DISSERTATION / DOCTORAL THESIS

Titel der Dissertation /Title of the Doctoral Thesis

Design and Development of Homologation and Related Strategies for Expanding the Chemical Space of Halogen-Containing Manifolds

verfasst von / submitted by

Margherita Miele

angestrebter akademischer Grad / in partial fulfilment of the requirements for the degree of

Doktorin der Naturwissenschaften (Dr.rer.nat)

Wien 2022 / Vienna 2022

Studienkennzahl lt. Studienblatt / degree programme code as it appears on the student record sheet:	UA 796 610 449
Dissertationsgebiet lt. Studienblatt / field of study as it appears on the student record sheet:	Pharmazie
Betreut von / Supervisor:	Vittorio Pace, Privatdoz. PhD

Design and Development of Homologation and Related Strategies for Expanding the Chemical Space of Halogen-Containing Manifolds

In recent years, carbenoid-based chemistry contributed to the development of novel homologating methodologies thus, enabling the access to a variety of functionalized carbon arrays of progressive molecular complexity. In this context, lithium carbenoids emerged as optimal C-1 synthons working under nucleophilic regime: once defined the conditions for their preparation, they engage in C-C bond forging operations in which an additional reactive appendix (C-X) is introduced within the recipient electrophile. Usually, the application of lithium carbenoids is restricted to sp^2-hybridized carbon electrophiles (C=Z, *e.g* Z = O, NR), which undergo homologation furnishing halomethyl alkyl derivatives suitable for further transformations. On the other hand, sp^3 -type alkyl halides remain elusive materials in these processes, as a consequence of undesired and non-controllable polyhomologations. Moreover, among the portfolio of nowadays available carbenoid-type homologating agents, those ones embodying one or more fluorine atoms manifest a higher tendency to decompose, thus making particularly challenging the innate synthetic potential.

The aim of this thesis is to boost the significance of homologative processes conducted on a variety of carbon and heteroatom-centered electrophiles, with the final goal of accessing functionalized molecular entities, ideally *via* a single synthetic operation. In particular, we directed our investigations towards: a) the development of a homologation – deoxygenation sequence for exploiting the innate reactivity of carbonyls towards carbenoids, followed by a chemoselective alcohol reduction, thus preparing (n+1)-haloakyl fragments; b) the synthesis of oxothioacetals *via* a consecutive homologation of thiosulfonates – nucleophilic displacement with oxygen nucleophiles; c) the use of the bench-stable $TMSCHF_2$ as pro-nucleophile (under alkoxide-activation) for delivering the valuable CHF_2 group to Weinreb amides (obtaining difluoromethyl ketones), to iso(thio)cyanates [giving difluoro(thio)amides] and to various electrophilic metals (yielding difluoromethyl-metal species. Additionally, a sustainable access to thioformamides *via* the Schwartz reagent-mediated reduction of isothiocyanate is presented. Lastly, we document that the usually deleterious Kirmse α-elimination of carbenoids may have synthetic potential as a controlled releasing process of LiX thus, enabling the opening of epoxides *en route* to halohydrins.

Design and Development of Homologation and Related Strategies for Expanding the Chemical Space of Halogen-Containing Manifolds

Die Weiterentwicklung der Chemie von Carbenoiden führte in den letzten Jahren zu neuartigen Homologationsmethoden und ermöglichte so den Zugang zu einer Vielzahl von funktionalisierten Kohlenstoffverbindungen zunehmender molekularer Komplexität. In diesem Zusammenhang stellten sich Lithium-Carbenoide als optimale, unter einem nukleophilen ‚Regime' arbeitenden, C-1-Synthone heraus. Nach ihrer Herstellung unter genau definierten Reaktionsbedingungen können sie C-C-Verknüpfungen bewerkstelligen, bei denen ein zusätzlicher, reaktiver Appendix (C-X) in das Empfänger-Elektrophil eingeführt wird. Üblicherweise beschränkt sich die Anwendung von Lithium-Carbenoiden auf die Reaktion mit sp^2-hybridisierten Kohlenstoff-Elektrophilen (C=Z, *z.B.* Z = O, NR), welche nach der dabei erfolgenden Homologation die entsprechenden Halomethylalkyl-Derivate liefern, die für weitere Transformationen verwendet werden können. Allerdings stellen sp^3-Alkylhalogenide in diesen Prozessen schwer fassbare Materialien dar, nicht zuletzt als Folge unerwünschter und nicht kontrollierbarer Polyhomologationen. Weiters zeigen Carbenoid-Homologatoren, welche ein oder mehrere Fluoratome enthalten, eine höhere Tendenz zur Zersetzung, was ihren Einsatz als Synthesebausteine besonders herausfordernd macht.

Ziel dieser Arbeit war es, homologative Prozesse an einer Vielzahl von kohlenstoff- und heteroatomzentrierten Elektrophilen so zu gestalten, dass gewünschte synthetische Ziele - idealerweise - über eine einzige synthetische Operation zugänglich werden. Insbesondere richteten sich die Untersuchungen auf:

a) die Entwicklung einer Homologations-Desoxygenierung-Sequenz – unter Ausnutzung der inheränten Reaktivität von Carbonylen gegenüber Carbenoiden– gefolgt von einer chemoselektiven Alkoholreduktion, wodurch (n+1)-Haloalkyl-Fragmente zugänglich werden

b) die Synthese von O,S-Acetalen durch Homologation von Thiosulfonaten und anschließende nukleophile Substitution des terminalen Halogenatoms mit Sauerstoffnukleophilen

c) die Verwendung des ‚bench-stabilen' Reagens $TMSCHF_2$ als Pro-Nukleophil (unter Alkoxid-Aktivierung) zur Abgabe der wertvollen CHF_2-Gruppe an Weinreb-Amide (Formierung von Difluormethylketonen), an Iso(thio)cyanate (Synthese von Difluor(thio)amiden) und an verschiedene elektrophile Metalle (Erzeugung von Difluormethyl-Metallspezies).

Zusätzlich wird ein nachhaltiger Zugang zu Thioformamiden über die von Schwartz-Reagenzien vermittelte Reduktion von Isothiocyanaten vorgestellt. Schließlich wird gezeigt, dass die bei Carbenoiden üblicherweise unerwünschte *Kirmse*-α-Eliminierung synthetisches Potenzial für die kontrollierte Freisetzung von LiX birgt, wodurch die Öffnung von Epoxiden hin zu Halohydrinen ermöglicht wird.

Abbreviations List

2-MeTHF	2-Methyltetrahydrofuran
B_2mpd_2	Bis(hexylene glycolato)diboron
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
B_2pin_2	Bis(pinacolato)diboron
Bu	Butyl
DMAc	Dimethylacetamide
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DTBB	Di-*tert*-butylbiphenyl
EDG	Electron donating group
EWG	Electron withdrawing group
HRMS	High Resolution Mass Spectrometry
LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
$LNCy_2$	Lithium dicyclohexylamide
LTMP	Lithium tetramethylpiperidide
Me	Methyl
MeCN	Acetonitrile
NMR	Nuclear Magnetic Resonance
PG	Protecting group
Ph	Phenyl
Pin	Pinacol
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Ts	Tosyl

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List of Publications

Publication 1 Monticelli, S.; Castoldi, L.; Touqeer, S.; **Miele, M.**; Urban, E.; Pace, V.
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Publication 5 **Miele, M**.; Ielo, L.; Pillari, V.; Senatore, R.; Mirabile, S.; Gitto, R.; Holzer, W.; Alcántara, A. R.; Pace, V.
Taking advantage of lithium monohalocarbenoid intrinsic α-elimination in 2-MeTHF: controlled epoxide ring-opening en route to halohydrins.
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Direct and Chemoselective Synthesis of Tertiary α,α-Difluoro-ketones via Weinreb Amides Homologation with CHF_2-Carbene Equivalent.
Org. Lett. **2019**, *21*, 8261-8265.

Publication 9 **Miele, M.**; D'Orsi, R.; Sridharan, V.; Holzer, W.; Pace, V.
Highly chemoselective difluoromethylative homologation of iso(thio)cyanates: expeditious access to unprecedented α,α-difluoro(thio)amides
Chem. Commun. **2019**, *55*, 12960-12963.

Publication 10 **Miele, M.**; Castoldi, L.; Simeone, X.; Holzer, W.; and Pace, V.
Straightforward Synthesis of Bench-Stable Heteroatom-Centered Difluoromethylated Entities via the Controlled Nucleophilic Transfer from Activated $TMSCHF_2$.
Submitted (ref. CC-COM-02-2022-000886).

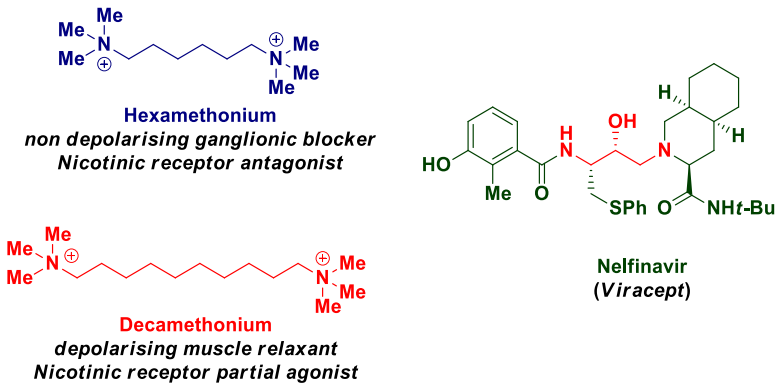
Publication 11 Touqeer, S.; Ielo, L.; **Miele, M.**; Urban, E.; Holzer, W.; Pace, V.
Direct and straightforward transfer of C1 functionalized synthons to phosphorous electrophiles for accessing gem-P-containing methanes.
Org. Biomol. Chem. **2021**, *19*, 2425-2429.

1. Introduction

1.1 Carbenoids: homologation tools and general properties

The synthetic operations consisting in the insertion of a formal unit C1 (*i.e.* CH_2 or CH) into a given reactant to form the next member of the homologated series are usually referenced as homologations.[1] They represent nowadays powerful and versatile tools in preparative chemistry, enabling the progressive increase of acyclic and cyclic systems.[2] Usually, methylenating agents – being constitutively C1-synthons - are common homologating tools, thus allowing the constant insertion of the CH_2 unit into a plethora of recipient manifolds.[3] In this sense, the reactive methylene unit may display different electronic behaviours including the carbanion-, the carbocation- and radical-type.[4] This preliminary differentiation introduces the reader to the intrinsic flexibility characterizing homologation chemistry: it consists in a variety of tactics highly tuneable by the operator and, thus the proper selection of reaction conditions becomes pivotal for accomplishing the formal C1-unit insertion into a general R-R^1 linkage.

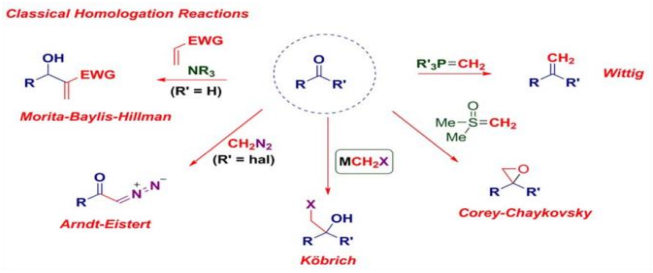
The significance of homologous series / homologation reactions in medicinal chemistry is a well-established concept,[5] as illustrated – for example – in the different pharmacodynamic profile manifested by decamethonium and hexamethonium towards the nicotinic receptor or, the first preparation of Nelfinavir (HIV-protease inhibitor) reported by Kaldor in 1997,[6] which contains a key homologation step for forging the chiral 1,3-diamino-propan-2-ol pharmacophore (**Scheme 1**).[7]



Scheme 1. Homologs in medicinal chemistry

The prototypal homologation reaction is represented by the carbon chain extension of carboxylic derivatives with diazomethane introduced by Arndt–Eistert in 1935.[8] However, the safety drawbacks concerning the use of diazomethane stimulated the research of risk-limited reagents to homologate

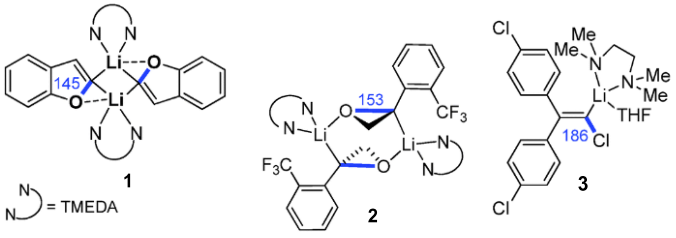
compounds under more sustainable conditions.[9] The wide portfolio of developed alternatives includes: Wittig-type,[10] Corey–Chaykovsky,[11] Morita–Baylis–Hillman[12] or Köbrich[13] reactions and, the metal carbenoids chemistry (**Scheme 2**).[14]



Scheme 2. Classical homologation reactions.

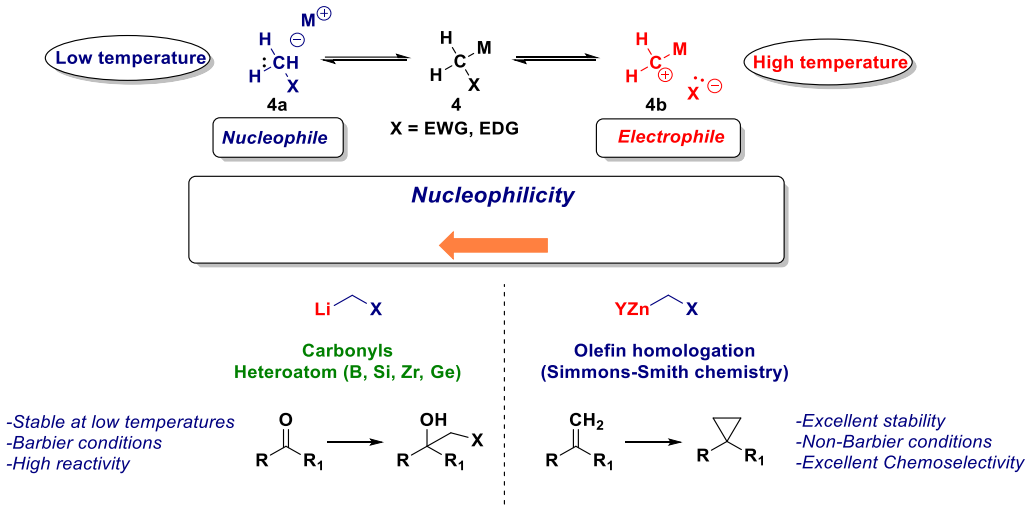
In recent years, the advancements of carbenes chemistry contributed to boost the role of carbenoid reagents in homologation chemistry.[15] The term carbenoid was introduced for the first time in 1964 by the pioneers Closs and Moss,[16] reporting the use of these species in cyclopropanation reactions. In this contest the distinction between carbene and carbenoids become essential to explain the stereocontrol in cyclopropanation reactions, as stated by them „*we propose the use of the term carbenoid for the description of intermediates which exhibit reactions qualitatively similar to those of carbenes without necessarely being free divalent carbon species*".

This evidence stimulated the scientific debate about the structures of carbenoids, defined as organometallic compounds containing a metal atom (*e.g.,* Li, Mg, and Zn) and at least one heteroatom-containing element (*e.g.*, halogen, N, and O) linked at the same carbon.[4,17] Due to the high reactivity and sensitivity the first structure elucidation was deducted *via* NMR experiments conducted by the group of Seebach.[18] Further investigations through the use of low temperature techniques – ensuring the termal-integrity of lithium carbenoids – culminated in the first X-ray structure (**1**) (**Scheme 3**) of a general carbenoid.[19]



Scheme 3. X-ray structures of lithium carbenoids.

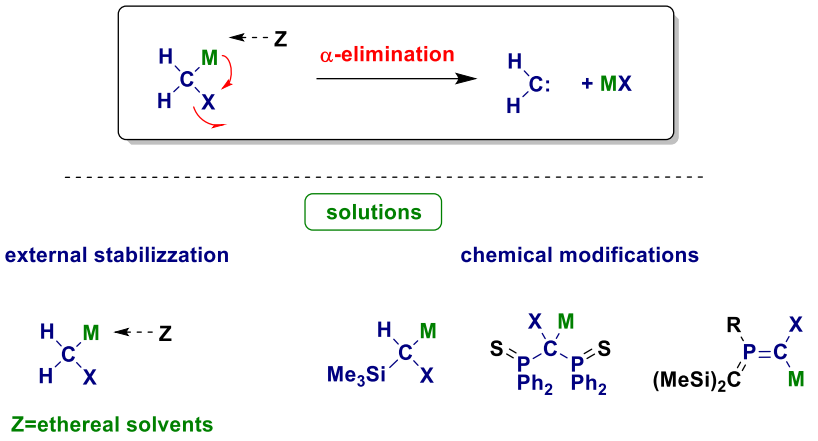
The constitutive essence of carbenoids, bearing electron-donating and electron-withdrawing substituent at the carbon center, determinates their ambiphilic character, showing nucleophilic or electrophilic behaviors depending on mostly two factors: temperature and nature of the metal.[17b,20]



Scheme 4. Ambiphilic character of carbenoids.

The ambivalent character of carbenoids is evident from the two limit forms **4a** and **4b** (**Scheme 4**): it is important to note that they cannot be considered resonance structures because of the breaking of C-M and C-X bonds.[2c] It is widely accepted that at low temperature and, usually in the presence of highly electropositive metal, such as lithium they show the nucleophilic behavior while, their electrophilicity is evidenced at higher temperature and in presence of less electropositive metals such as zinc, copper or tin.[2c,15,21]

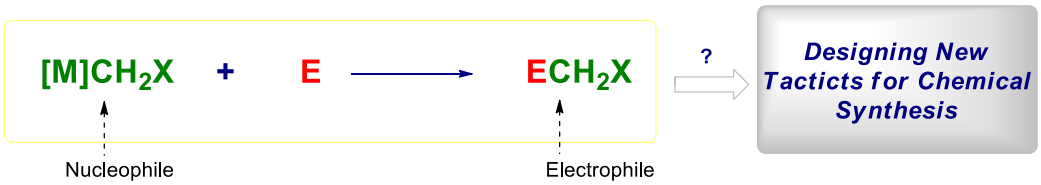
Due to the ionic nature of the carbon-metal bond, carbenoids of highly electropositive metals are suffering from a pronounced instability.[4,13,22] Therefore, typical increasing of stability follows the order Li < Mg < Zn, possibly due to the lower Lewis acidity of the heavier metals. Together with the nature of the metal, the leaving group X plays an important role in the stability and reactivity of carbenoids. In fact, seminal studies of Köbrich presented the halogenated carbenoids as the most reactive – in nucleophilic regime - species.[13] In general, halogenated lithium carbenoids are considered the most nucleophilic ones and thus, at some extent, it is conceivable regarding them as carbanion-like reagents.[17b] This intrinsic instability could be ascribed to the α-elimination process (**Scheme 5**) in which, the internal coordination between the metal and the halogen triggers the decomposition to a metal halide and a free carbene.[20,23]



Scheme 5. Kirmse α-elimination of carbenoids.

This limitation, pointed out by Köbrich does not imply shortcomings affecting their generation:[22a] as it will discussed in the next paragraphs, forming a carbenoid is *per se* a thermodynamically favoured process. What is the Achille's heel of these species is rather the instability once they are formed:[24] for this reason, their productive employment in synthesis requires a perfect control of the reaction conditions, thus enabling the generation and the preparative use. This is intrinsically related to ensure the chemical integrity during the course of the considered homologation event.[2c] Notable improvements have been accomplished for securing this paradigm. Extensive studies conducted by Köbrich,[22a] Matteson,[25] Villieiras[26] and Barluenga,[27] demonstrated that the use of low temperature (<-78°C) and of an ethereal solvent are effective solutions to overcome the fast α-elimination; thus, Cainelli introduced the adoption of the so called Barbier-type conditions for the correct generation of carbenoids.[28] This is, the carbenoid is generated through metal-exchangeable processes in the presence of the material to be homologated: accordingly, it is essential that the reagent employed for promoting the exchange does not react with this linchpin.[25c] An additional element preventing carbenoids's degradation is the introduction of stabilizing groups, such as silicon-based,[29] thiophosphoryl or phosphorano moieties,[30] whose use showed some benefit. Despite the advantages, these methodologies pose issues related to the inclusion of an additional removal step.

In recent years, our group showed that – regardless the limitations discussed above – carbenoids represent versatile reagents for C-C bond formation events and, the careful control of the reaction conditions can be advantageously exploited for triggering more complex rearrangement sequences, ultimately leading to sophisticated architectures obtainable through a single synthetic operation (**Scheme 6**).[2c,31]

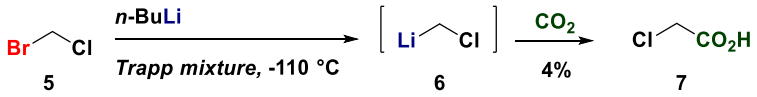


Scheme 6. Use of carbenoids in chemical synthesis.

1.2 Halogenated lithium carbenoids

The versatility of lithium carbenoids has been well recognized in homologation chemistry, providing an alternative to diazomethane-based[32] or sulfur ylides procedures.[11b,33] As said, despite their intrinsic instability, the introduction of CH_2 fragment *via* $LiCH_2X$-type reagents to a given electrophilic carbon, not only induce the formation of the C-C bond but also, owing to the inherent CH_2-X reactivity, enables further transformations at a later stage. [2c,34]

Köbrich and coworkers introduced the use of ethereal solvents – *i.e.* Lewis base systems - such as THF or diethyl ether to improve carbenoids stabilization.[13,22a] With the intent to trap chloromethyllithium **6** with carbon dioxide - generated at -110°C from bromochloromethane **5** and *n*-buthyllithium - they found beneficial to run the reaction in the so-called Trapp mixture (THF: Et_2O: petrol ether = 75:15:10):[35] although the formation of the carbenoid was detected, the limited yield (4%) of chloroacetic acid **7** obtained, suggested that the external trapping of lithium carbenoids is extremely elusive (**Scheme 7**). The addition to the reaction mixture of common Lewis base ligands such as TMEDA did not find extensive application, probably because these nucleophiles may interfere with the carbenoid generation event; however, in some instances it can benefit the stereocontrol of reactions.[24] Moreover, a strong polar Lewis base solvent as hexamethylphosporamide (HMPA) which coordinate the lithium atom *via* its oxygen, favors the degradative process by triggering the scission of the carbon-lithium bond.[26]

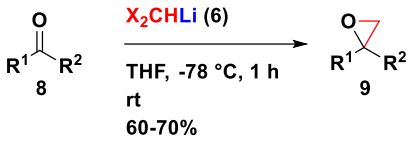


Trapp mixture = THF-Et_2O-*n*-pentane 75:15:10 *v/v*

Scheme 7. Köbrich trapping of lithium carbenoid with carbon dioxide.

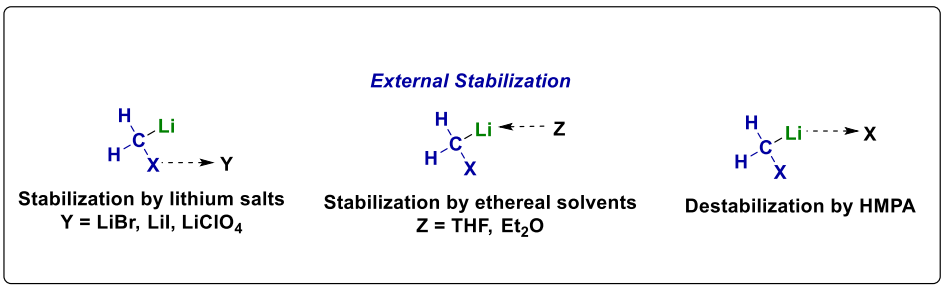
The pioneering studies by Cainelli and coworkers were fundamental because for the first time the *in situ* generation of halolithium carbenoids was accomplished under Barbier-type conditions which effectively suppressed the facile alpha-elimination they undergo.[28b] Accordingly, they reported the homologative conversion of carbonyls into epoxides (**Scheme 8**). The formation of the carbenoid species, in the presence of the carbonyl electrophile, was achieved in THF at-78 °C starting from the

dihalomethane which underwent a fast halogen-lithium exchange, thus permitting the genesis of the halocarbenoid. Importantly, no concomitant direct addition of the organolithium to the electrophile was noticed and, despite the extremely fast decomposition of the carbenoid, the desired compounds were obtained in good yields.



Scheme 8. Cainelli's bromomethyllithium-mediated epoxidation.

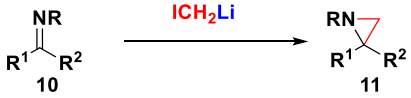
The instability of carbenoids depends also on the essence of the leaving group X (I > Br > Cl > F): in fact, due to its different polarizability, the deleterious α-elimination may be sensitively tuned, being mainly for fluorine containing species, very difficult to control.[22b] A practical and effective solution is constituted by adding to the reaction mixture a lithium salt (halide or perchlorate) which could coordinate with the halogen of the carbenoid, thus taming (or suppressing the α-elimination).[26] Collectively, the additional execution of reactions in ethereal type solvents – coordinating the lithium of the carbenoid – makes the procedure productive and applicable to synthesis' needings (**Scheme 9**).



Scheme 9. Stabilization of lithiumcarbenoids.

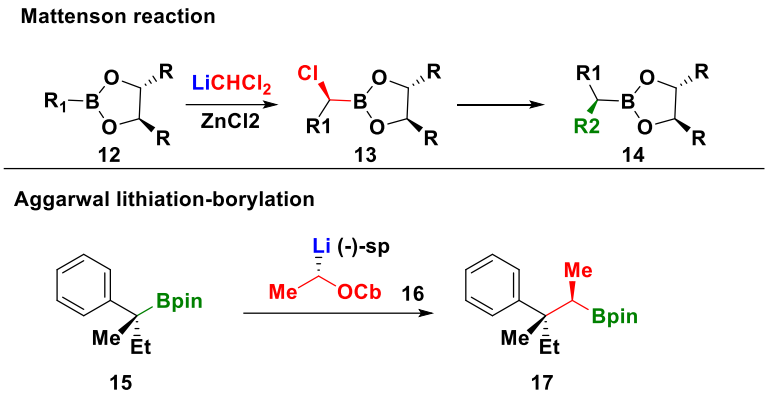
This so called salt effect was then confirmed by several groups, in particular Pace demonstrating the benefit in the use of the commercially available mixed metalating reagent MeLi-LiBr.[24] Moreover, Mattenson recognized the role of LiBr in decreasing the formation of the byproduct generated upon the attack of the methyl carbanion to the electrophile.[25c,36]

The attack of the carbenoid, in the case of epoxides and aziridines (**Scheme 10**), forms the formal intermediate alkoxide or amide, which spontaneously undergoes ring closure, as a result of the expulsion of the halogen, thus forming the three-membered rings.[37]



Scheme 10. Formation of aziridines using Lithium carbenoids.

In the case of boronic esters, the homologation was showed as powerful tool in asymmetric synthesis, as documented by Matteson[38] and Aggarwal[39] (**Scheme 11**).

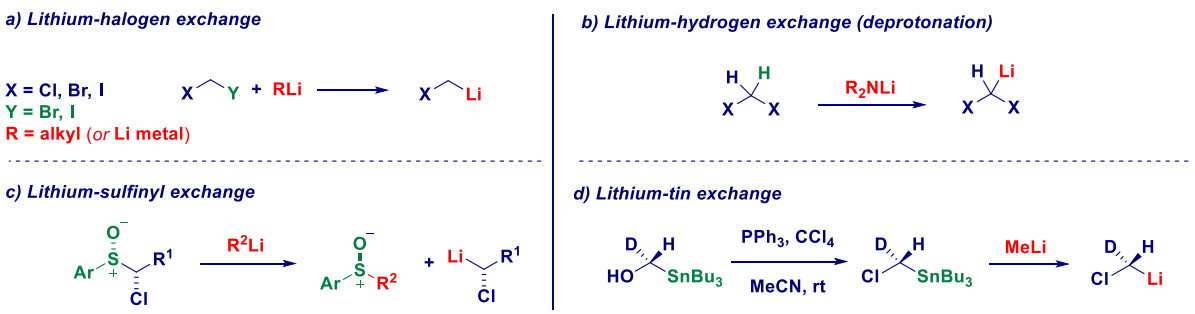


Scheme 11. Mattenson and Aggarwal lithiation of boronic esters.

The Matteson homologation involves the use of a chiral boronic ester (**12**) which reacts with dichloromethyllithium and, due to the presence of a Lewis acid as zinc (II) chloride, evolves to the C1-homologated boronic ester (**14**) under control of the stereochemistry.[25a,25b,38] Aggarwal adapted the tactic to chiral lithium reagents which – *coeteris paribus* – conducted to the formation of multiple stereogenic centers. Notably, these strategies found extensive application in the synthesis of natural products (*e.g.* kalkitoxin).[39b,39c,40]

1.3 Generation of Carbenoids Species

Despite halogen-lithium exchange represents the most common procedure for the preparation of halolithium carbenoids, all the standard preparative protocols for accessing classical organometallic reagents, can be conveniently adapted also to these species. Accordingly, it is possible to categorize as follows: a) lithium-halogen exchange; b) lithium-hydrogen exchange (*i.e.* deprotonation); c) lithium-sulfinyl exchange; d) lithium-tin exchange (**Scheme 12**).[24]

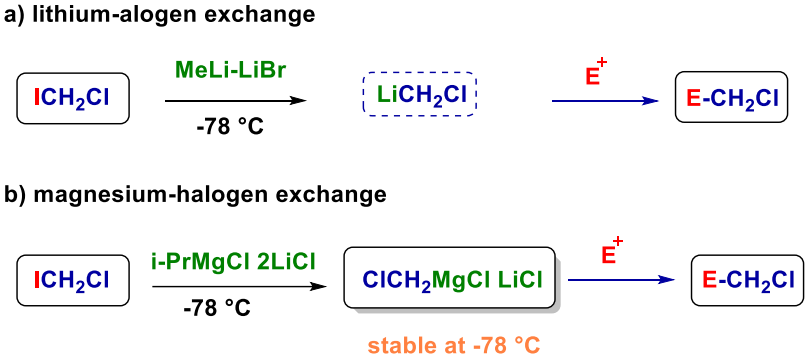


Scheme 12. Methods of preparation of halocarbenoids.

1.3.1 Lithiation via halogen-lithium exchange.

The lithiation *via* halogen-lithium exchange could be formally considered as an oxidative addition of the lithium to the precursor dihalomethane. The first studies conducted by Villieras, at -110°C using *s*-BuLi as base, showed the possible concomitance of deprotonation phenomena as a consequence of the extremely high basicity of this organolithium.[26] For this reason, the commercially available MeLi-LiBr and *n*-BuLi are nowadays the preferred lithium reagents for the purpose, being the former advantageous for imparting additional stability to carbenoids. Considering a general dihalomethane X-CH$_n$Y, one may argue about the selectivity of the halogen-lithium exchange: fortunately, only the heavier halogen is subjected to the exchange, thus leaving untouched the other one which therefore is embodied in the carbenoid. It is wise to employ a haloiodomethane (X-CH$_2$-I) in order to maximize the rate of exchange;[41] of course, in the case of using diiodomethane, only one iodine atom is exchanged yielding LiCH$_2$I. Alternatively, mainly for optimizing the industrial cost effectiveness of processes, a bromohalomethane can be employed; however, reaction yields are dwindled with this pronucleophile.[24]

The productive use of carbenoids requires some practical expertise which is fundamental for eclipsing deleterious phenomena: by adopting the Barbier-type conditions, the dihalomethane and the electrophilic linchpin are mixed in the ethereal solvent and cooled at -78 °C; then, the exchanging organolithium is slowly added (within 10-30 min, ideally with a syringe-pump), to ensure the continuous carbenoid formation and reactivity within the very short half-life it possesses.[24,42] The final consideration focuses on the stoichiometric ratio between procarbenoid and organolithium: although the reaction proceeds quantitatively, it is a common and wise practice using a slight excess of dihalomethane (usually 0.2-0.4 equiv), to suppress the collateral attack of the lithium base to the electrophilic partner.[41] Analogously, it is important freshly titrated organolithiums to avoid abnormal genesis of the carbenoids owing to concentration fluctuations.[24]



Scheme 13. Carbenoids generation through metal-halide exchange.

Is important to underline that magnesium carbenoids could be considered alternatives to lithium congeners (**Scheme 13**). Because of the tamed C-Mg ionic character (compared to C-Li), they are more stable than lithium ones and can be prepared *via* magnesium-halogen exchange using ICH_2Cl and *i*-PrMgCl in the absence of Barbier type condition at -78 °C.[17a,43] However, they manifest a lower nucleophilicity and can react only with strong electrophiles (aldehydes, carbon dioxide *but not* ketones or carboxylic derivatives, as indicated by Pace).[44]

1.3.2 Lithiation via lithium-hydrogen exchange.

Due to the constitutional acidity of the dihalomethane´s proton, the formation of carbenoids could be accomplished using a lithium base able to carry out the lithium-halogen exchange process.[34,45] Lithium base such as LDA, LMPT, LiHDMS or also *s*-BuLi could extract the proton of the dihalo-precursor at low temperature to form the corresponding di- and tri-halomethylcarbenoids. The latter species ($LiCX_3$) are inherently less nucleophilic than dihalo-analogues because of the additive electron-withdrawing effect displayed by the three halogens and, for instance for $LiCX_3$ reagents electrophilic-type reactivity cannot be neglected.[46] Regarding dihalomethyllithiums, the preparation under Barbier type conditions is not a mandatory requirement and thus, the operator may decide or not to adopt them taking into consideration the specific case he/she is dealing with (**Scheme 14**).[45a]

R = *i*-Pr, Cy, TMP, TMS
X, Y = Cl, Br, I

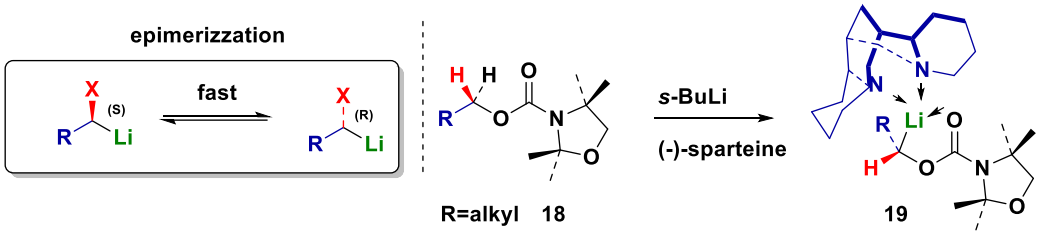
Scheme 14. Carbenoids generation through metal-hydrogen exchange.

Despite *s*-BuLi is an effective base to abstract an acidic proton from a dihalomethane, it shows a higher tendency to promote the halogen-lithium exchange rather than the deprotonation. In addition, the rapidity of halogen-lithium exchange implies that in the case of monohalolithium carbenoids, this represents the method of choice for their preparation.

1.3.3 Chiral carbenoids and Lithiation *via* lithium-sulfinyl exchange.

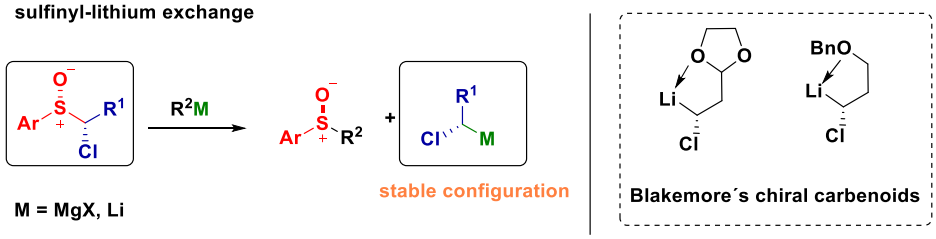
In modern organometallic chemistry, the possibility to obtain configurationally stable carbenoids have been regarded as a matter of high interest.[43c,47] The investigation on the chiral stability of halolithium carbenoids dates back to 1992, when the Hoffmann´s group during studies on 1-bromo-1-lithiopentane, reported that this species was configurationally stable at -110 °C.[48] Upon the reaction

with an electrophile, it was observed that the carbenoid preserved its stereochemical configuration: thus, it was a kinetically faster process than the inversion of the configuration leading to racemization (**Scheme 15**). Later, configurational stable lithiated carbamates (**19**) were reported by Hoppe and coworkers,[49] upon enantioselectively deprotonated the urethane (**18**) with a lithium base (*s*-BuLi*)* in the presence of a chiral base such as (-)- sparteine.[50]



Scheme 15. Configurational stable lithium carbamates in the presence of (−)- sparteine.

In 2013 Blakemore reported a series of enantioenriched carbenoids, prepared from chiral halo-arylsulfoxides *via* the lithium-sulfinyl exchange (**Scheme 16**).[51] The procedure introduced by Hoffmann for magnesium-carbenoids,[43c,47a] was validated also in the case of lithium carbenoids, thus leading to configurationally stable species. Mechanistically, the α-halosulfoxide undergoes the attack of the lithiating agent (*e.g t*-BuLi or PhLi in THF), furnishing the configurationally stable carbenoid and a sulfoxide featuring the inversion of stereochemistry at the sulfur atom. The formation of the exchange sulfoxide product – detectable through NMR or MS analyses - witnesses the effective formation of the carbenoid.

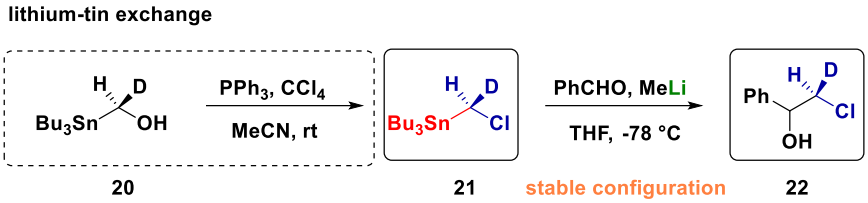


Scheme 16. Carbenoids formation via lithium-sulfinyl exchange.

1.3.4 Lithiation via lithium-tin exchange.

Installing four different substituents on a general carbon atom constitutes the *conditio sine qua non* for considering it a stereogenic center. In 2008, Hammerschmidt introduced chiral halocarbenoids featuring respectively: *i*) lithium; *ii*) halogen; *iii*) deuterium and *iv*) hydrogen (*i.e.* LiCHDX). These chiral α-substituted lithium carbenoids – existing as chloro-, bromo-, iodo-, and fluoro- methyllithium were formed from the corresponding chiral stannane precursors upon treatment with MeLi, at low

temperatures (**Scheme 17**).[52] In turn, the chiral chloromethylstannane-[D1] (**21**) was synthetized from tributylstannyl-[D1]-methanol (**20**) under Appel-type conditions (PPh_3/CCl_4).[53]



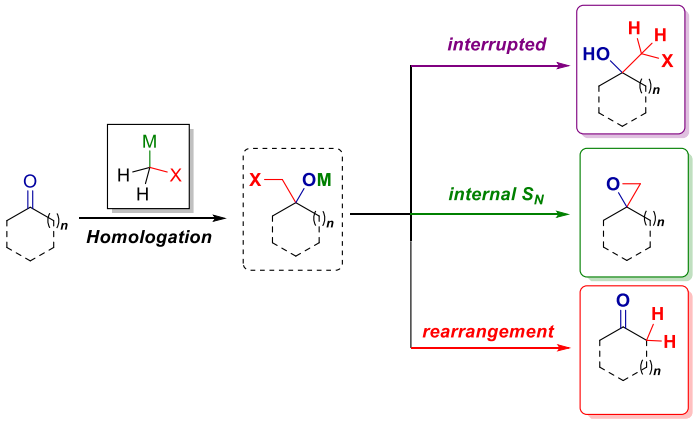
Scheme 17. Carbenoids formation via lithium-tin exchange.

The carbenoid genesis was dependent from the nature of the lithium reagent used: MeLi gave satisfying results, whereas *n*-BuLi, probably due to its higher basicity, was responsible for the formation of byproducts. If the chiral stability of bromo and chloromethyllithium reagents was retained at -78°C – enabling the trapping with the electrophile also after 30 s - the chiral stability of fluoro and iodomethyllithium was lower and require the cooling at -95°C.[52a,52b]

1.4 The role of lithium carbenoids in homologation reactions: an overview.

Starting from the seminal studies of Köbrich,[54] lithium carbenoids emerged as useful and versatile tools in homologation chemistry and their reactivity has been shown in processes involving a plethora of electrophiles. Importantly, not only carbon-centered electrophiles were employed but also heteroatoms such as boron,[38] germanium,[55] tin,[55] silicon,[56] and zirconium[57] could be employed. Our group focused its research in developing new homologation methodologies on a variety of electrophiles using in prevalence halomethyllithium.[2c,21a] The large applicability and versatility of these reagents can be ascribed to the carbanionic character and, the possible distinct outcomes of homologations conducted with such nucleophilic species can be categorized as follows (**Scheme 18**):[58]

a) The *interrupted* homologation (in which the halogen is still present in the final product and available for further modification).
b) The *ring-closure* in which the lithium intermediate (usually an alkoxide) undergoes internal nucleophilic rearrangement leading to an *in situ* ring closure to obtain a cycle.
c) The *pure* homologation, leading to a molecular rearrangement in which the halogen is replaced by a carbon atom upon fine tuning of the reaction conditions, being a typical example the ring enlargement of cyclic ketones.



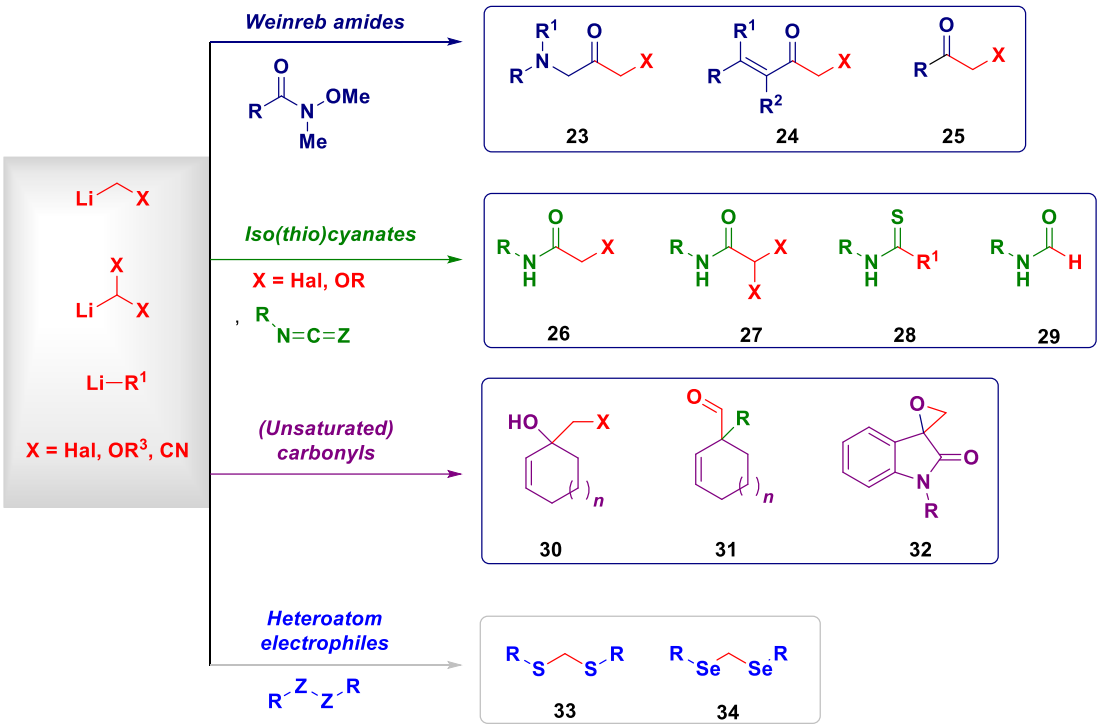
Scheme 18. Overview of lithium carbenoids homologation.

