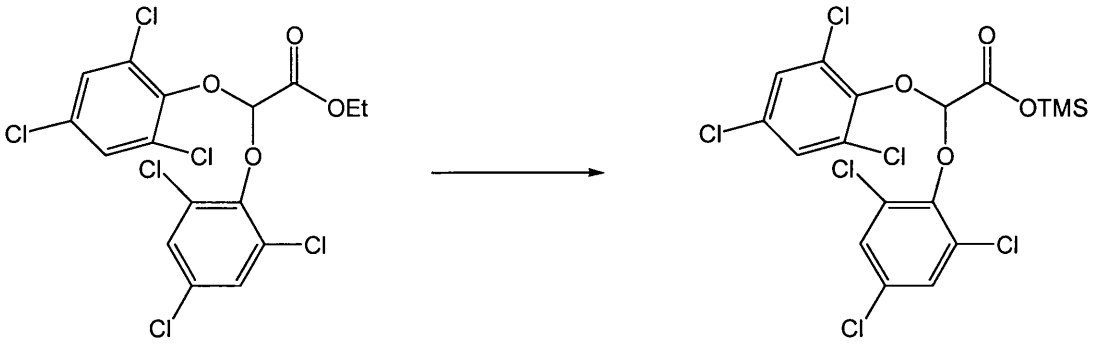
Attempted Reaction of Ethyl bis(2,4,6-trichlorophenoxy)acetate 327 with Iodotrimethylsilane-A Spectroscopic Study



326

Iodotrimethylsilane (42.7 µl, 0.30 mmol, 2 equiv.) was added to ethyl bis(2,4,6-trichlorophenoxy)acetate **327** (72.0 mg, 0.15 mmol, 1 equiv.) dissolved in dry deuterated chloroform (0.5 ml) under nitrogen at r.t. The reaction mixture was heated to 40°C and stirred for 1 h. A small aliquot was removed for spectroscopic analysis and only unreacted starting material and iodotrimethylsilane were detected from NMR analysis. The remaining reaction mixture was heated to reflux for a further 1 h and a second aliquot was removed. Only unreacted starting material **327** and iodotrimethylsilane were detected from NMR analysis.

Formation of Trimethylsilyloxy Bis(2,4,6-trichlorophenoxy)acetate 328-A Spectroscopic Study

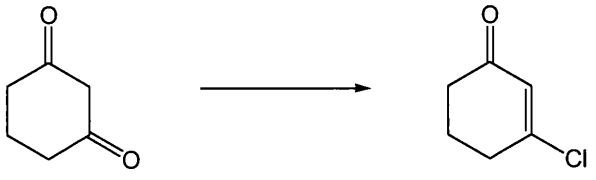


328

Iodotrimethylsilane (42.7 μl, 0.30 mmol, 2 equiv.) was added to ethyl bis(2,4,6-trichlorophenoxy)acetate **327** (72.0 mg, 0.15 mmol, 1 equiv.) at r.t. The reaction mixture was heated to 90°C and stirred for 15 h. An aliquot was removed for spectroscopic analysis (100% conversion by NMR). The instability of the *title compound* precluded complete characterisation.

δ_H (300 MHz, $CDCl_3$) 7.29 (4H, m, ArH), 6.00 (1H, s, CH), 0.31 (9H, s, $Si(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 163.9 (C=O), 146.8 (2 x C_{Ar}-O), 130.8, 130.0 (6 x C_{Ar}-Cl), 128.9 (4 x C_{Ar}-H), 99.5 (CH), 1.9 ($Si(CH_3)_3$).

Preparation of 3-Chloro-2-cyclohexenone 333[179]



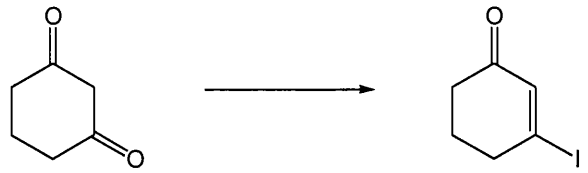
333

To an ice-cold, stirred solution of recrystallised triphenylphosphine (6.35 g, 24.2 mmol, 1.1 equiv.) in dry benzene (105 ml) was added chlorine (37.2 ml of a 0.65 M solution in dry carbon tetrachloride, 24.2 mmol, 1.1 equiv.). After the addition was complete, tlc analysis of the mixture indicated that triphenylphosphine was absent. To the resulting suspension was added successively triethylamine (3.37 ml, 24.2 mmol, 1.1 equiv.) and cyclohexane-1,3-dione (2.47 g, 22.0 mmol, 1 equiv.) and the mixture was stirred for a further 4 h at r.t. The suspension was filtered through a short column

of silica gel using ether (300 ml) as eluent and the solvents were then removed *in vacuo* to afford a yellow oil. Bulb to bulb distillation gave *β-chloro enone* **333** (2.15 g, 16.5 mmol, 75%) as a colourless oil, b.p. 66-69°C/1 mmHg (lit.,[206] 50°C/0.3 mmHg).

υ_{max} (NaCl; thin film)/cm^{-1} 2948 (m, C-H), 2872 (w, C-H), 1673 (s, C=O), 1601 (s, C=O), 1449 (w, C-H), 1421 (m, C-H), 749 (m, C-Cl); δ_H (300 MHz, $CDCl_3$) 6.16 (1H, t, *J* 1.5, CH), 2.63 (2H, m, CH_2), 2.34 (2H, m, CH_2), 2.03 (2H, m, CH_2); δ_C (75 MHz, $CDCl_3$) 196.7 (C=O), 158.4 (CCl), 128.4 (CH), 36.2, 33.8, 22.1 (CH_2); *m/z* (EI) 130 (42%, M^+), 112 (23%, M-H_2O), 102 (60%, M-CO), 84 (23%, M-H_2OCl), 67 (30%, $[C_5H_7]^+$), 55 (22%, $[C_4H_7]^+$).

