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Stability and reactivity control of carbenoids: recent advances and perspectives

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Metal carbenoids such as lithium or Simmons–Smith-type reagents are widely used in organic synthesis, particularly in cyclopropanation and homologation reactions. These reagents are often highly reactive and thermally labile, thus limiting their isolation and hampering the development of new synthetic applications. Recent years however, have shown that by means of systematic stabilization a control of reactivity and the development of new applications is possible. This feature article documents recent developments in the control of carbenoid reactivity and stability and highlights structural and electronic properties as well as applications in main group element and transition metal chemistry.

Introduction

In recent years, research in main group element and metal chemistry has experienced a remarkable renaissance due to their potential use in bond activation chemistry and catalysis.[1] Particularly low-valent main group species with vacant

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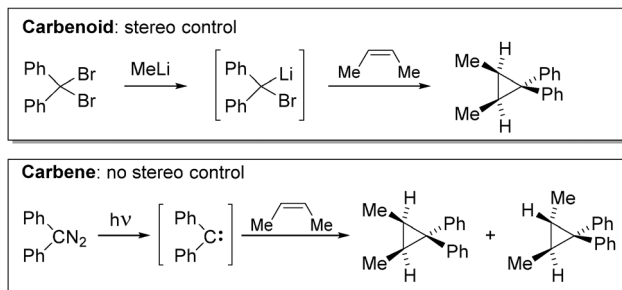
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Viktoria Gessner (born Oct. 1982 in Würzburg) obtained her diploma degree in 2007 from the University of Würzburg and her PhD in 2009 from the TU Dortmund working with C. Strohmann. After a postdoctoral stay at UC Berkeley with T. D. Tilley she started her independent academic career at the University of Würzburg affiliated to the group of H. Braunschweig and finished her Habilitation in 2015. She recently moved to the Ruhr-Universität Bochum, where she is now chair for inorganic chemistry. Her research interests involve organometallic and main group metal chemistry with focus on s-block metal compounds and unique carbon-based ligand systems. Her work has been recognized by several grants and awards, such as by an Emmy Noether Grant of the German Research Council, a Starting Grant of the European Research Council or the ADUC award and IUPAC prize for young scientists.

coordination sites and small energy gaps between their frontier orbitals have shown to be capable of transformations, which have long been considered the realm of transition metals.[2] The advancements in carbene chemistry have especially contributed to this research. Until today, many examples of carbenes capable of effecting oxidative addition reactions of E–H or E–E bonds (*e.g.* H–H, N–H, Si–H, P–P) or stabilizing main group element systems with unique reactivities have been reported.[3] Key step to these developments however, has been the stabilization of these usually highly reactive species, which have long been regarded as fleeting reaction intermediates and hence mainly been applied in the coordination sphere of transition metals or under extreme reaction conditions. Compared to carbenes, the reactivity of metal carbenoids (metal = s-block metal, Zn) towards E–H and E–E bonds is by far less explored. Since decades, these compounds have been utilized as potent reagents for cyclopropanation reactions.[4] However, only recent studies have focused on the stabilization of these usually highly reactive and thermally labile compounds and the development of reactivities beyond classical cyclopropanation reactions.

The term carbenoid was first introduced by Closs and Moss in 1964 to describe compounds, "which exhibit reactions qualitatively similar to those of carbenes without necessarily being free divalent carbon species."[5] This distinction to carbenes became necessary to explain the observed selectivity differences in cyclopropanation reactions with carbenes and carbenoids.[6] Thereby, the authors noticed that – contrary to diphenylcarbene – the use of the Li/Br carbenoid prepared from methyllithium and diphenyldibromomethane in the cyclopropanation of (*Z*)-2-butene allows for stereo control (Scheme 1), thus suggesting the presence of an intermediate which is similar, but not equal to a carbene.

In general, the carbenoid character was found to be realized in systems with a metalated carbon atom which additionally bears a leaving group X (Fig. 1), *i.e.* species of the general

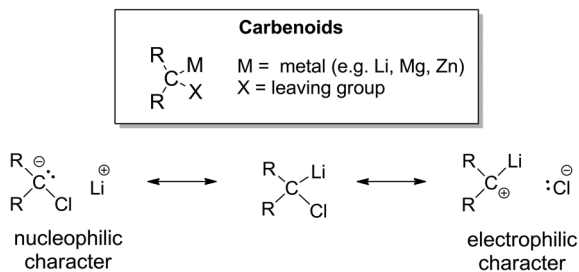**Scheme 1** Selectivity differences in cyclopropanation reactions with carbenes and carbenoids.

Fig. 1 (top) Definition of carbenoids; (bottom) resonance structures of Li/Cl carbenoids.

constitution $R_2C(X)M$ (M = s-block metal, Zn). This special constitution of carbenoids results in their ambiphilic character, which becomes evident from their resonance structures (see Fig. 1 for a Li/Cl carbenoid). Historically, cyclopropanations were one of the first reactions that demonstrated this ambiphilicity of carbenoids and their propensity to undergo salt eliminations.[4] The fact that metal organyls – despite of their carbanionic nature – exhibit an electrophilic character fascinated chemists ever since. Further reactivities were uncovered demonstrating this electrophilicity, such as C–H activation reactions (mostly intramolecular decomposition reactions) or rearrangements (e.g. the Fritsch–Buttenberg–Wiechell).[7] However, the high reactivity and the often observed thermal lability turned out to be the limiting factor to many studies and the development of broader synthetic applications. Hence, until today the most studied reactivity of carbenoids remains the cyclopropanation of olefins.

Recent years however, have experienced a renaissance in carbenoid chemistry. With the first isolation and the stabilization of these compounds novel reactivity patterns were uncovered and many different carbenoid systems – including transition metal species[8] – were developed. In this Feature article we highlight recent developments in this chemistry. Thereby, we will focus on s-block metal systems (including Zn carbenoids) with emphasis on the alkali metal compounds. Since the last detailed review on carbenoids published by Boche in 2001[9] many advances have been made in the stabilization, isolation and structural characterization of these reagents. Hence, we will start with general aspects on carbenoid stability – with special focus on its adjustability – and general preparation methods

as well as structural properties. Several reviews on the chemistry of carbenoids, especially on their application in organic synthesis, have appeared over the years.[10] Hence, reactivities towards carbon compounds will not be covered here. Instead, we will concentrate on recent developments in carbenoid chemistry towards applications in main group element and transition metal chemistry.

