

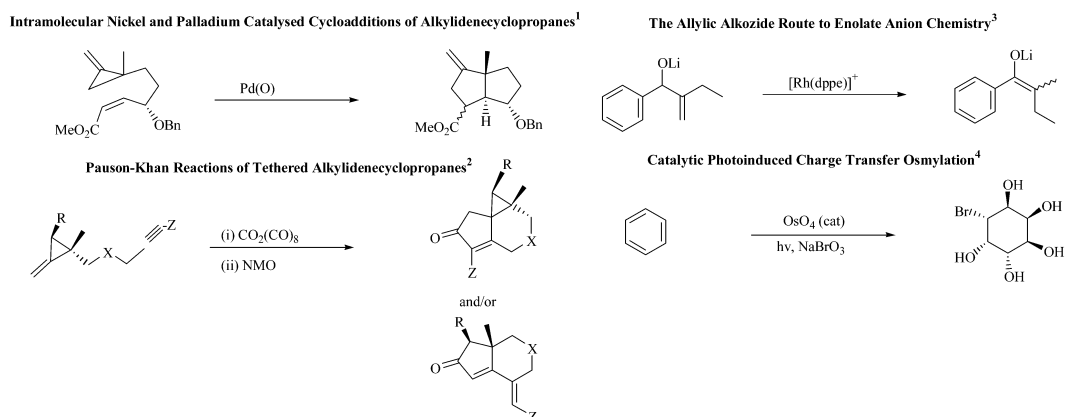
Curiosity and simplicity in the invention and discovery of new metal-mediated reactions for organic synthesis*

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Abstract: Two organometallic themes of current interest are presented. The scope and generality of the reductive deoxygenation of carbonyl compounds to organozinc carbenoids using zinc in combination with a silicon electrophile is discussed. Alkoxy-cyclopropanation can be achieved using orthoformates as substrates. Preliminary observations on the development of a rhodium-catalyzed tandem hydrosilylation–intramolecular aldol sequence are discussed.

The unparalleled power of metal-mediated reactions, either as stoichiometric reagents or as catalysts has, without question, revolutionized the art of organic synthesis, as witnessed by the ever-increasing armory of powerful but mild chemoselective and stereo- and enantiospecific transformations that have been placed at the disposal of the skilled practitioner. Within this framework of organometallic synthesis alone, it is now perfectly possible for the specialist to devote his/her entire career to the discovery of new and useful reactions based even on the use of a single metal. When viewed from this perspective, and given that metal-based reactions form only one facet of our own research activities, we must accordingly be considered amateurs rather than professional organometallic chemists. The joy and vicarious pleasure of the amateur, however, is of course that he is permitted to indulge his curiosity by ranging over the periodic table as shown in Scheme 1 by some of our own adventures in recent years.

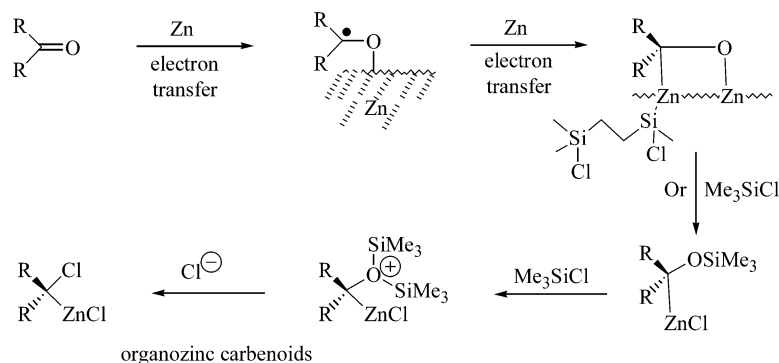


Scheme 1

*Lecture presented at the 11th IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS-11), Taipei, Taiwan, 22–26 July 2001. Other presentations are presented in this issue, pp. 1–186.

For the purpose of the present paper, however, two organometallic themes from our current research program have been selected for discussion.

