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Review

Zinc, Lithium and Magnesium Carbenoids: Chemical Properties and Relevant Applications in Organic Synthesis

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Carbenoids are a class of highly reactive reagents that play an important role in modern organic synthesis. These species are very similar to singlet state carbenes since they have an ambiphilic character and react by a concerted mechanism allowing stereospecific transformations. Herein, we discuss these and other chemical aspects of zinc, lithium and magnesium carbenoids as well as relevant applications of these intermediates in organic synthesis.

Keywords: carbenoid, organometallic, reactive intermediate, stereospecific synthesis

1. Introduction

The term carbenoid was first used in 1962[1] to describe highly reactive species having an ambiphilic character, presenting at same time nucleophilic features for its carbon-metal bond (C−M) and an electrophilic trait prevenient of a carbon-halogen bond (C−X).[2-5] These characteristics are similar to a singlet carbene that has a pair of electrons in a non-bonding sp^2 orbital (nucleophilic) and an empty p orbital (electrophilic), as illustrated in Figure 1.

More specifically, carbenoids can be described as organometallic species having both a good leaving group (such as a halogen) and a metal bonded to the same carbon. Moreover, such species may be related to metal carbenes when a mechanism of addition or elimination of the leaving group (X^-), which is influenced by the nature of the metal, is considered (Figure 2).[6-8]

The similarity between these reactive species has a strong influence on reaction mechanism and consequently on the stereochemistry of the formed products, i.e., both carbenoids and singlet carbenes react in a concerted manner resulting in stereospecific transformations. Therefore, carbenoids have emerged as an attractive alternative to carbenes, since they are generated by halogen-metal, metal-sulfoxide or hydrogen-metal exchange reactions.[4] These exchange reactions are easily controlled when compared to the photolysis or thermolysis of diazocompounds,[9] which can generate carbenes in both states (singlet and triplet).

In Scheme 1, one can observe that the reaction of the carbenoid **2** with *cis*- and *trans*- alkenes leads

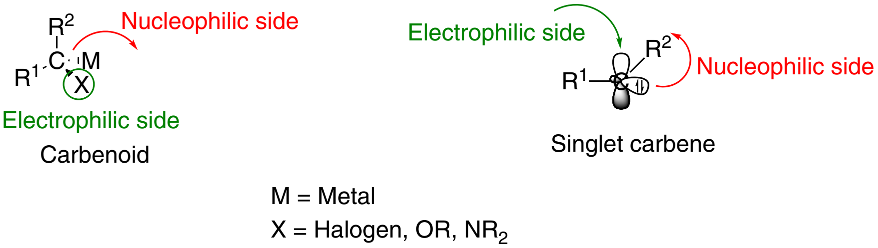

Figure 1. Similarities between a carbenoid and a singlet carbene.

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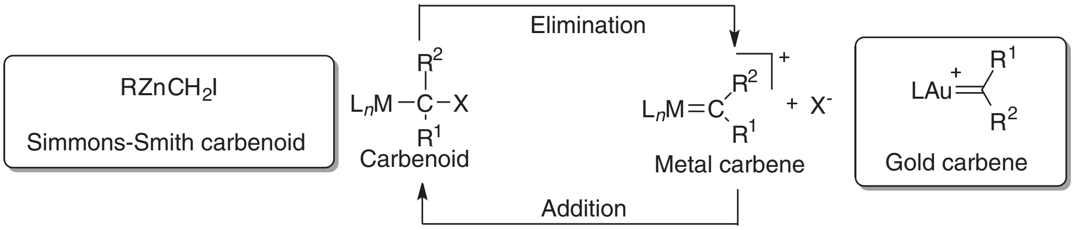
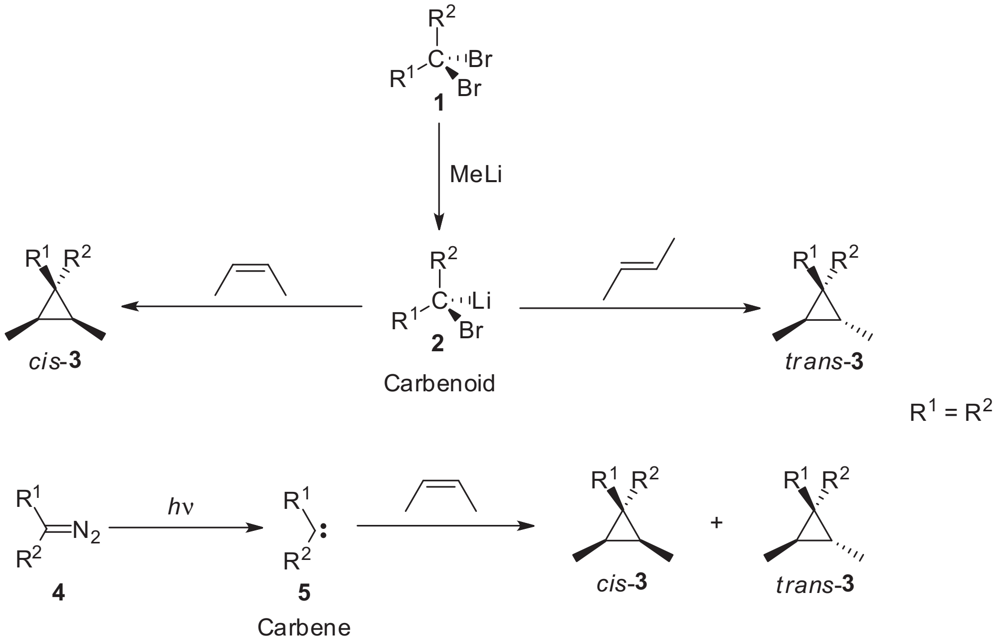


Figure 2. Structural relation of carbenoids and metal carbenes.

