A Practical Cyclopropanation Method using Direct Generation of Organozinc Carbenoids from Carbonyl Compounds

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A variety of readily available aryl and α,β-unsaturated carbonyl compounds, on treatment with zinc and 1,2-bis(chlorodimethylsilyl)ethane, afford organozinc carbenoids which may be trapped with alkenes to give cyclopropanes.

The cyclopropanation of alkenes using metallocarbenoids, especially those of rhodium, copper, mercury and zinc, is a reaction of proven synthetic utility.[1] In more complex systems, however, or in larger scale work, the preparation and handling of the generally required diazo or *gem*-dihalo precursors may prove problematic.

We have previously demonstrated[2] that the direct deoxygenation of a carbonyl compound to an organozinc carbenoid may be simply induced by reaction with zinc and chlorotrimethylsilane (Scheme 1) by a sequence which parallels the mechanism of the Clemmensen reduction. While the normal fate of the organozinc carbenoid is to undergo insertion into a neighbouring C–H bond to form an alkene,[2] we have shown that symmetrical dicarbonyl coupling involving carbenoid capture by a second molecule of carbonyl compound is also possible for certain aryl and α,β-unsaturated carbonyl compounds.[3] Most recently, we have improved the generation of organozinc carbenoids in this latter reaction through the selection of 1,2-bis(chlorodimethylsilyl)ethane **1** as a bis electrophile which enables intramolecular formation of the second silicon oxygen bond.[4] It was therefore of interest to examine the possibility of developing a simple cyclopropanation sequence involving the trapping of such organozinc carbenoids by alkenes.[5]

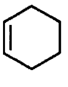
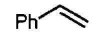
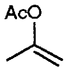
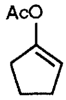
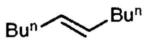
From the practical standpoint, it was important to minimise competitive dicarbonyl coupling (*vide supra*) and, hence, an experimental method was developed involving slow addition (36 h) of the carbonyl compound (1.0 mol equiv.) in diethyl ether *via* motor driven syringe to a vigorously stirred mixture of olefin (2.0 mol equiv.), 1,2-bis(chlorodimethylsilyl)ethane (1.5 mol equiv.) and amalgamated zinc (10 atom equiv.) in refluxing diethyl ether.

Initially, we elected to examine the behaviour of a series of simple *para*-substituted aromatic aldehydes **2** of varying electronic character. Inspection of the results in Table 1 not only confirms that preparatively useful yields of cyclopropanes can be obtained under mild conditions, but also presents some intriguing problems. Thus, it was of particular interest to note that the isolated yields of cyclopropanes **3** and **4** using cyclohexene as a trap (entries 1–4) parallel those obtained in Clemmensen reduction of the same substrates **2**, with electron releasing groups proving to be most effective.[6] Curiously, however, this trend is also mirrored by a concomitant increase in the stereoselective preference for formation of the more hindered *endo* isomer[7] **3**. Entries 5–7 show that other electron rich alkenes, such as enol acetates, can also be used and entry 8 reveals, as expected, that the original geometry of a *trans* alkene is preserved in the product. We have also carried out a competition experiment in order to probe the electronic character of these organozinc carbenoids. Reaction of *para*-methoxybenzaldehyde with zinc and **1** in the presence of equimolar amounts of cyclohexene and isopropenyl acetate afforded adducts **3**, **4** (44%) and **6** (37%), indicating that chemoselective discrimination between these functional groups was minimal.

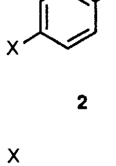
Our attention was then directed towards the use of non-aromatic organozinc carbenoids and, in particular, to those derived from acyclic and alicyclic α,β-unsaturated carbonyl compounds. We reasoned that the propensity for rearrangements of such intermediates to cyclopropenes and/or allenes would be more energetically demanding and, hence, afford opportunities for intermolecular trapping by alkenes. Moreover, they would also be of greater potential use in natural product chemistry.