Typical electrophilic partners for halolithium carbenoids are carbonyl compounds (aldehydes or ketones) which easily undergo homologation reactions and, often are also amenable for ring closure. We could identify 2 fundamental steps in the homologation process of carbonyls:[2c] 1) the addition of the nucleophile X-CH_2-M to the electrophilic carbon leading to the tetrahedral intermediate, which 2) upon subsequent protonation conducts to the formation of the homologated product (halohydrin). Evidently, assuring non-protonating conditions impedes the simple halohydrin formation and thus, is a conceptually simple tactic for late modifications of the intermediate alkoxide.

The interrupted homologation is typical for weak electrophiles, as Weinreb amides,[59] and is representing a prominent chapter of Pace´s group research (**Scheme 19**).[60] A variety of different XCH_2M reagents have been introduced to variously decorated Weinreb amides *en route* to highly chemoselective preparations of α-substituted ketones.[61] Notably, in the case of optically active Weinreb amides, full retention of configuration was observed.[62] This interesting aspect can be rationalized considering the intrinsic tamed basicity of a $LiCH_2X$ reagent compared to a pure $LiCH_2R$ analogue able to activate deprotonation and thus racemization phenomena. Mechanistic studies permitted to evidence for the first time tetrahedral intermediate in the process:[62b,63] upon the careful optimization of the work-up procedure, the group succeeded in isolating the corresponding *O*-TMS protected hemiaminal intermediates. Due to the high electrophilicity of the carbon, iso-and isothiocyanate were valuable reagents for the preparation of α-substituted *N*-methyl(thio)amides upon treatment of lithium carbenoids.[45b,64] The versatility of the procedure resulted also in the formation of thioamides, formamides, and thioformamides, switching to the use of hydrides or (enantio)-enriched organolithiums as nucleophiles.[64c,65] α,β-Unsaturated carbonyls give simple interrupted homologation products as halohydrins whereas, ring closure products as epoxides could be easily formed under basic conditions.[66] More complex structures such as spiro-epoxindoles and quaternary fully substituted aldehydes are obtainable by triggering the Meinwald-rearrangement.[31a] Chiral lithiated carbamates or chiral lithiated *N*-Boc pyrrolidines – generated under enantioselective

sparteine-imparted deprotonation - served to homologate Weinreb amides to novel α-oxy and cyclic α-aminoketones.[62b]

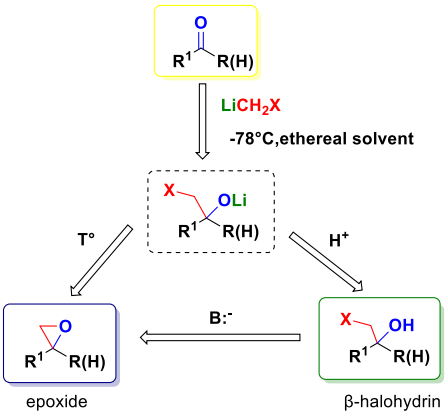
Non carbon electrophiles (R-Z-LG, Z = Se, Ge, S, Sn, P) undergo analogous homologation sequences upon treatment with lithium carbenoids.[55,67] The insertion of the methylenic unit to diselenides and disulfides furnishes the corresponding diseleno- and dithioacetals.[68] Halogermanes, halostannanes, phosphine, phosphine oxides and phosphonates show analogous reactivity towards a plethora of lithium carbenoids, thus expanding the set of the electrophilic partners.[55]



Scheme 19. Overview of homologation reactions in the Pace group.

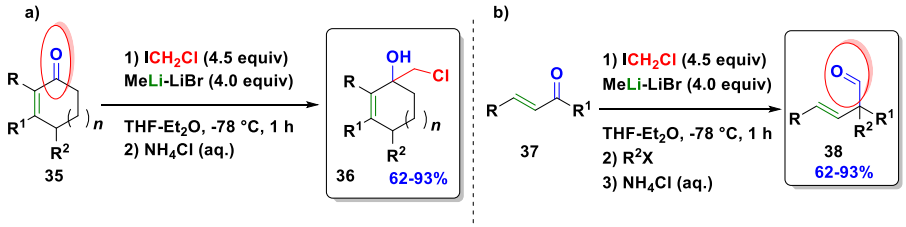
1.4.1 Carbonyl compounds as electrophilic partners

As reported independently previously by Cainelli,[28a] Villieras[26] and Matteson[25c,36] and later by Barlueng[27b] and Concellón[69] carbonyl compounds represent the most employed electrophiles homologation reactions with halomethyllithium carbenoids. Aldehydes and ketones are simply converted to the corresponding β-halohydrins, which upon increasing of temperature (from -78 °C to rt) or through a base-assisted process, undergo ring closure to give the corresponding epoxides (**Scheme 20**).



Scheme 20. Addition to carbonyl compounds.

The application of chloromethyllithium on more challangenging substrates such as unsaturated cyclic ketones was reported by Pace and coworkers.[34,66a] The 1,2-addition of the halolithium carbenoids gave access to allylic alcohols (**36**) as unique products, without observing any conjugate addition or Simmons–Smith-like cyclopropanation adducts.

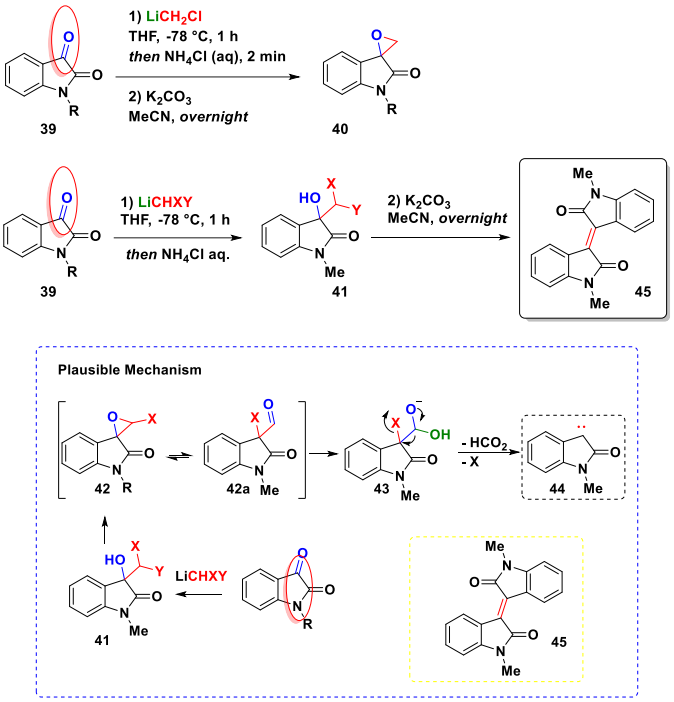


Scheme 21. a) Chemoselective addition of chloromethyllithium to cyclic ketones, b) formation of fully α-substituted aldehyde through Meinwald rearrangement.

On the other hand, the attempt to homologate α,β-unsaturated ketones into vinyl epoxides furnished fully α-substituted aldehydes (**38**) (**Scheme 21**).[31a] The mechanism elucidated *via* the use of deuterated halomethyllithium carbenoids can be summarized as follows: 1) C_1-homologation / ring closure to the epoxide; 2) epoxide-aldehyde Lewis acid mediated isomerization (*i.e.* Meinwald rearrangement)[70] and, 3) electrophilic trapping.

Pace reported a chemoselective synthesis of spiro-epoxyoxindoles (**40**) starting from functionalized isatines (**39**).[34] These manifolds represent extraordinary reactive ketones (at the level of the C-3 carbon) due to the presence of the vicinal electron-withdrawing lactam moiety.[71] Thus, the C-3 carbon undergo the nucleophilic addition of halomethyllithium carbenoids: no concomitant addition at the C2 carbon was observed and, for an unsubstituted isatin, the acidic NH group did not interfere with the process. The homologation with chloromethyllithium followed by a base-mediated ring closure – of the isolable

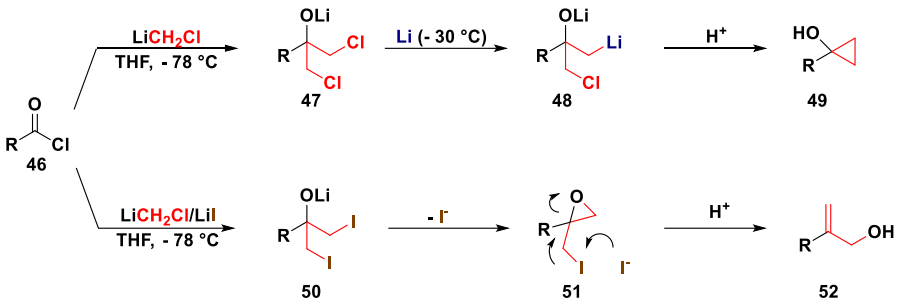
halohydrins – produced chemoselectively a variety of spiro-epoxyoxoindoles with different functionalization degree on both the nitrogen and the aromatic ring.



Scheme 22. Formation of epoxyoxoindoles and N,N-dimethyl-isoindigo structures with the proposed mechanism.

The optimized protocol spurred the group to evaluate dihalomethyllithium carbenoids for accessing valuable haloepoxides: surprisingly, the formation of unexpected *N,N*-dimethyl-isoindigo structure (**45**) was observed (**Scheme 22**).[34] The dihalomethyllithium species - generated *via* deprotonation of dihalomethane using LTMP-lithium base - furnished the intermediate dihaloydrines (**41**) which then rearranged upon K_2CO_3-treatment in acetonitrile at rt. It is possible to rationalize the transformation by assuming a Meinwald rearrangement yielding a quaternary α-haloaldehyde (**42a**) prone to undergo the base attack and elimination of the halide: collectively, a free carbene species (**44**) is formed and dimerizes into the observed iso-indigo motif.

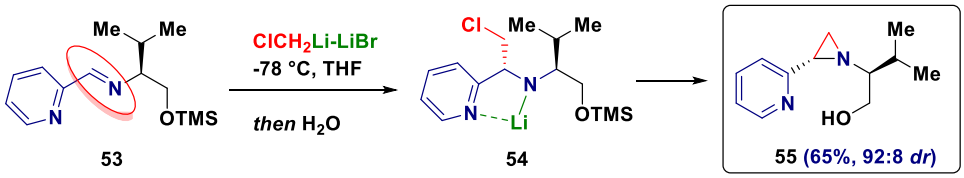
The homologation of acyl chlorides (**46**) using chloromethyllithium carbenoid is known since 1988 when Barluenga and coworkers reported the synthesis of cyclopropanols (**49**).[72] The strong reactivity of acyl halides causes the double addition of the lithium carbenoids with the formation of an alkoxide intermediate (**47**) which, in the presence of Li metal, provides a dilithiated species precursor (**48**) of the cyclopropane. Instead, by using LiI and epoxidation/elimination is activated, thus affording the corresponding allylic alcohols (**52**) (**Scheme 23**).



Scheme 23. Acyl chloride for the preparation of cyclopropanols and allyl alcohol.

1.4.2 imine as electrophilic partners

The first example of imines in homologation processes carried out with halolithium carbenoids was described by Savoia in 2006:[73] he reported the addition of chloromethyllithium to substituted 2-pyridinimines (**53**) to form diastereopure aziridines (**55**, dr 92:8) (**Scheme 24**). The β-haloamines intermediates (**54**) spontaneously undergo cyclization with the increase of the temperature (up to 20 °C). The presence of the 2-piridinimine fragment appeared to be crucial because the coordination of the carbenoids increases the nucleophilicity and thus, the attack to the low electrophilic imine carbon. However, the chemocontrol of the reaction is particularly challenging when additional electrophilic sites are present in the molecule (*e.g.* ester).

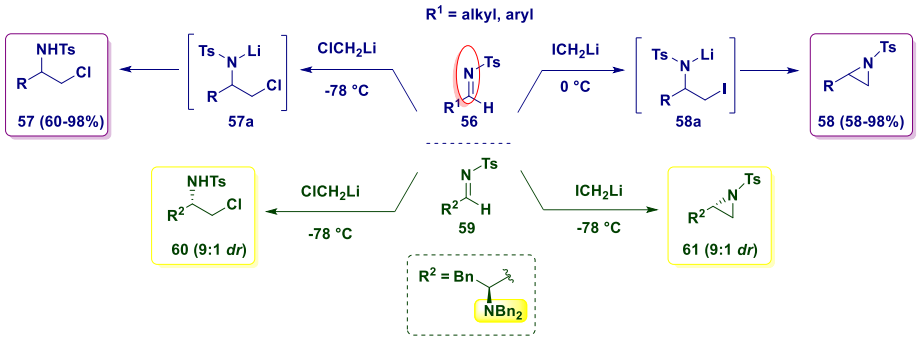


Scheme 24. Savoia's carbenoid-mediated 2-aziridination of 2-pyridinimines.

In order to increase the tamed electrophilicity of imines, Concellón proposed the installation of an electron-withdrawing element on the nitrogen (*N*-sulfonyl-type).[69,74] *N*-tosylaziridines (**56**) react with iodomethyllithium and the resulting β-iodoamide intermediates (**58a**) undergo a spontaneous cyclization to give the corresponding aziridines (**58**). The presence of the sterically hindered *N,N*-dibenzylamino group gave an excellent stereochemical control (9:1 *dr*). Notably, the use of $ClCH_2Li$ at -78 °C afforded the β-chloroamide (**57**), probably because of the tamed tendency of chlorine to act as a leaving group during the cyclization.

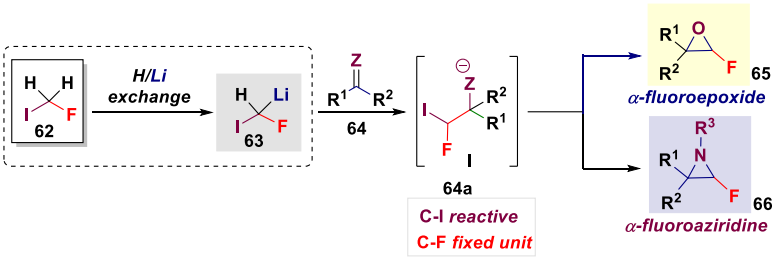
β-haloamines and aziridines are fundamental scaffolds for the synthesis of amino acids, β-lactams and alkaloids; thus, the conversion of imines into these derivatives spurred the development of several methodologies for accomplishing the task. Bull proposed *N*-Boc and *N*-Ts imines (**59**) as optimal

electrophilic partners for diiodomethyl lithium and magnesium carbenoids thus, accessing α-iodoaziridines (**Scheme 25**).[75]



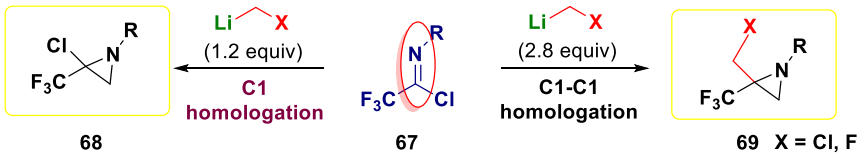
Scheme 25. Addition of lithium carbenoids to imine: divergent access to *N*-containing compounds.

In 2019, Pace and coworkers introduced for the first time the use of LiCHFI carbenoid (**63**), obtained via deprotonation of fluoroiodomethane (**62**) with a lithium base (LiN(*i*-Pr)Cy or LDA) at -78 °C under Barbier-type condition.[76] Accordingly, they used this unstable carbenoid for synthesizing rare α-fluoroepoxides (**65**) and α-fluoroaziridines (**66**) through a homologation-ring closure sequence on ketones and imines (**64**) (**Scheme 26**).



Scheme 26. Addition of fluoroiodomethyl lithium to ketones and imines.

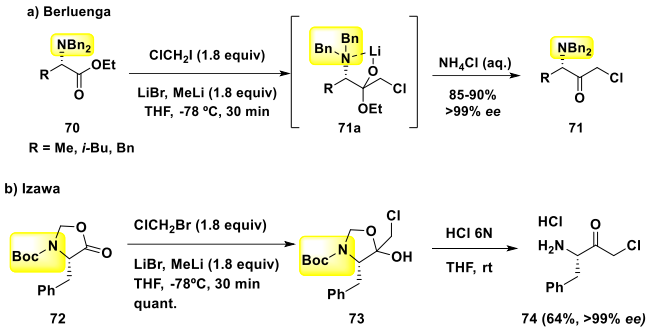
In the same year, Pace documented a novel single synthetic strategy to access all-substituted trifluoromethylaziridines (**Scheme 27***) via* mono- or bis- homologation of trifluoroacetimidoyl chlorides (**67**).[31b,31c] These easily accessible electrophiles underwent a stoichiometry-controlled addition of one or two methylene units, thus obtaining chloro- (**68**) and halomethylaziridines (**69**).



Scheme 27. Pace´s strategy to form trifluoromethylaziridines.

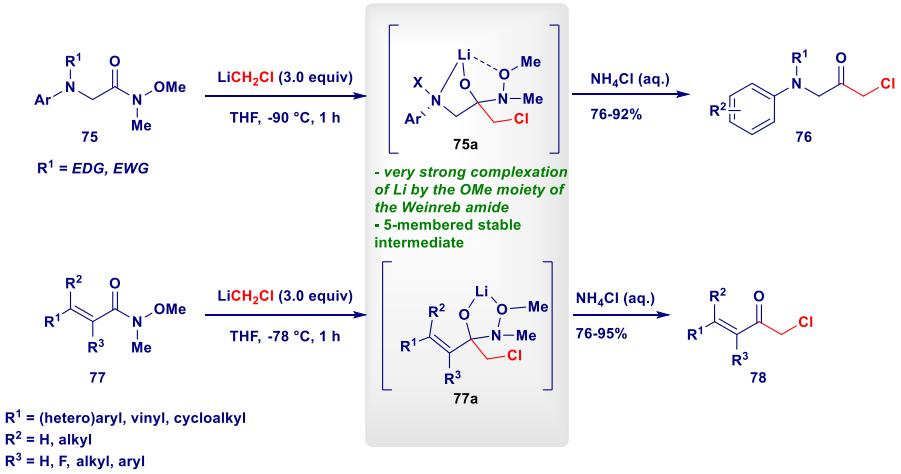
1.4.3 Weinreb amides

Weinreb and Nahm reported that „ *N-methoxy-N-methylamides combine cleanly with both Grignard reagents and organolithium species in THF to form ketones*“ avoiding the notorious undesirable overaddition of the carbanions to the substrates (carboxylic acids or esters).[59a] The constitutive *N*-methoxy group guarantees the stabilization of the five-membered tetrahedral intermediate, through the coordination of the metal and, thus ensuring the chemocontrol of the process.[59b] In order to guarantee the chemocontrol of the reaction, when for example esters are employed, it is necessary the presence of stabilizing groups such as disubstitued amino moieties, as reported by Barluenga[27b] and Izawa.[77] (**Scheme 28**).



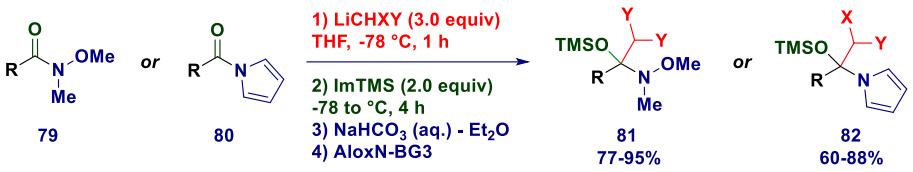
Scheme 28. a) Use of α-*N-dibenzyl* esters to access α-haloketones b) Izawa's homologation of esters

The stabilization of the tetrahedral intermediate, formed upon the addition of lithium carbenoids to Weinreb amides (**75, 77**), allowed high chemocontrol during the synthesis of α-haloketones, including α-amino substituted[61] (**76**) and α,β-unsaturated systems[66b] (**78**) (**Scheme 29**). The strategy was employed by Pace to access an important fragment for the synthesis of the HIV inhibitor Nelfinavir.[78] Moreover, the group succeeded to isolate and characterize the tetrahedral intermediates (**81,82**) from the reaction of (di)halocarbenoids with Weinreb amides (**79**) and *N*-acylpirroles (**80**) as *O*-TMS protected hemiaminals.[63]



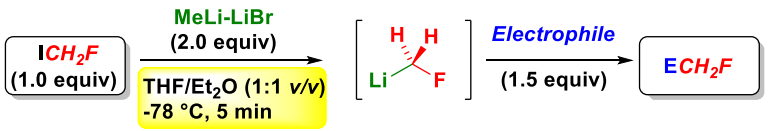
Scheme 29. Weinreb amides for the synthesis of α-substituted ketones.

It is important to highlight two fundamental points for the successful trapping of these unstable motifs: the use of TMS-imidazole as silylating agent and, the use of deactivated neutral alumina (Brockmann grade III) for the chromatographic purification (**Scheme 30**).



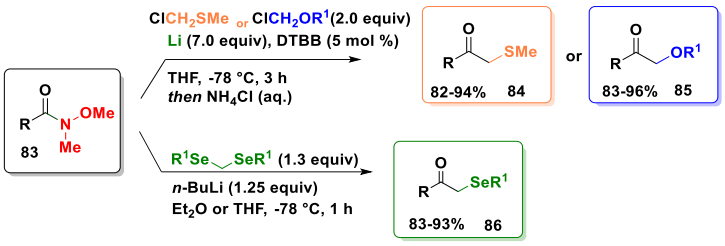
Scheme 30. Trapping of tetrahedral intermediates using TMS-imidazole.

Among the α-haloketones, α-fluoro derivatives are undoubtedly interesting due to the importance of fluorine in chemistry and, the limited synthetic tools available for their obtainment.[79] For long time, the access to these compounds represented a big challenge mainly because of the extreme instability of nucleophilic CH_2F fragments.[80] The homologation via fluorinated lithium carbenoids suffers from the high thermal instability due to the facile α-elimination of LiF.[30e] To overcome this limitation, different stabilizing groups - mostly electron-withdrawing elements - were proposed. For example, Hu introduced fluoromethylphenyl sulfone, whose use *per se* required an additional removing step under harsh conditions.[81] As anticipated, a preliminary solution was proposed by Hammerschmidt who showed the existence of the fluoromethyllithium carbenoid prepared under Barbier-type conditions through a lithium/tin exchange conducted on a fluoromethylstannane.[52d] This methodology unfortunately found limited preparative application, being validated in only two examples with modest yields (<40%). In 2017, Pace for the first time introduced the use of fluoroiodomethane as a valid precursor for $LiCH_2F$ which was generated under Barbier-type conditions at -78 °C with MeLi-LiBr.[82] The key points of the process are the accurate stoichiometry (1:1.5:2.0) with a small excess of organolithium reagent and, the use of a 1:1 (*v*/*v*) THF/Et_2O mixture for preserving the chemical integrity of the carbenoid. The versatility and feasibility of the method was demonstrated in the direct monofluoromethylation of Weinreb amides (among other electrophiles) to access in one step α-fluoromethyl ketones (**Scheme 31**).



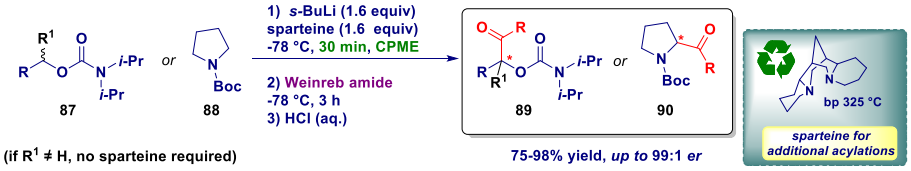
Scheme 31. Using the highly unstable LiCH2F for the direct monofluoromethylation of Weinreb amides.

Weinreb amides (**83**) react smoothly also in the case of nitrile-type carbanions - generated from acetonitriles to afford substituted α-cyanomethyl ketones[83] - α-oxyketones[62a,62b] (**85**) and β-oxothioethers (**84**),[84] *via* the nucleophilic addition of $LiCH_2OR$ and $LiCH_2SR$ generated under Yus' arene catalyzed reductive lithiation of $ClCH_2ZR$ reagents (Z = O, S).[85] Similarly, $LiCH_2SeR$ reagents were generated by lithium/selenium exchange starting from diselenoacetals. (**Scheme 32**).[62c,86]



Scheme 32. Versatility of Weinreb amides to generate substituted ketones.

Weinreb amides demonstrated their flexibility and capability of being unique acylating manifolds for organometallics also in the case of enantiopure organolithium reagents. In 2019, Pace and coworkers reported a high-yielding acylation of chiral lithium carbenoids revisiting the well-established Hoppe-Beak chemistry (**Scheme 33**).[62b] Generating the lithium carbenoid in the presence of the appropriate sparteine enantiomer and, using Weinreb amide as electrophilic partners, it was possible to achieve with an excellent stereofidelity novel configurationally stable α-oxy (**89**) and cyclic α-aminoketones (**90**).

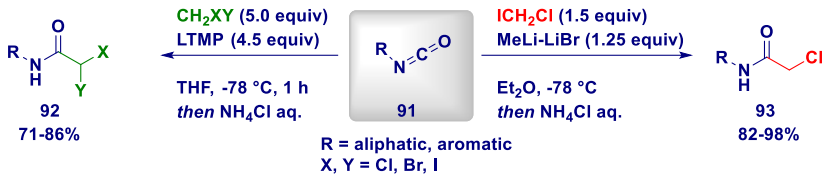


Scheme 33. acylation of chiral lithium carbenoids with Weinreb amides.

1.4.4 Heterocumulenes

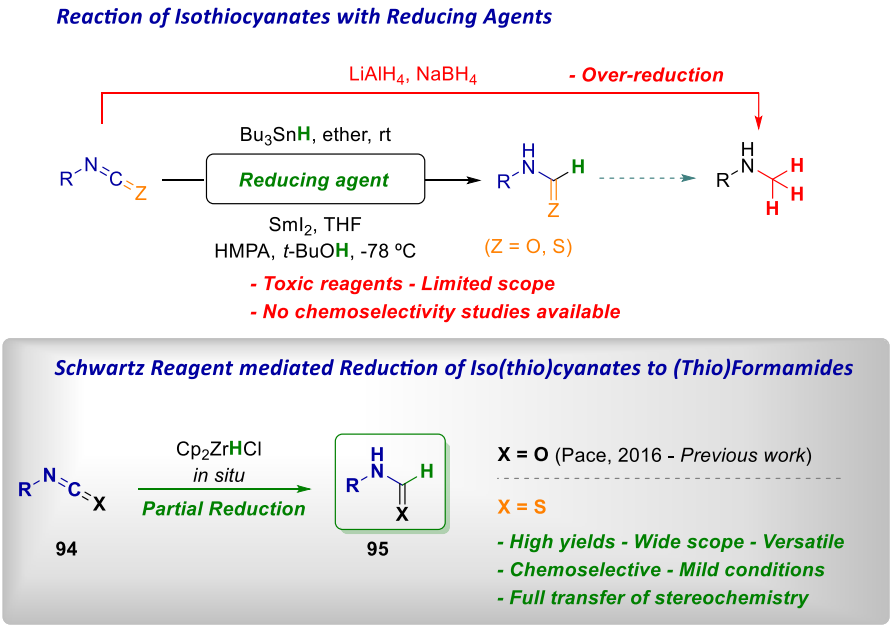
Heterocumulenes [*i.e.* iso(thio)cyanates] were recognized as optimal electrophilic partners for organometallic reagents since 1920s, when Gillman proposed them as preferred substrates for tritation procedures of both organolithium and organomagnesium reagents.[87] Chemically, these reagents add to the *sp*-hybrized carbon atom of electrophiles, thus forging an amide upon hydrolysis. Curiously, this strategy for accessing (thio)amides remained somehow eclipsed till Bode in 2012 underlined the full synthetic significance for the high-yielding preparation of sterically hindered amides.[88] Constitutively, heterocumulenes feature a high electrophilicity at the level of the carbon atom which therefore is not

modulated by possible deleterious effects (electronic and steric) displayed by the substituent on the nitrogen.



Scheme 34. Synthesis of α-haloamides from isocyanates and lithium carbenoids.

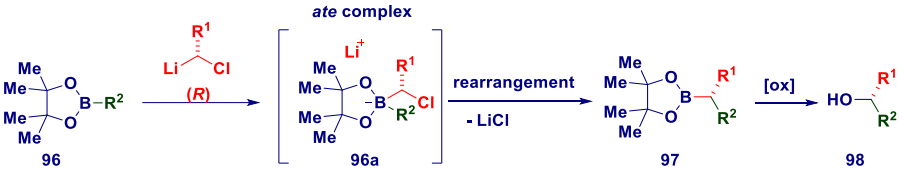
Our group explored these reagents employing halo- and dihalo lithium carbenoids to access α-haloacetamides (**93**),[64b] α,α-dihaloamides[45b] (**92**) and, lately thioamides (with organolithiums)[64c] or iminothietanes (with $LiCH_2Br$) *via* a sequential rearrangement.[64a] (**Scheme 34**) The protocols are characterized by an outstanding chemoselectivity, high yield and retention of chiral information embodied in chiral iso(thio)cyanates. The strategy documents a remarkable sustainable profile, as a consequence of avoiding, in the case of thioamides, the requirement of harsh conditions, long reaction times and the use of non-pleasant thionating agents.[89] Moreover, the group extended the applicability of iso(thio)cyanates (**94**) also for the nucleophilic hydride-transfer to afford formamides (**95**), employing the Schwartz reagent[90] as chemoselective H^- source, avoiding the full reduction of the isocyanate to *N*-methyl amines (**Scheme 35**).[65b]



Scheme 35. Nucleophilic hydride-transfer employing the Schwartz reagent.

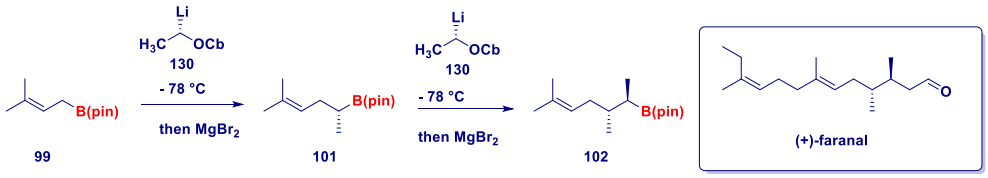
1.4.5 Boron as electrophilic partner

Boron chemistry is a well-established branch of organometallic chemistry, due to the increasing interest in borylated building blocks in academia and industry.[91] The first employment of boron-containing compounds in carbenoid chemistry dates back to 1980, when Matteson reported the first homologation of boronic ester with halocarbenoids.[25a] Based on the pioneer study of Matteson, the boronic chemistry moved toward a more stereoselective approach. In fact, Blakemore, used a diasteropure α-chloroalkyl sulfoxide to homologate organoboron derivatives, and lately, pinacol boronates (**96**) were recognized as optimal starting material to accomplish homologation reactions employing enantioenriched lithium carbenoids (**Scheme 36**).[47d,47e,92]



Scheme 36. Blakemore's stereocontrolled homologation of boronic esters.

A significant contribution in the field was introduced by Aggarwal and coworkers, that found the boronic esters reactive towards Hoppe`s chiral lithiated carbamates, thus opening the way to stereoselective homologation of pinacol boronates for accessing complex natural products such as the insect pheromone (+)-faranal (**Scheme 37**).[93]

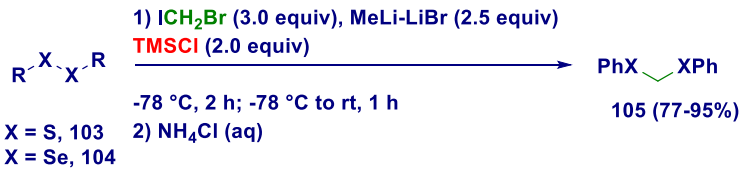


Scheme 37. Synthesis of (+)-faranal.

1.4.6 Homologation of Heteroatom Electrophiles

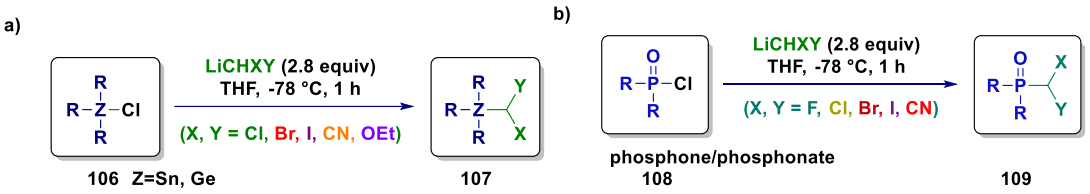
Other than boron homologations, the insertion of a [(di)halo]-methylenic fragment to non-carbon electrophiles represents a valid tool in organic synthesis. The heteroatoms electrophiles could be

homologated with the use of lithium carbenoids as showed by Pace and coworkers. Disulfides (**103**) and diselenides (**104**) were homologated with bromomethyllithium, leading to a stable α-halomethyl thiosulfide intermediate that, similarly to the Matteson reaction of boronic esters, undergo nucleophilic displacement by the mercapto anion (RS-) released during the first homologative step.[68a] The halogen of the carbenoid is present in the intermediate but not in the final product, being the use of TMSCl beneficial for triggering the displacement *via* a coordination effect. The procedure showed an excellent scope and the protocol could be extended also to the homologation of unsymmetrical disulfides (**105**) (**Scheme 38**).



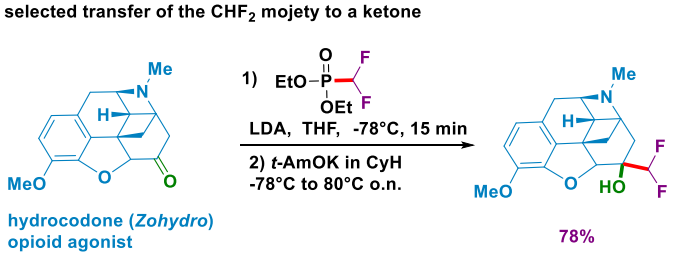
Scheme 38. Homologation of disulfides and diselenides *via* bromomethyllithium carbenoid.

In order to demonstrate the effectiveness of lithium carbenoids in the homologation of non-carbon electrophiles, different protocols were developed to access α- and α,α- difunctionalized organostannanes / organogermanes(**107**),[55] organophosphines , phosphine oxides and phosphonates (**109**) (**Scheme 39**).[67]



Scheme 39. Homologation of Organostannanes, organogermanes (a), organophosphines, phosphine oxides and phosphonates (b).

Notably, difluoromethylphosphonate esters were afterwards employed for functionalizing drug molecules (*vide infra*), as in the case of the carbonyl moiety of the narcotic agent Hydrocodone (**Scheme 40**).



Scheme 40. Difluoromethylationof Hydrocodone.

2. Organosilicon chemistry

Among organometallics, organosilicon compounds are experiencing a continuous interest across the chemical sciences. Nowadays, the number of available silicon compounds is considerable and is growing every year, mostly due to the stability, availability and versatility of this class of reagents.[94] It is important to highlight their characteristics before embarking in synthetic applications.[95] As a tetrahedral carbon atom, silicon shows an sp^3-hybridization, thus possesses the same formal structure of a carbon. The C-C bond shows a greater stability in comparison to the Si-Si bond and, a similar difference affects the C-H and Si-H bonds. In contrast, the Si-O is muchmore stable than a general C-O one. This makes clear the high applicability of Si-O containing compounds in resins and polimers, such as silicones (e.g. polydimethylsiloxane PDMS), silsesquioxanes (DDSQ's), or silica coating. The stability of the Si-O bond is documented by the broad use as silylating agents for protecting alcohols (e.g. alkoxide intermediate), phenols, amines, carboxylic acids, amides, thiols and alkynes or, for the derivatization of compounds.[96]

If the comparison of the bond strengths of Si-H and C-H does not show consistent differences, when we move to compare the electronegativity of Si, C, and H atoms (S i= 1.8, C = 2.5, H = 2.1),[97] it is evident the difference between the polarization of the Si–H, C–H and, accordingly the Si-C bonds. Carbon-hydrogen bonds are thus polarized in the direction $C^{\delta-}$ –$H^{\delta+}$, whereas Si–H bonds are $Si^{\delta+}$–$H^{\delta-}$, making organosilanes – presenting Si-H bonds - good sources of nucleophilic hydrides to be employed as versatile reducing agents.[96b] The higher electronegativity of carbon implies that, in the case of Si-C bonds, the carbon possesses a higher negative charge than silicon, making silicon-based reagents valuable and attractive species (*e.g.* Hiyama coupling).[94]

The functional groups attached to the silicon atom could profoundly influence the chemical behavior of these compounds and, for example, the presence of halogens (I, Cl, Br, F) confers high sensitivity to the nucleophilic attack. Halosilanes, in fact, react easily with organometallic reagents such as Grignards and organolithium to give the corresponding organosilanes.[98]

2.1. Organosilicon hydrides

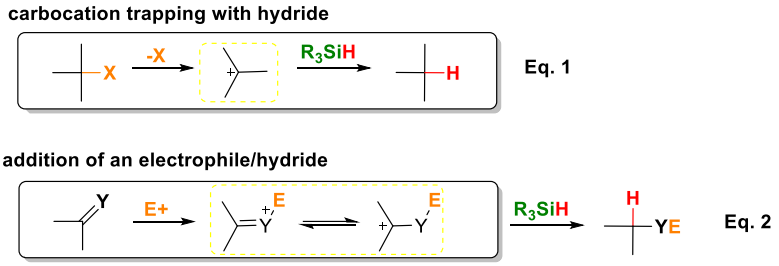
As anticipated, organosilicon compounds that contain at least one Si-H bond are valuable source of hydride and could be successfully employed as reducing agents.[99] As mentioned before, this is mainly due to the characteristic polarization of the Si-H bond, but the difference in electronegativity of such bond is not strong as in ionic hydrides (*e.g.*, LiH or NaH), thus, usually silanes allow reduction under mild conditions with an excellent selectivity towards sensitive functional groups. The Si-H bond could be described as a covalent bond, thus organosilicon

hydrides have little intrinsic nucleophilic character and, in general, react with organic compound only upon activation. Two are the possible mechanisms of reduction carried out by hydrosilanes: hydrosilylation and ionic reduction.[100]

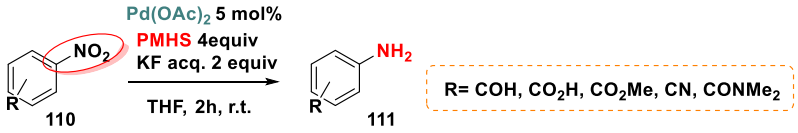
a) The catalyzed addition of a silane to a multiple bonded system, represents the hydrosilylation reduction and, thus it is a typical methodology to form Si-C bonds.

b) The ionic reduction could be defined as a reduction in which the hydride is transferred to a formal carbocation.

   The ionic reduction of organic compounds could be described with two different mechanisms: The formation of a carbocation which is trapped by the hydride delivered from the organosilicon (Eq. 1). The formation of the carbocation could be also due to the addition of an electrophile (proton or Lewis acid) on a double bound containing atoms such as *O, N, C*, or *S* (Eq. 2) and, then continuing to react following Eq. 1.



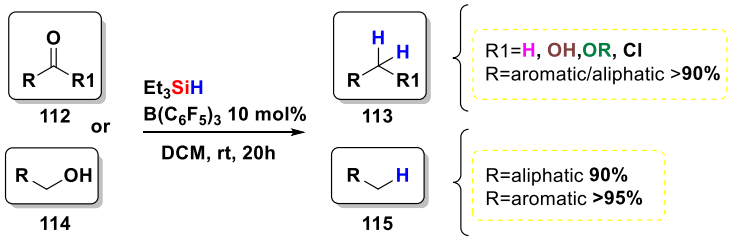
Thus, only for intermediates or complexes possessing considerable carbocationic character could be effective the hydride transfer and, ultimately this could enhance the selectivity of the process carried out by organosilicon hydrides. As discussed before, a catalyst is needed to promote the reduction, usually (Lewis) acids or, in the case of polymethylhydrosiloxane (PMHS) a metal such as Pd^0.[100a] The Pd-mediated reduction was showed to be an efficient alternative of the use of tri-*n*-butyltin hydride in the selective reduction of aromatic nitro group (**110**) to amine (**111**) (**Scheme 41**), avoiding the shortcomings associated with organotin compounds (toxicity).[101]



Scheme 41. selective reduction of aromatic nitro group to amine.

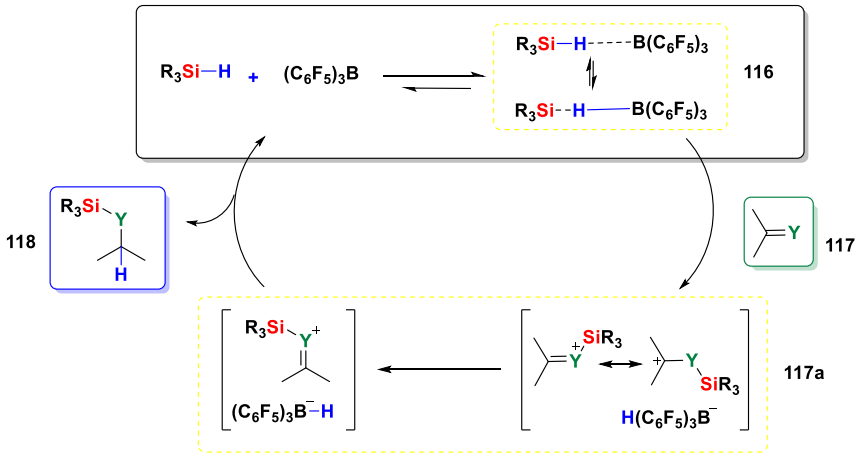
A variety of silanes are reported to accomplish the acid-promoted reduction, *e.g.* triethylsilane in the presence of trifluoroacetic acid (TFA) in DCM used for the reduction of alcohols to the corresponding hydrocarbons.[102] The process is reflecting the stability of the carbocation intermediate leading to clean and high yield products when the alcohol could produce a relatively

stable carbocation. Thus, tertiary alkyl alcohols undergo facile reduction when treated with acids in the presence of organosilicon hydrides, while primary alcohols do not produce the corresponding alkanes. Gevorgyan, Yamamoto, and co-workers, in 2000, reported an interesting reaction mechanism, introducing the use of catalytic amounts of tris(pentafluorophenyl)borane, [$B(C_6F_5)_3$] and an excess of triethylsilane thus, enabling the reduction of primary alcohols (**114**), carbonyl and carboxyl compounds (**112**) (**Scheme 42**).[103]



Scheme 42. Use of $B(C_6F_5)_3$ as catalyst to reduce carbonyls, carboxyl and primary alcohols.

The mechanism proposed involves the first formation of a hydrosilane–borane adduct (**116**) which undergoes the nucleophilic attack operated by the oxygen (**117**), leading to a *O*-silylated intermediate (**117a**); then, the hydride is transferred to the boron atom and, subsequently the boron hydride transfers the H^- to the carbon to generate the reduction product (**118**) and, concomitantly is regenerated the borane (**Scheme 43**).



