ChemComm

FEATURE ARTICLE

View Article Online
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Cite this: *Chem. Commun.*, 2018, **54**, 6692

Homologation chemistry with nucleophilic α-substituted organometallic reagents: chemocontrol, new concepts and (solved) challenges

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Received 28th March 2018,
Accepted 17th May 2018

DOI: 10.1039/c8cc02499e

rsc.li/chemcomm

The transfer of a reactive nucleophilic CH_2X unit into a preformed bond enables the introduction of a fragment featuring the exact and desired degree of functionalization through a single synthetic operation. The instability of metallated α-organometallic species often poses serious questions regarding the practicability of using this conceptually intuitive and simple approach for forming C–C or C–heteroatom bonds. A deep understanding of processes regulating the formation of these nucleophiles is a precious source of inspiration not only for successfully applying theoretically feasible transformations (*i.e.* determining how to employ a given reagent), but also for designing new reactions which ultimately lead to the introduction of molecular complexity *via* short experimental sequences.

Introduction

The introduction of C1 units into organic frameworks – usually referred to as homologation – represents a versatile tool with widespread applications in organic synthesis.[1] Historically, the prototypical example of homologation transformations is represented by the diazomethane-mediated Arndt–Eistert reaction[2] which opened the field for introducing analogous agents displaying a similar nucleophilic reactivity such as Corey–Chaykovsky sulfur ylides[3] and metal carbenoids.[4] The particular properties featured by the latter class of reagents make them unique entities in the synthetic panorama, *in primis* for their constitutive ambiphilicity enabling them to manifest a nucleophilic or electrophilic behaviour, depending on the reaction conditions.[4,5] Two main parameters are considered the *domini* governing such reactivity-switching equilibrium: (1) the nature of the metal and, (2) the temperature. Nowadays, it is well established that carbenoids of truly electron-positive metals (*e.g.* Li) usually behave as nucleophiles,[5a] while less-positive ones (Zn) show a

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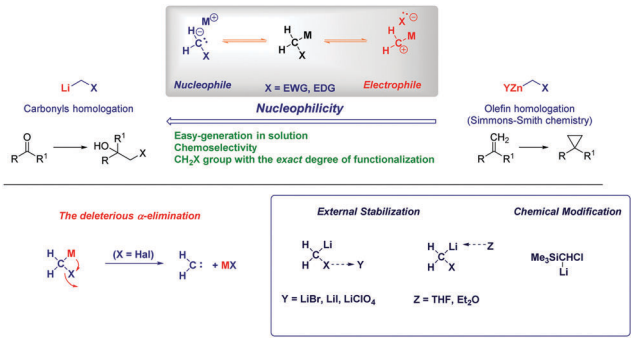
predominant electrophilic reactivity.[6] This is evidently a property arising from the fact that the carbon atom of a carbenoid is concomitantly linked to the metal and to the (usually) electronnegative group, *e.g.* halogen. In fact, the Achilles heel of carbenoids is the limited stability, the result of α-elimination triggered by the internal coordination of the metal with the halogen, finally leading to a free carbene and a metal halide.[4,7] As a result, the chemistry of carbenoids is somewhat conditioned by this intrinsic limitation and, in this context, the proper management of carbenoid preparation and stabilization becomes crucial for their synthetic exploitation.[8] Studies conducted by pioneers of the field (Villieiras and Barluenga)[9] revealed the beneficial activity of lithium halides and ethereal solvents in disrupting the internal coordination responsible for the undesired α-elimination (Scheme 1). The chemical modification of the halocarbenoid structure through the introduction of a stabilizing silicon-containing group is an equally effective solution as reported by Magnus, though an additional silicon-removal step should be considered.[10]



Scheme 1 General features of carbenoids.

Thus, it becomes evident that the preparation of these unstable species requires carefully controlled techniques and, with the judicious – but simple – selection of the methodologies, chemocontrolled strategies can be designed.

In this feature article, we will critically analyze selected examples from our own and others' research dealing with the modulation of carbenoidic reactivity by tuning mainly the reactive species formation event (*i.e.* how the preparation of the reagent influences the overall reactivity). In agreement with classical methods for preparing organometallic species, the following strategies are usually employed: (a) metal-halide exchange, (b) metal-proton exchange, (c) metal-sulfinyl exchange, and (d) tin-metal exchange.[11] Considering that lithium and magnesium halocarbenoids (although at a lesser extent)

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present nucleophilic attitude, our attention will be limited to these species.

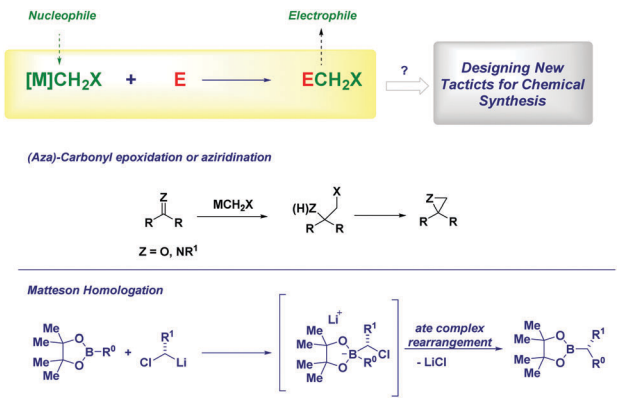
Vistas and potential in homologation chemistry with nucleophilic carbenoids

The versatility of lithium carbenoids as nucleophilic species can be advantageously employed for introducing a CH_2 group as a nucleophile (*i.e.* $LiCH_2X$) and, then, it reacts as an electrophile at a later stage of the synthetic sequence. Classical examples of this synthetic philosophy are the epoxidation[9c,12] or aziridination[13] of carbonyls and imines or the Matteson homologation of boronic esters[14] with (eventually) chiral carbenoids.[15] In the former case, the intermediate alkoxide (or amide) attacks the electrophilic halomethyl group, thus forming a three-membered cycle. On the other hand, the ate complex rearrangement causes the expulsion of the halide furnishing the homologated structure.[14a] Ultimately, there is a possibility to open the door for further chemistry on the now electrophilic CH_2X group. Accordingly, the design of new processes relies on: (1) generation of the nucleophilic reagent; (2) a deep understanding of mechanistic aspects which could play a determinant role (Scheme 2).

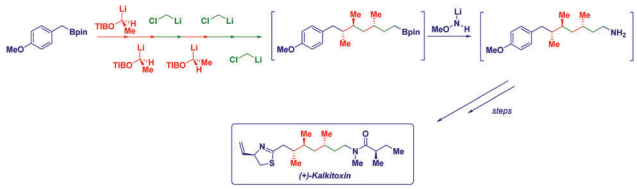
Lithiation–borylation has emerged as a powerful tool to control the stereochemistry along a carbon chain and to build up multiple stereogenic centers with high stereocontrol,[16] by using – *inter alia* – lithium carbenoids, lithium carbamates and benzoates.[17] Aggarwal and coworkers carried out a short synthesis of (+)-kalkitoxin and (+)-hydroxyphthioceranic acid by the iterative homologation of boronic esters, alternating chiral lithiated benzoate esters and chloromethyllithium, to insert the required methylene units (Scheme 3).[18]

Notably, purification between several homologations could be avoided, thus considerably improving the overall sequence. In the case of (+)-kalkitoxin, six iterative homologations were performed on the commercially available boronic ester to build up the carbon array before the C–B linkage was transformed into the required C–N bond without purification of the intermediates.

Thus, the assembly line strategy enabled the chain extension with full stereocontrol and, the simple increase of the temperature was found to be sufficient for decomposing the carbenoid



Scheme 2 Exploiting the introduction of a CH_2X fragment: general considerations.