In the event, however, the situation proved to be considerably more complex than the above analysis would suggest. In terms of cyclopropanation, the carbonyl compounds could be

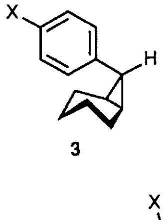
Table 1 Cyclopropanes from organozinc carbenoids derived from aromatic aldehydes

Entry	Aldehyde **2**	Alkene	Products	Ratio[a] (*endo* : *exo* or *cis* : *trans*)	Yield (%)
1	X = Cl		**3** : **4**	3 : 1	46
2	X = H			4 : 1	68
3	X = Me			8 : 1	75
4	X = OMe			15 : 1	96
5	X = OMe		**5**[b]	25 : 1	99
6	X = OMe		**6**[b]	2 : 1	89
7	X = OMe		**7**[b]	1 : 1	53
8	X = H		**8**	—	29

[a] Ratio determined by GC/NMR spectroscopy. [b] The *cis* isomer is shown.



2



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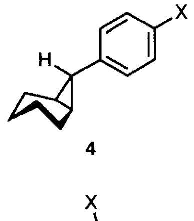
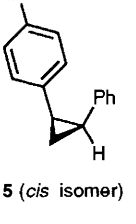
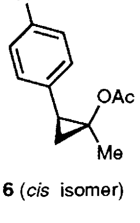


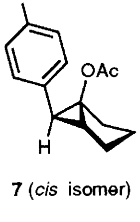
4



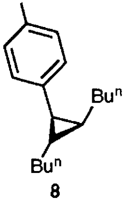
5 (*cis* isomer)



6 (*cis* isomer)



7 (*cis* isomer)



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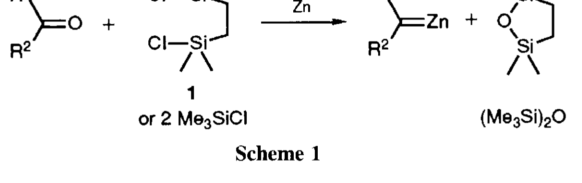
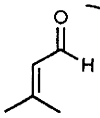
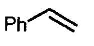
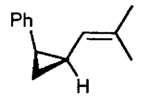
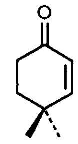
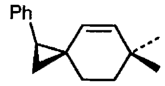
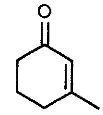
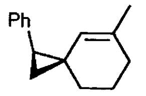
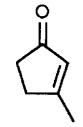
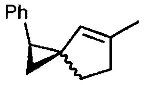
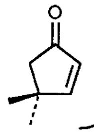
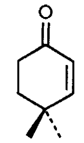
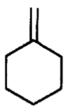
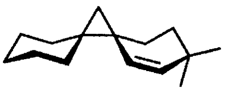


Scheme 1

Table 2 Cyclopropanes derived from alicyclic ketones and acyclic aldehydes

Entry	Carbonyl compound	Alkene	Products	Ratio[a] (*cis* : *trans*)	Yield (%)
1				all *cis*	53
2				20 : 1[b]	55
3				11 : 1[b]	59
4				1 : 1	44
5				1 : 1	19
6					34

[a] Ratio determined by GC/NMR spectroscopy. [b] For convenience, the *cis* isomer is shown.

cleanly divided into successful and unsuccessful categories. The latter included substrates such as cyclohexenone, cyclopentenone and 1-formylcyclopent-1-ene, and comparison of these with those which may be usefully trapped (Table 2) would suggest the empirical guideline that subtle substituent effects, notably crowding around the β-olefinic terminus of the enone or enal unit, have a profound beneficial influence on the outcome of the reaction.

Further inspection of the results in Table 2 indicates that the *cis* selective preference observed in the aromatic aldehydes is also maintained in the case of the isoprenoid enal (entry 1) and cyclohexenone derivatives (entries 2 and 3), but absent in the cases of the more planar cyclopentenone derivatives (entries 4 and 5). These observations reinforce the idea that the degree and nature of steric shielding around the β-olefinic terminus is also important in determining the stereochemical outcome. Once again, other alkenes may be used as traps (entry 6).

In summary, the present results extend the scope for direct generation of organozinc carbenoids from a range of aryl and α,β-unsaturated carbonyl compounds. As anticipated by analogy with the Simmons–Smith reaction,[8] these may then be trapped by alkenes to afford cyclopropanes. It is also of interest to note that a recent multistep application of this conceptual approach has been reported in organoiron chemistry[9] and, hence, to recognise that the use of a metal or organometallic complex capable of donating two electrons to a carbonyl group in the presence of two silicon electrophiles can, in principle, provide a general route to the important class of metallocarbenoids.

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