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Mini-Account

On the evolution of organozinc carbenoid chemistry from carbonyl compounds — a personal account

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Dedicated with respect, admiration and friendship to Professor Jean Normant, a creative scientist, a scholar and a gentleman.

Abstract

A variety of carbonyl compounds and related congeners react with zinc metal in the presence of silicon electrophiles to afford organozinc carbenoids which can undergo several useful reactions including direct deoxygenation to alkenes, dicarbonyl coupling and cyclopropanation. © 2001 Elsevier Science B.V. All rights reserved.

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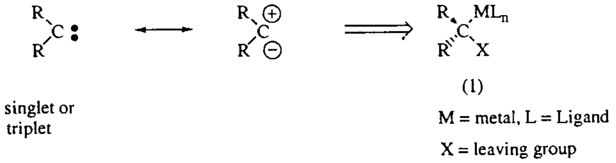
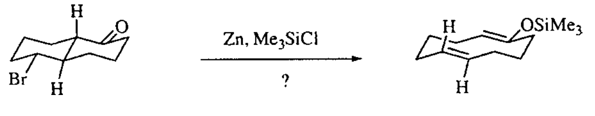
The fascination of organometallic carbenoids (**1**) lies in their ability to tame the indiscriminate chemical reactivity of 'free carbenes' through judicious control of the nature of the carbon–metal bond (M–C), the ancillary ligands, L_n, and the relative leaving group ability of the carbon–X bond as implied in Scheme 1. This apparently simple operation not only influences the nucleophilic or electrophilic character of reagents (**1**), but also, by selection of chiral ligands, L, has allowed organic chemists to develop highly enantioselective reactions. Although a myriad of reagents of general formula (**1**) remain to be explored, since the present account is concerned with the evolution of organozinc carbenoid chemistry within our own group, it is perhaps appropriate to illustrate the above points by specific reference to the well known Simmons Smith cyclopropanation reaction [1]. Over the years, the synthetic utility of this reaction has grown enormously, with the replacement of the original zinc or zinc–copper couple and diiodomethane combination by the Furukawa modification [2] using diethylzinc allowing homogenous reagents to be used and their structures investigated. This has culminated, most recently, in the elegant studies, especially by Denmark [3] and Charette [4], which have led, inter alia, to the introduction of chloroiodomethane, and the invention of highly enantio- and diastereoselective cyclopropanations [5].



Scheme 1.



Scheme 2.

All of these recent developments, however, are a long way from our own entry into the organozinc carbenoid area which began, as is so often the case, with the misconception of a young investigator. At that time, in the early 1970s, as the holder of an ICI Fellowship, I had the once in a lifetime opportunity to pursue my

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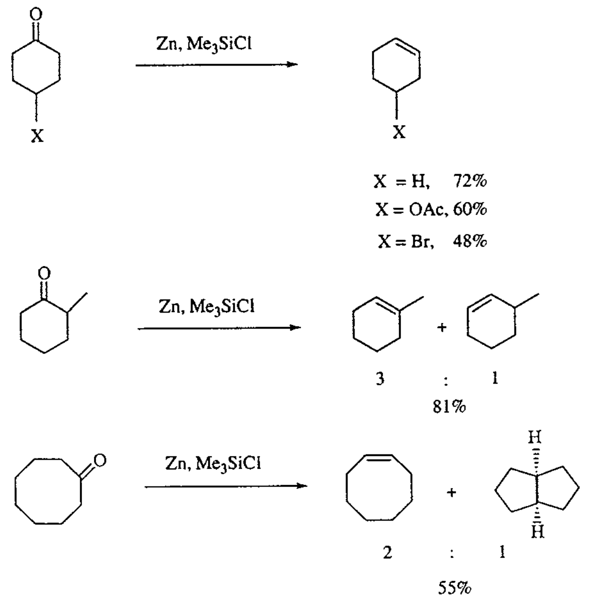


Scheme 3. Direct deoxygenation of cyclic ketones.

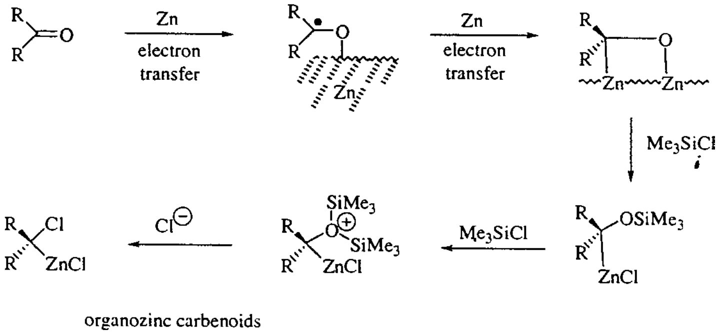
own independent research ideas, a very unusual privilege for a postdoctoral fellow immediately after his PhD. Since stereoelectronically controlled Grob type fragmentation reactions provided a very efficient entry into medium sized rings from bicyclic systems, I decided to examine the possibility indicated in Scheme 2, which would have led to a ten-membered ring possessing both a trans double bond and a useful regiospecific silyl enol ether moiety.