Preparation of 3-Iodo-2-cyclohexenone 334[179]

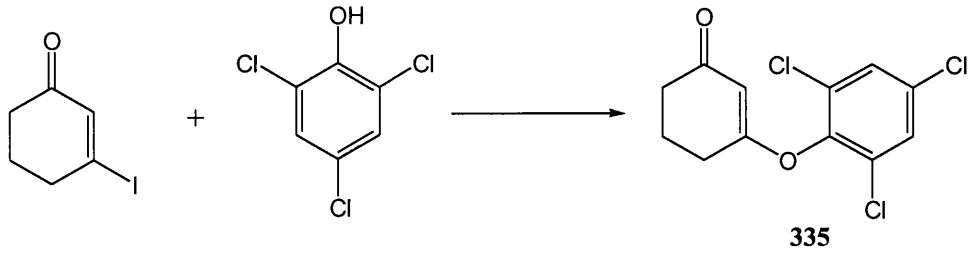


334

To a stirred solution of recrystallised triphenylphosphine (6.11 g, 23.3 mmol, 1.1 equiv.) in dry acetonitrile (212 ml) was added iodine (5.91 g, 23.3 mmol, 1.1 equiv.) and the mixture was stirred at r.t. for 2 h. To the resulting orange-yellow suspension was added successively triethylamine (3.25 ml, 23.3 mmol, 1.1 equiv.) and cyclohexan-1,3-dione (2.38 g, 21.2 mmol, 1 equiv.). The mixture was heated to reflux and stirred for 18 h, then concentrated *in vacuo* and the residual material was filtered through a short column of silica gel using ether (300 ml) as eluent. The solvent was removed *in vacuo* to afford a yellow oil. Bulb to bulb distillation gave *β-iodo enone* **334** (3.91 g, 17.6 mmol, 83%) as a colourless oil, b.p. 135-140°C/0.5 mmHg (lit.,[207] 110-120°C/0.1 mmHg).

υ_{max} (NaCl; thin film)/cm^{-1} 2946 (m, C-H), 2876 (w, C-H), 1670 (s, C=O), 1590 (s, C=C), 1450 (w, C-H), 1420 (m, C-H); δ_H (300 MHz, $CDCl_3$) 6.76 (1H, t, *J* 1.6, CH), 2.97 (2H, m, CH_2), 2.37 (2H, m, CH_2), 1.99 (2H, m, CH_2); δ_C (75 MHz, $CDCl_3$) 195.0 (C=O), 140.7 (CH), 126.7 (CI), 40.6, 36.5, 24.0 (CH_2); *m/z* (EI) 222 (99%, M^+), 127 (24%, I^+), 95 (100%, $[C_6H_7O]^+$), 67 (79%, $[C_5H_7]^+$), 55 (35%, $[C_4H_7]^+$).

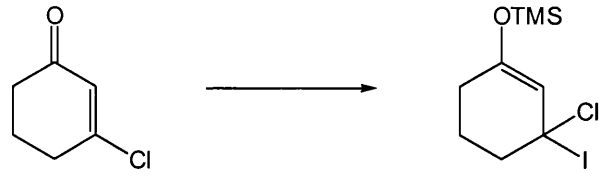
Preparation of 3-(2,4,6-Trichlorophenol)-2-cyclohexanone 335



335

A mixture of 2,4,6-trichlorophenol (2.67 g, 13.5 mmol, 2 equiv.) and potassium carbonate (1.87 g, 13.5 mmol, 2 equiv.) in dry DMF (10 ml) was heated for 15 min at 60°C. 3-Iodo-2-cyclohexenone **334** (1.50 g, 6.76 mmol, 1 equiv.) in dry DMF (5 ml) was then added dropwise and the resulting solution was stirred at 60°C for 72 h. The reaction mixture was cooled, filtered, and the residue was washed with ether (3 x 10 ml). The solvents were removed *in vacuo* and then distilled (bulb to bulb) under reduced pressure at 20 mmHg, 25°C to leave a dark oil. The crude product was chromatographed using 33% ether in light petroleum [40-60°C]) to give the *title compound* **335** (620 mg, 2.13 mmol, 32%) as a white crystalline solid, R_f= 0.21 (silica, 33% ether in light petroleum [40-60°C]), m.p. 121.5-124°C (from methanol). υ_{max} (KBr disc)/cm^{-1} 3132 (w, C-H), 3045 (s, C-H), 2958 (s, C-H), 1676 (s, C=O), 1613 (s, C=C), 1560 (s, C-H), 1445 (s, C-H), 1224 (s, C-O), 1127 (s, C-O); δ_H (300 MHz; $CDCl_3$) 7.37 (2H, s, ArH), 4.94 (1H, s, CH), 2.69 (2H, t, *J* 6.4, CH_2), 2.37 (2H, t, *J* 6.4, CH_2), 2.09 (2H, m, CH_2); δ_C (75 MHz; $CDCl_3$) 198.9 (C-O), 174.7 (C=O), 144.3, 132.2, 129.5, (3 x C_{Ar}-Cl), 129.1 (2 x C_{Ar}-H) 105.9 (CH), 36.5, 27.5, 21.0 (3 x CH_2); *m/z* (EI) 290 (63%, M+1), 196 (30%, $[C_6H_2Cl_3O]^+$), 95 (88%, M-$C_6H_2Cl_3O$), 67 (100%, $[C_5H_7]^+$), 55 (31%, $[C_4H_7]^+$); (Found: M^+, 289.9663. $C_{12}H_9Cl_3O_2$ requires *M*, 289.9668).

Formation of 3-Chloro-3-iodo(cyclohex-1-enyloxy)trimethylsilane 338-A Spectroscopic Study

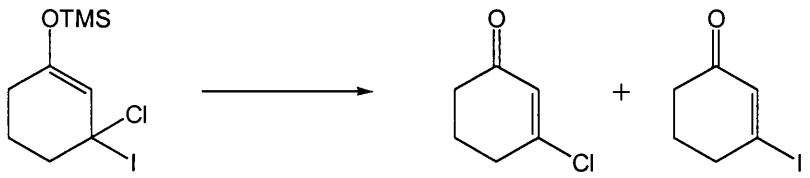


338

Iodotrimethylsilane (75.4 μl, 0.53 mmol, 1 equiv.) was added to a stirred solution of 3-chloro-2-cyclohexenone **333** (69.2 mg, 0.53 mmol, 1 equiv.) in dry deuterated chloroform (1.5 ml) under nitrogen at –78°C. The resulting mixture was stirred for 1 h at –78°C after which a small aliquot was removed for spectroscopic analysis (100% conversion by NMR). However, the instability of the *title compound* **338** precluded complete characterisation.