1. The carbenoid character and thermal stability

The fact that metal carbenoids – despite of their carbanionic nature – exhibit an electrophilic character early attracted interest of many synthetic chemists. However, the thermal lability involved with the "uncontrolled" α-elimination of the metal salt and the liberation of an extremely reactive carbene species, limited early investigations of the structural properties and reactivities. Later, X-ray crystallography[11] and NMR spectroscopy[12] as well by computational methods[13] showed that the instability of carbenoids can be rationalized by their unique hybridization compared to the protonated compounds. As such, carbenoids possess a higher p-character in the C–X bond compared to their protonated congeners, which results in the facilitated elimination of X⁻ and MX, respectively. However, there are several factors that influence the stability of a metal carbenoid and thus its carbenoid character (Fig. 2): (a) the M/X combination, (b) the substitution pattern and (c) the solvent and/or presence of additional donor bases or metal salts. By adjustment of these parameters the thermal stability and reactivity of carbenoids can be controlled, thus also allowing the preparation and isolation of systems that are stable at room temperature (vide infra). However, the fact that many parameters affect the carbenoid stability also results in the complexity of these systems. Only under the very same reaction conditions the stability of different carbenoids can be compared to each other. Hence, many examples exist in literature, which describe different stabilities for one and same carbenoid.[14] Reactivity and stability control in carbenoid chemistry however, is highly desirable not only to broaden the scope of applications, but also to offer alternatives to synthetic procedures which require the use of
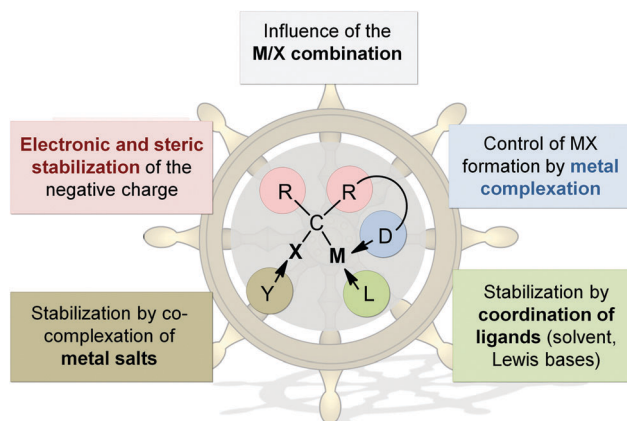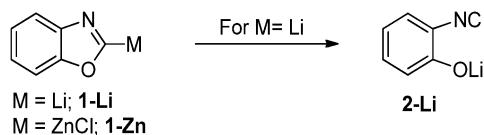

Fig. 2 Factors that determine the stability of carbenoids.

Scheme 2 Lithiated and zincated oxazoles **1-M**.

expensive transition metals and/or the use of highly reactive or toxic reagents mainly limited to aryl-functionalized systems, such as diazo or ylide compounds.[8]

The M/X combination

Regarding the nature of the metal, one typically observes an increased stability in the series Li < Mg < Zn. This trend follows the general observations made for simple metal organyls and is due to the decreasing polarity f the M–C bond within this series of metals. This has for example been demonstrated by Boche and co-workers by means of metalated oxazoles (Scheme 2).[13] While the zinc compound **1-Zn** could be isolated at −30 °C, the lithium compound was found to be unstable even at −78 °C decomposing via Li/OR elimination to the corresponding (Z)-2-isocyanolithium enolate **2-Li**. Computational studies also revealed a higher p-character in the C–OR bond in **1-Li** compared to **1-Zn** and thus confirmed the more pronounced carbenoid character for the lithium system. Very recently, our group reported on stability studies of a series of Li, Na and K carbenoids.[15] VT-NMR experiments revealed a higher thermal stability of the heavier congeners, which thus allowed – in contrast to the lithium compounds – their isolation at room temperature. The reason for this increased stabilization is presumably the lower Lewis acidity of the heavier metals, which weakens the M–X interaction in the carbenoid. This effect overcompensates the higher reactivity of the carbanion due to the higher polarity of the M–C bond.

Besides the nature of the metal, the leaving group X crucially determines the reactivity and stability of carbenoids. In general, halogens and ethers are the leaving groups leading to the most pronounced carbenoid character. Li/Hal carbenoids are regarded as the most reactive species, which often have to be handled at temperatures below −78 °C. This has already been noted in the late 1960s in seminal studies on simple systems such as Li–CH$_2$Cl or Li–CHBr$_2$, reported by Köbrich and coworkers.[14,16] Computational studies on the nucleofugal ability revealed a decreasing carbenoid character in the series LiCH$_2$F > LiCH$_2$Cl > LiCH$_2$Br > LiCH$_2$I.[17] In general, the carbenoid character for LiCH$_2$X was found to be more pronounced with groups of the second row of the periodic table (X = NH$_2$, OH, F) than with their heavier congeners (X = PH$_2$, SH, Cl). This was referred to the decreasing electronegativity and the increasing anion-stabilizing ability (via polarization and negative hyper-conjugation effects) when going down the group of the periodic table.[18] Until today, Li/F systems are regarded as the "beast" in carbenoid chemistry.

In contrast to ethers α-lithiated amines generally possess no carbenoid character.[19] One exception are aziridines, which undergo α-elimination reactions due to the strain in the three-membered ring.[20] Also lithiated thioethers have shown to undergo MSR elimination reactions, which however strongly depend on the substituent at sulfur. While most thioethers behave like simple organolithium compounds, α-lithiated arylthioethers such as LiC(SAr)$_3$[21] or PhSCH$_2$Li[22] behave like carbenoids.[23] Very recently, Steinborn and coworkers also demonstrated that sulf-oxides may exhibit a carbenoid character.[24]

The substitution pattern

As in the case of simple metal organyls the reactivity and stability of the carbanionic center can crucially be influenced by the substitution pattern. In general, electron-withdrawing groups stabilize the carbenoid and thus decrease their tendency for MX elimination. For example, tribromomethyllithium is more stable than the dibromo compound and can even be prepared from dibromomethyllithium and bromoform.[25] The right choice of the substitution pattern, even allows for the stabilization of the typically highly reactive Li/Cl systems at room temperature. This has first been demonstrated by Le Floch[26] and coworkers in 2007 and confirmed by Gessner,[27] Mézailles[28] and others.[29] Fig. 3 depicts a series of Li/Cl carbenoids and their decomposition temperature. The comparison impressively demonstrates the remarkable impact of the substituents and the tunability of carbenoid stability. For example, while dichloromethyllithium (**3**) is only stable at temperatures below −78 °C,[14] substitution of the carbenoid center by thiophosphoryl moieties produces the room temperature stable system **8**. It is interesting to note, that the thermal stability is not only determined by the stabilization of the carbenoid carbon center but also by the existence or absence of possible decomposition pathways. Hence, due to intra-molecular B–H activation the phosphino borane compound **6** is less stable than the symmetric bis(thiophosphoryl) system **8**.[28a] Besides the introduction of electron-withdrawing substituents the carbenoid carbon center can also be stabilized by a change in hybridization from sp^3 to sp^2. The higher s-character of the C–M bond results in its stabilization and hence in a generally greater stability of vinylic carbenoids.[30] Consequently, the first isolation of a Li/Hal carbenoid has been accomplished by Boche and coworkers with vinyl system **4** (vide infra), which is stable
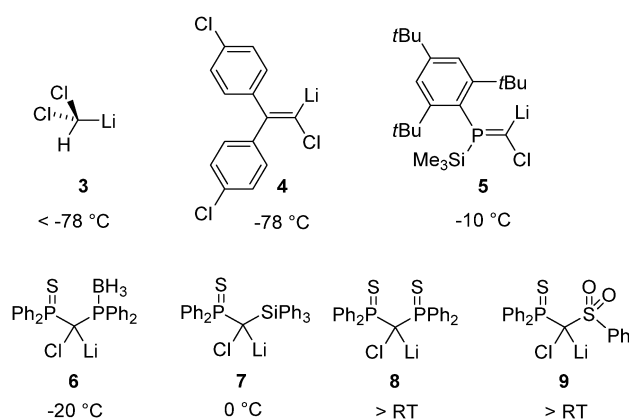