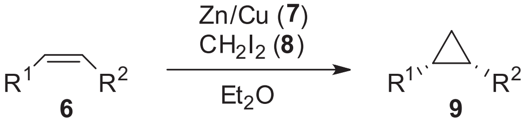


Scheme 1. Differences between a carbenoid and singlet carbenes.

stereospecifically to products from *syn*-type additions.[3] On the other hand, the reaction between carbene **5** and *cis*-alkene affords a mixture of addition products, indicating the presence of triplet carbenes that react by two-step radical processes. Moreover, singlet state carbenes can be preferentially obtained by introducing electron donor groups (R^1 and R^2), which act stabilizing the empty p orbital by delocalization of their electron pairs.[10,11]

2. Zinc Carbenoids

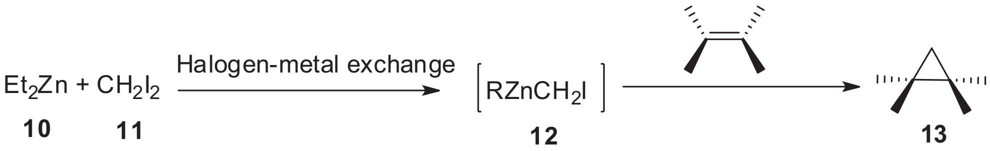
In the mid-twentieth century, Simmons and Smith[12] used diiodomethane (**8**) in the presence of zinc-copper couple (**7**) to generate a zinc carbenoid capable of producing stereospecifically cyclopropanes (**9**) from alkenes (**6**) (Scheme 2). This reaction has been termed the Simmons-Smith cyclopropanation and is currently widely employed in the preparation of many compounds such as natural products, steroids, terpenes, amino acids and others. Furthermore, due to their high-strained ring, cyclopropanes are important synthetic intermediates to the synthesis of highly complex molecules.[13-16]



Scheme 2. Simmons-Smith cyclopropanation reaction.

The applicability of this reagent prompted the interest of numerous research groups, which initiated detailed investigations in order to improve the knowledge regarding procurement methods, reactivity and selectivity of zinc carbenoids. Some years after the seminal report Simmons-Smith's studies, Furukawa *et al.*[17] were able to quickly prepare the carbenoid **12** by employing mild reaction conditions in a halogen-metal exchange reaction between diethylzinc (**10**) and diiodomethane (**11**). Nowadays, this is the most used protocol for preparing zinc carbenoids (Scheme 3).

In order to rationalize the experimental results, several investigations were conducted aiming to elucidate the



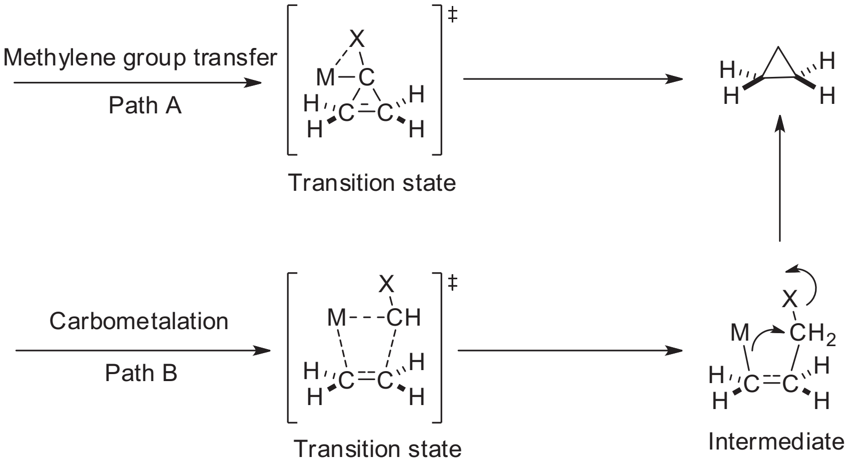
Scheme 3. Furukawa procedure for zinc carbenoids.

Simmons-Smith reaction mechanism. In this context, initial studies pointed in two directions: the first advocating for a methylene group transfer mechanism (path A) and the second for a carbometalation mechanism (path B, Scheme 4). Subsequent studies attempted to solve this dichotomy and assumed that a concerted methylene transfer would be the most likely mechanism since the zinc-carbon bond has a covalent nature and is unpolarized.[18,19]

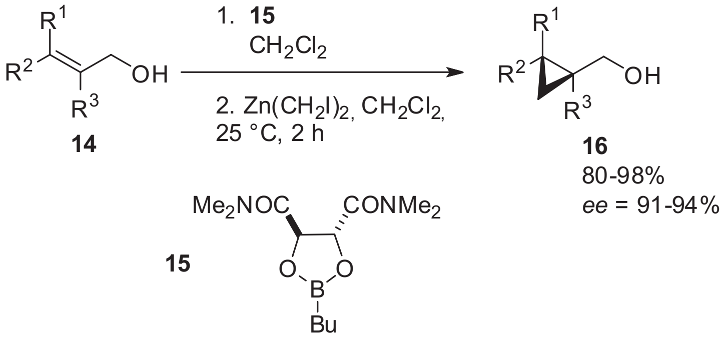
Denmark *et al.*[20,21] observed that the Simmons-Smith reagent was somehow stabilized by oxygen atoms near to the olefins (allylic alcohols) leading to an intriguing increased reaction rate (up to 1000-fold when compared to simple olefins). In order to better understand such amazing results they employed nuclear magnetic resonance spectroscopy (NMR) and X-ray crystallography techniques to study the behavior of these entities in the presence of chelating groups. These studies led to the conclusion that the large increase in reaction rate was not related to an inherent activation of the reagent, but to an induction effect caused by the proximity of the complex with the reaction site.

A milestone for the Simmons-Smith cyclopropanation occurred in 1994, when Charette *et al.*[22] developed an efficient methodology capable of producing cyclopropanes (**16**) from allylic alcohols (**14**) in high yields and enantiomeric excesses (*ee*). For this purpose the chiral auxiliary (**15**) with amphoteric characteristics and capable of chelating with both the allyl alcohol and the zinc carbenoid was designed (Scheme 5).

This methodology allowed the total synthesis of many natural products with potential biological activity and triggered the search for new chiral auxiliaries. For example, in the synthesis of the potent antifungal agent (FR-900848), selective for filamentous fungi, the Charette conditions were used in three steps of its synthetic route



Scheme 4. Possible mechanisms of Simmons-Smith cyclopropanation.



Scheme 5. Charette's approach for enantioselective synthesis of cyclopropanes.

