The role of zinc carbenoids in organic synthesis

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Reviewing the literature published up to February 1994

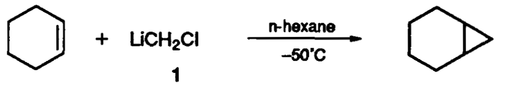
1 Introduction

1.1 Carbenes and carbenoids

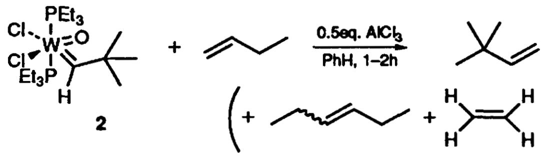
The unique electronic structure of the free divalent carbene intermediate,[1] either in its singlet state or in its biradical like triplet state, has proven, over many years, to be a fascinating area of study for the synthetic organic chemist. Thus the singlet carbene may be viewed simultaneously either as an electron-deficient species, comparable to the carbonium ion, or as a carbanion delivering a pair of non-bonding electrons. The overall reactivity in terms of nucleophilic or electrophilic character is strongly dependent on the electron-withdrawing or -donating ability of the two groups which are attached to the carbene carbon atom. However, to those synthetic organic chemists interested in the selective manipulation of sensitive polyfunctional molecules, such intermediates have often been rejected as being rather indiscriminate and hyperactive in their behaviour.

Fortunately, within the last thirty years, these schizophrenic and over-aggressive tendencies of the less electron-rich free carbenes have been 'domesticated' through the introduction of an ever increasing range of carbenoids which can generally be considered as derived by complexation of the free carbene with a metal.[2] The influence of the metal both in terms of structure, and as a control element in terms of reactivity, is of paramount importance. Furthermore, the nature of the ancillary ligands around the transition metal, and the selection of a cationic or a neutral complex, can also be used to great advantage as additional methods of attenuating reactivity.

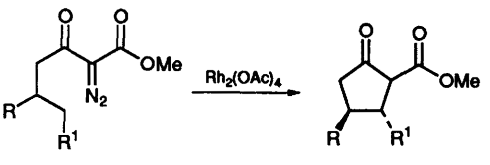
Many of these facets are encapsulated by the selected examples shown in **Schemes 1–4**.
Thus structures may vary from the tetrahedral lithium chlorocarbenoids **1**[3] (**Scheme 1a**) to those which possess a formal metal–carbon double bond **2**.
In terms of reactivity, there is an evident bifurcation between the behaviour of the early transition metal carbenoids or alkylidenes which undergo olefin metathesis (**Scheme 1b**),[4] and those which effectively mirror their free carbene counterparts in terms of insertion (**Scheme 2**),[5] cyclopropanation (**Scheme 3**),[6] and ylide formation and rearrangement reactions (**Scheme 4**).[7]



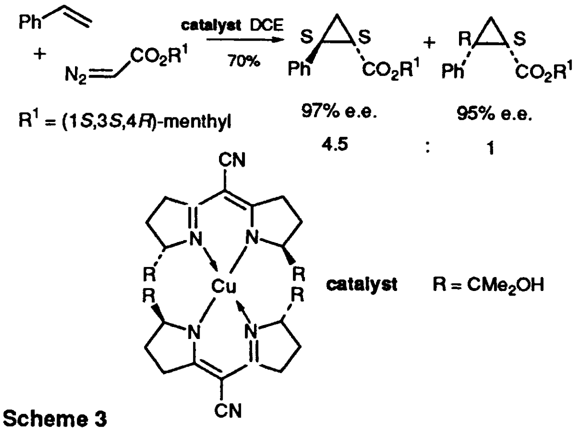
Scheme 1a



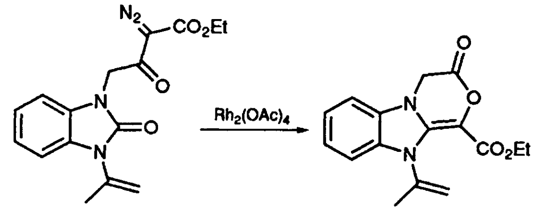
Scheme 1b



Scheme 2



Scheme 3



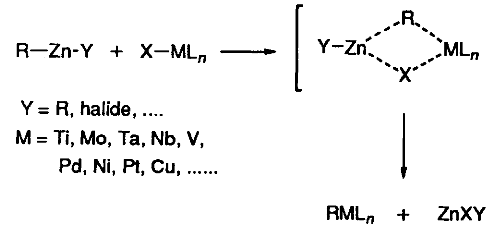
Scheme 4

A substantial number of extensive reviews dealing with the carbenoid behaviour of individual metals are currently available.[8-10] In recent years, however, it has become apparent that the use of stoichiometric metal carbenoids is less attractive than the development of catalytic cycles, especially when the latter involve chiral ligands. In this respect, the use of rhodium and copper carbenoids, invariably generated *in situ* from α-diazo carbonyl precursors, is proving to be the most popular choice at the present time.

1.2 Organozinc reagents and their carbenoid connection

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

In the wider context, it is interesting to reflect on the sinusoidal popularity of organozinc reagents for synthesis. Thus, although the reactivity of dialkylzinc reagents was studied for some thirty years after the first preparation of diethylzinc by Frankland in 1849,[11] by the turn of the century attention had turned to the more reactive Grignard reagents. The highly covalent character of the carbon–zinc bond which is responsible for the relative lack of reactivity of these organometallics is, however, the very reason for their current renaissance. With zinc possessing low-lying *p* orbitals, transmetallation with metallic salts is a facile process, as long as it is thermodynamically favoured. In this way, zinc can be used to convert a highly functionalized organic substrate into a stable organometallic, which can then be transmetallated to a more reactive organometallic (M = Cu, Pd, Ti, *etc*.), capable of reacting with an electrophile (**Scheme 5**).



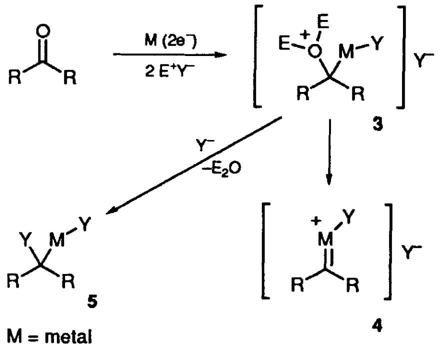
Scheme 5

Unfortunately, the intermediate species RZnY has frequently been referred to as an organozinc carbenoid, even when the carbenoid carbon is not geminally substituted with zinc and a leaving group. The reactivity of these very versatile, but non-carbenoid, organozinc compounds, whose use in synthesis has increased dramatically in the past 15 years, is the subject of a recent very comprehensive review.[12]

These fundamental properties of the carbon–zinc bond are also of course germane to the generation and behaviour of organozinc carbenoids. To the vast majority of synthetic organic chemists, such reagents are still only commonly encountered in the Simmons–Smith cyclopropanation reaction[13] and its variants, and recent developments in this area are highlighted in Section 3. The idea that a readily available carbonyl compound, rather than a *gem* dihalide, may be used as a direct precursor of an organozinc carbenoid, could still be somewhat foreign. The major portion of this review is accordingly devoted to this less frequently encountered area of organozinc carbenoid reactivity.

2 Zinc carbenoids from carbonyl compounds

From the most simplistic viewpoint of electronic stocktaking, the conversion of a carbonyl compound to an organometallic carbenoid requires only the delivery of two electrons from a metal or metal complex M and the addition of two equivalents of an electrophilic reagent (E^+Y^-) in order to generate the classical reactivity pattern of a geminally substituted carbon atom possessing both the carbon–metal bond and a leaving group shown in 3 (**Scheme 6**).



M = metal
E-Y = electrophilic reagent

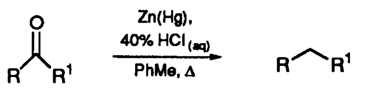
Scheme 6

The further evolution of this intermediate to other metallocarbenoid structures such as **4** and **5** is then a function of the leaving group ability of E_2O, the nucleophilicity of Y^-, and the nature of the metal M, in terms of wishing to sustain a carbon–metal double bond, or otherwise.

The substitution of zinc as the metal and the proton as the ultimate electrophile in **Scheme 6** immediately leads to the recognition of the Clemmensen reduction, and to the notion that some form of organozinc carbenoid should be involved in such reactions, even though further reduction steps are still required. As we shall see, however, considerable problems arise as soon as the timing of various electronic events is subject to scrutiny. It is therefore highly instructive in this section to discuss the behaviour and mechanisms involved in the Clemmensen reduction of various carbonyl substrates, since this provides valuable insight for the exploitation of other conceptually similar, but more controlled, methods of generating the same organozinc carbenoids.

2.1 The Clemmensen reduction

The Clemmensen reduction of a carbonyl group to give, in the simplest cases, a methylene unit, is perhaps one of the most familiar reactions in organic chemistry (**Scheme 7**). Since its discovery by Clemmensen[14] over 80 years ago, the original procedure employing amalgamated zinc and 40% aqueous hydrochloric acid, with an immiscible co-solvent, has undergone considerable modification. Commonly used procedures today are more suitable for use with compounds that were very labile under the original harsh conditions of Clemmensen's reaction. The reaction has been extensively reviewed.[15]

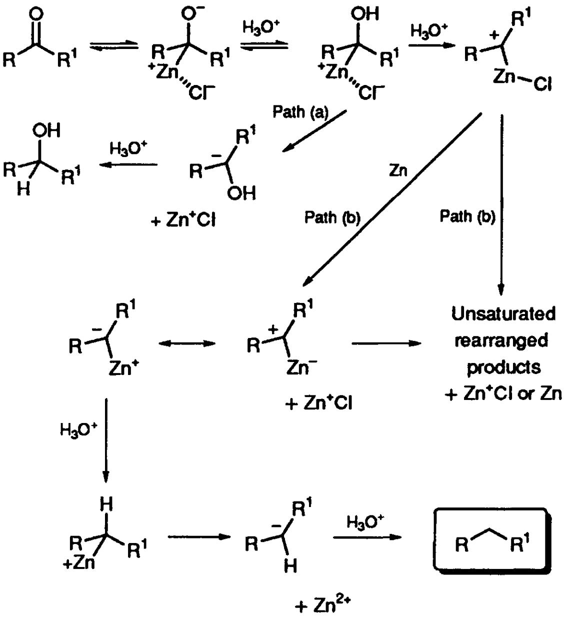


Scheme 7

2.1.1 Mechanistic studies

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

Some of the earliest detailed work was carried out by Brewster and co-workers.[16] In the first paper in this series, Brewster presented evidence that the mechanism involved direct metal intervention — *i.e.* formation of some metal-bound intermediate. He termed this process 'chemisorption' of the ketone on the metal surface (bonding *via* carbon or oxygen of the carbonyl group). Following on from this chemisorption theme, Brewster suggested that the zinc in the reduction acts essentially as an electron pump, and hence the mechanism demands the formation of partially reduced intermediates. Nakabayashi's[17] work also concluded that the mechanism was a stepwise process involving organozinc intermediates. As alcohols are not generally reduced under Clemmensen conditions, Brewster ruled free alcohols out as intermediates in the reduction. In Nakabayashi's studies, stopping the reduction of acetophenone or t-butyl phenyl ketone after five minutes, a complex product mixture was found, including saturated, unsaturated and rearranged hydrocarbons, alcohols and pinacol coupling-derived products. The hydrocarbon products were shown not to have arisen *via* alcohol intermediates — indeed when the alcohols isolated were separately subjected to the reaction conditions, no reduction was observed. He suggested that the major products of the reduction were derived from a carbocationic intermediate [Path (b)], and that there was a minor side reaction leading to the formation of the observed alcohol(s) [Path (a)] (**Scheme 8**). Furthermore, it was claimed that the pinacol coupling, which may occur at the one-electron reduction stage of a carbonyl compound, came about *via* a mechanism (termed as electrochemical) that shared no common intermediates with the Clemmensen reduction.



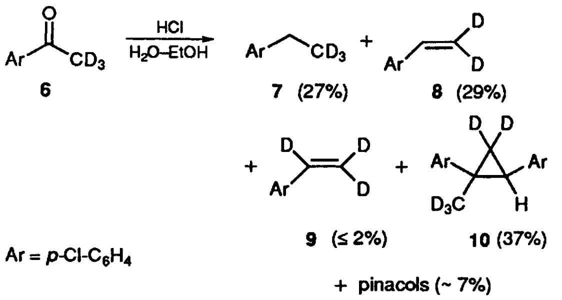
Scheme 8

Nakabayashi found in kinetic studies that the chloride ion concentration had a considerable influence on the reaction, and rationalized this as due to chloride ions being involved in the rate determining step. As the zinc concentration in the amalgam is also important, and the yields of Clemmensen-type products fall with the concentration of zinc in the amalgam, it was concluded that the rate determining step involved attack of zinc and chloride ion on the carbonyl group (the first step in the mechanism shown in **Scheme 8**). However, as an added complication, at very low zinc concentrations in the amalgam, Nakabayashi found that the one-electron pinacol processes dominated, with an absence of

Clemmensen-type products. It was on the basis of this result that he concluded that the mechanisms of the pinacol process and the Clemmensen reduction were quite different.