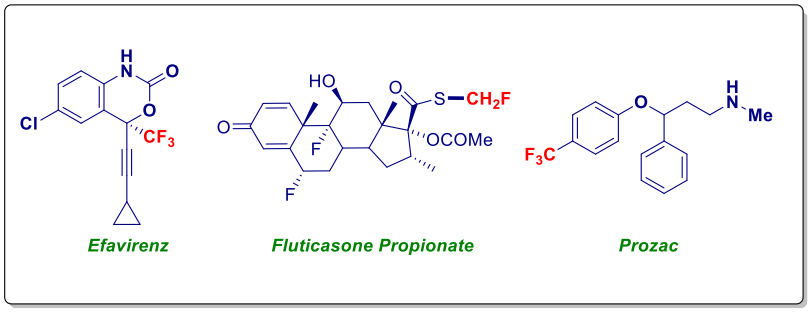
Scheme 43. Proposed mechanism involving an hydrosilane-borane adduct.

However, the reduction of secondary and tertiary alcohols was possible only with equimolar amount of triethylsilane, maybe due to a steric hindrance of the silicon-borane adduct.[104] An advance in the methodology was reported by McRae levered on the use of a less hindered *n*-$BuSiH_3$, thus allowing the reduction of secondary and tertiary alcohols.[105]

2.2. Organosilicon reagents in difluromethylation.

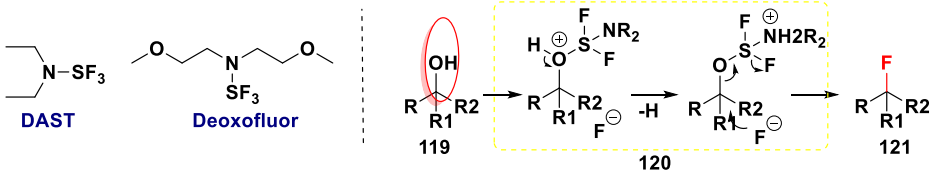
2.2.1 Importance of Fluorine in organic and medicinal chemistry.

Even if fluorine is almost absent in natural products, *ca.* 20% of drugs available on the market contain this halogen; representative examples are Fluoxetine (Prozac, antidepressant), Efavirenz (HIV-antiviral) or Fluticasone propionate (antiasthmatic) (**Scheme 44**).[79b,106] The selective insertion of the fluorine in an organic skeleton is one of the most used modifications in medicinal chemistry.[107] This is is mainly due to the fact that this small halogen appears to modulate chemical and biological properties of a compound; moreover, its insertion was showed to improve metabolic stability, bioavailability and interactions with proteins.[108]



Scheme 44. Examples of approved drugs containing the Fluorine.

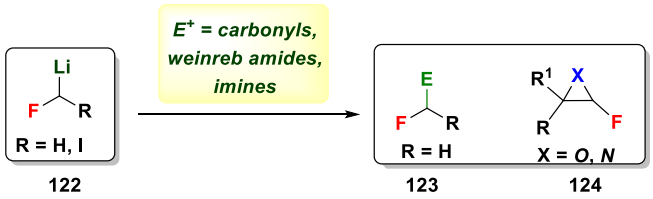
Thus, selective mono-, di-, and trifluoromethylation is a fast growing field in chemistry and the development of new tactics represent an intriguing challenge for synthetic chemists. Among the fluorinated organocompounds, a special attention has been given to compounds bearing the difluoromethyl fragment (CHF_2).[109] The interest towards the -CHF_2 insertion finds its bases on the fact that the presence of two fluorine atoms increases the acidity of the α-proton, thus the resulting CHF_2 unit is acting as H-donor in the hydrogen bonding.[110] Furthermore, it is a lipophilic isoster of the carbinol group CH_2OH.[109,111] We could rank in two groups the strategies allowing the insertion of a fluorine into a substrate: The fluorine is incorporated using fluorine sources in which the fluorine anion is the active species (DAST, Selectfluor or the safer Deoxo fluor **Scheme 45**), or the nucleophilic addition, in which we could observe the formation of new C-C bonds, well-illustrated by the reach chemistry available with the Ruppert–Prakash reagent ($TMSCF_3$).[112]



Scheme 45. fluorine sources and mechanism.

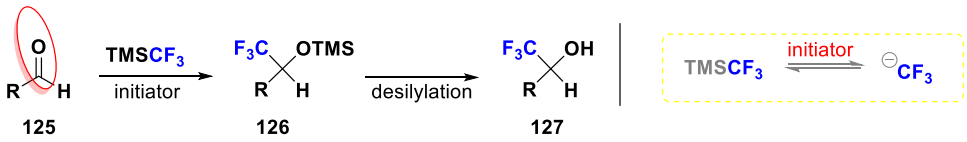
The fluorine anion addition is typical of organosulfur compounds (**120**) containing the N-SF_3 group that are transferring F from the source to the acceptor, usually alcoholic or carbonyls moieties (**119**). The methodology is unfortunately not regioselective (more than one fluorine could be added) to the substrate and strongly dependent on the reactivity of the nucleophile.[113]

The nucleophilic addition, in which the mono-, di-, or trifluoromethyl fragment is transferred from a pro-nucleophilic donor to the electrophilic acceptor with the formation of the new C-C bond, is formally an attractive homologation-based strategy.[80-81] The direct introduction of the mono-, di-, and trifluoromethylenic mojety has been thoroughly explored in the last decades, and appears to be one highly promising. However, the limitation of this tactic is mainly a consequence of the intrinsic instability of the CH_2F, CHF_2 and CF_3 fragments.[114] In this scenario the fluoromethyllithium carbenoid (**122**) demonstrated its versatility, as showed by Pace and coworkers in 2017 (**Scheme 46**).[82] On the other hand, for the trifluoro- and difluoro methylation the silicon-base reagents demonstrated to be an excellent alternative to accomplish these operations.[115]



Scheme 46. Pace fluoromethyllithium carbenoids to access fluoromethylated compounds.

Prakash, Olah, and co-workers reported an efficient trifluoromethylation of ketones and aldehydes (**125**) using $TMSCF_3$.[80] In fact, in the presence of a nucleophilic activator $TMSCF_3$ undergoes an easy cleavage of the Si-CF_3 bond leading to the active CF_3 carbanion-like species able to attack carbonyls for obtaining trifluoromethylated alcohols (**127**) (**Scheme 47**).[116]



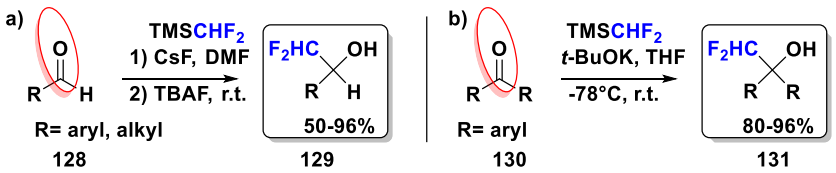
Scheme 47. Prakash reagent in the preparation of trifluoromethylated alcohols.

Fluoride anion derived from tetra-*n*-butylammonium fluoride (TBAF) or CsF have been extensively used as nucleophilic initiators for the trifluoromethylation of aldehydes, and nowadays the Ruppert-Prakash reagent represents the first choice for synthetic applications.[79b]

2.2.2 (difluoromethyl)trimethylsilane ($TMSCHF_2$)

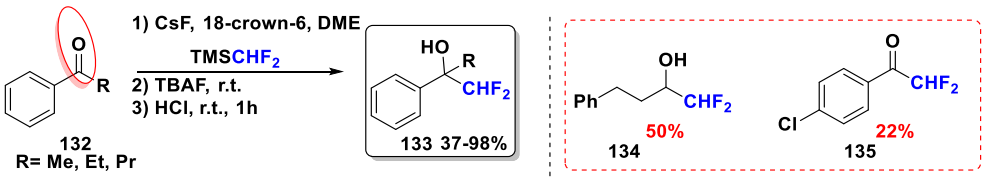
Moving the attention to the CHF_2 moiety, the scenario is notably changing. In fact, if the employing of $TMSCF_3$ is a well-established procedure, the use of $TMSCHF_2$ is much less explored.[117] The CHF_2 carbanion is less stable and less Lewis acid in comparison to the trifluoro counterpart, thus it is less reactive as nucleophile; in addition, the Si–CHF_2 bond is less polarized than the Si–CF_3 bond thus, determining a more difficult cleavage of the Si-C bond.[111b,118] The installation of alternative stabilizing electro-withdrawing groups (sulfones) appeared an effective solution but, the inherently requested removal step, affected the extensive use of the methodology.[119] Finally, in 2011 Hu reported the activation of $TMSCHF_2$ with the use of KF in DMF at room temperature, eventually in the presence of 18-crown-6.[120] Either CsF or TBAF were used as initiators, giving similar results (**Scheme 48a**). The procedure was effective in the case of aromatic aldehydes and ketones; however, diminished yields were observed in the case of the enolizable systems (**Scheme 48b**).

These aspects prompted to introduce the use of *O*-initiators, mostly alkoxides such as *t*-BuOK in THF, allowing the difluoromethylation of less reactive ketones at -78 °C.



Scheme 48. a) Use of CsF and TBAF as iniziator for the difluoromethylation of carbonyls. b) alkoxides as O-initiators.

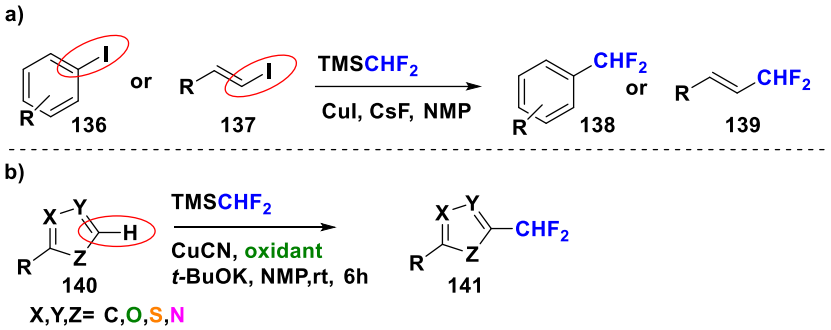
Hu also reported and efficient difluromethylation of enolizable ketones (**132**), using a mixture of CsF/18-crown-6 in 1,2-dimethoxyethane at room temperature to activate the $TMSCHF_2$ (**Scheme 49**).[121] Because of the interaction between the 18-crown-6 and the countercation, it was noticed the important role of the countercation (Cs+ > K+ > Na+).



Scheme 49. Hu´s difluoromethylation of enolizable ketones.

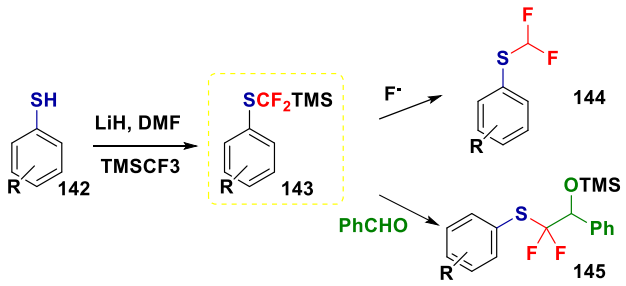
Notably, $TMSCHF_2$ was easily prepared from $TMSCF_3$ with the use of equimolar amount of $NaBH_4$ in dyglime solution at room temperature. The simplicity of the monodefluorurative reduction

protocol and the stability of $TMSCHF_2$ opened the way for the industrial production of this reagent.[117] With easy entries – perhaps nowadays commercially available - different protocols were developed: among them, Cu-mediated difluoromethylation cross coupling of aryl (**136**) and vinyl iodides (**137**) for accessing a variety of difluoromethyl arenes (**138,139**) and, the Cu-mediated oxidative coupling of (hetero)arenes (**140**) (**Scheme 50**).[122]



Scheme 50. a) cross coupling of aryl and vinyl iodides with $TMSCHF_2$, b)difluoromethylation of C-H bonds.

Notably, $TMSCHF_2$, could be also used to prepare a variety of electrophilic difluoromethylating agents. Interestingly, the direct *S*-difluoromethylation was attempted with the use of $TMSCF_3$ upon treatment with LiH in DMF (**Scheme 51**), forming the first trimethylsilyldifluoromethyl sulfide (**143**), which upon fluorine cleavage gives the desired difluomethyl sulfides (**144,145**).[123]



Scheme 51. S-difluoromethylation with the use of $TMSCF_3$ as electrophile.

We could anticipated that versatile protocols for accessing difluoromethyl-ketones, α,α-difluoromethyl (thio)amides and, a variety of difluoromethylated heteroatoms were prepared in the course of this PhD thesis.

3. References

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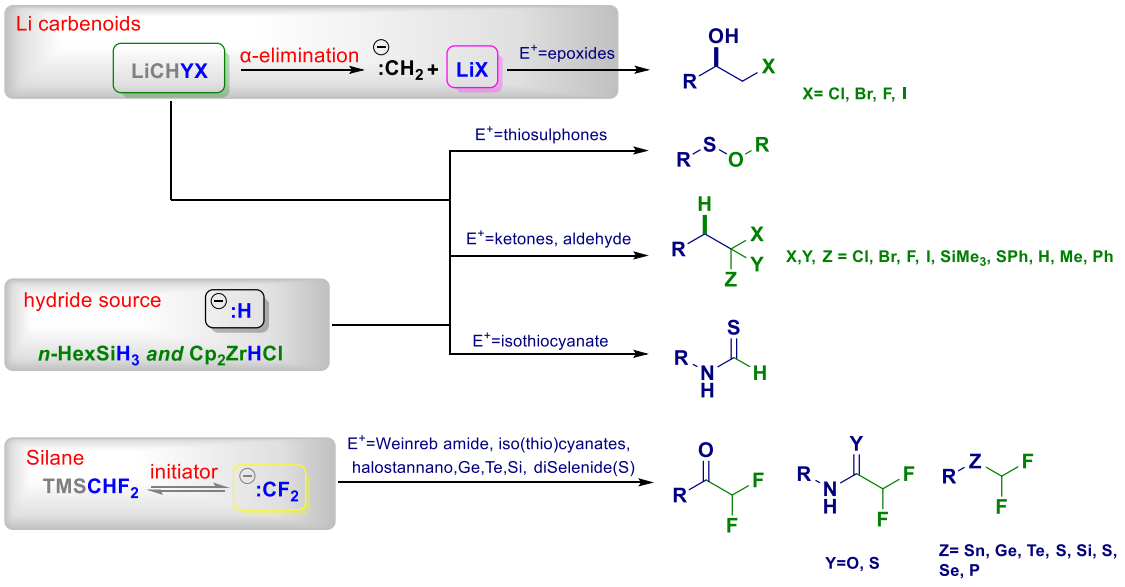
4. Results and Discussion

This section is dedicated to present the achievements obtained during my Doctoral Thesis. The use of halolithium carbenoids in homologation chemistry, and in particular the C1-unit transfer, becomes an important tools for accessing a variety of structural motifs by simply tuning conditions and the nature of these reagents. Thus, we developed simple strategies to access different, structurally complex, building blocks potentially useful in synthetic and medicinal chemistry. The first part of the work was focused to the application of these unique species to different electrophiles (carbon and non-carbon containing compounds) which serve as active intermediates for the sequential addition of a second nucleophile alkoxy- or hydride-type, for the preparation of (n+1)-haloalkyls arrays and oxothioacetals. In addition, by taking advantage of the degradative α-elimination process leading to the formation of a lithium halide, we proposed a controlled ring opening of epoxides *en route* to halohydrins.

The interest of a controlled reductive process carried out by a hydride gave us the possibility to identify a selective methodology to partially reduce isothiocyanates to thioamides, avoiding the over-reduction to amines. The key of the process is the *in situ* generation of the Schwartz reagent (Cp_2ZrHCl).

The recent developments in silicon chemistry (*e.g.* Ruppert-Prakash reagent) coupled with the increasing interest in mono-, and difluorinated substrates, motivated the design and the development of new direct methodologies allowing the insertion of the difluoromethyl-fragment into electrophiles. Once established the optimal activation protocol of $TMSCHF_2$, we reported a direct, high yielding methodologies to insert it in both carbon and non-carbon containing manifold under full chemocontrol and eventual retention of the chiral information.



The current state of art of lithium carbenoids is usually restricted to applications to sp^2 hybridized carbon electrophiles which undergo homologation-type transformations, as documented by the Pace group in recent years (*e.g.* spiro-epoxyoxindoles and aziridines) (*publication 1* and *2*) We established a consecutive sequence of homologation-deoxygenation, enabling the addition of two nucleophiles, namely lithium carbenoids (as the first nucleophile), followed by an hydride. The formal installation of a C-X functionality on the carbonyl of ketones and aldehydes, coupled with a deoxygenative process carried out by a silane hydride in the presence of $B(C_6F_5)_3$. Collectively, synthetically valuable (n+1)-haloalkyls were formed. (*publication 3*). Moving our attention from the carbon atom to the sulfur one, we reported a straightforward preparation of oxothioacetals, starting from thiosulfonates, which after the installation of the halomethyl fragment and the subsequent treatment of the (isolable) α-halothioether with a hydroxy-nucleophile [(hetero)-aromatic, aliphatic alcohols] furnished the desired oxothioacetals (*pubblication 4*). The halolithium carbenoids are characterized by an intrinsic instability due to the α -elimination process, in which the nucleophilic Li carbenoid leads to the free carbene specie and the coordinated product LiX. This typical instability always limited the use of them as homologating agents and is representing one of the critical points for their use in synthetic chemistry. Once established the optimal conditions enabling the use of a variety of lithium carbenoids on a plethora of electrophilic partners, we were interested to understand if the Kirsme´s elimination could have a preparative significance. We reported a controlled ring-opening of epoxides with the lithium halide obtained *via* the degradative process that the chloro-, bromo- and iodo- lithium carbenoids facilitated by the presence of the non-coordinating solvent 2-MeTHF *en route* to β-halohydrins. Pivotal for the process was identifying the role of LiX salt, acting both as Lewis acid – for the epoxide ring opening – and, as a source of the nucleophilic halide (*publication 5*). The controlled reductive process of commercially available isothiocyanate to form the partially reduced thioformamide was achieved by the *in situ* generation of the Schwartz reagent as optimal hydride source (*publication 6*).

If α-fluoromethyl ketones were for the first time accessible *via* the use of fluoroiodomethane, α,α-difluoromethyl ketones are less explored substrates. We rationalized the possibility and convenience in developing a direct, one step methodology for the installation of a difluoromethyl motif into an electrophile levered on the use of $TMSCHF_2$, acting as CHF_2 carbanion-like source upon proper activation (*publication 7*). The procedure allows the formation of α,α-difluoromethyl ketones, starting from the optimal acilating agent weinreb amides (*pubblication 8*), and shows a high versatility in the case of iso(thio)cyanates for accessing a variety of α,α-difluoromethyl (thio)amides (*publication 9*). The optimized procedure was also applied to different non-carbon electrophiles (Sn, Ge, Te, S, Se, Si), and in the case of phosphorus, the corresponding difluoromethylphosphonate which upon activation acted as an alternative difluomethyl unit donor a, affording a difluoromethyl alcohol in high yield (*publications 10 and 11*).

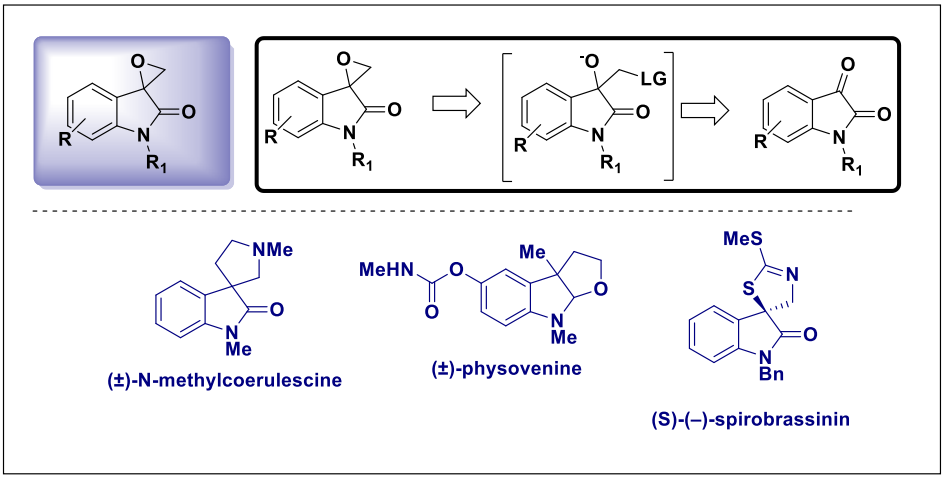
Publication n. 1

Monticelli, S.; Castoldi, L.; Touqeer, S.; **Miele, M.**; Urban, E.; Pace, V.

Recent advances in the synthesis and reactivity of spiro-epoxyoxindoles.

Chem. Heterocycl. Compd. **2018**, *54*, 389–393.

In this minireview, covering the literature of the last twenty years, we present recently introduced tactics for praparing spiroepoxyoxindoles with a particular focus on stereochemical aspects. This motif is featured in several natural and biologically active substances, such as (±)-*N*-methylcoerulescine and (±)-physovenine. Spiroepoxy-derivatives contain an highly reactive unsubstituted methylene fragment at the level of the oxirane ring, thus representing versatile building block in organic synthesis.



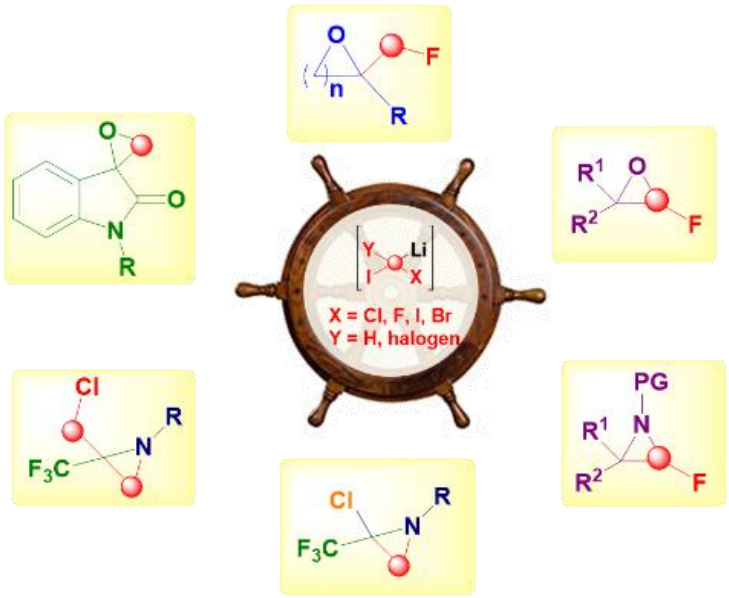
Publication n. 2

Ielo, L.; Pillari, V.; **Miele, M.**; Pace, V.

Carbenoids Mediated Homologation Tactics for Assembling Fluorinated Epoxides and Aziridines.

Synlett **2021**, *32*, 551–560.

In homologation chemistry, halomethyl lithium carbenoids represent an attractive alternative to diazomethane-like compounds and, nowadays they are routinary employed as methylene (CH_2) transfer reagents. The installation of a halomethylenic fragment into an electrophilic substrate leads to an intermediate susceptible of further manipulation thus, giving access to a variety of structurally different compounds. We focus the attention on the assembly of three-membered cycles featuring fluorinated substituents such as α-fluoroepoxides and aziridines, trifluoromethyl-containing halo- and halomethyl-aziridines. Inspired by previous work of our group, we demonstrated that also fluoromethyl-type organolithiums can be engaged as valuable synthons for preparing cyclic structures characterized by a different degree of fluorination.



Publication n. 3

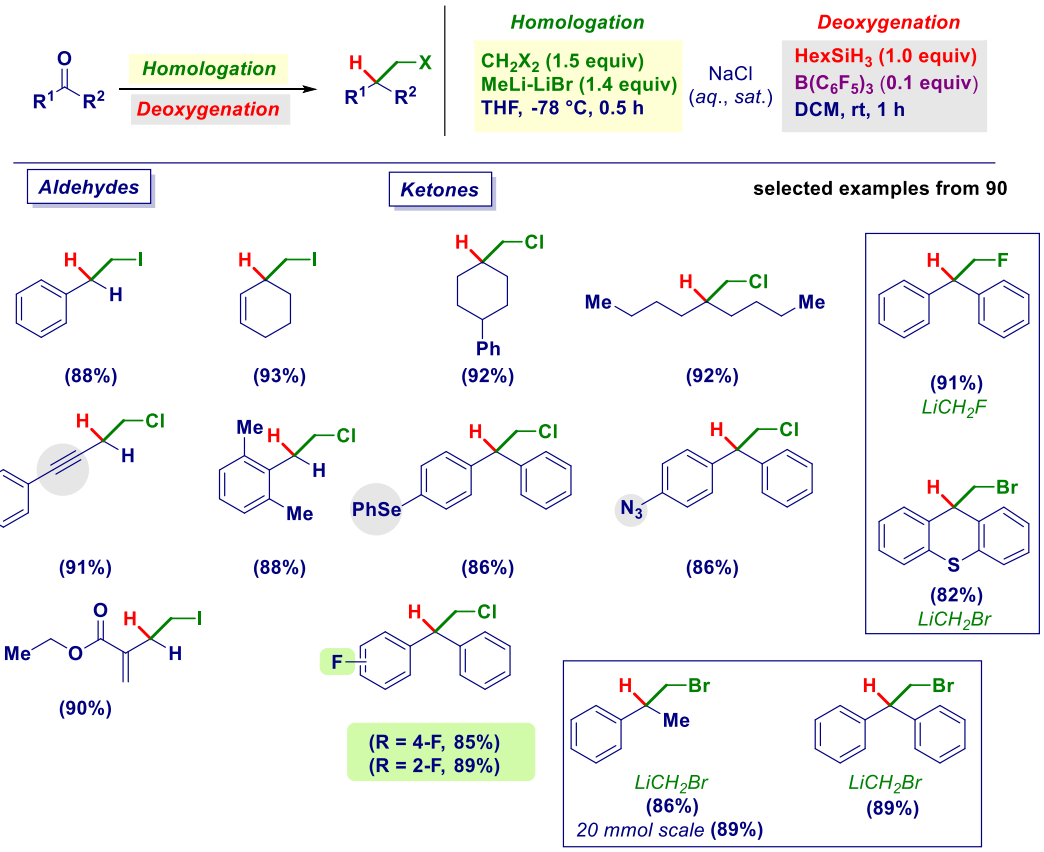
Miele, M.; Citarella, A.; Langer, T.; Urban, E.; Holzer, W.; Ielo, L.; Pace, V.

Chemoselective Homologation-Deoxygenation Strategy Enabling the Direct Conversion of Carbonyls into (n+1)-Halomethyl-Alkanes.

Org. Lett. **2020**, *22*, 7629.

Highlighted in Organic Chemistry Portal - https://www.organic-chemistry.org/abstracts/lit7/569.shtm

In this paper, we have documented the high-yielding installation of two nucleophiles (a carbenoid and an hydride) into the carbonyl carbon of aldehydes and ketones to access halomethyl alkyl derivatives with full chemocontrol. The methodology involves two distinct processes, homologation of the carbonyl thus, forming a new functionalized C-C bond, followed by a silane-mediated deoxygenation catalyzed by $B(C_6F_5)_3$. This conceptually intuitive sequence features high robustness (*ca.* 90 presented cases) and flexibility: not only homologative reagents can be used in the initial step but, also diverse carbanion-like species are compatible with the methodology.



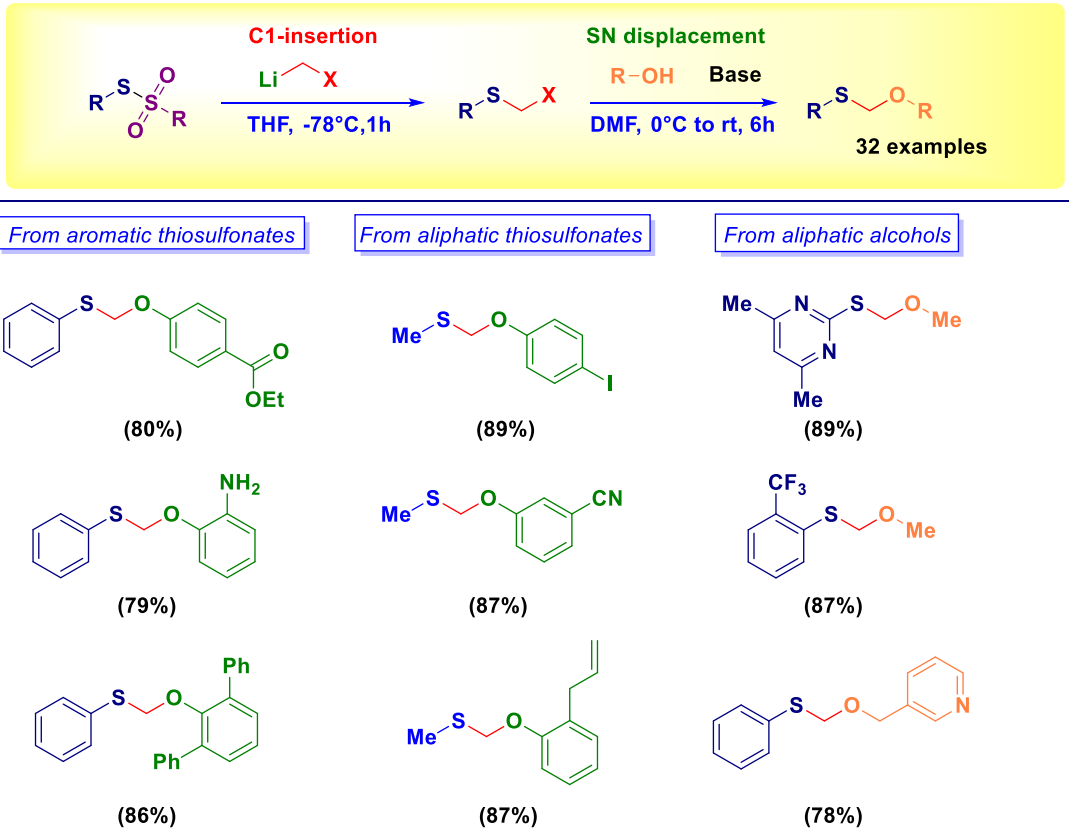
Publication n. 4

Ielo, L.; Pillari, V.; **Miele, M.**; Holzer, W.; Pace, V

Consecutive C1-Homologation / Displacement Strategy for Converting Thiosulfonates into O,S-Oxothioacetals.

Adv. Synth. Catal. **2020**, *362*, 5444– 5449.

An innovative synthesis of oxothioacetals has been developed for the selective installation of an halomethyl fragment on an electrophilic sulfur platform such as a thiosulfonate. pon the homologation event carried out with chloromethyllithium, the constitutive S-S bond is broken and, a non-nucleophilic sulfonate species is released, conducting to an intermediate (isolable) α-halothioether. The latter can sequentiallly undergo nucleophilic displacements with alcoholic groups [(hetero)-aromatic, aliphatic] furnishing the desired oxothioacetals in high yields and chemoselectivity.



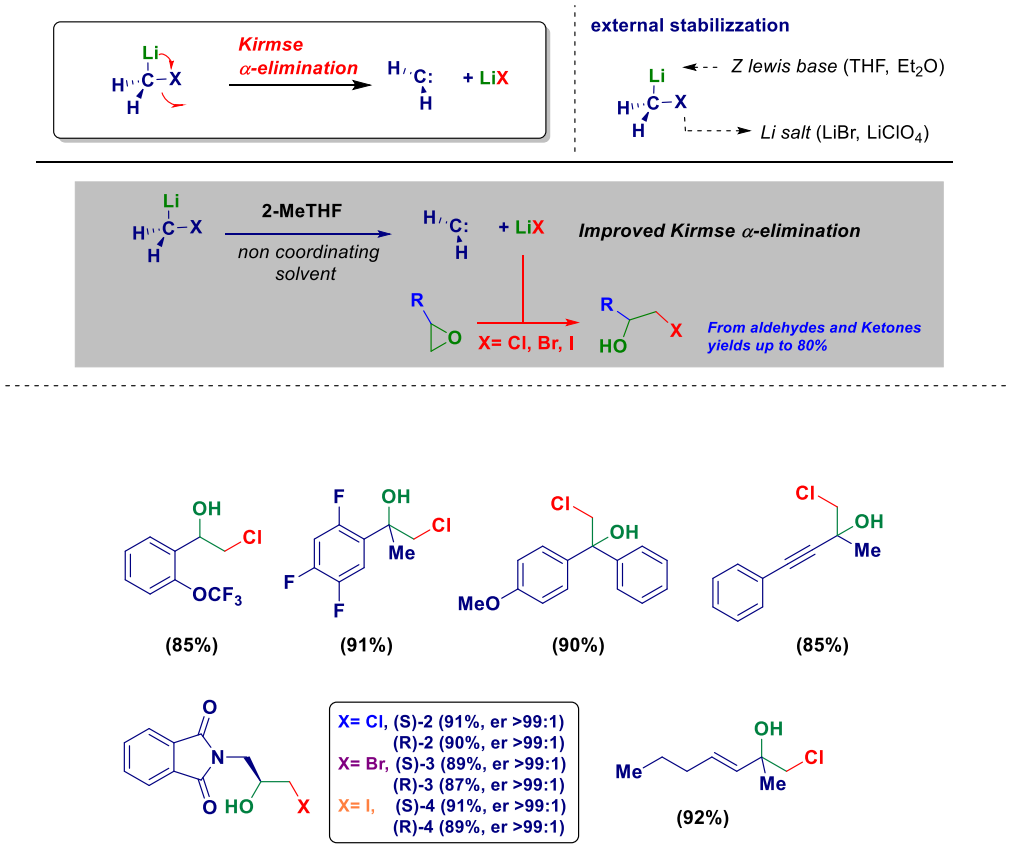
Publication n. 5

Ielo, L.; **Miele, M.**; Pillari, V.; Senatore, R.; Mirabile, S.; Gitto, R.; Holzer, W.; Alcántara, A. R.; Pace, V.

Taking advantage of lithium monohalocarbenoid intrinsic α-elimination in 2-MeTHF: controlled epoxide ring-opening en route to halohydrins.

Org. Biomol. Chem. **2021**, *19*, 2038-2043.

The α-elimination of lithium carbenoids, is usually regarded as problematic in homologation chemistry. We herein demonstrated that the boosting of the Kirmse's elimination can be advantageously employed for a controlled ring-opening of epoxides to access different β-halohydrins (chloro, bromo, and iodo) from the corresponding lithium monohalocarbenoids. The use of the eco-friendly and non-coordinating solvent 2-MeTHF forces the degradation of the monohalolithium, thus controlling the formation of LiX salts which act as competent ring-opening reagents. This method proceeds with high yields of the targeted compounds and regiocontrol; no racemization of enantiopure materials where observed, as well.



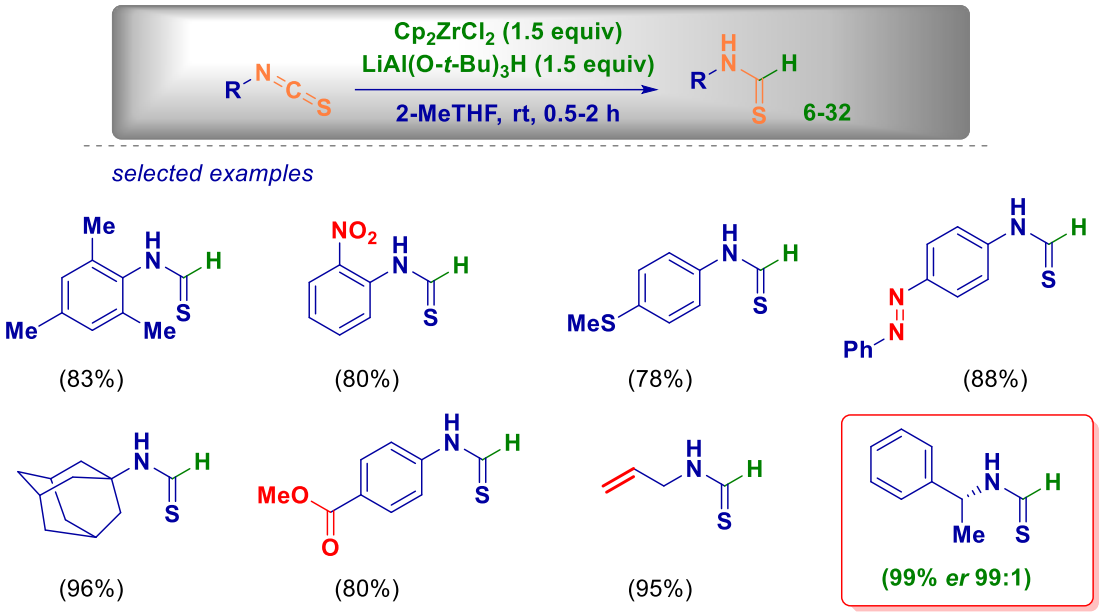
Publication n. 6

De la Vega-Hernàndez, K.; Senatore, R.; **Miele, M.**; Urban, E.; Holzer, W.; Pace, V.

Chemoselective reduction of isothiocyanates to thioformamides mediated by the Schwartz reagent.

Org. Biomol. Chem. **2019**, *17*, 1970-1978.

Thioformamides are valuable scaffolds in organic synthetis, covering a pivotal role as important intermediates for the construction of sulfur containing biologically active compounds. Despite this importance, strategies for accessing this class of compounds are rather limited. Here, we report a practical technique levered on the partial reduction of isothiocyanates in the presence of the Schwartz reagent generated *in situ* according to the Snieckus' procedure. A wide range of commercially available isothiocyanates can be partially reduced *via* hydride transfer, thus accessing a variety of *N*-substituted thioformamides in high yields under mild reaction conditions. The transformation occurs with good chemoselectivity, tolerates sensitive groups such as nitro, ester, alkene, azo, azide and keto groups and a full retention of the stereochemical information is observed.



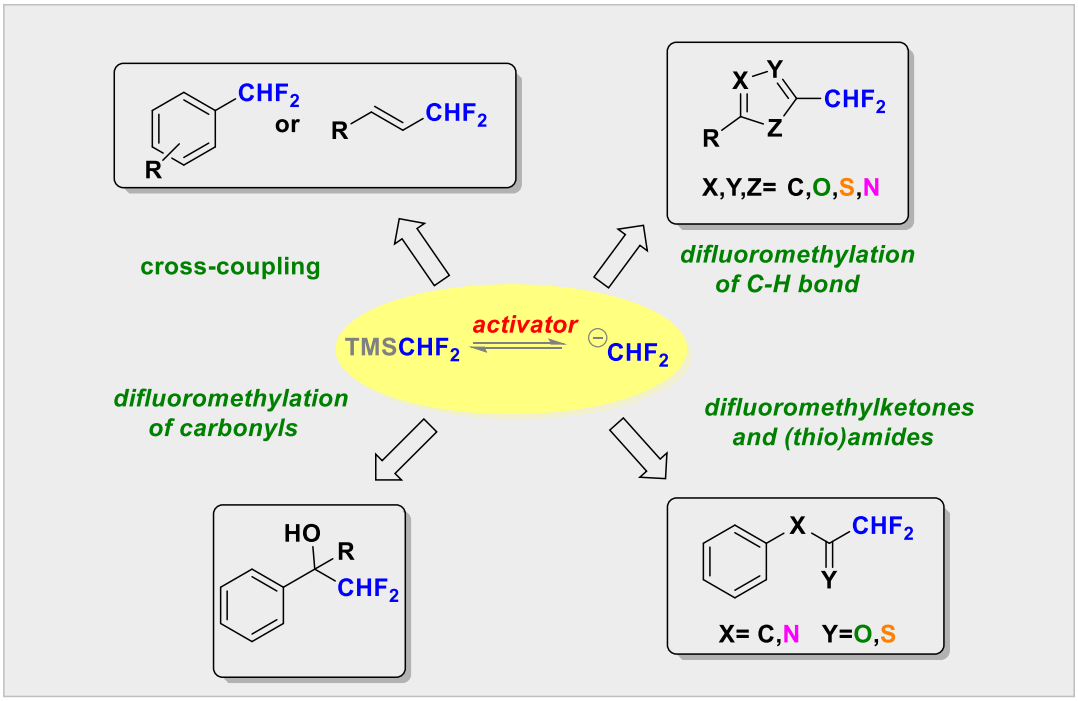
Publication n. 7

Miele, M.; Pace, V.

(Difluoromethyl)trimethylsilane ($TMSCHF_2$): A Useful Difluoromethylating Nucleophilic Source.

Aust. J. Chem. **2021**, *74*, 623–625.

We present recent and significant advancements levered on the use of the commercially available reagent (difluoromethyl)trimethylsilane ($TMSCHF_2$), as a versatile donor of the CHF_2 moiety under nucleophilic regime. The significance of difluoromethyl-analogues in medicinal and organic chemistry, boosted the development of simple and direct methodologies for the effective insertion of the CHF_2 group into organic arrays. $TMSCHF_2$ is a convenient liquid reagent characterized by a relatively acceptable boiling point (51–53 °C) and shows an excellent stability thus, accounting for a good experimental manipulability. Nowadays, it represents the first-choice reagent for difluoromethylation in both academic and industry research.



Publication n. 8

Miele, M.; Citarella, A.; Micale, N.; Holzer, W.; Pace, V.

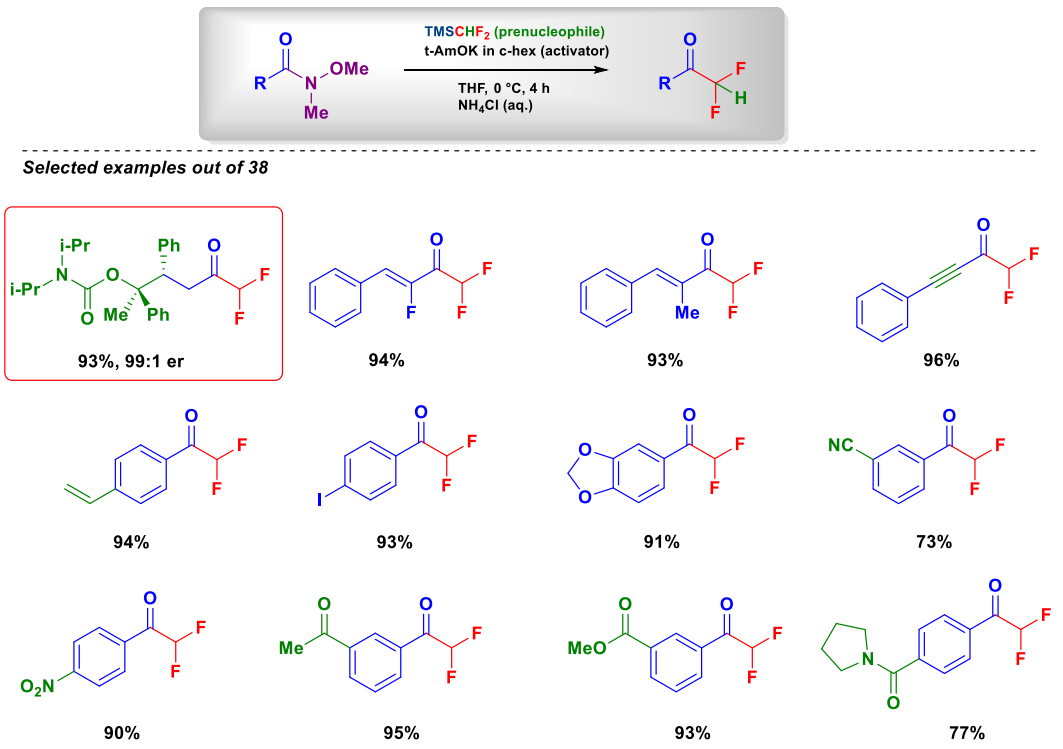
Direct and Chemoselective Synthesis of Tertiary α,α-Difluoro-ketones via Weinreb Amides Homologation with CHF_2-Carbene Equivalent.