Fig. 3 Examples of isolated Li/Cl carbenoids and their decomposition temperature in solution.

at -78 °C.[11] The phosphaalkene **5** reported by Niecke had long been the most stable Li/Cl system known.[31]

Additional donor bases and metal salts

The decomposition of carbenoids by α-elimination can significantly be controlled by complexation of the metal by donor bases. This coordination can occur in an intramolecular fashion in case of donor-functionalized substituents (*cf.* carbenoids **6–9**) or in an intermolecular fashion when using coordinating solvents or additional Lewis bases. Typically, complexation of the metal by donor bases results in a decreased Lewis acidity of the metal, its increased solubility and presumably in many systems in the disruption of the M–X interaction. This considerably hampers metal salt elimination and thus increases the thermal stability. Although systematic studies on the stability of a given carbenoid in different solvents and/or in the presence of different Lewis bases are rare, solvent effects have early been reported. For example, Köbrich *et al.* noticed in seminal studies on simple lithium carbenoids higher selectivities when reactions were performed in THF relative to those in diethyl ether.[32] They also determined critical ratios of Et_2O/THF, which still gave selective conversion and suggested the so-called Trapp mixture (THF : Et_2O : petrol ether = $4:1:1$) as ideal solvent mixture for the preparation of carbenoids. The employment of strong (often multidentate) N- or O-donor ligands such as TMEDA or PMDETA is also beneficial for the isolation of carbenoids, as has been shown in the case of the Li/Cl systems **3–5** (*vide infra*), and can also affect the stereochemistry of their transformations.[33]

Besides influencing carbenoid stability by complexation of the metal by donor bases, the stability can also be affected by coordination to the nucleofugal group. Salt effects in α-elimination reactions have already been noted in the 1960s,[34] and were later also confirmed for metal halide carbenoids by Villieras and coworkers, who observed higher yields in reactions of bromomethyllithium, $BrCH_2Li$, when adding one equivalent of LiBr.[35] This was confirmed by several groups – particularly Matteson[36] and Pace[37] – highlighting the effectiveness of using the mixed metalating reagent, MeLi·LiBr, for carbenoid formation. The stabilizing effect of metal salt is assumed to origin from co-aggregation of the carbenoid with LiX, which weakens or disrupts the internal M–X interaction within the carbenoid (Fig. 4).[35]

Overall, thermolability due to MX α-elimination is a typical and characteristic property of carbenoids. This property however, is influenced by many factors, which – on the one hand – makes it difficult to predict stabilities under certain reaction conditions. On the other hand, the versatile adjustability of the stability also allows for the fine-tuning and control of reactivity (*vide infra*).
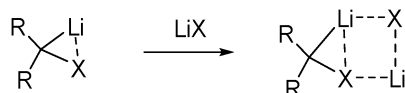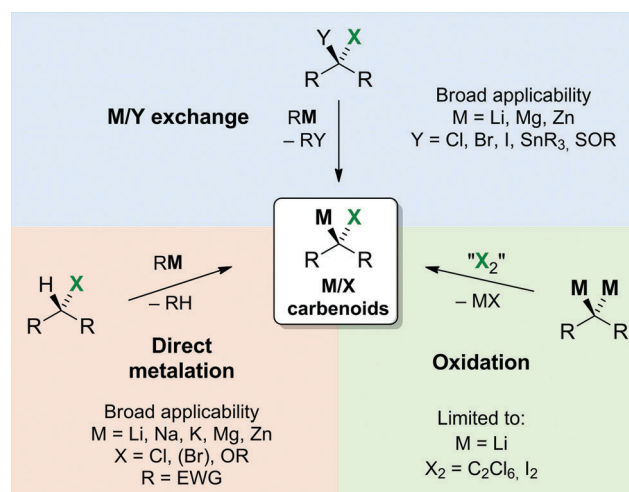
2. Preparation of carbenoids

Despite their thermal sensitivity several routes for the preparation of carbenoids have been developed over the years. Typically carbenoid generation is performed at low reaction temperatures. In most of the cases no isolation of the generally highly sensitive compounds has been attempted. Instead they were usually applied *in situ* shortly after their preparation to prevent decomposition. In most of the cases, the choice of the right reaction conditions (*vide supra*), above all the solvent, temperature, metalation reagent and/or the presence of additional donor bases turned out to be critical for the successful and selective preparation.

The preparation of carbenoids either proceeds *via* introduction of the metal or the leaving group in the last step of the synthesis. Due to the requirement of geminal dimetalated compounds in the latter case, metalation is the common route to carbenoids. In the majority of reports, this includes the two classical pathways *via* deprotonation (direct metalation) or halogen–metal exchange (Scheme 3). Particularly bromine– or iodine–metal exchange reactions are widely used for the generation of lithium carbenoids. On the contrary, only a limited number of halogen–magnesium exchange reactions have been reported.[38] In case of halomethyllithium compounds often the Barbier method is applied for the generation and reaction of the carbenoid.[39] This includes the synthesis of the carbenoid (mostly by Li/I or Li/Br exchange *e.g.* ICH_2Cl + MeLi) already in the presence of the electrophile, which thus ensures immediate reaction of the reactive halomethyllithium species directly after its formation. Although this strategy has successfully been employed for the application of the carbenoid in organic synthesis,[40] limitations have been noticed in cases when formation of the carbenoid is slower than the reaction of the substrate with the alkyllithium reagent.[41]

Besides the classical pathways *via* deprotonation or halogen–metal exchange reactions a number of other strategies to access carbenoid species have been reported, yet most of them only

Fig. 4 Stabilization of lithium carbenoids by lithium halide complexation.

Scheme 3 Preparation methods for carbenoids.

applicable to a limited number of substrates. The most successful routes include further exchange reactions using tin compounds or sulfoxides. Tin/lithium exchange for example has only recently been used by Hammerschmidt to access enantiomerically pure chloromethyllithium.[14d] Sulfoxide/metal exchange was first reported by Satoh and coworkers by means of magnesium carbenoids[42] and later transferred to the lithium compounds.[43] In case of lithium carbenoids the advances in the preparation of dilithiomethanes resulted in the development of an elegant method, namely the mild oxidation of the dilithium salt. This was first demonstrated by Le Floch with the synthesis of a Li/Cl carbenoid using hexachloroethane as oxidation reagent (R = $Ph_2P(S)$ in Scheme 2).[26] Later the analogous iodo compound could be accessed by employment of iodine.[29] Because of the limited number of readily available methandiide precursors this method remains applicable for only a few systems.[27,44]

3. Structures and characterization of carbenoids

NMR-spectroscopy

The unique reactivity of carbenoids, particularly compared to simple metal organyls, early raised the question of their electronic and structural properties. Due to the high reactivity, and thermal lability, early studies were restricted to *in situ* preparation and characterization without isolation or even purification. First informative spectroscopic studies were thus solution NMR experiments, which are mostly connected with the group of Seebach.[45] Detailed studies on different lithium carbenoids showed a distinct deshielding of the carbenoid carbon atom with a down-field shift relative to the protonated analogue of up to $\Delta\delta_C = 280$ ppm in the ^{13}C NMR spectrum. For example, lithation of chloroform to trichloromethyllithium resulted in a down-field shift by $\Delta\delta_C = 65.9$ ppm, lithation of bromoform to tribromomethyllithium in a shift by $\Delta\delta_C = 142.5$ ppm (Table 1).[45b]

This observation contrasts the typical high-field shift for simple organolithium compounds,[46] but compares well with the NMR spectroscopic properties of free carbenes.[47] The ^{13}C NMR shifts and the typically observed deshielding of the carbenoid carbon atom could also be reproduced by IGLO (individual gauge for localized orbitals) calculations. Origin of the deshielding is not the partial charge at the carbon atom – which is often similar to that of the protonated congener – but the energy of the bonding σ(CLi)- and the antibonding σ*(CX) orbitals. The higher the σ(CLi) and the lower the σ*(CX) orbital, the greater the deshielding.