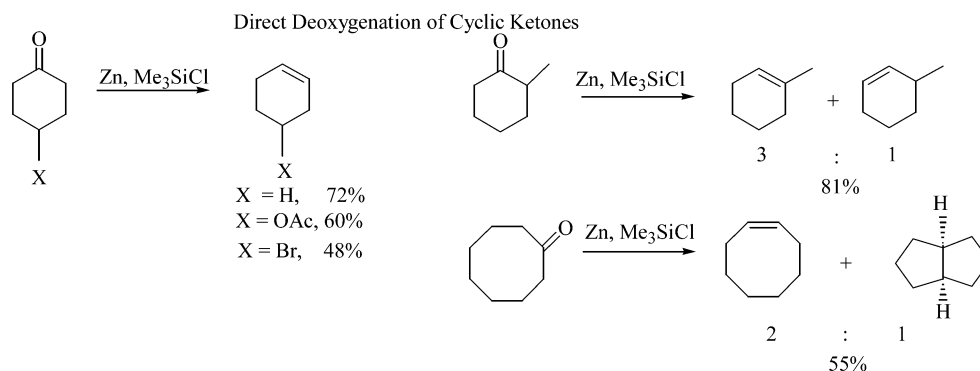
The first of these, and of long-term interest in our group [5], is concerned with the generation and reactivity of functionalized organozinc carbenoids [6] from carbonyl compounds, as encapsulated in Scheme 2, which views the growth of the organozinc carbenoid as resulting from a series of single-electron transfer steps from the zinc surface. From a mechanistic standpoint, the reaction sequence therefore bears a close resemblance to the Clemmensen reduction, except that the proton is replaced by a highly oxophilic silicon electrophile, which presumably provides a strong thermodynamic driving force with the formation of hexamethyldisiloxane or the related cyclic congener which may be produced when the entropically favored bis silicon electrophile, 1,2-bis(chlorodimethylsilyl) ethane is used.



Scheme 2

The advantage and inherent simplicity of such an approach is not only that it avoids the use of dangerous and/or toxic *gem* dihalo and diazo precursors, but also that the carbonyl group and its related congeners have always been considered as cornerstone building blocks for organic synthesis.

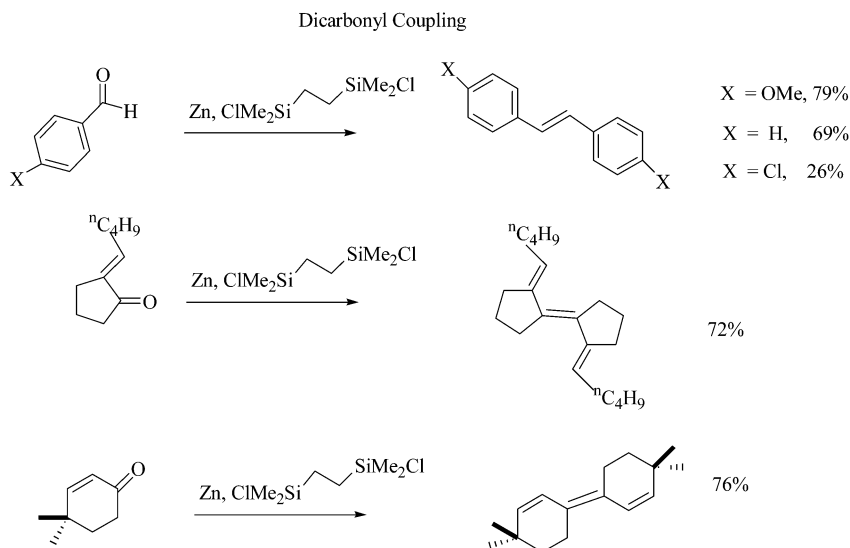
The subsequent reactivity of the resultant organozinc carbenoids is of course determined by the structure of the carbonyl compound that was selected for study. Thus, as shown in Scheme 3, for a series of cyclic ketones, insertion into the neighboring C–H bond is the predominant reaction for 6-membered rings, thereby providing a direct and useful chemo- and regioselective method for alkene formation [7]. The formation of bicyclo [3,3,0] octane from cyclooctanone by transannular insertion is also representative of carbenoid reactivity.