Org. Lett. **2019**, *21*, 8261-8265.

Highlighted in Org. Proc. Res. Devel. **2019**, *23*, 2583-2591.

Highlighted in Chemistry Views - https://www.chemistryviews.org/details/news/11190152/Turning_Weinreb_Amides_into_Difluoromethylketones.html

The selective insertion of a difluoromethyl unit into an organic compound profoundly regulates the chemico-physical properties of the resulting scaffold. The presence of the CHF_2 fragment at the vicinal position of a ketone carbonyl, modulates the reactivity of both the carbonyl and the difluorinated methylenic group, increasing the electrophilicity of the carbonyl carbon. Despite the significance of difluoroketones, practical methodologies for accomplishing the task are rather rare. We propose an effective protocol for synthesizing difluoromethyl ketones *via* the homologation of variously functionalized Weinreb amides. The formal nucleophilic CHF_2 fragment results from the activation of $TMSCHF_2$ with potassium tert-amylate under Barbier-type conditions. Attractive characteristics of the methodology are uniformly high-yields, excellent tolerance to sensitive functionalities, retention of the stereochemical information embodied in the starting materials.



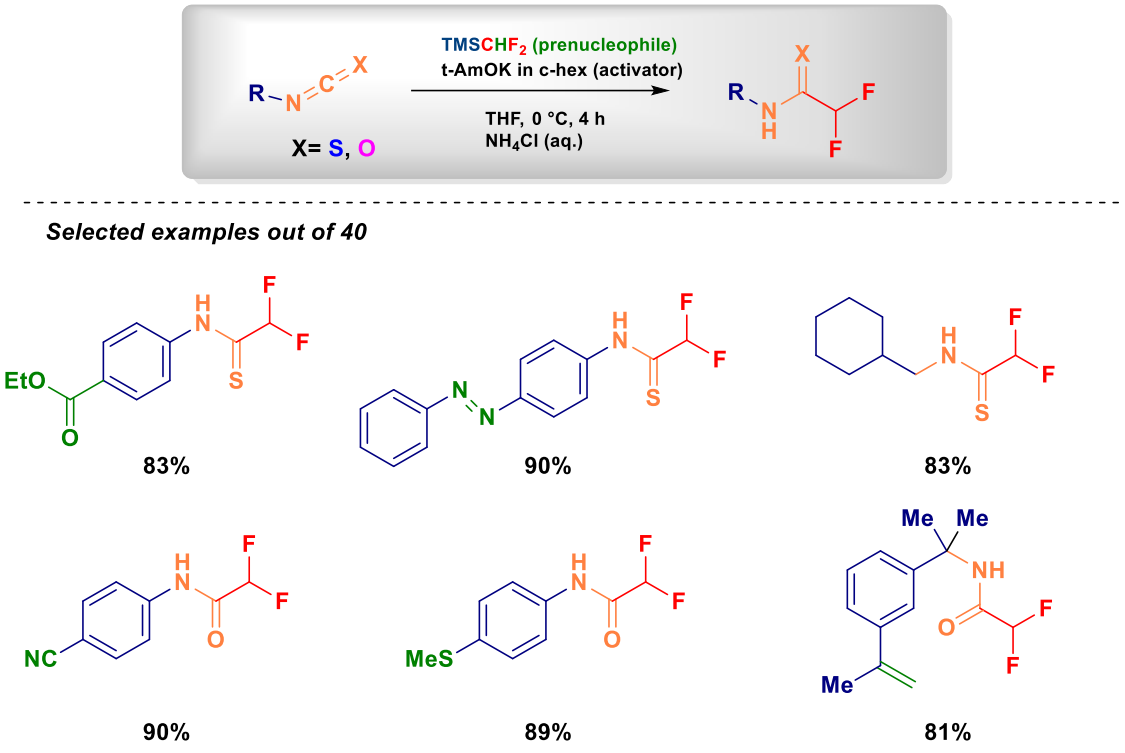
Publication n. 9

Miele, M.; D'Orsi, R.; Sridharan, V.; Holzer, W.; Pace, V.

Highly chemoselective difluoromethylative homologation of iso(thio)cyanates: expeditious access to unprecedented a,a-difluoro(thio)amides

Chem. Commun. **2019**, 55, 12960—12963.

Unprecedented α,α-difluoromethyl oxo- and thio-amides were prepared through the formal difluoromethylcarbanion-like homologation of iso(thio)cyanates. The proper activation of the commercially available $TMSCHF_2$ with potassium *tert*-amylate gives the opportunity to synthesize the title compounds with high chemocontrol and substrate scope.



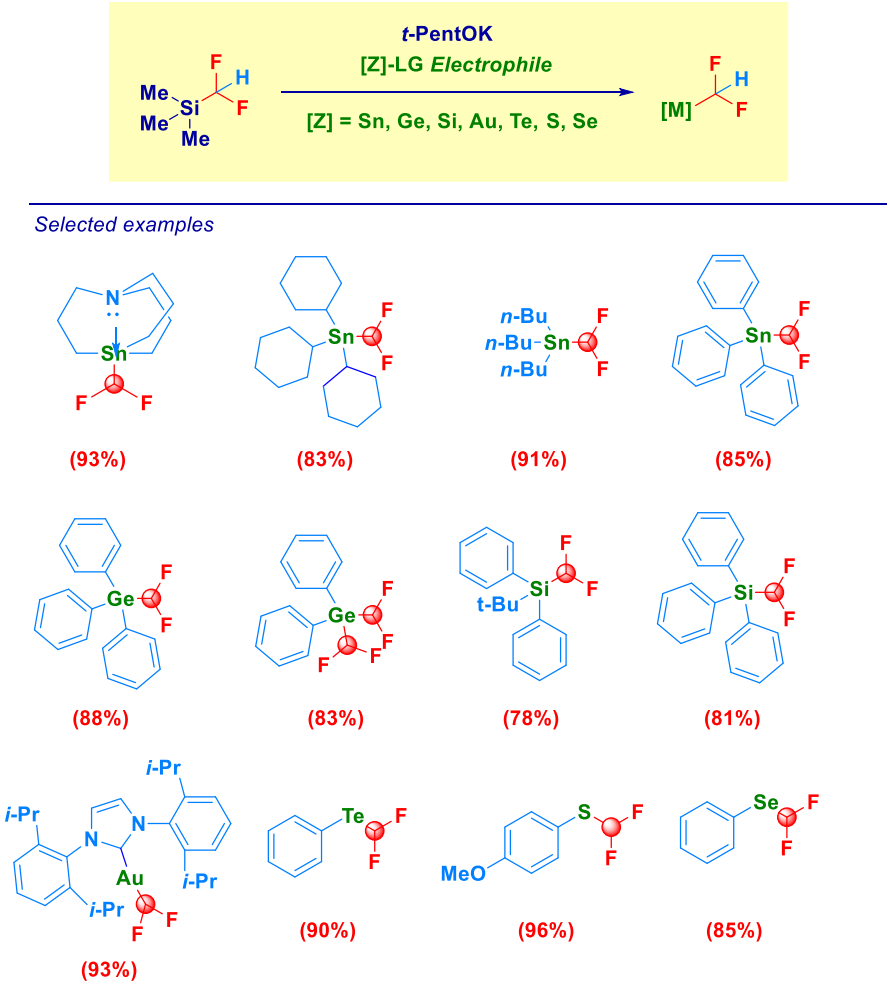
Publication n. 10

Miele, M.; Castoldi, L.; Simeone, X.; Holzer, W.; and Pace, V.

Straightforward Synthesis of Bench-Stable Heteroatom-Centered Difluoromethylated Entities via the Controlled Nucleophilic Transfer from Activated $TMSCHF_2$.

Submitted (ref. CC-COM-02-2022-000886)

The commercially available and experimentally convenient (bp 65 °C) difluoromethyltrimethylsilane ($TMSCHF_2$) is proposed as a valuable difluoromethylating transfer reagent for delivering the CHF_2 moiety to various heterotom-based electrophiles (Sn, Ge, Si, Au, S, Se, Te). Upon the activation with an alkoxide, a conceptually intuitive nucleophilic displacement directly furnishes in high yields the bench-stable analogues. The X-ray structural analysis of the corresponding stannatrane supports a valuable reactivity - as also noticed for the triphenylsilane derivative - thus introducing novel difluoromethylating agents suitable for both Pd-catalyzed sequence and classical nucleophilic regime.



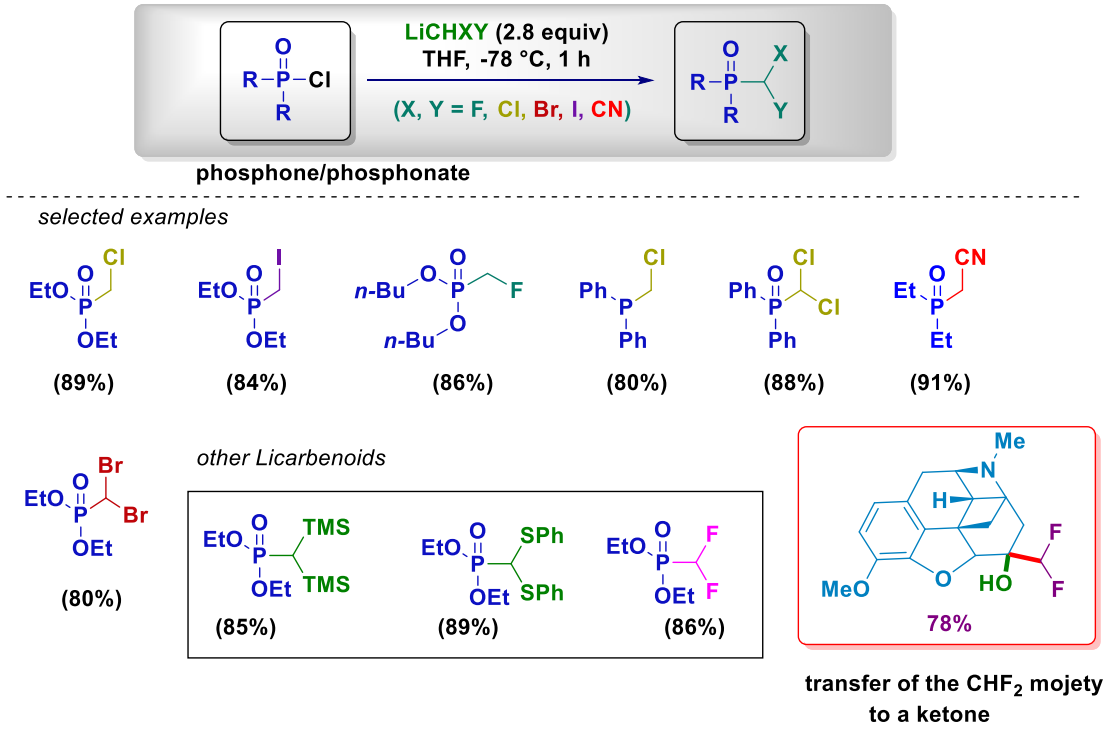
Publication n. 11

Touqeer, S.; Ielo, L.; **Miele, M.**; Urban, E.; Holzer, W.; Pace, V.

Direct and straightforward transfer of C1 functionalized synthons to phosphorous electrophiles for accessing gem-P-containing methanes.

Org. Biomol. Chem. **2021**, *19*, 2425-2429.

We reported a direct and straightforward transfer of different α-substituted methyllithium reagents to access α-functionalized organophosphines, phosphine oxides and phosphonates. The methodology relies on the nucleophilic substitution carried out on chlorinated phosphorous electrophiles *via* the employing of different lithium carbenoids ($LiCH_2Hal$, $LiCHHal_2$, $LiCH_2CN$, $LiCH_2SeR$ etc.). The homologated compounds are obtained in high yields and *via* a single step functionalization. The difluoro *P*-containing carbanion have been evaluated in the carbonyl-difluoromethylation of the opioid agent Hydrocodone.



5. Conclusions

The main objective of this Thesis is to extend the portfolio of available methodologies in homologation chemistry, focusing on organometallic species of lithium and silicon-based reagents.

The success of strategies levered on the use of halolithium carbenoids is crystallized in the achievement of transformations featuring high level of chemocontrol thus, leading to complex molecular architectures mostly conducted on sp^2 hybridized carbon electrophiles. In this scenario, the synthetic value of sp^3-hybridized platforms remained a long-standing issue mostly due to the difficulties of inserting a *single* carbon unit on these linchpins. We successfully designed a consecutive sequence of homologation-deoxygenation on carbonyls, using as first nucleophiles a variety of lithium carbenoids and carbanion-like species which could be easily reduced with Si-H reagent under $B(C_6F_5)_3$ catalytic conditions. Thus, formal homologated haloalkyl arrays were prepared in high yield under full chemocontrol. A conceptually analogous tactic of installing a reactive halomethylenic fragment suited for a sequential nucleophilic displacement was realized on the electrophilic sulfur of thiosulfonates which upon reaction with a lithium carbenoid furnished an intermediate α-halomethyl mercaptane amenable for substitution with a oxygen-centered nucleophile, thus leading to oxothioacetals.

The selective and controlled hydride transfer, in the case of the challenging partial reduction of isothiocyanates, affordered *N*-substituted thioformamides in high yields under mild reaction conditions overpassing the disadvantages of the already reported synthetic procedures.

Considering the chemical instability of halolithium carbenoid species, the α -elimination process has been regarded as the Achille's heel of these entities. We took advantage of this limitation and accordingly developed an effective synthesis of β-halohydrins (Cl, I, Br) *via* a controlled ring-opening of epoxides operated by the lithium halide derived from the boosting of the Kirme´s elimination.

Although nowadays mono- and trifluoromethylation procedures benefit of well-established synthetic methodologies, the difluoromethylation remains a less explored field. In this context, the silicon-chemistry is offering valuable alternatives to access difluoromethylated compounds under nucleophilic regime using an activated form of the commercially available and safe reagent $TMSCHF_2$. We extended the applicability of this versatile reagent as CHF_2 carbanion-like source for introducing the CHF_2 fragment into a variety of carbon and non-carbon electrophiles. As an additional evidence of the synthetic versatility and flexibility of Weinreb amides, we prepared α,α-difluoromethyl ketones through an intuitive tactic characterized by full chemocontrol and retention of the optical purity. Moreover, by treating heterocumulenes (isocyanates and isothiocyanates) we discovered a novel route to α,α-difluoromethyl oxo- and thio-amides, again with excellent chemoselectivity.

Publication n. 1

Recent advances in the synthesis and reactivity of spiro-epoxyoxindoles.

Monticelli, S.; Castoldi, L.; Touqeer, S.; **Miele, M.**; Urban, E.; Pace, V.*
Chem. Heterocycl. Compd. **2018***, 54,* 389–393. (DOI: 10.1007/s10593-018-2280-4)

Латвийский институт органического синтеза

Химия гетероциклических соединений **2018**, *54*(4), 389–393

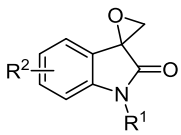
Химия гетероциклических соединений

Recent advances in the synthesis and reactivity of spiro-epoxyoxindoles

Serena Monticelli[1], Laura Castoldi[1], Saad Touqeer[1], Margherita Miele[1], Ernst Urban[1], Vittorio Pace[1]*

[1] *Department of Pharmaceutical Chemistry, University of Vienna, 14 Althanstrasse, Vienna 1090, Austria; e-mail: vittorio.pace@univie.ac.at*

Submitted March 15, 2018
Accepted April 19, 2018



Spiro-epoxyoxindoles containing an unsubstituted methylene fragment in the oxirane ring are excellent building blocks in organic synthesis due to the high reactivity conferred by the three-membered oxygenated cycle. In this minireview, a concise survey of the methods of their synthesis and examples of reactivity with carbon and nitrogen nucleophiles is presented, with a particular focus on the stereochemical aspects. The review covers the literature for the last twenty years.

Keywords: epoxides, isatins, spiro compounds, Friedel–Crafts reaction, nucleophilic addition.

The 3,3'-disubstituted oxindole core is featured in several natural products and biologically active substances, thus representing an important target for the synthetic chemists.[1] The corresponding spiro-epoxy derivatives induce a particular interest – they are characterized by the high reactivity conferred by the oxirane ring and can be employed for the construction of complex molecular structures.[2]

Synthesis of spiro-epoxyoxindoles

Despite the availability of strategies to construct functionalized spiro-epoxyoxindoles under full stereocontrol,[3] unsubstituted analogs received much less attention and only recently reliable methods for their preparation have been disclosed. The retrosynthetic analysis indicates isatins[4] as valuable starting materials which upon a conceptually simple homologation would transform the carbonyl into the epoxide. Accordingly, three main protocols based on common homologating agents have been proposed, namely diazomethane, sulfur ylides, and halomethyllithium reagents (Fig. 1). Arndt, Eistert, and Ender[5] in the course of their seminal studies on the use of diazoalkanes in synthesis noticed the formation of rearrangement products, later confirmed by Alcaide, Almendros, and coworkers.[6] Epoxidation of isatin carbonyl group in Corey–Chaykovsky reaction, reported by Howe and coworkers[7] in the early 1970s, appeared a versatile strategy, as evidenced in more recent studies by Nair and coworkers[8] and applied further by Hajra and coworkers.[9]

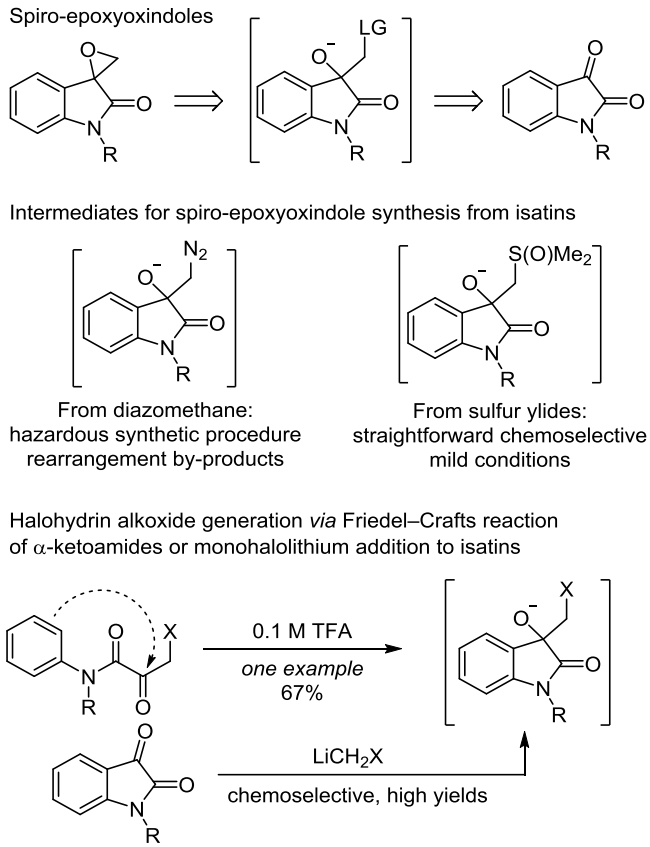


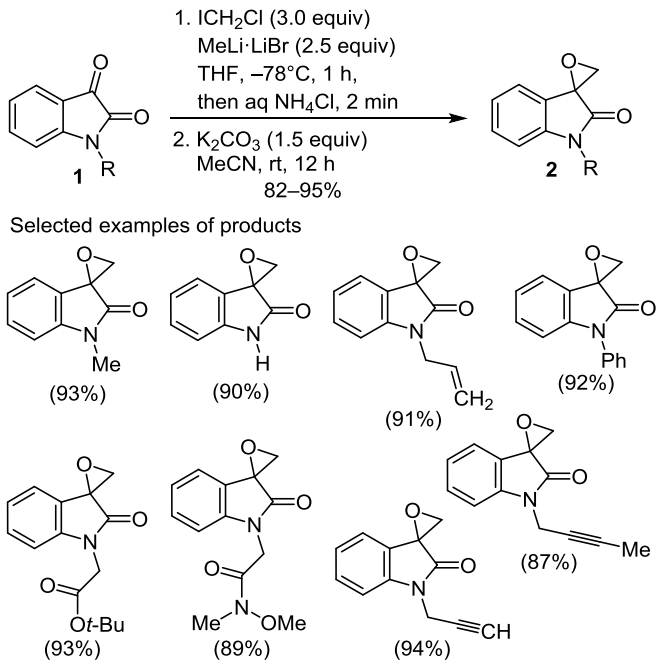
Figure 1. Spiro-epoxyoxindole synthesis strategies.

Upon reaction with a sulf(ox)onium ylide in the presence of a base, spiro-epoxyoxindoles are also smoothly obtained in good yields. The protocol is adaptable to isatins containing alkyl substituents on the nitrogen, as well as to the simplest member of the series – with unsubstituted NH. Notably, generating the ylide *in situ* from a sulfoxide and benzyne, as described by Zhang, Wang, and coworkers, could represent a useful alternative to the classical sulfoxonium deprotonation.[10] In 2011, Zhu and coworkers documented the synthesis of a spiro-epoxyoxindole *via* the intramolecular Friedel–Crafts reaction of an α-oxoanilide triggered by trifluoroacetic acid followed by basic treatment.[11] Overall, the process involves the formation of a halohydrin alkoxide which undergoes ring closure yielding a spiro compound.

A critical analysis of the strategies discussed above clearly evidences the requirement for a quaternary alkoxide featuring a β-substituent with good leaving group ability as the pivotal intermediate for the synthesis of spiro-epoxyoxindoles.

In this context, Pace and coworkers documented a robust and operationally simple tactic involving the addition of a lithium halomethylcarbenoid ($LiCH_2Cl$)[12] to isatin carbonyl,[13] thus giving the same Zhu's alkoxide intermediate through a conceptually different route. The protocol proceeds under high chemocontrol, as deducted from the selective attack of the nucleophilic $LiCH_2Cl$ to the carbonyl of isatin **1**, even in the presence of additional electrophilic functionalities (esters, Weinreb amides, amides, nitrile) or moieties which can be sensitive to organolithium reagents such as alkenes, alkynes, or bromine atoms (Scheme 1). Notably, the presence of acidic NH groups such as in secondary amides or in simple lactam (i.e., isatin) did not affect the outcome of the desired spiro-epoxyoxindoles **2**.[14]

Scheme 1. Lithium carbenoid-mediated isatin epoxidation

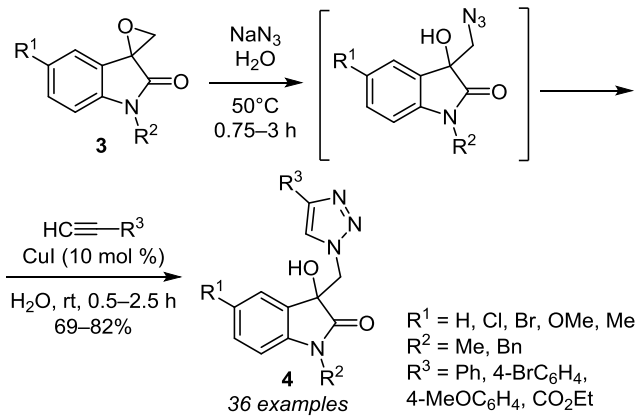


New reactivity concepts in spiro-epoxyoxindole chemistry

Reactions with nitrogen nucleophiles

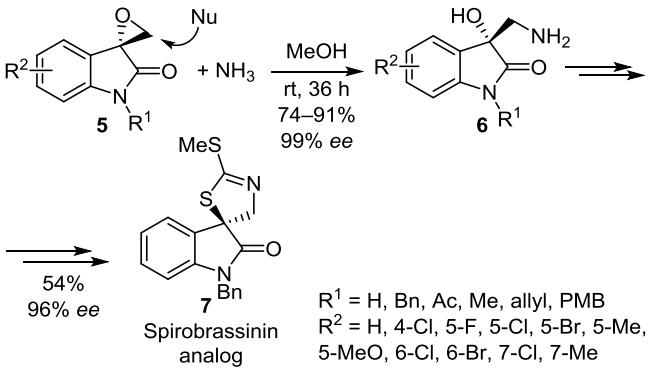
Nair and coworkers reported the regioselective aminolysis of spiro-epoxyoxindoles with both aliphatic and aromatic amines in water to give 3-aminomethyl-3-hydroxyindolin-2-ones.[8a] The same group extended the epoxide ring opening of spiro-epoxyoxindoles **3** by azidolysis followed by the Cu-catalyzed azide-alkyne cycloaddition, finally leading to diverse 1-alkyl-3-[(4-aryl(alkyl)-1*H*-1,2,3-triazol-1-yl)methyl]-3-hydroxyindolin-2-ones **4** (Scheme 2).[8b]

Scheme 2. Regiospecific azidolysis and Cu-catalyzed azide-alkyne cycloaddition on spiro-epoxyoxindoles



Sun, Hong, Wang, and coworkers demonstrated the selective, catalyst-free epoxide ring opening with a weak nucleophile such as ammonia, enabling the synthesis of the relevant 3-aminomethyl-3-hydroxyoxindoles.[15] Starting from optically active spiro-epoxyoxindoles **5**, enantiopure amino alcohols **6** with retained configuration were obtained. The reaction could be scaled up to gram quantities and be used in the synthesis of spirobrassinin derivative **7** (Scheme 3).

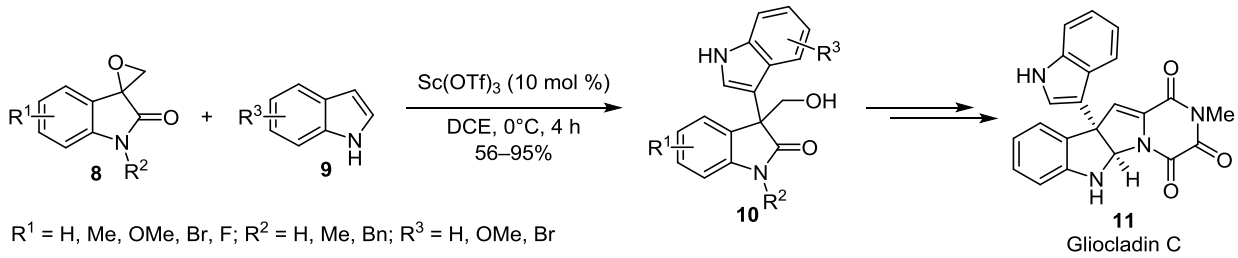
Scheme 3. Regioselective ring opening of spiro-epoxyoxindoles with ammonia



Reactions with carbon nucleophiles

Hajra and coworkers employed spiro-epoxyoxindoles **8** as convenient electrophiles in regioselective Friedel–Crafts-type reaction with indoles **9** under Lewis acid catalysis in

Scheme 4. Hajra's Lewis acid-catalyzed reaction of spiro-epoxyoxindoles and indoles



R^1 = H, Me, OMe, Br, F; R^2 = H, Me, Bn; R^3 = H, OMe, Br

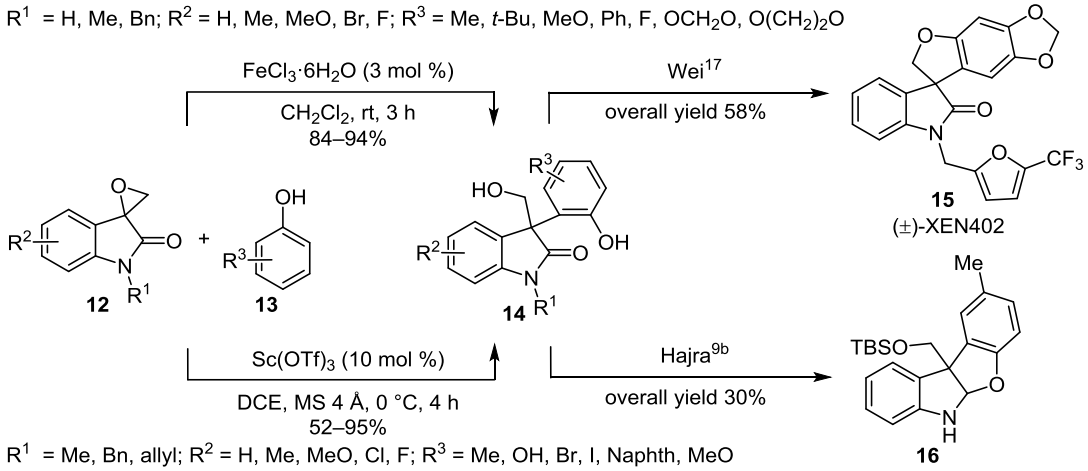
the presence of $Sc(OTf)_3$ for the synthesis of 3-(hydroxymethyl)-3-(1*H*-indol-3-yl)indolin-2-one derivatives **10**.[9a] The reaction, involving the attack of the indolic C-3 carbon atom to the sterically congested C-3 atom of the epoxyoxindole **8** has been employed in a formal synthesis of gliocladin C (**11**) (Scheme 4). The tactic is notable since the regioselective ring opening with a C-nucleophile leads to an all-carbon quaternary center. The same authors demonstrated its usefulness also in the case of related chiral spiro-aziridines in the absence of catalyst, emphasizing the key role of water as the solvent in activating the cascade.[16]

Almost contemporaneously, the same group of Hajra[9b] and the group of Wei[17] demonstrated independently the efficiency of the tactic in the case of spiro-epoxyoxindoles **12** reacting with electron-rich phenols **13** as nucleophiles leading to 3-(hydroxymethyl)-3-(2-hydroxyaryl)indolin-2-ones **14** under Fe (Wei)[17] and Sc (Hajra)[9b] catalysis (Scheme 5). Mechanistically, the overall process constists of a tandem arylation–*O*-cyclization sequence. Notably, the method of Hajra is not limited to aromatic alcohols, but can be conveniently employed for non-hydroxy electron-rich benzenoid arenes.[9b] In both methodologies, the primary alcohol can be further activated and advantageously employed in a intramolecular nucleophilic displacement with a phenol, finally leading to a tetracyclic dihydrobenzofuro-[2,3-*b*]indoline scaffold.[9b,17] It should be mentioned that both methods are valuable tools for rapid assembly of the benzofuroindole skeleton found in biologically active substances, as demonstrated by Wei in the gram-scale total synthesis of drug candidate (±)-XEN402 (**15**) which is under IIb phase clinical trial for pain treatment and Hajra in the synthesis of benzofuroindoline **16**.

Sun, Hong, Wang, and coworkers documented the catalytic kinetic resolution (selectivity factor up to 1060) of racemic spiro-epoxyoxindoles **17** with the simultaneous regio- and enantioselective Friedel–Crafts alkylation of indoles **18** using a chiral phosphoric acid **19** as catalyst (Scheme 6).[18] The protocol provides the two highly versatile (*R*)-building blocks **17** and **20**, in excellent yields and optical purities, which can undergo subsequent transformations, as illustrated by authors in the formal total syntheses of (+)-gliocladin C or (*S*)-(–)-spirobrassinin. Interestingly,

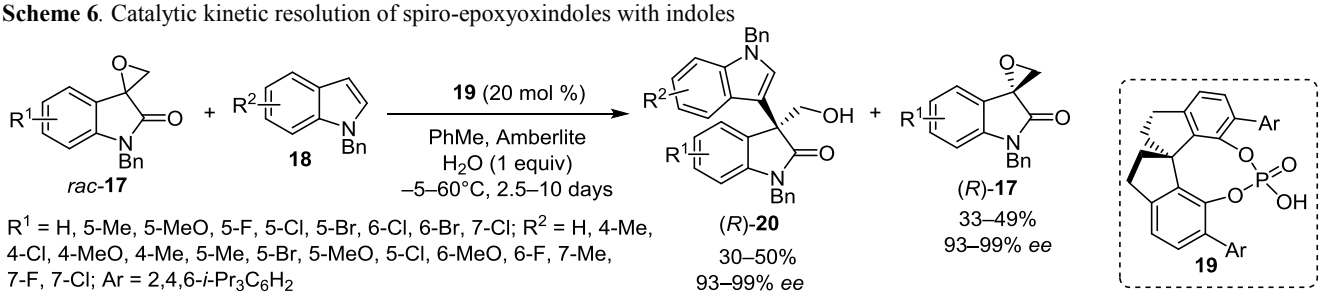
Scheme 5. Tandem Friedel–Crafts arylation – *O*-cyclization starting from spiro-epoxyoxindoles

R^1 = H, Me, Bn; R^2 = H, Me, MeO, Br, F; R^3 = Me, *t*-Bu, MeO, Ph, F, OCH_2O, $O(CH_2)_2O$



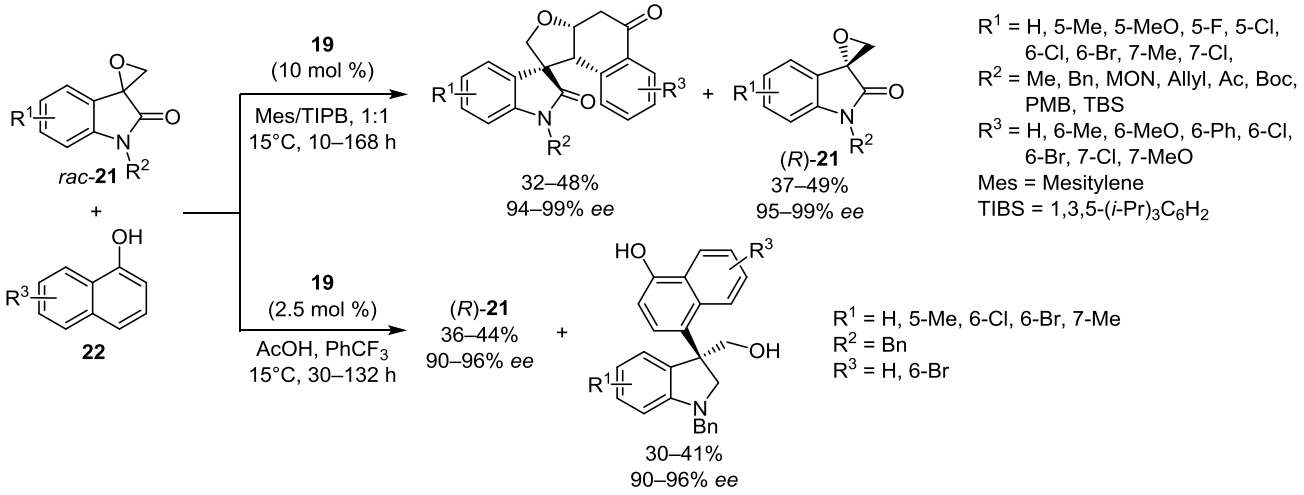
R^1 = Me, Bn, allyl; R^2 = H, Me, MeO, Cl, F; R^3 = Me, OH, Br, I, Naphth, MeO

Scheme 6. Catalytic kinetic resolution of spiro-epoxyoxindoles with indoles

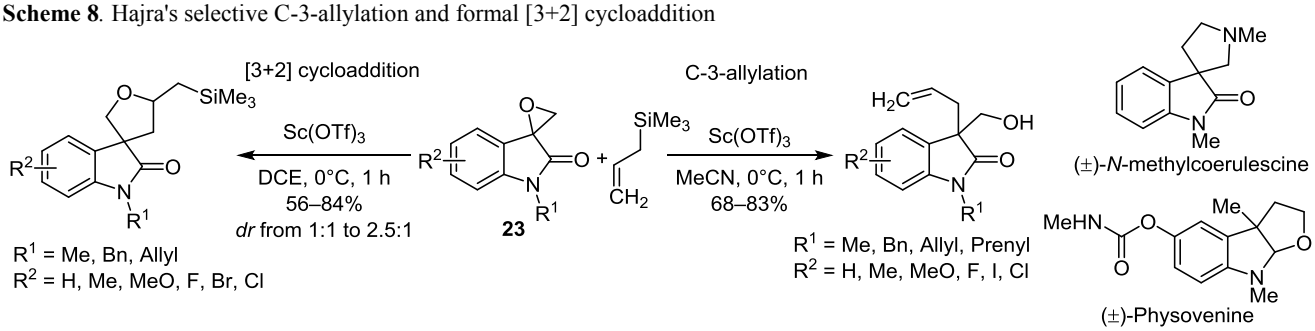


R^1 = H, 5-Me, 5-MeO, 5-F, 5-Cl, 5-Br, 6-Cl, 6-Br, 7-Cl; R^2 = H, 4-Me, 4-Cl, 4-MeO, 4-Me, 5-Me, 5-Br, 5-MeO, 5-Cl, 6-MeO, 6-F, 7-Me, 7-F, 7-Cl; Ar = 2,4,6-*i*-$Pr_3C_6H_2$

Scheme 7. Catalytic kinetic resolution of spiro-epoxyoxindoles with naphthols



Scheme 8. Hajra's selective C-3-allylation and formal [3+2] cycloaddition



the enantiopure alkylated (*S*)-product (*S*)-**20** can be obtained by the regioselective ring opening of (*R*)-spiro-epoxyoxindole (*R*)-**17** with the indole without the use of the catalyst.

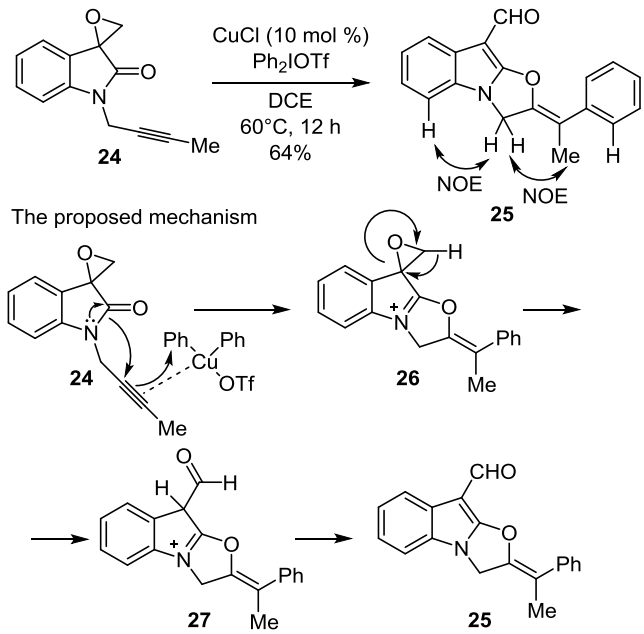
The same group succeeded in demonstrating that 1-naphtols **22** are able to act as C-4 regioselective nucleophiles in a tandem dearomatization–oxa-Michael and Friedel–Crafts alkylation with spiro-epoxyoxindoles **21**. The chemoselectivity of the process shows a significant dependence on the solvent (Scheme 7). Both chemoselective reactions were accompanied by simultaneous kinetic resolution of the racemic starting spiro-epoxyoxindoles. Notably, the protocol shows excellent diastereo- and enantioselectivity in the formation of three contigous stereocenters including a quaternary one.[19]

Hajra developed a Lewis acid-catalyzed regioselective C-3-allylation and a formal [3+2] annulation protocol of spiro-epoxyoxindoles **23** by simple change of the reaction conditions (Scheme 8). The method has been applied for the synthesis of various natural products – (±)-*N*-methylcoerulescine, (±)-physovenine, and 3a-allylhexahydropyrrolo[2,3-*b*]indole, a subunit of a large number of members of the HPI-alkaloid family.[20]

Selective rearrangements

Spiro-epoxyoxindole **24** featuring a propargylic substituent on nitrogen atom undergoes copper-catalyzed iodonium-mediated arylation – rearrangement to a tricyclic system **25** with well defined *Z*-configuration at the exocyclic C=C bond, as established by NOE experiments. This one-pot transformation is assumed to be the sequence of an intramolecular oxyarylation of spiro-epoxyoxindole **24** to give epoxy-iminium intermediate **26**, which through Lewis acid-promoted epoxide-aldehyde isomerization followed by rearomatization of intermediate **27** affords the desired product **25** (Scheme 9).[13a]

Scheme 9. Intramolecular electrophilic oxyarylation



In conclusion, in this review, the latest aspects of the methods of the synthesis and examples of reactivity of 3,3'-spiro-epoxyoxindoles were presented. The objective of the review was not to completely cover the research area but rather to introduce the reader to the recent advances in the field.

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Publication n. 2

Carbenoids Mediated Homologation Tactics for Assembling Fluorinated Epoxides and Aziridines.

Ielo, L.; Pillari, V.; **Miele, M**.; Pace, V.*

Synlett **2021**, *32*, 551–560. (DOI: 10.1055/s-0040-1706404)

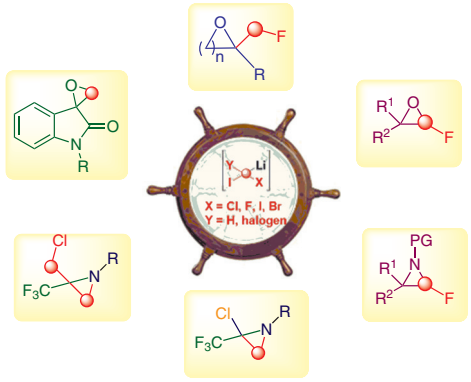
Synlett L. Ielo et al. Account

Carbenoid-Mediated Homologation Tactics for Assembling (Fluorinated) Epoxides and Aziridines

Laura Ielo *[a]
Veronica Pillari[a]
Margherita Miele[a]
Davide Castiglione[a]
Vittorio Pace *[b]

[a] University of Vienna, Department of Pharmaceutical Chemistry, Althanstrasse 14, 1090 Vienna, Austria
laura.ielo@univie.ac.at
[b] University of Turin, Department of Chemistry, Via P. Giuria 7, 10125 Turin, Italy
vittorio.pace@unito.it

In memory of Professor Hans Reich, a pioneer in organolithium chemistry.



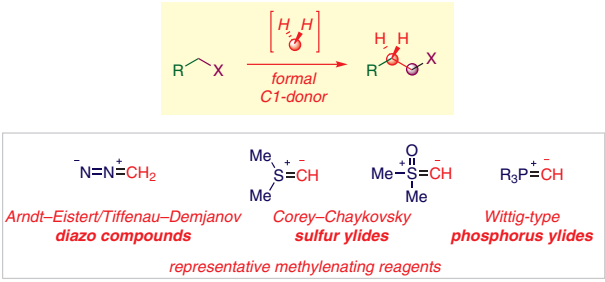
Received: 11.06.2020
Accepted: 10.07.2020
Published online: 26.08.2020
DOI: 10.1055/s-0040-1706404; Art ID: st-2020-a0340-a

Abstract Homologation strategies provide highly versatile tools in organic synthesis for the introduction of a CH_2 group into a given carbon skeleton. The operation can result in diverse structural motifs by tuning of the reaction conditions and the nature of the homologating agent. In this Account, concisely contextualizing our work with lithium carbenoids ($LiCH_2X$, LiCHXY *etc*) for homologating carbon-centered electrophiles, we focus on the assembly of three-membered cycles featuring fluorinated substituents. Two illustrative case studies are considered: (1) the development and employment of fluorinated carbenoids *en route* to rare α-fluoroepoxides and aziridines, and (2) the installation of *up to* halomethylenic groups on trifluoroimidoylacetyl chlorides (TFA-ICs) for preparing CF_3-containing halo- and halomethylaziridines. Collectively, we demonstrate that the initial homologation event generated by the installation of the carbenoid, upon modulation of the conditions, serves as a tool for creating fluorinated building blocks in a single operation.

