Anatomy of Long-Lasting Love Affairs with Lithium Carbenoids: Past and Present Status and Future Prospects

Vito Capriati* and Saverio Florio*[a]

Abstract: After a long adolescence, the chemistry of lithium carbenoids has currently been entering its maturity bringing a dowry of a more in-depth and less empirical knowledge of the structure and configurational stability of such double-faced intermediates; this, thanks in particular to the synergistic and harmonic cooperation between calculations and the most modern NMR techniques now at our disposal. Such knowledge has stimulated the development of fruitful stereoselective applications in the field of organic synthesis, providing in addition a rationale to observed selectivities. Such aspects together with the role played by aggregation and solvation on the structure–reactivity relationship are highlighted throughout this Minireview with selected examples extracted from recent literature.

Keywords: carbenoids · density functional calculations · lithium · NMR spectroscopy · stereochemistry

Introduction

In the "collection" of organolithium compounds available for the organic chemist, lithium carbenoids undoubtedly represent some of the most astonishing "precious stones". Because of their intriguing ambiphilic behavior (nucleophilic and electrophilic reactivity), they are generally recognized as useful reagents capable of modifying their reactivity by "umpolung".

Over the years, their synthetic utility for carbon–carbon and carbon–heteroatom bond formation (e.g., cyclopropane formation from alkenes, C–H insertion, reaction with RLi, alkynes and carbonyl compounds, etc.) has been amply demonstrated and the interest for their nature and structure has stimulated numerous theoretical studies and NMR investigations.[1] Curiously, the term "carbenoid" itself has been characterized by an intrinsic dichotomy over time: employed for the first time as an adjective by Friedman and Shechter[2] to describe a carbene-like reactivity, Closs and Moss[3] were later to suggest the appellation (as a noun) of "carbenoid" to those species capable of undergoing electrophilic reactions without necessarily being free carbenes. In this Minireview, some selected features of lithium carbenoids such as their structure and configurational stability, the stereochemistry of their coupling reactions with electrophiles as well as the influence of aggregation and solvation on the structure–

[a] Prof. V. Capriati, Prof. S. Florio
Dipartimento Farmaco-Chimico, Università di Bari "Aldo Moro"
Consorzio Interuniversitario Nazionale Metodologie e
Processi Innovativi di Sintesi C.I.N.M.P.I.S.
Via E. Orabona 4, 70125 Bari (Italy)
Fax: (+39)080-5442231
E-mail: capriati@farmchim.uniba.it
        florio@farmchim.uniba.it

reactivity relationship will be (re)considered in the light of literature recent advances. The authors hope this survey may further increase the interest toward these intriguing reactive species, stimulate new ideas and the scientific discussion around them, and promote at the same time more "surgical" stereoselective applications in the near future.

Structural Features of Lithium Carbenoids

Structurally, a lithium carbenoid is a species such as **1b** (Scheme 1) carrying a lithium and a peculiar nucleofugal heterosubstituent on the same carbon atom. The "chame-

X = nucleofugal heterosubstituent (e.g., halogen, OR, NR₂)
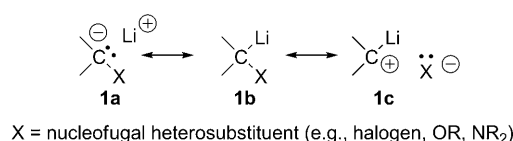
Scheme 1. Conceivable resonance structures of the lithium carbenoid **1b**.

leon-like" character becomes evident from a closer look at the resonance structures (**1a** and **1c**) associated with **1b**; indeed, the extreme ionization of the polar bonds could lead, in principle, to the liberation of a carbanionic species (**1a**) and a carbocation (**1c**) from **1b**.

Elongation of the C–X bond: A common structural feature of lithium carbenoids is the elongation of the C–X bond upon metalation, which enhances its p character; at the same time, the s character of the C–Li bond is increased as well (Figure 1).
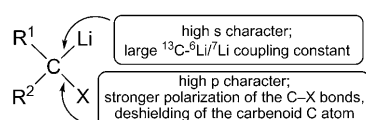

Figure 1. Carbenoid carbon atom of Li/X carbenoids in the ^{13}C NMR spectrum and conclusions thereof.

This particular hybridization of the carbenoid carbon atom has been experimentally proven by recent X-ray structure analyses and multinuclear magnetic resonance investigations.[1a,b] Indeed, there is an increase in the value of the ^{13}C–^{6}Li/^{7}Li coupling constant, because of the Fermi-contact term involving s-orbital contributions from both atoms,[4] and, very often, also a deshielding of the ^{13}C NMR chemical shift of the lithiated carbenoid center, because of the paramagnetic contribution of the σ^*_{C-X} orbital to the shielding constant.[1b,c] However, the presence of a "generic" acceptor substituent X at the anionic carbon atom is not sufficient to

label the corresponding lithiated species as a carbenoid. In the first place, one should take into consideration that an important common feature of many polar organometallic compounds is, in contrast, the shortened C−X bond compared with that of the corresponding nonlithiated species; this is the case, for instance, of α-lithiated sulfones, sulfoxides, thioethers, nitro compounds, and so on.[5] In the second place, not all those α-heterosubstituted lithiated species experiencing a lengthening of the C−X bond can be regarded a priori as real carbenoids. For instance, the C−O bond elongation also found for other classes of compounds such as α-lithiated carbamates[6] did not find confirmation in electrophilic reactivity. To date, compounds that have undoubtedly shown a remarkable electrophilic/nucleophilic character are lithiated alkyl[1b,c] and vinyl halides,[1d,e] lithio derivatives of ethers in general[7] and epoxides in particular,[8] and, very recently, also terminal and ring-fused lithiated aziridines.[9]

Thermal lability: Another characteristic feature one would expect to find for a lithium carbenoid is thermal lability. However, this is not universally true. The first example of a Li/halide (Li/Hal) carbenoid (**2**, Figure 2), stable at room
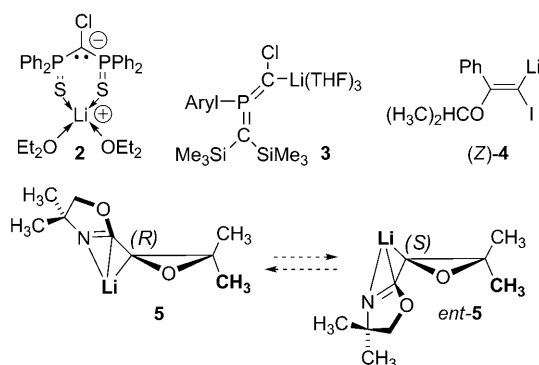

Figure 2. Thermally stable lithium carbenoids.

temperature, has recently been reported by Le Floch and co-workers.[10] An X-ray analysis has revealed a strong stabilization occurring for the lithium cation provided by the two sulfur atoms and two molecules of diethyl ether that prevent LiCl elimination, thus accounting for the observed increase in thermal stability. Surprisingly, a shielding of $\delta = 15.2$ ppm was at the same time detected for the central ^{13}C atom further to lithiation. This phenomenon, rather unusual for a lithium carbenoid, has been interpreted by the authors by noting that the central lithiated carbon possesses its lone pair in a pure p orbital, thereby being efficiently stabilized by negative (anionic) hyperconjugation[11] into the phosphorus antibonding orbitals; this leads to a rather strong C−Cl bond. The above peculiar structural characteristics have also been successfully exploited to transform the carbenoid into "carbene complexes" with electron-rich metal centers.