As a simple prelude, the reaction of 4-bromocyclohexanone with zinc and chlorotrimethylsilane was investigated. To my initial surprise, the major product to be isolated from this reaction was 4-bromocyclohexene, the result of direct deoxygenation of the carbonyl group to an alkene. Frenetic activity then ensued to demonstrate that this mild and simple 'one-pot' method exhibited a useful degree of chemoselectivity and regioselectivity, and the reaction of cyclooctanone, which furnished not only *cis*-cyclooctene but also the transannular insertion product bicyclo[3,3,0]octane, provided the first mechanistic clue that an organozinc carbenoid intermediate might be involved. Some selected examples of the reaction, which are taken from my first paper as an independent investigator, are shown in Scheme 3 [6]. At that stage, little did I know that a period of apprenticeship with Sir Derek Barton, first in the Imperial College and then in France, was to follow, and it was almost a decade before we could continue to explore this area of chemistry!

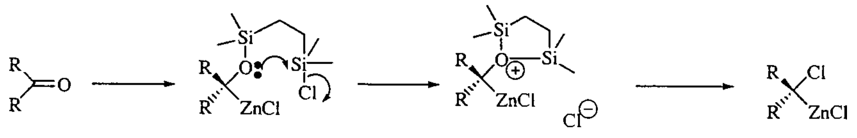
Further reflection on the results immediately led to the analogy that the essence of this reaction finds a mechanistic parallel as a simple variant of the classical Clemmensen reduction, with the silicon electrophile replacing the proton in the initial stages of the reaction. In this way, as implied in Scheme 4, the growth of an organozinc carbenoid species can be viewed as resulting from a series of electron transfer steps from zinc, and this, when coupled with the strong affinity of the silicon electrophile for the oxygen atom of the carbonyl group, leads to deoxygenation. The organozinc carbenoids thus formed then diverge from the Clemmensen pathway and undergo insertion reactions as opposed to further reactions with silicon electrophiles.

The similarity with Clemmensen reduction surfaced again when we began to study the behaviour of aromatic and α,β-unsaturated carbonyl substrates and discovered that these were particularly prone to undergo pinacolic coupling or dimerisation at the softer β-carbon atom, presumably as a consequence of the longevity of the carbon centred radicals produced by a single electron transfer from zinc. In order to combat this problem, since the overall stoichiometry of carbenoid generation requires two molecules of chlorotrimethylsilane per carbonyl group, we elected to use 1,2-bis (chlorodimethylsilyl) ethane as the silicon electrophile, reasoning, as shown in Scheme 5, that this would lead to intramolecular delivery of the second silicon electrophile, and hence facilitate carbenoid generation.

The selection of the bis silicon electrophile then allowed us to improve the yields, in a non McMurry like symmetrical dicarbonyl coupling [7] reaction which we had discovered some time earlier [8] when we had



Scheme 4.



Scheme 5.

attempted to prepare 1,3-diene derivatives from α,β-unsaturated carbonyl compounds. The method was also applicable to the preparation of stilbene derivatives and some typical examples of both classes of compound are collected in Scheme 6.

From a mechanistic standpoint, we were already aware that vicinal diols or their bis trimethylsilyl ethers did not undergo deoxygenation to alkenes, whilst α,β-unsaturated epoxides and stilbene epoxides could undergo ring opening and zinc induced elimination via siloxychlorohydrin derivatives [9]. These observations, when taken in conjunction with the isolation of 2,6-diphenyldihydropyran from an attempted intramolecular coupling of 1,5-diphenylpentane-1,5-dione provide strong presumptive evidence for the mechanism shown in Scheme 7 which involves trapping of an organozinc carbenoid by a carbonyl compound to give a carbonyl ylide as an intermediate. For the particular intramolecular case shown, epoxide formation is of course disfavoured, both in terms of electronic stabilisation and the strain produced on ring closure.