Key words epoxides, aziridines, fluorine, homologation, carbenoids

The Concept of Homologations and Carbenoids

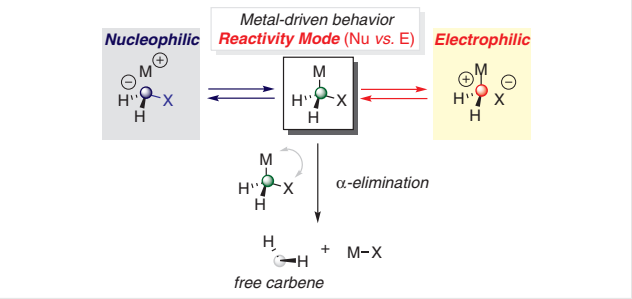
Homologation refers to a synthetic operation that enables the formation of a new carbon–carbon bond through the formal insertion of a constant unit (usually a methylene, i.e., CH_2) within an existing bond (Scheme 1).[1] In this context, examples of homologations of widespread use in synthesis are canonical reactions involving the transfer of C1 units supplied in the form of formal CH_2-X fragments, such as diazomethanes (Arndt–Eistert[2] and related Tiffenau–Demjanov[3]), sulfur ylides (Corey–Chaykovski),[4] or phosphorus ylides (Wittig).[5]



Scheme 1 General context of homologation reactions and canonical homologating agents

Since the launch of our group,[6] we have focused on the employment of carbenoids (metalated α-halomethyl reagents, M-CH_2-X) for realizing homologation processes.[7] Introduced by Closs and Moss in the early 1960s,[8] such carbenoids exhibit a reactivity profile that is related to the aforementioned C1 donors, although the dynamic switching from a nucleophilic to electrophilic behavior makes them unique entities.[9] This is well illustrated in the tunable reactivity of halomethyl carbenoids of different metals: highly electropositive ones (e.g., Li) manifest (almost) predominantly nucleophilic activity, whereas decreasing the electropositivity (e.g., Zn) leads to a significant switch to overall electrophilic character (Scheme 2).[9] In agreement with this assumption, carbenoids of metals featuring moderate electropositivity (e.g., Mg) react according to a nucleophilic or electrophilic mode, mainly depending on the reaction conditions.[10] A series of points are recognized as critical when using carbenoids in synthesis. The main limitation is represented by the significant thermal instability, resulting in a degradation process through α-elimination, due to an internal coordination of the metal with the halogen, which ultimately leads to a free carbene and a

metal halide salt.[7b,c] However, careful selection of the reaction conditions enables the homologation chemistry with carbenoids to be productive.



Scheme 2 Basics of carbenoid reactivity

Conducting the reactions in the presence of lithium halides in ethereal solvents constitutes an effective tool for disrupting the internal coordination responsible for the undesired α-elimination. Additionally, running the reaction under Barbier-type conditions (i.e., the electrophile must be present in the medium when the carbenoid is generated), and fixing the temperature at a reasonably low temperature (–78 °C), further contribute to avoid deleterious phenomena. Such a temperature not only impedes the degradation of the carbenoid, but, in the case of optically active ones, is fundamental for minimizing the risk of racemization events, which would result in loss of stereochemical integrity of both the electrophile and the carbenoid. Because of the adoption of halogen, hydrogen, metalloid or sulfoxide exchange strategies to generate the carbenoid, it could be convenient to use a small excess of these carbenoid precursors (compared to metalating agent) in order to preserve the electrophile from undesired attacks of these highly reactive nucleophiles/bases.[7b] Although the controlled addition of the metalating agents via a syringe pump represents an adequate technique for preparing carbenoids,[11] the advent of microfluidic technologies contributed to further improve the critical methodological aspect of their generation, thus avoiding the requirement for Barbier-type conditions in some circumstances.[12]

The chemistry of halocarbenoids attracted significant interest because of the innate potential of the approach to constitute a valid and effective alternative to classical diazomethane-based procedures.[7c] Applications of lithium carbenoid homologations at industrial level to access key building blocks en route to antiretroviral agents are known.[13] Undoubtedly, the high value of halolithiums is illustrated in the pioneering work of Matteson on boron-ate complexes,[14] and further extended to assembly line and iterative homologations by Aggarwal[15] and Blakemore.[16]

A Survey of Designed Homologations with Carbenoids

The prototypal nucleophilic homologative transformation of a representative carbonyl platform involves two key events: (1) the formation of an addition-type intermediate accomplished with a M-CH_2-X reagent (M = metal, X = leaving group, e.g., halogen, N_2 etc.) and (2) the eventual molecular rearrangement of this intermediate through the expulsion of the leaving group, finally evolving to the homologated architecture.

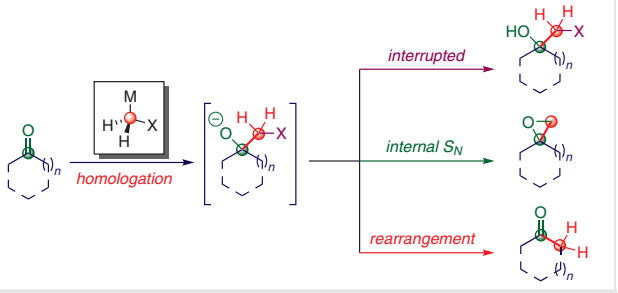
We devoted several studies to design and develop synthetic methodologies building on the initial C–C bond forged with nucleophilic halomethyl lithiums.[7c] Depending on the inclusion (or not) of the halogen(s) inserted with the carbenoid in the final compound, we could individuate three different outcomes for the processes: (1) the *inter-*

Biographical Sketches

Vittorio Pace has been a Full Professor of Organic Chemistry at the University of Torino since March 2020. He graduated in Pharmacy in 2005 from the University of Perugia (Italy) and subsequently received his PhD in Chemical Sciences *cum laude* from the Complutense University of Madrid in 2010 working with Profs. Alcántara and Sinisterra. After postdoctoral training at Vienna (Prof. Holzer, 2010–2011), Manchester (Prof. Procter, 2011–2013) and Stockholm (Prof. Olofsson, 2013–2014), he obtained a group leader position at the University of Vienna in 2014, before holding the Tenure-Track Professorship in Drug Synthesis at the University of Vienna between 2018 and 2020. In 2016 he received the *Habilitation* in Pharmaceutical Chemistry from the University of Vienna and, in 2017, the *Habilitation* for Full Professor of Organic Chemistry from the Italian Ministry of University.

He has received several awards including the *Ciamician Medal* of the Italian Chemical Society, the *Caglioti Prize* of the Accademia Nazionale dei Lincei, the *Young Investigator Award* of the Faculty of Life Sciences at Vienna, the *La Roche-Hoffmann Prize* of the European Society of Medicinal Chemistry, the *Viennese Innitzer Award* in 2017, the *Habilitation Award* of the Austrian Chemical Society in 2019 and the *Thieme Journal Award* in 2020. His research core is represented by the design and development of new synthetic concepts with functionalized organometallic reagents.

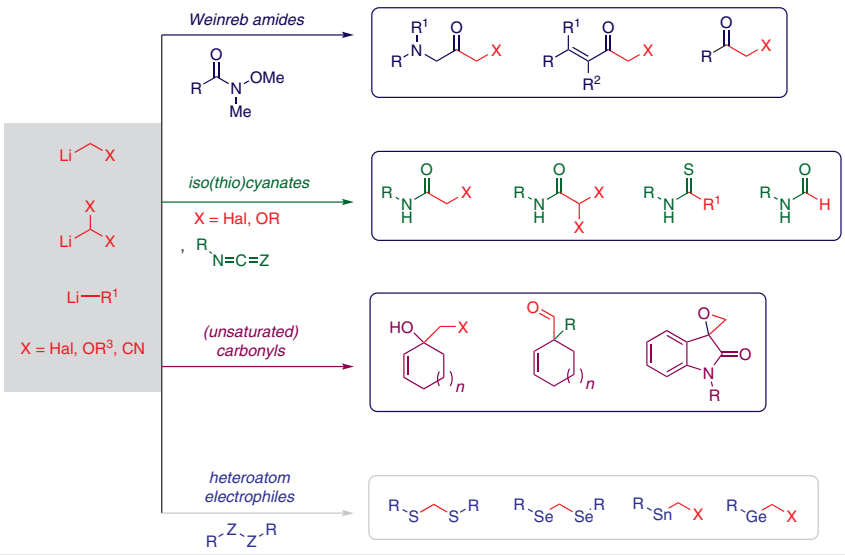
rupted homologation in which the halogen(s) remains in the resulting structures, thus being available for later functionalization;[17] (2) the *ring-closure* through simple internal nucleophilic displacement[18] (e.g., Corey–Chaykovski mode), and (3) the *pure* homologation in which the halogen is conveniently displaced during the molecular rearrangement of the carbon skeleton, often exploited in ring-enlargement operations (Scheme 3).[19] Evidently, the pathway followed by a given addition intermediate is governed by both the nature of the substrate and the carbenoid. Under nucleophilic regime, more reactive electrophiles (ketones, aldehydes, and, in general, carbonyl-like substrates) are more prone to undergo ring-closure phenomena compared to less reactive electrophiles (Weinreb amides, esters, etc.), for which the interrupted homologation is preferentially observed.[20]



Scheme 3 The outcome of canonical homologations of a carbonyl with MCH_2X reagents

Extensive work from our group dealt with – but was not limited to – interrupted homologations of Weinreb amides, which proved to be excellent manifolds for preparing α-substituted methyl ketones according to an intuitive logic.[21]

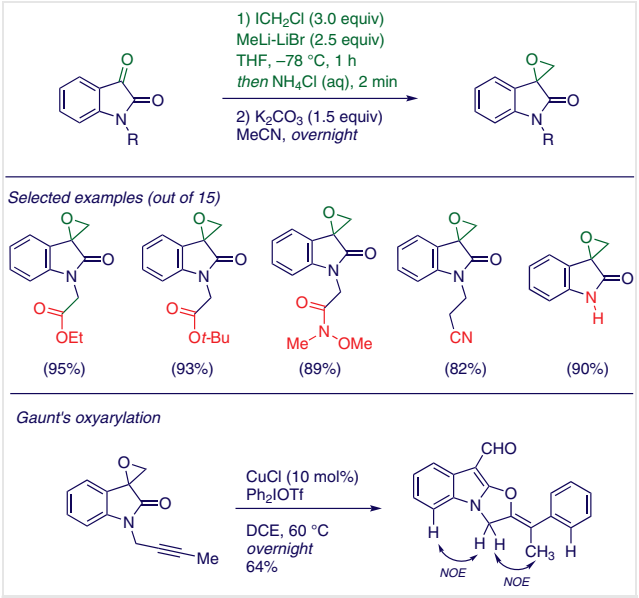
Once the metalating conditions were defined, a series of M-CH_2-X agents delivered the fragment to the recipient acylating agents (Scheme 4). Notably, no undesired overaddition or loss of stereointegrity was generally observed, as also confirmed by the isolation of hemiaminal addition intermediates.[22] α-Substituted methyllithium derivatives were the nucleophiles of choice to accomplish the reactions, whereas the tamed nucleophilic – although more stable – magnesium analogues were not productive with these electrophiles.[23] We also became interested in rejuvenating Gilman's seminal chemistry for forging the (thio)amide bond starting from iso(thio)cyanates and polar organometallics.[24] We installed halomethyl- and dihalomethyl fragments via the carbenoidic pathway to prepare α-halomethyl and α,α-dihalomethyl amides.[25] Switching to simple (enantio)-enriched organolithiums or hydrides as the nucleophiles, the methodology was further extended to synthesize thioamides, formamides, and thioformamides.[26] Intriguingly, the halomethylation of carbonyl-type compounds possessing unsaturated elements in the adjacent position was an excellent tool for accessing complex motifs ranging from simple interrupted homologated products[17] to naturally relevant spiro-epoxyoxindoles (see below)[18,27] or more complex fully substituted quaternary aldehydes resulting from Meinwald rearrangement sequences.[28] Moreover, the higher nucleophilicity of lithium carbenoids compared to other homologating agents (e.g., sulfur ylides and diazomethane) was crucial for solving elusive transformations such as the homologation of disulfides and diselenides to the corresponding dithio- and diselenoacetals.[29] Finally, we also succeeded in achieving related homologations (in interrupted mode) of halo-stannanes and halo-germanes to halomethyl-analogues in a single synthetic operation.[30]



Scheme 4 Overview of homologation reactions developed in the Pace group

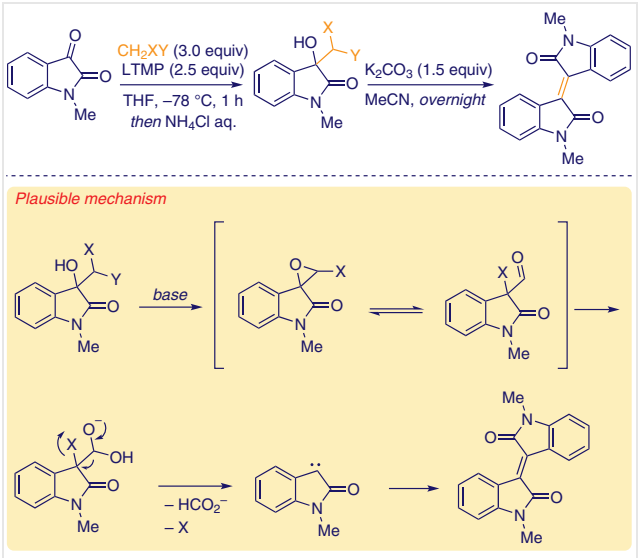
Early Work on Homologation of Isatine Derivatives en Route to Spiro-epoxyoxindoles

Given the relevance of isatins as precursors of natural products,[31] we reported a convenient direct epoxidation of the highly electrophilic 3-carbonyl functionality by direct treatment with $LiCH_2Cl$ followed by alkaline aqueous ring closure (Scheme 5).[18,27b] The scope of this method was investigated and a plethora of spiro-epoxyoxoindoles featuring a wide range of functionalities both on the nitrogen and the aromatic ring of the isatin core were prepared in high yield. Excellent chemoselectivity for the attack of the carbenoid to the isatin carbonyl was uniformly observed, as showcased in the case of esters, Weinreb amide, amide, nitrile or even in the simple (unprotected, NH) isatin. Notably, *N*-propargyl-type spiro-epoxyoxindole were amenable to Gaunt's Cu-catalyzed intramolecular electrophilic oxyarylation with an hypervalent iodonium salt to yield a complex tricyclic system.[32]



Scheme 5 Chemoselective homologations of isatins

It is interesting to note the completely different behavior of intermediate dihaloalcohols and isatins towards the standard base-mediated ring closure (Scheme 6). Although the initial homologation event with LiCHXY carbenoids,[22,25b] generated via deprotonation of the corresponding dihalomethane CH_2XY with LTMP (lithium 2,2,6,6-tetramethylpiperidide) in THF at –78 °C, proceeded smoothly, the following alkali treatment resulted in iso-indigo compounds. We postulate the intermediacy of an extremely labile haloepoxide (chloro, bromo), rearranging in Meinwald fashion to a quaternary α-haloaldehyde[28] that is susceptible to base attack, followed by elimination of formate and halide. The so-formed free carbene furnishes the observed iso-indigo scaffold upon dimerization.



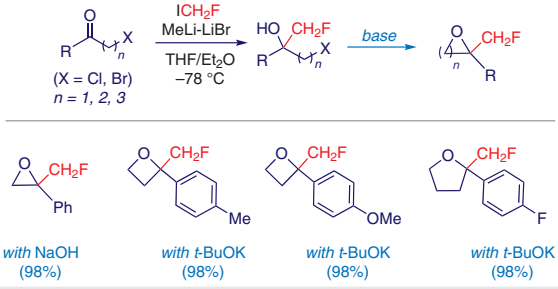
Scheme 6 Genesis of iso-indigo type compounds from the rearrangement of unstable α-haloepoxides of isatins under basic conditions

Developing Fluorinated Carbenoids for Homologations

The three-word paradigm 'single synthetic operation' spurred the group to continue to work in the field because, probably, the lessons learned from carbenoids were not exhaustive. *In primis*, as could be deducted from the discussion above, no mention was made of fluorine-containing carbenoids. The unique effects, in terms of reactivity and molecular properties tuning, imparted by this halogen would be highly desirable and involve intuitively simple logics for its introduction.[33] And, surely a reagent such as MCH_2F would have met these requirements! It was difficult to conceive that generations of chemists working in the field did not consider the possibility of generating $LiCH_2F$, *simili modo* to chloro-, bromo- or iodo-methyllithiums. The efficient development of this reagent could definitively provide a direct installation of the valuable fluoromethyl-group into organic skeletons without needing additional transformations. In this context, Hammerschmidt reported the first description of fluoromethyllithium in 2014 through a convenient lithium–tin exchange conducted on $(n\text{-Bu})_3SnCH_2F$, highlighting a series of unique features of this reagent:[34] (1) its chemical stability was definitively lower than its stereochemical integrity, as deducted by observing the behavior of a chiral deuterated species (LiCHDF); (2) the reagent proved to be valuable for transferring the CH_2F unit to an aldehyde (one example), thus preparing a fluorohydrin, albeit in moderate yield. This prece-

dent clearly demonstrates the existence and usefulness of $LiCH_2F$, thus suggesting that properly identifying the optimal conditions for its generation could represent the key to finally include this reagent among the usable halolithium for preparative purposes. In 2017 we proposed a solution to the challenge built on an intuitive approach (Scheme 7):[35] the commercially available fluoroiodomethane undergoes an extremely fast lithiation at –78 °C. A series of interesting points emerged during the optimization study: (a) a precise 1:1.5:2.0 stoichiometry was essential for properly forming and using the fluoro carbenoid; (b) although there was a slight excess of MeLi·LiBr, no detectable concomitant addition to the carbonyl manifold by the methyl carbanion was observed; (c) the overall limited existence of the species benefited from using a 1:1 (*v*/*v*) THF/Et_2O mixture, with other solvents being deleterious for its formation or stability. It is worth noting that employing a single-carbon fluorinated unit as carbenoid precursor (ICH_2F) was highly convenient in terms of practicability as a consequence of the liquid physical state (bp 53 °C),[36] which is practically analogous to the prototypal dichloromethane. This is indeed one of the most attractive characteristic of the methodology: a simple and available carbenoid precursor in which the constitutive iodine atom confers three fundamental features: easy experimental manipulability, innate tendency for iodine–lithium exchange, and flexibility for different uses imparted by the acidic methylene unit (e.g., deprotonation; see below). The addition of this novel carbenoid demonstrated an excellent versatility and flexibility, as demonstrated by a wide portfolio of carbonyl containing platforms that are amenable for the protocol, including aldehydes, ketones, imine and Weinreb amides. Interestingly, the addition of $LiCH_2F$ to the latter amides, probably because of the intrinsic lower electrophilicity, was very recently improved by Luisi and Nagaki through a microfluidic approach enabling its external trapping.[12a]

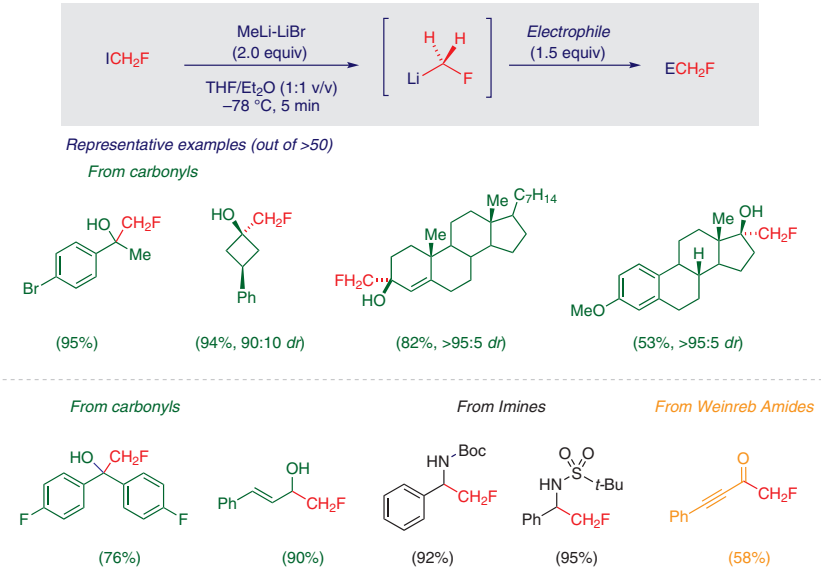
This fluoromethylation of α-, β-, or γ-halogenated ketones could be efficiently coupled with a subsequent base-triggered ring closure, finally delivering epifluorohydrins[37] and their corresponding homologues (oxetanes and tetrahydrofurans) characterized by the pendant fluoromethyl fragment in the *vic*-position to the oxygen (Scheme 8).[35]



Scheme 8 Successive haloketone fluoromethylation/ring closure strategy

From Fluoromethyllithium to Fluoroiodomethyllithium

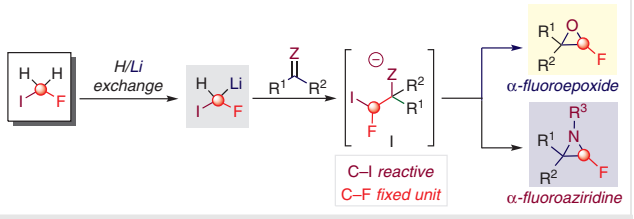
As anticipated, ICH_2F constitutes a C1-unit presenting two reactive sites for organolithium reagents: the iodine and the methylene. More importantly, the two halogens connected to the carbon impart a significant acidity to the methylene protons. In analogy to the well-established practice for preparing dihalocarbenoids starting from a dihalomethane,[22,25b] a lithium amide base could selectively deprotonate the CH_2 group, thus giving the unprecedented LiCHFI



Scheme 7 Generation and use of $LiCH_2F$

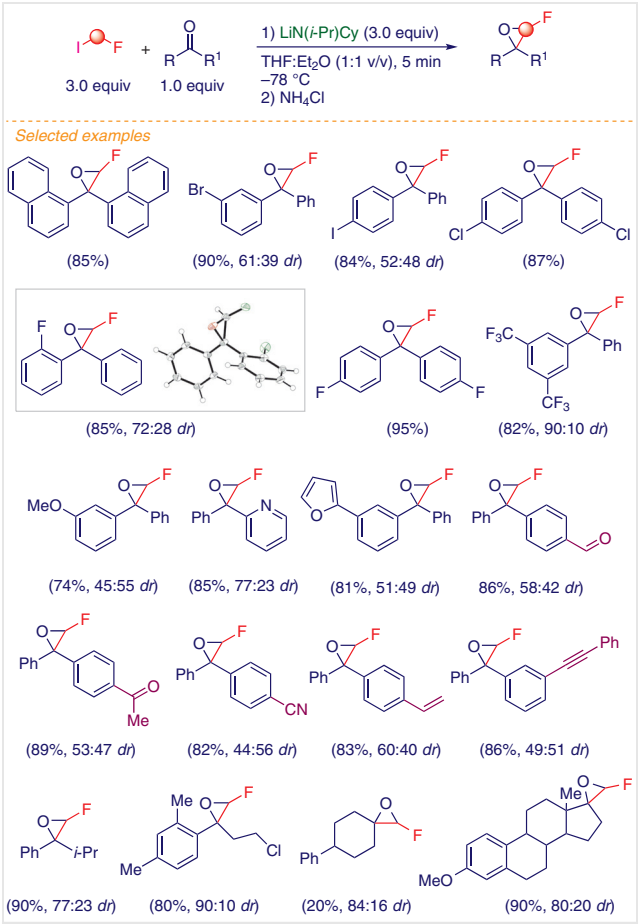
carbenoid. In previous studies, we reported selective methodologies for obtaining $LiCHCl_2$, LiCHBrCl and LiCHICl by treating the corresponding carbenoid precursor (common reagents such as CH_2Cl_2 etc) with LDA or LTMP.[22,25b] There is no doubt that LiCHIF is *per se* a fascinating carbenoid, being itself formally a single carbon atom presenting four different substituents. At the outset of our study, we recognized its unique potential because of the different inherent reactivity of the two halogens: iodine and fluorine. In particular, the former, under suitable conditions, could advantageously undergo a nucleophilic displacement (C–I bond dissociation energy = 57 kcal/mol),[38] thus leaving the fluorine (C–F bond dissociation energy = 115 kcal/mol)[38] on the organic array.

With this background in hand, in 2019, we reported the first application of LiCHFI in synthesis in a homologation–ring closure sequence of ketones and imines, leading to rare[39] α-fluoroepoxides and α-fluoroaziridines (Scheme 9).[40] Effectively, the conditions required for generating $LiCH_2F$ (primarily the solvent mixture THF/Et_2O) were found adaptable to the case of LiCHFI, thus making practicable the introduction of this carbenoid to the synthetic chemist toolbox. Notably, previous studies by Hiyama found severe difficulties in using analogous Si-substituted fluorinated species, with strict control of temperature (–130 °C) being required to avoid the α-elimination.[41]



Scheme 9 Deprotonation of fluoroiodomethane for preparing fluoroiodomethyllithium and reactions with (aza)carbonyls

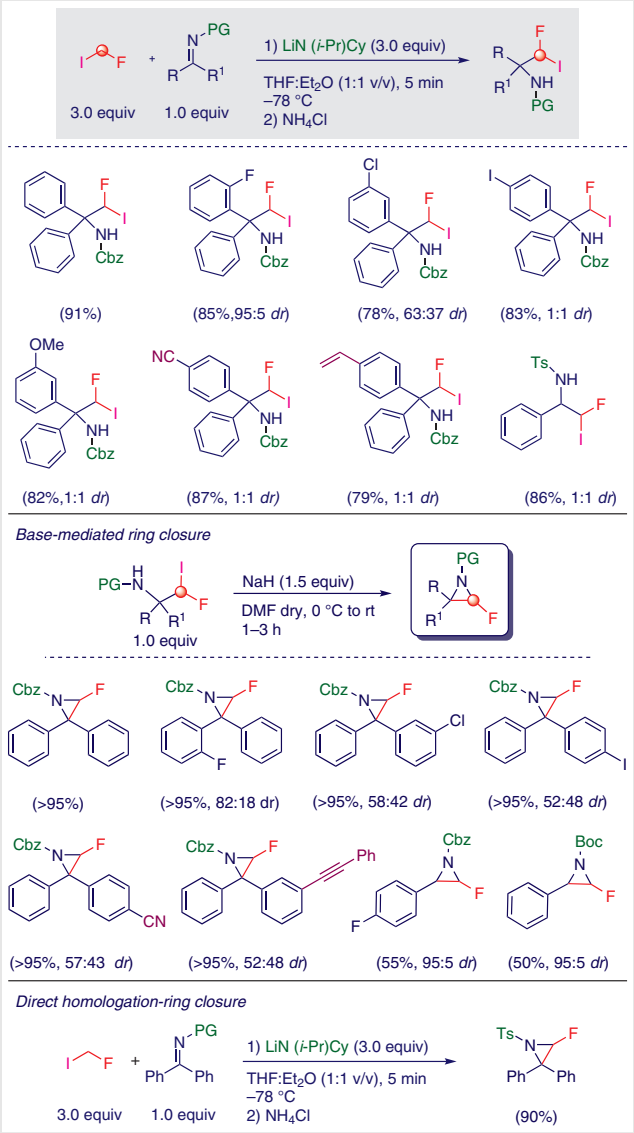
In our optimization study on benzophenone as a model electrophile, the lithium amide base LiN(*i*-Pr)Cy, emerged as the preferred option under Barbier-type conditions at –78 °C. However, the more common LDA could also be advantageously employed, as reported in following studies by Aggarwal[42] and Luisi.[36c] To ensure the full generation of the instable carbenoid, a convenient three-fold excess of carbenoid was used (3 equiv ICH_2F, 3 equiv Li base). The scope of the reaction was investigated in detail with both (hetero)diaryl ketones and aryl-alkyl ketones presenting a variety of substituents such as halogens, electron-donating and electron-withdrawing groups placed on the (hetero)aromatic ring (Scheme 10). We were pleased to observe genuine chemoselectivity in reactions involving additional carbonyl groups (aldehyde and ketone) that were potentially susceptible to nucleophilic attack by LiCHFI. Analogously, the electrophilic manifolds could embody nitrile and unsaturated functionalities (olefins and alkynes), which were fully retained during the homologation event.



Scheme 10 Synthesis of α-fluoroepoxides via homologation/ring closure of ketones

The opportune activation of the poorly electrophilic azamethinic carbon of imines through the installation of an electron-withdrawing element on nitrogen was fundamental[43] to also applying these species to the homologation–ring closure sequence en route to valuable α-fluoroaziridines (Scheme 11).[44] However, probably because of the additional steric hindrance introduced by the activating element and the low temperature demanded to preserve the chemical integrity of the carbenoid, the direct ring closure was possible only in the case of the strong electron-withdrawing benzensulfonyl group. Indeed, the isolation of unprecedented α-fluoro-α-iodo amines at the end of the interrupted homologation step, followed by NaH-mediated cyclization, allowed the corresponding target α-fluoroaziridines to be finally obtained. It is worth noting – again – the high chemoselective profile of the transformation, as, for example, indicated by the tolerance of an iodo-

aromatic substituent. The latter did not affect the generation of the carbenoid, thus indicating the higher tendency of ICH_2F to undergo the crucial Li–I exchange.



Scheme 11 Synthesis of α-fluoroiodoamines through homologation of EWG-substituted imines and their transformation into α-fluoroaziridines

Telescoped Homologations for Accessing Quaternary *gem*-Halo(methyl)trifluoromethyl Aziridines

Considering the importance of the presence of a fluorine atom in an organic framework, the incorporation of a trifluoromethyl group (CF_3) within a three-membered nitrogen cycle would also lead to unique species (CF_3-aziridines) in terms of reactivity, synthetic versatility and potential pharmacological properties.[33b,45] This importance is underlined by the intense efforts that have been undertaken towards the development of efficient tactics for preparing CF_3-aziridines. To this end, in 2019, our group reported the synthesis of unprecedented quaternary α-chloro and α-halomethyl trifluoromethyl aziridines[46] employing a telescoped carbenoid homologation of trifluoroacetimidoyl chlorides (TFAICs) as a key tool.[47] Such electrophiles present a unique reactivity profile because of the excellent electrophilicity of the azomethinic carbon imparted by the trifluoromethyl group and the chlorine atom (Figure 1).

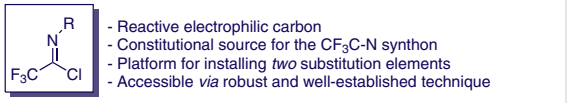


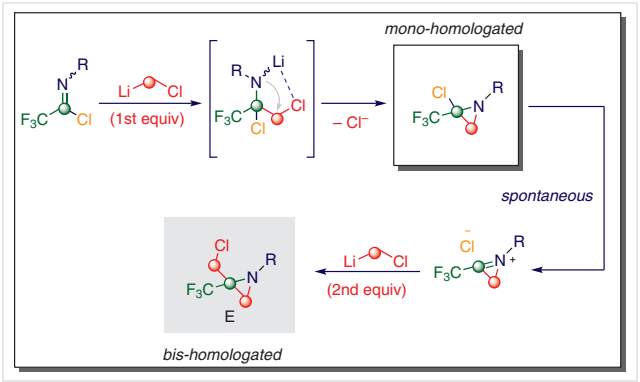
Figure 1 Trifluoromethylimidoyl chlorides (TFAICs): Reactivity fundamentals

Accordingly, our rationale was harnessed by tailoring TFAICs as ideal electrophilic imine surrogates, thus circumventing the innate low reactivity of the classical imines which have often required activating groups (e.g., strong EW),[43] as highlighted before. Moreover, the sp^2 C–N double bond could be efficiently considered as a manifold for installing two nucleophilic elements. We immediately recognized the potential of these electrophiles in reactions with carbenoids, as the switchable carbenoid stoichiometric-driven chemoselectivity was evident from preliminary experiments (Scheme 12). One C1 unit – giving a *gem*-halotrifluoromethyl-aziridine – was inserted in the presence of 1.2 equiv of $LiCH_2Cl$, while increasing the loading up to 2.8 equiv, resulting in an unprecedented C1–C1 bis-homologation, furnishing *gem*-halomethyl-trifluoromethyl-aziridine. Remarkably, in both instances, the quaternary carbon of the aziridinyl motif was assembled during the telescoped homologation event. Notably, the chemocontrol of the methodology was superb. Indeed, in the presence of substrates featuring functionalities that are highly sensitive to organolithium reagents, such as nitrile, ester, Weinreb amide, and halogen atoms, the attack of the carbenoid was extremely selective for the electrophilic TFAIC carbon. Moreover, nitrogen-containing substituents on the aromatic ring such as morpholine, pyrrolidine, lactam, diazo, and unsaturated motifs such as olefins or alkynes, were perfectly tolerated.

The telescoped homologation can be explained by considering a tetrahedral intermediate **B**, formed upon the addition of the first equivalent of $LiCH_2Cl$. We hypothesize that an internal coordinative effect between the cation (Li) of the amide and the chlorine (introduced during the homologation) would foster an internal nucleophilic substitution leading to the mono-homologated chloroaziridine **C**. In case of higher loading of carbenoid (2.8 equiv) such an intermediate **C** spontaneously yields the highly electrophilic

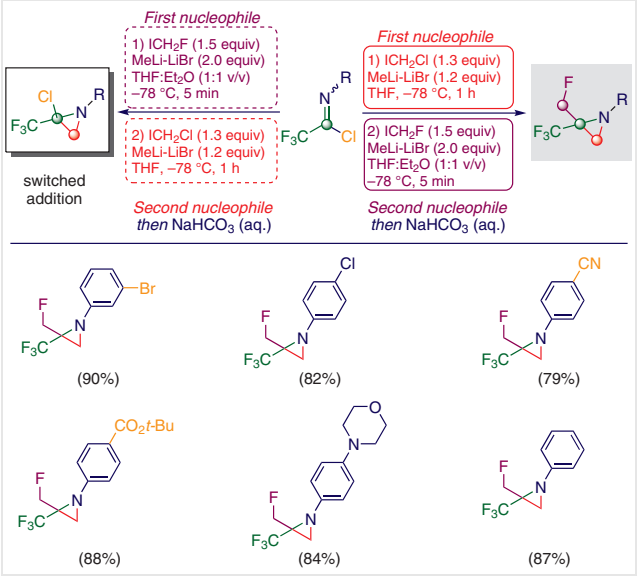
azirinium ion **D**, which is susceptible to the second homologation, finally giving the C1–C1 di-homologated chloromethylaziridine **E** (Scheme 13).

The mechanism proposed is consistent with additional experimental evidence obtained using two distinct homologating agents ($LiCH_2Cl$ and $LiCH_2F$). The chloro carbenoid intervenes in both phases of the process, thus it serves in both aziridine ring assembly and homologation of the azirinium to finally give the bis-homologated adduct. On the other hand, fluoromethyllithium – presenting a non-optimal leaving fluorine atom – cannot be employed for constructing the three-membered ring, but it manifests enough nucleophilicity to attack the azirinium species. As a consequence, fluoromethyl-trifluoromethyl-aziridines can



Scheme 13 Plausible mechanism governing C1 vs. C1–C1 telescoped homologations

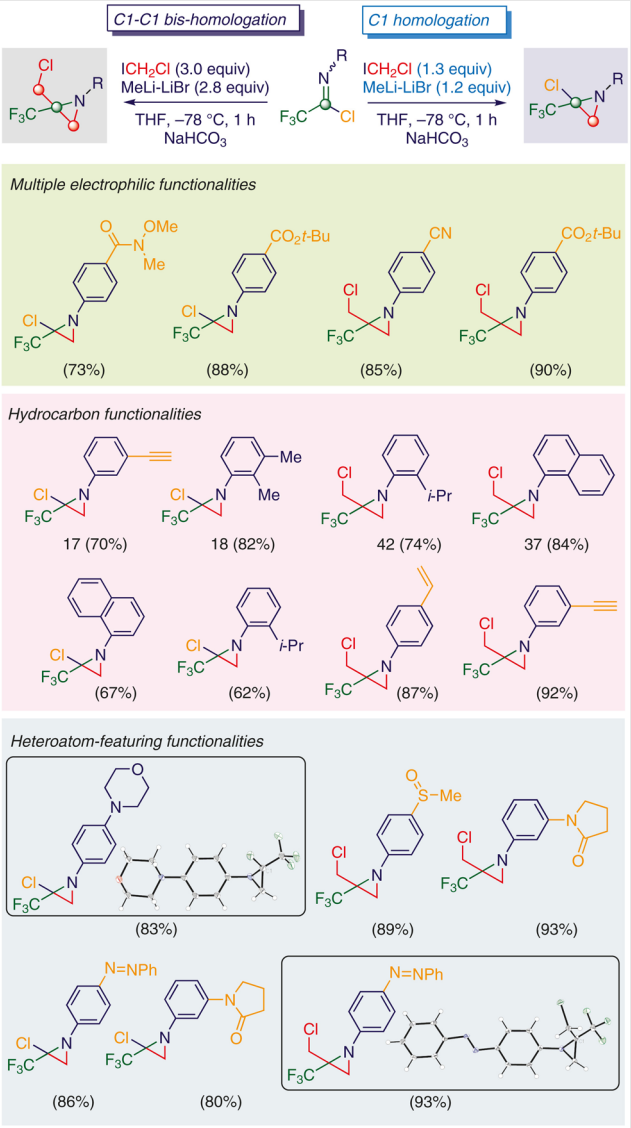
be easily accessed through a two-carbenoid addition procedure: $LiCH_2Cl$ furnishes the CH_2 unit for the ring, whereas $LiCH_2F$ installs the pendant fluoromethyl fragment. Overall, a series of crossover experiments, in which the nature of the carbenoid (first nucleophile and second nucleophile) was changed one by one, are supportive for the mechanistic rationale proposed (Scheme 14).



Scheme 14 Addition of two different carbenoids: $LiCH_2Cl$ and $LiCH_2F$

Conclusions

Homologation chemistry offers a privileged perspective for assembling cyclic motifs through an intuitive and highly predictable strategy. The proper installation of a halomethylenic fragment into an electrophilic platform uniformly leads to tetrahedral intermediates that are amenable for additional manipulation and, thus diversification into a wide portfolio of final compounds. Importantly, the chemoselectivity – often considered elusive with organolithiums –



Scheme 12 Telescoped homologations of TFAICs to chloro-trifluoromethylaziridines and chloromethyl-trifluoromethyl aziridines

seems to be controllable with carbenoids, probably because of their tamed nucleophilicity. The work from our group on fluoro carbenoids enabled the existing gap of introducing fluorinated carbenoids into electrophiles to be filled. Indeed, the previously established use of stabilizing elements for ensuring the preservation of the chemical integrity of putative fluorinated carbanions are *de facto* eliminated by adopting the carbenoid approach. Thus, the three-step sequence involving (1) preparation of the pronucleophile by installing the formal protecting group, (2) effective nucleophilic reaction and, (3) removal (usually under forcing conditions) of the stabilizing element, can now be executed in a single synthetic operation with a fluoro carbenoid.

Funding Information

We acknowledge the University of Vienna and the University of Turin for financial support.

Acknowledgment

We thank our colleague Prof. R. Luisi (University of Bari) for having shared adventures on fluoro-carbenoids.

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Publication n. 3

Chemoselective Homologation-Deoxygenation Strategy Enabling the Direct Conversion of Carbonyls into (*n+1*)-Halomethyl-Alkanes.

Miele, M.;,Citarella, A.; Langer, T.; Urban, E.; Holzer, W.; Ielo, L.; Pace, V.*

Org. Lett. **2020**, 22, 7629-7634. (DOI: 10.1021/acs.orglett.0c02831)

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Chemoselective Homologation–Deoxygenation Strategy Enabling the Direct Conversion of Carbonyls into (*n*+1)-Halomethyl-Alkanes

Margherita Miele,[⊥] Andrea Citarella,[⊥] Thierry Langer, Ernst Urban, Martin Zehl, Wolfgang Holzer, Laura Ielo, and Vittorio Pace*

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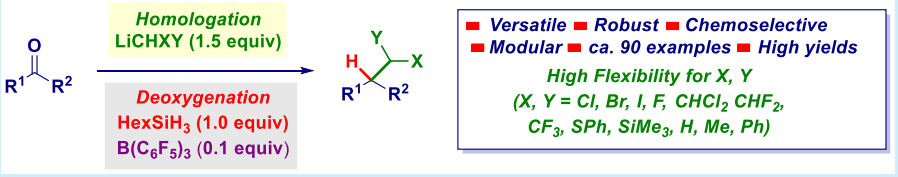
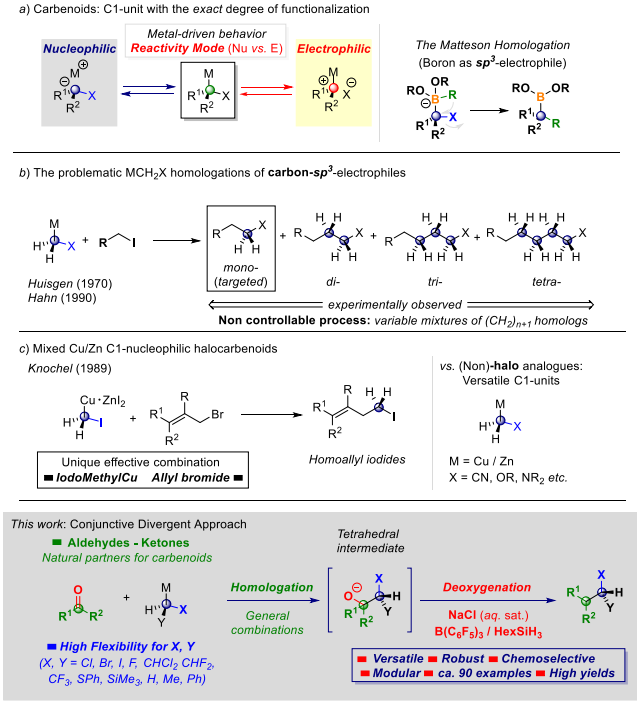


ABSTRACT: The sequential installation of a carbenoid and a hydride into a carbonyl, furnishing halomethyl alkyl derivatives, is reported. Despite the employment of carbenoids as nucleophiles in reactions with carbon-centered electrophiles, sp^3-type alkyl halides remain elusive materials for selective one-carbon homologations. Our tactic levers on using carbonyls as starting materials and enables uniformly high yields and chemocontrol. The tactic is flexible and is not limited to carbenoids. Also, diverse carbanion-like species can act as nucleophiles, thus making it of general applicability.