A remarkable thermal stability has also been reported for the methylene(phosphoranylidene) carbenoid **3** (Figure 2)

by Niecke et al.[12] Interestingly, in spite of the potential carbene-like reactivity this carbenoid would have (as shown by the strong deshielding experienced by the carbenoid ^{13}C nucleus), it tends to undergo LiCl elimination only above −10°C to give a λ^3-phosphirene. Most probably, the fact that the carbenoid center is a component of a delocalized π-electron framework extending over three atoms may enhance the kinetic stability of such a Li/Hal carbenoid. Another alkylidenecarbenoid that surprisingly revealed to be kinetically stable almost up to ambient temperature is (Z)-**4** (Figure 2).[13] Apparently, the presence of a stationary substituent, such as the isopropyloxy group, hampers both the expected phenyl migration through a Fritsch–Buttenberg–Wiechell rearrangement and the 1,5-CH insertion into isopropyl CH$_3$ groups as the temperature is increased; in addition, this intermediate does not even undergo a possible dimerization to furnish a butatriene. Although ab initio calcu-

Vito Capriati obtained his M.Sc. degree with honours in Chemistry and Pharmaceutical Technology from the University of Bari in 1990. After working as a forensic chemist officer within the Carabinieri's RIS (Scientific Investigation Department) of Rome and earning a two-year graduate fellowship within the National Research Council (CNR) centre "M.I.S.O.", in 1993 he became Assistant Professor at the University of Bari before taking up his current position of Associate Professor of Organic Chemistry at the same University in 2002. His current research interests revolve around lithium chemistry and the elucidation of the structure–reactivity relationships, asymmetric synthesis of small-ring heterocycles and their functionalization, stereochemistry, and multinuclear magnetic resonance investigations on highly reactive intermediates aimed at solving their solution structures and dynamic behavior. Recently, he has been honoured for his work with the C.I.N.M.P.I.S. Prize "Innovation in Organic synthesis" awarded by the Interuniversities Consortium C.I.N.M.P.I.S.

Saverio Florio received his "Laurea" in Chemistry at the University of Bari (Italy). After being first Assistant Professor and then Associate Professor of Organic Chemistry in 1986, he was appointed Full Professor of Organic Chemistry at the University of Lecce. In 1990 he moved to the University of Bari on the chair of organic chemistry. Currently, he is Director of "Consorzio Interuniversitario sulle Metodologie e Processi Innovativi di Sintesi" (CINMPIS). President of the Division of Organic Chemistry of the Italian Chemical Society from 1997 to 2001, at present he acts as the vice president of the Italian Chemical Society. He is member of the Scientific Advisory Board of the Ischia IASOC School and member of the "Academy of Science and Arts of Salsburg". Prof. Florio's research interests are concerned with mechanistic studies, stereochemistry, asymmetric synthesis of small-ring heterocycles. He has published more than 200 papers and for his research work has been awarded with "Ziegler–Natta Lecture" from the German Chemical Society (GDCh) in 2005 and with the "Angelo Mangini Gold Medal" from the Division of Organic Chemistry of the Italian Chemical Society in 2007.

lations,[14] in line with experimental findings, proved the higher thermodynamic stability of the *Z* isomer with respect to the *E* isomer, in spite of the fact the former could not benefit from a stabilizing O−Li chelation, the reluctance of **4** to display an electrophilic reactivity as the majority of alkylidenecarbenoids do remains to date unexplained.

The first case of a chiral Li/O carbenoid undergoing a very slow isomerization to the corresponding ketone in ethereal solvents as the temperature is increased has recently been described by Capriati, Florio, and co-workers.[15] Oxazolinyloxiranyllithium **5** (Figure 2), generated by H/Li exchange, was successfully trapped with a deuterium source also at 25 °C in 85 % yield (>98 % D) and 65 % yield (>98 % D) starting from 0 and −78 °C, respectively. A multinuclear magnetic resonance investigation, jointly with IR-spectroscopic studies, suggested that at least in a range of concentration of 0.08–0.3 M, **5** mainly exists as a monomeric η^3-aza-allyl coordinated species rapidly equilibrating, on the NMR timescale, with a complex mixture of diastereomeric oxazoline-bridged dimeric species variously intra-aggregated. Here, too, as in the case of **2**, intramolecular coordination of lithium seems to be a key factor in controlling the kinetic stability of such a lithium carbenoid in spite of its potential carbenoid reactivity, which is more apparent in nonpolar solvents; indeed, the carbenoid carbon atom is deshielded by 36.3 ppm in THF. At the same time, the bias that lithium has to be strongly coordinated by the iminic oxazoline moiety seems also to be a crucial factor in causing a fast racemization of **5** on the NMR timescale ($t_{1/2} = 6.05$ s, $\Delta G^{enant}_{\neq} = 8.8$ kcal mol^{-1} at −130 °C in 3:2 THF/Et$_2$O). An exchange mechanism by which the two enantiomeric monomers **5** and *ent*-**5** (Figure 2) would interchange their Li atoms via an oxazoline-bridged dimeric species, detectable at NMR level, has been proposed.[15]

Influence of the leaving group: The influence of the leaving group on the structure and reactivity in the carbenoid series LiCH$_2$X (X = Hal, OH) toward a "classic" cyclopropanation reaction has also been studied by Boche et al. from a theoretical point of view.[16] At the end of such an investigation, the authors concluded that there is no special halide effect in the reaction of the carbenoids LiCH$_2$Hal with ethene, because the energy of the C−Hal bond cleavage in the transition states is essentially compensated by the energy of the Li−Hal bond formation; in contrast, the higher energy for the reaction of LiCH$_2$OH (chosen as a model system of a Li/OR carbenoid) with ethene results from the high C−OH bond energy.

studying the mechanism and the stereochemistry of reactions of chiral lithium carbenoids (in particular those of chiral cyclopropyl and vinyl lithium carbenoids) with nucleophiles.[17] By using stereochemistry as a probe they were able to distinguish between the carbenoid and carbene mechanisms. In order to explain the stereochemical results of the substitution reaction on such carbenoid species, the concept of "metal-assisted ionization" (MAI) was introduced (Figure 3). In practice, according to this model, as a consequence of a lithium-assisted partial ionization of the carbon–halogen bond, the carbenoid species acquires a certain carbocationic character, but still retaining its configuration because of the permanent coordination of lithium to the halogen. Thus, a nucleophile is allowed to attack the lithiated carbon atom from the backside giving rise to a product that, in the case of chiral cyclopropyl and vinyl lithium carbenoids, often (but not always) displays an overall inversion of configuration.

Figure 3. Metal-assisted ionization (MAI) in a typical lithium/halogen carbenoid.

The development of new pathways for the stereoselective generation of chiral nonracemic lithium carbenoids and their employment in asymmetric processes is an amazing goal that is being pursued more and more today. However, the question of configurational stability of these chiral intermediates under the conditions of their generation as well as the steric course of their coupling reactions with electrophiles (retentive or invertive pathways)[18] are important issues that need always to be preliminarily addressed before planning an asymmetric synthesis.[19]

Configurational stability of α-haloorganolithiums: While chiral nonracemic α-oxygen and α-nitrogen-substituted lithium carbenoids are known to be nearly always configurationally stable at temperatures as low as −78 °C and during the time needed to generate and to trap them with electrophiles,[20] enantiomeric α-halolithium compounds still have not been deeply investigated.[1f,21] However, the results reported to date are pleasingly surprising and encouraging for stereoselective transformations. The first racemic bromocarbenoid investigated was **6** (Figure 4).[22] Generated by a bromine–lithium exchange reaction from the corresponding dibromo derivative, it showed a remarkable configurational stability at −120 °C on a macroscopic timescale when sub-
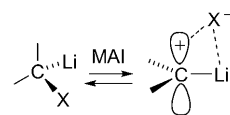
Configurational Stability of Lithium Carbenoids and Stereochemistry of their Coupling Reactions with Electrophiles