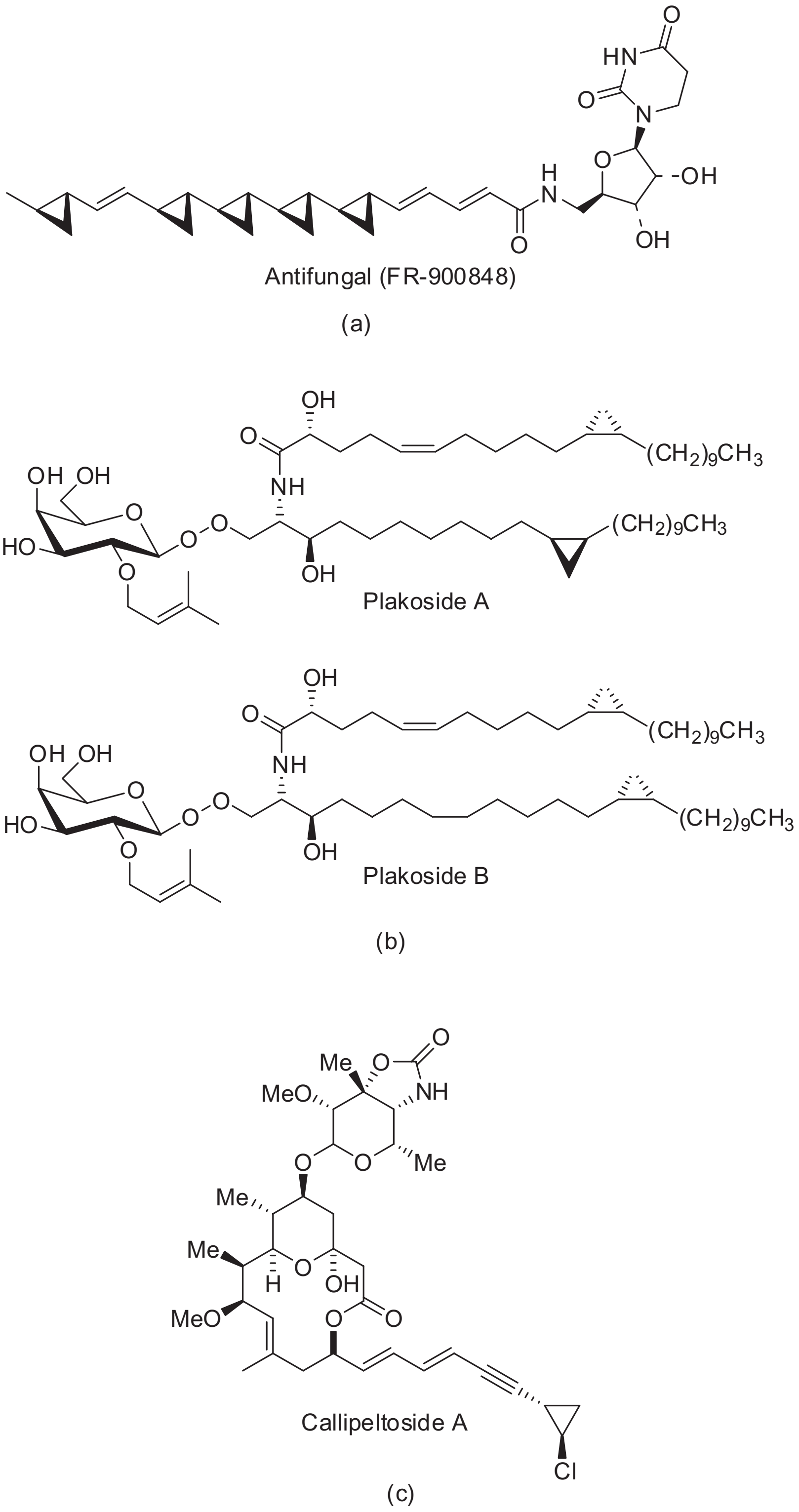


Figure 3. Some natural products that were synthesized using the Charette methodology.

to generate stereogenic centers in a controlled manner and with high overall yields (Figure 3a).[23] Years later, Nicolaou *et al.*[24] used these conditions to synthesize two glycosphingolipids (Figure 3b), whose biological properties were related to immunosuppressive activity. Similarly, a marine macrolide with cytotoxic activity against cell lines P388 and NSCLC-N6 was synthesized using this versatile and efficient synthetic methodology (Figure 3c).[25]

In the last decade, considerable efforts have been dedicated to the enantio- and diastereoselective Simmons-

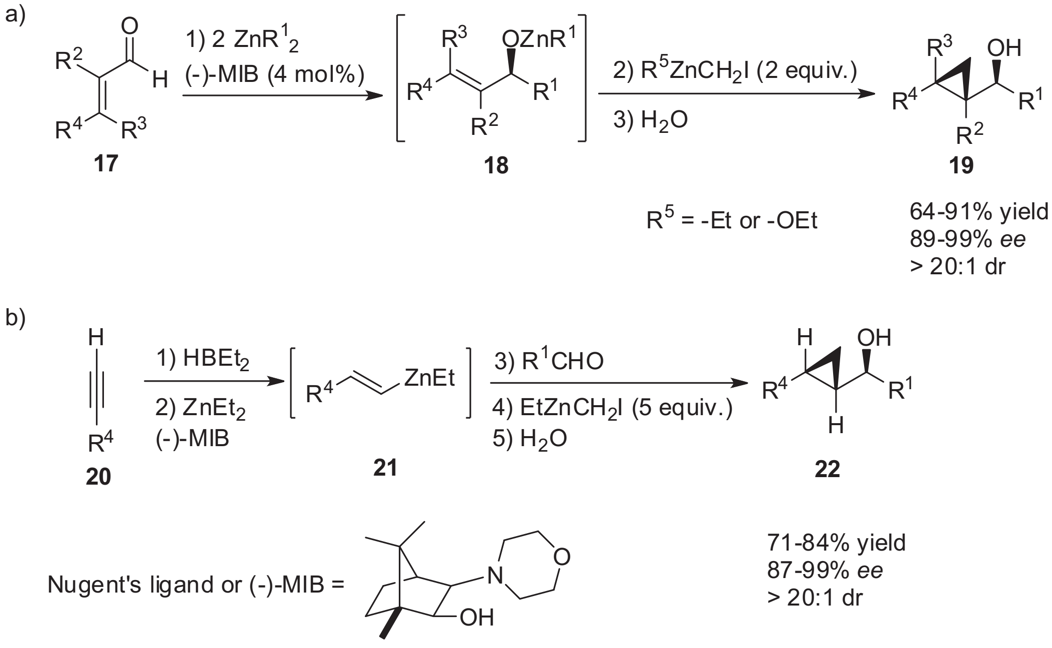
Smith cyclopropanations. In this context, it should be highlighted two methods developed by the Walsh's group:[26,27] the first (Scheme 6a) generates an allylic zinc alkoxide intermediate (**18**) by the asymmetric reaction between α,β-unsaturated aldehydes (**17**) and dialkyl zinc reagents in the presence of 4 mol% of Nugent's ligand. Then, this intermediate is treated with Simmons-Smith reagent to achieve the cyclopropyl alcohols (**19**) in good yields and enantiomeric excesses. The second method (Scheme 6b) consists in a sequence of reactions starting with a hydroboration of an alkyne followed by a transmetalation with zinc chloride. The produced vinyl zinc (**21**) is then allowed to react with an aldehyde to give an allylic alkoxide, which is further submitted to a diastereoselective cyclopropanation with $EtZnCH_2I$ to afford **22**. The high diastereoselectivity observed is a result of a transition state in which the zinc reagent is coordinated to the chiral allylic alcohol.[28]