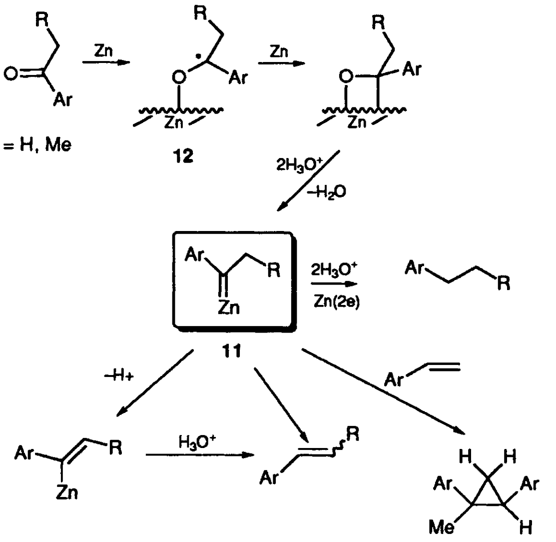
Indication that the mechanism of the Clemmensen reduction involved a carbenoid intermediate was, in fact, present in Clemmensen's original work on the reaction. He noted that on the reduction of acetophenone at low acid concentration, styrene rather than ethylbenzene was obtained. With this result strongly suggesting a C—H insertion reaction of an intermediate carbenoid, this aspect of the reaction became the subject of further investigations by other workers.[18] The effect of acid concentration on the reduction of 11 different carbonyl compounds was examined, and the ratio of alkane to alkene found. Generalizing the results, the formation of alkenes is favoured over alkanes as the acid concentration falls. It was interesting to note that under all reaction conditions cyclohexanone gave exclusively cyclohexene, but that *p*-ethoxy- and *p*-methoxy-acetophenone gave exclusively the corresponding alkane, presumably due to electronic influences which facilitate further reduction of the carbenoid. When the derived alcohol corresponding to several of the ketones was subjected to the reaction conditions, different product distributions were obtained to those from the parent compound, strongly suggesting yet again that alcohols are not free intermediates in the reduction.

In 1986, an elegant study by Burdon[19] provided results further indicative of a carbenoid mechanism. Under the reduction conditions studied — zinc in 50% aqueous ethanol at 20°C — the chosen substrates, acetophenone, substituted acetophenones, and propiophenone, were found to give classic Clemmensen reduction products, and products formed *via* 'carbenoid chemistry'. Cyclopropanes were formed, in the first instance by the trapping of alkenes formed in the reaction, and later by trapping alkenes added to the reaction mixture. The alkenes formed during the reaction are proposed to have been formed by a C—H insertion process, another classic carbene reaction. Deuterium labelling studies provided further backing for the intervention of a zinc carbenoid in the reduction. The product distribution from the reduction of **6** is shown in **Scheme 9**.



Scheme 9

Thus, **7**, the alkane product, occurs *via* the transfer of two electrons and two protons to the carbenoid. Compound **8** results from the loss of D^+ from the carbenoid to give a vinyl zinc species, and hence for this substrate this is almost exclusively the route to the unsaturated products. Compound **9**, the other olefinic product, results from a C—D insertion of the carbenoid (*i.e.* a 1,2-shift). The cyclopropane **10** results from the cyclopropanation of styrene formed during the reaction by further carbenoids. The high percentage yield of this species suggests that cyclopropanation by the carbenoid is a very facile process. These results allowed Burdon to propose the mechanism shown in **Scheme 10**. The route shown for the formation of the carbenoid **11** was only tentatively proposed by Burdon, although he did suggest that radical intermediate **12** could explain the pinacol type products obtained in the reaction (in direct opposition to Nakabayashi's earlier conclusions on the mechanism of these two processes).[17(c)]



Scheme 10

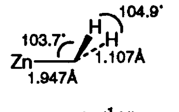
A recent series of papers by Rosnati and co-workers,[20] has also examined the particular cases of mono- and diaryl-carbonyl compounds, in which sequential halide anion displacement may, not surprisingly, also intervene.

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

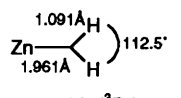
2.1.1.1 Spectral studies on prototypical zinc carbenoids

The carbenoid mechanism that Burdon[19] invoked for the Clemmensen reduction prompted the publication of a study on the isolation and characterization of the parent methylene zinc carbenoid, $ZnCH_2$.[21] A 1:1 adduct was produced by co-deposition of zinc atoms with diazomethane and argon onto a rhodium-plated copper mirror at 12K. Under photolysis conditions ($\lambda > 400$ nm), the adduct was converted to $ZnCH_2$, whose structure was examined by Fourier Transform IR. The frequencies measured for the adduct, as well as for isotopically labelled species, agreed well with those calculated by a normal coordinate analysis. Later, *ab initio* quantum mechanical calculations[22] showed that the species Billups and co-workers had isolated[21] was a triplet carbene, and predicted that the singlet state species would lie only 49.6 kJmol^{-1} higher in energy.

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



13 ($^1A'$)

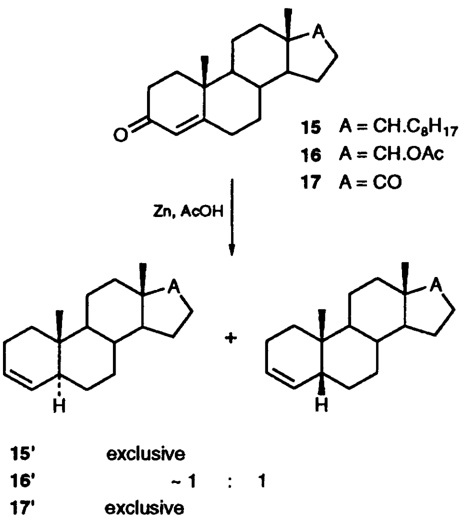


14 ($^3B_1$)

2.1.2 α,β-Unsaturated ketones in the Clemmensen reduction

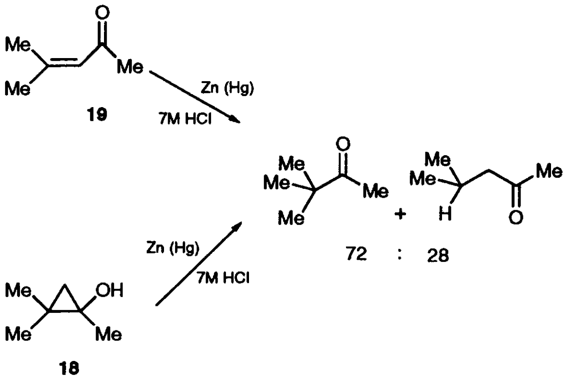
Whilst strong presumptive evidence for the intermediacy of an organozinc carbenoid may be found in the reactions of simple carbonyl compounds, the reduction of α,β-unsaturated compounds under Clemmensen conditions presents a very different picture. Typical products include the saturated ketone and derived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

Steroidal enones have proved interesting substrates in many studies.[15(c)] An example of such work is that of McKenna and co-workers.[23] They examined the reduction of many different steroidal enones, amongst which were cholest-4-en-3-one **15**, testosterone acetate **16**, and androst-4-ene-3,17-dione **17**. It is interesting to note that the reduction of the carbonyl group in the enone proceeds with shift of the alkene towards what was the carbonyl carbon. The isolated 17-ketone in androst-4-ene-3,17-dione remains untouched under the conditions employed (**Scheme 11**).



Scheme 11

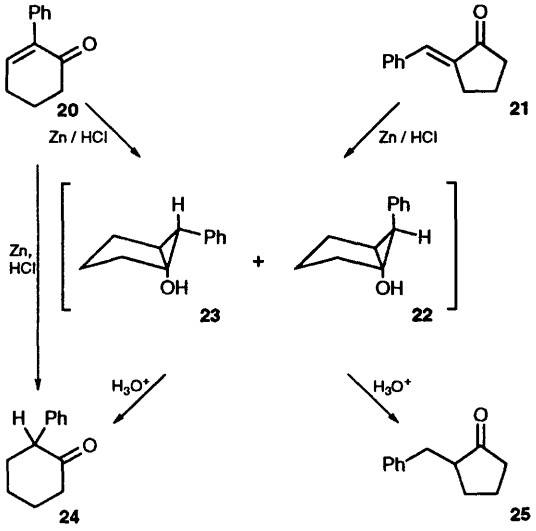
In terms of the more often observed rearrangement process, Davis and Woodgate had proposed[24] that the reduction of α,β-unsaturated ketones under Clemmensen conditions proceeded *via* a cyclopropanol, which, depending upon its mode of ring-opening, could give two structurally isomeric saturated ketones. In their study, the authors also synthesized the cyclopropanol **18** they believed to be an intermediate in the reduction of 4-methylpent-3-en-2-one **19** (**Scheme 12**). On acid-catalysed cleavage of this cyclopropanol, they formed the two isomeric ketones isolated from the reduction of the α,β-unsaturated ketone, in the same ratio.



Scheme 12

In a very beautifully conceived study, Elphimoff-Felkin and Sarda examined the reductive behaviour of the two α,β-unsaturated ketones **20** and **21**, which could be expected to undergo reduction *via* rearrangement of the same cyclopropanol intermediates *endo*-**22** and *exo*-**23**.[25] The latter were not only isolated from the reactions as their acetates by carrying out the reactions in acetic anhydride, but also subjected to solvolytic proton-catalysed rearrangement to give the final product ketones **24** and **25**. On the basis of the differing ratios of ketonic products formed from **20**, **21**, **22**, and **23**, it was concluded that direct reductive routes with skeletal preservation also exist in competition with the bicyclic cyclopropanol pathway (**Scheme 13**).

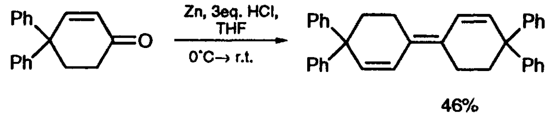
In a very comprehensive study, a wide range of enones were subjected to the Clemmensen reduction, in anhydrous conditions [Zn(Hg), Et$_2$O–HCl, Ac$_2$O].[26] For each enone, the product ratios were determined,



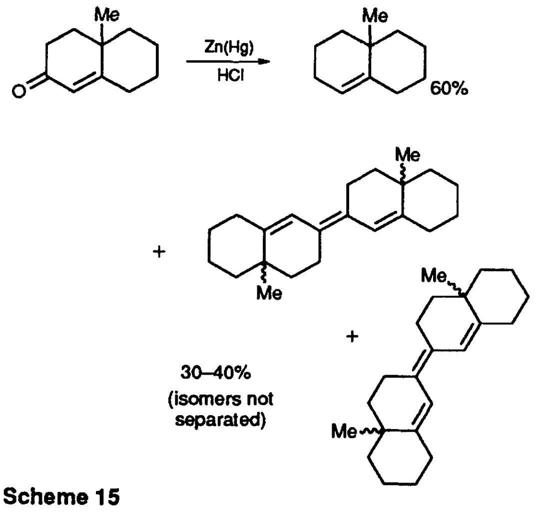
Scheme 13

but in all cases a cyclopropanol acetate was isolated, adding further weight to the evidence suggesting that such species are intermediates in the reduction. Their results also reinforced the idea that the configuration of the starting enone dictated the stereochemical outcome of the cyclopropanol formed and hence the regiochemical outcome of the reaction, and that an allylic anion was the key intermediate. This postulate arose partly due to the dismissal of radical intermediates, as the addition of a radical quench had no influence on the reaction.

From the above examples, it might well be concluded that such competing pathways preclude access to α,β-unsaturated organozinc carbenoids. By way of contrast, however, two isolated reports of 'carbene dimers' have been described, **Schemes 14** and **15**.[15(c), 27]



Scheme 14



Scheme 15

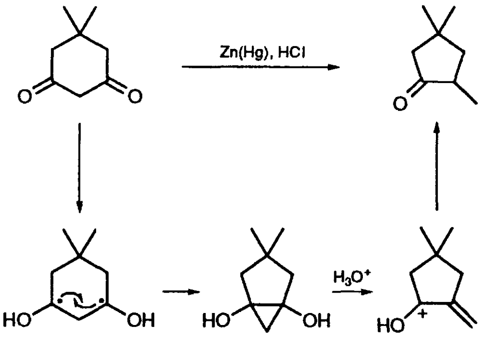
In both of these cases, neither double bond reduction nor skeletal rearrangement were observed, and, on the basis of later studies of dicarbonyl coupling using zinc and chlorotrimethylsilane (*vide infra*), it is highly probable that the carbenoid is in fact involved.

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

2.1.3 Diketones in the Clemmensen reduction

Diketones, particularly 1,3- and 1,4-diketones, are rarely found to give useful yields of the normal products expected from the Clemmensen reduction. Instead, they are frequently found to undergo intramolecular pinacol couplings at the one-electron reduction stage, with the products observed deriving from this pathway. This type of reaction has been reviewed,[28] and numerous examples are available to show the generality of the reaction.[29]

The mechanism for dimedone, the first example studied in 1935 by Dey and Linstead,[30] **Scheme 16**, is illustrative, and carbenoid chemistry has not been observed in these cases.