Stereochemistry has always been a recurring theme when dealing with lithium carbenoids that have a stereogenic lithium-bearing carbon atom. Walborsky et al. were pioneers in
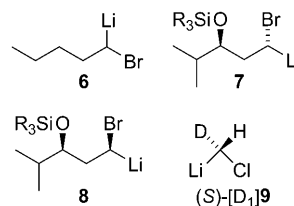

Figure 4. Chiral lithium halogen carbenoids.

jected to the Hoffmann test, which is based on kinetic resolution. Likewise, diastereomeric 1-bromoalkyllithium compounds **7** and **8** (Figure 4), generated by bromine–lithium exchange, were found to be configurationally stable at −110 °C.[22] Interestingly, Hammerschmidt et al. have recently reported[23] that an enantiomerically enriched chloromethyllithium such as (S)-[D$_1$]**9** (Figure 4), generated by tin–lithium exchange, in spite of its chemical lability, is configurationally stable on both microscopic and macroscopic timescales up to the temperature of its rapid decomposition, which is −78 °C. Although its half-life at this temperature has been estimated in the range of seconds, it rather decomposes than racemizes! This suggests that the pathway of racemization (whenever it occurs) may not be as simple as predicted. In the case of the configurationally labile oxazolinyloxiranyllithium **5**, for instance, an inverting tetrahedral configuration is very likely to take place rather than an inverting planar configuration,[15] the latter being the favorite racemization pathway radical intermediates usually follow. Therefore, a proper understanding of such an inversion occurring at a stereogenic lithium-bearing carbon atom of a carbenoid cannot disregard either the "cocktail" of components in which these reagents are formed and the reaction conditions or, above all, their aggregation states.[24]

Coupling reactions of stereodefined lithium carbenoids: An enantioenriched Li–carbenoid species such as (S)-**10** (Scheme 2), generated by in situ sulfoxide-ligand exchange,
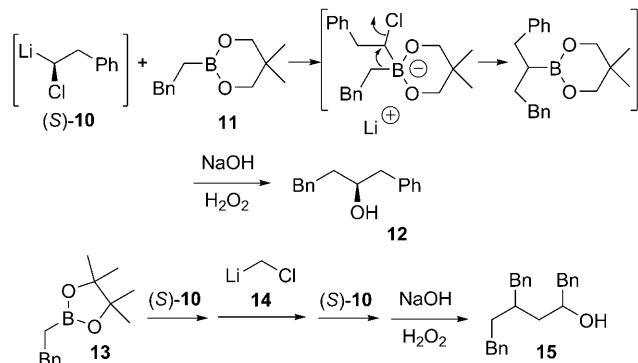
Scheme 2. Homologation of boronic esters and iterative stereospecific reagent-controlled homologation.

has recently been shown to undergo a coupling reaction under Barbier conditions with the boronate **11** to give the carbinol **12** in a remarkable 96 % ee and 70 % yield after oxidative workup, thus providing an interesting asymmetric route to homologate boronic esters.[25a] Under an optimized protocol, Blackmore et al. then set up a programmed synthesis of a stereodiad motif leading to targeted carbinols **15** by iteratively reacting chiral carbenoid **10** with boronate **13** interspersing a homologation step with chloromethyllithium **14** (Scheme 2).[25b]

Terminal epoxides could be lithiated with lithium tetramethylpiperidide (LTMP) and trapped with boronic esters to give syn-1,2-diols with complete diastereoselectivity.[26] In addition, also in this case, the whole process could successfully be iterated, thus creating triols containing up to four stereogenic centers with total control over their relative and absolute stereochemistry. In the selected example depicted in Scheme 3, the iterative homologation of boronic acid pi-
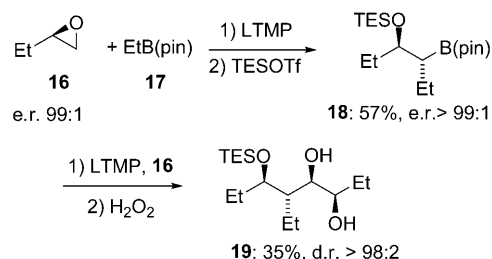
Scheme 3. Homologation of boronic esters using terminal lithiated epoxides.

nacol ester **17** using (R)-butenoxide **16** is shown. It furnished first the β-silyloxy boronic ester **18** and then, after a second homologation and final oxidative workup, the stereodefined triol **19**. When the above protocol was applied to lithiated styrene oxide, 1,2-diols bearing quaternary stereogenic centers could also be successfully generated. In a similar way, terminal N-Boc aziridines (Boc = tert-butyloxycarbonyl) have been stereospecifically β-lithiated and trapped in situ with boronic esters to give syn-β-amino alcohols as single enantiomers and with a complete control of the diastereoselectivity.[27]
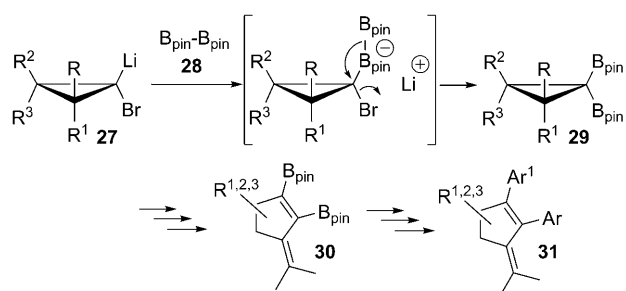
Lithiated carbamates **20**, derived from primary alcohols and prepared in the presence of (−)-sparteine (sp), proved to be effectively configurationally stable chiral lithium carbenoids able to react with both boranes or boronates **21** to give, through the collapse of ate complexes **22** and final oxidative workup, secondary alcohols **23** in good yield, high enantioselectivity and complete retention of configuration (Scheme 4).[28] Similarly, chiral nonracemic carbenoids derived from secondary alcohols have also been successfully employed by Aggarwal and co-workers to prepare highly enantiomerically enriched tertiary alcohols.[29] The most intriguing outcome of this reaction is that either enantiomer of the tertiary alcohol can be obtained with high level of stereocontrol from the same enantiomer of the secondary alcohol, simply depending on whether a borane or a boronic ester is used. The above versatile methodology, the power of which lies just in its potential iterative use, has recently been applied by Aggarwal and co-workers in natural product synthesis.[30] Thus, a stereocontrolled total synthesis of (+)-faranal **26** has been set up exploiting as key steps one-pot iterative boronic ester homologations (which run without detriment to selectivity) between chiral lithiated carbamate **24** and boronic ester **25**. The stereocontrolled addition
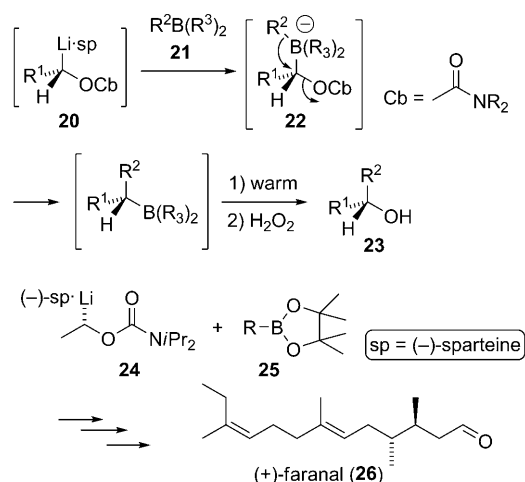
Scheme 4. One-pot lithiation/borylation of carbamates and total synthesis of (+)-faranal through iterative boronic ester homologations.

Scheme 6. Geminal difunctionalization of alkenylidene-type carbenoids and stereocontrolled approach to tetrasubstituted olefins.
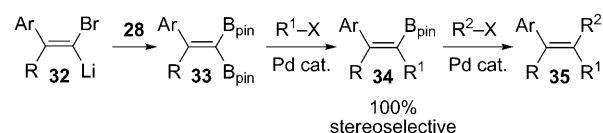
of successive groups to the growing chain finally leads to the insect pheromone **26** (Scheme 4).