The deshielding of the carbenoid carbon atom was also observed for Li/OR carbenoids, albeit less pronounced than in case of Li/Hal systems. As such, shift changes of only $\Delta\delta_C = 7$–40 ppm have been reported (*cf.* entries 4–6, Table 1).[55] The weaker deshielding for Li/OR compared to Li/Hal carbenoids is well in line with the generally stronger carbenoid character of the halide systems. However, similarly to the stability of carbenoids, the NMR shift changes are also dramatically influenced by the complexation of the metal or the substitution pattern. The room temperature stable Li/Cl carbenoids **8** and **9** for example showed no deshielding, although exhibiting reactions with LiCl elimination. Likewise, disruption of the C–M bond by strongly coordinating donor bases (*e.g.* PMDETA or crown ether) leads to smaller shifts than found for structures with a direct metal carbon linkage.[55] Hence, the deshielding of the carbenoid carbon atom is indicative for the carbenoid character, but no exclusion criterion. Compared to lithium carbenoids, this property is much less pronounce for zinc and magnesium system. Above all the zinc carbenoids often showed no distinct downfield shift relative to their protonated analogue (see entries 9 and 10).[50–54]

Besides the ^{13}C NMR chemical shifts also the $J(^{13}C,^{6}Li)$ coupling constant has found to be indicative for a carbenoid character. Typically a large $^{1}J(^{13}C,^{6}Li)$ value of around 17 Hz is observed due to the higher s-character of the carbenoid carbon

Table 1 Comparison of ^{13}C NMR chemical shifts of different carbenoids relative to their protonated congeners

Entry	Carbenoid	$\delta(^{13}C)$ [ppm]	$\Delta\delta(^{13}C)$ Li/H [ppm]	Ref.
1	LiCH$_2$Cl	57.9	32.3	48
2	LiCHCl$_2$	105.5	50.0	39
3	LiCCl$_3$	145.9	65.9	39
4	Li⌒OPh	74.5	19.7	55
5	Li⌒OC$_6$F$_5$	92.2	29.9	55
6	(CF$_3$-aryl epoxide, Li)	≈ 83.3	≈ 31.3	49
7	Ph$_2$P(S)—C(Cl)(SiPh$_3$)M	M = Li: 37.6 / M = Na: 42.9 / M = K: 42.6	M = Li: −4.7 / M = Na: 0.6 / M = K: 0.3	15
8	iPrMg—C(Bu)(Cl)	68.8	24.8	50
9	L·Zn(CH$_2$Cl)(Cl)	L = DME: 29.6 / L = Bipy: 32.9	L = DME: 4.0 / L = Bipy: 7.3	51 and 52
10	XZnCH$_2$I	X = (BuO)$_2$P(O)O: −23.7 / X = RO $\approx$ −27.0	X = (BuO)$_2$P(O)O: −0.1 / X = RO $\approx$ −3.4	53 and 54

atom compared with simple organolithium reagents, which usually show coupling constants between 8 and 10 Hz.[48] Accordingly, smaller ^1J-coupling constants are found to the other substitutents. For example, lithiation of dichloromethane ($^1J_{CH}$ = 178 Hz) to LiCHCl$_2$ results in a by 68 Hz smaller $^1J_{CH}$ coupling constant.[48]

Computational studies

The molecular structures of carbenoids were first studied by computational methods.[56] Seminal studies by the Schleyer group focused on simple systems such as LiCH$_2$X and LiCHX$_2$.[57] They revealed a preference of a bridged structure such as **I** (Fig. 5) with contacts between lithium and both, the carbon atom and the nucleofugal group X. This bridged structure was found to be favored over a classical structure **II** and carbene donor **III** and acceptor **IV** complexes. Although these calculations only considered monomeric structures and no involvement of solvent molecules, experimental structure elucidations later confirmed the existence of all structural motifs **I–IV** (*vide infra*). The energetically most disfavoured carbene–acceptor complex has so far only been observed with NHCs.[58] Aggregation and Lewis base coordination was later also considered by computational methods, confirming their importance for the structure formation and for mirroring experimental observations.[59] Analogous geometries to those reported for halomethyllithium carbenoids were also observed for vinylcarbenoids, also considering solvent effects.[60] Overall, structure formation of carbenoids is a rather complex subject. Even the metal salt MX formed upon decomposition of the carbenoid can influence the structure formation. However, such mixed aggregates with lithium halides and lithium methoxide have only poorly been studied computationally as well as experimentally.[61]

Besides identifying different structural motifs, the computational studies revealed also the elongation of the C–X bond as characteristic structural feature of carbenoids. This elongation is well in line with the electrophilicity and the deshielding of the carbenoid carbon atom found in the NMR experiments. The extent of the elongation however, strongly depends on the M/X combination and the structural motif formed. This is shown in Fi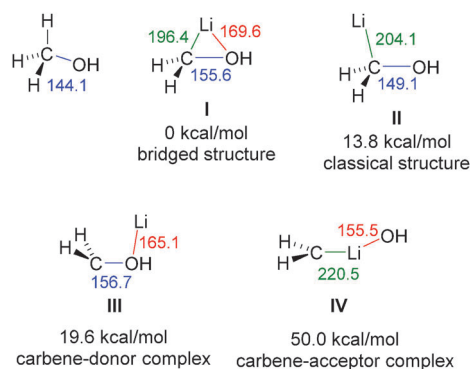g. 5 for the hypothetical carbenoid LiCH$_2$OH, in which the C–O bond elongates by 5–16 ppm relative to methanol depending on the structure. In line with the general reactivities and the carbenoid behaviour, the bond elongation was found to be most pronounced for Li/Hal carbenoids and less significant in the magnesium and zinc compounds.[62] However, no direct correlation between the carbenoid character and the C–X bond elongation exists. There are even systems known, which exhibit no C–X bond shortening, despite showing an ambiphilic nature.[26–29] For example, thioethers generally show a shortening of the C–S bond upon lithiation, although several examples are known that show carbenoid bahaviour.[21,22]

DFT studies were also used to elucidate the electronic structure of carbenoids. Thereby, it was found that carbenoids possess a higher p-character in the C–X bond relative to their protonated congeners owing to the higher s-character in the metal carbon bond. This was first demonstrated by calculations on lithium carbenoids[17] but also confirmed for zinc and magnesium systems.[62] One exception to that rule is the room temperature stable Li/Cl carbenoid **8** (Fig. 3) reported by Le Floch and coworkers.[26] Here, no significantly higher p-character was observed in the C–Cl bond.