υ_{max} (NaCl; thin film)/cm^{-1} 2942 (w, C-H), 2861 (w, C-H), 1656 (s, C=C), 1452 (w, C-H), 1417 (m, C-H), 1330 (s, C-H), 1284 (m, Si-C), 1182 (m, Si-O), 1131 (m, Si-O), 882 (m, Si-C); δ_H (300 MHz, $CDCl_3$) 6.81 (1H, m, CH), 2.90 (2H, m, CH_2), 2.41 (2H, m, CH_2), 2.01 (2H, m, CH_2), 0.40 (9H, s, $Si(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 196.9 (CClI), 140.3 (CH), 131.2 (CO), 40.9, 36.3, 23.9 (CH_2), 3.2 ($Si(CH_3)_3$); *m/z* (EI) 332 (6%, M+1), 222 (46%, M-TMSCl), 129 (17%, $[C_6H_6OCl]^+$), 128 (47%, IH), 95 (41%, $[C_6H_7O]^+$), 67 (40%, $[C_5H_7]^+$), 55 (33%, $[C_4H_7]^+$).

Formation of 3-Chloro-2-cyclohexenone 333 and 3-Iodo-2-cyclohexenone 334 from 3-Chloro-3-iodo(cyclohex-1-enyloxy)trimethylsilane 338

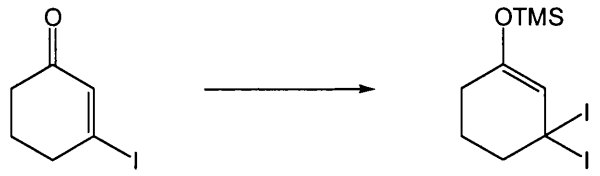


333 **334**

Iodotrimethylsilane (75.4 μl, 0.53 mmol, 1 equiv.) was added to a stirred solution of 3-chloro-2-cyclohexenone **333** (69.2 mg, 0.53 mmol, 1 equiv.) in dry deuterated chloroform (1.5 ml) under nitrogen at –78°C. The resulting mixture was stirred for 1

h, warmed to r.t., then diluted with ether (20 ml) and poured onto cold sodium thiosulfate solution (10 ml, 5%). The organic layer was separated, washed with brine (10 ml), dried ($MgSO_4$) and filtered. Evaporation of the solvent yielded a dark red oil (68.4 mg; 6.7:1 mixture of 3-iodo-2-cyclohexenone **334** and starting 3-chloro-2-cyclohexenone **333**). The products were spectroscopically identical to material prepared before.

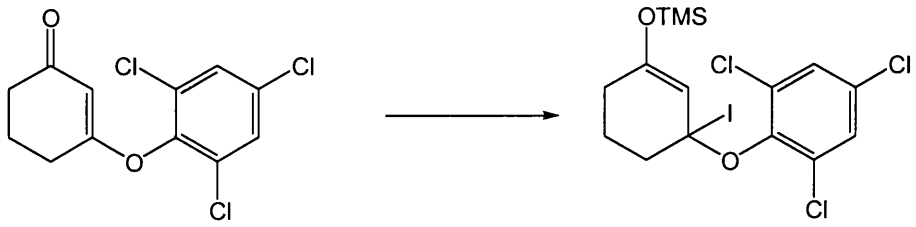
Formation of 3,3-Diiodo(cyclohex-1-enyloxy)trimethylsilane 339-A Spectroscopic Study



339

Iodotrimethylsilane (71.2 μl, 0.50 mmol, 1 equiv.) was added to a stirred solution of 3-iodo-2-cyclohexenone **334** (111 mg, 0.50 mmol, 1 equiv.) in dry deuterated chloroform (1.5 ml) under nitrogen at –78°C. The resulting mixture was stirred for 1 h at –78°C, after which a small aliquot was removed for spectroscopic analysis (100% conversion by NMR). The product **339** was characterised spectroscopically as defined below. However, it proved to be extremely labile and work up involving dilution with ether (20 ml) followed by washing with cold sodium thiosulfate solution (10 ml, 5%) and brine (10 ml), drying ($MgSO_4$), filtering and evaporation of the solvent yielded the starting 3-iodo-2-cyclohexenone **334** (85.0 mg, 0.38 mmol, 77%) as a dark red oil. υ_{max} (NaCl; thin film)/cm^{-1} 2947 (w, C-H), 2859 (w, C-H), 1651 (s, C=C), 1446 (w, C-H), 1411 (m, C-H), 1333 (m, C-H), 1289 (m, Si-C), 1181 (m, Si-O), 1132 (m, Si-O), 883 (m, Si-C); δ_H (300 MHz, $CDCl_3$) 6.81 (1H, m, CH), 2.90 (2H, m, CH_2), 2.41 (2H, m, CH_2), 2.01 (2H, m, CH_2), 0.40 (9H, s, $Si(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 197.4 (CI_2), 140.3 (CH), 131.2 (CO), 40.9, 36.3, 23.9 (CH_2), 1.9 ($Si(CH_3)_3$); *m/z* (EI) 299 (3%), 254 (45%, I_2), 222 (67%, M-TMSI), 147 (16%), 127 (19%, I^+), 95 (79%, $[C_6H_7O]^+$), 67 (48%, $[C_5H_7]^+$), 55 (32%, $[C_4H_7]^+$).

Formation of 3-Iodo-3-(2,4,6-trichlorophenol)cyclohex-1-enyloxy)trimethylsilane 340-A Spectroscopic Study

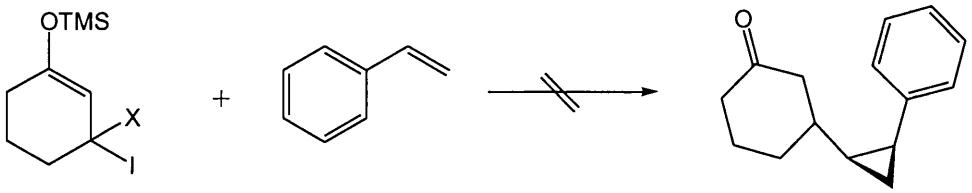


340

Iodotrimethylsilane (37.0 µl, 0.26 mmol, 1 equiv.) was added to a stirred solution of 3-(2,4,6-trichlorophenol)-2-cyclohexanone **335** (75.0 mg, 0.26 mmol, 1 equiv.) in dry deuterated chloroform (1.5 ml) under nitrogen at –78°C. The resulting mixture was stirred for 1 h, after which a small aliquot was removed for NMR analysis (100% conversion by NMR). The product **340** was characterised spectroscopically as defined below. However, it proved to be extremely labile and work up involving dilution with ether (20 ml) followed by washing with cold sodium thiosulfate solution (10ml, 5%) and brine (10 ml), drying ($MgSO_4$), filtering and evaporation of the solvent yielded the starting 3-(2,4,6-trichlorophenol)-2-cyclohexanone **335** (54.8 mg, 0.19 mmol, 73%) as a red crystalline solid.