In 2009, the Charette group demonstrated the first asymmetric synthesis of cyclopropanes employing zinc carbenoids generated *in situ* by the reaction between diazo compounds and zinc salts.[29] Furthermore, in this work an innovator introductory methodology using a catalytic amount of zinc to generate the corresponding carbenoid was reported. More recently, the same group exploited the scope of this catalytic approaching with a number of substituted alkenes (**23**) to furnish substituted cyclopropanes (**24**) in yields ranging from moderate to excellent (Scheme 7).[30]

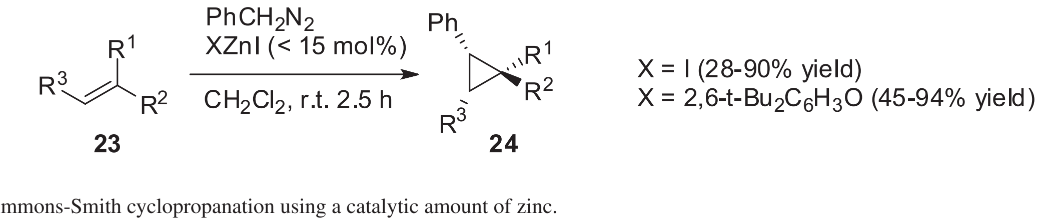
3. Lithium Carbenoids

The lithium carbenoids were little explored for a long period,[31] due to their low thermal stability inherent to the carbon-lithium bond (C−Li), which has a predominantly ionic nature. This feature emphasizes its ambiphilicity that is strongly dependent of the temperature, acting as nucleophile at low temperatures and as electrophile at high temperatures.[32-34]

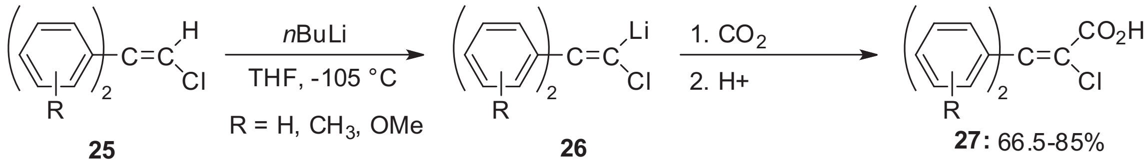
In a pioneering study, Köbrich *et al.*[35] prepared some lithium carbenoids (**26**) by directed metalation of 1-chloro-2,2-diarylethylenes (**25**) using *n*-butyllithium, and these species demonstrated themselves to be stable at low temperature (−105 °C). Moreover, reaction of the intermediates with carbon dioxide allowed isolation of the desired carboxylic acids (**27**) in good isolated yields (Scheme 8).



Scheme 6. Tandem asymmetric cyclopropanation reactions.

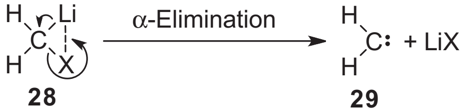


Scheme 7. Simmons-Smith cyclopropanation using a catalytic amount of zinc.



Scheme 8. Carboxylation using lithium carbenoids.

As a result of this work several studies employing lithium carbenoids began to emerge and, therefore, new problems have hatched. Among them it can be highlighted the preparation of α-halomethyllithium species (**28**), which are important synthetic intermediates that appeared to be extremely unstable leading to α-elimination even at very low temperatures (–130 °C). Since Köbrich's work it was already known that the instability of carbenoids is related to the electrophilic behavior of these species. Based on previous studies by Seebach's group,[36,37] Villieras and co-workers[38] suggested that decomposition of α-halomethyllithium (**28**) is due to an intramolecular coordination between metal and halogen, which leads to a carbene (**29**) as α-elimination product (Scheme 9).

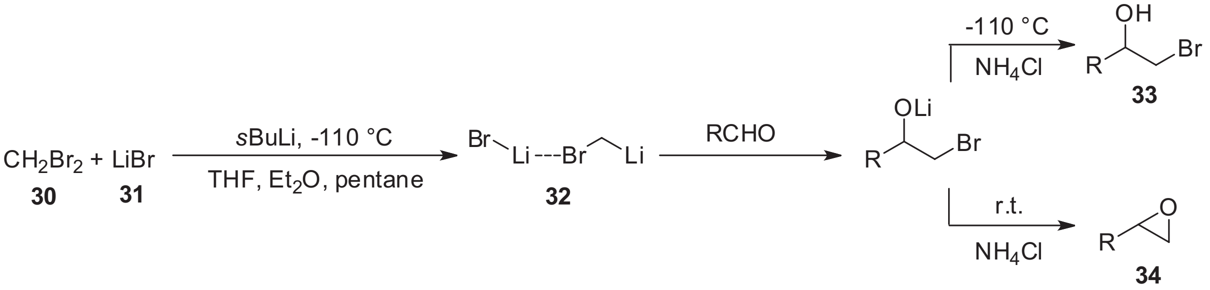


Scheme 9. Reagent degradation due to α-elimination as suggested by Villieras and co-workers.[38]

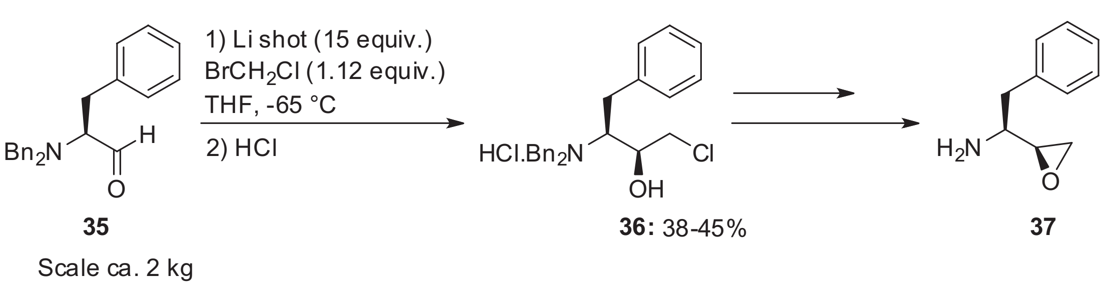
Based on the suggested degradation mechanism, the authors added a lithium salt (**31**) in order to disrupt the interaction between the halogen and the metal and, consequently, avoiding the degradation of reagent. This strategy showed to be effective and was applied in the synthesis of various halohydrins (**33**) and even some epoxides (**34**), depending on the reaction completion temperature (Scheme 10).[38]