X-Ray diffraction analyses

Alkali metals. Due to the high reactivity and sensitivity of most of the carbenoids the first structure elucidations of carbenoids came far after seminal studies on their reactivity and NMR spectroscopic properties. However, owing to the developments in inert gas and low-temperature techniques this limitation could be overcome in the past decades. The first structure of a lithium carbenoid was reported in 1989 by Harder and coworkers with lithiated benzofuran **10** (Fig. 6).[63] The dimeric TMEDA aggregate showed a long C–O bond of 145 pm as well as a bridging motif of the lithium atom. Similar observations were made for the 2-bromo-substituted congener.[64] However, both compounds were found to be stable at room temperature and showed no Li/OR elimination reactions, thus suggesting only a weak carbenoid character. On the contrary, the ethoxyvinyllithium compound **11** featured an elongated C–O bond along with a strongly deshielded carbenoid carbon atom.[65]

Fig. 5   Calculated structures of model carbenoid LiCH$_2$OH and their corresponding energies.
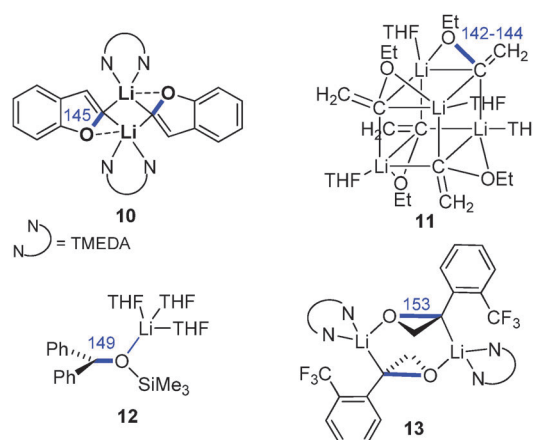

Fig. 6   Isolated and structurally characterized Li/OR-carbenoids.

It formed a tetrameric structure in the solid state with lithium in a bridging position. The first carbene–donor motif was reported by Boche in 1993 with silylether **12**.[66] Despite the missing C–Li contact a downfield shift of the carbenoid carbon atom was observed in the ^{13}C NMR spectrum, thus confirming its carbenoid nature. The tetrameric nature of **12** also exemplifies the structure diversity of carbenoids, analogous to simple organolithium compounds.[67] Here, structure formation is mainly influenced by the substituents at the carbenoid carbon atom (steric as well as electronic properties) as well as intra- and intermolecular donor functions (solvents, Lewis bases). A dimeric structure has also been reported by Capriati, Stalke and coworkers for the oxiranyllithium **13**. Lithiated epoxides have long been considered as fleeting intermediates. They possess a high reactivity and pronounced carbenoid character due to the strain in the three-membered ring. Accordingly, a long C–O bond has also been observed in the molecular structure of **13**.

Owing to their extreme thermal lability, the number of isolated and structurally characterized Li/Cl carbenoids has long been limited to compounds **3–5** (Fig. 7).[11,26,31] This changed in 2007 with the report of the first room temperature stable Li/Cl system **8** by Le Floch and coworkers. Since then a number of compounds with similar stabilities have been isolated and structurally characterized, all making use of strongly stabilizing substituents. Notably, none of the molecular structures reported so far exhibited the bridged structural motif which was predicted by computational studies and also confirmed in case of Li/OR carbenoids (Fig. 6). Most structures showed either a classical structural motif with a C–Li interaction (*cf.* **3–5**) or exclusive coordination of the lithium by additional donor functions in the carbenoid or solvent molecules (*e.g.* **8** and **14/15**). Owing to the high reactivity and sensitivity of Li/Hal carbenoids, sufficient complexation of the metal is necessary to prevent or hamper uncontrolled α-elimination. The molecular structures generally showed the expected lengthening of the C–Cl bond. This is particularly true for the thermally labile systems, while the room temperature

stable compounds showed no or only slight bond length changes. For example the pyridine adduct of LiCHCl$_2$ (**3**) exhibited a C–Cl bond elongation of approx. 10 ppm, whereas the bis(thiophosphoryl) system **8** and its derivatives **6**, **14** and **15** showed no change relative to the protonated congener.[26,28] Interestingly, the iodo congener of **8** was found to be less stable than the chloro compound and decomposed *via* LiI elimination at room temperature.[29] However, the molecular structure also showed no distinct C–I bond elongation, thus demonstrating that the C–X bond lengthening does not necessarily correlate with the carbenoid stability. This is particularly true, when metalation is also accompanied by changes in the hybridization at the carbenoid carbon atom, which – in addition to the structural motif formed – affects bond lengths and angles. The only solvent-separated ion-pair structure of a lithium carbenoid was only recently reported with the crown-ether coordinated compound **7**.[15] Despite the missing C–Li interaction a slight C–Cl bond elongation was observed. Most remarkably, the crown-ether complex showed a by 20 °C higher thermal stability than its THF analogue (decomposition at 0 °C).

Besides the iodo congener of **8** no other Li/I carbenoid has been isolated and structurally characterized until today. Similarly, the structures of Li/Br and Li/F carbenoids are also much less explored than their chloro analogues. The only structure of a Li/Br system has been reported by Niecke and coworkers with the bromo congener of **5**.[68] The analogous Li/F system[69] showed an extraordinary stability even at −50 °C, which thus facilitated its isolation. Here, the stability was not limited by α-elimination of LiF, but by solvent degradation and protonation of the carbenoid. In the molecular structure, the Li/Br and Li/F systems formed monomers analogous to **5** with no contact between the lithium and the halide. This is particularly noteworthy in case of the fluoro compound, because of the usually stronger Li–F interactions. The bromo as well as the fluoro carbenoids showed elongation of the C–X bonds, which was more pronounced in the Li/F (7.0%) than in the Li/Br (4.5%) system. The first sp^3-hybridized Li/F carbenoid was recently reported by Hoge, Mitzel and coworkers.[70] They succeeded in the isolation of the highly reactive F$_3$CCF$_2$Li as its diethyl ether adduct **16**. LiC$_2$F$_5$ is potentially explosive and has to be handled below −60 °C to exclude decomposition reactions.[71] **16** forms a dimeric structure in the solid state, which is dominated by Li–F interactions. Accordingly, the C–F bonds at the carbenoid carbon atom are elongated by 7 and 12 ppm compared to the protonated congener.
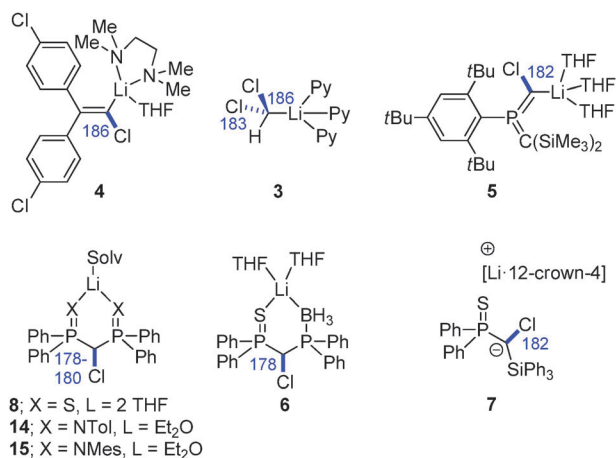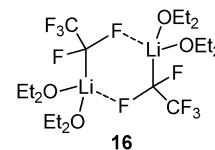

Fig. 7 Isolated and structurally characterized Li/Cl-carbenoids (C–Cl bond lengths are given in blue [pm]).