Embodying a halogen-containing functionality within a carbon skeleton profoundly influences the physicochemical features, thus properly modulating the reactivity profile of the array.[1] Accordingly, solid synthetic methodologies levered on different logics (e.g., radical, electrophilic, and nucleophilic) have been designed and thoroughly applied.[2] In this sense, the introduction of metalated α-halogenated carbon species (MCR^1R^2Hal, i.e., the so-called carbenoid reagents) reacting under a nucleophilic or electrophilic regime (Scheme 1, path a), depending on the nature of the metal, has emerged as a valuable tool for delivering synthons featuring the exact degree of functionalization requested (i.e., halogen loading).[3] As a result, common downsides associated with the use of conceptually different approaches, such as polyhalogenations, can be conveniently skipped. The initial installation of the CR^1R^2Hal unit, that is, a homologative event, is later exploited en route to the construction of more complex molecular architectures accessible through a single synthetic operation, as, for example, illustrated in the versatile Matteson homologation of sp^3-hybridized boron electrophiles, elegantly adapted by Aggarwal to the assembly line concept.[4] Regrettably, carbon-based platforms suitable for homologations with halocarbenoids are restricted to sp^2-type systems: For example, our group demonstrated that homologations of carbonyl-type derivatives conduct, through a single operation, to more sophisticated architectures (quaternary aldehydes[5] and aziridines).[6] Also, olefins are amenable substrates for C1 insertions into cyclopropanes.[7] In this scenario, the endeavored homologations of (primary) sp^3-carbon platforms resulted in uncontrollable multi-insertion phenomena (up to four consecutive homologations) of questionable synthetic value,

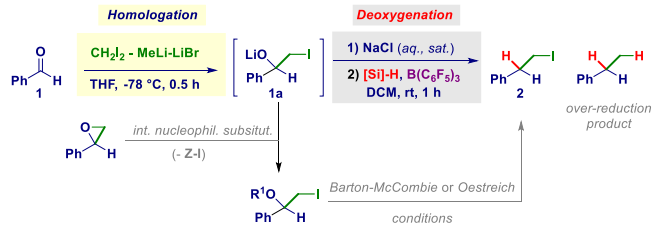
Scheme 1. General Context of the Presented Work



Received: August 24, 2020
Published: September 10, 2020

https://dx.doi.org/10.1021/acs.orglett.0c02831
Org. Lett. 2020, 22, 7629–7634

Table 1. Model Reaction: Optimization[a]



entry	$LiCH_2I$ (equiv)/time (h)	deoxygenation reductant/solvent	Lewis acid	yield of **2** (%)[a]
1[b]	1.4/0.5	*BMC*		11
2[c]	1.4/0.5	*Oestreich*	$B(C_6F_5)_3$	46
3[d]	1.4/0.5	Et_3SiH/DCM	$B(C_6F_5)_3$	52
4[e]	1.4/0.5	Et_3SiH/DCM	$B(C_6F_5)_3$	66
5	1.4/0.5	Ph_2SiH_2/DCM	$B(C_6F_5)_3$	68
6	1.4/0.5	Et_2SiH_2/DCM	$B(C_6F_5)_3$	77
7	1.4/0.5	$PhSiH_3$/DCM	$B(C_6F_5)_3$	84
8	*1.4/0.5*	*hexSiH$_3$/DCM*	*$B(C_6F_5)_3$*	89
9	1.4/0.5	$hexSiH_3$/DCM	$InCl_3$	60

[a]Isolated yield after the homologation/deoxygenation sequence. [b]BMC, Barton−McCombie (R^1 = PhCS, Bu_3SnH, AIBN, toluene, reflux). [c]Oestreich (R^1 = Ts, Et_3SiH, $B(C_6F_5)_3$, DCM). [d]Upon quenching with H_2O, DCM was added, and the two phases were separated. [e]Sat. NaCl (aq) and DCM were added prior to phase separation. Unless otherwise stated, $B(C_6F_5)_3$ (0.1 equiv) was used.

first noticed in the seminal works by Huisgen[8] and later observed by Hahn[9] (Scheme 1, path b). An initial solution to the polymethylene homologation problem is offered by the Knochel's mixed copper−zinc mono-iodocarbenoids introduced in 1989, which, to the best of our knowledge, represent unique C1-halogenated units able to selectively control the process (Scheme 1, path c). Unfortunately, the attainable chemical space is narrowed by specific structural characteristics demanded of reactions partners, an allylic bromide as the recipient electrophile and an iodo-methyl-Cu-ZnI_2 as the nucleophile, with the final result being the preparation of exclusively homoallylic iodides. This significant aspect is in contrast with the wide applications described for diverse halo methyl zinc carbenoids developed and thoroughly applied, for example, by Marek[11] or different (non)-halomethyl Cu/Zn mixed carbenoids of Knochel.[10a−d]

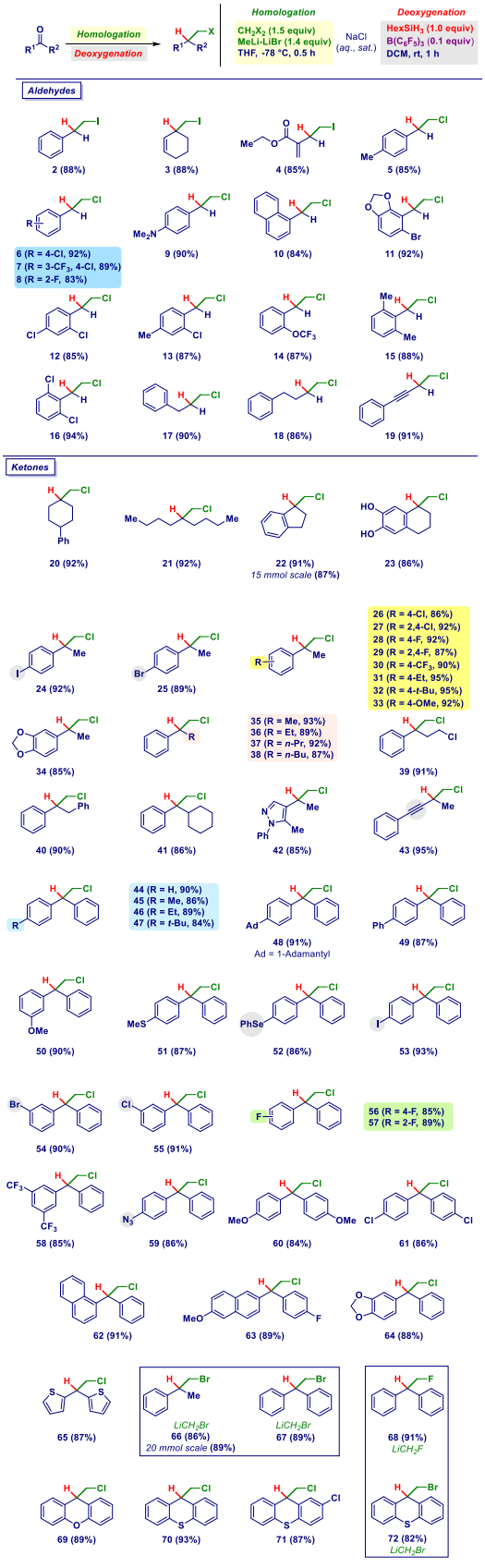
We reasoned that realizing the carbenoid installation on a carbonyl sp^2-carbon followed by the deoxygenation[12] of the intermediate carbinol would represent a general and modular synthesis of homologous alkyl halides not dependent on the specific layout of reagents. Collectively, the strategy can be regarded as the employment of sp^2-carbonyl systems as naked sp^3-C-LG systems (LG = leaving group), which, after the envisaged sequence, would release the targeted motifs. We anticipate that this tactic will offer a robust and highly flexible solution for streamlining homologous (n+1)-haloalkyls that are tunable by selecting, at the operator's discretion, both reaction partners: the electrophilic carbonyls and the nucleophilic carbenoids.

We selected benzaldehyde (**1**) as the model substrate for the homologative deoxygenation with $LiCH_2I$ to gain insights into both separate moments of the process (Table 1). In principle, installing an iodo-containing motif would be critical because, on one hand, it could trigger an internal nucleophilic displacement, giving an epoxide[5] (**1b**, homologation side reduction), whereas, on the other hand, it could suffer from over-reduction to C−H (**1c**, deoxygenation side reduction).[13] The optimized homologation step proceeded quantitatively within 0.5 h at −78 °C in THF using 1.4 equiv of $LiCH_2I$, as deduced by ^1H NMR and GC-MS analyses, thus yielding the tetrahedral intermediate **1a**. Leaving the reaction mixture for a longer time or increasing the temperature to −50 °C resulted in significant epoxidation. (For full details, see the SI.) Direct treatment under Barton−McCombie conditions[14] gave iodoalkane **2** in low yield after a long time and at a high temperature (entry 1). We next applied the extremely versatile and convenient Oestreich's formal reduction of alcohols,[15] upon their conversion to tosylates, followed by $B(C_6F_5)_3$-catalyzed dehydroxylation[16] with Et_3SiH and obtained a good 46% yield (entry 2). Further refinement was secured by simply quenching the homologation reaction crude product with water, thus making a formal iodohydrin that was directly suitable for deoxygenation after a trivial separation of the organic phases. Although the reduction took place in moderate yield (52%), we hypothesized that the THF (used for the homologation) still present in the reaction mixture, upon dilution with DCM, could interfere with the C−O breaking event (entry 3). Indeed, the prior complete removal of THF (washing of the homologation crude product with sat. NaCl (aq)) benefited the dehydroxylation, giving a 66% yield (entry 4). Less hindered silanes such as Ph_2SiH_2, Et_2SiH_2, $PhSiH_3$, and $hexSiH_3$ were also effective: Excellent selectivity (i.e., no side reduction was noticed) was observed, suggesting the latter as the ideal agent (entries 5−8). Replacing $B(C_6F_5)_3$ with a different Lewis acid such as $InCl_3$[17] had a negative effect on the process (entry 9).

Once the reaction conditions were set, we studied the scope of the sequential process (Scheme 2). The chemocontrol was superb, as illustrated in the case of sensitive substrates such as a cyclic enone (**3**) and an α,β-unsaturated ester (**4**): No over-reduction of the olefinic and ester carbonyl motifs was noticed. The protocol was highly flexible, as deduced when using a different carbenoid homologating agent. The chloromethylation−deoxygenation methodology was effective in the case of benzaldehyde derivatives decorated with several functionalities of diverse electronic behavior, including alkyl (**5**), amino (**9**), and polyaromatics (**10**), among others. Notably, the acetal-containing bromo derivative (**11**) did not interfere in either

https://dx.doi.org/10.1021/acs.orglett.0c02831
Org. Lett. 2020, 22, 7629−7634

Scheme 2. Scope of the Sequential $LiCH_2X$ Homologation/Deoxygenation



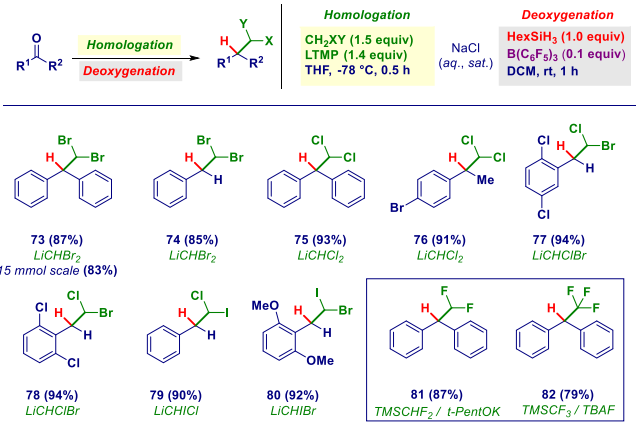
the homologation or the reduction steps. Positioning differently constituted halogen substituents is permitted (**6**−**8**, **12**−**14**), as is increasing the sterical hindrance close to the carbonyl (e.g., 2,6-disubstituted systems, **15** and **16**). Aliphatic aldehydes could be subjected to the reaction conditions, giving ω-chloro phenylalkanes (**17** and **18**) in high yields. Remarkably, a propargylic aldehyde smoothly gave the homologated analogue (**19**), preserving the chemical integrity of the alkyne. The protocol could be extended to ketones as starting substrates. Aliphatic derivatives reacted well, giving α-chloro tertiary centers in the case of both cyclic (**20**) and acyclic (**21**) derivatives. Analogously, indanone and tetralone derivatives (**22** and **23**) underwent the transformation; remarkably, scaling up to 15 mmol validated the method (**22**, 87% yield). During the reduction step, concomitant bis-demethoxylation was observed, thus affording the interesting biologically relevant dihydroxyphenyl (catechol-like) scaffold **23**.

Acetophenone derivatives were excellent materials, further documenting the high degree of chemocontrol associated with the reductive homologation. The presence of sensitive groups is fully tolerated, as illustrated by sensitive halogen iodo (**24**), bromo (**25**), chloro (**26** and **27**), fluoro (**28** and **29**), and trifluoromethyl substituents (**30**). Substituents on the aromatic ring of the opposite electronic effect maintain an unaltered efficiency: ethyl (**31**), *tert*-butyl (**32**), methoxy (**33**), and acetal (**34**). The progressive enlargement of the aliphatic terminus of the acetophenone core (**35**−**38**) was not detrimental. The genuine homologative conditions were further deduced by the precise nucleophilic attack, reduction on the carbonyl of ω-chloro-propiophenone, without noticing any collateral effect (e.g., side homologation) on the constitutive CH_2Cl appendix (**39**). Analogously, chloromethyl derivatives of 1,2-diphenylethane (**40**), cyclohexyl-toluene (**41**), and alkylpyrazol (**42**) could also be synthesized in high yield with high selectivity. Again, a propargyl fragment did not touch its integrity under the reaction conditions, giving **43**. Diaryl ketones proved to be highly effective substrates for the transformation, as indicated by a series of (mono)-substituted alkyls (**44**−**47**), including an adamantyl derivative (**48**) and aryl (**49**) benzophenone functionalities. Alkoxy (**50**), alkylthio (**51**), and arylseleno (**52**) groups could be opportunely incorporated on the benzophenone core, highlighting the fact that no simultaneous Se−Li exchange occurred during the carbenoid genesis. As a further confirmation of the chemoselectivity, potentially exchangeable halogens, such as iodine (**53**), bromine (**54**), chloro (**55**), and fluoro (**56** and **57**), or modifications thereof (trifluoromethyl (**58**)) were unambiguously endured. It is noteworthy that an azido substituent did not undergo a concomitant reduction and was intact at the end of the transformation (**59**), thus remarking on the chemoselectivity profile. Disubstituted symmetric (**60** and **61**) and asymmetric (**62** and **63**) benzophenones could react in high yields regardless of the electronic orientation of the substituents, including cases of heteroaromatic systems such as benzofuran (**64**) and dithienyl (**65**). The versatility of the method was also gathered by modifying the nature of nucleophilic carbenoids: When $LiCH_2Br$[4g] was conducted to the bromomethyl analogues (**66** and **67**), also on a higher scale (20 mmol, **66**), while using the highly unstable $LiCH_2F$,[18] an efficient synthesis of the fluoro derivative (**68**) could be performed. Notably, tricyclic-type ketones of xanthene (**69**) and thioxanthene (**70**−**72**) types also reacted under similar chloro- or bromo-methylation/deoxygenation conditions.

https://dx.doi.org/10.1021/acs.orglett.0c02831
Org. Lett. 2020, 22, 7629−7634

The successful outcome inferred by reacting monohalocarbenoids as the first nucleophiles spurred us to widen the method to dihalomethyl analogues, notoriously challenging entities for which unified, general, and reliable strategies are still underdeveloped.[19] Benefiting from the tunable intrinsic versatility of carbenoid precursors, the simple switching from a halogen−lithium exchange (shown above) to a hydrogen−lithium exchange (i.e., deprotonation with lithium tetramethylpiperidide (LTMP)) resulted in the formation of diverse dihalomethyl fragments that expeditiously reacted with ketones and aldehydes prior to deoxygenation, thus giving dibromo (**73** and **74**, further suitable for scaling in the case of the former) and dichloro (**75** and **76**) derivatives. When a halo-halo′-methane (XCH_2Y) was selected as the pro-carbenoid, the treatment with the same LTMP afforded the corresponding mixed carbenoids (LiCHXY)[20] deliverable to carbonyls with comparable efficiency and chemoselectivity: After the deoxygenation, chlorobromo (**77** and **78**), chloroiodo (**79**), and bromoiodo (**80**) analogues were prepared in high yield with high control (Scheme 3). As an additional proof of the

Scheme 3. Dihalomethyl Homologation/Deoxygenation Sequence

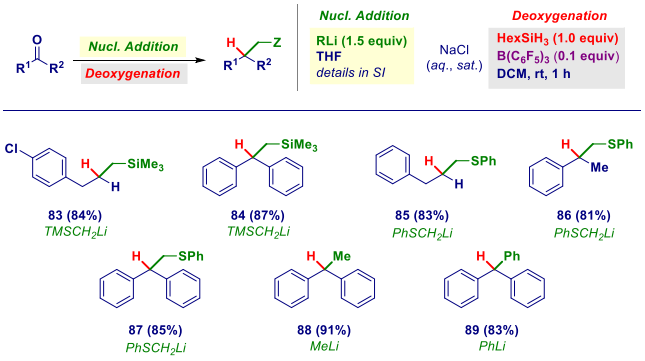


modularity of the concept, we were pleased to prepare difluoromethyl (**81**) and trifluoromethyl (**82**) derivatives. The well-known reluctance of using polyfluoromethyllithiums[21] was circumvented with silylated suitable precursors ($TMSCHF_2$[22] and $TMSCF_3$[23]), which, upon adequate activation, furnished the corresponding formal carbanions.

This conceptually intuitive carbonyl nucleophilic addition−deoxygenation sequence represents a formidable tool for forging C−C bonds, as documented by the perfect extensibility to nonhalogenated carbanions (Scheme 4). Hence, by adding an α-silyl methyl carbanion ($TMSCH_2Li$), terminal silanes were produced from both an aldehyde (**83**) and a ketone (**84**), whereas terminal thioethers were prepared through the reaction of carbonyls with an α-thio methyllithium reagent (**85**−**87**).[24] More generally, two unfunctionalized organolithiums, MeLi and PhLi (selected as model representatives for alkyl and aryl species), were amenable to reaching the corresponding trisubstituted methanes (**88** and **89**).

In summary, we have documented the high-yielding addition of two nucleophiles, a halo-carbenoid and a hydride, to the carbonyl carbon of aldehydes and ketones, thus increasing their (already) high potential and versatility in synthesis.[25] The overall operation consisting of two distinct processes, namely, homologation and silane-mediated deoxygenation under B-

Scheme 4. General Nucleophilic Addition/Deoxygenation Protocol with Various Carbanion-like Reagents



$(C_6F_5)_2$ catalysis, enables access to a plethora of halomethyl−alkyl derivatives. The conditions established for both phases of the sequence feature very high chemocontrol, thus guaranteeing safe and reliable transformations in the presence of several sensitive functionalities, such as halogens, olefins, alkynes, esters, and so on. The robustness of the logic proposed, assessed across ca. 90 presented cases, entails adding not only a wide range of monohalo- and dihalomethyl carbenoids but also fluorinated, silylated, mercapto, and, more generally, simple alkyl and aryl organolithiums.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02831.

Experimental procedures, NMR spectra, and analytical data for all of the compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Vittorio Pace − *Department of Pharmaceutical Chemistry, University of Vienna, 1090 Vienna, Austria; Department of Chemistry, University of Turin, 10125 Turin, Italy;* orcid.org/0000-0003-3037-5930; Email: vittorio.pace@univie.ac.at, vittorio.pace@unito.it

Authors

Margherita Miele − *Department of Pharmaceutical Chemistry, University of Vienna, 1090 Vienna, Austria*

Andrea Citarella − *Department of Pharmaceutical Chemistry, University of Vienna, 1090 Vienna, Austria; Department of Chemical, Biological, Pharmaceutical and Environmental Sciences, University of Messina, 98166 Messina, Italy*

Thierry Langer − *Department of Pharmaceutical Chemistry, University of Vienna, 1090 Vienna, Austria;* orcid.org/0000-0002-5242-1240

Ernst Urban − *Department of Pharmaceutical Chemistry, University of Vienna, 1090 Vienna, Austria*

Martin Zehl − *Faculty of Chemistry − Department of Analytical Chemistry, University of Vienna, 1090 Vienna, Austria;* orcid.org/0000-0001-9685-0373

Wolfgang Holzer − *Department of Pharmaceutical Chemistry, University of Vienna, 1090 Vienna, Austria*

Laura Ielo − *Department of Pharmaceutical Chemistry, University of Vienna, 1090 Vienna, Austria*

https://dx.doi.org/10.1021/acs.orglett.0c02831
Org. Lett. 2020, 22, 7629−7634

Complete contact information is available at:
https://pubs.acs.org/10.1021/acs.orglett.0c02831

Author Contributions

[⊥]N.N. and A.C. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the University of Vienna and Fondazione Ri.Med (Palermo, Italy) for financial support and abcr Germany for the generous supply of fluoroiodomethane. M.M. and A.C. thank the OeAD for a Blau grant and the University of Messina for predoctoral grants.

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https://dx.doi.org/10.1021/acs.orglett.0c02831
Org. Lett. 2020, 22, 7629−7634

Publication n. 4

Consecutive C1-Homologation / Displacement Strategy for Converting Thiosulfonates into O,S-Oxothioacetals.

Ielo, L.; Pillari, V.; **Miele, M**.; Holzer, W.; Pace, V.*

Adv. Synth. Catal. **2020**, *362*, 5444– 5449. (DOI: 10.1002/adsc.202000919)

FULL PAPER DOI: 10.1002/adsc.202000919

Advanced Synthesis & Catalysis

Consecutive C1-Homologation / Displacement Strategy for Converting Thiosulfonates into *O,S*-Oxothioacetals

Laura Ielo,[a] Veronica Pillari,[a] Margherita Miele,[a] Wolfgang Holzer,[a] and Vittorio Pace[a, b,*]

[a] University of Vienna, Department of Pharmaceutical Chemistry, Althanstrasse 14 – 1090 Vienna (Austria)
+43-1-4277-55035
E-mail: vittorio.pace@univie.ac.at
Homepage: http://drugsynthesis.univie.ac.at/
[b] University of Turin, Department of Chemistry, Via P. Giuria 7 – 10125 Turin (Italy)
E-mail: vittorio.pace@unito.it

Manuscript received: August 3, 2020; Revised manuscript received: August 26, 2020;
Version of record online: October 6, 2020

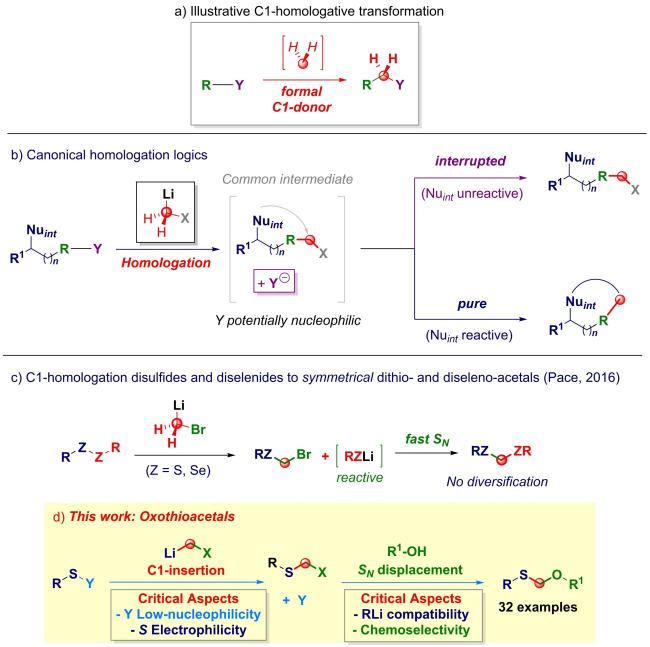
Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202000919

Abstract: A conceptually intuitive synthesis of oxothioacetals is reported starting from thiosulfonates as electrophilic sulfur donors. The installation of a reactive CH_2Cl motif with a homologating carbenoid reagent, followed by the immediate nucleophilic displacement with alcoholic groups [(hetero)-aromatic, aliphatic] offer a convenient access to the title compounds. Genuine chemoselectivity is uniformly observed in the case of multi-functionalized systems.

Keywords: Homologation; Carbenoids; Oxothioacetals; Sequential processes; Sulfur

Introduction

Homologation chemistry represents a valid tactic for selectively introducing a methylene group ($-CH_2$) into a given array.[1] This operation underpins significant modifications of the organic skeleton, thus modulating important physical-chemical parameters such as the lipophilicity and the overall chemical reactivity, *inter alia*.[2] Ideally, the homologation event would precisely deliver the methylene fragment between a preformed R–Y linkage (Scheme 1a). Among the plethora of reagents developed to this end (*e.g.* diazomethane, ylides),[3] carbenoid reagents constitute important players for the release of the methylene under tuneable nucleophilic or electrophilic regime governed (mainly) by the nature of the metal.[4] Two main – intimately connected (Scheme 1b) – mechanistic pathways can be devised for the reaction of a metal carbenoid (*e.g.* $LiCH_2X$ – usually nucleophilic) with an electrophilic manifold (**R–Y**):[5] *i*) the *interrupted homologation* in which upon forming the new **R-CH$_2$X** bond, the X defining element remains constitutively in the final scaffold;[6] *ii*) the *pure* homologation leading through an *internal* displacement of the X element – carried out with an internal nucleophilic species (*e.g.* Nu_{int}) –



Scheme 1. General context of the presented work.

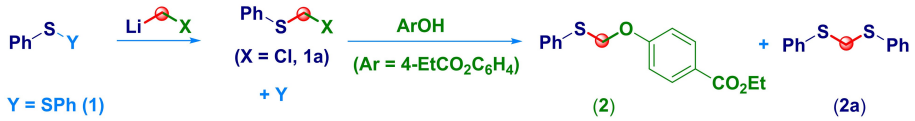
to the homologue, as illustrated by the (aza)-carbonyl homologation to aziridines and epoxides[7] or by the elegant Matteson-type boronic esters homologation.[8] Motivated by the interest towards such chemistry, we designed selective processes characterized by the triggering of molecular rearrangements once the initial homologation was accomplished, *e.g.* fully α-substituted aldehydes from vinyl ketones[9] or, aziridines *via* telescoped homologations of TFAICs.[10] To the best of our knowledge, classical manifolds for conducting the C1-insertions have been restricted to X–Y systems (X, Y = carbon-carbon, carbon-heteroatom, heteroatom 1 – heteroatom 2)[11] whereas, analogous operations on homo-dimeric materials (X–X, X = heteroatom) are much less developed. In this context, in 2016 we reported a direct procedure for converting disulfides and diselenides into symmetrical dithioacetals and diselenoacetals, respectively (Scheme 1c).[12] This transformation, regarded as elusive for decades,[13] was successfully conducted with the highly nucleophilic $LiCH_2Br$, which by attacking the di-chalcogen link furnished an intermediate α-halo thio- or seleno-ether.[12] The subsequent internal nucleophilic displacement – with the anion released during the homologation (RS^- or RSe^-) – yielded the final homologated products. We wondered if an *externally* added (second) oxygen-centered nucleophile could be analogously employed and thus, diversifying the strategy for a modular synthesis of oxothioacetal (Scheme 1d). The following critical points had to be properly addressed during the protocol design: 1) to be productive, the expulsed leaving group (**Y**) on the sulfur electrophile should manifest (almost) no nucleophilic behaviour to ensure no competitive phenomena with the external nucleophile; 2) the same **Y** group should impart a strong electrophilic behaviour to the RS-platform to ensure the attack of the nucleophilic carbenoid; 3) the oxygen-type reagent used for activating the displacement should be compatible with the adopted lithiating conditions, ideally ensuring wide flexibility of the substituents incorporated on the alcoholic partner.

Results and Discussion

As the model substrates we selected diphenyl disulfide (Y = SPh) and the ester substituted phenol **1 b** as the attacking nucleophile to gather initial information on the chemoselectivity. This was motivated by the innate reactivity of carbenoids towards carboxylic derivatives which may result in poor chemocontrol (Table 1).[7b,14] Introducing the C1 unit in the form of $LiCH_2Br$ leaded to almost exclusive formation of the dithioacetal **2 a**, probably because of the higher nucleophilicity of the released mercapto anion compared to the EWG-substituted phenol (entry 1). No improvement was noticed when $LiCH_2I$ – affording a more reactive methylene-iodide bond – was used (entry 2), while a detectable amount of the desired product **2** was formed in the presence of $LiCH_2Cl$ (entry 3). By solubilizing **1 b** in a polar solvent such as DMF prior to the addition to the homologation mixture benefited the reaction, providing a detectable amount of the desired product **2** (entry 4). Raising the temperature from −78 °C to rt was pivotal for activating the phenoxide attack, since keeping the mixture at −78 °C or increasing up to 0 °C resulted in no reactivity (entries 5–6). In order to tame the nucleophilicity of the Y leaving group, as well as, to enhance the sulfur electrophilicity, we focused on different sulfenylating agents fulfilling these requirements. Accordingly, chloro-, cyano-phenylsulfide and *N*-phenylthiophtalimide (entries 7–9) were effective in suppressing the formation of the symmetrical dithioacetal **2 a**, though chemical yields did not exceed 55% even in the presence of significant loadings of both carbenoid and second nucleophile (entry 10). Collectively, these initial experiements suggested that taming the nucleophilicity of the Y group had to be adequately complemented by a strong sulfur electrophilicity enhancing element. Thus, we turned our attention towards a *S*-thiosulfonate ester[15] which, pleasingly under the homologation /displacement conditions was transformed into the desired compound **2** in 78% isolated yield and excellent selectivity (entry 11). Moreover, the Finkelstein reaction with the phenol benefited from the addition of catalytic amount of NaI (0.1 equiv), thus delivering **2** in a 86% isolated yield (entry 12). From a practical and environmental perspective the use of the *S*-thiosulfonate is attractive because of the good manipulability and the avoiding of common drawbacks affecting sulfurating chemicals (odor, toxicity, instability).[16] It should be noted that the overall process was positively influenced by the basic conditions – due to the organolithium – of the mixture: by quenching the reaction with stoichiometric HCl (1 N) after realizing the homologation and, then adding the phenol, the full recovery of the α-halothioether **1 a** was obtained (entry 13).

With the optimized condition in hand, we then studied the scope of the reaction (Scheme 2). The high chemocontrol of the sequential process was not only evident in the case of an ester-substituted phenol (**2**) but, also in the case of a more reactive (towards carbenoids) ketone-substituted system (**3**) presenting the benzoyl group in the phenol *ortho* position. The X-ray analysis of this derivative gave useful structural information on the oxothioacetal motif. The O1–C1 bond (1.421 Å) is significantly shorter than the S1–C1 bond (1.819 Å), whereas the distance between the heteroatoms (O1–S1) is 2.736 Å and the dihedral angle S1–C1 O1–C1 is 114.68 °. The presence of potentially exchangeable halogen on the core of the phenol did not minimally affect the transformation, as evidenced in the cases of bromo (**4**) or chloro (**5–8**) derivatives. The employment of nitrogen-substituted phenol at

Table 1. Reaction optimization.[a]



Entry	Y group *Homologation*	$LiCH_2X$ (X, equiv)	Solv. [a] *Nu Substitution*	Ratio **2**/**2a**[b]	Yield of **2** (%)[c]
1	PhS	(Br, 1.8)	THF	>1:99	–
2	PhS	(I, 1.8)	THF	>1:99	–
3	PhS	(Cl, 1.8)	THF	7:93	4
4	PhS	(Cl, 1.8)	DMF	11:88	7
5[d]	PhS	(Cl, 1.8)	DMF	1:99	–
6[e]	PhS	(Cl, 1.8)	DMF	2:98	–
7	Cl	(Cl, 1.8)	DMF	>99:1	25
8	CN	(Cl, 1.8)	DMF	>99:1	39
9	PhN-Phth	(Cl, 1.8)	DMF	>99:1	48
10[f]	PhN-Phth	(Cl, 2.8)	DMF	>99:1	55
11	SO_2Ph	(Cl, 1.8)	DMF	>99:1	78
12[g]	SO_2Ph	(Cl, 1.8)	DMF	>99:1	86
13[h]	SO_2Ph	(Cl, 1.8)	DMF	–	–

Carbenoids were formed in Barbier-type conditions using a dihalomethane (2.0 equiv) as precursors: *i.e.* ICH_2Br ($LiCH_2Br$), ICH_2I ($LiCH_2I$), ICH_2Cl ($LiCH_2Cl$) – respectively - and MeLi-LiBr (Et_2O solution 1.5 M, 1.8 equiv) in THF at −78 °C.

[a] Otherwise stated after the addition of the phenol (1.3 equiv) at −78 °C, the cooling bath was removed and the mixture was allowed to reach rt.

[b] The ratio has been calculated by ^{1}H-NMR analysis using 1,3,5-trimethylbenzene as an internal standard.

[c] Isolated yield.

[d] Reaction kept at −78 °C for 12 h.

[e] Reaction kept at 0 °C for 8 h after the addition of the nucleophile and removing of the cooling bath.

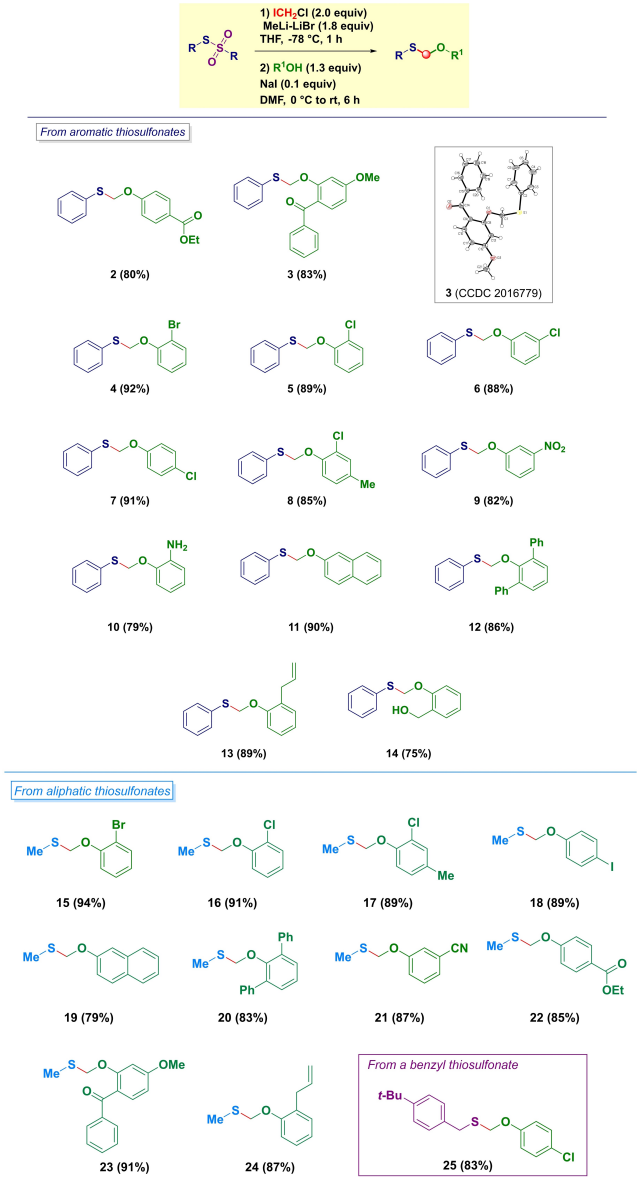
[f] 4-$EtCO_2C_6H_4OH$ (3.0 equiv) were used.

[g] NaI (0.1 equiv) was added.

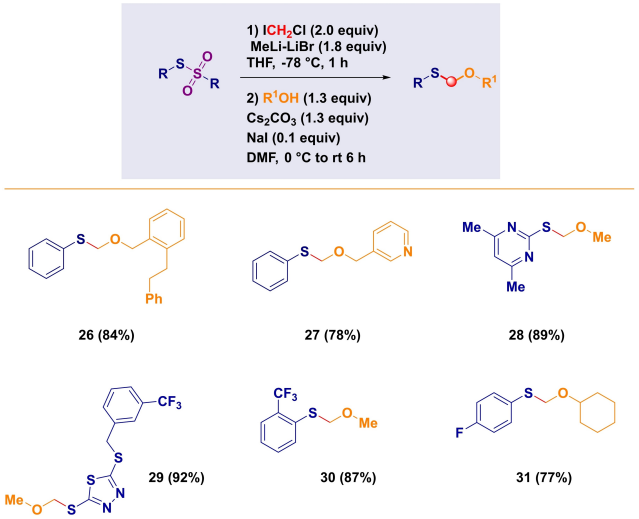
[h] **1a** was obtained in 89% isolated yield.

different oxidation state is fully compatible with the methodology, as indicated by the somehow reluctant (to organolithium carbenoids)[17] nitro compound **9**. With much of our delight, *o*-aminophenol was exclusively alkylated at the oxygen, thus leaving untouched the *per se* nucleophilic amino group (**10**). 2-Naphtol- (**11**) and the sterically demanding 2,6-diphenylphenol- (**12**) derivatives additionally illustrates the versatility of the method. Moreover, the installation of a sensitive element such as a terminal olefin – a cyclopropane manifold[18] – is tolerated (**13**). The different acidity between a phenol and a benzylic alcohol enabled to selectively functionalize the aromatic alcohol, thus preparing the hydroxymethyl-containing scaffold **14**. The protocol was flexible to prepare *S*-alkyl type oxothioacetals starting from the corresponding thiosulfonates. With comparable efficiency we could synthesize under full chemocontrol analogues embodying the aforementioned sensitive functionalities on the aromatic nucleus such as bromo (**15**), chloro (**16**–**17**) and even the highly reactive iodo compound (**18**). Polyaromatic (**19**) or encumbered systems (**20**) efficiently promoted the nucleophilic substitution upon completion of the homologation. In analogy to aromatic thiosulfonates, carboxylic (**22**), carbonyl (**23**) and alkenyl (**24**) oxothioacetals were assembled without compromising the chemical integrity of these reactive handles. The chemoselectively profile was further maintained when a nitrile-substituted phenol was used (**21**): this is particularly interesting because of the well-established chemistry dealing with the addition of carbanion-like reagents to the CN group *en route* to ketones.[19] Notably, also a benzylic thiosulfonate smoothly underwent the sequential homologation/displacement giving **25**.

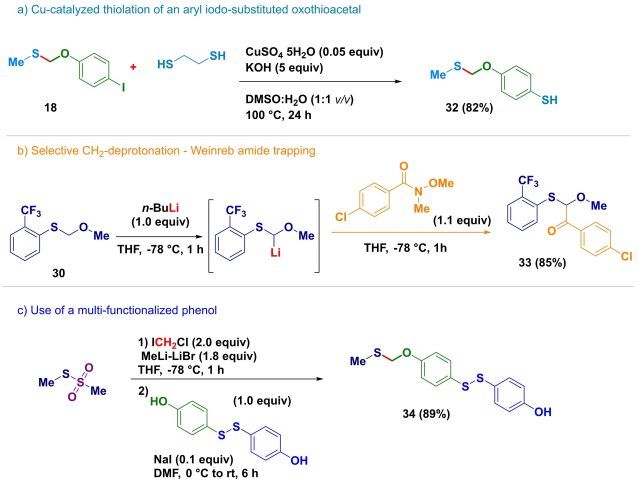
To gain full advantage of the methodology the employment of aliphatic alcohols was also studied (Scheme 3). Based on the above seen evidence that a benzylic alcohol (**14**) was not alkylated under the reaction conditions, we found that by pre-treating the hydroxyl-derivative with stoichiometric Cs_2CO_3 in DMF at 0 °C – *i.e.* forming a caesium alkoxide – enabled to address the shortcoming. Thus, analogues **26** (from a *ortho*-substituted benzylic alcohol) and **27** (from 3-pyridinylmethanol) were easily prepared in high yield. Similarly, upon the formation of caesium



Scheme 2. Scope of the thiosulfonate homologation/nucleophilic displacement with aromatic alcohols.



Scheme 3. Thiosulfonate homologation/nucleophilic displacement with aliphatic alcohol derivatives.



Scheme 4. Selective functionalizations of dithioacetals.

methoxide, a series of *O*-methylated oxothioacetals (**28**–**30**) could be smoothly accessed. As showcased by the challenging poly-nitrogenated requested for synthesizing the pyrimidinyl-(**28**) and the 1,3,4-thiodiazolyl-(**29**) analogues, no alkylating effect was displayed by chloroiodomethane, thus allowing the correct genesis of the carbenoid.

Finally, selective manipulations on particular synthesized skeletons were realized for briefly screening their reactivity profile (Scheme 4). The iodo-substituted derivative **18** underwent a smooth I/SH interchange under Chae's Cu-catalyzed conditions[20] with 1,2-ethanedithiol as the mercapto source, yielding the oxothioacetal **32** presenting a free thiol group (*path a*). The selective deprotonation of the oxothioacetal methylene of **30** with *n*-BuLi furnished an intermediate oxo-thio geminal lithium anion which was intercepted with a Weinreb amide *en route* to a mixed oxo-thio ketone **33**, thus complementing our previous achievements on the synthesis of α-substituted ketones (*path b*).[6,21] Finally, we were pleased in using a bis-disulfide-containing diphenol as the displacing alcohol for the tandem protocol: upon completing the carbenoid homologation, the nucleophilic substitution could be executed on only one of the phenolic groups with full retention of the labile S–S bond (**34** – *path c*).

Conclusion

In summa, we have developed a straightforward preparation of oxothioacetals starting from widely

available thiosulfonates. The tactic relies on the selective installation of a halomethyl fragment with chloromethyllithium. Crucial for the success of the methodology is employing the thiosulfonate as a competent electrophilic sulfur manifold, which upon the homologation event releases a non-nucleophilic (reactive) sulfinate species. The subsequent treatment of the (isolable) α-halothioether with a hydroxy-containing nucleophile [(hetero)-aromatic, aliphatic alcohols] triggers the displacement, thus furnishing the desired oxothioacetals. Uniformly high yields and chemocontrol are observed: reaction partners may embody sensitive groups whose chemical integrity was not affected in the course of the sequential process.

Experimental Section

General Procedure for the Homologation of *S*-Thiosulfonate Ester to Asymmetric Dithioacetals

The *S*-thiosulfonate ester ($RSSO_2R$, 1.0 equiv) was dissolved in dry THF under Argon and cooled down to −78 °C. Chloroiodomethane (2.0 equiv) was added and, after 5 min, MeLi-LiBr (2.2 M solution in Et_2O, 1.8 equiv) was added *via* syringe pump (rate 0.2 mL/min) and then, the resulting mixture was stirred for 1 h. After increasing the temperature up to 0 °C, a solution of alcohol (R^1OH, 1.3 equiv) and NaI (0.1 equiv) in dry DMF was added dropwise. Upon reaching room temperature, the reaction mixture was further stirred for 6 h and, subsequently was quenched with aqueous saturated NH_4Cl solution. The resulting organic phase was extracted 3 times with Et_2O, washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude compounds were purified as reported below through column chromatography.

The crystal structure of compound **3** is available at http://www.ccdc.cam.ac.uk/conts/retrieving.html with the CCDC code 2016779.

Acknowledgements

We thank the University of Vienna, the University of Turin and Fondazione Ri.Med (Palermo, Italy) for generous support. V. Pillari acknowledges the university of Vienna for a Uni:docs doctoral fellowship. M. Miele is grateful to the OEAD for a Blau grant. We thank A. Roller and N. Gajic for X-ray analysis and D. Dobusch for HRMS data. We thank Lisa Kernler for her help in the experimental work.