Scheme 3 Aggarwal's assembly-line synthesis of (+)-kalkitoxin.

in excess and, as a consequence, allowing the next homologation step to be performed directly.[19]

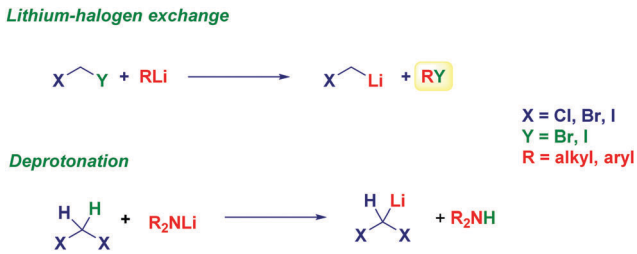
Reagents of $LiCH_2X$ and $LiCHX_2$ type: preparation

The metal halogen exchange – formally an oxidative addition – run on a given dihalomethane precursor is undoubtedly the most common method for preparing halocarbenoids for synthetic purposes.[8a] In line with the general theory that heavier halogens are exchanged first, iodo-containing derivatives represent excellent manifolds for generating carbenoids. Accordingly, an alkyl or aryl-lithium reagent promotes the exchange on $XCH_2I(Br)$ furnishing the corresponding Li carbenoid. Because of the acidity of dihalomethanes conferred by the electron-withdrawing halogens, the proton abstraction is easily achieved with a lithium amide base such as LDA and LTMP (Scheme 4).[20]

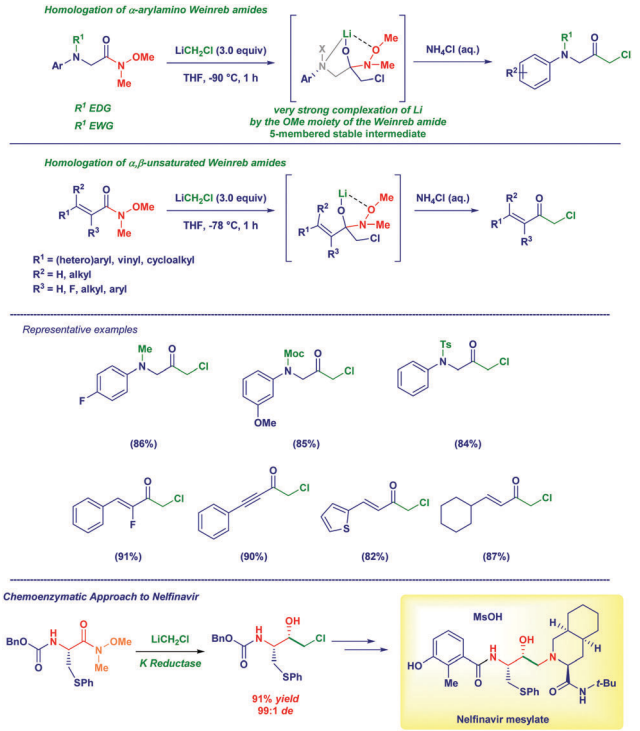
Lithium halocarbenoids are regarded as extremely labile entities because of the aforementioned α-eliminationthey suffer: however, operating in batch mode by adopting Barbier-type conditions makes it possible to efficiently form these reagents and, therefore to react them with the appropriate electrophile.[8] It should be observed that the extremely rapid halogen-lithium exchange is so fast that no concomitant attack of the nucleophilic organolithium reagent to the electrophile already present in the reaction medium takes place. Indeed, as suggested by Matteson, the generation of a carbenoid in the presence of LiBr further decreases the occurrence of such undesired events.[21]

Carbon-electrophilic partners for $LiCH_2X$ reagents

Weinreb amides. Weinreb amides are considered excellent acylating manifolds for organometallics including carbenoids.[22] The coordinating capability of the constitutively present OMe group provides an excellent stabilizing factor to the putative 5-membered tetrahedral intermediate which cannot be ensured by using esters. In fact, the success of homologations on the



Scheme 4 Preparation of monohalolithium and dihalolithium carbenoids *via* halogen-Li and proton-Li exchange.



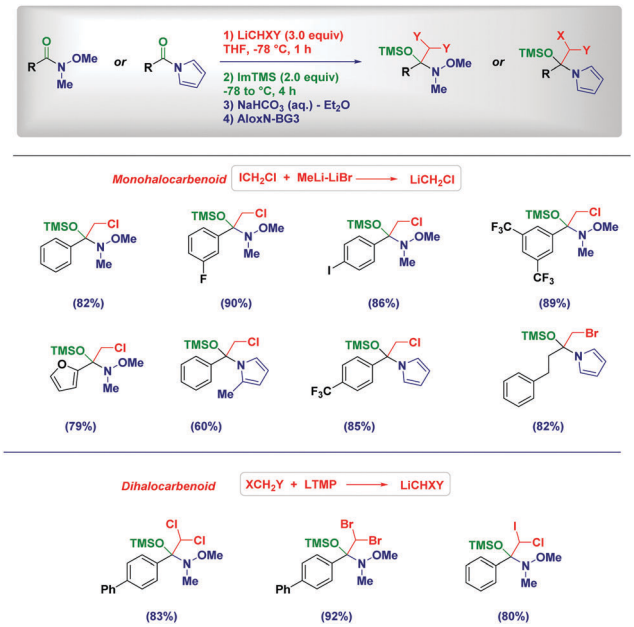
Scheme 5 Versatility of Weinreb amides for preparing α-haloketones.

latter class of electrophiles may depend on the presence of elements able to guarantee the sufficient stability to the intermediate.

The homologation of Weinreb amides with carbenoids emerged as a versatile tool for preparing different α-haloketones (α-amino and α,β-unsaturated) under controlled conditions.[23] In particular, no undesired phenomena such as the overaddition of the organometallic reagent (observed with esters), Michael-type processes or, the reaction with sensitive functionalities decorating the structure could be noticed. We employed this technique for preparing an important scaffold for the synthesis of the HIV inhibitor Nelfinavir (Scheme 5).[24]

The excellent stability of tetrahedral intermediates formed upon the addition of lithium (di)halocarbenoids to Weinreb amides is showcased by their isolation as *O*-TMS protected hemiaminals (Scheme 6).[25] As documented by our group in 2017, such labile species constitute the first example of isolated and fully characterized intermediates from Weinreb amides and organolithiums known since their introduction in 1981.[22a] Again, the process preserves the chemoselectivity in the presence of different other reactive functionalities, including a potentially exchangeable aromatic iodide. Analogous intermediates formed from *N*-acylpyrroles[26] could be isolated under identical conditions, even in the presence of sterically demanding moieties.[25] Crucial factors enabling the isolation of these intermediates where the use of TMS-imidazole (Im-TMS) as the silylating agent and deactivated neutral alumina (Brockmann grade 3) for chromatography.