Simultaneous incorporation of two metals into organic substrates is a crucial and challenging task in organic synthesis in order to obtain multisubstituted target organic frameworks.[31] In particular, the preparation of novel *gem*-diborylated compounds has been successfully accomplished taking advantage of *gem*-diborylation of lithium carbenoids with diboron compounds. The synthesis of 1,1-diborylated cyclopropanes **29**, for instance, has been performed by *gem*-diborylation of cyclopropylidene lithium carbenoids **27** with bis-(pinacolato)diboron **28** ($B_{pin}-B_{pin}$). Cyclopropanes **29** showed their synthetic utility as useful precursors of *vic*-diborylated methylenecyclopentenes **30** amenable to further functionalization by regioselective cross-coupling reactions with aryl halides to the corresponding derivatives **31** (Scheme 5).[32]

Scheme 5. Synthesis and application of 1,1-diborylated cyclopropanes.

Analogously, geminal difunctionalization of stereodefined alkylidene-type carbenoids **32**, by using interelement compounds such as **28**, also serves as an efficient preparative method for the obtainment of 1,1-diboryl-1-alkenes **33**[33] (Scheme 6). Palladium-catalized cross-coupling reaction of **33** with R^1-X proceeds stereoselectively to give (*E*)-alkenyl-

boronates **34** as single diastereomers with no trace of dicoupled products. Irrespective of the vinyl substituent R, the stereochemical outcome is always uniform. Further coupling reaction with another halide R^2-X allows the obtainment of tetrasubstituted ethenes **35** with overall complete stereocontrol (Scheme 6).[34]

Now, what about the stereochemical integrity of an alkylidene Li/Hal carbenoid such as **32** when subjected to a 1,2-metalate rearrangement? In an interesting survey that reports full details of the insertion reactions of 1-chloro-1-lithioalkenes into organozirconocenes, Whitby et al. investigated the stereochemistry of such a carbenoid insertion.[35] The insertion of 1-chloro-lithioalkenes **36** into organozirconocene chlorides **37** effectively provides a stereocontrolled synthesis of terminal dienes, trienes, dienynes, and other unsaturated systems (Scheme 7). To explain the experimental results in terms of stereochemistry, the proposed mechanism envisages a clean inversion of configuration at an sp^2 center of an "ate" complex **38** with the formation of a new organozirconium species **39** which may be further elaborated (Scheme 7).
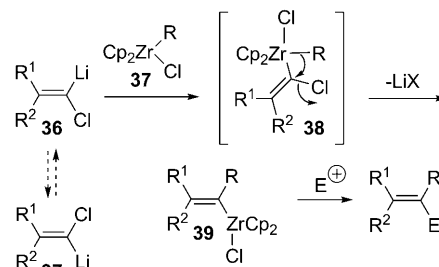
Scheme 7. Insertion of 1-chloro-1-lithioalkenes into organozirconocene chlorides.

However, only the insertion of β-monosubstituted 1-halo-1-lithioalkenes strongly supports a concerted 1,2-migration mechanism, as depicted in Scheme 7, that finally leads to stereodefined unsaturated systems. Indeed, β,β′-dialkyl-substituted 1-lithio-1-alkenes also insert but with a loss of stereochemical integrity of the starting vinyl halide. The authors ascertained that such a loss of stereochemistry arises from a rapid isomerization of **36** into **37** that occurs prior to 1,2-metalated rearrangement on the zirconium and is most probably mediated by a "metal-assisted ionization". Interestingly, Harada et al. have reported[36] that lithium carbenoids derived from 1,1-dibromoalkenes are configurationally stable at low temperature, whereas they undergo rapid iso-

merization at the carbenoid atoms in the presence of the un-reacted starting dibromoalkenes probably through a rapid reversible bromine/lithium exchange. Substitution reactions promoted by organolithiums at unactivated 1-chloro-1-al-kenes have been recently investigated by Knorr and co-workers;[37] an alkylidenecarbenoid chain reaction has been proposed to occur in the case of 2-(halogenomethylidene)-1,1,3,3-tetramethylindan derivatives. Now, the questions needed to be addressed would be the following: what is the real "identity" of a lithium carbenoid responsible of a di-chotomous reactivity according to the employed experimen-tal conditions? What are the factors responsible of its con-figurational integrity/lability and that govern the stereo-chemistry of its coupling reactions with electrophiles?

The Influence of Aggregation and Solvation on the Structure–Reactivity Relationship

The structure–reactivity relationship is an important feature of organolithium compounds to be always taken into consid-eration for both the elucidation of reaction mechanisms and an improved understanding of observed selectivities.[38] Lith-ium compounds, often schematically depicted as monomeric species (especially for educational purposes), are instead known to be typical self-assembling molecules par excel-lence, reputed to exhibit an astonishing array of struc-tures;[39] lithium carbenoids are no exception. As a conse-quence, their solution structures tend to be much more com-plicated than expected, because of the formation of higher aggregates in which the metal may be associated with more than one carbanion center. Such rule-breaking structures, in Schleyer's terminology,[40] illustrate the interplay of ionic and covalent bonding. Lithium carbenoids are similarly vari-ously aggregated in solution and an understanding of their peculiar reactivity cannot leave out the consideration of their structure elucidation. In particular, some structural fea-tures are noteworthy when dealing with these reactive inter-mediates. As supported by X-ray analyses,[1c,d,7] NMR inves-tigations,[1c,d,7] and calculations,[41] the presence of a heteroa-tom (e.g., halogen, O) in the organic framework of a lithiat-ed system allows it preferentially to form bridged structures with the heteroatom bridging the carbon–lithium bond. In addition, in the case of bridged dimers[42] or higher aggre-gates,[43] it is not unusual that such architectures may differ in their basic structural features from those of the most common symmetric types, because of the presence of addi-tional intramolecular coordinations that might induce a dis-tortion of their geometries. This is particularly true also when solvation is considered: an ethereal solvent, competing with the heteroatom for coordination sites on lithium, might indeed increase both lithium–carbon and lithium–heteroa-tom bond lengths in a different way in a higher aggregate. In this context, NMR spectroscopic data, suggestive of a cer-tain aggregation state of a lithium carbenoid, should always be treated with caution. Let's consider, for instance, the case of the Li/Hal carbenoids LiCHCl$_2$ and LiCCl$_3$ examined by

Seebach et al.[44] The ^{6}Li,^{13}C triplet observed in their ^{13}C NMR spectra would be suggestive of a carbon coupled to only one lithium atom (^{6}Li $I=1$) such as would occur in monomeric structures. However, performing calculations on LiCH$_2$F (**40**; Figure 5) (chosen as a model system), Boche
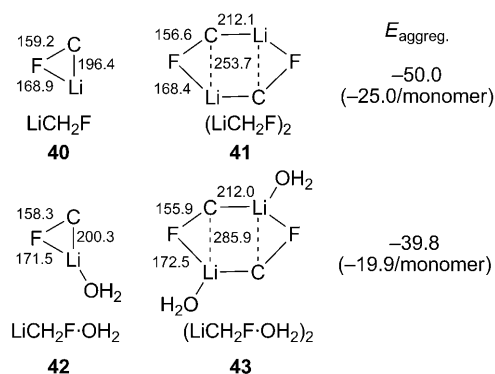

Figure 5. MP2/6-31G(d)//3-21G energies [kcal mol^{-1}] and bond lengths [pm] of bridged LiCH$_2$F, LiCH$_2$F·OH$_2$, [LiCH$_2$F]$_2$ and [LiCH$_2$F·OH$_2$]$_2$.

et al.[7] found a more stable bridged dimer (LiCH$_2$F)$_2$ (**41**) with respect to the monomer in which the bridging lithium exhibited two different bond lengths to carbon. Solvation of Li in the monomer to form LiCH$_2$F·OH$_2$ (**42**) increased the difference even more in the corresponding disolvated dimer (LiCH$_2$F·OH$_2$)$_2$ (**43**) (Figure 5). This implies that the above Li/Hal carbenoids, namely LiCHCl$_2$ and LiCCl$_3$, might indeed be themselves aggregated as dimers and the single ^{6}Li,^{13}C coupling observed be just due to the large distance of the bridging ^{6}Li to the carbenoid ^{13}C atom.