Since then many synthetic applications using lithium carbenoids have been developed. Among them, it should be highlighted the large scale preparation of the aminoepoxide (**37**), which is an important intermediate of HIV-protease inhibitors.[39,40] The key step of this synthetic route is the diastereoselective preparation of the chlorohydrin (**36**) through the reaction between the aldehyde (**35**) derived of the *L*-phenylalanine and the chloromethyllithium generated *in situ* (Scheme 11).[41]

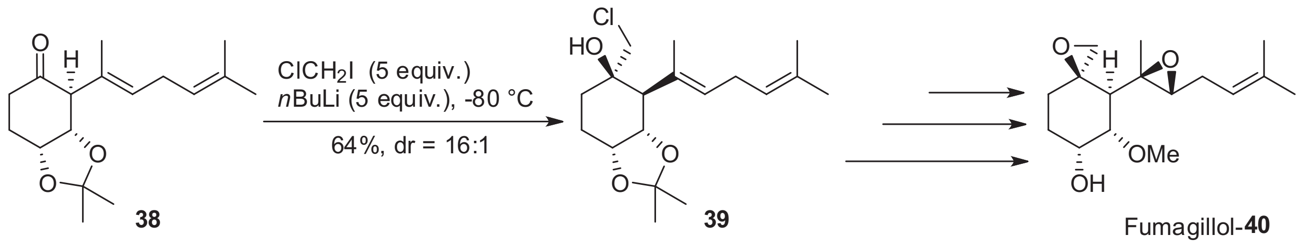
At the beginning of the XXI century, the inhibition of angiogenesis was seen as a promising approach for cancer therapy and some compounds such as fumagillin and analogs appeared as targets of interest for this type of treatment.[42] Among analogues, fumagillol (**40**) was a major synthetic challenge only achieved by fumagillin degradation. Therefore, in 2001, Hutchings *et al.*[43] synthesized fumagillol employing the α-chloromethyl lithium in one of its synthetic steps, which converted the



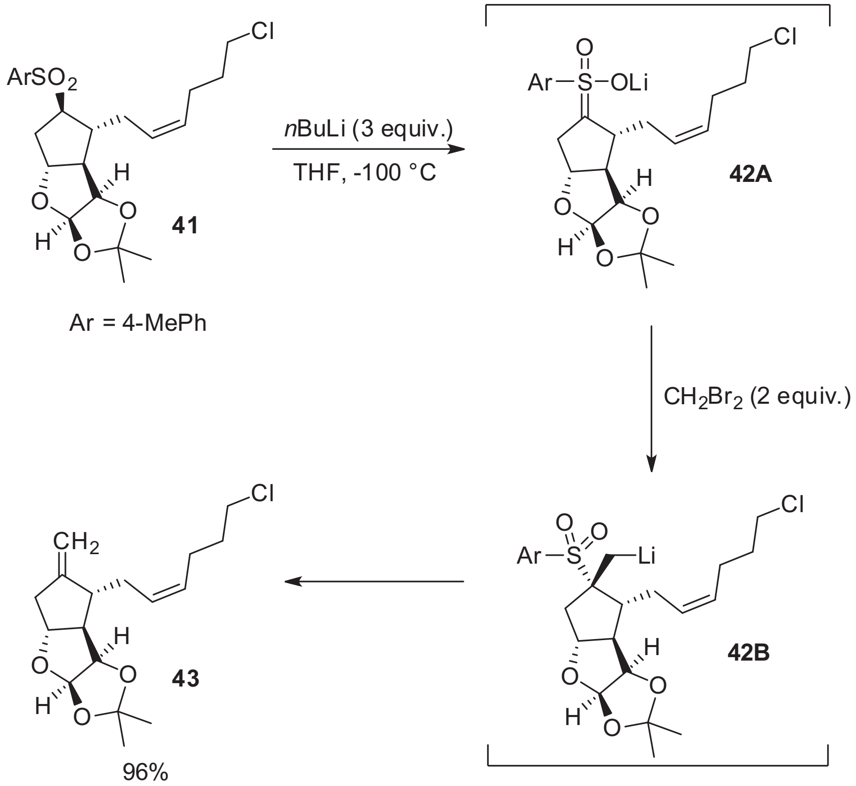
Scheme 10. Synthesis of bromohydrins and epoxides from carbenoids.



Scheme 11. Large scale synthesis of aminoepoxide **37**.



Scheme 12. Fumagillol synthesis.

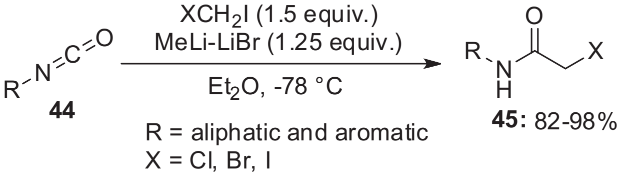


Scheme 13. Olefination using a lithium carbenoid.

ketone **38** to the chlorohydrin **39** in a good isolated yield and with high diastereoselectivity (Scheme 12).

An interesting work involving α-bromomethyl lithium demonstrates the ability of this reagent to perform methylenation of sulfones in a one-pot synthesis. Initially, treatment of the sulfone **41** with excess of *n*BuLi led to the formation of the intermediate **42A** due to abstraction of the proton in the α-sulfonyl position. This reaction mixture was then treated with dibromomethane and immediately allowed to react with excess of *n*BuLi to produce the carbenoid which suffered a nucleophilic attack leading to the intermediate **42B**. Finally, the olefin **43** was obtained after the elimination of the sulfonyl group (Scheme 13).[44]

Recently, in order to explore the scope of applications of these reagents in organic synthesis, many methodological studies have been carried out and three of them deserve to be highlighted. The first investigated the addition reaction between lithium carbenoid and various aliphatic and aromatic isocyanates (**44**), leading to the formation of α-haloacetamides (**45**) in good isolated yields (Scheme 14).[45]



Scheme 14. Preparation of α-haloacetamides from isocyanates.