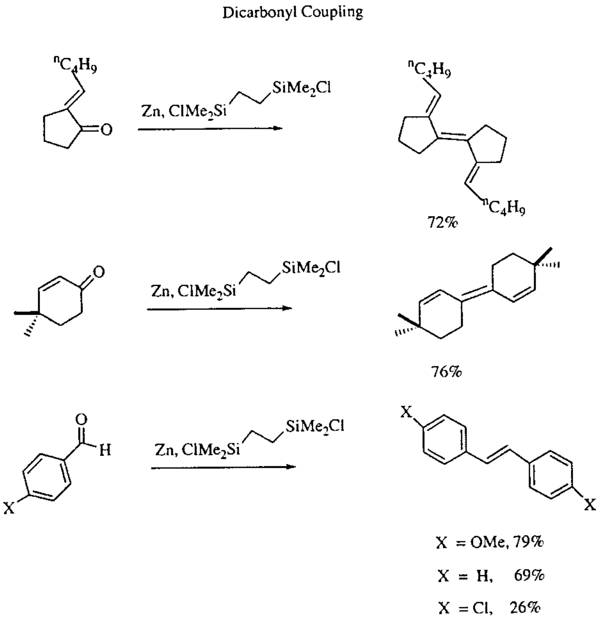
Almost inevitably, however, because of the formal similarity of the active species with the Simmons Smith carbenoid, we were drawn towards the possibility of developing a simple and attractive cyclopropanation method which would not require the necessity for handling and preparing either the gem dihalo compounds or the diazo precursors used as reagents in typical metallocarbenoid chemistry. It is said that patience is a virtue, but in this instance the interval between the preliminary experiment, in my own laboratory notebook, using benzaldehyde, cyclohexene, zinc and chlorotrimethylsilane, and the following study was some 15 years. Needless to say, the PhD student, Lee Roberts, improved considerably over my own efforts.

The results for a series of aromatic aldehydes using 1,2-bis(chlorodimethylsilyl) ethane to avoid pinacolic coupling problems are shown in Scheme 8, and, from a preparative standpoint, it is pertinent to note that only two molar equivalents of the alkene were employed [10].

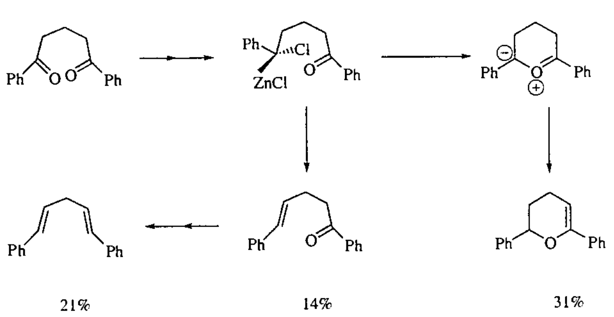
Clearly, electron releasing groups increase the efficiency of carbenoid generation, as might be expected for the step involving expulsion of hexamethyldisiloxane (Scheme 4). The intriguing preference for the formation of the more hindered *endo* isomer has also been noted in other metallocarbenoid cyclopropanations and an elegant explanation involving electron donation via the *ipso* carbon of the aromatic ring has been advanced by Casey [11].

The carbenoids derived from a variety of acyclic and alicyclic α,β-unsaturated aldehydes and ketones also proved to be useful for cyclopropanation. Some typical yields are shown in Scheme 9, which also reveals that the precursor carbonyl derivatives could be cleanly divided into successful and unsuccessful categories. Comparison of ‘those which work’ and ‘those which do not’ suggested that some degree of substitution either at or around the β carbon of the unsaturated carbonyl group was beneficial, but it was only at a later stage (vide infra) that we appreciated the significance of these observations.

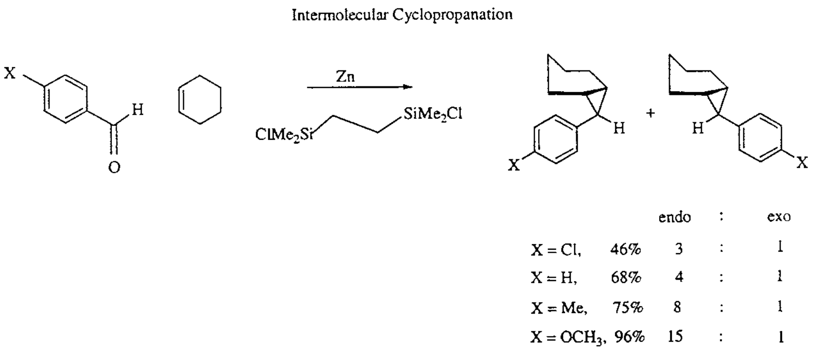
As a student, I was always fascinated by the diversity and molecular acrobatics of the terpenoids, and we



Scheme 6.