Scheme 16

2.1.4 Practical advances in the Clemmensen reduction

With the Clemmensen reduction classically being carried out using amalgamated zinc and 40% aqueous hydrochloric acid, with an immiscible co-solvent, typically toluene, the conditions are simply too harsh for many highly functionalized substrates to tolerate. Although the process was modified relatively early on to use organic solvents such as alcohols and acetic acid,[15(b)] such a homogeneous system was found to favour the formation of pinacols. Perhaps the most significant advance was made by Yamamura and co-workers.[31] They showed that by employing a large excess of activated zinc dust in diethyl ether saturated with hydrogen chloride at 0°C, optimum results could be obtained in the reduction, with reactions typically complete in 1 hour.

Surprisingly, little study seems to have been made of the effect of sonication on the reaction. Reeves and co-workers have published results on the reduction of ketones to the corresponding methylene compound using zinc amalgam and hydroiodic acid in methanol, with sonication (5 hours).[32] For the ketones selected, yields were high in most cases, with aromatic ketones generally giving better results than their aliphatic counterparts. It was found that amalgamation of the zinc was crucial to the reaction; without amalgamation, yields were found to be significantly lower.

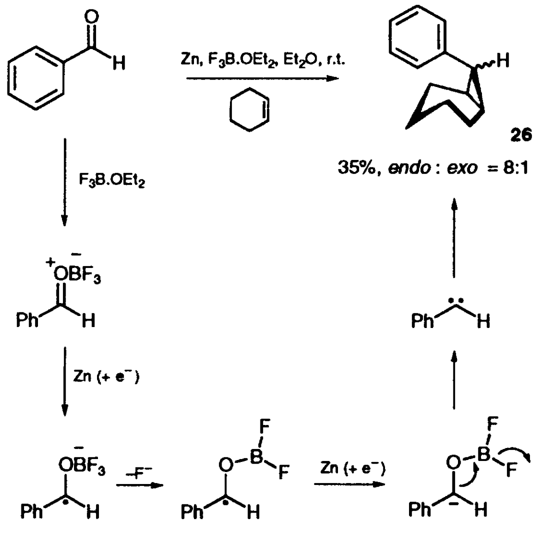
Finally, report of an electrochemical reduction of a diketone has been made that permitted the isolation of the labile cyclopropanediol as its diacetate.[33] Triangular wave cyclic voltammetry was used on a hanging drop mercury electrode. With such electrochemical reductions being a powerful yet simple technique in organic synthesis, it is indeed surprising that these methods have not been exploited more, particularly using a zinc anode.

2.2 Controlled reductive deoxygenation of carbonyl compounds

2.2.1 The demise of the proton

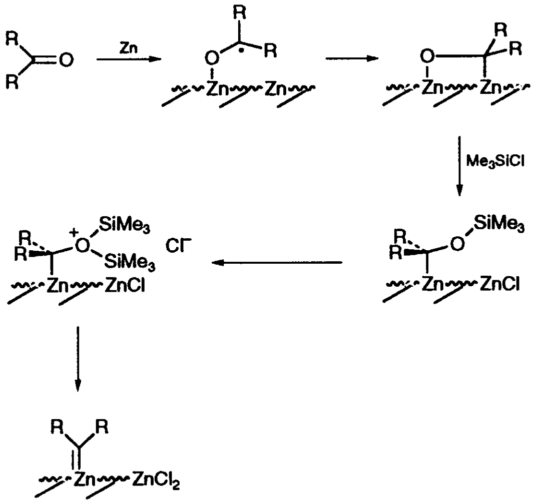
Although convincing evidence has accumulated over the years for the intermediacy of a zinc carbenoid in the Clemmensen reduction, classic carbenoid reactivity is not routinely observed since the vigorous reaction conditions employed are also ideal for further protonations and two-electron reduction to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

Two conceptually similar solutions, both involving replacement of the proton, have evolved. In the first of these, reported by Elphimoff-Felkin in 1969,[34] the use of boron trifluoride etherate as a Lewis acid under Clemmensen-type reductive conditions allowed the carbenoid from benzaldehyde to be trapped by an alkene, to give cyclopropanes (**Scheme 17**). The yield of 7-phenylnorcarane **26** obtained was almost doubled (60%) by the use of the alkene as the reaction solvent. In the few examples studied, whilst yields were only moderate, a notable feature was that cyclic alkenes gave the more hindered *endo* isomer preferentially (*vide infra* Section 2.2.4).



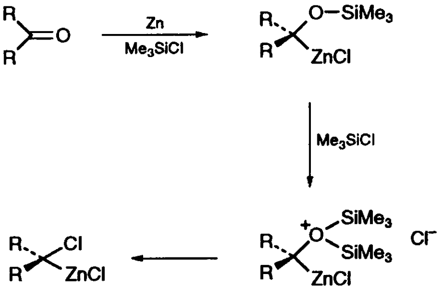
Scheme 17

Our own independent approach began in 1973,[35] with a study of the behaviour of alicyclic ketones using chlorotrimethylsilane as a replacement for hydrogen chloride. This selection was made since the silicon electrophile is also capable of forming a very strong bond to oxygen. When viewed in this way, a mechanistic pathway for the formation of a heterogeneous organozinc carbenoid analogous to that proposed by Burdon[19] (Section 2.1.1) for the Clemmensen reduction may be proposed (**Scheme 18**).



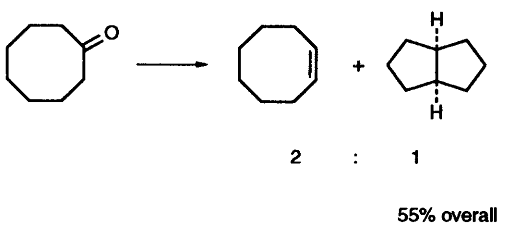
Scheme 18

Alternatively, by analogy with the Simmons–Smith reaction, the carbenoid may be viewed as a tetrahedral chloro congener, arising from the series of electron-transfer steps indicated in **Scheme 19**.



Scheme 19

Fortunately, further reduction of the organozinc carbenoid in the presence of silicon reagent to give a *geminal* disilane was not observed, presumably as a result of prohibitive steric interactions. The fate of the organozinc carbenoid in these cases was to undergo C—H insertion reactions (*vide infra* Section 2.2.2), and the case of cyclooctanone, which furnished not only *cis*-cyclooctene, but also bicyclo[3,3,0]octane as a result of transannular interaction (**Scheme 20**), was particularly indicative of carbenoid intermediacy.



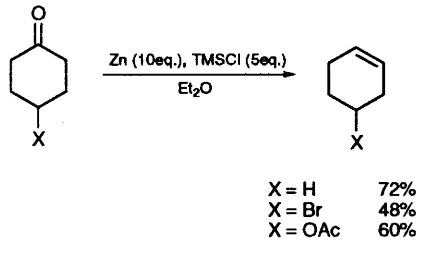
Scheme 20

Although the ratio of olefin to bicyclic hydrocarbon was different from that observed in the Bamford–Stevens reaction *via* the free carbene, this was not surprising since the metal might well be expected to have a considerable moderating influence. Following on from these original observations, a variety of useful reactions have been developed, based on the above methods and variants thereof. In the following sections, these have been conveniently grouped from a synthetic standpoint according to the fate of the carbenoid involved.

2.2.2 Direct deoxygenation of carbonyl compounds to give alkenes

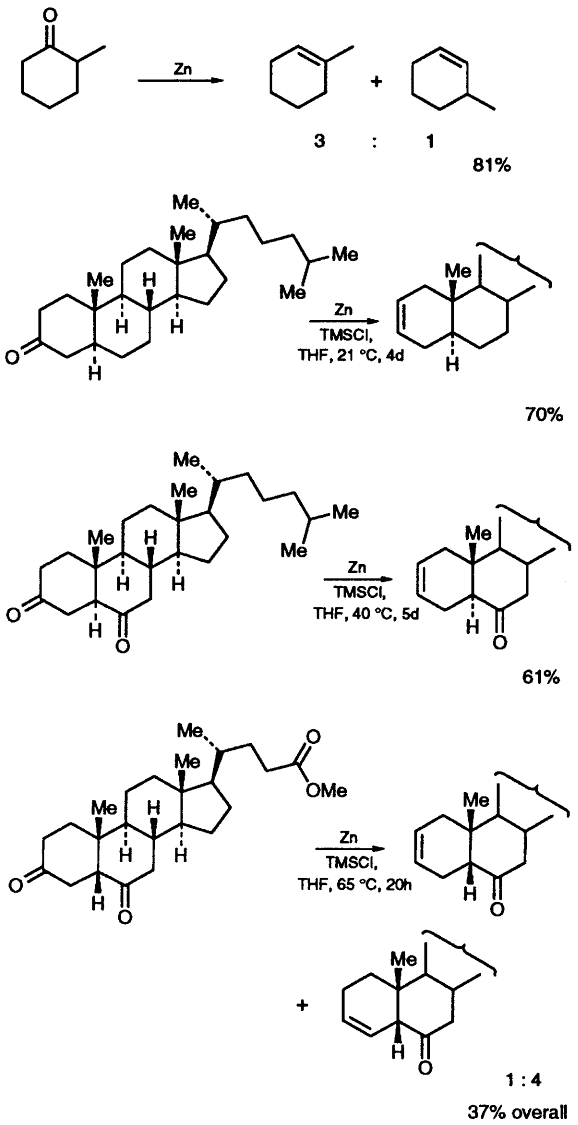
The reaction of a variety of cyclic ketones with zinc and chlorotrimethylsilane offers a very simple 'one-pot' method for the conversion of this functional group to an alkene, without any need for prior formation of derivatives such as enol phosphonates, enamines, or tosylhydrazones.[35] Trimethylsilylenol ethers are not intermediates in this reaction, and can in fact be recovered unchanged after exposure to zinc and chlorotrimethylsilane. As in the case of the Clemmensen reduction performed at very low acid concentrations, alkene formation most probably arises by insertion of the organozinc carbenoid into the neighbouring C—H bond.

In chemoselective terms, the reaction conditions are very mild, and remote ester functionality and even alkyl bromides are tolerated, as shown by the examples in **Scheme 21**.



Scheme 21

The behaviour of unsymmetrical ketones also reveals some features of interest (**Scheme 22**). Thus, for 2-methylcyclohexanone,[35] although a relative series of migratory aptitudes for alkyl, hydrogen, and aryl substituents remains to be established, there is a preference for formation of the more substituted alkene.

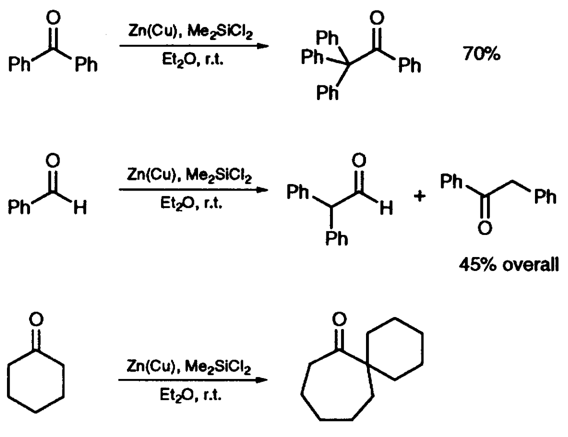


Scheme 22

A useful study by Hodge and Khan[36] in the steroidal series revealed that, as in the Clemmensen reduction, an unhindered 3-oxo steroid can react while carbonyl functionality in 6, 7, 12, 17, and 20-oxo steroids remain intact. The regioselectivity in the reactions is also noteworthy, with a preference for formation of the less strained Δ^2-alkene from the *trans*-fused decalin moiety in 5α-cholestan-3-one derivatives, presumably as a result of a relatively late transition state for the C—H insertion reaction. This notion is supported by the isolation of a mixture of Δ^2- and Δ^3-alkenes from the *cis*-fused methyl 3-oxo-5β-cholanate derivative.

2.2.3 Dicarbonyl coupling reactions

The first report of a dicarbonyl coupling reaction appeared in 1980, using a zinc-copper couple and dichlorodimethylsilane as the silicon electrophile.[37] The vast majority of the products from benzophenone, benzaldehyde, and cyclohexanone, shown in **Scheme 23**, were most readily rationalized by invoking pinacolic coupling followed by rearrangement.



Scheme 23

However, the isolation of 2-phenylacetophenone was indicative of the intermediacy of stilbene epoxide, and led the authors to propose that oxirans could be formed by reaction of a derived organozinc carbenoid with the carbonyl partner. Support for the presence of such an intermediate was adduced from a trapping experiment using cyclohexene and benzaldehyde to give 7-phenylnorcarane in 15% yield. Clearly, however, the major products need not necessarily have been involved in this pathway.