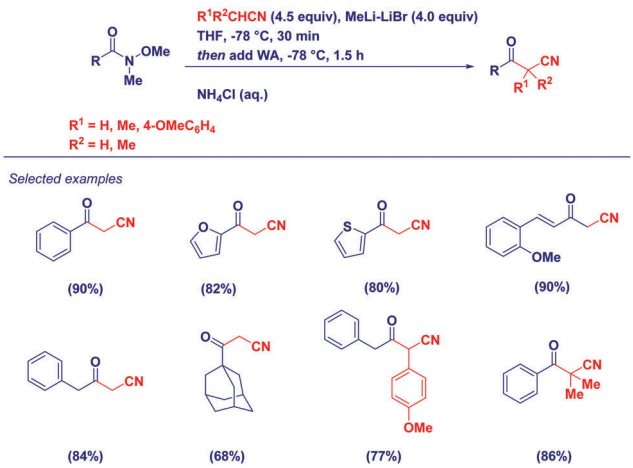
Given the nucleophilicity of nitrile-type carbanions[27] and the unique acylating properties of Weinreb amides, we have



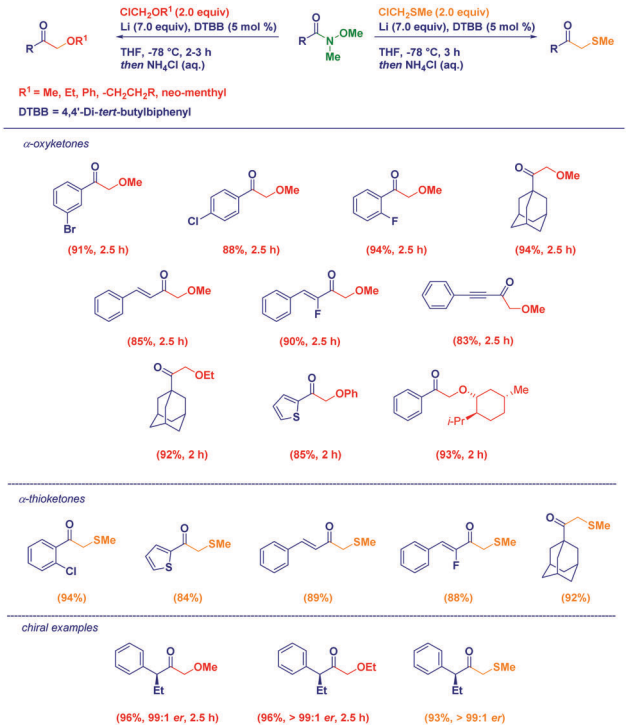
Scheme 6 Trapping of tetrahedral intermediates formed from Weinreb amides and (di)halocarbenoids.

developed a simple, efficient, protocol for the synthesis of variously functionalized α-cyanoketones (Scheme 7).[28] Key features of the method are: (a) uniformly high yields, employing both different substituted acetonitriles and/or Weinreb amides; (b) easy work-up procedure when reactions are carried out in the presence of an excess of $LiCH_2CN$; (c) possibility to access multi-substituted cyanomethylketones by simply selecting the proper R^1R^2CLiCN carbanion; and (d) excellent chemoselectivity observed in particular systems such as α,β-unsaturated Weinreb amides.

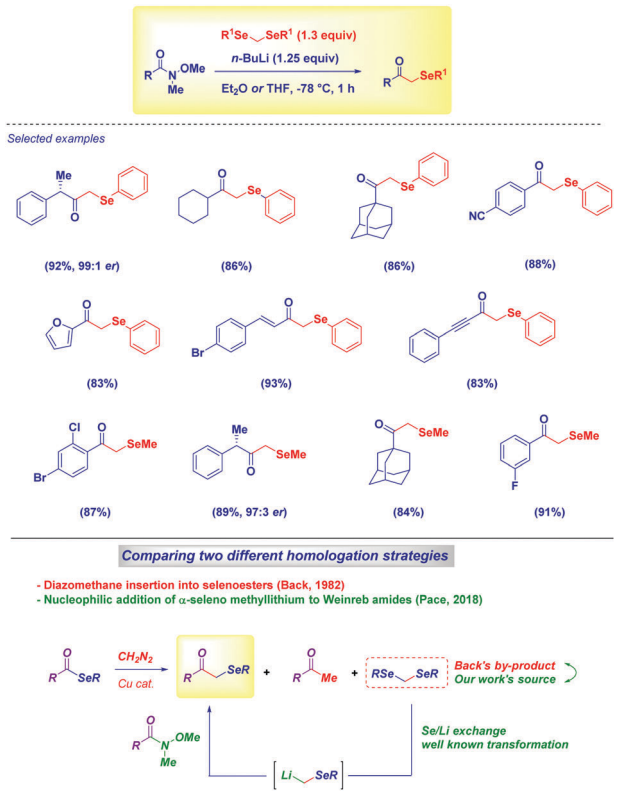
The Weinreb amides-based approach is also amenable for the preparation of α-oxyketones, through the generation of nucleophiles of type $LiCH_2OR$[29] *via* Yus' arene catalyzed reductive lithiation of chloromethyl ethers.[30] Broad scope in terms of



Scheme 7 Synthesis of α-cyanoketones from Weinreb amides and lithiated acetonitriles.



Scheme 8 Synthesis of α-oxo- and α-thio methylketones from Weinreb amides and organolithiums generated *via* reductive lithiation.



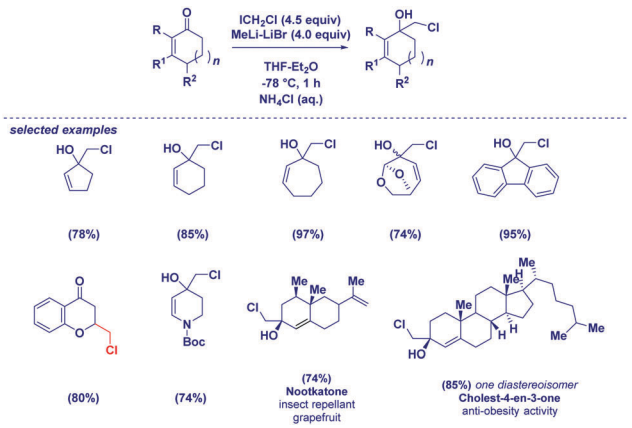
Scheme 9 Synthesis of α-seleno methylketones from Weinreb amides using diselenoacetals as precursors.

acylating agents and carbanions used was observed without any detrimental effect displayed by electronic and steric factors. Despite the basic conditions, the stereochemical information could be fully transferred from the Weinreb amide or from a chiral α-alkoxyorganolithium (Scheme 8). Similarly, the proper generation of α-thiomethyllithium reagents *via* reductive lithiation or deprotonation conditions (for systems of LiCHRAr type) followed by the reaction with variously functionalized Weinreb amides represents an excellent method to access β-oxo thioethers.[31] The procedure, adaptable to the case of both alkyl- or aryl-thiomethyllithiums, combines the conceptual simplicity and versatility of the addition of organometallics to Weinreb amides with the possibility to fully preserve the optical information contained in the starting materials.

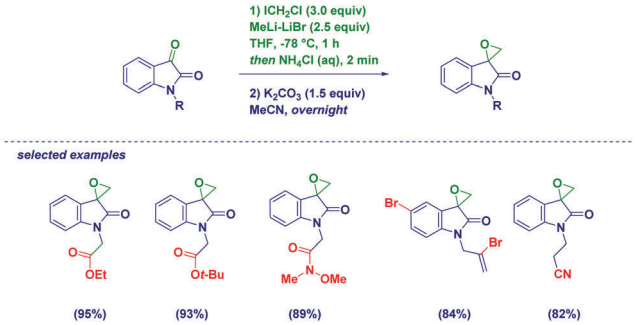
These tactics represent a practical and valuable solution for access to α-substituted ketones which can be problematic when direct nucleophilic substitutions on α-haloketones[32] or enolate trapping methods with the corresponding electrophiles are attempted.[33]

Very recently, our group demonstrated the feasibility of such an approach for preparing challenging α-aryl- and α-alkyl-selenomethyl ketones under full chemocontrol from Weinreb amides and diselenoacetals (Scheme 9).[34] The straightforward lithium/selenium exchange these compounds undergo represents an excellent entry to selenomethyllithium reagents ($LiCH_2SeR$), which then are trapped with several Weinreb amides to give – upon hydrolysis – the desired compounds. Remarkably, previous work by Back in the 1980s on the Cu-catalyzed diazomethane homologation of selenoesters[35] (to α-selenoketones) pointed out that diselenoacetals were by-products of the reaction. In our tactic – just cognizant of the easiness of the Li/Se exchange[36] – these materials were identified as valuable sources for the corresponding carbanions.