δ_H (300 MHz; $CDCl_3$) 7.43 (5H, m, ArH), 5.98 (1H, s, CH), 2.99 (4H, m, CH_2), 2.26 (2H, m, CH_2), 0.02 (9H, s, $Si(CH_3)_3$); δ_C (75 MHz; $CDCl_3$) 207.9 ($COSi(CH_3)_3$), 189.2 (C-O), 143.1, 133.9 (2 x C_{Ar}-Cl), 129.5 (2 x C_{Ar}-H), 128.4 (C_{Ar}-Cl), 104.2 (CH), 33.6, 28.5, 20.5 (CH_2), 1.8 ($Si(CH_3)_3$).

Attempted Cyclopropanation of Styrene using 3-Halo-3-iodo(cyclohex-1-enyloxy)trimethylsilane 338/339 and Diethylzinc

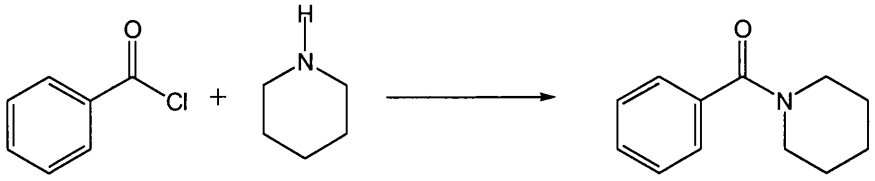


X=Cl, I

341

Iodotrimethylsilane (285 μl, 2.00 mmol, 1 equiv.) was added to a stirred solution of 3-halo-2-cyclohexenone **333** or **334** (2.00 mmol, 1 equiv.) in dry DCE (3 ml) under nitrogen at –78°C. The reaction mixture was stirred for 1 h to form 3-halo-3-iodo-cyclohex-1-enyloxy)trimethylsilane **338** or **339** as a highly labile oil which was used without complete characterisation. The compound was transferred *via* cannula into a mixture containing diethylzinc (1.42 ml of 12% solution in hexane, 1.00 mmol, 0.5 equiv.) and styrene (115 μl, 1.00 mmol, 0.5 equiv.) in dry DCE (2 ml) at 0°C. The reaction mixture was then stirred for 12 h at r.t. and then quenched with ammonium chloride solution (20 ml). The organic layer was separated and dried ($MgSO_4$), filtered and the solvents were removed *in vacuo*. No products were isolated after attempted purification by column chromatography using 10% ether in petroleum ether [40-60°C].

Preparation of 1-Benzoylpiperidine 345



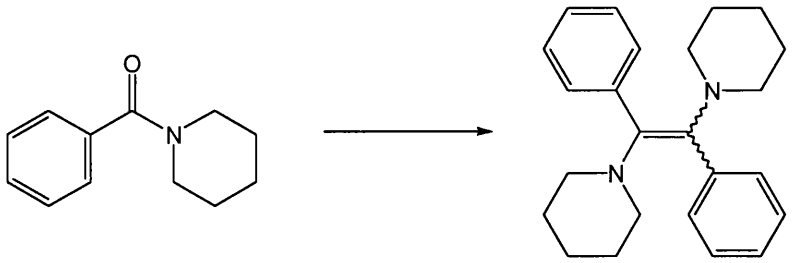
345

To a stirred solution of piperidine (10.9 ml, 110 mmol, 1 equiv.), triethylamine (18.4 ml, 132 mmol, 1.2 equiv.) and 4,4-dimethylaminopyridine (0.67 g, 5.50 mmol, 0.05 equiv.) in DCM (150 ml), was added benzoyl chloride (12.8 ml, 110 mmol, 1 equiv.) dropwise at 0°C. The reaction mixture was stirred for 4 h at r.t. Water (150 ml) was added and the organic layer was separated. The aqueous layer was further washed

with DCM (2 x 50 ml) and the combined organic layers were washed with aqueous hydrochloric acid (100 ml, 2 M), and brine (2 x 100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude oil was distilled to give the *amide* **345** (16.2 g, 85.6 mmol, 78%) as a colourless oil which crystallised on standing to give a colourless crystalline solid, b.p. 169-172°C/10 mmHg (lit.,[208] 165-168°C/10 mmHg), m.p. 47-49°C (from methanol) (lit.,[209] 46-51°C).

υ_{max} (KBr disc)/cm^{-1} 3237 (m, C-H), 2997 (m, C-H), 2939 (m, C-H), 2853 (m, C-H), 1658 (s, C=O), 1606 (w, C-N), 1430 (s, C-H); δ_H (300 MHz; $CDCl_3$) 7.33 (5H, s, PhH), 3.64 (2H, br s, CH_2), 3.31 (2H, br s, CH_2), 1.62 (6H, br m, CH_2); δ_C (75 MHz; $CDCl_3$) 170.1 (C=O), 136.5 (C(Ar)-), 129.2, 128.2, 126.7 (CH(Ar)-), 48.5, 43.0, 26.2 x 2, 24.5 (5 x CH_2); *m/z* (EI) 189 (39%, M^+), 188 (100%, M-1), 105 (88%, $[C_6H_5CO]^+$), 77 (43%, $[C_6H_5]^+$).