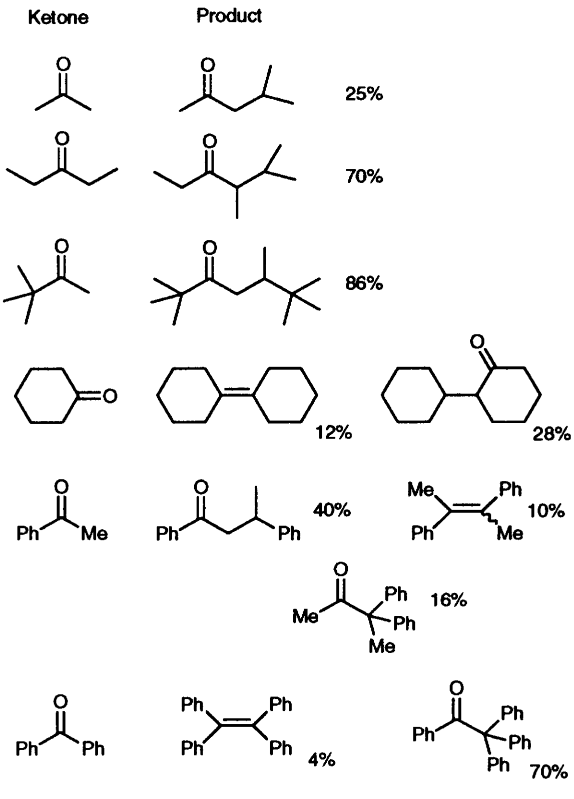
Curiously, in the same year, Ando and Ikeno[38] found that it was only possible to achieve the reduction of ketones using zinc and diiododimethylsilane in dichloromethane. These authors stated that 'dichlorodimethylsilane did not show any reaction with ketones'. Their results (**Table 1**) were also at variance with those of Smith and co-workers[37] for the product(s) derived from cyclohexanone, and, with the exception of aromatic carbonyl compounds, their major products are most readily explicable in terms of an aldol condensation followed by dehydration and subsequent zinc reduction of the α,β-unsaturated carbonyl compound (**Table 1**).

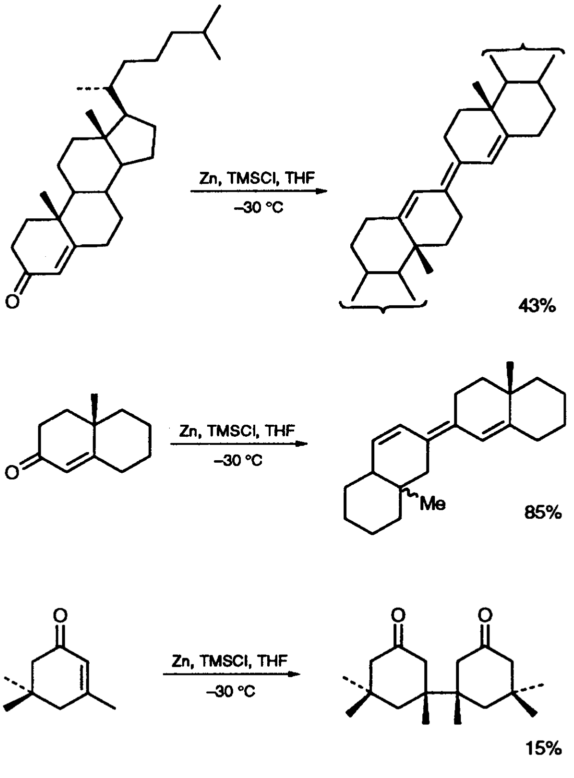
Our own investigations[39] in this area began in collaboration with the group of Banerjee, who had discovered that certain aryl and α,β-unsaturated carbonyl compounds could be induced to undergo a McMurry-like dicarbonyl coupling under Clemmensen conditions (Section 2.1.2, **Scheme 15**).[27] Although several coupling reactions could be achieved in a very high yield using the basic chlorotrimethylsilane – zinc system (**Scheme 24**), other substrates such as isophorone yielded complex mixtures which included one-electron induced dimerization at the softer β-carbon atom.

It soon became apparent that these reactions were not only highly substrate dependent, but also crucially influenced by the relative concentrations of substrate, reagents, and the presence or absence of small amounts of hydrogen chloride. The case of α-tetralone (**Scheme 25**), where the reaction could be channelled to unimolecular C—H insertion, to pinacolic coupling followed by dehydration, or to dicarbonyl coupling, is illustrative.

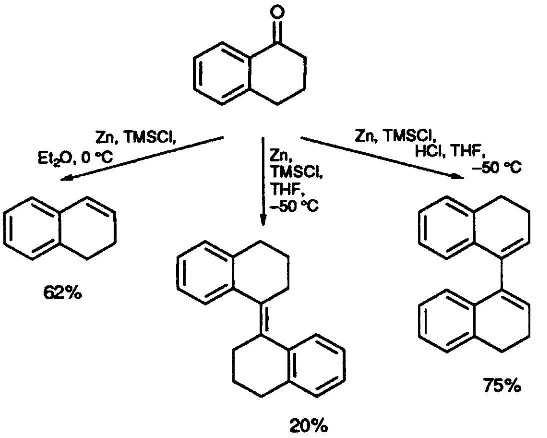
A series of control experiments in the case of the formation of stilbene from benzaldehyde indicated

Table 1 Products derived from ketone reduction using zinc and diiododimethylsilane in dichloromethane[38]





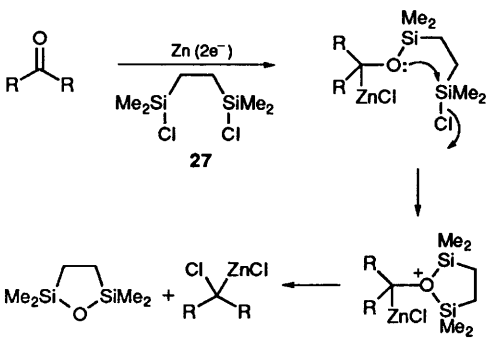
Scheme 24



Scheme 25

that neither benzpinacol nor its silylated derivative was a precursor of the alkene. As in the work of Smith,[37] however, when *trans*-stilbene-oxide was subjected to the reaction conditions, alkene formation was observed, together with diphenylacetaldehyde, thereby implying that the epoxide was a viable intermediate. Interestingly, a sonochemical study of the coupling of aromatic and α,β-unsaturated carbonyl compounds in the presence of zinc and chlorotrimethylsilane,[40] which was published shortly afterwards, indicated that pinacolic coupling was a dominant pathway under these conditions.

Faced by the obvious problem of competing intermolecular reactions at the one-electron reduction level, it therefore became necessary to reduce the 'longevity' of these radical intermediates, and enhance the efficiency of carbenoid generation, in order to improve the yields in dicarbonyl coupling. Consideration of the overall stoichiometry of the reaction, which requires two silicon electrophiles to produce hexamethyldisiloxane as a leaving group, suggested the simple solution shown in **Scheme 26**.

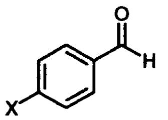
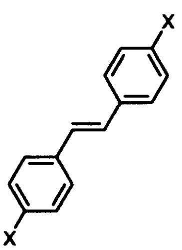
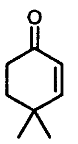
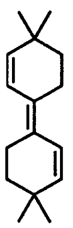
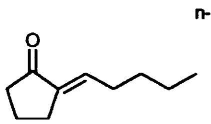
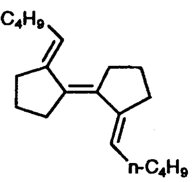
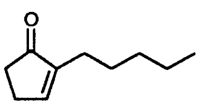
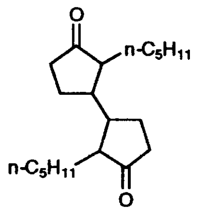


Scheme 26

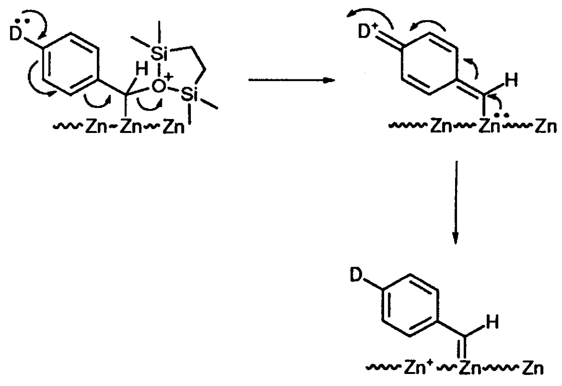
Thus, selection of 1,2-bis(chlorodimethylsilyl)ethane **27** as a bis electrophile would permit *intramolecular* delivery of the second necessary silicon atom.

The use of this reagent in the symmetrical dicarbonyl coupling reaction with aryl and α,β-unsaturated carbonyl compounds led to a significant improvement in yield.[41] Some examples are shown in **Table 2**, and reveal several aspects worthy of comment.

Table 2 Reaction of aromatic aldehydes and α,β-unsaturated carbonyl compounds with 1, 2-bis(chlorodimethylsilyl)ethane and zinc

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

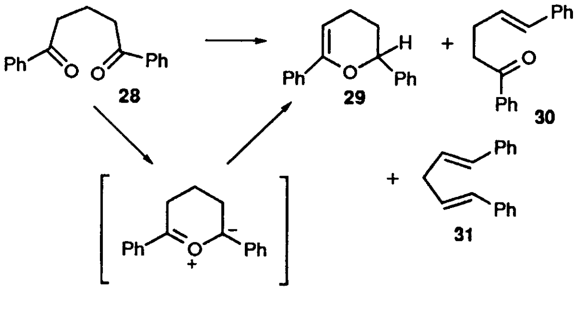
The best yields of stilbene derivatives are obtained from aromatic aldehydes possessing electron-releasing groups. This trend is also mirrored in the Clemmensen reduction of some substrates, and may well be a consequence of anchimeric assistance towards the departure of the cyclic siloxane (or water) as a leaving group, as implied in **Scheme 27**.



Scheme 27

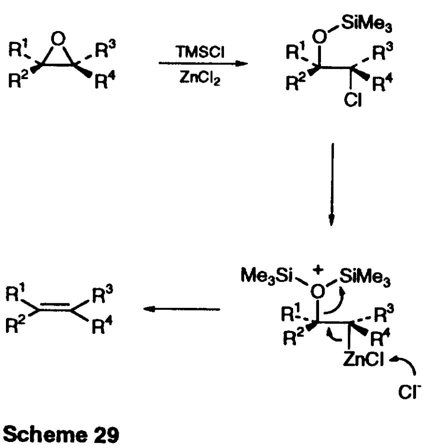
Examination of the enone substrates reveals that the construction of oxygen sensitive s-*trans*-trienes which contain a highly hindered tetra-substituted central double bond is possible. As with cyclopropanation studies, however (Section 2.2.4), the generation of an α,β-unsaturated organozinc carbenoid is very substrate dependent, as emphasized by the two cyclopentenone derivatives, of presumably similar redox potential, which behave in a very different fashion.

In mechanistic terms, a very significant result came from the attempted intramolecular dicarbonyl coupling of **28**, to give three products **29** (31%), **30** (14%), and **31** (21%) (**Scheme 28**), without any indication for formation of a cyclopentanoid. The isolation of the dihydropyran **29** is most readily understood in terms of the carbonyl ylide shown, whose ring closure to the epoxide, necessary for deoxygenation to an alkene, is retarded by a combination of electronic effects and ring strain.



Scheme 28

At the present time, the convoluted mechanistic pathway from carbonyl to organozinc carbenoid, and then *via* carbonyl oxide to epoxide followed by deoxygenation, has been restricted to symmetrical coupling and to aryl and α,β-unsaturated carbonyl substrates. A separate study of the epoxide deoxygenation step using chlorotrimethylsilane and zinc has also been carried out,[42] and reveals that *one* of the pathways for this transformation involves ring-opening to a siloxychlorohydrin followed by zinc induced elimination of hexamethyldisiloxane, as implied in **Scheme 29**.



Scheme 29

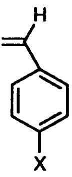
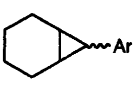
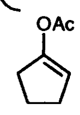
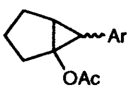
A limiting factor is that the chloride formed must be at least tertiary in order for further zinc-induced elimination to occur. Benzylic and allylic substrates which are formed in the observed dicarbonyl coupling are therefore particularly favoured. While a range of unsymmetrical couplings may be possible, it is nevertheless unlikely that this approach will replace the inherently more flexible and mechanistically simpler McMurry reaction.[43]

2.2.4 Cyclopropanation reactions

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

As we have seen (Section 2.2.1), the first observations of useful trapping of an organozinc carbenoid by an alkene were made by Elphimoff-Felkin and Sarda.[34] At a later stage the same authors published a series of cyclopropanation reactions for a range of olefins with benzaldehyde, and for the same olefin, various *para*-substituted benzaldehydes.[44] These, together with a selection of our own results[45] for aromatic aldehydes using the zinc — 1,2-bis(chlorodimethylsilyl)ethane system (which, not surprisingly exhibit similar trends), are displayed in **Table 3**.