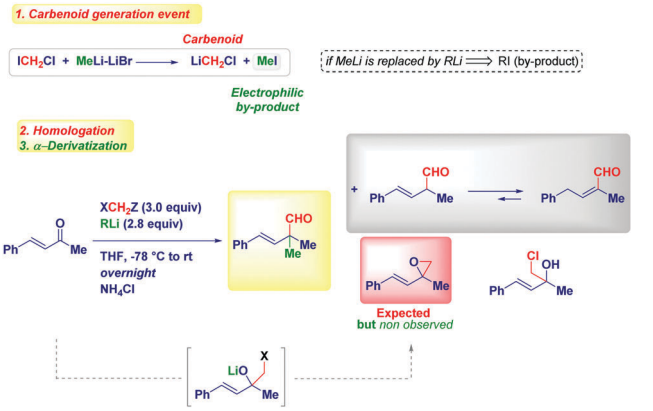
α,β-Unsaturated-type ketones: expected outcomes. α,β-Unsaturated cyclic ketones undergo a highly chemoselective addition of chloromethyllithium to give quaternary allylic halohydrins (Scheme 10).[37] The process is uniformly high-yielding and adaptable to ketones of different ring-sizes, as well as, to more complex materials. The 1,2-chemoselectivity of the method



Scheme 10 Chemoselective addition of lithium carbenoids to α,β-unsaturated cyclic ketones.



Scheme 11 Preparation of spiro-epoxyoxindoles from isatins and $LiCH_2X$ reagents.



Scheme 12 Surprising discovery of the formation of full-quaternary α-aldehydes instead of vinyl epoxides.

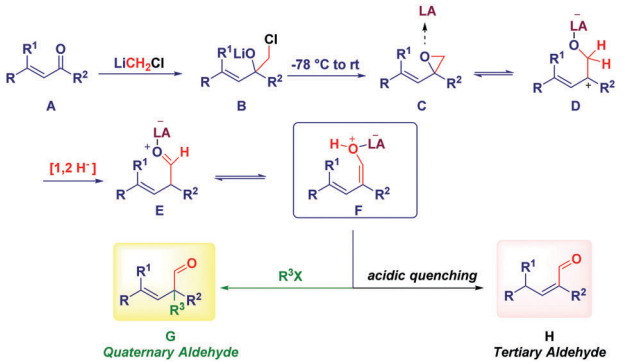
is significant considering that similar carbenoids could add in a 1,4-fashion as documented by Phillips[38] and Hernández-Galán.[39] It is conceivable that LiBr may not only exert a stabilizing effect on the carbenoid, but also display a mild Lewis acid activity enhancing the electrophilicity of the carbonyl-carbon.[40] Notably, mesomeric effects can govern the chemoselectivity in particular instances, as observed in the case of chromone (formal 1,4-addition).

Isatins are particularly reactive unsaturated carbonyl compounds, featuring an extremely high electrophilic C3 carbon due to the constitutive presence of the electron-withdrawing lactam.[41] Halocarbenoids can be added to C3 with precise chemoselectivity, even in the presence of functionalities which are known to be placeholders for halomethylating reagents (Scheme 11).[42] Notoriously, organometallic sensitive groups such as Weinreb amides, esters, nitriles, alkenes and alkynes do not alter the chemoselectivity of the process. Pleasingly, also the incorporation of bromine on aromatic or olefinic residues is tolerated, as well as an acidic N–H lactam proton. This is particularly relevant and indicative of the excellent electrophilicity of the C3 of isatins compared to other electrophiles. In fact, Kunisuke,[43] Hilpert[44] and our own group[23a] evidenced the difficulties of homologating esters or Weinreb amides in systems presenting free (*i.e.* unprotected) amidic or aminic NH groups. The carbenoid addition, ensued by the rapid base-triggered ring-closure of the so-formed halohydrin, enables valuable spiro-epoxyoxindoles to finally be produced through an extremely simple and reliable procedure. It should be observed that the key halohydrin-alkoxide required for cyclization was previously prepared by Zhu *via* a more complex intramolecular Friedel–Crafts strategy.[45] However, considering also the effectiveness of Corey–Chaykovsky strategies recently presented by Nair[46] and Hajra,[47] it appears preferable to prepare unsubstituted spiro-epoxyoxindoles through a homologation tactic.

Unexpected adventures: the merging of three chemical concepts. In the course of further investigations aimed at directly accessing vinyl epoxides[48] *via* the thermal-mediated ring closure of halohydrin alkoxides – a well established technique for the epoxidation of saturated ketones[12a,b] – we were quite surprised in observing the exclusive formation of an aldehyde featuring full substitution at the α-position (Scheme 12).[49]

This unexpected outcome spurred us to critically analyse the transformation. The presence of an additional carbon (*i.e.* the aldehydic one) was diagnostic of the homologation process, while the additional α-methyl group could not be rationalized at first sight. The carbenoid formation event has a deep influence on the reaction mechanism, as evidenced by properly selecting the reaction conditions. In fact, by considering the carbenoid generation equation *via* lithium/halogen exchange run with MeLi–LiBr, the formation of an electrophilic by-product (MeI) seems plausible and thus, it can indicate the origin of the α-methyl group in the final product. Simply by replacing MeLi–LiBr with *n*-BuLi, PhLi or $TMSCH_2Li$, we observed the formation of a homologated α,β-unsaturated aldehyde showing no quaternarization at the α-position. Should the hypothesized carbenoid formation event be the key to control the process, the less electrophilic by-products (compared to MeI formed in the presence of MeLi–LiBr) obtained with these organolithiums – *n*-BuI, PhI or $TMSCH_2I$ – would not be able to promote the α-functionalization, in agreement with the experimental result. A similar reactivity was deduced by generating $LiCH_2Cl$ *via* Sn/Li exchange. Moreover, two additional parameters were considered fundamental for the transformation: (a) the presence of LiBr as a mild Lewis acid and, (b) the increase of temperature from −78 °C to room temperature. Taken together these three aspects (organolithium employed, the presence of LiBr, temperature increasing), it is conceivable assuming a mechanism constituted by three-different separation processes: (1) $LiCH_2X$-mediated homologation followed by ring-closure to an epoxide; (2) LiBr-mediated Meinwald-type rearrangement of the epoxide into an aldehyde[50] and, (3) electrophilic functionalization of a putative enolate. Notably, the formation of this enolate *via* 1,2-hydride shift[51] on the allylic carbocation **D**, is in agreement with the impossibility to observe such transformation in saturated ketones, thus identifying α,β-alkenyl type carbonyls as privileged substrates. As a consequence, the enolate-intermediate **F** is amenable for further treatment with electrophilic species, finally leading to α-quaternary aldehydes or homologated α,β-unsaturated aldehydes (*via* tautomerization) by simply selecting the quenching reagent (alkyl halide or acid) (Scheme 13).