Preparation of 1,2-Dipiperidinostilbene 346[181]



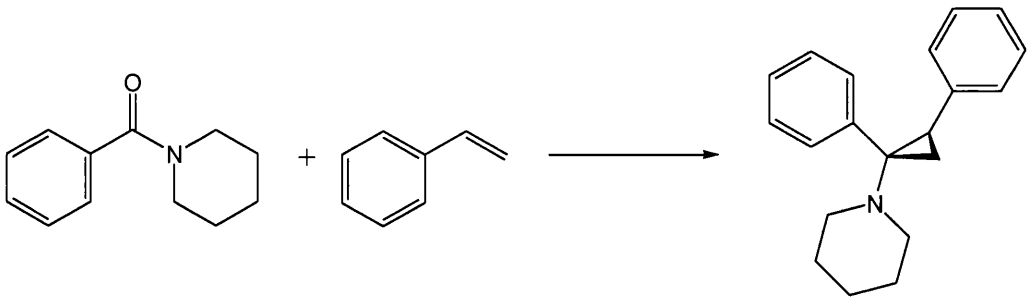
346

Samarium powder (481 mg, 3.20 mmol, 3.2 equiv.) was placed under an argon atmosphere in a three-necked flask, and purified 1,2-diiodoethane (620 mg, 2.20 mmol, 2.2 equiv.) in dry THF (6 ml) was added. The mixture was warmed to 67°C and stirred for 1 h to give a blue solution of samarium metal/samarium diiodide mixed reagent (Sm/SmI_2). To the reaction mixture, 1-benzoylpiperidine **345** (189 mg, 1.00 mmol, 1 equiv.) in dry THF (16 ml) was added dropwise. The reaction mixture was stirred at 67°C for 14 h and was then quenched with saturated aqueous sodium bicarbonate solution (40 ml). The product was extracted with ether (3 x 20 ml) and the combined extracts were washed with brine (30 ml), dried ($MgSO_4$), and the solvent evaporated *in vacuo*. Purification by column chromatography on basic alumina (deactivated 15wt% water) using petroleum ether [40-60°C] provided an inseparable diastereomeric mixture of *E*- and *Z*-1,2-dipiperidinostilbene **346** (87.9 mg, 0.51 mmol,

51%, *E/Z*, 84:16 as determined by NMR) as a yellow crystalline solid, whose spectral properties were in accord with the literature,[181] m.p. 111.0-112.5°C (from methanol) (lit.,[181b] 112.0-112.5°C).

υ_{max} (KBr disc)/cm^{-1} 3054 (m, C-H), 3018 (m, C-H), 2929 (s, C-H), 2850 (s, C-H), 2812 (m, C-H, 1594 (w, C-N), 1489 (m, C-H); δ_H (300 MHz; $CDCl_3$) [*E*-isomer] 7.61-7.33 (8H, br d, ArH), 7.26-7.20 (2H, m, ArH), 2.36 (8H, br s, CH_2), 1.26 (12H, br s, CH_2); [*Z*-isomer] 7.10-7.01 (4H, m, ArH), 6.99-6.91 (6H, m, ArH), 2.98 (8H, br s, CH_2), 1.56 (12H, br s, CH_2); δ_C (75 MHz; $CDCl_3$) 142.4, 140.6, 137.7, 136.5, 131.3, 129.7, 127.7, 127.1, 126.2, 125.4, 52.9, 51.9, 27.2, 27.0, 24.8, 24.4; *m/z* (FAB) 346 (100%, M^+).

Preparation of 1-(1,2-Diphenylcyclopropyl)piperidine 347[180]



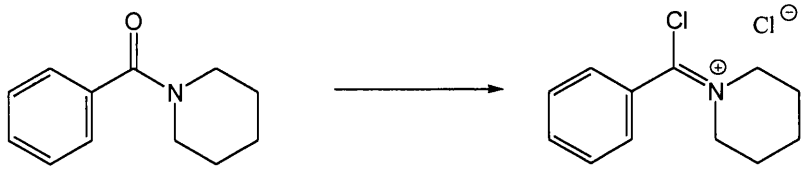
347

Samarium powder (752 mg, 5.00 mmol, 2 equiv.) was placed under an argon atmosphere in a three-necked flask, and purified 1,2-diiodoethane (705 mg, 2.50 mmol, 1 equiv.) in dry THF (12.5 ml) was added. The mixture was warmed to 67°C and stirred for 1 h to give a blue solution of samarium metal/samarium diiodide mixed reagent (Sm/SmI_2). To the reaction flask, were added 1-benzoylpiperidine **345** (473 mg, 2.50 mmol, 1 equiv.) and styrene (12.5 ml, 109 mmol, 43.6 equiv.), and the resulting solution was stirred at 67°C for 4 h. The reaction mixture was then quenched with saturated aqueous sodium bicarbonate solution (50 ml), and the product was extracted with ether (3 x 30 ml). The combined organic extracts were washed with brine (2 x 30 ml), dried ($MgSO_4$), and the solvent was removed *in vacuo*. The styrene was removed by distillation *via* a water aspirator at 65°C. Purification by column chromatography on silica using 10% ether in light petroleum [40-60°C] as an eluent gave the *cyclopropane* **347** (332 mg, 1.20 mmol, 48%) as an orange oil, whose

spectral properties were in accord with literature,[180] R_f= 0.63 (silica, 10% ether in light petroleum [40-60°C]).

υ_{max} (NaCl; neat)/cm^{-1} 3057 (s, C-H), 3024 (m, C-H), 2930 (s, C-H), 2851 (m, C-H), 2801 (m, C-H), 1601 (m, C-N), 1494 (m, C-H), 1445 (s, C-H); δ_H (300 MHz; $CDCl_3$) 7.43 (2H, d, *J* 7.7, PhH), 7.30-7.15 (8H, m, PhH), 2.30 (3H, t, *J* 7.9, cyclopropyl CH and CH_2), 2.06 (2H, m, CH_2), 1.36 (2H, d, *J* 7.9, CH_2), 1.24 (4H, m, CH_2), 1.13 (2H, m, cyclopropyl CH_2); δ_C (75 MHz; $CDCl_3$) 138.9, 138.8 (C_{Ar}), 130.5, 128.3, 127.5, 127.1, 126.9, 125.4 ($C_{Ar}H$), 55.9 (C), 50.9 (CH_2), 32.1 (CH), 26.2, 24.4, 21.5 (CH_2); *m/z* (EI) 346 (9%), 277 (42%, M^+), 276 (32%, M-1), 186 (100%, M-$[C_7H_7]^+$), 117 (11%, $[C_{10}H_9]^+$), 104 (17%, $[C_8H_8]^+$), 91 (14%, $[C_7H_7]^+$), 84 (14%, $[NC_5H_{10}]^+$), 77 (10%, $[C_6H_5]^+$).