The first sodium and potassium carbenoids have only recently been reported by our group.[15] Interestingly, Na/Cl carbenoid **17** and its potassium analogue **18** showed higher stabilities than their lithium counterpart (Fig. 8). Both formed carbene–donor complex-like structures in the solid state with a
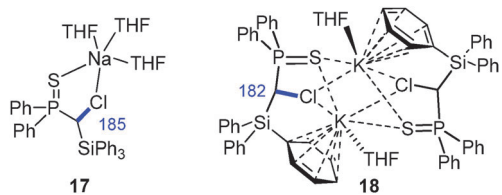
Fig. 8 Isolated sodium and potassium carbenoids (C–Cl bond lengths are given in blue [pm]).
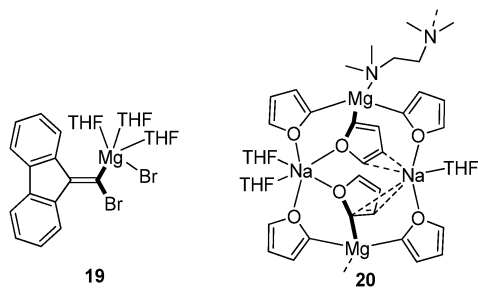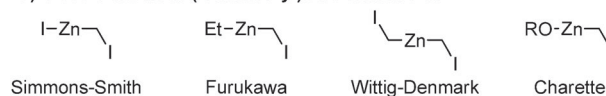

Fig. 9 Isolated and structurally characterized Mg carbenoids.

Fig. 10 Isolated and structurally characterised Mg and Zn carbenoids.

contact between the metal and the chloride, but not C–M interaction. While the sodium compound formed a monomeric complex, **18** exhibited a dimeric structure with additional metal arene interactions. In both structures, the C–Cl bond was found to be slightly elongated (Δd = 3 and 5 pm).

Magnesium and zinc. Inspite of the use of magnesium carbenoids in organic synthesis, Mg/Br carbenoid **19** reported by Boche and coworkers in 1994 remains the only structurally characterized magnesium halide system until today (Fig. 9).[11b] Mulvey and coworkers also succeeded in the isolation of magnesiated furan, which forms a complex polymeric structure such as **20** with TMEDA-linked subunits.[72] While no carbenoid character was discussed for **20**, the fluorene system **19** showed the expected elongation of the C–Br bond by 5.4% as well as a large C–C–Mg angle of 147.3(8)°, being well in line with a substantial vinylidene character of the carbenoid.

Zinc carbenoids possess a considerably higher stability than their lithium congeners (*vide supra*). Accordingly, a number of zinc carbenoids, including simple halomethylzinc systems, have been isolated and the structures of several Zn/Hal, Zn/OR and Zn/SR systems have been reported until today, although the carbenoid character of many systems hasn't been explored.[73] The class of (iodomethyl)zinc carbenoids are – without doubt – the most important and most frequently applied zinc carbenoids. Depending on the substitution pattern at zinc, these systems are typically classified as Simmons–Smith ($IZnCH_2I$),[4] Furukawa ($EtZnCH_2I$),[74] Wittig–Denmark (ICH_2ZnCH_2I)[75] or Charette-type ($ROZnCH_2I$)[54] reagents (Fig. 10a). Until today, nine (iodomethyl)-zinc carbenoids have been characterized by X-ray diffraction analysis,[76] while, no structure of a Furukawa-type reagent has been reported. The first structure elucidation of a zinc carbenoid was accomplished by Denmark and coworkers in 1991 with the bis(iodomethyl)zinc complex **21**.[77] Coordinated by a bis(ether) carbenoid **21** formed a monomeric structure in the solid state.
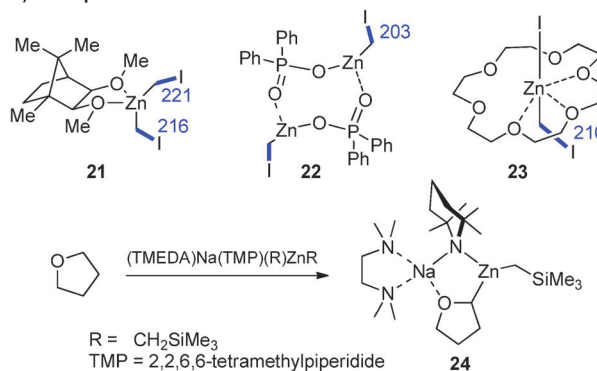
Although no deshielding of the carbenoid carbon atom was observed, the C–I bond lengths were longer than those later determined in other (iodomethyl)zinc compounds such as **22** or **23** (Fig. 10b).[78] The phosphate system **22** and derivatives thereof are particularly interesting, since they were found to be highly stable systems that can be stored for days at −22 °C, while keeping their reactivity in cyclopropanation reactions.[78b] A remarkable Zn/OR system was reported by Mulvey and coworkes with compound **24**, which was obtained by direct metalation of THF using a mixed metal base.[79] While the use of lithium bases typically results in the degradation of THF after its metalation **24** could be isolated at room temperature and was used for further functionalization reactions.

4. Reactivity of carbenoids towards main group element compounds

Boron chemistry

While carbenoids are widely applied in organic synthesis, their reactivity towards main group element compounds and transition metals is much less explored. In the case of main group element chemistry boron compounds are the by far most intensively studied compounds in carbenoid chemistry. One of the earliest examples was reported by Köbrich in the 1960s. He observed the homologation of triphenylborane *via* a 1,2-metalate rearrangement in the intermediate ate-complex **26-Int** when treated with different Li/Cl carbenoids (Scheme 4).[80] However, the real potential of this transformation, particularly in organic synthesis, has only recently been discovered. This was particularly connected with the observation that also boronates[40c] – as well as diboranes and silylboranes[81] – can be used in this reaction providing starting point for further functionalizations. In the past years Aggarwal, Blakemore and others impressively extended this lithiation–borylation reaction, thus establishing stereoselective procedures as well as iterative
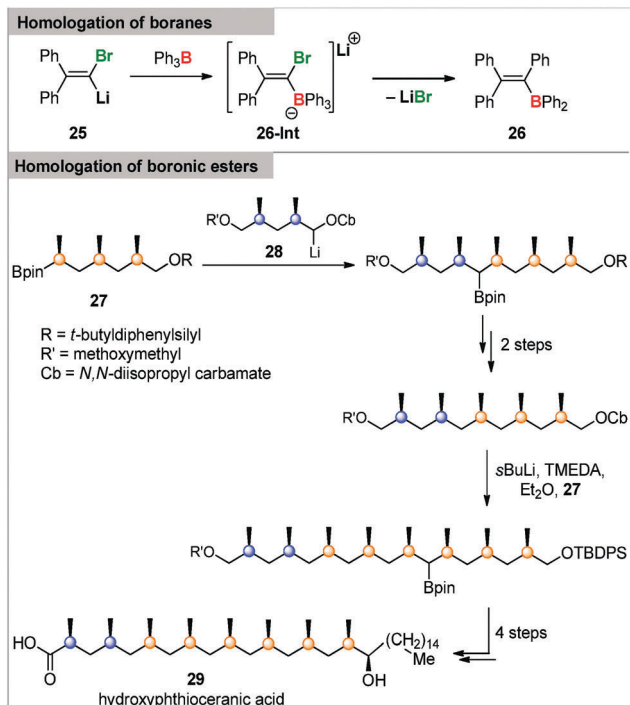
Scheme 4 Triphenylborane homologation and total synthesis of hydroxy-phthioceranic acid **29** *via* a lithiation–borylation–protodeboronation sequence.