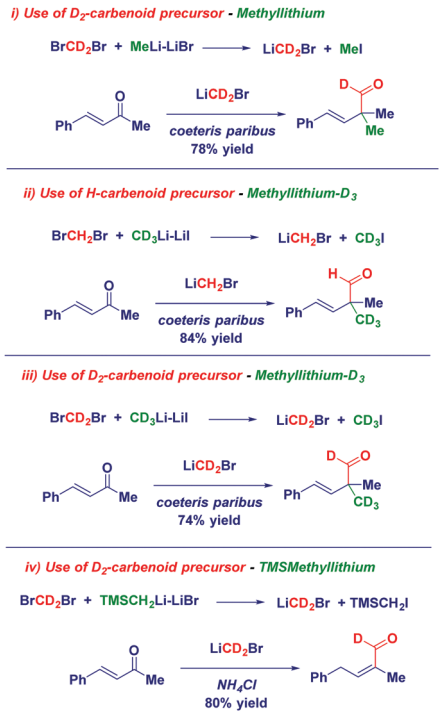
The use of labelled carbenoids and/or labelled methyl iodide provided convincing evidence for the hypothesized enolate-type



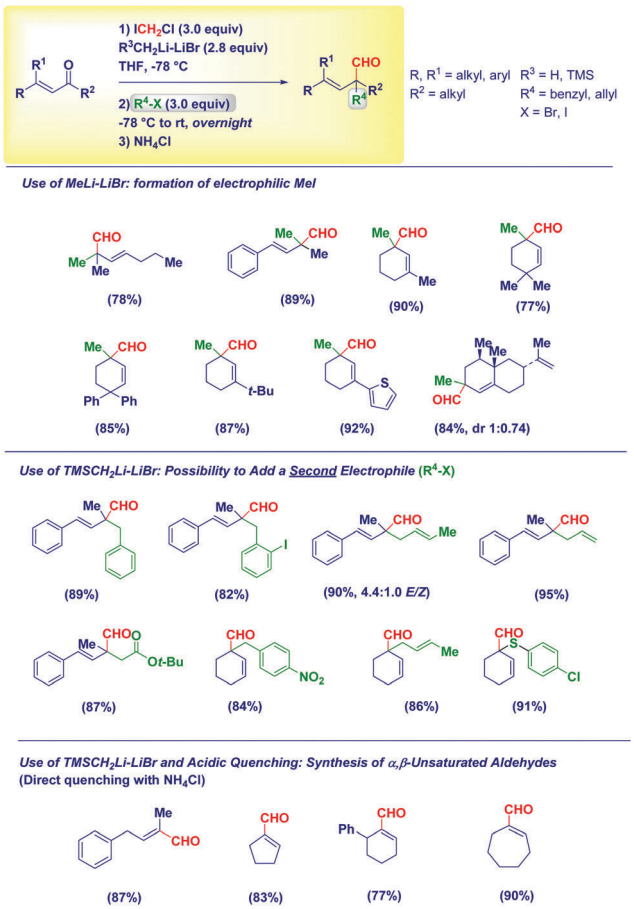
Scheme 13 Plausible rational for the transformation.

mechanism: (i) the use of deuterated carbenoid $LiCD_2Br$ generated from CD_2Br_2 and MeLi–LiBr afforded the aldehyde presenting a α-CH_3 group and a deuterated carbonyl. (ii) The employment of $CD_3Li{\cdot}LiI$ and CH_2Br_2 – which evidently forms $LiCH_2Br$ – gave the *H*-aldehyde featuring the CD_3 group at the α-position. (iii) Homologation with $LiCD_2Br$ – formed from CD_2Br_2 and $CD_3Li{\cdot}LiI$ – yielded the aldehyde showing deuteration at both sites: the aldehyde and the α-position. (iv) Homologating with $LiCD_2Br$ generated with $TMSCH_2Li$ and quenching with an acid, delivered the deuterated α,β-unsaturated aldehyde (Scheme 14). Thus, it appeared demonstrated that the whole reactivity is determined by the general equation for forming the nucleophilic carbenoid.

Based on these mechanistic indications, we designed a direct and finely tuned transformation by simply selecting the carbenoid precursor, the organolithium and the electrophilic



Scheme 14 Labelled experiments supporting the mechanism.



Scheme 15 Scope of the all-carbon quaternary and tertiary α-functionalized homoallyl-type aldehydes.

trapping agent. For example, generating $LiCH_2Cl$ from ICH_2Cl and MeLi–LiBr allowed the preparation of a series of cyclic and acyclic α-methyl aldehydes, including derivatives of natural products. On the other hand, $TMSCH_2Li$–LiBr is the reagent of choice for introducing at the α-position a residue from a different electrophile subsequently added to the reaction mixture (Scheme 15). Reactive alkyl-type halides (*i.e.* benzyl, allyl, crotyl and propargyl) are excellent partners for the transformation and, the concomitant presence of sensitive groups such as exchangeable halides or esters does not affect the chemoselectivity. Although a heteroatom electrophile such as a disulfide can be used for the trapping of the enolate, unfortunately no reactivity was observed with acyl-type partners (carbonyls, amides, isocyanates and carboxylic derivatives). In the absence of an external electrophile, the simple acidic quenching of the enolate results in the formation of α,β-unsaturated aldehydes through the spontaneous tautomerization of the corresponding (less stable) β,γ-unsaturated analogues. Thus, our method introducing the concept of synthetic equivalence between a vinyl oxirane and a β,γ-unsaturated aldehyde, complements previously available tactics for accessing homoallylic-type aldehydes such as the α-allylation of aldehydes *via* transition metal-catalyzed chemistry[52] or *via* an aldehyde enolate approach.[53] It should be mentioned that these strategies, based on the

formal allylation of a pre-existing aldehyde motif, could display full stereocontrol under careful selection of the conditions. In this context, a nice and elegant selective fragmentation of diastereomerically pure and enantioenriched cyclopropanols was introduced by Marek for accessing *n*-butenals with all-carbon quaternary centers.[54]

Homologation of heterocumulenes. The amide bond is the most ubiquitous chemical functionality in nature, and thus its formation ranks among the hottest challenges in modern organic synthesis.[55] In the 1920s, Gilman introduced iso-(thio)cyanates as valuable reagents for titrating organometallic reagents (RLi and RMgX):[56] the process entailed the acylation of these carbanions resulting in the formation of (thio)amides. Surprisingly, the high efficiency of this conceptually intuitive access to the amide-type linkage was not thoroughly recognized[57] until Bode reported in 2012 a straightforward synthesis of sterically hindered amides from Grignard reagents and isocyanates.[58] Nowadays, they are regarded as privileged starting materials as in metal-catalyzed amidations as elegantly introduced by Martin in 2016.[59] The following factors account for the excellent performance of heterocumulenes in acylation processes: (a) the high electrophilicity of the carbon; (b) the practically negligible deleterious effect (electronic and steric) displayed by the substituent on the nitrogen.[60]

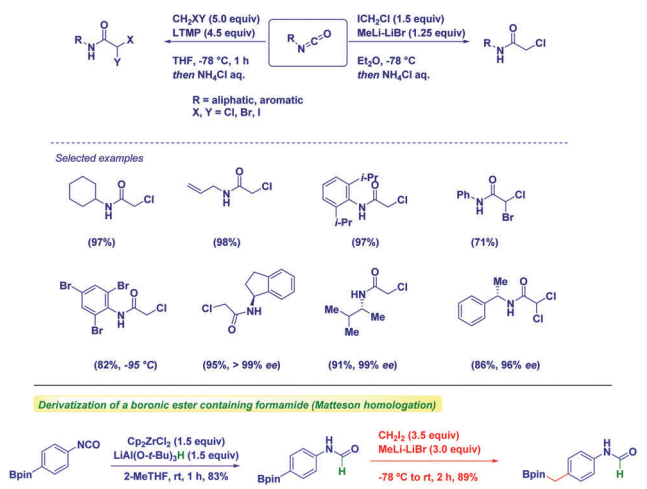
Our group exploited this tactic for the chemoselective preparation of α-haloacetamides through the addition of halocarbenoids to isocyanates (Scheme 16).[61] The protocol features a robust scope, as observed in the case of both aromatic and aliphatic isocyanates. As underlined above, common problematic elements limiting the synthesis of sterically hindered amides *via* classical strategies – *e.g.* the condensation of an amine and a carboxylic derivative – are practically suppressed by using such an approach. Some additional points merit mention: (1) chemoselectivity is still preserved in the case of bromine-containing aryl nuclei by just reducing temperature; (2) enantiopure isocyanates undergo the transformation under full retentive conditions; (3) no concomitant Simmons–Smith type cyclopropanations could be observed in the presence of an olefinic functionality; (4) uniformly high yields demonstrate the robustness of the methodology. The methodology could also be extended to the synthesis of α,α-dihaloamides, which is a demanding task because of the chemoselective difficulties associated with the use of halogenation procedures. The generation of dihalolithium carbenoids (LiCHXY) through the deprotonation of a dihalomethane with a lithium amide base under Barbier conditions in the presence of isocyanate gives the expected compounds in high yields and chiral integrity.[20] We found LTMP as the optimal base for selectively generating dihalocarbenoids.