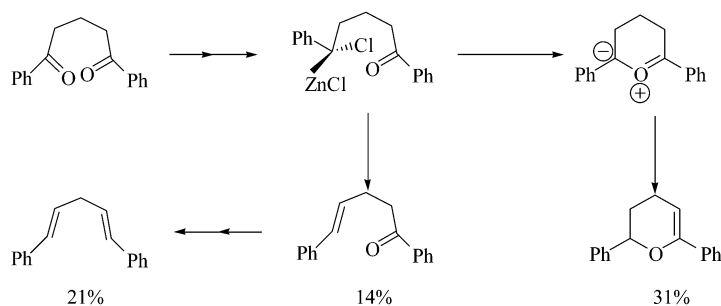
Scheme 3

By way of contrast, the selection of either an aromatic aldehyde or certain enones as substrates led to the discovery of the unusual symmetrical dicarbonyl coupling reaction [8] shown in Scheme 4.

The use of the silicon *bis* electrophile in these reactions is mandatory and avoids formation of pinacolic coupling products derived by single-electron transfer. From a mechanistic standpoint, the reaction differs from the McMurry protocol and most probably involves the intermediacy of a carbonyl ylide that then undergoes ring closure to an epoxide and subsequent deoxygenation. Some support for this pathway comes from the isolation of 2,6-diphenyldihydropyran from attempted intramolecular coupling of 1,5-diphenylpentane 1,5-dione as shown in Scheme 5.



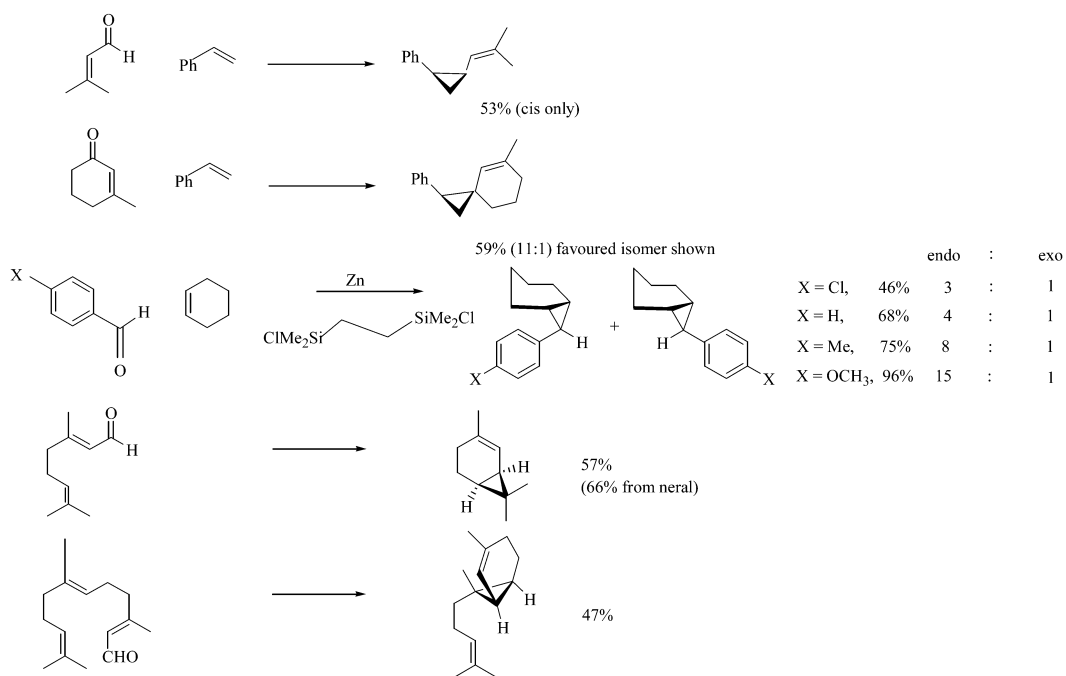
Scheme 4



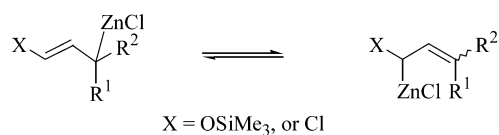
Scheme 5

In view of the formal similarity between our functionalized organozinc carbenoids and the Simmons–Smith reagent, it was inevitable that our attention was then directed toward cyclopropanation and, as revealed in Scheme 6, a similar range of carbonyl partners could be effectively trapped in both the inter- [9] and intramolecular [10] modes.