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Publication n. 5

Taking advantage of lithium monohalocarbenoid intrinsic α-elimination in 2-MeTHF: controlled epoxide ring-opening en route to halohydrins

Ielo, L.; **Miele, M**.; Pillari, V.; Senatore, R.; Mirabile, S.; Gitto, R.; Holzer, W.; Alcántara, A. R.;Pace, V.*

Org. Biomol. Chem. **2021***,19*, 2038-2043. (DOI: 10.1039/D0OB02407D)

Organic & Biomolecular Chemistry

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PAPER

Cite this: *Org. Biomol. Chem.*, 2021, **19**, 2038

Taking advantage of lithium monohalocarbenoid intrinsic α-elimination in 2-MeTHF: controlled epoxide ring-opening *en route* to halohydrins†

Laura Ielo, [a,d] Margherita Miele,[a] Veronica Pillari,[a] Raffaele Senatore,[a] Salvatore Mirabile,[b] Rosaria Gitto,[b] Wolfgang Holzer, [a] Andrés R. Alcántara *[c] and Vittorio Pace *[a,d]

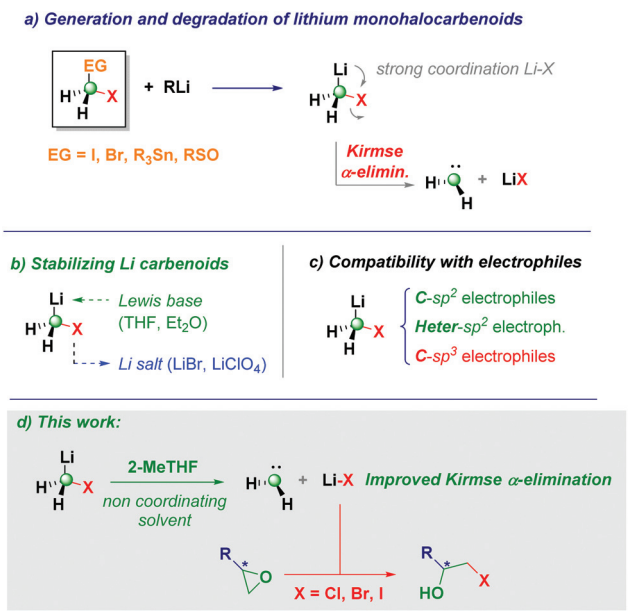
Received 2nd December 2020,
Accepted 8th January 2021

DOI: 10.1039/d0ob02407d

rsc.li/obc

The intrinsic degradative α-elimination of Li carbenoids somehow complicates their use in synthesis as C1-synthons. Nevertheless, we herein report how boosting such an α-elimination is a straightforward strategy for accomplishing controlled ring-opening of epoxides to furnish the corresponding β-halohydrins. Crucial for the development of the method is the use of the eco-friendly solvent 2-MeTHF, which forces the degradation of the incipient monohalolithium, due to the very limited stabilizing effect of this solvent on the chemical integrity of the carbenoid. With this approach, high yields of the targeted compounds are consistently obtained under very high regiocontrol and, despite the basic nature of the reagents, no racemization of enantiopure materials is observed.

Lithium monohalocarbenoids ($LiCH_2X$, X = halogen) constitute highly versatile C1-synthons for accomplishing homologation processes in both nucleophilic and electrophilic regimes, the former being the usual mode of action for lithium derivatives.[1] Accordingly, upon releasing the CH_2X unit onto a proper electrophilic manifold, a plethora of useful synthetic transformations could be designed.[2] The coexistence of C–Li and C–halogen bonds on the same carbon atom promotes an extremely high tendency to induce degradative Kirmse's α-elimination phenomenon, triggered by the strong Li–X internal coordination, with the final result of making the carbenoid unproductive for homologation purposes (Scheme 1a).[1c,3] This constitutive aspect of carbenoid chemistry is profoundly reflected in the strict operational details requested for their correct use in batch mode:[1e,4] (1) to overcome the intrinsic instability, the carbenoid generation event from a given precursor (dihalomethane, stannane, or sulfoxide) must be conducted under Barbier conditions to ensure that no degradation takes place; (2) running the process in coordinative solvents (THF and diethyl ether) in the presence of lithium halide salts contributes to attenuating (if not eliminating) Kirmse's α-elimination to a free carbene and a LiX species (Scheme 1b).[5] Notably, these paradigms represent the



Scheme 1 General context of the presented work.

[a]*University of Vienna – Department of Pharmaceutical Chemistry, Althanstrasse, 14, 1090 Vienna, Austria. E-mail: vittorio.pace@univie.ac.at, vittorio.pace@unito.it; http://drugsynthesis.univie.ac.at/*

[b]*University of Messina – Department of Chemical, Biological, Pharmaceutical and Environmental Sciences, Viale Palatucci, 13, 98168 Messina, Italy*

[c]*Complutense University of Madrid – Department of Chemistry in Pharmaceutical Sciences, Plaza de Ramón y Cajal, s/n, Madrid, Spain. E-mail: andalcan@ucm.es; https://www.ucm.es/qffa/transbiomat*

[d]*University of Turin – Department of Chemistry, Via P. Giuria 7, 10125 Turin, Italy*

†Electronic supplementary information (ESI) available. See DOI: 10.1039/d0ob02407d

necessary guidelines for the convenient application of carbenoid-mediated strategies in synthetic methodologies.[6]

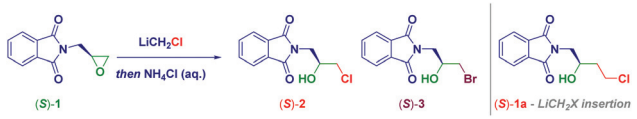
Due to our continued interest in this chemistry over the years, we wondered if Kirmse's elimination could have a synthetic significance behind the well-known degradative effect on the chemical integrity of these C1-synthons. The current state-of-the-art of carbenoid-guided processes, clearly evidences that sp^2-hybridized carbon electrophiles are privileged platforms for accomplishing homologation-type transformations, as well as various heteroatoms (*e.g.* B,[7] Sn,[8] *inter alia*). Unfortunately, the corresponding sp^3-hybridized carbon electrophiles remain elusive materials for accomplishing homologations with $LiCH_2X$, as documented in the seminal work by Huisgen[9] and Hahn (Scheme 1c).[10] In this context, our group very recently documented the formal homologation of C–X functionalities through a sequential installation of the carbenoid into a carbonyl group followed by Si–H-mediated deoxygenation.[11]

Herein, we report the controlled ring-opening of epoxides with the lithium halide liberated during Kirmse's α-elimination for obtaining a high-yield of β-halohydrins (Scheme 1d). Pivotal for the success of the method is the generation and rapid degradation of the carbenoid in 2-MeTHF[12] (a green solvent increasingly becoming more useful in classical organic chemistry and biotransformations, as well as for polymerization or extractive purposes),[13] therefore leading to the degradation of the monohalolithium. We anticipate the genuine regioselectivity of the transformation harnessed on the formation of LiX which plays the dual role of Lewis acid (facilitating the C–O cleavage) and source of the attacking halide.[14]

We selected the enantiomerically pure epoxide-containing phthalimide (*S*)-**1** as the starting material to gather, additionally, information on the stereochemical outcome of the process. $LiCH_2Cl$ was generated under our previously established reaction conditions[6d] from ICH_2Cl (3.0 equiv.) and MeLi–LiBr (2.8 equiv.) in THF at −78 °C (Table 1). Surprisingly, no attack of the nucleophile leading to the homologated adduct (*S*)-**1a** was observed, but rather a mixture of two enantiopure halohydrins [(*S*)-(**2**) and (*S*)-(**3**)] was recovered in an 84 : 16 ratio (entry 1). The subsequent HPLC analysis of both reaction products indicated the full preservation of the stereochemical information embodied, thereby confirming our previous findings on the retention of configuration in reactions involving basic α-substituted methyllithiums.[2a,12k,15] This initial experiment was indicative of the ring-opening of the epoxide with a LiX salt.[16] On the other hand, the simultaneous presence of the chloro (*S*)-(**2**) and bromo-(*S*)-(**3**) derivatives points towards a ring-opening mediated by two different species, namely LiCl and LiBr. Presumably, LiCl was formed during Kirmse's α-elimination of the carbenoid, thus yielding the chlorohydrin, whereas LiBr, complexing the metalating agent MeLi (*i.e.* MeLi-LiBr complex in Et_2O), directly furnished bromohydrin (*S*)-**3**. To ascertain this hypothesis, LiX-free MeLi (MeLi in Et_2O) was employed for generating the carbenoid under identical conditions: exclusively the chlorohydrin (*S*)-**2** was formed, thus confirming that LiCl (carbenoid degradation product) was responsible for the attack on the oxirane (entry 2). Some important aspects of the process were deduced by running the reaction in different solvents: thus, decreasing the medium-coordination effect on the carbenoid allowed an increase of the yield of the chlorohydrin, as a consequence of a positive modulating effect on Kirmse's elimination. Accordingly, the formation of (*S*)-**2** increased when using Et_2O, CPME,[17] and TBME (entries 3–5) and it was maximized in 2-MeTHF, giving an excellent yield of 93% (entry 6). Some additional points merit mention: (a) decreasing the loading of carbenoid to 2.0 equiv. has practically no effect (91% yield), thus suggesting that it is optimal in terms of efficiency-costs (entries 7 and 8); (b) the presence of the additive TMEDA did not improve the process (entry 9); (c) the reaction conducted in toluene considerably lowered the yield (entry 10); (d) by running the process at higher temperatures (−40 °C and −10 °C), the effectiveness decreased, probably because of the non-optimal generation of the carbenoid (prior to its decomposition, entries 11 and 12); (e) the process is independent of the pro-carbenoid source, as evidenced using a stannane or a sulfoxide for accomplishing the corresponding metal exchange (entries 13 and 14), though the procedure on ICH_2Cl afforded the best results; (f) the other Kirmse's elimination product, CH_2 (free carbene), had no effect on the whole transformation (*vide infra*); and (g) the adoption of non-Barbier-type conditions for forming the carbenoid did not provide any material because of the inadequate formation of the carbenoid (entry 15). Collectively, these results confirmed the previous evidence that $LiCH_2Cl$ is not a competent nucleophile for C-sp^3 hybridized electrophiles.

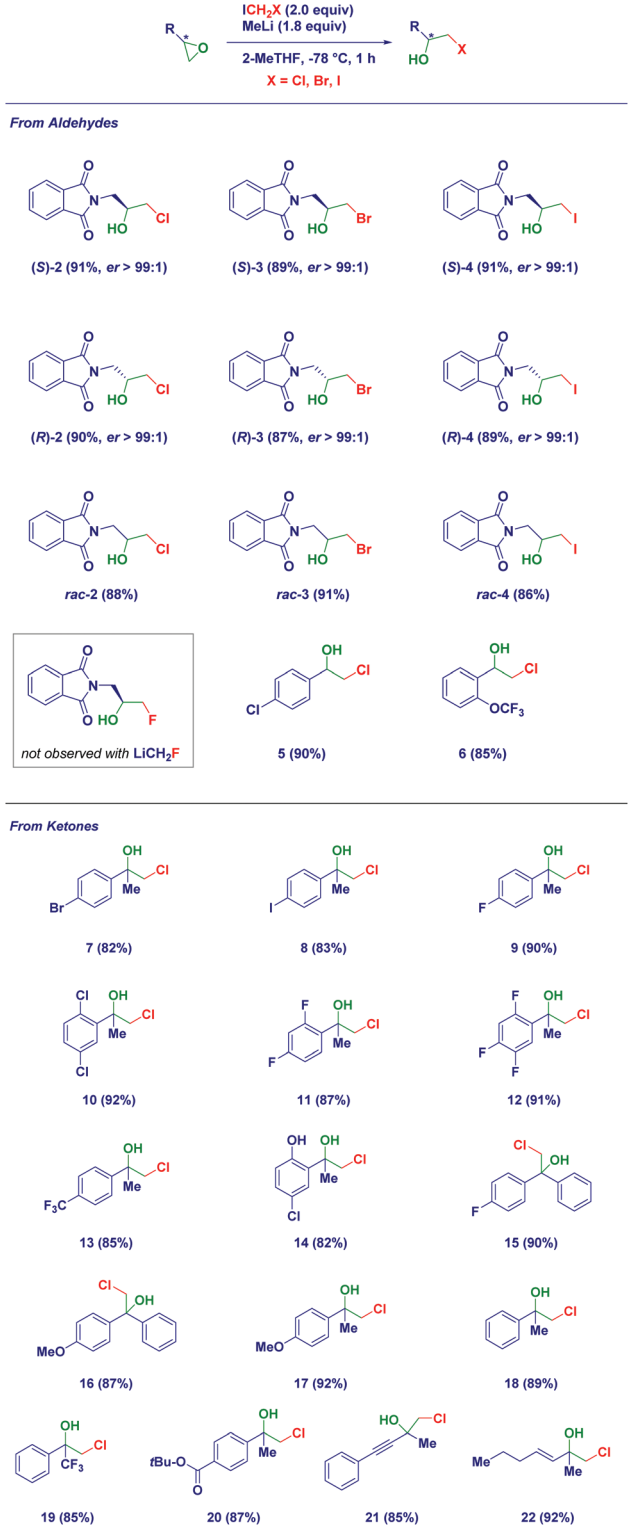
Having established the reaction conditions, we then studied the scope of the reaction (Scheme 2). The use of the other enantiomer of **1**, *i.e.* [(*R*)-**1**], afforded the corresponding epimeric halohydrin (*R*)-**2** with analogous efficiency and enantiomeric purity. This aspect was further evidenced in the case of different halocarbenoids, such as $LiCH_2Br$ [(*S*)-**3** and (*R*)-**3**] and $LiCH_2I$ [(*S*)-**4** and (*R*)-4], thus indicating the flexibility of the methodology. The procedure was then extended to *rac*-**1** with the three different carbenoids confirming the average yields obtained with the chiral platform. Unfortunately, the methodology could not be applied for the LiF ring-opening *en route* to a fluorohydrin. Considering the key role of the solvent in generating $LiCH_2F$,[6b,c,18] the use of the optimal mixture THF : Et_2O (1 : 1 v/v) was tested as an alternative to the herein employed 2-MeTHF, without observing the formation of the desired compound. Therefore, regardless of the proper generation of the unstable carbenoid, the degradation salt LiF may not be efficient in promoting the ring opening.[19] Epoxides derived from aldehydes could also be subjected to the reaction conditions leading to decorated aromatic β-chlorohydrins (**5**–**6**). Analogously, disubstituted epoxides (derived from ketones) easily underwent the ring-opening despite the substitution pattern on the aromatic ring. Notably, the carbenoid formation was not affected by the presence of functionalities sensitive to the organolithium environment. Thus, bromo-(**7**), iodo-(**8**), fluoro-(**9**, **11**, **12**), chloro-(**10**) and trifluoromethyl-(**13**) β-chlorohydrins were smoothly prepared in 2-MeTHF. The

Table 1 Reaction optimization



Entry	Solvent	$LiCH_2Cl$ (equiv)	Ratio **2**/**3** [a]	Yield of (*S*)-**2** [b] (%)	er of (*S*)-**2**
1[c]	THF	2.8	84 : 16	66	>99 : 1
2	THF	2.8	>99 : 1	74	>99 : 1
3	Et_2O	2.8	>99 : 1	78	>99 : 1
4	CPME	2.8	>99 : 1	81	98 : 2
5	TBME	2.8	>99 : 1	85	97 : 3
6	2-MeTHF	2.8	>99 : 1	93	>99 : 1
7	2-MeTHF	1.8	>99 : 1	91	>99 : 1
8	2-MeTHF	1.5	>99 : 1	77	>99 : 1
9[d]	2-MeTHF	2.0	>99 : 1	87	>99 : 1
10	Toluene	2.0	>99 : 1	61	>99 : 1
11[e]	2-MeTHF	2.0	>99 : 1	67	>99 : 1
12[f]	2-MeTHF	2.0	>99 : 1	48	>99 : 1
13[g]	2-MeTHF	2.0	>99 : 1	85	>99 : 1
14[h]	2-MeTHF	2.0	>99 : 1	79	>99 : 1
15[i]	2-MeTHF	2.0	—	—	—

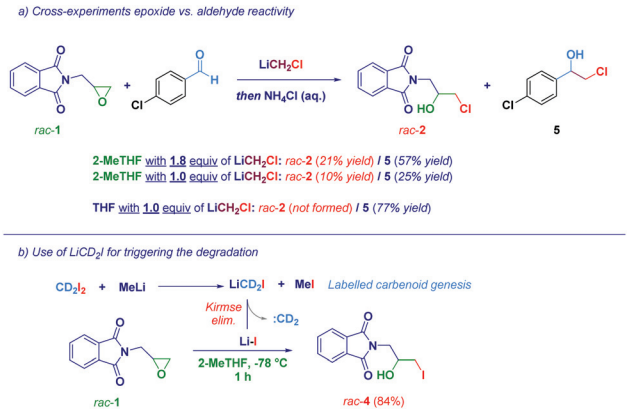
Unless otherwise stated, the carbenoid was generated under Barbier-type conditions starting from ICH_2Cl and MeLi (Et_2O solution 1.6 M) in THF at −78 °C. [a] The ratio has been calculated by ^{1}H-NMR analysis using 1,3,5-trimethylbenzene as an internal standard. [b] Isolated yield. [c] MeLi–LiBr complex (Et_2O solution 1.5 M) was used; compound (*S*)-**3** was obtained in 12% yield and >99 : 1 er. [d] TMEDA (2.0 equiv.) was added. [e] Reaction was run at −40 °C. [f] Reaction was run at −10 °C. [g] The carbenoid was prepared from $(n\text{-Bu})_3SnCH_2Cl$. [h] The carbenoid was prepared from $PhS(O)CH_2Cl$. [i] The carbenoid was generated under *non*-Barbier conditions.



Scheme 2 Scope of the reaction.

additional presence of an acidic aromatic alcohol did not constitute a limitation for the method when deprotonation (with the same MeLi) was carried out prior to carbenoid formation (**14**). Epoxides formally derived from benzo- or acetophenones were amenable substrates for the reaction furnishing derivatives **15–16** and **17–18**, respectively, in high yields. The use of an α-trifluoromethyl-epoxide enabled the straightforward formation of analogue **19**, while, much to our delight, even a labile ester group was tolerated during the carbenoid generation–degradation sequence, giving compound **20**. The installation of unsaturated fragments (alkyne and alkene) on the epoxide core was particularly attractive not only for the synthetic importance of the so-obtained halohydrins (**21–22**) but, more importantly, for constituting unambiguous proof of the lack of reactivity of the free carbene generated during the carbenoid degradation.[18b,20] No cyclopropanation-like process was detected, as judged by NMR analysis of the crude product, thus confirming the initial hypothesis of the higher reactivity of the lithium halide salt.

With the aim to gather useful insights into the mechanistic aspects of the transformation, a 1 : 1 molar mixture of epoxide *rac*-**1** and an aromatic aldehyde was reacted with $LiCH_2Cl$ (1.8 equiv.) in 2-MeTHF (Scheme 3a). Two halohydrins were obtained upon the attack of the carbenoid on the aldehyde (major compound, **5**) and the attack of the degradation product (LiCl) on the epoxide (minor compound, *rac*-**2**). This fact can be rationalized taking into account the higher electrophilicity of the carbonyl group compared to that of the epoxide: although not optimal for stabilizing $LiCH_2Cl$, the carbonyl nucleophilic addition still takes place, as the predominant process, in 2-MeTHF. Concomitantly, the epoxide ring-



Scheme 3 Additional mechanistic proof.

opening product was observed, though in a lesser yield (21% yield of *rac*-**2**), promoting itself the degradation of the carbenoid. Notably, when only 1 equiv. of $LiCH_2Cl$ was used, no significant differences in the ratio of *rac*-**2** and **5** were observed, probably indicating that, due to its short life, the carbenoid reacted (again) with the more activated substrate (aldehyde) before the decomposition took place, so that the degradation product (LiCl) attacked the epoxide. However, when the reaction was carried out in the carbenoid stabilizing THF, the attack of 1 equiv. of $LiCH_2Cl$ on the aldehyde was a practically uniquely occurring phenomenon, since no significant Kirmse's elimination took place. Finally, as an additional proof of the formation of LiX, we carried out an experiment using the labelled carbenoid $LiCD_2I$ (formed upon treatment of CD_2I_2 with MeLi),[6d] observing the iodohydrin *rac*-**4**, as the sole product (Scheme 3b). This could be explained considering that Kirmse's elimination of $LiCD_2I$ provided CD_2 (unreactive) and LiI, responsible for the oxirane opening.

In summary, we have developed a straightforward preparation of different β-halohydrins (chloro, bromo, and iodo) through boosted Kirmse's elimination of the corresponding lithium monohalocarbenoids starting from epoxide. The degradative process – usually conceived as problematic in canonical homologation chemistry – is herein implemented in the eco-friendly and non-coordinating solvent 2-MeTHF. Accordingly, the controlled formation of LiX salts is triggered, leading ultimately to the ring-opening of the epoxides. The uniformly high-yield, the full preservation of the embodied stereochemical information and the high chemocontrol – deduced by selectively preparing variously decorated motifs – further document the potential of this operationally simple and intuitive methodology.

Experimental part

General procedure 1

To a cooled (−78 °C) solution of the suitable epoxide (1.0 equiv.) in dry 2-MeTHF was added iodochloromethane (2.0 equiv.). After 2 min, an ethereal solution of MeLi (1.8 equiv., 1.6 M) was added dropwise, using a syringe pump (flow: 0.200 mL min^{-1}). The resulting solution was stirred for one hour at −78 °C. A saturated solution of NH_4Cl was added (2 mL $mmol^{-1}$ substrate), and then extracted with Et_2O (2 × 5 mL) and washed with water (5 mL) and brine (10 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and, after removal of the solvent under reduced pressure, the so-obtained crude mixture was subjected to chromatography on silica gel to afford pure compounds.

2-(3-Chloro-2-hydroxypropyl)-1*H*-isoindole-1,3(2*H*)-dione (*rac*-2). By following the general procedure **1**, starting from 2-[(oxiran-2-yl)methyl]-1*H*-isoindole-1,3(2*H*)-dione (203 mg, 1.0 mmol, 1.0 equiv.), ICH_2Cl (353 mg, 0.15 mL, 2.0 mmol, 2.0 equiv.), MeLi (1.6 M, 1.1 mL, 1.8 mmol, 1.8 equiv.) and 2-MeTHF (3 mL), the desired product was obtained in 91% yield (218 mg) as a white solid (m.p.: 95 °C) after chromatography on silica gel (50 : 50 v/v, *n*-hexane/diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.81 (m, 2H, Phthal H-4,7), 7.70 (m, 2H, Phthal H-5,6), 4.16 (brs, 1H, CHOH), 3.91 (dd, J = 14.3, 7.4 Hz, 1H, NCH_2), 3.83 (dd, J = 14.3, 4.4 Hz, 1H, NCH_2), 3.64 (dd, J = 11.5, 4.7 Hz, 1H, CH_2Cl), 3.59 (dd, J = 11.5, 5.5 Hz, 1H, CH_2Cl), 3.18 (brs, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.6 (Phthal C-1,3), 134.2 (Phthal C-5,6), 131.7 (Phthal C-3a,7a), 123.4 (Phthal C-4,7), 69.5 (CHOH), 47.2 (CH_2Cl) 41.5 (NCH_2). HRMS (ESI), m/z: calcd for $C_{11}H_{11}ClNO_3^+$: 240.0422 $[M + H]^+$; found: 240.0426.

1-Chloro-2-(4-iodophenyl)-2-propanol (8). By following the general procedure **1**, starting from 2-(4-iodophenyl)-2-methyloxirane (260 mg, 1.0 mmol, 1.0 equiv.), ICH_2Cl (353 mg, 0.15 mL, 2.0 mmol, 2.0 equiv.), MeLi (1.6 M, 1.1 mL, 1.8 mmol, 1.8 equiv.) and 2-MeTHF (3 mL), the desired product was obtained in 83% yield (246 mg) as a colourless oil after chromatography on silica gel (90 : 10 v/v, *n*-hexane/diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70 (m, 2H, Ph H-3,5), 7.21 (m, 2H, Ph H-2,6), 3.79 (A-part of an AB-system, $^2J_{AB}$ = 11.2 Hz, 1H, CH_2Cl), 3.73 (B-part of an AB-system, $^2J_{AB}$ = 11.2 Hz, 1H, CH_2Cl), 2.60 (brs, 1H, OH), 1.60 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.0 (Ph C-1), 137.5 (Ph C-3,5), 127.1 (Ph C-2,6), 93.2 (Ph C-4), 73.7 (COH), 55.0 (CH_2Cl), 27.3 (CH_3). HRMS (ESI), m/z: calcd for $C_9H_{11}ClIO^+$: 296.9538 $[M + H]^+$; found: 296.9542.

1-Chloro-2-(2,4,5-trifluorophenyl)-2-propanol (12). By following the general procedure **1**, starting from 2-methyl-2-(2,4,5-trifluorophenyl)oxirane (188 mg, 1.0 mmol, 1.0 equiv.), ICH_2Cl (353 mg, 0.15 mL, 2.0 mmol, 2.0 equiv.), MeLi (1.6 M, 1.1 mL, 1.8 mmol, 1.8 equiv.) and 2-MeTHF (3 mL), the desired product was obtained in 91% yield (204 mg) as a colourless oil after chromatography on silica gel (90 : 10 v/v, *n*-hexane/diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52 (ddd, J = 11.5, 9.0, 7.3 Hz, 1H, Ph H-6), 6.91 (m, 1H, Ph H-3), 4.01 (d, J = 11.2 Hz, 1H, CH_2Cl), 3.86 (dd, J = 11.2, 1.1 Hz, 1H, CH_2Cl), 2.79 (brs, 1H, OH), 1.64 (d, J = 1.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.8 (ddd, J = 244.1, 9.3, 2.9 Hz, Ph C), 149.3 (ddd, J = 251.5, 14.6, 12.8 Hz, Ph C), 146.8 (ddd, J = 244.6, 12.0, 3.4 Hz, Ph C), 127.9 (dt, J_d = 15.0 Hz, J_t = 4.4 Hz, Ph C-1), 116.4 (ddd, J = 21.4, 5.9, 1.3 Hz, Ph C-6), 106.4 (dd, J = 29.9, 21.0 Hz,

Ph C-3), 72.6 (d, J = 4.7 Hz, COH), 53.4 (d, J = 6.5 Hz, CH_2Cl), 25.8 (d, J = 3.5 Hz, CH_3). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −141.9 (m, F), −134.7 (m, F), −115.7 (m, F). HRMS (ESI), m/z: calcd for $C_9H_9ClF_3O^+$: 225.0289 $[M + H]^+$; found: 225.0286.

2-Chloro-1-(4-fluorophenyl)-1-phenylethanol (15). By following the general procedure **1**, starting from 2-(4-fluorophenyl)-2-phenyloxirane (214 mg, 1.0 mmol, 1.0 equiv.), ICH_2Cl (353 mg, 0.15 mL, 2.0 mmol, 2.0 equiv.), MeLi (1.6 M, 1.1 mL, 1.8 mmol, 1.8 equiv.) and 2-MeTHF (3 mL), the desired product was obtained in 90% yield (225 mg) as a colourless oil after chromatography on silica gel (90 : 10 v/v, n-hexane/diethyl ether). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.43 (m, 2H, Ph2 H-2,6), 7.42 (m, 2H, Ph1 H-2,6), 7.36 (m, 2H, Ph2 H-3,5), 7.30 (m, 1H, Ph2 H-4), 7.03 (m, 2H, Ph1 H-3,5), 4.18 (A-part of an AB-system, $^2J_{AB}$ = 11.7 Hz, 1H, CH_2Cl), 4.16 (B-part of an AB-system, $^2J_{AB}$ = 11.7 Hz, 1H, CH_2Cl), 3.17 (brs, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.2 (d, J = 246.9 Hz, Ph1 C-4), 143.0 (Ph2 C-1), 139.1 (d, J = 3.2 Hz, Ph1 C-1), 128.4 (Ph2 C-3,5), 128.3 (d, J = 8.2 Hz, Ph1 C-2,6), 127.9 (Ph2 C-4), 126.3 (Ph2 C-2,6), 115.2 (d, J = 21.4 Hz, Ph1 C-3,5), 77.5 (COH), 53.1 (CH_2Cl). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −114.7 (m, F). HRMS (ESI), m/z: calcd for $C_{14}H_{13}ClFO^+$: 251.0633 $[M + H]^+$; found: 251.0659.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

L. I. and M. M. contributed equally to the work. We thank the University of Vienna, the University of Turin, the Complutense University of Madrid and Fondazione RiMed (Palermo, Italy) for generous support. M. M. acknowledges OEAD for a *Blau* grant. V. Pillari thanks the University of Vienna for a *Uni:docs* fellowship. S. M. thanks the University of Messina for a visiting pre-doctoral grant.

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Publication n. 6

Chemoselective reduction of isothiocyanates to thioformamides mediated by the Schwartz reagent.

De la Vega-Hernàndez, K.; Senatore, R.; **Miele, M.**; Urban, E.; Holzer, W.; Pace, V.*

Org. Biomol. Chem. **2019***, 17*, 1970-1978*.* (DOI: 10.1039/C8OB02312C)

Publication n. 7

(Difluoromethyl)trimethylsilane (TMSCHF2): A Useful Difluoromethylating Nucleophilic Source.

Miele, M.; Pace, V.*

Aust. J. Chem. **2021***, 74,* 623–625. (DOI: 10.1071/CH21045)

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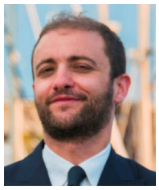
Aust. J. Chem. **2021**, *74*, 623–625
https://doi.org/10.1071/CH21045

Focus

(Difluoromethyl)trimethylsilane ($TMSCHF_2$): A Useful Difluoromethylating Nucleophilic Source



Margherita Miele,[A] *and Vittorio Pace* [A,B,C]

[A]Department of Pharmaceutical Chemistry, University of Vienna, Althanstrasse 14, 1090 Vienna, Austria.
[B]Department of Chemistry, University of Turin, Via P. Giuria 7, 10125 Turin, Italy.
[C]Corresponding author. Email: vittorio.pace@univie.ac.at

Keywords: fluorination, fluorine, silicon, organosilicon compounds, difluoromethyl, nucleophilic addition, nucleophilic substitution, cross-coupling.

Received 16 February 2021, accepted 20 April 2021, published online 19 May 2021

Vittorio Pace has been a full professor of organic chemistry at the University of Torino (Italy) since March 2020. He earned his Ph.D. in chemical sciences at the Complutense University of Madrid (Spain) and, after three post-doctoral stays in Vienna (Austria), Manchester (UK), and Stockholm (Sweden), he started his independent career in Vienna in 2014, launching a group with a strong focus on homologation chemistry.

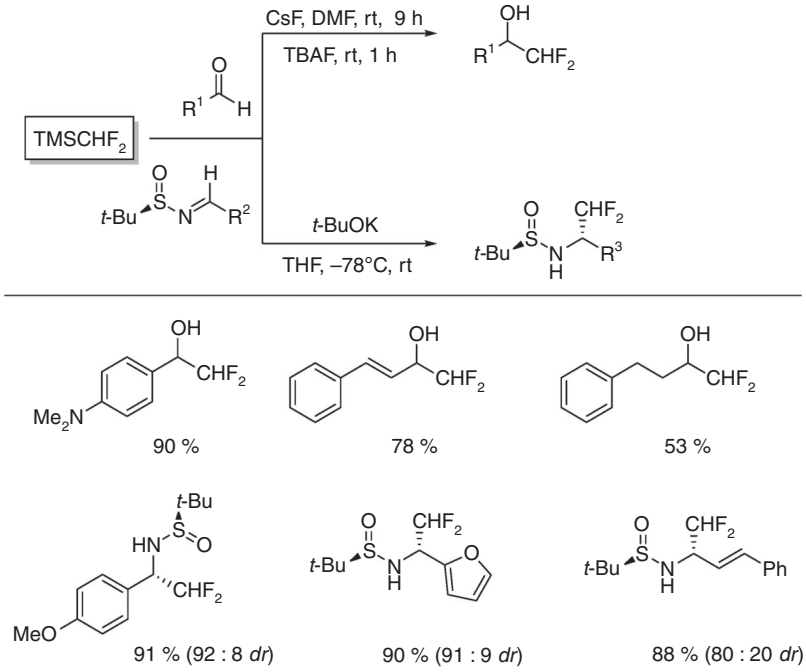
Introduction

Because of the significance of difluoromethyl-analogues as privileged fluoro-containing scaffolds across the chemical sciences,[1] in recent years significant advancements have been achieved thanks to the excellent versatility of the commercially available (difluoromethyl)trimethylsilane ($TMSCHF_2$) as a competent donor of the CHF_2 group under nucleophilic regime.[2] It is a commercially or easily accessible liquid documenting excellent experimental manipulability due to its relatively high boiling point (51–53°C). As such it may be regarded nowadays as the first choice reagent for difluoromethylation in both academic and industry research. Crucial for its productive use is the proper activation easily achieved through treatment with CsF or alkoxides acting as Lewis bases. However, its inherent reactivity is tamed compared with the more common $TMSCF_3$ (Ruppert–Prakash reagent)[3] thus, requiring somewhat harsher conditions. Notably, the installation of the silicon-residue on the putative CHF_2 carbanion imparts excellent stability to the reagent, thus preserving its chemical integrity.

Nucleophilic Addition to Carbonyl-Type Platforms

Aldehydes–Ketones–Imines

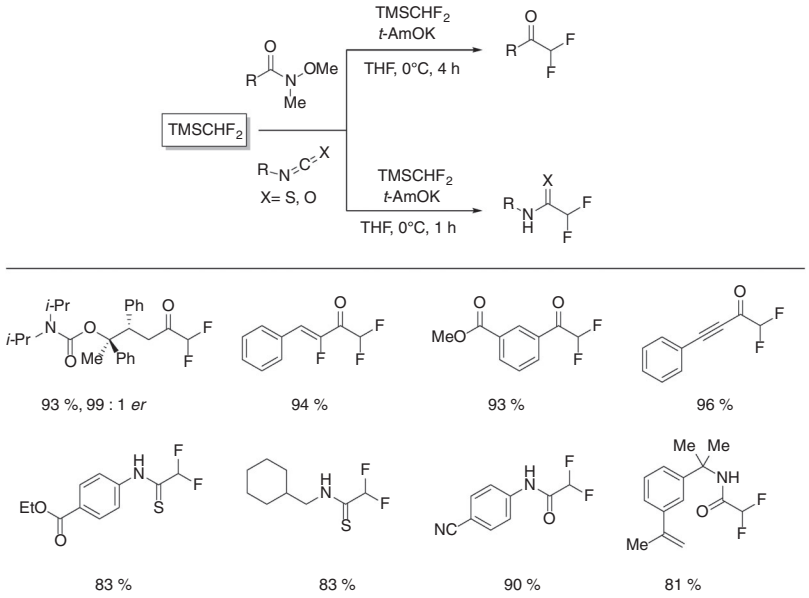
Hu and coworkers recognised the first synthetic use of the $TMSCHF_2$ in 2011 by realising selective difluomethylation of aldehydes and Ellman's aldimines (Scheme 1).[4] By simply selecting the activation conditions of the reagent, various difluomethyl carbinols (CsF) and sulfinyl-amines (*t*-BuOK) were prepared. The transformation is also extendible to ketones, including elusive enolizable ones,[5] and to combined difluoromethylation-deoxygenative strategies.[6]



Scheme 1. Delivery of CHF_2-units to carbonyl-like electrophiles.

Weinreb Amides and Heterocumulenes

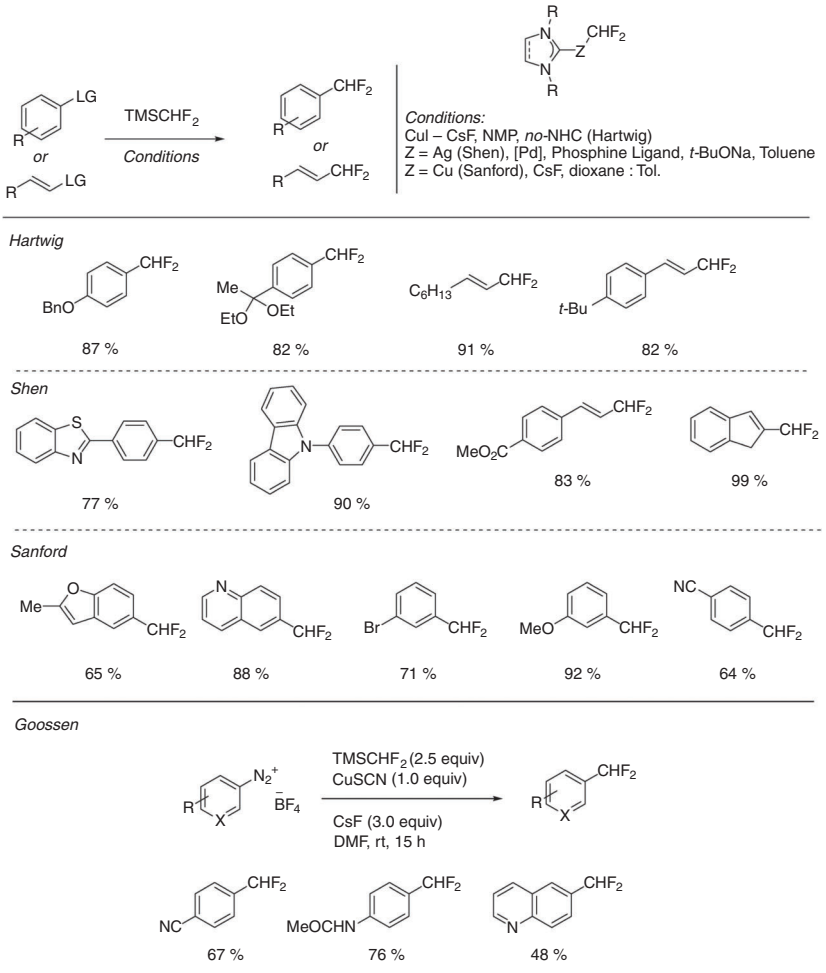
Miele et al. used $TMSCHF_2$ for the delivery of the CHF_2 unit to Weinreb amides en route to difluoromethyl-ketones.[7] The activation of $TMSCHF_2$ with potassium *tert*-amylate (*t*-AmOK) ensured higher yields compared with different Lewis bases, thus enabling an efficient synthesis of these ketones under full chemocontrol, as evidenced in the case of variously functionalized acylating linchpins. Notably, no epimerization was observed when a chiral Weinreb amide was used. Taking advantage of the versatility of using isocyanates and isothiocyanates in forging (thio)-amidic linkages,[8] Miele et al. used $TMSCHF_2$ – activated with *t*-AmOK – for preparing in a single synthetic operation difluoromethyl analogues with very high chemoselectivity (Scheme 2).[9]



Scheme 2. Synthesis of difluoromethyl ketones and (thio)amides.

Cross Couplings

Fier and Hartwig introduced in 2012 an effective protocol for the Cu-mediated difluoromethylation of aryl and vinyl iodides with $TMSCHF_2$.[10] This seminal discovery stimulated intensive research for introducing the CHF_2 group into a plethora of C–X (X = halogens, OTf, hypervalent iodonium salts, etc.) sp^2-electrophiles.[11] In this context, particular significance is attributed to the generation of (NHC)–Ag–CHF_2 and (NHC)–Cu–CHF_2 complexes developed by Shen and coworkers[12] and Sanford and coworkers,[13] respectively, acting as competent difluoromethylating elements for a portfolio of substrates under catalytic conditions (Scheme 3). Notably, $TMSCHF_2$ can



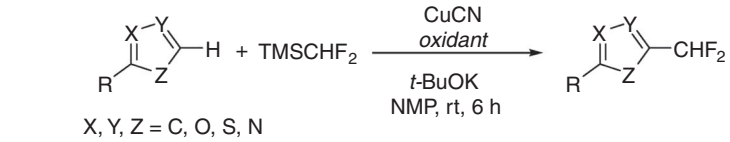
Scheme 3. Use of $TMSCHF_2$ in cross-coupling chemistry.

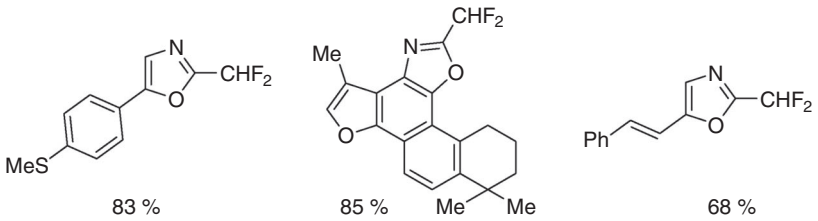
also be used for obtaining highly versatile electrophilic difluoromethylating agents, as illustrated by Shen and coworkers, in the case of *N*-difluoromethylthiophtalimide.[14]

Analogous operations have also been conducted via diazonium chemistry, as showcased by Goossen and coworkers.[15]

Difluoromethylation of C–H Bonds

The Cu^I-catalytic treatment of (hetero)arenes with $TMSCHF_2$ in the presence of an oxidizing agent (e.g. 9,10-phenanthrenequinone) to rearomatize is conducive to the direct formal insertion of the difluoromethyl unit (Scheme 4).[16]





Scheme 4. Direct difluoromethylation of C–H bonds.

Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of Funding

This research did not receive any specific funding.

Acknowledgements

The authors thank the Universities of Vienna and Turin for financial support.

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Publication n. 8

Direct and Chemoselective Synthesis of Tertiary α,α-Difluoro-ketones via Weinreb Amides Homologation with CHF2-Carbene Equivalent.

Miele, M.; Citarella, A.; Micale, N.; Holzer, W.; Pace, V.*

Org. Lett. **2019***, 21,* 8261-8265. (DOI: 10.1021/acs.orglett.9b03024)

OL | Organic Letters

Letter

Cite This: Org. Lett. 2019, 21, 8261−8265

pubs.acs.org/OrgLett

Direct and Chemoselective Synthesis of Tertiary Difluoroketones via Weinreb Amide Homologation with a CHF_2-Carbene Equivalent

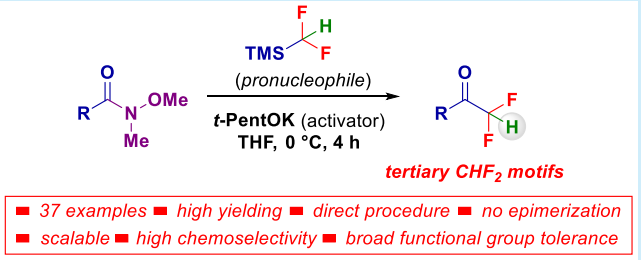
Margherita Miele,[†,§] Andrea Citarella,[†,‡,§] Nicola Micale,[‡] Wolfgang Holzer,[†] and Vittorio Pace*[,†]

[†]University of Vienna, Department of Pharmaceutical Chemistry, Althanstrasse, 14, 1090 Vienna, Austria

[‡]University of Messina, Department of Chemical, Biological, Pharmaceutical and Environmental Sciences, Viale F. Stagno D'Alcontres, 31, 98166 Messina, Italy

Supporting Information

ABSTRACT: The homologation of Weinreb amides into difluoromethylketones with a formal nucleophilic CHF_2 transfer agent is reported. Activating $TMSCHF_2$ with potassium *tert*-amylate enables a convenient access to the difluorinated homologation reagent, which adds to the acylating partners. The high chemoselectivity showcased in the presence of variously multifunctionalized Weinreb amides, jointly with uniformly high yields, enables the strategy of general applicability without requiring any stabilization element for the putative carbanion.