Moreover, we employed the hydride-transfer *via* nucleophilic addition to isocyanates en route to formamides.[62] The Schwartz reagent proved to be the optimal H^- source in terms of chemoselectivity. In fact, this long-waiting transformation was previously limited by the full reduction of isocyanates to *N*-methyl amines.[63] Moreover, full chemocontrol emerged in the Matteson homologation of a boronic ester featuring a formamide unit, thus indicating how selecting the order of the transformation is critical for the target-oriented synthesis.

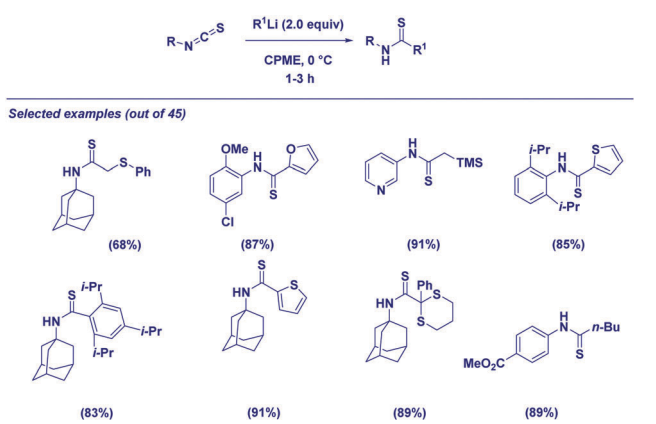
Intriguingly, attempts to halomethylate the corresponding isothiocyanates for preparing α-halothioamides were unsuccessful presumably because of the instability of these species, as indicated by the few reports available on this class.[64]

However, it spurred us to deeply investigate the reactivity of isothiocyanates, bearing in mind that accessing thioamides through such an approach would have allowed the severe limitations related to the synthesis of these building blocks (*e.g.* harsh conditions, long reaction times and the use of non-pleasant thionating agents) to be overcome.[65] The procedure is applicable for a set of different combinations of isothiocyanates and α-substituted organolithiums giving thioamides in excellent yields (Scheme 17). We were delighted in applying the protocol to the straightforward synthesis of complex thioamides including highly sterically demanding structures. It is important to note that the transmetallation of a lithium carbanion to a Gilman reagent (R_2CuLi)[66] enables the chemoselective addition exclusively at the isothiocyanate moiety, thus leaving the ester group untouched.

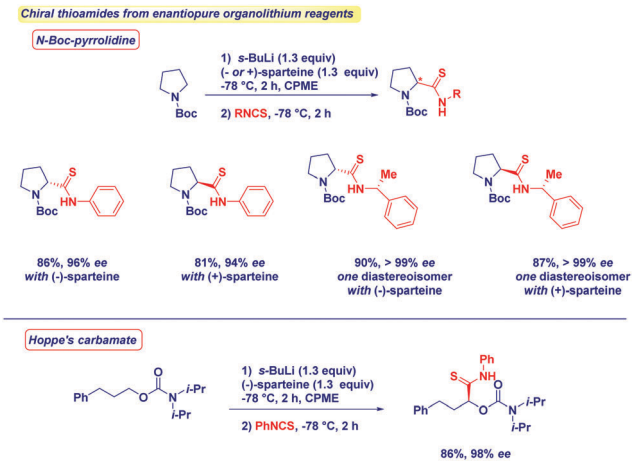
No racemization takes place upon the addition of various organolithium reagents to optically active isothiocyanates.



Scheme 16 Synthesis of α-haloamides from isocyanates and carbenoids.



Scheme 17 Synthesis of thioamides from isothiocyanates and organolithiums.

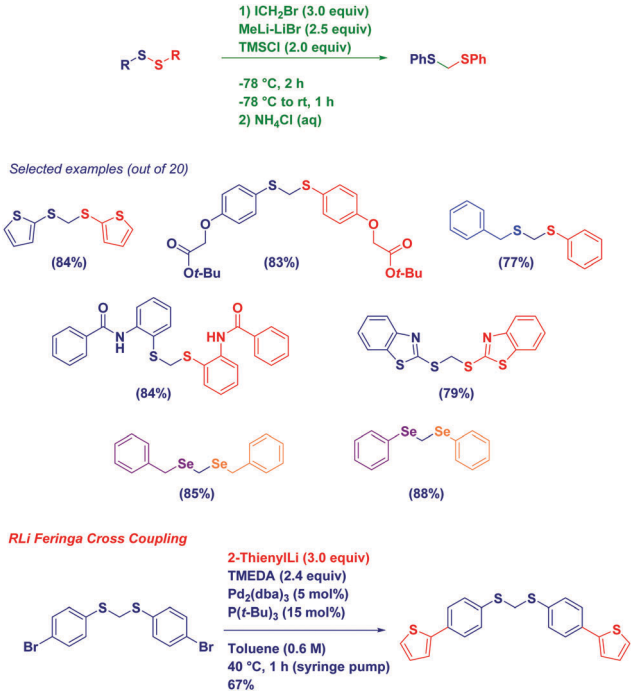


Scheme 18 Preparation of optically active thioamides from isothiocyanates.

The formation of enantiopure *N*-Boc-pyrrolidine or Hoppe's carbamate,[11c,67] through deprotonation in the presence of chiral ligands (−)- or (+)-sparteine[68] affords the corresponding thioamides with full retention of stereochemistry and in excellent diastereomeric ratio (Scheme 18). As expected, by switching from one enantiomer of sparteine to the other, it is possible to get both asymmetric forms of a given thioamide with comparable optical integrity. The simplicity of the reaction conditions developed, and the results in terms of enantiopurity allow the conclusion to be drawn that the present method shows better performances compared with sulfurating protocols in which ee's erosion can be problematic.[69]

Heteroatom electrophiles. Besides boron homologations,[14a,16] non-carbon electrophiles undergo analogous transformations such as ring-enlargement in the cases of zirconium,[70] silicon or germanium.[71]

An indicative example of the good nucleophilicity of lithium carbenoids – towards heteroatom electrophiles – is the homologation of disulfides to the corresponding dithioacetals (Scheme 19).[72] Inspired by the known synthesis of thioethers from a disulfide and an organolithium reagent,[73] we were pleased to observe its adaptability to the more challenging homologation. In fact, such a transformation, previously realized with different nucleophilic homologating reagents (diazomethane[74] and sulfur ylides[75]) or with electrophilic zinc carbenoids,[76] proved to be in both instances highly difficult and, in general, low yielding. Our idea of employing the highly nucleophilic Li carbenoid consisted of forming an (isolable) α-halomethyl thiosulfide intermediate, whose halide was then displaced by the mercapto anion (RS^-) released during the first homologation step. We noticed a beneficial activity of TMSCl in promoting such a second nucleophilic displacement, presumably *via* a coordination effect. This strategy illustrates the true concept of homologation with CH_2X reagents: the introduction of this reactive unit is followed by the subsequent expulsion of the halide, thus finally leading to the formal insertion of the methylene moiety. In analogy, such an overall process recalls the Matteson reaction of boronic esters or the epoxidation of carbonyls, in which the halogen of the



Scheme 19 Homologation of disulfides and diselenides.