The controversy of the mechanistic dichotomy for carbe-noid-promoted cyclopropanation reactions (that is, the methylene-transfer pathway and the carbometalation path-way; Scheme 8), has recently been deeply re-investigated by Zhao and co-workers[45] by means of DFT calculations taking into account both aggregation and solvation states for lithium carbenoids. These calculations reveal, first, that the carbometalation pathway cannot compete with the
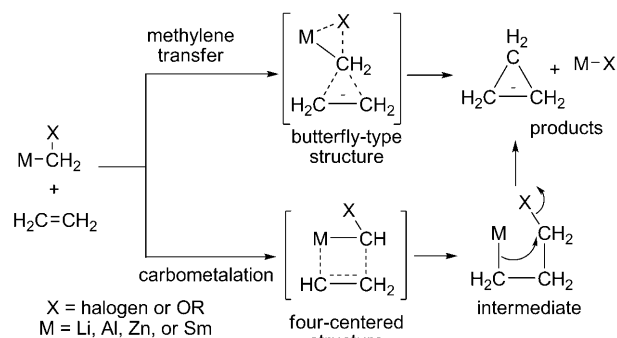
Scheme 8. The methylene-transfer mechanism and carbometalation mechanism for carbenoid-promoted cyclopropanation reactions.

methylene-transfer pathway once aggregation states are considered. Second, the aggregated lithium carbenoids are the most likely reactive species in the reaction systems; indeed, the reaction barrier of the methylene-transfer pathway for a lithium carbenoid such as **40** decreases from 16.0 kcal mol^{-1} for the monomer to 10.1 kcal mol^{-1} for the dimer (LiCH$_2$F)$_2$ (**41**), and to 8.0 kcal mol^{-1} for the tetramer (LiCH$_2$F)$_4$. By investigating the solvation effect, introducing explicitly coordinating solvent molecules to the lithium ion of **40**, it transpires that solvation helps make the methylene-transfer pathway even more favored than the carbometalation pathway. DFT calculations have also been employed to examine the possible formation of mixed aggregates (mixed dimers, trimers and tetramers) between halomethyllithium carbenoids and lithium halides in both the gas phase and THF solution. As highlighted by L. M. Pratt et al.,[46] these mixed aggregates, whenever formed, can affect the activation barrier of carbenoid reactions (e.g., that of cyclopropanation reactions) and may cause, at the same time, a change in the mechanism during the course of the same reaction. In addition, such mixed aggregates may also have a potential in synthetic reactions of lithium carbenoids.

Similarly, aggregation and solvation proved to be crucial factors also for a proper elucidation of the dichotomous reactivity of α-lithiated ethers. As reported,[7] the carbenoid nature of α-lithiated ethers has always allowed them to react with nucleophiles like RLi. Moreover, whenever spectroscopic data are available, α-lithiated ethers have often been described as having bridged dimeric structures in solution. One of the rare exceptions is represented by the Li/O carbenoid **44** (Figure 6), which is a monomer in THF at −108 °C and has an ylide nature, with the lithium bound to oxygen; the stabilization of the negative charge at the anionic carbon is, most probably, the prerequisite for the removal of Li from this carbon. Curiously, attempts to react this monomeric species **44** in various solvents with RLi nucleophiles have always failed. A recent multinuclear magnetic resonance investigation performed by Capriati, Florio, and co-workers on α-lithiated [α,β-$^{13}C_2$] styrene oxide (also in an enantiomerically enriched form), nicely supported by both DFT and GIAO chemical shift calculations, showed that in [D$_8$]THF at 173 K this oxiranyllithium is mainly present as a solvated monomeric species in equilibrium with a complex mixture of stereoisomeric dimeric aggregates (with/without O−Li coordinations) as well as with a fluxional tetrameric aggregate.[47] The reduced symmetry of some aggregates, mainly because of the partial breaking of some C$_\alpha$−Li bonds, complicates their NMR spectra even more. Thus, for a certain dimeric aggregate such as **45** (Figure 6), two diastereomers, namely **45a·2THF** and **45b·2THF**, under slow equilibration on the NMR timescale in absence of tetramethylethylenediamine (TMEDA), could be seen each one exhibiting a pair of diastereotopic lithiated carbons. Interestingly, DFT and GIAO chemical shift calculations suggested that the trisolvated monomeric aggregate **46·3THF** is very likely to exist in solution without any coordination between Li and the oxirane oxygen, thus exhibiting an almost tetra-
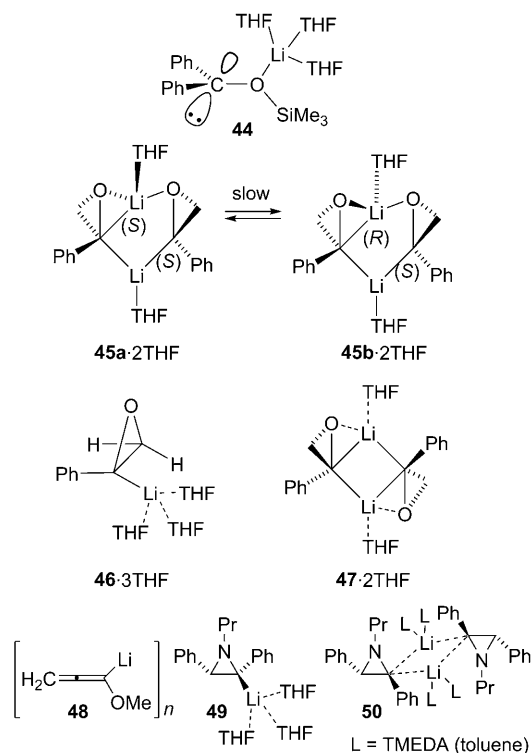

Figure 6. Li/O carbenoid **44**, selected aggregation states of lithiated styrene oxide (**45–47**), lithiated allenyl ether **48**, and lithiated diphenylaziridines **49** and **50** in two different geometries and aggregation states according to the nature of the solvent.

hedral arrangement around the carbanionic carbon. At the same time, bridged O-coordinated dimeric aggregates of the type of **47·2THF** are most probably the expression of a higher "carbene-like" reactivity of lithiated styrene oxide with respect to the monomer **46·3THF** (Figure 6). This supposition was supported by both natural bond analysis (NBA) and experimental results. Therefore, the dichotomous reactivity exhibited by lithium carbenoids may be properly rationalized on the basis of a close structure–reactivity relationship; aggregates are, indeed, the real species formed in solution—each one being preferred with respect to another one under certain experimental conditions and each one characterized by its own reactivity. A combined computational and ^{13}C NMR study has been analogously used to determine the solution structures of a lithiated allenyl ether such as 1-methoxyallenyllithium (**48**; Figure 6).[48] The NMR spectra in THF, together with the calculated aggregation energies and chemical shifts, are consistent with a dimer–tetramer equilibrium, the dimer being favored by lower temperatures whereas the tetramer by higher temperatures. An opposite stereochemical course has been observed in different solvents by Florio and co-workers in the lithiation-trapping sequence of *trans-N*-alkyl-2,3-diphenylaziridines with electrophiles.[49] This phenomenon has recently been spectroscopically rationalized just in terms of a switch occurring between two differently configured lithiated intermediates according to the nature of the solvent em-

ployed.[50] A monomeric species *cis*-49 (presumably solvated up to three molecules of THF), has been postulated in THF, whereas a *trans*-50, a homomeric dimer with TMEDA tightly bonded to lithium, is most probably the aggregate favored in toluene (Figure 6).