The second involved the chemoselective addition of α-chloromethyllithium to cyclic enones (**46**), leading to the formation of chlorohydrins (**47**) in good yields through a 1,2-addition mechanism (Scheme 15a). Interestingly, the mesomeric effects due to the presence of an electron donor group bonded to the β carbon makes this position susceptible to nucleophilic attack favoring the 1,4-addition (Scheme 15b).[46]

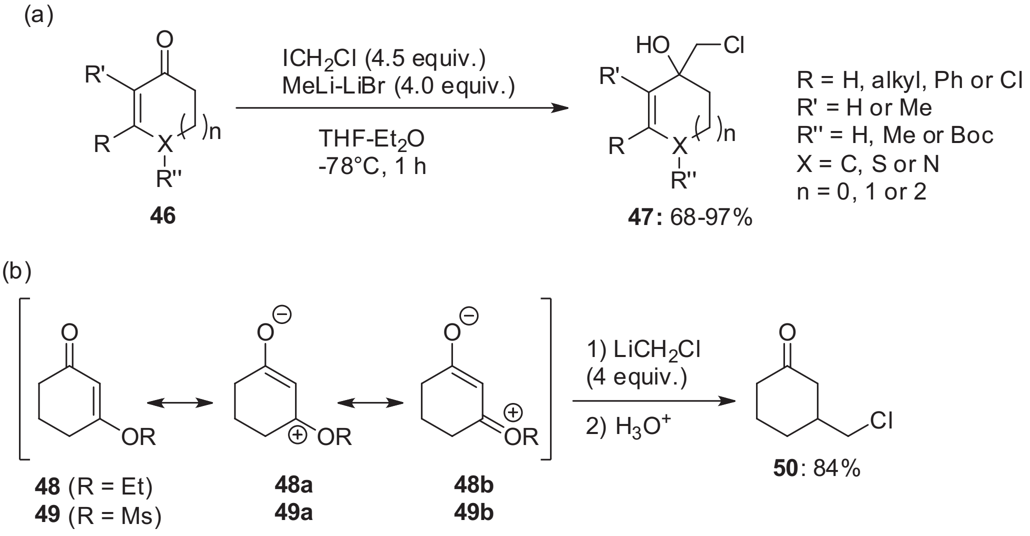
The third study we wish to mention investigated the preparation of vinyl carbenoids from chloro-substituted alkynes. The first step of the reaction consisted of an expected lithium-iodine exchange that generated an aryl lithium intermediate, which was quickly subjected to a carbolithiation with complete regio-, stereo- and chemoselectivity, leading to the carbenoid **52**. Subsequently, various electrophiles were used to quench the reaction leading to the corresponding derivatives (**53**) in excellent chromatographic conversions. A drawback, however, was the double bond isomerization (exo- to endo-cyclic) under the purification step in a silica gel column, resulting in low yields of the isolated product **53** (Scheme 16). It is worth mentioning that while PhLi enabled, in all cases, the total conversion to vinyl carbenoid **52**, *n*BuLi provided a parallel reaction of chlorine-lithium exchange (5-25%).[2]

Recently, the α-chloromethyllithium reagent could be generated under flow conditions at moderate temperatures (−20 °C) using a microreactor. Moreover, external trapping with a number of eletrophiles such as aldehydes, ketones, imines and Weinreb amides allowed the isolation of the expected products in yields ranging from good to excellent.[47]

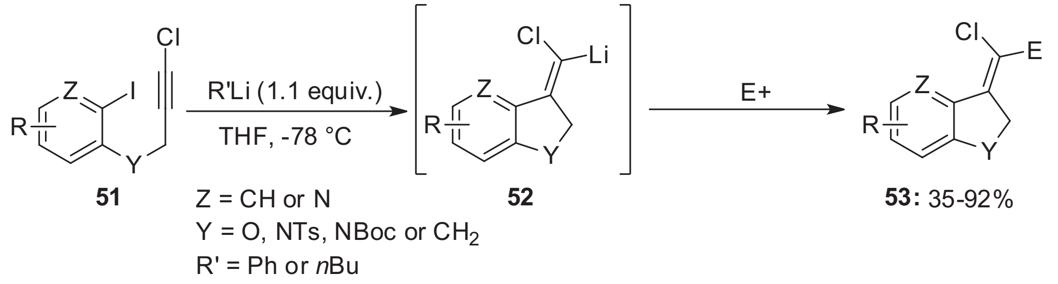
In summary, the main notable characteristics on chemical reactivity of lithium carbenoids are: (*i*) the need for low reaction temperatures (≤ −78 °C) due to their pronounced thermolability,[48,49] (*ii*) the stability of these reagents can be improved in ethereal solvents (such as Et_2O and tetrahydrofuran-THF) and in the presence of lithium salts, since the solvation of the lithium atom and the coordination of the carbenoid with lithium salts avoid degradation of the reagent,[50,51] (*iii*) the main method of preparing these reagents is the halogen-metal exchange between a dihaloalkyl and an organolithium reagent,[52] (*iv*) its' ambiphilic character allows it to act as both nucleophile and as an electrophile.[53]

4. Magnesium Carbenoids

Currently, organomagnesium reagents are an excellent alternative to the corresponding organolithium reagents in a broad range of reactions since they exhibit better thermal stability and excellent reactivity for a broad spectrum of electrophiles. Due to the increased covalent character of the carbon-magnesium bond, Grignard reagents offer a



Scheme 15. Chemoselective addition of α-chloromethyllithium to cyclic enones.