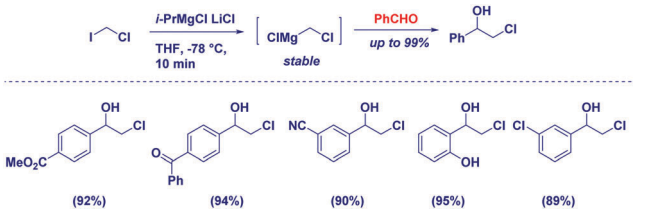
carbenoid is only present at an intermediate level, but not in the final compound. The protocol shows an excellent scope, and the chemoselectivity is fully maintained in the presence of additional sensitive functionalities such as aryl halides, heterocycles, esters and a secondary amide (*i.e.*, again the NH group does not affect homologations!). Importantly, the procedure could be employed for homologating an asymmetric disulfide and aryl or alkyl diselenides.[72]

The presence of a reactive aromatic bromide opened up the field to evaluate the Pd-catalyzed coupling of an aryl bromide-containing substrate with an organolithium reagent reported by Feringa as an effective method for generating C–C bonds with lithium carbanions.[77]

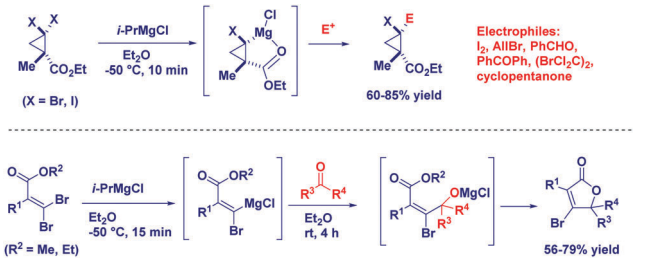
Nucleophilic magnesium carbenoids

Considering that taming the nucleophilicity can be a fine expedient for improving chemoselectivity – as, for example, seen above in the case of a Gilman reagent – magnesium carbenoids are regarded as more stable, but less reactive nucleophiles than the corresponding lithium analogues.[78] That is, the use of non-Barbier conditions is compatible with these carbenoids and, from a chemoselective perspective, it is worth mentioning the excellent discriminating capability between two distinct reactive carbonyls. Clososky reported a highly chemocontrolled synthesis of chlorohydrins – in the presence of ketones – using $ClCH_2MgC{\cdot}LiCl$ prepared by the metallation of ICH_2Cl with the Turbo Grignard reagent (Scheme 20).[79] Notably, the chemoselectivity of the protocol was further demonstrated in the cases of other sensitive functionalities, such as nitrile, ester, and alcohol.

Knochel and co-workers prepared diastereopure multisubstituted cyclopropane carboxylates through the selective



Scheme 20 Chemoselective addition of magnesium carbenoids to aldehydes.



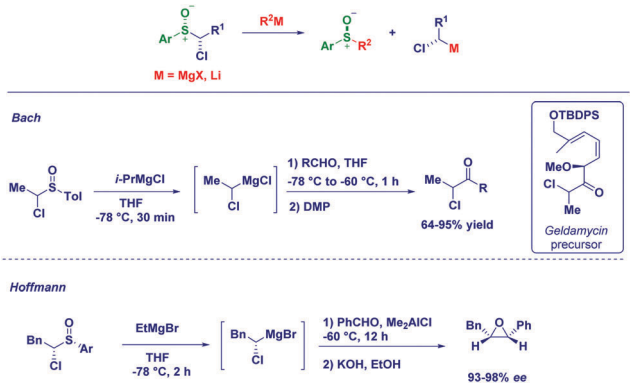
Scheme 21 Chemoselective elaboration of complex architectures with magnesium carbenoids.

metalation of halogen *cis* to the ester (Scheme 21). The stereochemical integrity is maintained after trapping with different electophiles.[80] Similarly, starting from *gem*-dibromoalkene – possessing an alkoxycarbonyl group – they were able to prepare β-bromobutenolide.[81] Mechanistically, the magnesium carbenoid generated through bromo/magnesium exchange reacted with a carbonyl compound, giving an alkoxide intermediate that attacks the ester furnishing the cyclization product.

An excellent alternative for the preparation of magnesium carbenoids is based on the metal exchange on a α-halosulfoxide moiety.[82] It should be observed that magnesium carbenoids manifest an excellent electrophilic behaviour, as recently reviewed by Satoh[78a] and Kimura.[78c] Bach employed Mg-sulfoxide exchange for preparing secondary magnesium carbenoids which upon reaction with aldehydes, followed by Dess–Martin oxidation, produced a crucial α-chloroketone for the synthesis of geldamycin analogues.[83] Hoffmann and co-workers focused their attention on the generation of chiral magnesium carbenoids from optically active 1-chloroalkyl aryl sulfoxides. The treatment of pure 1-chloroalkyl aryl sulfoxides with EtMgBr at −78 °C affords configurationally stable magnesium carbenoids that promptly react with benzaldehyde. The stereochemical information contained in the reagent is fully transferred to the product, allowing the synthesis of an enantioenriched epoxide *via* a homologation/ring closure sequence (Scheme 22).[82,84]

New directions in halocarbenoids

Fluoromethyllithium. Due to the outstanding importance of fluorine containing frameworks in chemistry, the development of a direct and straightforward fluoromethylation tactic represents a significant advancement in the field.[85] In fact, the highly pronounced instability of fluoromethyl-type carbanions – as a consequence of the so-called "negative fluorine effect" – posed strict requirements for use in synthesis.[86] The installation

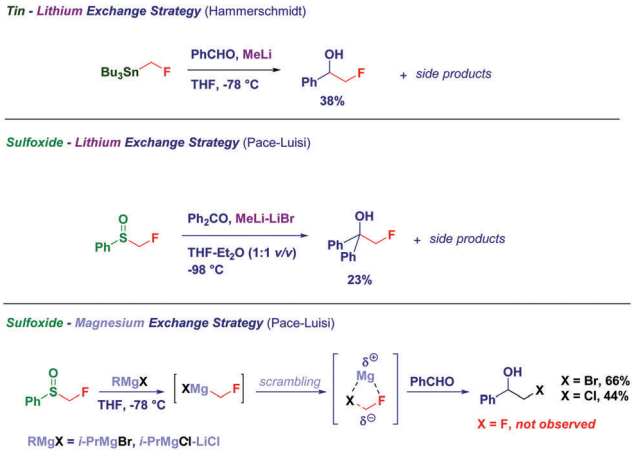


Scheme 22 Use of the sulfoxide-metal exchange for preparing carbenoids.

of strongly electron-withdrawing groups on the carbon was pivotal for ensuring stability and thus, reactivity with a given electrophile.[87] As such, the synthetic sequence for installing a CH_2F group has to be constituted by three different operations: (1) synthesis of the protected fluoromethyl-carbanion; (2) reaction with the desired electrophile and, (3) non-easy removal of the stabilizing auxiliary. It becomes evident that establishing the conditions for generating a MCH_2F-type reagent would *de facto* implement and simplify the overall introduction of the fluoromethyl group.[88] That is, realizing in one-step the exclusive transformation for which it is conceived. A similar radical type approach was designed by Hu for the fluoromethylation of O-, S-, N- and P-nucleophiles: however, it was not applicable to carbon nucleophiles.[89] The extremely high chemical instability of fluorocarbenoids – even at very low temperatures – was observed in recent work by Hammerschmidt[90] who also noticed a significant configurational stability in the case of LiCHDF. This author generated the carbenoid under Barbier conditions *via* a Sn/Li exchange on a fluoromethylstannane prepared in two steps from paraformaldehyde. Unfortunately, the scope of the methodology was limited to the case of benzaldehyde and simple acetophenone analogues, thus leaving undisclosed the innate potential of the protocol. Despite the Barbier-type conditions used, the chemocontrol was not optimal, and products formed through the direct attack of the non-fluorinated organolithium to the carbonyl were observed. This result suggests no efficient Sn/Li exchange and therefore justifies the quest for suitable more-easily exchangeable groups.