Scheme 7.



		endo	:	exo
X = Cl,	46%	3	:	1
X = H,	68%	4	:	1
X = Me,	75%	8	:	1
X = OCH$_3$,	96%	15	:	1

Scheme 8.

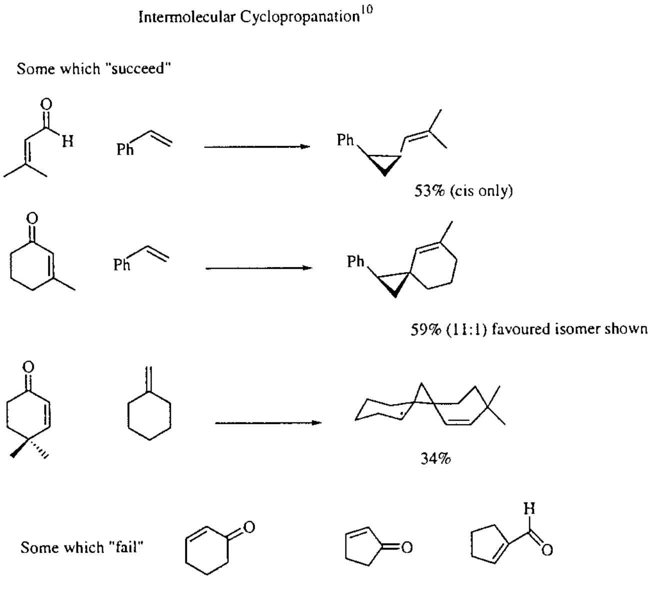
therefore decided to examine a series of intramolecular cyclisations in this area in which the prenyl motif embodied in the enal unit served as the carbenoid precursor for a tethered alkene [12]. The most surprising feature to emerge from this study was that a highly efficient cyclopropanation could occur even when the initial geometry around the enal unit was unfavourably located with respect to the alkene trap, as shown for all three of the examples selected in Scheme 10.

These results, when taken in conjunction with the necessity for some degree of steric hindrance around the β-carbon atom of the α,β-unsaturated carbonyl unit (Scheme 9) suggest that 1,3-allyl migration of the carbon zinc bond leading to relief of steric congestion, but with consequent loss of alkene geometry, may well be a very facile process at some stage (Scheme 11). As shown by the examples in Scheme 10, however, the fact that enal geometry need not be controlled can also offer synthetic advantages.

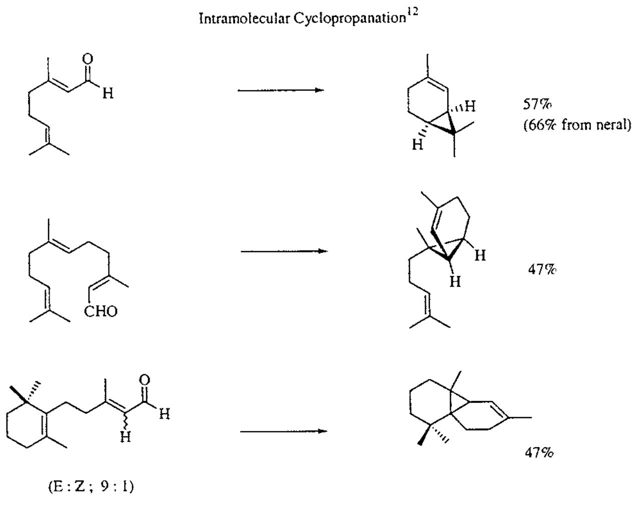
All of the above reactions have relied on the carbonyl group as an electron acceptor and, as pointed out by Burden [13] in his study of the Clemmensen reduction, pinacolic coupling is most readily explained by the early formation of a carbon centred radical which is bound to the zinc surface through the oxygen atom. More recently, in view of the fact that isolable organochromium [14] and organoiron carbenoids [15] have been prepared by two electron delivery from a metal salt to an oxocarbenium ion derived from an orthocarbonate or acetal, we decided to investigate the use of acetals and ketals as substrates for organozinc carbenoid generation [16]. We reasoned that such a pathway should avoid the formation of carbon centred radicals bound to the zinc surface and also hoped that an oxonium ion intermediate, by virtue of its positive charge, would be more susceptible to accept two electrons from zinc.

The transformations shown in Scheme 12 served, inter alia, to convince us that this possibility did indeed exist, particularly since the reaction of the neopentyllic ketal derived from 4-*tert*-butyl cyclohexanone was unlikely to undergo alkyl oxygen cleavage with regeneration of the parent carbonyl compound.