Scheme 16. Some synthetic applications of lithium carbenoids.

higher tolerance for functional groups. These features have enabled many industrial applications and therefore many of these compounds are nowadays commercially available.[54]

Similarly to the lithium reagents, organomagnesium compounds may be obtained by either direct oxidative insertion, halogen-metal exchange or directed metalation. In this context, the halogen-metal exchange, discovered by Wittig (1938)[55] and Gilman (1939)[56] assumes a prominent position, since this methodology is extremely efficient for a wide range of compounds. It should be emphasized that the halogen-metal exchange occurs in an equilibrium which favors the formation of a weaker base, i.e., the formation of the most stable organometallic. Moreover, it is believed that the most likely mechanism involves an intermediate called by Wittig as an "ate" complex.[57,58]

It's well known that Grignard reagents may coexist in dimeric forms, thus excess of the reagents and heating are frequently need in order to accomplish reactions with electrophiles. However, production of byproducts from side reactions may be a drawback. To address these issues, Knochel and co-workers[59-64] recently developed a method for preparing more reactive organomagnesium reagents. In this context, the turbo Grignard reagent *i*PrMgCl·LiCl appeared to be highly reactive and selective in halogen-magnesium exchange reactions. In addition, this reagent is nowadays an important precursor for mixed lithium-magnesium amides of great synthetic relevance.[65-74]

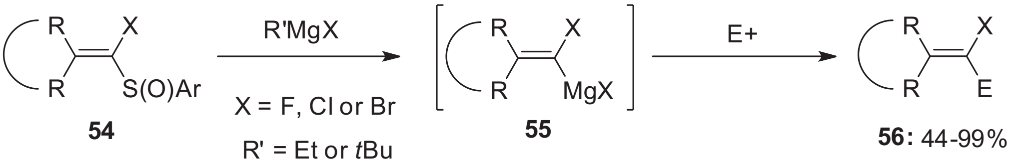
A better understanding of the chemistry of Grignard reagents led many researchers to seek new synthetic applications for this type of compound. As a consequence, magnesium carbenoids began to gain prominence in the 1990s and since then many reports on its reactivity have been published. These reagents are efficiently generated under milder conditions compared to their lithium counterparts. Furthermore, its ambiphilic nature is noted in several reactions involving these species.

One of the first synthetic applications of magnesium carbenoids was reported by Satoh and co-workers[75] in 1995 who *in situ* prepared the reagents of type **55** through a sulfoxide-metal exchange reaction between the sulfoxides (**54**) and ethyl or *tert*-butylmagnesium halides. Subsequently, the carbenoid **55** was subjected to reactions with some electrophiles leading to the desired products (**56**) in yields ranging from moderate to excellent (Scheme 17).

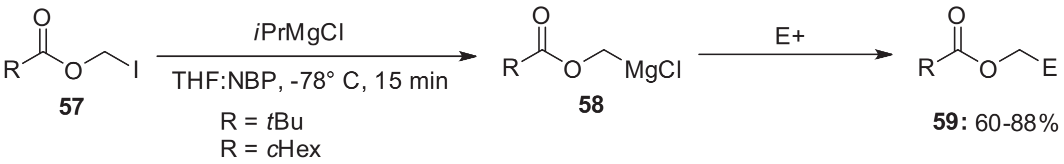
In order to demonstrate the tolerance for sensitive functional groups, it can be highlighted the preparation of a magnesium carbenoid containing the ester function **58**, which was prepared by the reaction between the iodomethyl carboxylate (**57**) and isopropylmagnesium chloride in THF:NBP at −78 °C for 15 minutes. Carbenoid **58** was subjected to the reaction with a number of electrophiles such as aldehyde, ketone, immonium salt, chlorophosphine and allylic halide and led to products of type **59** in yields ranging from 60 to 88% (Scheme 18).[76]

The electrophilic character of magnesium carbenoids may be observed in recently reported reactions involving nucleophiles, for instance, *N*-lithio arylamines, 2-lithiothiophenes, lithium acetylides, Grignard reagents, among others.[77-83] In these reactions the magnesium carbenoids **61** are generated through the sulfoxide-metal exchange between α-halosulfoxides **60** and isopropylmagnesium chloride. Posteriorly, the nucleophilic attack leads to intermediates **62** with inversion of configuration,[84,85] which reacts with electrophiles generating products of type **63** (Scheme 19).

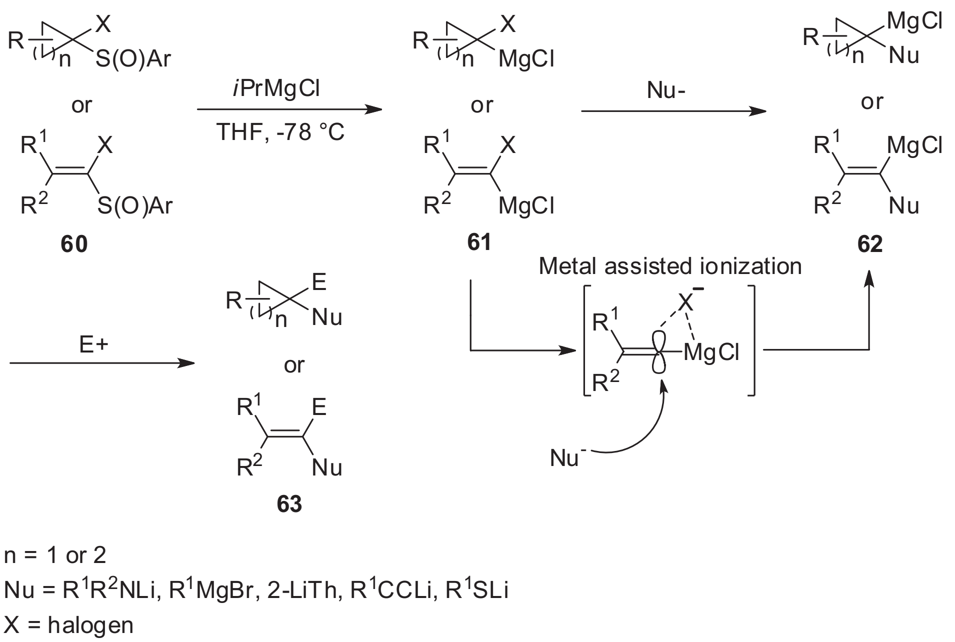
Activation of relatively inert C–H bonds is of great interest for modern organic synthesis, since the directed functionalization provides a method for obtaining desired products more efficiently, eliminating the need of pre-activation and promoting both atoms and steps economy.[86-88] Among the various reactions employing this synthetic methodology, the C–H insertion is one of the most attractive reactions performed by carbenoids



Scheme 17. Preparation of magnesium alkylidene carbenoids **55** and reaction with electrophiles.



Scheme 18. Preparation of functionalized magnesium carbenoids.