Examination of those α -, β -unsaturated carbonyl substrates that have been successfully employed for cyclopropanation reveals that some degree of steric hindrance around the β carbon atom of the enone or enal unit is necessary for efficient generation of unsaturated organozinc carbenoids. This observation, when taken in conjunction with the fact that the initial geometry of the enal unit can be effectively “scrambled” in intramolecular cyclopropanations leads us to speculate, as shown in Scheme 7, that 1,3-allyl migration of the carbon–zinc bond, which would lead to relief of steric congestion, can certainly occur.



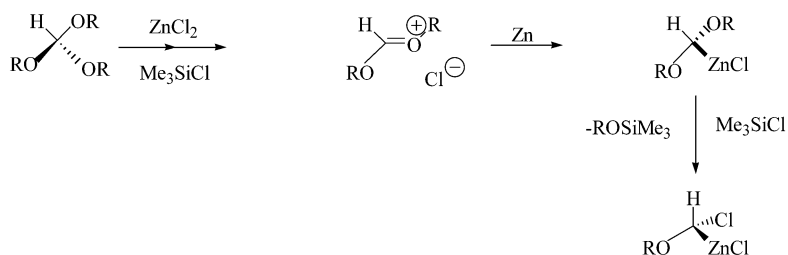
Scheme 6



Scheme 7

Most recently, in view of the considerable versatility of alkoxy-cyclopropanes as synthetic intermediates, we have been interested in extending the range of our functionalized organozinc carbenoids to this area.

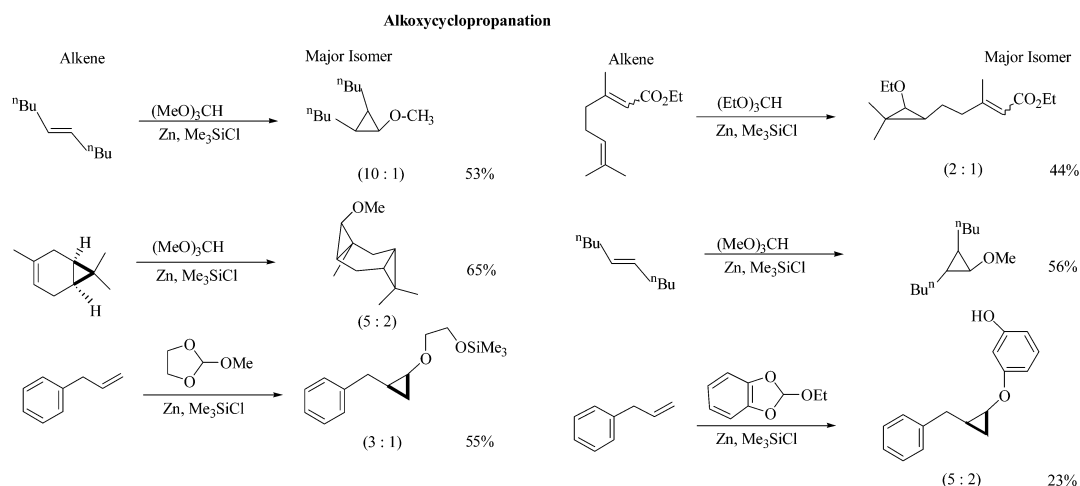
A preliminary study using acetals and ketals [11] served to convince us that such congeners could also be used and that it was therefore possible to deliver two electrons from zinc to an oxocarbenium ion. The selection of simple, inexpensive orthoformates as precursors for alkoxyorganozinc carbenoids then followed as a logical progression as formalized in Scheme 8.