Only very recently, in the course of a collaboration with R. Luisi, we addressed this long standing challenge on the use of $LiCH_2F$ at preparative scale.[91]

The use of a sulfoxide as the precursor of the lithium carbenoid provides the model fluorohydrin in 23% yields, together with side reaction products. On the other hand, the corresponding magnesium fluorocarbenoids generated *via* sulfoxide-magnesium exchange suffered from halogen-scrambling similarly to zinc fluorocarbenoids noticed by Charette.[92] However, these results further confirm the existence of $LiCH_2F$, though it appears evident that neither tin- nor sulfoxide-fluoromethylstannanes are the ideal carbenoid precursors (Scheme 23).



Scheme 23 Formation of α-fluoromethyl metal carbanions from tin and sulfoxide precursors.

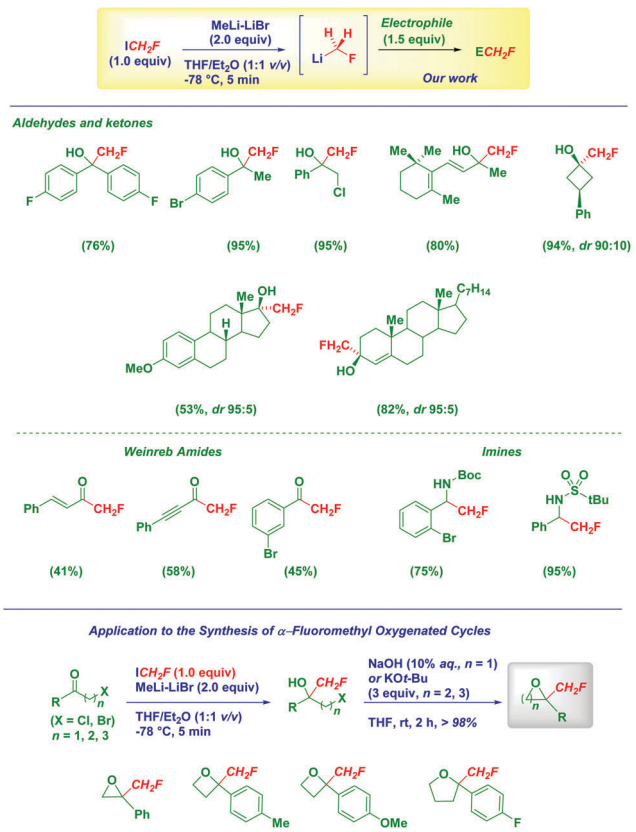
An effective solution was finally found by adopting a highly effective iodine–lithium exchange on the currently commercially available and easy to manipulate (liquid, bp 53 °C) fluoroiodomethane (Scheme 24).[93] The fine tuning of the reaction conditions allows the model compounds to be obtained in an excellent 88% isolated yield, thus making it suitable for preparative processes.[91] In depth optimization studies defined the crucial factors accounting for the successful preparation of $LiCH_2F$: (1) MeLi–LiBr as the lithiating agent; (2) generation of the carbenoid under Barbier conditions; (3) stoichiometry (electrophile : MeLi–LiBr : ICH_2F = 1 : 1.5 : 2); and (4) solvent mixture THF : Et_2O 1 : 1 v/v.

Our fluoromethylation strategy presents an excellent scope as indicated by the variety of functionalized electrophiles used (*e.g.* carbonyls, Weinreb amides and imines). Ketones and aldehydes were converted into α-fluoro alcohols in very high yields and remarkable chemocontrol, even in the presence of a double bond or potentially exchangeable halogens. Biologically relevant and complex scaffolds such as 3-*O*-methylestrone and 4-colesten-3-one efficiently undergo the transformation furnishing the corresponding fluorohydrins as single stereoisomers. The reactivity of $LiCH_2F$ was also evaluated towards α-, β- or γ-halo ketones giving mixed fluoro-halohydrins which upon base-mediated cyclization resulted in practically quantitative yields of interesting fluoromethyl-oxygenated 3, 4 or 5 membered cycles.

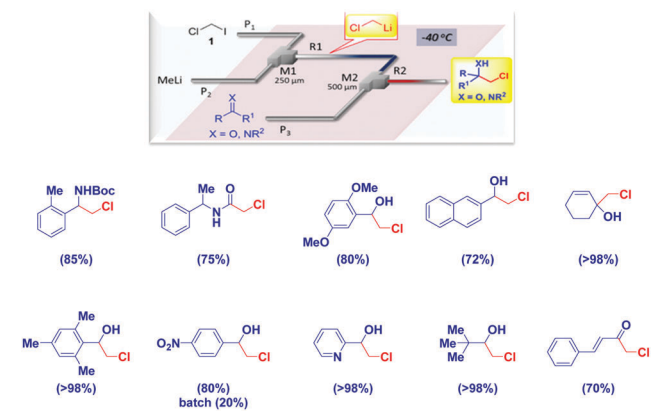
Microfluidic techniques. Recently, in order to minimize the α-elimination degradation pathway to the free carbene species, flow methodologies became attractive tools in the field. These strategies allow the effective external trapping of the labile lithiated species formed prior to the addition of the electrophile.

Luisi and coworkers elegantly demonstrated how microfluidic systems are effective in the generation of the thermolabile $LiCH_2Cl$, followed by trapping with electrophiles at high temperatures (up to −20 °C).[94] This methodology – constituting a significant advancement in the field – works quite well with different electrophiles from carbonyl compounds, imines, Weinreb amides and isocyanates, thus paralleling the substrate scope observed under classical Barbier-type conditions (Scheme 25).

Sedelmeier's group employed a similar technique to generate dichloromethyllithium, by treating DCM with *n*-butyllitium at −30 °C, followed by the addition of aldehydes to form dichlorocarbinols or boronic esters to access the corresponding α-chloro analogues.[95] The flow procedure is also amenable for preparing α,α-dibromoketones from esters and $LiCHBr_2$ – which were practically unreactive under classical batch conditions – as shown by Ley.[96]



Scheme 24 Fluoromethyllithium: generation and use in synthesis.



Scheme 25 In flow generation of chloromethyllithium and trapping with electrophiles under non Barbier conditions.

Conclusions

The addition of a nucleophilic CHRX fragment to an electrophile can not only be conveniently used for obtaining the result of the (expected) transfer, but also can be envisaged as the first step of a sequence leading to more complex molecular architectures. The instability of α-organometallic substituted species has represented in the past a severe limitation for the design of novel strategies. Fortunately, nowadays the understanding of the mechanisms regulating the formation and the decomposition of these species, contributes to expanding the synthetic versatility of these tactics. The demonstration that analogous reagents are configurationally stable clearly defines one of the next huge challenges in the field: the use at the preparative level of such chiral carbenoids.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors thank the University of Vienna for financial support and for a *Unidocs* fellowship to S. M., and ABCR Germany for the generous supply of fluoroiodomethane (ref. AB291947). L. C. acknowledges the Austrian Academy of Sciences for a postdoctoral L'OREAL grant. We deeply appreciate the collaboration of Prof. Dr Renzo Luisi (University of Bari) for breakthrough studies we conducted on fluorinated organometallics.

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