Table 3 Cyclopropanes derived from aromatic aldehydes

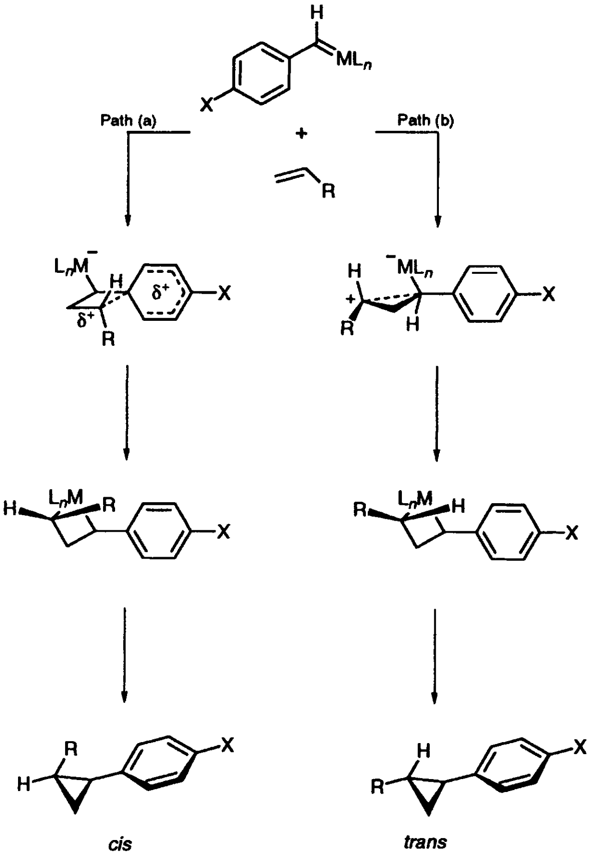
Substrate	X	Method	Alkene	Product	Yield, Ratio (*endo*:*exo*)
	OMe	A			60%, 19:1
	OMe	B			96%, 15:1
	Me	A			63%, 7.5:1
	Me	B			75%, 8:1
	H	A			43%, 5:1
	H	B			68%, 4:1
	Cl	A			43%, 4.5:1
	Cl	B			46%, 3:1
	H	A			20%, 1:1
	OMe	B			53%, 1:1

Method A: Zn, $F_3B.OEt_2$
Method B: Zn, $(CH_2SiMe_2Cl)_2$

Once again, as in the dicarbonyl coupling reaction, yields are best for electron rich substrates, thereby lending additional credence to the idea that these participate most efficiently in carbenoid generation. The virtually quantitative yield in the trapping of the carbenoid from *para*-anisaldehyde in the presence of only two equivalents of cyclohexene, using the zinc and silicon electrophile system is particularly noteworthy.

Reactions with *cis*- and *trans*-but-2-ene lead to retention of the original alkene geometry, and there is a highly stereoselective tendency for formation of the more hindered isomer, which is particularly marked in the case of *para*-anisaldehyde, but apparently falls off as a function of decreasing electron-release from the aromatic ring.

An elegant rationalization of these trends has been published by Casey[46] in a study of cyclopropanation by stoichiometric tungsten alkylidenes (**Scheme 30**), and would also seem to be applicable in the case of zinc carbenoids.



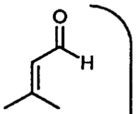
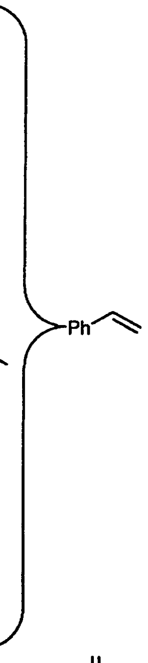
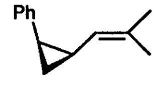
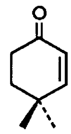
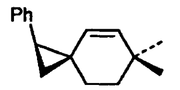
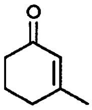
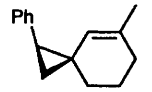
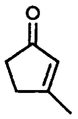
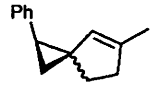
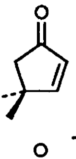
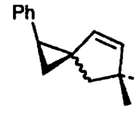
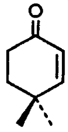
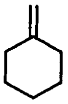
Scheme 30

Thus, approach of the alkene to the metal carbenoid always occurs in such a way as to place any substituents on the alkene *trans* to, or away from, the metal. As the bulk of the substituent increases, this tendency increases, and Path (b), resulting in formation of the *trans* isomer, is favoured. However, in less sterically demanding cases, opportunities exist for additional electronic stabilization of the developing positive charge on the alkene, through electron-donation *via* the *ipso* carbon of the aromatic ring, and Path (a), leading to the more hindered *cis* substituted cyclopropane, is then followed. This model also rationalizes the general observation that yields in the metallocarbenoid cyclopropanation of *trans* disubstituted alkenes always tend to be lower than in the case of their *cis* counterparts, as a result of increased demands in steric approach control.

We were also intrigued to examine the behaviour of non-aromatic α,β-unsaturated organozinc carbenoids in cyclopropanation reactions.[45] In this instance, of course, conventional wisdom relating both to the isolation of cyclopropanol acetates by Elphimoff-Felkin,[25] and to the reductive ring contractions observed under Clemmensen conditions (Section 2.1.3) would argue that carbenoid reactivity should not be observable.

In the event, however, as shown in **Table 4**, a useful range of carbenoids from both cyclic and acyclic enones and enals may be trapped.

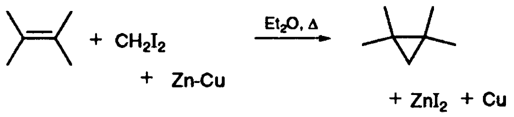
Table 4 Cyclopropanes derived from alicyclic ketones and acyclic aldehydes

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

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

3 The Simmons–Smith reaction and Furukawa modification

The Simmons–Smith reaction, first reported in 1958,[13] involves the cyclopropanation of an alkene with a reagent prepared *in situ* from a zinc-copper couple and diiodomethane (**Scheme 31**). The reaction is stereospecific with respect to the geometry of the alkene, and unlike reactions involving free carbenes, is generally free from side reactions.



Scheme 31

Since that time, it has become the most frequently used method for the preparation of simple cyclopropanes. The reaction has been reviewed very comprehensively,[47] and hence our intention is to present an overview of the more recent key synthetic modifications and applications of the reaction, as well as the methodological advances. Of these, the most significant variation lies in the use of diethyl zinc and diiodomethane in place of a zinc couple and diiodomethane (or substituted diiodides). First reported by Furukawa,[48] this adaptation will be considered in this section, as it is frequently used to provide a comparison with the Simmons–Smith reagent system. The other reagent system of importance involved the reaction of diazomethane with zinc iodide to give a cyclopropanating agent, and will be discussed in Section 4.

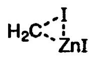
3.1 The Simmons–Smith reaction

In their first report of the reaction,[13] the authors obtained cyclopropanes in yields ranging from 10–70%, depending on the type of couple employed. They considered that the reactive intermediate, *i.e.* the cyclopropanating agent, was iodomethylzinc iodide, and that it would be displaced by the π-bond of an olefin to give a cyclopropane and zinc iodide. A full paper was later published on the reaction,[49] and was followed by two papers which sought to define the nature of the intermediate, and the optimum conditions for synthesis.[50]

Studies indicated that di-iodomethane formed a 1:1 complex with zinc (from a zinc-copper couple), which existed as a colourless homogeneous solution, capable of forming cyclopropanes with alkenes.[49] It was proposed that this complex may best be represented as **32** or **33**, and was also shown in the same study that the copper simply acted *via* activation of the zinc surface, and had no other role.

$H_2C \rightarrow ZnI_2$

32



$H_2C \overset{I}{\underset{ZnI}{\vdots}}$

33

Mechanistically, it was suggested that the reaction proceeded by a one-step methylene transfer, where the quasi-trigonal methylene group of the active cyclopropanating agent **33** adds to the alkene, with essentially simultaneous formation of two bonds. This interpretation fitted well with the following experimental observations: (i) few side reactions are found, suggesting that free methylene is not an intermediate; and (ii) the reaction follows second-order kinetics, in accordance with a bimolecular process; and, cyclopropane formation is stereospecific. It was also shown that the iodomethylzinc iodide behaves as a weak electrophile, since alkene reactivity increased with alkyl substitution although, of course, at the price of a balanced steric pay-off.

3.2 The Furukawa modification

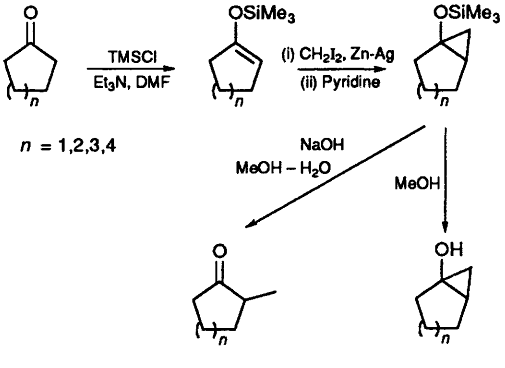
In many ways, the reagent generated by Furukawa's method,[48] is very similar to the Simmons–Smith reagent. The major advantages of Furukawa's system are the following: (i) the reaction is homogeneous; (ii) reagent formation is rapid under mild conditions; (iii) it is suitable for the cyclopropanation of vinyl ethers and similar substrates that are prone to undergo polymerization under Simmons–Smith conditions;[51] and (iv) the reaction is not restricted to methylene transfer, but may also be used with alkyl and phenyl carbenoids.[52] As with the Simmons–Smith reaction, cyclopropanes were found to form stereospecifically. The observed *syn*-selectivity was augmented with increased electron-donating ability of the substituents on the carbenoid.[53] It was also found that electron-donating substituents on the olefin increase both the yield and rate of reaction, strongly indicating that the cyclopropanating agent is electrophilic (and hence analogous to the Simmons–Smith reagent).[54] Reactions were found to give the highest yields when a hydrocarbon solvent was employed. Polar solvents, such as ethers, gave far lower yields.[51]

Denmark has made an extensive study of the nature of the reagent generated by the Furukawa procedure.[55] The research demonstrated that the highly reactive bis(halomethyl)zinc reagents generated are stabilized by coordination to ethers or acetone. The first *X*-ray crystallographic analysis of an (iodomethyl)zinc complex was also undertaken, and gave a strong indication as to the structural parameters of reagent stabilization by proximal oxygenated functionality.

3.3 A synthetic overview

The Simmons–Smith reaction provides a route for the introduction of a methyl group to a molecule bearing an alkene unit suitable for cyclopropanation. Cleavage of such an introduced cyclopropane furnishes an angular methyl group. Conia and co-workers published some very elegant work on this theme.[56] In essence, by a three step sequence, it was possible to introduce an α-methyl group to a ketone. A silyl enol ether was generated from the desired ketone, and this cyclopropanated with zinc-silver couple and diiodomethane, using a pyridine work-up. The cyclopropane thus generated could then undergo either a standard deprotection sequence to yield the

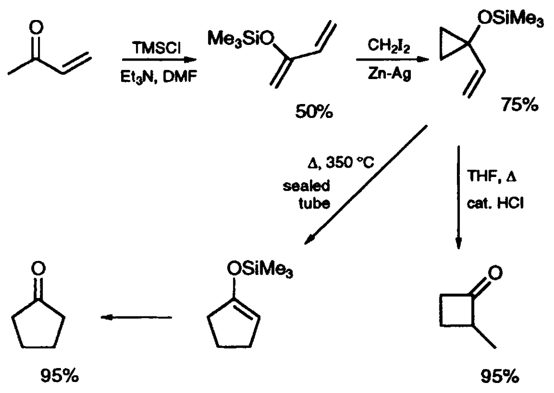
cyclopropanol, or hydrolysis to yield the α-monomethylated ketones (**Scheme 32**).
The reaction sequence was found to work for cyclopentanones, cyclohexanones, cycloheptanones, and cyclooctanones, as well as aldehydes.[56(a)] In the case of unsymmetrical ketones, it was possible, through selection of the appropriate silyl enol ether, to orientate methylation to the α or α' position. In all cases, the yields were good.



Scheme 32

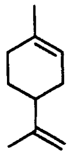
When 2-trimethylsiloxycycloalka-1,3-dienes were examined,[56(b)] it was found that monocyclopropanation occurred almost exclusively on the double bond bearing the trimethylsiloxy group (using 1.1 equivalents of diiodomethane). The 2-trimethylsiloxycycloalka-1,3-dienes were prepared from the corresponding α,β-unsaturated ketones. In the presence of 3 equivalents of diiodomethane, cyclopropanation of both double bonds occurred in 80–90% yields.[56(d)] The relative stereochemistry of the two cyclopropane rings was believed to be *anti*, since the second cyclopropanation reaction of the 3,4-alkene would be directed to occur on the same face as the siloxy group.

Using the same methodology, Conia accessed cyclobutanones and cyclopentanones *via* the rearrangement (either acid-catalysed or thermal) of 1-siloxy-1-vinyl cyclopropanes, formed *via* the cyclopropanation of silyl enol ethers of cisoid or labile α-ethylenic ketones (**Scheme 33**).[56(c)]



Scheme 33

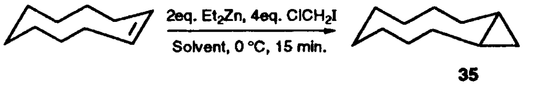
Since the initial studies made on the Simmons–Smith reagent, there have been several studies on the influences which affect its reactivity. Recently, work was published comparing the regioselectivities of the mono-cyclopropanation of such substrates as limonene **34** and 4-vinylcyclohexene with the classic Simmons-Smith reagent (diiodomethane, zinc, and copper(I) chloride in diethyl ether), the modified Furukawa conditions (diiodomethane with diethyl zinc in toluene) and the Yamamoto conditions[57] (diiodomethane and triethylaluminium in toluene-dichloromethane).[58]



34

The relative reactivity of dibromomethane, zinc, and copper(I) chloride in diethyl ether was also examined. Earlier results had suggested that CH_2I_2–Zn–Cu gave rise to an electrophilic cyclopropanating agent, which was sterically hindered,[50(a)] whilst the Furukawa system was known to provide a less sterically hindered reagent, especially in non-coordinating solvents. The final triethylaluminium based system[59] had been found to cyclopropanate exclusively at an alkene distant from a hydroxyl group, the opposite of the other two systems, although this facet of the systems's reactivity was not relevant in this particular study.