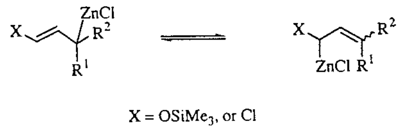
Whilst the direct conversion of an acetal or a ketal to an alkene may prove to be a useful functional group interconversion in its own right, it was in fact the



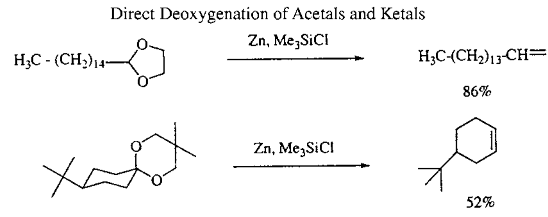
Scheme 9.



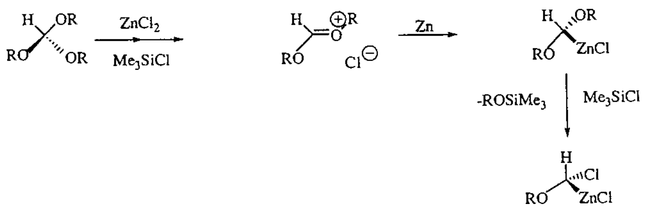
Scheme 10.



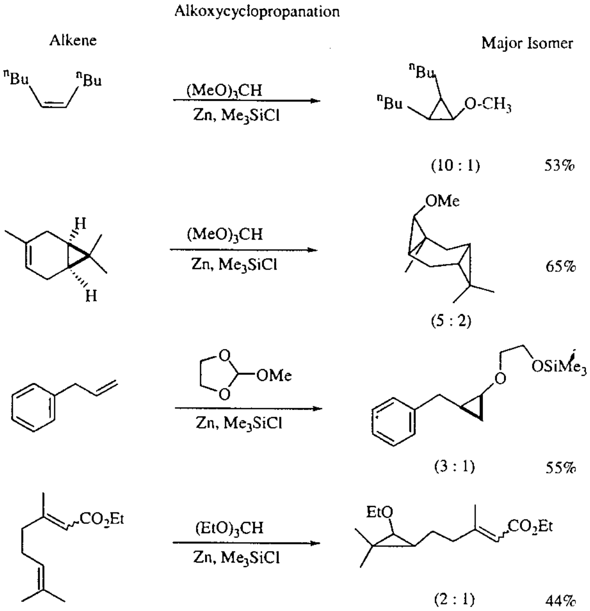
Scheme 11.



Scheme 12.



Scheme 13.



Scheme 14.

preliminary study for the first generation of alkoxyorganozinc carbenoids from orthoformates.

Thus, as implied in Scheme 13, provided that alkyl oxygen cleavage of oxocarbenium ions does not intervene, two electron delivery from zinc can then be followed by the oxygen atom assisted departure of a second alkoxy group to provide intermediates whose subsequent reactivity in alkoxycyclopropanation is consistent with the expected behaviour of an alkoxyorganozinc carbenoid.

In practice, a useful range of synthetically valuable alkoxy- and aryloxycyclopropanes can be simply prepared by selection of the appropriate orthoformate and reaction with an alkene in the presence of zinc and chlorotrimethylsilane [17], thereby avoiding the manipulation of highly carcinogenic α halo or α,α-dihalo ethers. Some examples are shown in Scheme 14. Interestingly, although both electron rich and electron poor alkenes can react, a chemoselective preference for the former is evident.

Whilst the chemistry of organozinc carbenoids [18] has formed only one small branch of our research programme, it has always remained as an area of fascination and interest over the years and, hopefully, the foregoing personal account has demonstrated that several new reactions of practical value have emerged. As always in organic synthesis, new reactions can be discovered by conception, by misconception and by chance and, within the evolution of our own studies, all of these facets have been involved. Thus, the initial misconception which led to direct deoxygenation to alkenes was followed by the 'chance' observation of dicarbonyl coupling products during separation of unwanted pinacolic products. As mechanistic insight grew however, the introduction of the silicon bis electrophile and the resultant cyclopropanation and alkoxycyclopropanation studies can be regarded as originating from a more conceptual approach. Young investigators should certainly take advantage of all three! At every single stage however, progress has only been possible through the dedication, curiosity, insight and experimental skills of those postgraduate students and postdoctoral fellows with whom I have had the joy and privilege of being associated, and those involved appear in the list of references. It is not perhaps by chance, that chance favours the prepared mind.

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