Formation of 1-(Chlorophenylmethylene)piperidinium chloride 350-A Spectroscopic Study



350

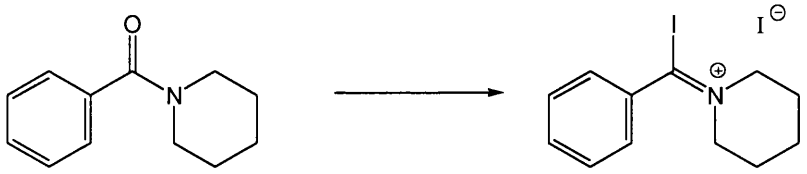
Oxalyl chloride (174 µl, 2.00 mmol, 1 equiv.) was added dropwise to a stirred solution of 1-benzoylpiperidine **345** (378 mg, 2.00 mmol, 1 equiv.) in dry DCM (1.8 ml) under nitrogen at r.t. The reaction mixture was then stirred at the stated temperature (°C) and time (h). The solvent was removed *in vacuo* to give the *title compound* **350**, whose instability precluded complete characterisation (490 mg, 2.00 mmol, 100%) as an extremely hygroscopic white crystalline solid (Table 24).

υ_{max} (KBr disc)/cm^{-1} 2925 (m, C-H), 2849 (w, C-H), 1624 (m, C=N), 1434 (m, C-H), 731 (w, C-Cl); δ_H (400 MHz; $CDCl_3$) 8.09 (2H, d, *J* 8.0, PhH), 7.72 (1H, t, *J* 6.7 and 8.3, PhH), 7.62 (2H, t, *J* 7.0 and 8.3, PhH), 4.83 (2H, br s, NCH_2), 4.59 (2H, br s, NCH_2), 2.23 (2H, s, CH_2), 2.02-1.95 (4H, br m, CH_2); δ_C (100 MHz; $CDCl_3$) 169.3 (C-Cl), 133.3, 129.8, 128.4, 128.1 (5 x C_{Ar}), 58.3, 57.2, 25.6, 24.8, 21.1 (CH_2); *m/z* (EI) 346 (54%, 2 x M^+), 208 (22%, M^+), 188 (91%), 105 (100%), 84 (14%, $[NC_5H_{10}]^+$), 77 (66%, $[C_6H_5]^+$); (Found: M^+, 208.0895. $C_{12}H_{15}NCl$ requires *M*, 208.0893).

Table 24: Formation of 1-(Chlorophenylmethylene)piperidinium chloride 350

Reaction temperature (°C)	Reaction time (h)	Yield (% conversion by NMR)
25	1	64
25	4	77
25	16	85
25	24	100
40	1	100

Formation of 1-(Iodophenylmethylene)piperidinium iodide 351-A Spectroscopic Study



351

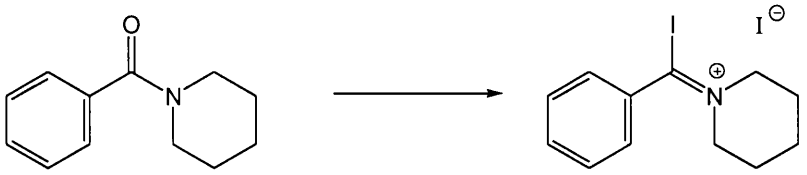
Iodotrimethylsilane (474 μl, 3.33 mmol, 3 equiv.) was added dropwise to 1-benzoylpiperidine **345** (210 mg, 1.11 mmol, 1 equiv.) under nitrogen at r.t. The reaction mixture was then stirred at the stated temperature (°C) and time (h). The top layer was removed by syringe under nitrogen to leave a dark red viscous oil. Small aliquots were removed for spectroscopic analysis. However, the instability of the *title compound* **351** precluded complete characterisation (Table 25).

δ_H (400 MHz; $CDCl_3$) 7.87 (2H, d, *J* 7.8, PhH), 7.65 (1H, t, *J* 6.5 and 9.5, PhH), 7.57 (2H, t, *J* 7.6 and 8.5, PhH), 4.13 (2H, br s, NCH_2), 3.77 (2H, br s, NCH_2), 1.96 (2H, s, CH_2), 1.76 (4H, m, CH_2); δ_C (100 MHz; $CDCl_3$) 167.7 (C-I), 132.2, 128.6, 127.5, 126.5 [C(Ar)], 51.1, 47.9, 24.8, 24.2, 21.8 (CH_2).

Table 25: Formation of 1-(Iodophenylmethylene)piperidinium iodide 351

Reaction Temperature (°C)	Reaction Time (h)	Yield (% conversion by NMR)
25	1	0
106	16	63
106	23	80

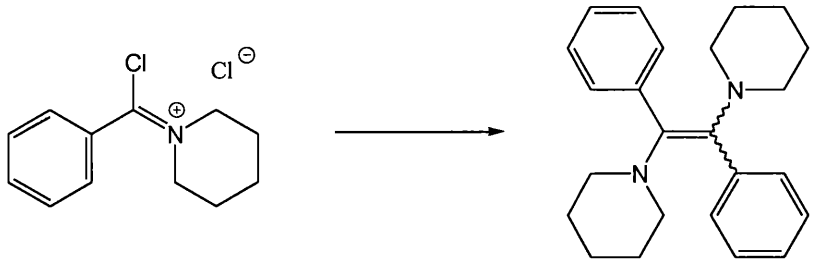
Formation of 1-(Iodophenylmethylene)piperidinium iodide 351-A Spectroscopic Study



351

Iodotrimethylsilane (474 μl, 3.33 mmol, 3 equiv.) was added dropwise to a stirred mixture of distilled trimethylsilyl trifluoromethanesulfonate (10.9 μl, 0.06 mmol, 0.05 equiv.) and 1-benzoylpiperidine **345** (210 mg, 1.11 mmol, 1 equiv.) under nitrogen at r.t. The reaction mixture was then heated to reflux (106°C) and stirred for 19 h. The top layer was removed by syringe under nitrogen to leave a dark red viscous oil. A small aliquot was taken for spectroscopic analysis (100% conversion by NMR). The spectral properties were identical to those reported above.