Throughout the last three decades, the structural analysis of an organolithium compound has benefited a lot from the tremendous evolution of new NMR techniques. Today, in particular, the aggregate size of an organolithium intermediate may be deduced not only from NMR line multiplicities due to $^{13}C,^{6,7}Li$ coupling,[51] but also from the measurements of diffusion constants (related to the individual lithiated species present in solution) by pulsed gradient spin-echo (PGSE) NMR methods. The incorporation of the PGSE sequence into a two-dimensional experiment leads to the so-called diffusion-ordered NMR spectroscopy (DODY).[52] Starting in the year 2000, many efforts have been made by Williard and co-workers to employ multinuclear DOSY techniques in the characterization of reactive organolithium aggregates in order to correlate solid-state crystal structures (determined by X-ray diffraction) with solution structures and also to discover the role of aggregate formation and solvation states in reaction mechanisms.[53] The combination of ^7Li NMR and PGSE methods also proved to be quite useful for recognizing both ion pairing and aggregation of organolithium species in THF.[54]

Summary and Outlook

Organolithium compounds, in general, because of the predominantly ionic nature of their C−Li bonds are often aggregated in solution, the molecular structure being affected by various factors such as solvent/cosolvent coordination of the lithium atom, (de)localization of the negative charge into the organic framework, and the steric demand around the lithiated carbon. Li carbenoids, in particular, because of additional coordination promoted by the heteroatom toward lithium (which compete with those arising from both the lithiated carbon and the solvent), may exhibit even more complex architectures in solution with a lower symmetry than expected. Any proposal for the solution structures of these aggregates should therefore result, preferentially, from a synergistic interaction between theoretical and experimental work. Solid-state structures (if any) may also be of further help for the interpretation of experimental results. A new synthesis making use of this class of compounds cannot disregard (particularly in terms of selectivity) the knowledge of the structure–reactivity relationship, which with these systems becomes particularly crucial; their dichotomous reactivity is indeed related to the different aggregates formed in solution. Such lithium aggregates can be considered, in all respects, as supramolecular entities in Lehn's terminology, because they are the result not only of additive but also of cooperative interactions between monomeric units.

The challenge from now on is to pay great attention to all of the "secondary interactions" (mainly noncovalent interac-

tions) that may be responsible of the geometries of these clusters and in which a "lithium bond"[55] and/or close "agostic"-type Li···H−C interactions[56] also might be playing an important role. Topological analysis of the charge densities from high resolution X-ray data exploiting the "atoms in molecules" (AIM) approach,[57] may shed some brighter light in unveiling such interactions.[11b] This type of knowledge is important not only in the field structure–reactivity relationships, but also because these higher ordered structures could also display an interesting chirality at the supramolecular level. This, in turn, could inspire the proper planning of an asymmetric synthesis as well as its optimization. As an example of a successful self-assembly in the organolithium field, suffice it to say that one of the simplest nonchiral organolithiums, methyllithium, in the presence of diethoxymethane, forms tetrameric $(MeLi)_4$ units linked to each other through Li_3−C···Li intertetrameric long-range interactions, each tetramer also interacting completely with its eight adjacent tetramers, thus leading to a three-dimensional network characterized by hexagonal channels.[58] A further example of the formation of high-order supramolecular structures has been provided by Collum: an achiral lithium acetylide and a lithium ephedrate containing two stereogenic centers self-assemble into mixed tetramers containing up to 14 stereogenic centers with complete stereocontrol.[59]

Studying the spontaneous or induced self-assembly of organolithiums[60] in order to get functional architectures at a supramolecular level may be one of the most challenging breakthroughs in the near future, because this would also smooth the way toward a proper understanding of the circumstances under which these "reagents" become able to "communicate" with each other or, better, they start to "live"!

Acknowledgements

[1] For selected general reviews on lithium carbenoids, see: a) H. Siegel, *Top. Curr. Chem.* **1982**, *106*, 55–78; b) G. Boche, J. C. W. Lohrenz, A. Opel, in *Lithium Chemistry: A Theoretical and Experimental Overview* (Eds.: A.-M. Sapse, P. von R. Schleyer) Wiley, New York, **1995**; pp. 195–226; c) G. Boche, J. C. W. Lohrenz, *Chem. Rev.* **2001**, *101*, 697–756 and references therein; d) the reactivity of alkylidenecarbenoids has also been extensively reviewed: M. Braun, *Angew. Chem.* **1998**, *110*, 444–465; *Angew. Chem. Int. Ed.* **1998**, *37*, 430–451; e) R. Knorr, *Chem. Rev.* **2004**, *104*, 3795–3849; f) M. Braun, in *The Chemistry of Organolithium Compounds, Vol. 2* (Eds.: Z. Rappoport, I. Marek), Wiley, New York, **2004**, Chapter 13, pp. 829–900; g) for a recent review on α-lithiated α-chloroalkylheterocycles and their utility in synthetic organic chemistry, see: S. Florio, V. Capriati, R. Luisi, *Curr. Org. Chem.* **2004**, *8*, 1529–1545.
[2] The reaction refers to a base-catalyzed decomposition of tosylhydrazones in aprotic solvents, which most probably implies the release of

a carbene fragment: L. Friedman, H. Shechter, *J. Am. Chem. Soc.* **1959**, *81*, 5512–5513.

[3] G. L. Closs, R. A. Moss, *J. Am. Chem. Soc.* **1964**, *86*, 4042–4053.

[4] H.-O. Kalinowski, S. Berger, S. Braun, *^{13}C-NMR Spektroskopie*, Thieme, Suttgart, **1984**, Chapter 4.

[5] G. Boche, *Angew. Chem.* **1989**, *101*, 286–306; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 277–297.

[6] M. Marsch, K. Harms, O. Zschage, D. Hoppe, G. Boche, *Angew. Chem.* **1991**, *103*, 338–339; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 321–323.

[7] G. Boche, F. Bosold, J. C. W. Lohrenz, A. Opel, P. Zulauf, *Chem. Ber.* **1993**, *126*, 1873–1885.

[8] For leading references on the carbanionic/carbenoid reactivity of α-lithiated oxiranes, see: a) T. Satoh, *Chem. Rev.* **1996**, *96*, 3303–3325; b) Y. Mori, *Rev. Heteroat. Chem.* **1997**, *17*, 183–211; c) D. M. Hodgson, K. Tomooka, E. Gras, *Top. Organomet. Chem.* **2003**, *5*, 217–250; d) F. Chemla, E. Vranken in *The Chemistry of Organolithium Compounds, Vol. 2* (Eds.: Z. Rappoport, I. Marek), Wiley, New York, **2004**, Chapter 18, pp. 1165–1242; e) V. Capriati, S. Florio, R. Luisi, *Synlett* **2005**, 1359–1369; f) D. M. Hodgson, C. D. Bray in *Aziridine and Epoxides in Organic Synthesis* (Ed.: A. K. Yudin), Wiley-VCH, Weinheim, **2006**, Chapter 5, pp. 145–184; g) D. M. Hodgson, P. G. Humphreys, S. P. Hughes, *Pure Appl. Chem.* **2007**, *79*, 269–279; h) V. Capriati, S. Florio, R. Luisi, *Chem. Rev.* **2008**, *108*, 1918–1942 and references therein; i) L. Degennaro, V. Capriati, C. Carlucci, S. Florio, R. Luisi, I. Nuzzo, C. Cuocci, *Tetrahedron* **2009**, *65*, 8745–8755.