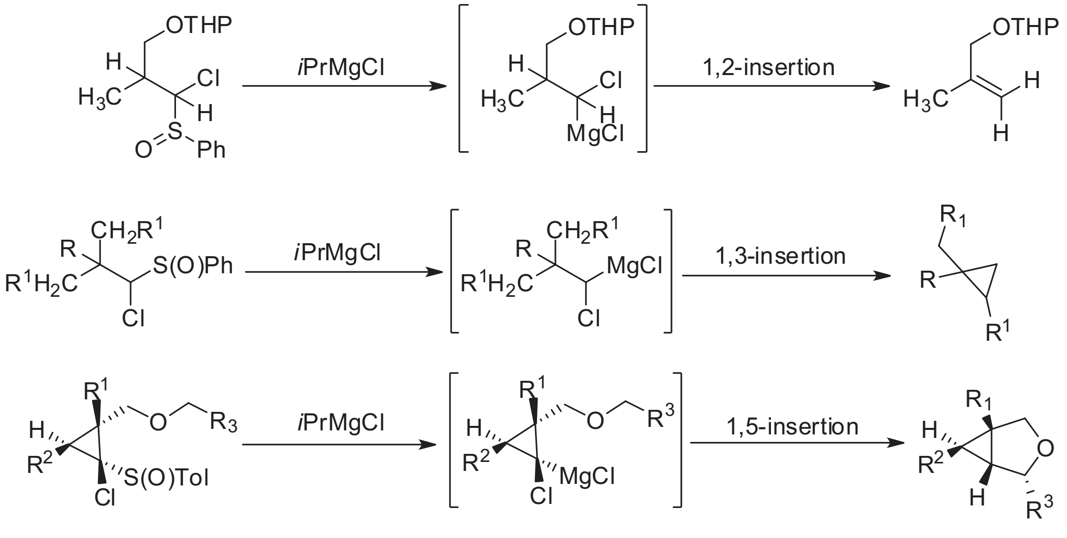
Scheme 19. Preparation of magnesium carbenoids and reactions with nucleophiles.

and carbenes. Indeed, intramolecular insertions may provide an alternative route for the preparation of highly tensioned molecules, which are not easily obtained using conventional synthetic strategies. In this context, Satoh have generated *in situ* a number of magnesium carbenoids capable of performing C–H insertions of types 1,2, 1,3 and 1,5 (Scheme 20).[89-93]

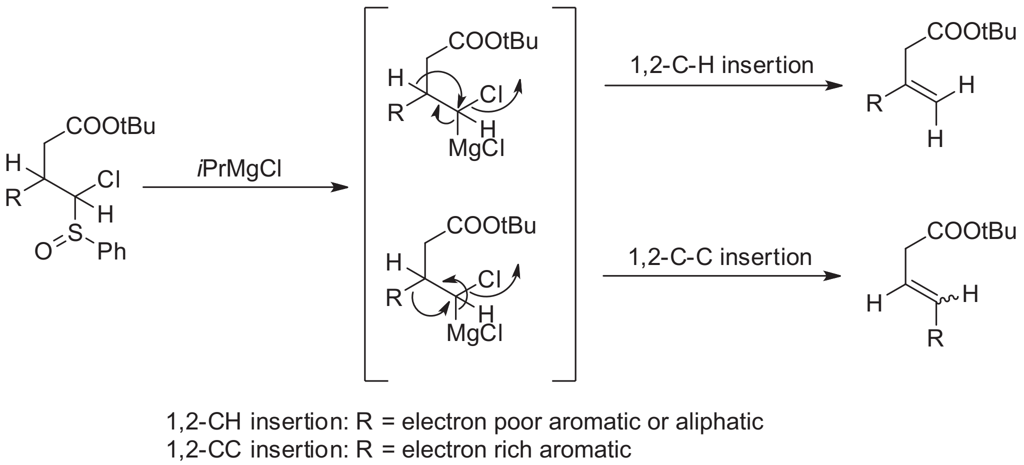
Interestingly, the nature of certain groups that are present in magnesium carbenoids may influence insertion reactions, inducing migration of different groups (especially electron-rich aryl groups) which can lead to C–C instead of C–H insertion (Scheme 21).[94]

Recently, our group investigated the preparation of a mixed lithium-magnesium carbenoid complexed with lithium chloride, which was generated *in situ* by the reaction of chloroiodomethane (**64**) with *i*PrMgCl·LiCl. Subsequently, this reagent was reacted with a number of aromatic, aliphatic and heterocyclic aldehydes (**65**) to give the corresponding chlorohydrins (**66**), which are important synthetic intermediates, in good yields (Scheme 22).[95,96]

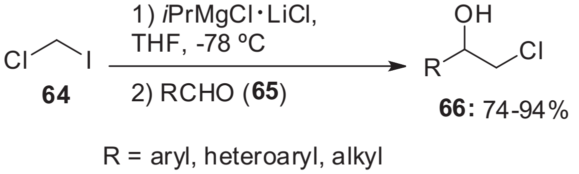
The scope of this methodology was further evaluated with a range of aromatic aldehydes substituted with various functional groups (**67**). This reagent proved to be very chemoselective, allowing the efficient synthesis of a number of ring-functionalized chlorohydrins (**68**) in good yields (Scheme 23).[97]



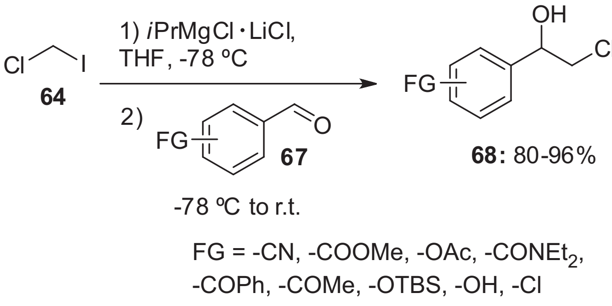
Scheme 20. C–H insertion reactions with magnesium carbenoids.



Scheme 21. C–H or C–C insertion reactions competition.



Scheme 22. Chlorohydrins synthesis using $ClCH_2MgCl·LiCl$.



Scheme 23. Synthesis of functionalized aromatic chlorohydrins using a magnesium carbenoid.

5. Conclusion

Since the 1950s, the Simmons-Smith reaction is one of the most important approaches for the synthesis of cyclopropanes, which are found in several natural products with a range of biological properties and are useful intermediates in organic synthesis as cyclopropanes undergo ring-opening reactions. However, although there are still questions concerning zinc carbenoids, these reagents have a very well established chemistry and therefore prospects of new findings in their field is narrowing. In contrast, although their synthetic relevance, literature data on lithium carbenoids is scarce thus the chemistry of these compounds offers great opportunities for exploration. A major limitation of these reagents is related to their low thermal stability, mainly due to their predominantly ionic nature. Finally, since the 1990s, the magnesium carbenoids have emerged as a powerful tool for applications in organic synthesis, as these species require milder reaction conditions and lead to more selective products when compared with their lithium counterparts.

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