Preparation of 1,2-Dipiperidinostilbene 346 *via* Zinc Reduction of 1-(Chlorophenylmethylene)piperidinium chloride 350

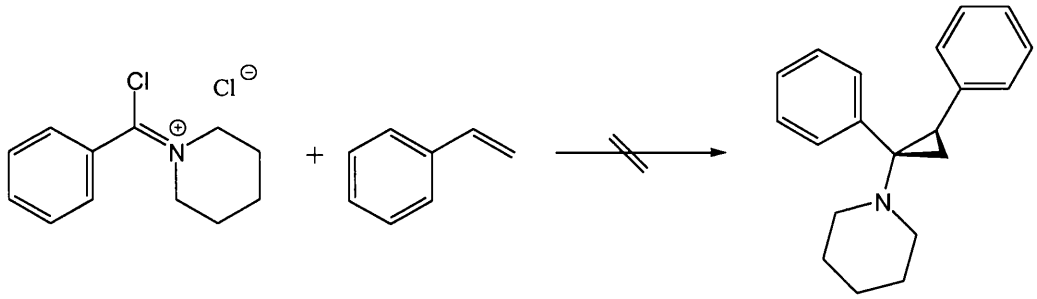


346

Oxalyl chloride (174 μl, 2.00 mmol, 1 equiv.) was added dropwise to a stirred solution of 1-benzoylpiperidine **345** (378 mg, 2.00 mmol, 1 equiv.) in dry DCE (1 ml). The mixture was stirred for a further 30 min under nitrogen at 40°C to form 1-(chlorophenylmethylene)piperidinium chloride **350** which was used without complete characterisation. This solution was added to acid-washed zinc dust (1.31 g, 20.0 mmol, 10 equiv.) in dry DCE (10 ml) under nitrogen at r.t. The resulting mixture was warmed to 90°C and vigorously stirred for 60 h. The reaction mixture was cooled to ambient temperature, quenched by addition of saturated aqueous sodium bicarbonate

solution (25 ml), and the mixture was stirred for 5 min. The resultant suspension was filtered through Hyflo, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (3 x 20 ml) and the combined organic layers were washed with brine, dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude material was dried *in vacuo* for 5 h. Purification by column chromatography on basic alumina (deactivated with 15wt% water) using petroleum ether [40-60°C] provided an inseparable diastereomeric mixture of *E*- and *Z*-1,2-dipiperidinostilbene **346** (21.6 mg, 0.06 mmol, 6%, *E*/*Z*, 85:15) as a yellow solid, which was spectroscopically identical to material already prepared and starting 1-benzoylpiperidine (247 mg, 1.29 mmol, 65%).

Attempted Aminocyclopropanation of Styrene *via* Zinc Reduction of 1-(Chlorophenylmethylene)piperidinium chloride 350

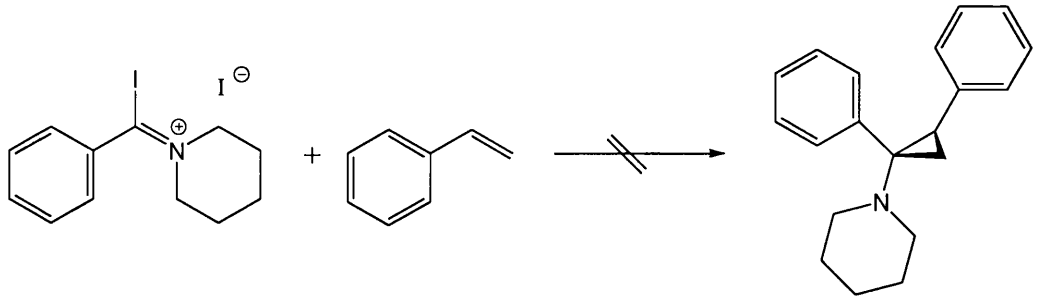


347

Oxalyl chloride (174 µl, 2.00 mmol, 1 equiv.) was added dropwise to a stirred solution of 1-benzoylpiperidine **345** (378 mg, 2.00 mmol, 1 equiv.) in dry DCM or DCE (1 ml). The mixture was stirred for a further 30 min under nitrogen at 40°C to form 1-(chlorophenylmethylene)piperidinium chloride **350** which was used without complete characterisation. This solution was then added to a mixture of acid-washed zinc dust (3.27 g, 50.0 mmol, 25 equiv.) and styrene (4.58 ml, 40.0 mmol, 20 equiv.) in dry DCM or DCE (5 ml) under nitrogen at r.t. The resulting mixture was vigorously stirred at reflux temperature (42°C or 86°C) for 18 h. The reaction mixture was quenched with saturated aqueous sodium bicarbonate solution (40 ml) and the layers were separated. The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude material was dried *in vacuo* to remove the styrene for 5 h and column chromatography on basic alumina (deactivated with 15wt% water) using

petroleum ether [40-60°C] gave an inseparable diastereomeric mixture of *E*- and *Z*-1,2-dipiperidinostilbene **346** (19.0 mg, 0.05 mmol, 3%, *E*/*Z*, 85:15), which was spectroscopically identical to material already prepared, and starting 1-benzoylpiperidine **345** (271 mg, 1.43 mmol, 71%).

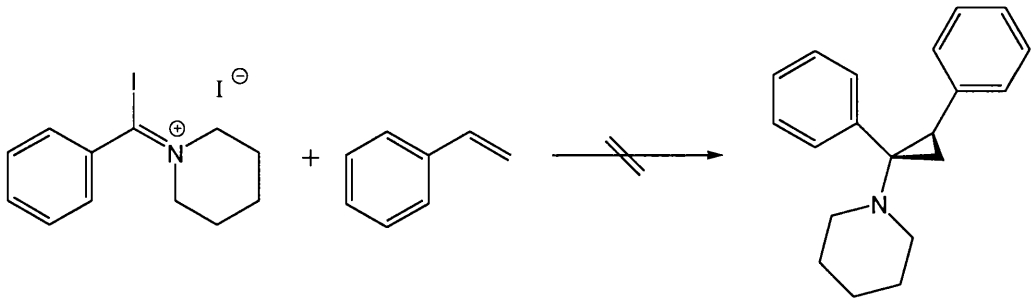
Attempted Aminocyclopropanation of Styrene *via* Zinc Reduction of 1-(Iodophenylmethylene)piperidinium iodide 351