Scheme 8

In the event, a useful range of alkoxy- and aryloxy-cyclopropanes can be simply prepared [12] from the appropriate orthoformate and alkene in the presence of zinc and chlorotrimethylsilane, thus avoiding the necessity for handling α , halo- or α,α -dihaloether precursors or the alternative preparations involved with Fischer carbenoids.

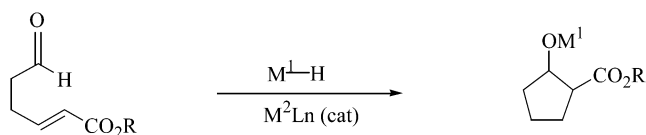
Some representative results are shown in Scheme 9 and reveal several features of interest. Thus mono di- and tri-substituted alkenes undergo alkoxy-cyclopropanation in good yield with preservation of alkene geometry and, as with other functionalized organozinc carbenoids, there is a distinct preference for formation of the more hindered *cis* (or *endo*) isomer. From the standpoint of chemoselectivity, although both electron-rich and electron-poor alkenes can be used as substrates, there is a preference for the former, although it might be argued, *a priori*, that such carbenoids should exhibit nucleophilic character.



Scheme 9

The foregoing overview of our work in organozinc carbenoid chemistry has hopefully demonstrated that this simple deoxygenation approach from the carbonyl group can lead to a variety of useful practical reactions. Moreover, given that the principle involved requires only two-electron delivery from a metal or metalloid reducing agent in the presence of a silicon electrophile, and that the nature of the metal will certainly influence the subsequent reactivity of the carbenoid, it is clear that many further opportunities exist.

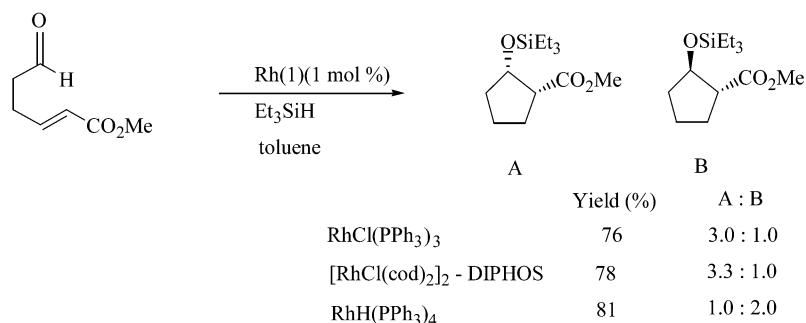
We turn now from the world of organometallic reagents to that of transition-metal catalysis, and to a research project of much more recent vintage within our group. The reaction that we chose to examine is shown in Scheme 10, and it involves the intramolecular variant of the increasingly popular reductive approach to the aldol reaction [13] featuring an acrylate ester as the acceptor in a transition metal-mediated hydrometallation sequence.



Scheme 10

Since both the catalyzed and noncatalyzed versions of the sequential two-step intermolecular acrylate reduction/aldol addition protocol are known [13], most organic chemists would argue that, in the absence of severe geometric constraints, the intramolecular variant of this reaction must automatically be successful. As we shall see, however, this is not necessarily the case for the situation where a three-component sequence is reduced to two, since the correct kinetic balance between competing reactions must be achieved.

Thus, for the prototypical reaction involving the parent unit, methyl (*E*)-6-oxo-2-hexenoate, selection of the rhodium-catalyzed, borane-mediated method developed by Evans [13] led only to the reduction of the aldehyde, whereas, as shown in Scheme 11, the use of triethylsilane in the presence of Wilkinson's catalyst afforded the silylated cyclopentanols in good yield and with a 3:1 ratio in favor of the *cis* diastereomer.