pathways to build-up long alkyl chains.[82] Li/Cl carbenoids as well as lithium carbamates and benzoates were employed in this chemistry, whereat the latter showed higher stabilities and have thus more successfully been employed until today.[83,84] The broad utility of the reaction has led to its application in total synthesis.[85] A particularly impressive example reported by Aggarwal and coworkers is shown in Scheme 4. Iterative lithiation–borylation–protodeboronation allowed the coupling of smaller fragments such as **27** and carbenoid **28** to finally build up hydroxyphthioceranic acid **29**.[82a]

Besides supporting the homologation of triarylboranes and boronates carbenoids were also found to insert into the B–H bond of simple BH₃ Lewis base adducts. This was first reported in 2013 by Mézailles, So and coworkers by means of the phosphino-borane functionalized Li/Cl system **6** (Scheme 5).[28a] This carbenoid – contrary to the bis(thiophosphoryl) system **8** – was found to be unstable at room temperature undergoing an intramolecular B–H bond activation at temperatures above −20 °C. The reaction lead to the elimination of LiCl and the formation of the corresponding borane **30** stabilized through intramolecular coordination *via* the thiophosphoryl moiety. This reactivity was extended to an intermolecular activation reaction using carbenoid **8** and BH₃·THF. Interestingly, B–H bond activation with the more reactive Li/Cl silyl substituted system **7** did not result in an analogous borane formation but selectively delivered borate **31**.[86] The reaction was found to require a slight excess of borane and was accompanied by chloroborane formation.

Despite the different products formed the B–H bond activation reactions were found to proceed *via* an analogous step-wise
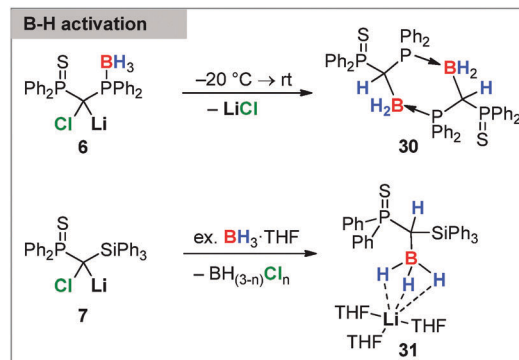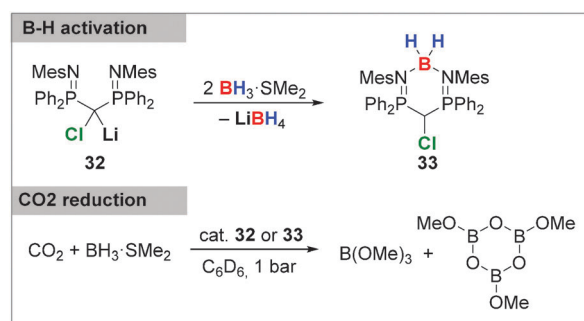
Scheme 5 B–H activation with Li/Cl carbenoids.

mechanism including nucleophilic attack of the carbenoid at the borane followed by H/Cl exchange. The activation barrier of the nucleophilic attack with replacement of the corresponding Lewis base was found to determine the viability of the processes. As such, more stable Lewis base adducts, such as BH₃·NEt₃, were found to be unreactive due to the elevated activation barrier.

The potential of carbenoids in catalytic transformations was only recently demonstrated by Mézailles and coworkers by means of the reduction of CO_2 with BH₃.[28b] Starting point of these studies was the B–H activation with the bis(iminophosphoryl) substituted carbenoid **32**, resulting in the formation of compound **33**, in which a BH_2^+ group is stabilized by the two PN moieties (Scheme 6). Both, the carbenoid **32** as well as the activation product **33** were successfully used as catalyst in the CO_2 reduction to selectively deliver methanol derivatives in up to quantitative yields and TONs of up to 2646.

Phosphorus chemistry

Applications of carbenoids in phosphorus chemistry have only scarcely been explored. Early reports by Märkl focussed on the reactivity towards phosphabenzenes. Thereby, 2,4,6-triphenyl-phosphabenzene was found to react with LiCHCl₂ to benzene derivatives *via* phosphorus elimination.[87] The reaction proceeds at −80 °C *via* the anionic intermediate **34-Int**, which was identified by *in situ* trapping reactions, but quickly "decomposes" to **34** upon warming to room temperature (Scheme 7).

Scheme 6 B–H bond activation with carbenoid **32** and its application in CO_2 reduction.
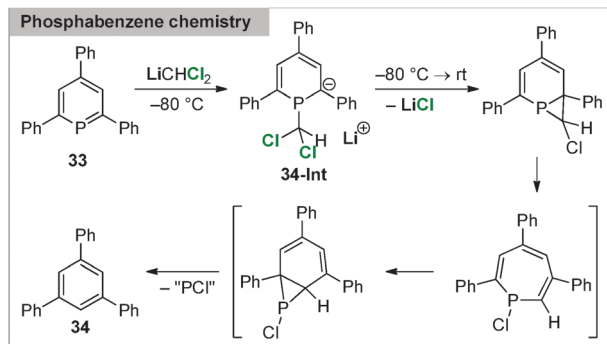
Scheme 7 Reaction of dichloromethyllithium with phosphabenzene **33**.

Scheme 9 Homologation of disulfides and diselenides.

diselenides, thus underlining the synthetic benefit of this reaction.

A surprising reactivity of electronically stabilized carbenoids was only recently discovered in our laboratories. Treatment of the stabilized Li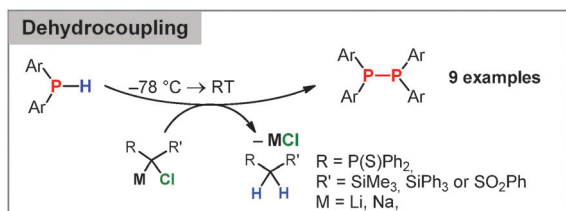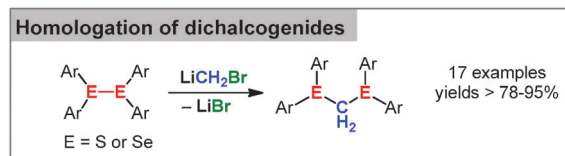/Cl carbenoids **7** and **9** (as well as the potassium and sodium derivatives of **7**) with secondary phosphines did not result in a P–H activation or homologation analogous to boranes, but in the selective formation of diphosphines (Scheme 8).[88] Such a carbenoid-mediated dehydrocoupling reaction has never been observed before with any other substrate. The reaction protocol was transferrable to a series of functionalized phosphines, including chloro-substituents, and provided the diphosphines in high yields. The selectivity of this reaction was found to strongly depend on the stability of the carbenoids. Only the highly stabilized systems gave way to selective dehydrocoupling, while the more labile carbenoids, *e.g.* LiCHCl₂, provided complex product mixtures. This was explained by the mechanism, which first proceeds *via* deprotonation and phosphide formation. This step is prefered for the stabilized carbenoids, whereas LiCl elimination is competing in case of the labile systems, thus showing that electronic manipulation may give rise to new applications in carbenoid chemistry.