Thus it was found that in the case of limonene **34**, the Et_2Zn–CH_2I_2 system exhibited the lowest regioselectivity for mono-cyclopropanation, and was hence determined to have the lowest steric requirements of all the systems examined. CH_2I_2– or CH_2Br_2–Zn–Cu both gave similar regioselectivities, with an average of 3:1 preference for the exocyclic disubstituted alkene. The regioselectivity of the Et_3Al system was found to lie between the other two systems. These findings were confirmed with 4-vinylcyclohexene.
Denmark and co-workers made a comparison of (chloromethyl)- and (iodomethyl)zinc as cyclopropanation reagents in the modified Furukawa process,[60] using the reaction shown in **Scheme 34**.

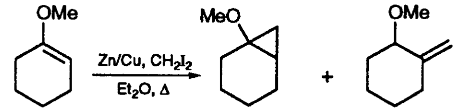


Scheme 34

Initially, the influence of the solvent was examined. Dichloroethane was found to be the superior solvent for the reaction, giving **35** in a yield of 94%, while other solvents assessed included diethyl ether (< 1%), toluene (75%), benzene (83%), and hexane (7%).
In the cyclopropanation of a variety of alkenes using diethyl zinc and either $ClCH_2I$ or CH_2I_2, $ClCH_2I$ was found to give far superior reaction rates. NMR spectra of the solution state species formed indicated that each gave rise to a different organometallic species. As is generally expected, the presence of an allylic oxygen led to a large rate enhancement, and more remote neighbouring oxygen atoms were also found to direct

the stereochemical course of the reaction. The evident superiority of the chloromethylzinc reagent examined here over the more normal iodomethylzinc would suggest that this should become the reagent of choice for Furukawa modified Simmons–Smith cyclopropanations.

The Simmons–Smith cyclopropanation of enol ethers has been found to give different results depending on the concentration of the reaction mixture.[61] Under dilute conditions (~ 0.5 M with respect to the substrate), it was found that cyclopropanation occurred exclusively, whereas under much higher concentrations, allylic ethers were generally found to be the exclusive product (**Scheme 35**). The allylic ether products were assumed to have formed *via* zinc iodide catalysed rearrangment of the initially formed cyclopropane. The isomerization step was also examined, although less successfully, using diiodomethane and diethylzinc. It was found that although the isomerization of the cyclopropane occurred, the resulting allyl ether then underwent rapid cyclopropanation itself. In general, the isomerization reaction proceeds more smoothly in less coordinating solvents.

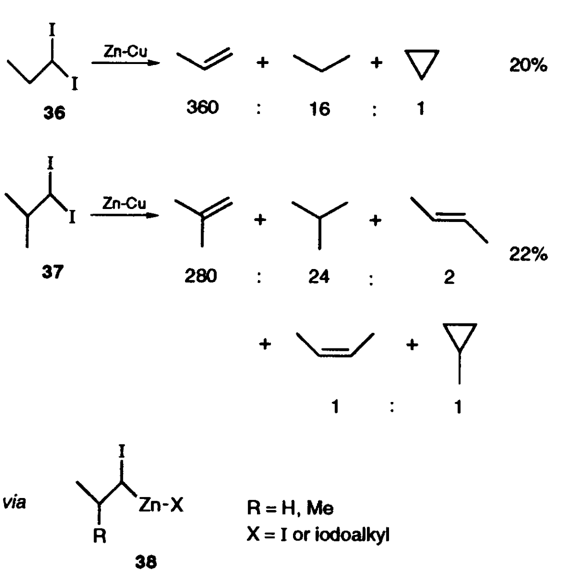


Concentration	Product Ratio	Total Yield (%)
~0.5M	98 : 2	72
~1.25M	83 : 17	59
~2.0M	2 : 98	66

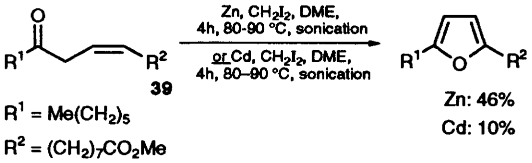
Scheme 35

In an early study, the carbenoid nature of the Simmons–Smith cyclopropanation reagent was shown by the ability of a modified reagent to undergo intramolecular C—H insertion reactions.[62] The reagents concerned were prepared from the reaction of 1,1-diiodopropane **36** or 1,1-diiodo-2-methylpropane **37** with a zinc-copper couple. After a short induction period, volatile products were found to form (**Scheme 36**), and were proposed to have arisen *via* the intermediacy of **38**.

The heterogeneity of the Simmons–Smith reaction would suggest that reactivity would be increased enormously by sonication. Repic and Vogt undertook such a study,[63] and found that whereas the Simmons–Smith reaction normally requires prior activation of the zinc, *i.e.* formation of a couple (a capricious process), by sonicating the reaction, ordinary unactivated zinc is sufficiently reactive. They also found that it was possible to cyclopropanate alkenes with consistently higher yields than in the literature. It is surprising in view of these results that sonication of such reactions has not met with wider use. Lie Ken Jie and Lam later published on the influence of sonication in the cyclopropanation of unsaturated long chain keto esters, and the effect of changing the metal employed (zinc *versus* cadmium *versus* copper).[64] It was found that under sonication at 80–90°C in DME, copper metal and diiodomethane were able to effect alkene cyclopropanation. Interestingly, when **39** was sonicated in the presence of either cadmium or zinc and diiodomethane, furan formation was observed (**Scheme 37**).



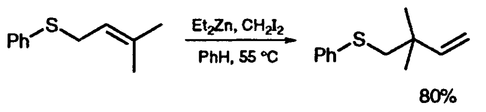
Scheme 36



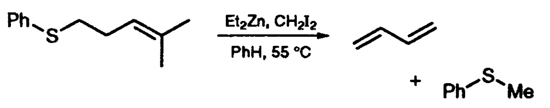
Scheme 37

Sibille and co-workers examined what may be considered an electrochemical version of the Simmons–Smith reaction.[65] The optimized reaction conditions were found to be a 9:1 dichloromethane : dimethylformamide solvent mixture, using a carbon fibre cathode and zinc anode. Zinc bromide was then generated *in situ* by the electrolysis of 1,2-dibromoethane, in the presence of the alkene, and then dibromoethane added to facilitate cyclopropanation. In this manner cyclopropanes were obtained in yields ranging from 8–75 per cent, with the best yields for allylic or unfunctionalized alkenes. *Syn* addition was observed in all cases. The authors suggested that the cyclopropanating agent formed in this process is a zinc carbenoid 'as proposed for the classical chemical reaction', on the basis of similarities in reactivity observed.

The use of allyl thioethers[66] and α-oxoketene dithioacetals[67] as substrates in the Simmons–Smith reaction has led to some interesting reactions. It was found that the cyclopropanation of cyclohexene was completely suppressed in the presence of an allyl or alkyl thioether using diiodomethane and either a zinc-copper couple, zinc-silver couple or copper powder.[66] However, taking 3-methyl-1-phenylthio-2-butene, diethyl zinc, and diiodomethane, a methylene homologation reaction is observed, which presumably proceeds *via* the formation of a sulfur ylide and a 2,3-sigmatropic rearrangement (**Scheme 38**). If a homoallylic sulfide is used, it can form an ylide capable of elimination to form dienes (**Scheme 39**).

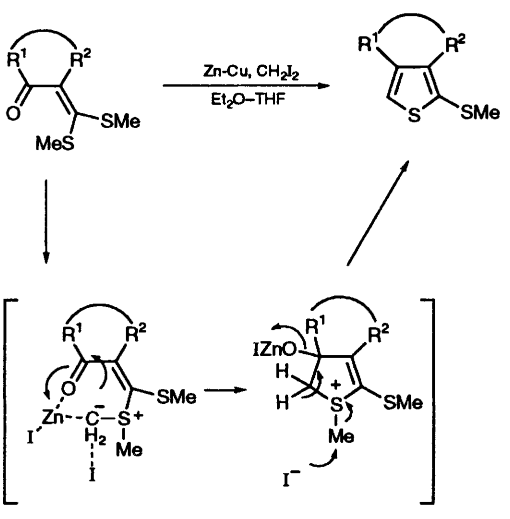


Scheme 38



Scheme 39

The attempted cyclopropanation of α-oxoketene dithioacetals gave rise to a new route to 3,4-substituted and annelated thiophenes.[67] In essence, under normal Simmons–Smith conditions, the carbenoid intermediate forms a sulfur ylide with α-oxoketene dithioacetal, which then reacts intramolecularly to yield a thiophene (**Scheme 40**).



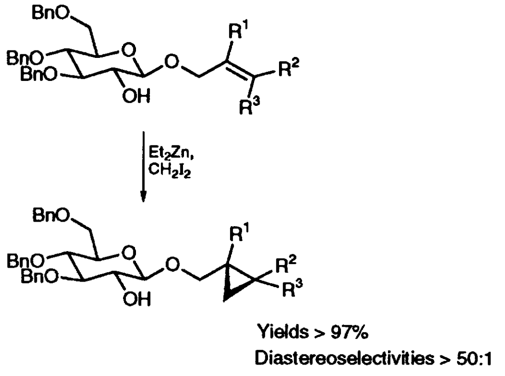
Scheme 40

The reaction was found to be unaffected by the presence of additional alkene units, and in the examples examined, yields of the thiophenes ranged from 53–65%. In some cases, dethiomethylation of the resulting thiophene was possible using Raney nickel in methanol.

It is thus possible that a whole range of ylide chemistry could be accessed *via* the zinc carbenoid formed in the Simmons–Smith reaction. One interesting aspect of this is that in the Simmons–Smith reaction a neighbouring oxygen (alcohol) serves to promote the rate of cyclopropanation, an effect considered to be due to coordination of the zinc *via* the oxygen. There have apparently been no similar examples of oxonium ylide chemistry, which reflects on the relative availability of the lone pairs of electrons in divalent sulfur and oxygen, and the rate of cyclopropanation *versus* ylide formation.

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

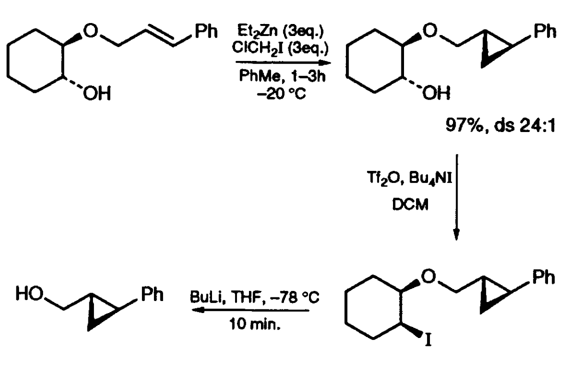
Charette has published some particularly elegant work recently, employing carbohydrates as a chiral auxiliary to achieve a highly stereoselective cyclopropanation of allylic alcohols.[68] This methodology capitalizes on the fact that one of the oxygen atoms in the auxiliary (the free hydroxyl at the 2-position) proximal to the alkene undergoes direct attack by the reagent to facilitate prior coordination of the zinc. This anchoring of the reagent was found to give good diastereoselection and high yields of the cyclopropane (**Scheme 41**). A large excess of reagents is required, and the exact reagent ratios were found to be important.



Scheme 41

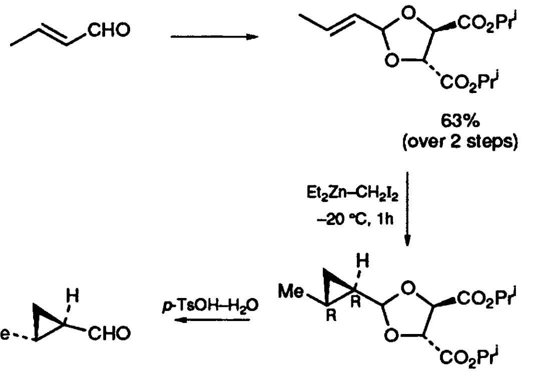
Cleavage to the cyclopropylmethanol was achieved *via* the conversion of the product into the corresponding triflate, and then heating in DMF–water at 160°C, yielding the free cyclopropane (90%) *via* a novel fragmentation of the 2-hydroxyglucopyranoside. Preliminary results using the auxiliary with the opposite anomeric configuration indicate formation of the cyclopropane of opposite relative configuration with a good level of asymmetric induction (diastereoselection > 12:1, yield > 97%).

Developing and simplifying this strategy, Charette later published results on the use of 1,2-*trans*-cyclohexanediol as the chiral auxiliary for the asymmetric cyclopropanation of allylic ethers.[69] After optimization studies the auxiliary was found to give a high level of stereochemical induction (> 20:1) if bis(chloromethyl)zinc was used instead of bis(iodomethyl)zinc. In this instance, in contrast to the sugar-based auxiliaries, only three equivalents of the reagent in toluene were necessary to maximize yields and diastereoselection. Furthermore, protection of the secondary alcohol was found to be detrimental to the diastereoselectivities, indicating the pivotal importance of zinc coordination to the free hydroxyl group on the stereochemical outcome. A typical reaction, and the sequence for removal of the auxiliary, is shown in **Scheme 42**.