[9] a) ref. [8 f]; b) P. O'Brien, C. M. Rosser; D. Caine, *Tetrahedron* **2003**, *59*, 9779–9791; c) P. Müller, D. Riegert, G. Bernardinelli, *Helv. Chim. Acta* **2004**, *87*, 227–239; d) D. M. Hodgson, B. Stefane, T. J. Miles, J. Witherington, *Chem. Commun.* **2004**, 2234–2235; e) D. M. Hodgson, S. M. Miles, *Angew. Chem.* **2006**, *118*, 949–952; *Angew. Chem. Int. Ed.* **2006**, *45*, 935–938; f) D. M. Hodgson, C. D. Bray, P. G. Humphreys, *Synlett* **2006**, 1–22; g) D. M. Hodgson, P. G. Humphreys, J. G. Ward, *Org. Lett.* **2006**, *8*, 995–998; h) B. Musio, G. J. Clarkson, M. Shipman, S. Florio, R. Luisi, *Org. Lett.* **2009**, *11*, 325–328.

[10] T. Cantat, X. Jacques, L. Ricard, X. F. Le Goff, N. Mézailles, P. Le Floch, *Angew. Chem.* **2007**, *119*, 6051–6054; *Angew. Chem. Int. Ed. Angew. Chem. Int. Ed. Engl.* **2007**, *46*, 5947–5950.

[11] For other examples dealing with the role played by negative hyperconjugation in stabilizing carbanions, see: a) C. Gaul, P. I. Arvidsson, W. Bauer, R. E. Gawley, D. Seebach, *Chem. Eur. J.* **2001**, *7*, 4117–4125; b) W. Scherer, P. Sirsch, D. Shorokhov, M. S. McGrady, S. A. Mason, M. G. Gardiner, *Chem. Eur. J.* **2002**, *8*, 2324—2334; c) for an interesting theoretical work showing how negative hyperconjugation may control chemical reactivity, see: S. O. Nilsson Lill, G. Rauhut, E. Anders, *Chem. Eur. J.* **2003**, *9*, 3143–3153; d) recent structure/reactivity studies performed on an α-lithiated highly enantiomerically enriched benzylsilane revealed that negative hyperconjugation seems to play a key role in stabilizing this carbanion: H. Ott, C. Däschlein, D. Leusser, D. Schildbach, T. Seibel, D. Stalke, C. Strohmann, *J. Am. Chem. Soc.* **2008**, *130*, 11901–11911.

[12] E. Niecke, P. Becker, M. Nieger, D. Stalke, W. W. Schoeller, *Angew. Chem.* **1995**, *107*, 2012–2015; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1849–1852.

[13] a) J. Barluenga, M. A. Rodríguez, P. J. Campos, *J. Am. Chem. Soc.* **1988**, *110*, 5567–5568; b) A. Maercher, B. Böss, *Main Group Met. Chem.* **1991**, *14*, 67–71; *Chem. Abstr.* **1993**, *119*, 226014v; c) see reference [1 d].

[14] J. Barluenga, J. M. González, I. Llorente, P. J. Campos, M. A. Rodríguez, W. Thiel, *J. Organomet. Chem.* **1997**, *548*, 185–189.

[15] V. Capriati, S. Florio, R. Luisi, F. M. Perna, A. Spina, *J. Org. Chem.* **2008**, *73*, 9552–9564.

[16] H. Hermann, J. C. W. Lohrenz, A. Kühn, G. Boche, *Tetrahedron* **2000**, *56*, 4109–4115.

[17] a) M. Duraisamy, H. M. Walborsky, *J. Am. Chem. Soc.* **1984**, *106*, 5035–5037; b) M. Topolski, M. Duraisamy, J. Rachón, J. Gawronski,

K. Gawronska, V. Goedken, H. M. Walborsky, *J. Org. Chem.* **1993**, *58*, 546–555.

[18] a) R. E. Gawley, *Tetrahedron Lett.* **1999**, *40*, 4297–4300; b) in a quite recent and interesting paper (ref. [11d]), Strohmann et al. also tackle the question of invertive and retentive pathways occurring in enantiomerically or diastereomerically enriched alkyllithium compounds. Moreover, apart from steric interactions, substitution and geometry of the carbanionic carbon and the coordination sphere of the lithium, the three-dimensional distribution of the negative electrostatic potential (as a whole) seems to be vital (rather then a local charge concentration at a formal carbanionic carbon) in guiding the incoming electrophile towards the more nucleophilic reactive center; see: H. Ott, U. Pieper, D. Leusser, U. Flierler, J. Henn, D. Stalke, *Angew. Chem.* **2009**, *121*, 3022–3026; *Angew. Chem. Int. Ed.* **2009**, *48*, 2978–2982.

[19] a) J. Claiden, In *Organolithiums: Selectivity for Synthesis*; Pergamon, Amsterdam, **2002**; b) P. Beak, T. A. Johnson, D. D. Kim, S. H. Lim, *Top. Organomet. Chem.* **2003**, *5*, 139–176; c) D. Hoppe, F. Marr, M. Brügemann, *Top. Organomet. Chem.* **2003**, *5*, 61–137; d) G. Wu, M. Huang, *Chem. Rev.* **2006**, *106*, 2596–2616.

[20] a) R. E. Gawley, I. Coldham, in *The Chemistry of Organolithium Compounds, Vol. 2* (Eds.: Z. Rappoport, I. Marek), Wiley, New York, **2004**, Chapter 16, pp. 997–1053; b) D. Hoppe, G. Christoph, in *The Chemistry of Organolithium Compounds, Vol. 2* (Eds.: Z. Rappoport, I. Marek), Wiley, New York, **2004**, Chapter 17, pp. 1055–1164; some enantiopure oxygen-substituted methyllithiums, deuterated on their primary lithiated carbon atoms, have also been recently described by Hammerschmidt et al. and their configurational stability discussed on both microscopic and macroscopic timescales: c) D. Kapeller, R. Barth, K. Mereiter, F. Hammerschmidt, *J. Am. Chem. Soc.* **2007**, *129*, 914–923; d) D. C. Kapeller, F. Hammerschmidt, *J. Org. Chem.* **2009**, *74*, 2380–2388.

[21] a) A. Basu, S. Thayumanavan, *Angew. Chem.* **2002**, *114*, 740–763; *Angew. Chem. Int. Ed.* **2002**, *41*, 716–738; b) ref. [19].

[22] a) R. W. Hofmann, T. Ruhland, M. Bewersdorf, *J. Chem. Soc. Chem. Commun.* **1991**, 195–196; b) R. W. Hoffmann, M. Julius, F. Chemla, T. Ruhland, G. Frenzen, *Tetrahedron* **1994**, *50*, 6049–6060.

[23] D. C. Kapeller, F. Hammerschmidt, *J. Am. Chem. Soc.* **2008**, *130*, 2329–2335.

[24] The mechanism of one of the most powerful method for the preparation of organolithium compounds, that is the lithium-metalloid exchange, is still controversial; both radical and carbanionic mechanisms seem, indeed, plausible and recurrent according to the nature of the reactants and reaction conditions. For leading references about the outcome of such lithium-metalloid exchanges and fruitful discussions on the nature of possible intermediates involved, see: a) H. J. Reich, M. A. Medina, M. D. Bowe, *J. Am. Chem. Soc.* **1992**, *114*, 11003–11004; b) H. J. Reich, M. J. Bevan, B. Ö. Gudmundsson, C. L. Puckett, *Angew. Chem.* **2002**, *114*, 3586–3589; *Angew. Chem. Int. Ed.* **2002**, *41*, 3436–3439; c) N. S. Nudelman, G. V. García, S. Velurtas, *J. Phys. Org. Chem.* **2002**, *15*, 903–910; d) ref. [19a].