Sulfur and selenium chemistry

Group 16 element compounds have only recently been employed in carbenoid chemistry. Pace and coworkers observed that lithium carbenoids effectively insert into the S–S bond of disulfides.[89] Different Li/X combinations were tested with bromo derivatives giving the best results. The protocol allowed the homologation of a series of functionalized disulfides thus providing a valuable tool for the formation of dithioacetales (Scheme 9). Most remarkably, the same reaction conditions were applicable for the insertion of the carbenoid into the Se–Se bond in

# 5. Reactivity of carbenoids towards transition metal compounds

Despite their carbene-like reactivity carbenoids have only scarcely been employed in the synthesis of carbene complexes. This can probably also be referred to the fact that the reaction of carbenoids with transition metal precursors does not necessarily result in the formation of carbene species. For example, the reaction of carbenoids with organo zirconocenes such as **35** results in an insertion of the carbenoid into the Zr–C bond. Protic work-up thus gives way to the corresponding C–C bond formation product (*e.g.* **36**, Scheme 10a). This has first been demonstrated by means of acyclic systems[90] and was subsequently transferred to zirconacycles, resulting in ring expansion reactions.[91] The reactions presumably proceed *via* nucleophilic attack of the carbenoid to an ate-complex, which undergoes 1,2-rearrangement to the final product (Scheme 10b). An analogous reactivity has also been reported with other metals,[90a] yet in a less selective manner than was observed for the zirconium compounds, which also proved to be applicable in total synthesis.[92]

The use of carbenoids as carbene-transfer reagents for the synthesis of carbene complexes has only been demonstrated at a handful of selected examples. One of the first examples focused on the carbocyclic carbene species **39** (Scheme 11), which provides a valuable alternative route to the reaction with a diazo precursor.[93] In 2007 Milstein and coworkers reported the first application of a zinc carbenoid in carbene complex formation. Treatment of [Zn(CH₂I)₂] or [Zn(CHPhCl)₂] with the ruthenium(II) precursor [(PPh₃)₃RuCl₂] delivered the corresponding carbene

Scheme 8 Carbenoid-mediated dehydrocoupling of secondary phosphines.
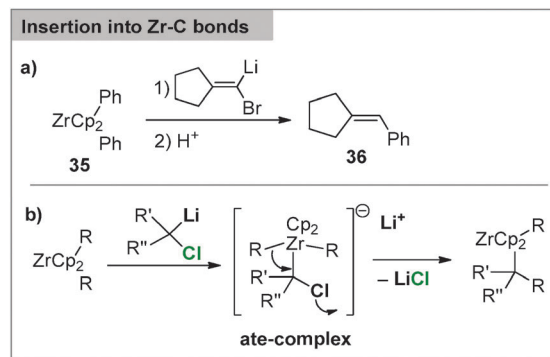
Scheme 10 (a) Reaction of lithium carbenoids with organozirconium reagents and (b) the proposed mechanism.
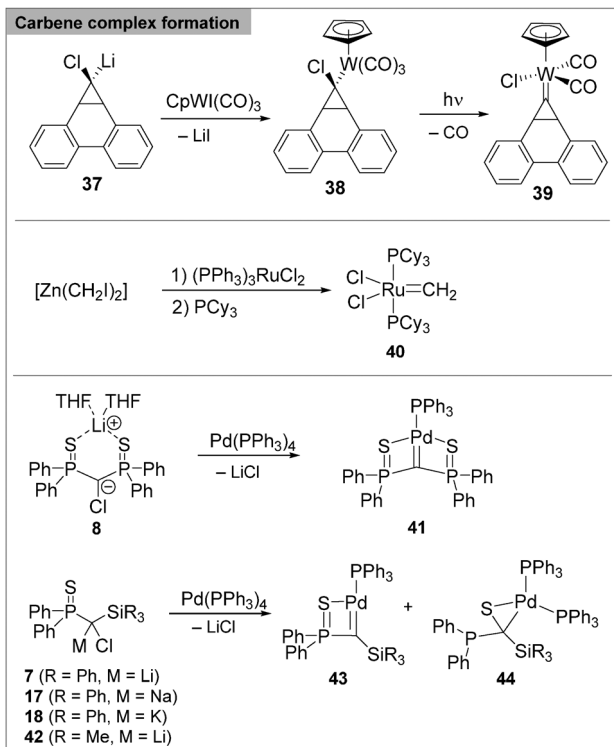
Scheme 11 Carbenoids as carbene transfer reagents for the synthesis of transition metal carbene complexes.

complexes such as **40**, including the Grubbs catalyst.[94] Mechanistically, the authors suggested a concerted pathway similar to the methylene transfer in cyclopropanation reactions. In contrast, a step-wise mechanism was postulated by Le Floch and coworkers for the formation of the nucleophilic palladium carbene complex **41** from the corresponding room-temperature stable Li/Cl carbenoid **8**. The formation of **41** is remarkable, since nucleophilic carbene complexes of late transition metals are still difficult to synthesize *via* alternative routes. However, our group also experienced limitations to this apparently straight-forward carbene transfer reaction. Employment of the more reactive silyl carbenoids **7** and **42** gave mixtures of the carbene species **43** and thioketone complex **44** formed *via* sulfur transfer from phosphorus to carbon. This reaction however, turned out to nicely reflect a stability reactivity relationship of carbenoids. As such, the selectivity of palladium carbene complex formation was found to strongly depend on the stability of the carbenoid.[95] While the $SiMe_3$ substituted Li/Cl carbenoid **42** selectively delivered thioketone complex **44**, introduction of the $SiPh_3$ moiety in **7** – leading to increased carbenoid stabilization through negative hyperconjugation effects – resulted in a 50% conversion to **43**. Most remarkably, replacement of lithium by the heavier congeners, Na and K, provided access to the stable carbenoids **17** and **18**, which allowed selective carbene complex formation. The examples in Scheme 11 demonstrate that carbenoids can serve as valuable transfer reagents for carbene complex formation. The scope of this reactivity is still by far underexplored. Yet, the recent developments suggest that manipulation of the carbenoid stability may present a useful tool

to control the transfer reaction and thus establish carbenoids as viable precursors for carbene complexes.

6. Conclusions

Carbenoid chemistry has quite a long history, beginning with seminal studies on cyclopropanation reactions, which were followed by a myriad of organic transformations. However, the last two decades have experienced a renaissance in their application with the development of transformations beyond classical organic syntheses. On the one hand this can be ascribed to the nowadays convenient handling of these often highly reactive and thermally sensitive species by standard inert gas techniques. On the other hand, fundamental studies have provided a profound understanding of the electronic structure and aggregation of these species which now allows their controlled stabilization and electronic tuning. This has paved the way for the isolation of carbenoids and their stoichiometric applications as well-defined complexes, which facilitated the development of new reactivity patterns also in main group element and transition metal chemistry. As such, coupling reactions as well as carbene transfer reactions and even catalytic transformations are now part of the repertoire of carbenoid reactivity. With many discoveries only made in the last couple of years the revelation of further applications can be expected, which will further underline the unique reactivity and behaviour of metal carbenoids and their role as extraordinary organometallic reagents.

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