Scheme 42

A considerable body of work has been published using homochiral ketals as auxiliaries in the cyclopropanation reaction. The first results in this area were published simultaneously by Yamamoto[70] and Mash.[71] Yamamoto had employed an acetal of an α,β-unsaturated aldehyde, derived from diisopropyl tartrate, as the chiral auxiliary (since this substrate was found to give slightly higher enantiomeric excesses than that derived from diethyl tartrate). Cyclopropanation was then carried out using diethyl zinc and diiodomethane. Yields were high, as were the diastereomeric excesses (**Scheme 43**).

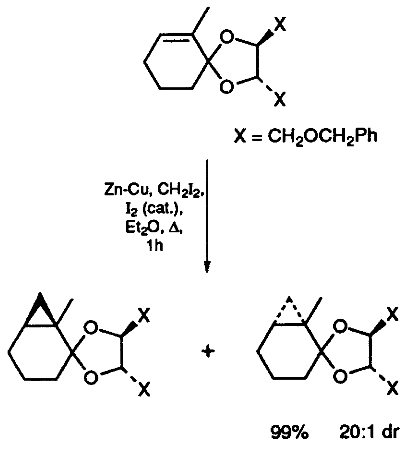


Scheme 43

The acetal could be transformed to the aldehyde (p-TsOH-H_2O) or to the ester (ozonolysis). The ready availability of both the (*R,R*)- and (*S,S*)-tartaric acid esters allows the synthesis of both enantiomers of cyclopropanes from α,β-unsaturated aldehydes.

Yamamoto then used this methodology in the synthesis of (5*R*,6*R*)-5,6-methanoleukotriene A_4.[72] In the same paper results were also presented on the use of acetals derived from (2*R*,4*R*)-2,4-pentanediol, which gave the corresponding (*R,R*)-cyclopropane in good to high yield (69–95%) and moderate diastereomeric excess (29–75%). The mechanism for the action of these auxiliaries was suggested to be *via* the coordination of the incoming cyclopropanating agent to the more exposed acetal oxygen on the auxiliary.

Mash employed homochiral cycloalkenone ketals, prepared by the direct ketalization of the corresponding α,β-unsaturated ketones and aldehydes using 1,4-di-*O*-benzyl-L-threitol as the diol component.[71] These ketals were then cyclopropanated using zinc-copper couple, diiodomethane, and a crystal of iodine in refluxing diethyl ether. After a short reaction time (~ 1 h), yields were found to be in the range 90–98%, with, in the case of the cycloalkenone ketals, a good diastereomeric excess (**Scheme 44**). However, acyclic ketals derived from α,β-unsaturated aldehydes were found to give very poor diastereoselection.



Scheme 44

In a later paper the methodology was expanded successfully to synthesize tricyclo[m.n.1.0]-alkanones as well as bicyclo[m.1.0]-alkanones of the sort shown in **Scheme 44**.[73] As with Yamamoto's method, both cyclopropane enantiomers could be accessed by using either the L- or D-forms of 1,4-di-*O*-benzyl-threitol, readily available from natural and unnatural tartaric acids. The ketal was readily hydrolysed in acidic methanol, and the auxiliary easily recovered. The stereochemistries of the cyclopropanes thus synthesized suggested that a common mode of reagent delivery is operative (**Figure 1**). The major drawback, however, with this method, was found to be that the diastereomers produced were neither crystalline nor chromatographically separable, and so it was not possible to obtain enantiomerically pure cyclopropyl ketones by this route.

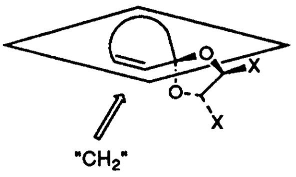
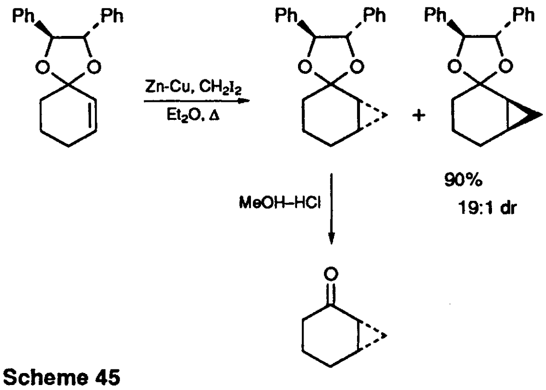


Figure 1

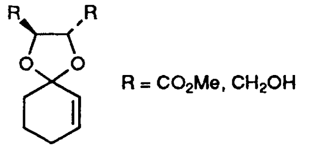
This work was later applied by Mash in the total synthesis of (+)-modhephene, using a slightly modified auxiliary. The first steps in the synthesis involved an enantioselective cyclopropanation, which, on ring-opening of the cyclopropane, eventually furnished an angular methyl group.[74]

Mash went on to examine other diols, which allowed more successful separation of the diastereomers produced, and all recent work has employed the diol (*S,S*)-(−)-hydrobenzoin, giving the corresponding 2-cycloalken-1-one (*S,S*)-(−)-hydrobenzoin ketals. These were found to give good yields of the cyclopropane, and high diastereomeric ratios (**Scheme 45**).[75]



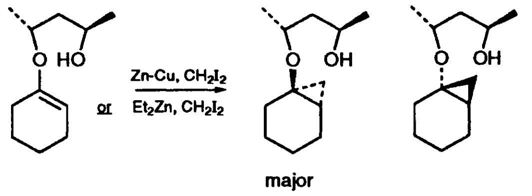
Scheme 45

An interesting study was also made on the influence on the diastereoselectivities of having strongly Lewis basic oxygenated appendages on the ketals **40**.[76] These were found to both lower yields and diastereoselectivity, and the results were in contrast to those of Yamamoto, shown in **Scheme 43**.[70] Yamamoto had reported similar yields and diastereomeric excesses to Mash, who was employing either ether or alkyl appendages on the ketal, using diisopropyl tartrate as the chiral auxiliary, *i.e.* R = CO_2Pr^i in **40**. Mash discusses the mechanistic implications of the observed effects. Studies were also carried out on the effect of ring conformation on diastereoselectivity.[77]



40

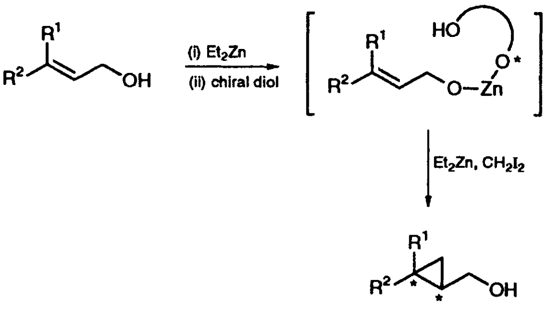
Tai and co-workers examined the use of 2,4-pentanediol or 2,6-dimethyl-3,5-heptanediol as an auxiliary. Early work employing 2,4-pentanediol gave moderate yields (~ 55%) and high diastereomeric excesses (> 95%) (**Scheme 46**).[78] The use of both the classic Simmons–Smith reagent, and the Furukawa modified procedure was examined. The chiral auxiliary was removed by PCC oxidation followed by treatment with potassium carbonate in methanol.



Scheme 46

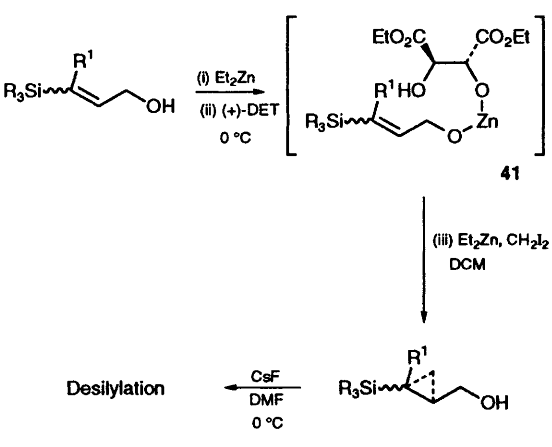
Using the more sterically congested chiral auxiliary 2,6-dimethyl-3,5-heptanediol, and cyclopropanating using diethylzinc and diiodomethane in diethyl ether at 20°C, yields were elevated up to 86%, with excellent diastereomeric excesses (> 99.5%).[79] The major drawback to this auxiliary appears to be that, as with the 2,4-pentanediol derivative, a two step deprotection protocol is necessary.

In an interesting variant on the chiral auxiliary theme Fujisawa and co-workers found that they were able to take an allylic alcohol, form *in situ* a complex with diethyl zinc and (+)-diethyl tartrate (DET) (other esters of *R,R*-tartaric acid were also examined), such that the tartrate moiety still had one free pendent hydroxyl group. On the addition of the second equivalent of diethyl zinc and diiodomethane, the cyclopropanating agent formed carried out a stereospecific methylene delivery by virtue of the transient auxiliary-substrate complex formed (**Scheme 47**).[80] Although the results reported were variable, this approach to the enantioselective synthesis of cyclopropanes from allylic alcohols seems promising.



Scheme 47

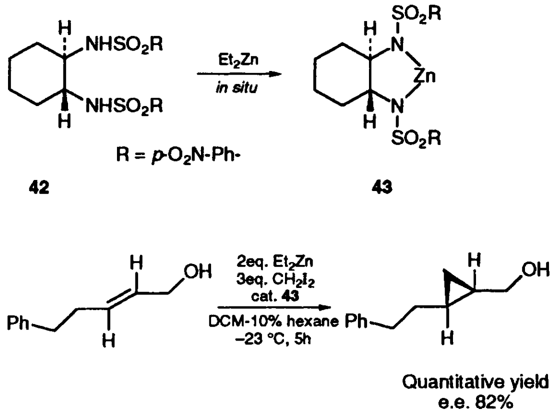
Fujisawa's preliminary results in this area were extended by Ukaji and co-workers.[81] Optically active silicon substituted cyclopropylmethyl alcohols were prepared by the reaction of γ-trimethylsilyl substituted allylic alcohols with diethyl zinc, diiodomethane, and (+)-DET (**Scheme 48**). The products were formed with a high diastereoselectivity (up to 92% e.e.), and in most cases in high yield. It was found that using dichloroethane as the reaction solvent lowered the selectivity compared with dichloromethane, and that



Scheme 48

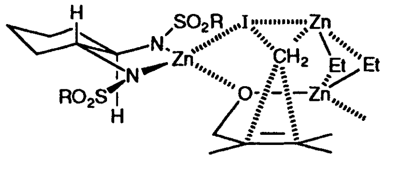
lowering the reaction temperature enhanced selectivity. It was assumed as before that the addition of the first equivalent of the diethyl zinc and (+)-DET led to the formation of the zinc bridging intermediate **41**.

In a very exciting development, allylic alcohols have also been enantioselectively cyclopropanated in a catalytic fashion *via* the use of a C_2-symmetric disulfonamide as a chiral ligand.[82] Thus, a catalytic quantity of the disulfonamide **42** is reacted with diethyl zinc to generate what is assumed to be species **43**. When diiodomethane is added, a chiral cyclopropanating agent is formed, giving excellent chemical yields, and good enantiomeric excesses (**Scheme 49**). The free hydroxyl group of the allylic alcohol was found to be very important, and when ether derivatives were subjected to these reaction conditions, racemic mixtures of cyclopropanes resulted.



Scheme 49

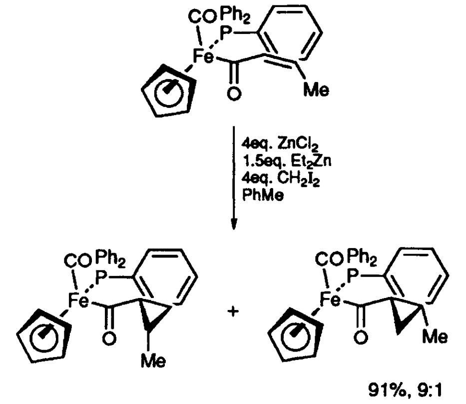
The authors suggested, in view of the experimental results, that the chiral Lewis acid zinc complex **43**, formed a chiral complex of type **44** in the transition state, which must of course react even faster than the normal achiral reagent. Thus the oxygen atom of a zinc alkoxide and an iodine atom of iodomethylzinc coordinate to the zinc atom in **44**, giving rise to a trinuclear complex. The enhanced reactivity observed by the authors could thus be attributed to the coordination of the zinc atom of **43** with an iodine atom of iodomethylzinc.