[25] a) P. R. Blakemore, S. P. Marsden, H. D. Vater, *Org. Lett.* **2006**, *8*, 773–776; b) P. R. Blakemore, M. S. Burge, *J. Am. Chem. Soc.* **2007**, *129*, 3068–3069.

[26] E. Vedrenne, O. A. Wallner, M. Vitale, F. Schmidt, V. K. Aggarwal, *Org. Lett.* **2009**, *11*, 165–168.

[27] F. Schmidt, F. Keller, E. Vedrenne, V. K. Aggarwal, *Angew. Chem.* **2009**, *121*, 1169–1172; *Angew. Chem. Int. Ed.* **2009**, *48*, 1149–1152.

[28] J. L. Stymiest, G. Dutheuil, A. Mahmood, V. K. Aggarwal, *Angew. Chem.* **2007**, *119*, 7635–7638; *Angew. Chem. Int. Ed.* **2007**, *46*, 7491–7494.

[29] J. L. Stymiest, V. Bagutski, R. M. French, V. K. Aggarwal, *Nature* **2008**, *456*, 778–782.

[30] G. Dutheuil, M. P. Webster, P. A. Worthington, V. K. Aggarwal, *Angew. Chem.* **2009**, *121*, 6435–6437; *Angew. Chem. Int. Ed.* **2009**, *48*, 6317–6319.

[31] For a recent review on the preparation and synthetic applications of *gem-* and *vic-*diborylated compounds, see: M. Shimizu, T. Hiyama, *Proc. Jpn. Acad. Ser. B* **2008**, *84*, 75–85.

[32] M. Shimizu, M. Schelper, I. Nagao, K. Shimono, *Chem. Lett.* **2006**, *35*, 1222–1223.

[33] T. Hata, H. Kitagawa, H. Masai, T. Kurahashi, M. Shimizu, T. Hiyama, *Angew. Chem.* **2001**, *113*, 812–814; *Angew. Chem. Int. Ed.* **2001**, *40*, 790–792.

[34] M. Shimizu, C. Nakamaki, K. Shimono, M. Schelper, T. Kurahashi, T. Hiyama, *J. Am. Chem. Soc.* **2005**, *127*, 12506–12507.

[35] A. Kasatkin, R. J. Whitby, *J. Am. Chem. Soc.* **1999**, *121*, 7039–7049.

[36] T. Harada, T. Katsuhira, K. Hattori, A. Oku, *Tetrahedron* **1994**, *50*, 7987–8002.

[37] R. Knorr, C. Pires, C. Behringer, T. Menke, J. Freudenreich, E. C. Rossmann, P. Böhrer, *J. Am. Chem. Soc.* **2006**, *128*, 14845–14853.

[38] V. H. Gessner, C. Däschlein, C. Strohmann, *Chem. Eur. J.* **2009**, *15*, 3320–3334.

[39] a) A. Streitwieser, S. M. Bachrach, A. Dorigo, P. von R. Schleyer in *Lithium Chemistry: A Theoretical and Experimental Overview* (Eds.: A.-M. Sapse, P. von R. Schleyer) Wiley, New York, **1995**, pp. 1–43; b) A.–M. Sapse, D. C. Jain, K. Raghavachari in *Lithium Chemistry: A Theoretical and Experimental Overview* (Eds.: A.-M. Sapse, P. von R. Schleyer) Wiley, New York, **1995**, pp. 45–65.

[40] P. von R. Schleyer, *Chem. Eng. News* **2003**, 36.

[41] a) L. M. Pratt, N. V. Nguyên, L. T. Lê, *J. Org. Chem.* **2005**, *70*, 2294–2298; b) L. M. Pratt, B. Ramachandran, *J. Org. Chem.* **2005**, *70*, 1688–1696. For an interesting systematic investigation aimed at determining which levels of theory are required to obtain accurate geometries and dimerization energies for lithium carbenoids, see: L. M. Pratt, D. H. T. Phan, P. T. T. Tran, N. Van Nguyen, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1587–1596.

[42] S. Harder, J. Boersma, L. Brandsma, J. A. Kanters, W. Bauer, R. Pi, P. v. R. Schleyer, H. Schöllhorn, U. Thewalt, *Organometallics* **1989**, *8*, 1688–1696.

[43] K. Sorger, W. Bauer, P. v. R. Schleyer, D. Stalke, *Angew. Chem.* **1995**, *107*, 1766–1768; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1594–1596.

[44] D. Seebach, R. Hässig, J. Gabriel, *Helv. Chim. Acta* **1983**, *66*, 308–337.

[45] Z. Ke, C. Zhao, D. L. Phillips, *J. Org. Chem.* **2007**, *72*, 848–860.

[46] L. M. Pratt, S. Merry, S. C. Nguyen, P. Quan, B. T. Than, *Tetrahedron* **2006**, *62*, 10821–10828.

[47] V. Capriati, S. Florio, F. M. Perna, A. Salomone, A. Abbotto, M. Amedjkouh, S. O. Nilsson Lill, *Chem. Eur. J.* **2009**, *15*, 7958–7979; it is worth noting that in the ^{13}C NMR spectrum of lithiated styrene oxide, measured at natural carbon abundance, α-lithiated carbon only appeared as a very broad singlet at 173 K in [D$_8$]THF.

[48] D. D. Dixon, M. A. Tius, L. M. Pratt, *J. Org. Chem.* **2009**, *74*, 5881–5886.

[49] R. Luisi, V. Capriati, S. Florio, B. Musio, *Org. Lett.* **2007**, *9*, 1263–1266.

[50] V. Capriati, S. Florio, R. Luisi, A. Mazzanti, B. Musio, *J. Org. Chem.* **2008**, *73*, 3197–3204.

[51] W. Bauer, In *Lithium Chemistry: A Theoretical and Experimental Overview* (Eds.: A.-M. Sapse, P. von R. Schleyer) Wiley, New York, **1995**; pp. 125–172.

[52] H. Barjat, G. A. Morris, S. Smart, A. G. Swanson, S. C. R. Williams, *J. Magn. Reson. Ser. B* **1995**, *108*, 170–172.

[53] D. Li, I. Keresztes, R. Hopson, P. G. Williard, *Acc. Chem. Res.* **2009**, *42*, 270–280.

[54] I. Fernández, E. Martínez-Viviente, F. Breher, P. S. Pregosin, *Chem. Eur. J.* **2005**, *11*, 1495–1506.

[55] A. B. Sannigrahi, T. Kar, B. G. Niyogi, P. Hobza, P. v. R. Schleyer, *Chem. Rev.* **1990**, *90*, 1061–1076.

[56] W. Scherer, P. Sirsch, M. Grosche, M. Spiegler, S. A. Mason, M. G. Gardiner, *Chem. Commun.* **2001**, 2072–2073.

[57] a) R. F. W. Bader, *Atoms in Molecules: A Quantum Theory*, Oxford University Press, New York, **1990**; b) see also: P. Macchi, *Angew. Chem.* **2009**, *121*, 5905–5907; *Angew. Chem. Int. Ed.* **2009**, *48*, 5793–5795.

[58] B. Walfort, L. Lameyer, W. Weiss, R. Herbst-Irmer, R. Bertermann, J. Rocha, D. Stalke, *Chem. Eur. J.* **2001**, *7*, 1417–1423.

[59] A. Thompson, E. G. Corley, M. F. Huntington, E. J. J. Grabowski, J. F. Remenar, D. B. Collum, *J. Am. Chem. Soc.* **1998**, *120*, 2028–2038.

[60] For a recent review on lead structures in lithium organic chemistry, see: T. Stey, D. Stalke in *The Chemistry of Organolithium Compounds, Vol. 1* (Eds.: Z. Rappoport, I. Marek), Wiley, New York, **2004**, Chapter 2, pp. 47–120.