347

Iodotrimethylsilane (1.28 ml, 9.00 mmol, 3 equiv.) was added dropwise to a stirred mixture of distilled trimethylsilyl trifluoromethanesulfonate (27.1 μl, 0.15 mmol, 0.05 equiv.) and 1-benzoylpiperidine **345** (568 mg, 3.00 mmol, 1 equiv.) under nitrogen at r.t. The reaction mixture was then heated to reflux (110°C) and stirred for 19 h. The top layer was removed by syringe to give 1-(iodophenylmethylene)piperidinium iodide **351** as an unstable oil which was used without complete characterisation. A solution of 1-(iodophenylmethylene)piperidinium iodide **351** in dry DCE (5 ml) was then added to a mixture of acid-washed zinc dust (4.90 g, 75 mmol, 25 equiv.) and styrene (6.87 ml, 60.0 mmol, 20 equiv.) in dry DCE (5 ml) under nitrogen at r.t. The resulting mixture was heated to reflux and vigorously stirred for 18 h. The reaction mixture was quenched with saturated aqueous sodium bicarbonate solution (40 ml) and the layers were separated. The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude material was dried *in vacuo* to remove the styrene for 5 h and column chromatography on silica with 20% ether in light petroleum [40-60°C] gave starting 1-benzoylpiperidine **345** (371 mg, 1.96 mmol, 65%).

Attempted Aminocyclopropanation of Styrene *via* Samarium Reduction of 1-(Iodophenylmethylene)piperidinium iodide 351



347

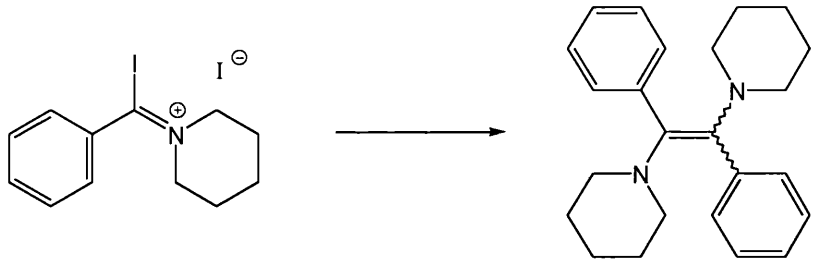
Iodotrimethylsilane (1.28 ml, 9.00 mmol, 3 equiv.) was added dropwise to a stirred mixture of distilled trimethylsilyl trifluoromethanesulfonate (27.1 μl, 0.15 mmol, 0.05 equiv.) and 1-benzoylpiperidine **345** (568 mg, 3.00 mmol, 1 equiv.) under nitrogen at r.t. The reaction mixture was then heated to reflux (110°C) and stirred for 19 h. The top layer was removed by syringe to give 1-(iodophenylmethylene)piperidinium iodide **351** as an unstable oil which was used without complete characterisation. A solution of 1-(iodophenylmethylene)piperidinium iodide **351** in dry DCE (5 ml) was then added to a mixture of styrene (6.87 ml, 60.0 mmol, 20 equiv.) and samarium diiodide formed from heating a mixture of samarium (451 mg, 3.00 mmol, 1 equiv.) and 1,2-diiodoethane (846 mg, 3.00 mmol, 1 equiv.) in dry THF (5 ml) under nitrogen at 70°C for 2 h. The resulting mixture was stirred at 70°C for 12 h. The solution gradually changed from blue to yellow indicating the presence of samarium(III) species. The reaction mixture was then quenched with saturated aqueous sodium bicarbonate solution (20 ml), and washed with ether (3 x 20 ml). The combined organic layers were washed with brine (20 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude oil was chromatographed on silica with 20% ether in light petroleum [40-60°C] to give starting 1-benzoylpiperidine **345** (345 mg, 1.82 mmol, 61%).

Reaction of Samarium Diiodide with 1,2-Dichloroethane

Samarium powder (451 mg, 3.00 mmol, 1 equiv.) was placed under an argon atmosphere in a three-necked flask, and purified 1,2-diiodoethane (846 mg, 3.00

mmol, 1 equiv.) in dry THF (5 ml) was added. The resulting mixture was heated to 70°C and a blue solution formed showing the presence of samarium diiodide. Dry DCE (1.20 ml, 15.0 mmol, 5 equiv.) was added dropwise to samarium diiodide at r.t. The reaction mixture was then continued to stir at 70°C for a further 1 h. Gradually, the reaction mixture changed from blue to yellow and after 1 h all of the blue samarium diiodide had been converted to yellow samarium triiodide.

Preparation of 1,2-Dipiperidinostilbene 346 *via* Samarium Reduction of 1-(Iodophenylmethylene)piperidinium iodide 351



346

Iodotrimethylsilane (1.28 ml, 9.00 mmol, 3 equiv.) was added dropwise to a stirred mixture of distilled trimethylsilyl trifluoromethanesulfonate (27.1 µl, 0.15 mmol, 0.05 equiv.) and 1-benzoylpiperidine **345** (568 mg, 3.00 mmol, 1 equiv.) under nitrogen at r.t. The reaction was then heated to reflux (110°C) and stirred for 19 h. The top layer was removed by syringe to form 1-(iodophenylmethylene)piperidinium iodide **351** as an unstable oil which was used without complete characterisation. A solution of 1-(iodophenylmethylene)piperidinium iodide **351** in dry THF:DMPU (5 ml, 1:1) was then added to samarium diiodide formed from heating a mixture of samarium (451 mg, 3.00 mmol, 1 equiv.) and 1,2-diiodoethane (846 mg, 3.00 mmol, 1 equiv.) in dry THF:DMPU (10 ml, 1:1) under nitrogen at 70°C for 2 h. The resulting mixture was stirred at 70°C for 12 h, then quenched with saturated aqueous sodium bicarbonate solution (20 ml), and washed with ether (3 x 20 ml). The combined organic layers were washed with brine (20 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography on basic alumina (deactivated with 15wt% water) using light petroleum [40-60°C] provided an inseparable diastereomeric mixture of *E*- and *Z*-1,2-dipiperidinostilbene **346** (43.0 mg, 0.12 mmol, 4%, *E*/*Z*, 85:15) as a yellow solid.

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