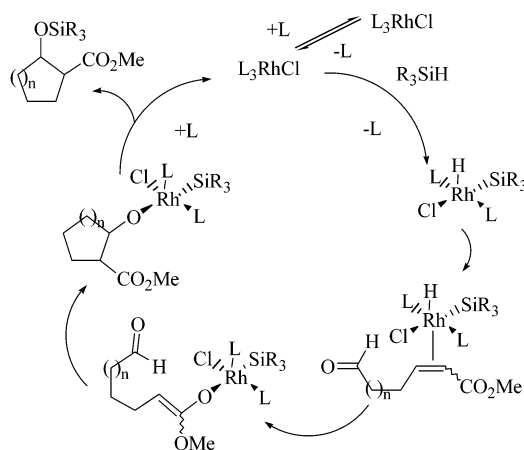


Scheme 11

Interestingly, and clearly of preparative value, this stereochemical preference was not altered in an otherwise identical reaction using the *Z* isomer, thereby indicating that the initial alkene geometry is not a determinant factor in influencing the transition state adopted for the subsequent aldol cyclization.

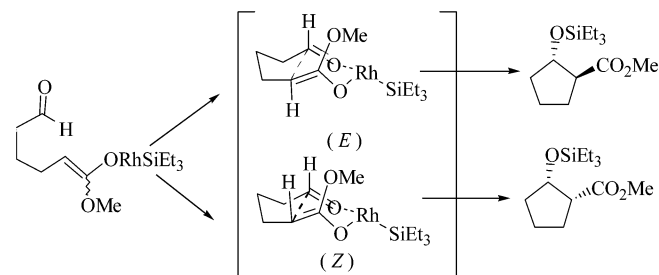
Constrastingly, however, the nature of the rhodium catalyst clearly plays a vital stereochemical role with the [(cod)-RhCl]₂-DIPHOS catalyst system, providing the best combination of yield and *cis* stereoselectivity and the hydridotetrakis (triphenylphosphine) rhodium(1) proving not only to be the most active catalyst but also leading to a reversal of selectivity with predominant formation of the *trans* product (Scheme 11).

A plausible mechanistic sequence for the reaction, and featuring the intermediacy of a rhodium-bound ester enolate of the type suggested by Heathcock [14], is shown in Scheme 12, and the stereo-



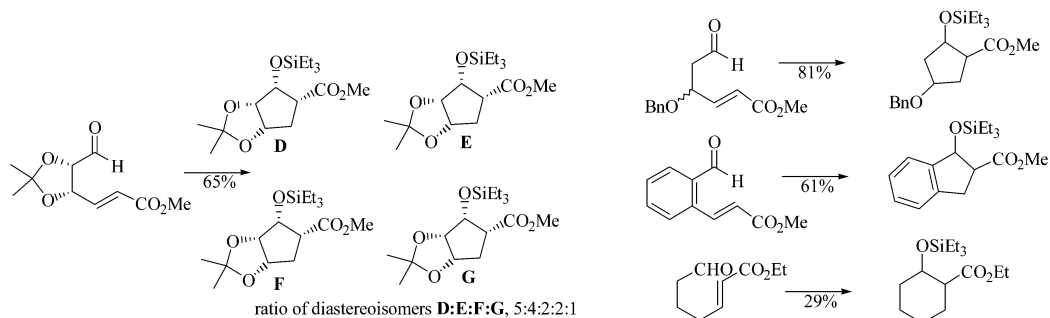
Scheme 12

chemical outcome can then be formally rationalized in terms of the preferential formation of either geometrical isomer of this enolate as depicted in Scheme 13. The alternative is, of course, that the rhodium catalyst may also be involved as a Lewis acid in controlling the stereochemical outcome of the intramolecular aldol reaction involving the derived silyl ester enolate.



Scheme 13

Finally, as shown in Scheme 14, we have extended this reaction to several usefully functionalized derivatives in order to demonstrate their tolerance of the reaction conditions and also shown in a preliminary experiment that ring closure to form a 6-membered cyclohexanol derivative is also possible.



Scheme 14

Given the most recent advances in this area, which include the first intermolecular asymmetric catalytic reductive aldol reaction [14] and diastereoselective aldol and Michael cycloreductions [15] we are encouraged that the present rhodium(1)-catalyzed tandem hydrosilylation intramolecular aldol reaction sequence will provide a versatile and mild method for the construction of usefully functionalized carbocyclic skeletons [16].

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