R = p-O2N-Ph-

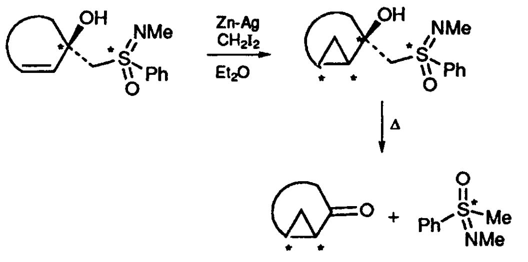
44

The asymmetric synthesis of cyclopropane carboxylic acid derivatives has been examined using an iron complex as the chiral auxiliary.[83] When $[(\eta^5\text{-}C_5H_5)\text{-}Fe(Co)(PPh_3)]$ was complexed with a Z-α,β-unsaturated acyl ligand, and cyclopropanated using diethyl zinc and diiodomethane, in the presence of zinc chloride in toluene, the corresponding cyclopropanes were isolated in 91% yield (**Scheme 50**). Stereoselectivity was found to increase with increasing size of the terminal alkene substituent. However, it was found that this method could not be used for the corresponding E-α,β-unsaturated acyl ligands, as these appeared to require a nucleophilic methylene transfer reagent.[83(b)]



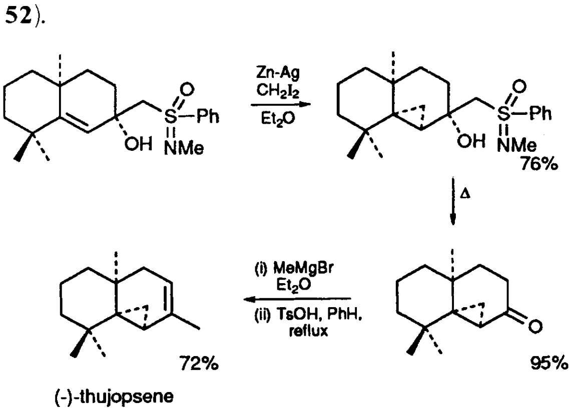
Scheme 50

Optically active cyclopropyl ketones were accessed *via* the cyclopropanation of β-hydroxysulfoximines using a zinc-silver couple and diiodomethane, refluxing in diethyl ether for 72 h (**Scheme 51**).[84]



Scheme 51

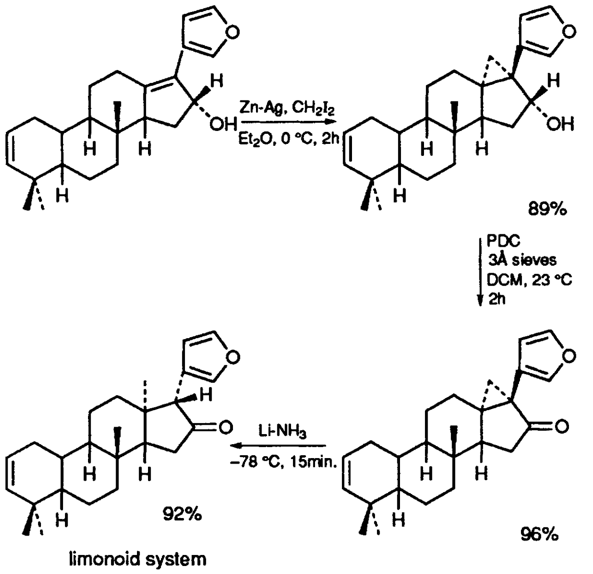
The cyclopropanation was found to occur *cis* to the hydroxyl group of the allylic β-hydroxysulfoximine. As both the enantiomers of the β-hydroxysulfoximine can be accessed, it is possible to synthesize both cyclopropane enantiomers. Removal of the β-hydroxysulfoximine group is achieved simply by a thermal elimination. This technology has been applied to the synthesis of (−) and (+)-thujopsene (**Scheme 52**).



Scheme 52

Finally, in this section, some of the more recent uses of the Simmons–Smith reaction in natural product synthesis will be outlined. Cyclopropanes feature in many important synthetic targets, and their introduction has also been used to furnish angular methyl groups *via* a ring cleavage protocol.
In the first total synthesis of the limonoid skeleton, Corey utilized a hydroxyl-directed Simmons–Smith reaction to stereospecifically generate a cyclopropane, which was then cleaved using lithium–liquid ammonia, to create the C/D angular methyl group (**Scheme 53**).[85] Generally this group is difficult to introduce, and the Simmons–Smith methodology provides a useful entry.

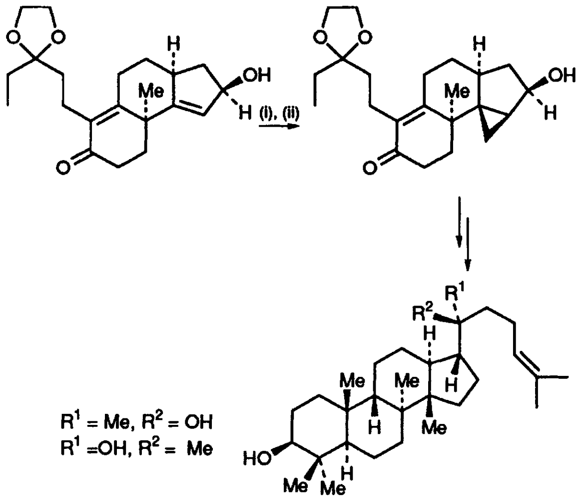
The same synthetic strategy for the introduction of the C/D angular methyl group was also applied in the synthesis of azadiradione, a tetracarbocyclic member of the limonoid family.[86]



Scheme 53

The first enantioselective total synthesis of 3β,20-dihydroxyprotost-24-ene **45**, a protostenediol of the protosterene system, again used a hydroxyl-directed cyclopropanation to furnish eventually an angular methyl group (**Scheme 54**).[87] In this instance, however, the yield in the cyclopropanation step was only moderate (66%).
The enantiospecific synthesis of ring system **46**, characteristic of the crenulide diterpenes was recently published.[88] In this instance, the cyclopropane moiety was introduced through reagent delivery from the least hindered face of the alkene, using diethyl zinc and diiodomethane to give a high yield (83%) to give the desired product (**Scheme 55**).

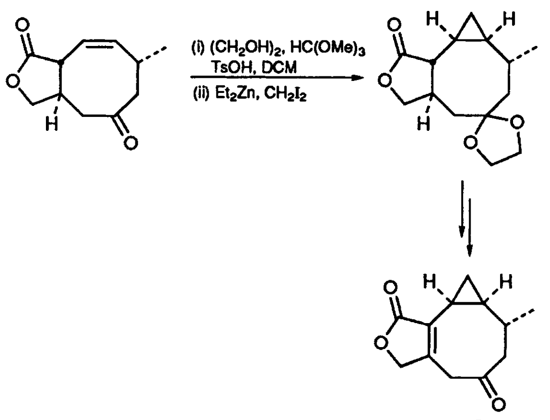
As part of a strategy towards the linearly fused sesquiterpene hirsutene, Hudlicky and co-workers demonstrated the first example of an intramolecular Simmons–Smith reaction.[89] The reaction examined is illustrated in **Scheme 56**. Although the yields of the cyclopropanes were relatively low, the authors suggested that this was due to the purity of the precursor, which had to be generated *in situ* due to its instability.



45

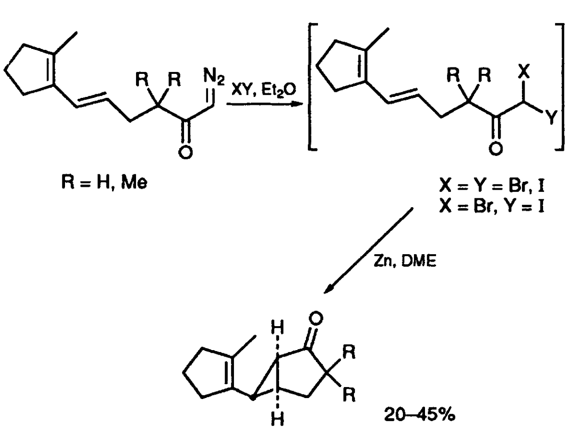
Reagents: (i) 1eq. Bu^{n}Li; (ii) 15eq. ICH$_2$ZnI, Et$_2$O, 23 °C, 12h

Scheme 54



46

Scheme 55



Scheme 56

4 Simmons–Smith reagents from the reduction of a zinc(II) salt with a diazoalkane

This method for the generation of Simmons–Smith type reagents for the cyclopropanation of olefins was first reported by Wittig,[90] and has since received relatively little attention. The active cyclopropanating species is formed by the addition of diazomethane or aryldiazomethane to an ethereal suspension of a zinc (II) halide, **Schemes 57 and 58**, with the active species being either the 'monomer' **47** or 'dimer' **48**.

$$ZnI_2 + CH_2N_2 \xrightarrow{-N_2} ICH_2{\cdot}ZnI$$

47

Scheme 57

$$ICH_2{\cdot}ZnI + CH_2N_2 \xrightarrow{-N_2} ICH_2{\cdot}ZnCH_2I$$

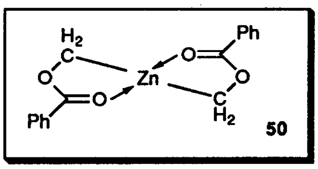
48

Scheme 58

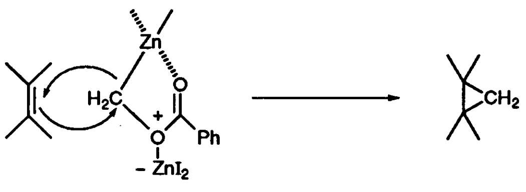
Wittig proceeded to publish a series of papers on this reaction,[91] where salt effects were examined, and the influence of other metals such as magnesium and lithium. It was possible to cyclopropanate alkenes with the reagent derived from diazomethane in moderate to good yields.[91(a)] Whilst cyclohexene could only be cyclopropanated in 30% yield, aromatic substituted alkenes such as styrene and 4-propenylanisole gave far higher yields, 85% and 80% respectively. In a variant of this reaction[91(e)] it was found that taking dibenzoyloxy zinc and diazomethane, an effective methylene insertion occurred to give the benzoyloxymethyl zinc derivative **49**. Characterization by IR suggested structure **50**. This reagent could then be used to cyclopropanate alkenes in the presence of zinc(II) halides (**Scheme 59**).

$$(PhCO_2)_2Zn + CH_2N_2 \xrightarrow{-N_2} (PhCO_2\text{-}CH_2)_2Zn$$

49

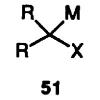


50

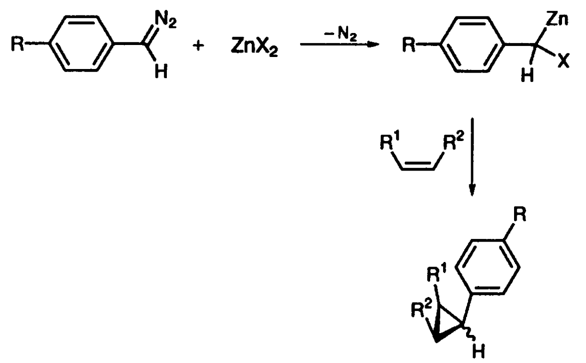


Scheme 59

Apart from Wittig, few groups have examined this reaction, and it is primarily of academic interest. Closs[92] published a detailed study on the influences on the decomposition of aryldiazomethanes with lithium and zinc halides (**Scheme 60**). In effect, by considering the carbenoid generated by this method as having a general formulation **51**, the study examined the effect of the R (aryl only), M (metal), and X (leaving group).



51



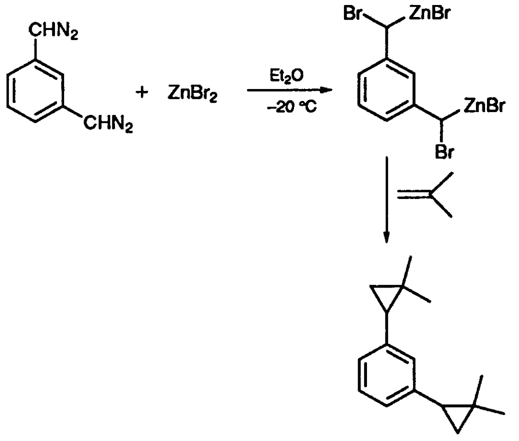
Scheme 60

Zinc halide catalysis of the reaction (**Scheme 60**) was found to give excellent yields of cyclopropanes, with the *syn* isomer always predominating. The reaction also worked for catalytic quantities of zinc halide, although most results were for the use of stoichiometric quantities.

For any one olefin and zinc halide, increasing electron-donating ability of the *para*-substituent on the aromatic ring of the aryldiazomethane led to a marked increase in the *syn* to *anti* ratio of the resulting cyclopropane, although this was surprisingly mirrored by a decrease in yield, in contrast to our own observations.[45] It would seem likely that this yield reduction was in fact due to increased substrate instability, and not inefficiency of carbenoid formation *per se*. Interestingly, a systematic study of the variation of the zinc halide used revealed that the chloride ion caused the smallest *syn* to *anti* ratio and iodide the largest (with bromide in between). The influence of the zinc halides on the reaction was measured using kinetic studies on the relative rates of additions of the various reactive intermediates to different olefins. Over all substrates, the rate increases markedly chloride to bromide to iodide, with iodide being significantly faster. A substrate (olefin) dependency also became apparent from this study: the greater the degree of substitution around the olefin, the faster the addition; as a corollary to this, the greater the degree of substitution, the larger the rate difference across the series from chloride to bromide to iodide.

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

Extending this principle, Goh and co-workers[93] examined the formation of dicarbenoid species from the reaction of 1,3-bis(diazomethyl)benzene with zinc halides. Best results were obtained using isobutylene, with the decomposition of the diazo compound being carried out in the presence of zinc bromide at -20°C in diethyl ether (**Scheme 61**). These reaction conditions gave a 62% yield of the dicyclopropane. In the absence of an alkene trap, the dicarbenoid was found to insert into the α-CH of diethyl ether (12%) and THF (34%), depending on the solvent employed for the reaction. Similar insertion reactions were also observed by Closs.[92] Attempted addition of the dicarbenoid to a di-olefin (diallyl ether) failed to give any of the expected adduct.



Scheme 61

5 Conclusions

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

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

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