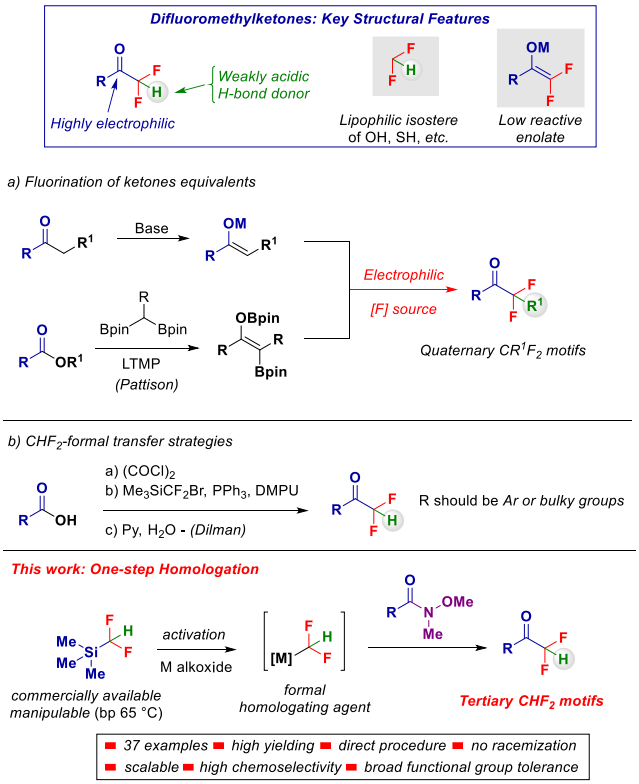


Embodying a difluoromethyl unit into an organic array profoundly tunes the chemico-physical properties of the resulting scaffold.[1] In more detail, the weakly acidic CHF_2 motif represents a rare example of a methinic carbon capable of establishing hydrogen-bonding interactions[2] to improve the binding selectivity of pharmaceuticals.[3] Thus, valuable optimization processes in drug design can be realized by introducing the CHF_2 unit acting as a competent more lipophilic isostere of widespread functionalities such as hydroxyl, mercapto, hydroxamic, or amidic species.[3a,4] Placing the CHF_2 fragment at the vicinal position of a ketone carbonyl results in the simultaneous modulation of the reactivity profile of both moieties: the carbonyl and the difluorinated C−H group (Scheme 1).[5] Evidently, the electron-withdrawing effect exerted by CHF_2 guarantees a significant increase of the electrophilicity of the carbonyl carbon, whereas it causes a remarkable inertness of the corresponding enolates.[6] However, the remarkable significance of difluoroketones in the general context of the chemical sciences is somehow counterbalanced by the lack of a general tactic to access them.[7] Accordingly, the most common logical approaches to the motif can be summarized as follows: (1) progressive introduction of fluorine through C−F bond formation operations (Scheme 1a) and (2) transfer of the difluorinated building block onto a proper acceptor, thus formally constituting a C−C bond formation event (Scheme 1b). Techniques belonging to the first tactic (e.g., use of enolate-like materials, alkynes, etc.) are often plagued by important concerns on the regioselectivity of the transformation observed during the fluorination under electrophilic regime, also manifesting a strong dependence on the structure of the nucleophilic scaffold (mainly in the presence of different enolization centers).[7a,8] A breakthrough in the field has been introduced by Pattison through the homologative ester difluorination coupling with lithiated bis(boron) species: accordingly, *quaternary* difluoromethyl ketones can be prepared under full regio- and chemocontrol.[9] As a common feature, these strategies are valuable platforms for accessing fully substituted difluoroketones, but unfortunately, the flexibility and adaptability to prepare *tertiary* α-CHF_2 analogues appear limited. A conceptually different disconnection would suggest adopting an intuitive C−C bond formation strategy by transferring the formal CHF_2-containing nucleophile onto an electrophilic partner.[10] To be productive, the tactic should overcome the inherent high instability of putative CHF_2-type carbanions.[11] In this context, the installation of stabilizing electron-withdrawing elements on them emerged as an effective solution to tackle the challenge; however, the requirement of unnecessary extra steps (installation and removal of these stability enhancing factors under forcing conditions) undoubtedly decreases the overall synthetic efficiency as, for example, evidenced in recent work by Kuhakarn.[12] In 2011, Hu and co-workers introduced Me_3SiCF_2H (**I**) as a valid equivalent of the CF_2H carbanion, pointing out some remarkable characteristics of the reagent:[1g,13] unlike the similar Ruppert−Prakash reagent (Me_3SiCF_3),[14] **I** requires proper activation to be synthetically useful as a consequence of the very strong Si−C bond it possesses.[13] We reasoned a homologation event carried out with a formal CHF_2 nucleophile, i.e., presenting the exact degree of substitution as the targeted structures, on a Weinreb amide acting as the electrophilic acylating partner[15] would represent an effective solution to the problem of preparing tertiary difluoromethylketones. As documented in recent work

Received: August 24, 2019
Published: October 10, 2019

DOI: 10.1021/acs.orglett.9b03024
Org. Lett. 2019, 21, 8261−8265

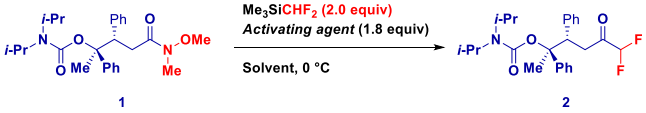
Scheme 1. Difluoromethyl Ketones: State of the Art



by our group, these amides act as highly competent acylating agents for α-substituted methyl-type carbanions,[16] including the unprecedented lithium *mono*fluoromethyl nucleophile ($LiCH_2F$).[17] Additionally, structural limitations, e.g., needing aromatic or bulky groups, pointed out by Dilman in the case of using difluorinated phosphorus ylides could be advantageously circumvented.[18]

We selected the optically active Weinreb amide **1**[19] as the model substrate for gaining insight into both chemical reactivity and preservation of the stereochemical information (Table 1). Cognizant of the requirement of activating $TMSCHF_2$, we screened a set of conditions for generating the formal CHF_2-transfer nucleophilic agent. Nonoptimal efficiency was noticed by using TBAT (tetrabutylammonium difluorotriphenylsilicate) or an alkaline metal fluoride in DMF, accompanied by minor but still noticeable racemization (entries 1−3). Moreover, the use of the amidic solvent DMF is responsible for self-difluoromethylation phenomena, as indicated by ^{1}H NMR analysis of reaction crudes. The process manifested a strong solvent-activating agent dependence, as deducted by the complete lack of reactivity when switching—*coeteris paribus*—from DMF to THF (entry 4). Activating the pronucleophile Me_3SiCHF_2 with a stoichiometric amount of a low nucleophilic alkoxide in THF (potassium *tert*-butoxide) allowed us to produce in satisfying yield the desired difluoroketone **2**, albeit with minor epimerization (entry 5). Changing to a commercially available THF solution of *t*-BuOK had a positive effect on the yield, although epimerization could not be fully avoided (entry 6). Pleasingly, the activation of $TMSCHF_2$ with a commercially available solution of the more sterically hindered potassium *tert*-pentoxide (i.e., amylate, 0.9 M in cyclohexane)[20] resulted in an excellent 91% yield of the targeted ketone with full preservation of the optical purity (entry 7). Some additional points merits mention: (a) Despite

Table 1. Model Reaction: Optimization.[a]



entry	solvent	base	reaction time (h)	yield of **2**[a] (%)	er of **2**
1	DMF	TBAT	8	traces	
2	DMF	KF/18-crown-6	8	27	95:5
3	DMF	CsF	8	15	96:4
4	THF	KF/18-crown-6	8	traces	
5[b]	THF	*t*-BuOK	4	63	96:4
6[c]	THF	*t*-BuOK	4	75	96:4
7	***THF***	***t*-PentOK**	**4**	**91**	***99:1***
8	Et_2O	*t*-PentOK	8	52	97:3
9	toluene	*t*-BuOK	8	75	98:2
10[d]	THF	*t*-PentOK	8	77	99:1
11[e]	THF	*t*-PentOK	4	36	98:2
12[f]	THF	*t*-PentOK	4	<10	

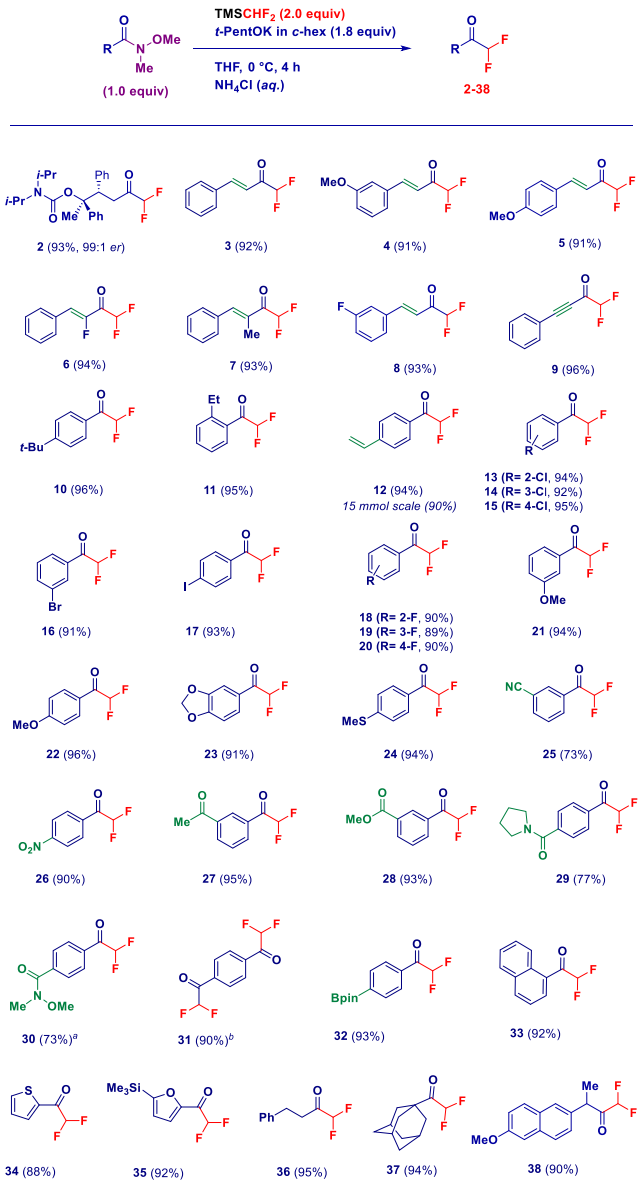
[a]Otherwise stated reactions were run at 0 °C with *t*-PentOK 1 M solution in cyclohexane under Barbier-type conditions. [b]*t*-BuOK solid. [c]*t*-BuOK 1.0 M in THF. [d]Me_3SiCHF_2 (1.5 equiv) and *t*-PentOK (1.4 equiv) were used. [e]Reaction run at rt (23 °C). [f]Non-Barbier-type conditions (e.g., CHF_2-transfer agent generated from Me_3SiCHF_2 (2.0 equiv) and *t*-PentOK (1.8 equiv)) and then Weinreb amide **1** was added.

the existence of an enolization site at the α-position of the starting Weinreb amide, no deleterious effect was evidenced, thus making the reaction productive. This is a particularly remarkable result compared to the elusive attitude of similar enolizable ketones to undergo difluoromethylation observed by Hu.[13] (b) THF represented the ideal solvent for the transformation as indicated by compared with diethyl ether and toluene even after prolonged reaction times (entries 8 and 9). (c) Decreasing the nucleophile loading to 1.4 equiv was detrimental for the yield (entry 10). (d) By increasing the temperature up to rt, a dramatic lost of efficiency was observed, presumably as a consequence of the nucleophile thermal stability (entry 11). It is worth mentioning that the use of Barbier-type conditions not only compromised the chemoselectivity but also constituted a *conditio sine qua non* to enable reactivity, in analogy to the highly unstable monofluoromethylating agent $LiCH_2F$ we introduced in 2017.[17] In fact, when the nucleophile was generated prior to the acylation event (3 min, i.e., non-Barbier conditions) compound **2** was formed in only <10% yield.

With the optimized conditions in hand, we then studied the scope of the reaction (Scheme 2). Unsaturated Weinreb amides smoothly undergo the homologative difluoromethylation, providing the resulting ketones (**3**−**8**) in excellent yields (>91%). Interestingly, substitution across the cinnamoyl core (both on the aromatic ring—with functionalities of diverse electronic behavior—or on the exocyclic olefin) are perfectly tolerated, thus affording interesting products, including the unprecedented ketone **6** presenting two different fluorine-containing substituents (sp^2 C−F) and (sp^3 CHF_2) at the α and α'-position, respectively. Moreover, incorporating a triple bond into the Weinreb amide core maintains untouched the efficiency (**9**). The excellent yields observed in the case of aromatic Weinreb amides, delivering difluoroketones (**10**−**33**), accounts for the robustness and versatility of the process. Substitution on the aromatic nuclei is uniformly permitted

DOI: 10.1021/acs.orglett.9b03024
Org. Lett. 2019, 21, 8261−8265

Scheme 2. Scope of the Reaction: Synthesis of Difluoromethylketones



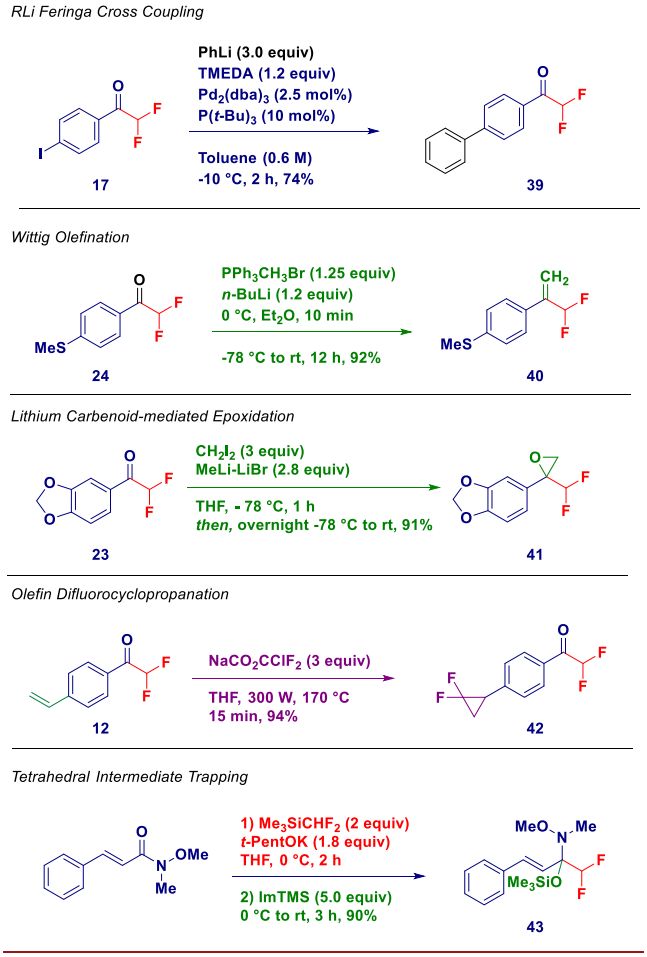
with both electron-donating (**10**, **11**, **21**−**24**) and electron-withdrawing substituents (**13**−**20**). Significantly, positioning the substituent on delicate sites (*ortho*, **11**, **13**) does not influence the yield. In analogy to the compatibility of the reaction conditions with the presence of unsaturated C−C bonds seen above, a vinyl fragment (**12**) does not suffer any modification during the generation of the carbene-like species. Scaling-up the process (15 mmol, compound **12**) resulted in comparable efficiency, thus making it of potential interest for nonacademic audiences. We anticipate these mild conditions enable further elaboration of the scaffold upon tuning of the difluoromethylation methodology en route to difluorocyclopropanes (vide infra). The whole set of halogens (**13**−**20**) can be placed on the aromatic ring as well as ether (**21**, **22**), acetal (**23**), or thioether (**24**) functionalities, thus adding reliability to the technique. The compatibility of the procedure with highly sensitive groups to the nucleophilic environment is undoubtedly one of the main advantages of the methodology.[21] In fact, susceptible electrophilic decorating elements such as nitrile (**25**), nitro (**26**), ketone (**27**), ester (**28**), or a pyrrolidinyl amide (**29**) remain completely untouched during the transformation, presumably due to the excellent performance of Weinreb amides in reaction with α-functionalized carbanions. Additionally, a bis-Weinreb amide is amenable for mono- or bis-difluoromethylation by simply tuning the stoichiometry: in the case of using 1.0 equiv of nucleophile and cooling the mixture at −20 °C, it is possible to introduce a single CHF_2 group, leaving untouched the remaining Weinreb amide site (**30**). Alternatively, by increasing the nucleophile loading up to 3.0 equiv, both Weinreb amides undergo the difluoromethylation, affording the symmetric bis-difluoroketone **31** in an excellent 90% yield through a single operation. A synthetically useful boronate ester—a benchmark for further chemistry—is analogously tolerated (**32**), pointing out the unique characteristics of the CHF_2 nucleophile compared to different $CHHal_2$ carbenoids whose addition to boronate esters follows a Matteson-type homologation pathway.[22] Moreover, polyaromatic (**33**) or thiophene (**34**) Weinreb amides can be employed, further highlighting the stability of a sensitive TMS group on the furan ring (**35**). Finally, additional aliphatic Weinreb amides including the highly sterically demanding adamantyl substituted (**37**) or the one generated from the nonsteroidal anti-inflammatory drug naproxen could be conveniently employed for preparing the targeted scaffolds in very high yield.

The availability of a highly efficient preparative procedure for tertiary difluoroketones spurred us to undertake a survey on their use in chemical synthesis. By simply selecting the reaction conditions, high chemoselective processes with strong nucleophiles can be designed (Scheme 3). The Feringa Pd-catalyzed cross-coupling of *p*-iodoketone **17** with PhLi gave the corresponding *p*-phenyl derivative **39** in very high yield without touching the sensitive difluorocarbonyl unit.[23] Also, a selective Wittig reaction on the ketone functionality of **24** conducted to the difluoroallyl compound **40**. The carbonyl of **23** undergoes the attack of the carbenoid iodomethyllithium ($LiCH_2I$)[24] to prepare in a single operation the extremely rare α-difluoromethyl epoxide core[25] (**41**). Moreover, the pendant vinyl substituent of **12** could be used to construct a difluoromethyl cyclopropane,[26] furnishing the unknown ketone **42**, featuring contemporaneously two different difluoromethyl fragments. Finally, the tetrahedral hemiaminal generated by the addition of the CHF_2 unit to a Weinreb amide could be trapped and fully characterized according to our previous established procedure.[27] It is worth noting that analogous stable tetrahedral adducts derived from difluoromethyl ketones are relevant for enzymatic inhibition studies of potential pharmacological interest.[7a]

In summary, we have disclosed a conceptually intuitive and smooth access to difluoromethyl ketones via the straightforward homologation with a formal CHF_2-type carbanion equivalent of variously functionalized Weinreb amides. The methodology paves on the activation of the commercially available reagent $TMSCHF_2$ in the presence of potassium *tert*-amylate in THF. Particularly attractive characteristics of this uniformly high-yielding and general methodology are (1) the excellent tolerance of sensitive functionalities (including challenging ketone, ester, amide, nitro, nitrile groups, inter alia), (2) the perfect flexibility to Weinreb amides of diverse electronic behavior; (3) the negligible effect of sterically demanding elements positioned on the acylating partner; and

DOI: 10.1021/acs.orglett.9b03024
Org. Lett. 2019, 21, 8261−8265

Scheme 3. Synthetic Versatility of α,α-Difluoromethylketones



(4) the complete retention of the stereochemical information contained in an optically active Weinreb amide.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03024.

Experimental procedure, NMR spectra, HPLC traces, and analytical data for all the compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: vittorio.pace@univie.ac.at. Web: https://drugsynthesis.univie.ac.at/. Twitter: @LabPace.

ORCID

Nicola Micale: 0000-0002-9294-6033

Vittorio Pace: 0000-0003-3037-5930

Author Contributions

§M.M. and A.C contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the University of Vienna for financial support. A.C. acknowledges the University of Messina for a predoctoral mobility grant.

■ DEDICATION

Dedicated to Professor Norbert Haider in the occasion of his retirement.

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DOI: 10.1021/acs.orglett.9b03024
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Publication n. 9

Highly chemoselective difluoromethylative homologation of iso(thio)cyanates: expeditious access to unprecedented a,a-difluoro(thio)amides.

Miele, M.; D'Orsi, R.; Sridharan, V.; Holzer, W.; Pace, V.*

Chem. Commun. **2019***, 55,* 12960-12963. (DOI: 10.1039/C9CC06929A)

ChemComm

COMMUNICATION

Cite this: *Chem. Commun.*, 2019, 55, 12960

Received 5th September 2019,
Accepted 3rd October 2019

DOI: 10.1039/c9cc06929a

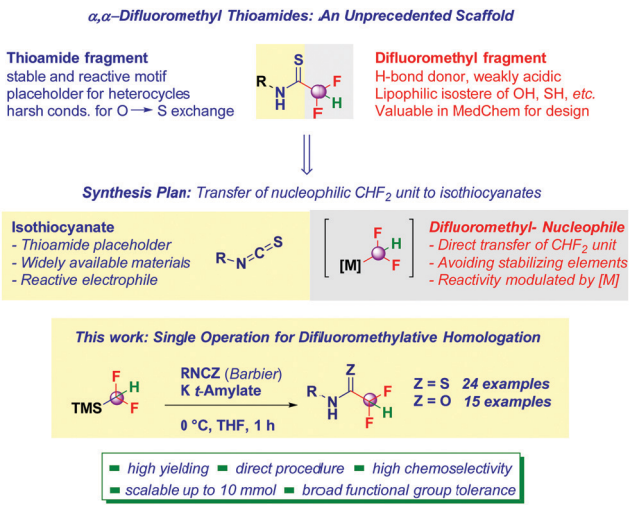
rsc.li/chemcomm

Highly chemoselective difluoromethylative homologation of iso(thio)cyanates: expeditious access to unprecedented α,α-difluoro(thio)amides†

Margherita Miele,[a] Rosarita D'Orsi,[b] Vellaisamy Sridharan,[c] Wolfgang Holzer[a] and Vittorio Pace *[a]

The new motif – α,α-difluoromethyl thioamide – has been assembled starting from isothiocyanate (as thioamide precursor) and a formal difluoromethyl-carbanion generated from commercially available $TMSCHF_2$. Upon proper activation of this reagent with potassium *tert*-amylate, the high-yielding transfer of the difluorinated nucleophile takes place under high chemocontrol. Various sensitive functionalities (*e.g.* ester, nitrile, nitro, azido groups) can be accommodated across the isothiocyanate core, thus allowing a wide scope. The methodology is highly flexible and adaptable to prepare analogous α,α-difluoromethyl oxoamides by conveniently using isocyanates as the electrophilic building-blocks.

Chemical entities featuring a difluoromethyl substituent (CHF_2) are receiving prominent interest within different audiences because of the fine modulation of physico-chemical parameters achievable by its introduction into organic skeletons.[1] The relatively acidic proton confers a unique capability to establish H-bond phenomena;[2] moreover, the CHF_2-group acts as a valuable – more lipophilic isostere – of important moieties such as OH or SH, *inter alia*.[3] These properties are regarded as highly valuable during drug optimization processes, in which the continued demand for CHF_2-containing scaffolds has boosted the design of novel tactics for their preparation.[4] In the frame of a medicinal chemistry project, we became interested in preparing α,α-difluoromethyl thioamides – completely unprecedented scaffolds – conjugating the versatility of the CHF_2 group with unique structural/chemical aspects (stability, crystallizability, good reactivity towards nucleophiles or placeholders for heterocycles) conferred by the formal replacement of oxygen (in oxoamides) with sulfur (Scheme 1).[5]



Scheme 1 General context of the presented work.

At the outset of our investigations, we were cognizant of the stability risk of α-halogenated thioamides,[6] thus requiring a straightforward synthetic route – ideally high yielding – to be adopted, in which critical steps such as the formal thionation (O → S substitution) could be advantageously skipped. For this purpose, we conceived an approach dealing with the transfer of a putative nucleophilic CHF_2-unit to isothiocyanates – as (thio)amides precursors – which proved to be highly effective in addition processes,[6b,7] thus enabling the limitations observed with thionating reagents (*e.g.* Lawesson) to be circumvented.[8] Because of the excellent electrophilicity of the heterocumulene carbon a wide array of nucleophilic elements could be installed, thus providing a reliable technique operating under chemocontrol and mild reaction conditions.[9] However, the well-known instability of F-containing carbanions[10] posed important risks on the success of the technique. In fact, to make the strategy productive, two key requirements had to be fulfilled: (1) the conditions to generate the formal CHF_2-carbanion must ensure its (limited) chemical integrity and, (2) the *per se* reactive

[a] *Department of Pharmaceutical Chemistry, University of Vienna, Althanstrasse 14, A-1090, Vienna, Austria. E-mail: vittorio.pace@univie.ac.at; Web: http://drugsynthesis.univie.ac.at/*

[b] *Department of Sciences, University of Basilicata, Via dell'Ateneo Lucano 10, 85100 Potenza, Italy*

[c] *Department of Chemistry and Chemical Sciences, Central University of Jammu, Rahya-Suchani (Bagla), 181143, India*

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c9cc06929a

isothiocyanate had to be fully preserved during the carbanion generation event.

The direct use of $MCHF_2$ reagents (M = metal), limited in terms of versatility and toxicity, stimulated the development of alternative pro-nucleophilic sources for the difluoromethyl anion.[10a] In fact, through the positioning of the TMS-group on the putative carbanion,[11] Hu and co-workers demonstrated the effectiveness of employing $TMSCHF_2$ in difluoromethylation under nucleophilic regime of carbonyls (ketones and aldehydes) and imines.[12] Remarkably, it manifests a series of positive features including easy manipulability (bp 65 °C) and, the protecting TMS group is advantageously cleaved during the activation event imposed by the presence of the strong Si–CF_2H bond. This is a particularly attractive characteristic compared to the use of different protecting elements, mainly strong electron-withdrawing groups,[13] which would have required two additional undesirable operations: the installation and the removal. An analogous approach has been documented by Dilman who demonstrated the effectiveness of difluorinated phosphorus ylides as nucleophilic reagents.[14] Herein, we present a straightforward preparation of α,α-difluoromethyl thioamides consisting of the nucleophilic CHF_2-transfer agent generation/chemoselective addition to isothiocyanates. We anticipate that the strategy is modular and adaptable to the synthesis of analogous α,α-difluoromethyl oxoamide derivatives by simply switching to isocyanates as the starting materials.[7a,15]

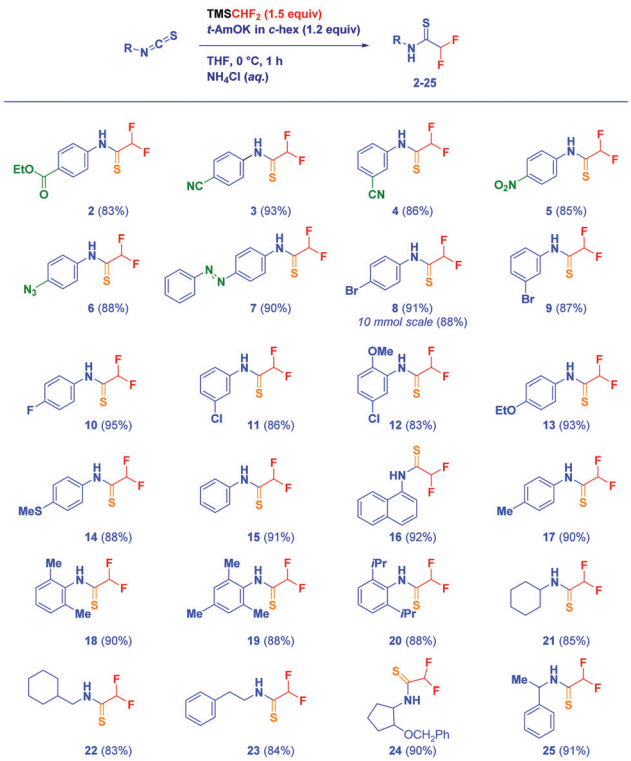
With the aim of verifying the initial hypothesis and evaluating the chemoselectivity of the transformation, the challenging ester-substituted isothiocyanate **1** – potentially susceptible of nucleophilic addition at the carbonyl – was selected as the model substrate (Table 1). The activation of $TMSCHF_2$ with CsF was inefficient regardless of the solvent used, thus indicating a distinct behaviour – governed by the nature of the electrophile – compared to Hu's work on carbonyls (entries 1 and 2).[12] Potassium *tert*-butoxide activated the pro-nucleophile enabling the desired transformation, though significant attack of the *t*-BuO anion on the isothiocyanate was observed (entry 3). Unfortunately, cooling the reaction at −78 °C did not suppress the side product formation (entry 4); interestingly, by switching the solvent to toluene or CPME an increase of the undesired thiocarbamate was noticed (entries 5 and 6). These initial indications suggested us to activate the donor with a more sterically hindered alkoxide, the commercially available *tert*-amylate being a valid alternative.[16] Pleasingly, the desired difluoromethylthioamide **2** was obtained in high yield as the major product together with a minimal amount of thiocarbamate **2b** (entry 7). Additional considerations merit mention: (1) by decreasing the nucleophile loading to 1.2 equiv. complete suppression of the undesired product was achieved, thus allowing **2** to be prepared with high chemocontrol (entry 8); (2) the putative carbanion needs to be generated under Barbier-type conditions, since late addition (even after 1 min at −78 °C) of the electrophile results in destruction of the species (entries 9 and 10); (3) the reaction is quite fast reaching completion within 1 h at 0 °C. Moreover, the use of a small excess of $TMSCHF_2$ compared to *t*-AmOK (0.3 equiv.) guarantees the nucleophile generation event to proceed quantitatively (entry 8 *vs.* 11).

With the optimized conditions in hand (entry 8 – Table 1), we then studied the scope of the reaction (Scheme 2). Not only a sensitive ester (**2**) could be placed on the reactive aryl isothiocyanate core, but also additional susceptible electrophilic functionalities such as nitrile (**3–4**) and nitro (**5**) which remained completely untouched during the nucleophile formation/homologation sequence. Moreover, nitrogen-containing groups did not interfere with the transformation, as deduced in the case of azide (**6**) and diazo (**7**). Different halogens – bromine (**8–9** – eventually performing the reaction in 10 mmol scale), fluorine (**10**), chlorine (**11–12**) – decorating the aryl nucleus at diverse positions are tolerated, thus allowing their reactivity in late transformations (*vide infra*) to be exploited. Moving to substituents of opposite electronic behaviour (electron donating groups) – alkoxy (**12–13**) or alkylmercapto (**14**) – resulted in clean reactions of

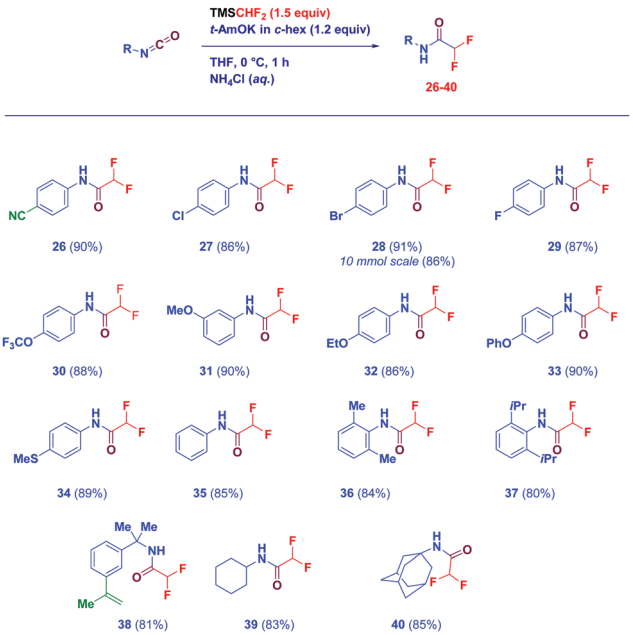
Table 1 Reaction optimization

Entry	Activator (equiv.)	$TMSCHF_2$ (equiv.)	Solvent	Temperature [°C]	Ratio **2**/**2ab**[a]	Yield of **2**[b] (%)
1	CsF (2.0)	1.8	DMF	rt	—	—
2	CsF (2.0)	1.8	THF	rt	—	—
3	*t*-BuOK (1.9)	2.0	THF	0	70 : 30	61[c]
4	*t*-BuOK (1.9)	2.0	THF	−78	79 : 21	66[d]
5	*t*-BuOK (1.9)	2.0	Toluene	0	58 : 42	47[e]
6	*t*-BuOK (1.9)	2.0	CPME	0	55 : 45	41[f]
7	*t*-AmOK (1.9)	2.0	THF	0	88 : 12	72[g]
8	***t*-AmOK (1.2)**	**1.5**	**THF**	**0**	**>99 : 1**	**83**
9[h]	*t*-AmOK (1.2)	1.5	THF	0	—	—
10[h]	*t*-AmOK (1.2)	1.5	THF	−78	—	—
11	*t*-AmOK (1.2)	1.2	THF	0	93 : 7[i]	67

[a] The ratio has been calculated by ^{1}H-NMR analysis using 1,3,5-trimethylbenzene as an internal standard. [b] Isolated yield. [c] **2a** (20%). [d] **2a** (14%). [e] **2a** (31%). [f] **2a** (32%). [g] **2b** (9%). [h] Non-Barbier conditions were used (*i.e.* the nucleophile was generated 1 min prior to the addition of **1**). [i] **2b** (4%).



Scheme 2 Scope of the nucleophilic difluoromethylation of isothiocyanates.

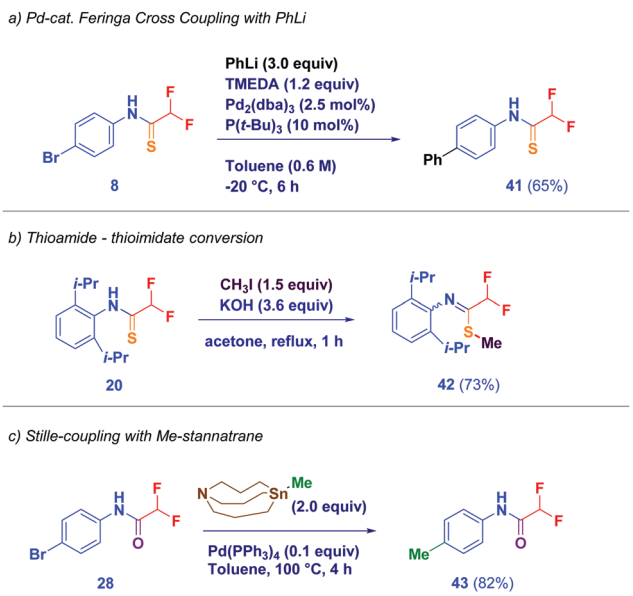


Scheme 3 Synthesis of α,α-difluoromethyl amides starting from isocyanates.

comparable efficiency. Moreover, simple aromatic groups – phenyl, *p*-tolyl (**15**, **17**) or 1-naphthyl (**16**) – provide the expected difluoromethyl thioamides in excellent yields. An intriguing and significantly valuable opportunity of the methodology is the one-step construction of highly sterically demanding scaffolds: accordingly, the introduction of methyl groups at the critical 2 and 6 positions of the phenyl moiety documents the validity of the tactic giving analogues **18** and **19**. This aspect is further showcased in the case of the more crowded 2,6-di-i-propylphenyl analogue **20**. The nature of the isothiocyanate does not influence the effectiveness of the technique: also aliphatic materials undergo the difluoromethylation giving the corresponding thioamides in high yields (**21**–**25**), thus confirming the positive trend manifested by aromatic counterparts.

The success of the procedure motivated us to evaluate the reactivity of oxo-analogues (isocyanates) en route to valuable α,α-difluoromethyl amides, synthetically and structurally relevant scaffolds,[17] previously prepared *via* classical amide-linkage forging chemistry.[18] The transformation is perfectly flexible affording the targeted motifs in high yield under full chemocontrol (Scheme 3). A series of functionalized aryl isocyanates are amenable for the direct difluoromethylation, including cyano (**26**), halogen-containing (**27**–**29**), alkoxy (**30**–**33**), and alkylthio (**34**). Again, scaling up to 10 mmol is compatible with the protocol (**28**). Clear confirmation of the suitability of the methodology for preparing challenging sterically demanding substrates arises from the outcome noticed with examples **36** and **37** (aromatic). Additionally, aliphatic congeners afford difluoromethyl amides with similar efficiency, it being worth noting the congested vinyl-substituted (**38**) and the adamantyl derivative **40**.

With the aim to explore the potential behaviour of the α,α-difluoromethyl thioamide motif, we realized a series of manipulations on the synthesized scaffolds (Scheme 4). Notably, the new motif withstands the Feringa Pd-catalyzed cross-coupling[19] of PhLi, thus allowing the phenylation on the bromine-containing nucleus **8** to be selectively conducted giving the bis-phenylated structure **41** (path a). Under alkylative conditions (MeI, KOH), the difluoromethyl thioamide group of **20** is conveniently converted into the thioimidate **42** (path b). Because of our interest towards C_1–Sn



Scheme 4 Synthetic versatility of α,α-difluoro(thio)amides.

reagents,[20] we were pleased to use a stannatrane[21] for the transfer of the methyl unit to oxoamide **28** under Stille-coupling conditions, thus evidencing the stability of the difluoromethyl amide **43** (path c).

In summary, we have developed a straightforward synthesis of previously undisclosed α,α-difluoromethyl thioamides *via* a tactic based on the nucleophilic transfer of a difluoromethyl carbanion equivalent to isothiocyanates. The treatment of the commercially available and experimentally convenient reagent $TMSCHF_2$ with potassium *tert*-amylate allows the efficient formation of the difluorinated nucleophile. Full chemocontrol is uniformly manifested as indicated in the cases of challenging isothiocyanates embodying chemical moieties susceptible of nucleophilic attack. This high yielding methodology fully preserves its effectiveness when applied to the synthesis of α,α-difluoromethyl oxoamide using isocyanates as amide precursors.

We thank the University of Vienna and the OEAD for generous support. Dr R. Bartolotta is acknowledged for initial contributions and D. Dobusch for HRMS data. R. D'O. thanks the University of Basilicata for a visiting doctoral fellowship. This paper is dedicated to Professor Marko Mihovilovic in the occasion of his 50th birthday.

Conflicts of interest

There are no conflicts to declare.

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Publication n. 10

Straightforward Synthesis of Bench-Stable Heteroatom-Centered Difluoromethylated Entities via the Controlled Nucleophilic Transfer from Activated TMSCHF2.

Miele, M.; Castoldi, L.; Simeone, X.; Holzer, W.; and Pace, V.*

Submitted (ref. CC-COM-02-2022-000886).

Journal Name

COMMUNICATION

Straightforward Synthesis of Bench-Stable Heteroatom-Centered Difluoromethylated Entities *via* the Controlled Nucleophilic Transfer from Activated $TMSCHF_2$

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

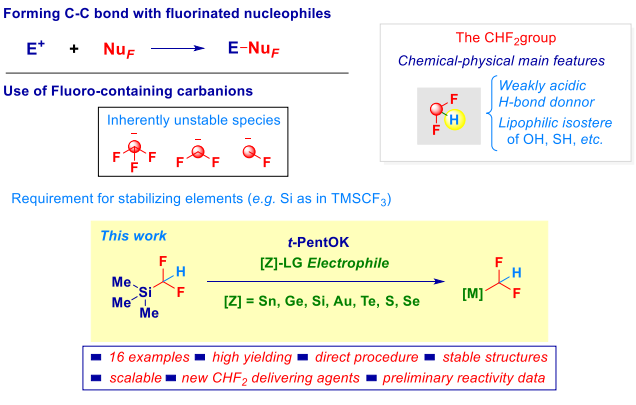
www.rsc.org/

Margherita Miele,[a] Laura Castoldi,[b] Xenia Simeone,[a] Wolfgang Holzer[a] and Vittorio Pace[a,b*]

The commercially available and experimentally convenient (bp 65 °C) difluoromethyltrimethylsilane ($TMSCHF_2$) is proposed as a valuable difluoromethylating transfer reagent for delivering the CHF_2 moiety to various heterotom-based electrophiles (Sn, Ge, Si, Au, S, Se, Te). Upon the activation with an alkoxide, a conceptually intuitive nucleophilic displacement directly furnishes in high yields the bench-stable analogues. The X-ray structural analysis of the corresponding stannatrane supports a valuable reactivity - as also noticed for the triphenylsilane derivative - thus introducing novel difluoromethylating agents suitable for both Pd-catalyzed sequence and classical nucleophilic regime.

Among the techniques enabling the modulation of pivotal physical-chemical properties (*e.g.* pharmaco- kinetic and dynamic aspects) of organic arrays, the introduction of fluorine atoms became a powerful tool, nowadays thoroughly applied in chemistry.[1] Synthetic chemists tackling the challenge of embodying fluorine into molecules, quickly recognized that well-established methodologies in classical halogen chemistry could not be validated for this member of the series.[2] Ideally, the use of fluorinated carbanion-like entities would enable – upon a conceptually intuitive nucleophile-electrophile logic - the forging of a new carbon-carbon bond presenting the exact and desired fluorination degree of the targeted compound (Scheme 1).[3] However, F-containing nucleophiles are notoriously reluctant species mainly due to their inherent limited chemical integrity which for long time eclipsed their employment in synthesis.[2a,4] In this sense, the introduction of trifluoromethyltrimethylsilane ($TMSCF_3$, Ruppert-Prakash reagent)[5] made productive trifluoromethylations under nucleophilic regime by exploiting the stabilizing effect imparted by the silicon atom. Analogous nucleophilic difluoromethylations[6] and monofluoromethylations[7] remained somehow obscured and thus, underdeveloped till recently because of the high tendency of $MCHF_2$ and MCH_2F carbanions to undergo α-elimination. On the other hand, the introduction of difluoromethyltrimethylsilane ($TMSCHF_2$), a commercially available and experimentally convenient CHF_2-donor source (bp 65 °C)[8] boosted the flourishing of synthetic protocols for the introduction of this group[9] featuring some unique properties – H-bond donor, weakly acidic, lipophilic isostere of OH and SH motifs - which make it highly valuable *inter alia* in drug design.[10]

Compared to the Ruppert-Prakash reagent, the reactivity of $TMSCHF_2$ is tamed[11] and its proper activation under Lewis basic conditions is essential, as demonstrated by Hu in 2011 in the course of difluoromethylations of ketones and imines,[12] later extended also to other sp^2-hybridized carbon electrophiles by our group.[13]. Collectively, these precedents showcase that replacing a putative ionic (*e.g.* Li) M-CHF_2 bond with a covalent one (*e.g.* Si) represents the *conditio sine qua non* for accessing bench stable difluoromethylating agents. With this rationale in mind, we wondered if a unified strategy enabling the release of the nucleophilic CHF_2 moiety from a competent donor to a recipient heteroatom-centered electrophile - [Z]-LG, Z = heteroatom, LG = leaving group - could be designed. Should this concept be experimentally validated, we would establish a smooth access to versatile Z-CHF_2 agents not relying on more complex routes such as the Prakash-Olah modification[14] of the Cullen CF_2 carbene insertion into the Sn-H bond of a trialkyltin hydride.[15] Herein, we present the feasibility of this rationale through an alkoxide mediated activation of $TMSCHF_2$: we anticipate the protocol – working like a CHF_2 shuttle – enables to prepare in high chemical yields α,α-difluoromethyl-derivatives of tin, germanium, tellurium, gold, selenium and sulfur.



Scheme 1. General context of the presented work.

[a] University of Vienna - Department of Pharmaceutical Chemistry. Althanstrasse, 14 1090 Vienna, Austria. E:mail: vittorio.pace@univie.ac.at
Web: http://drugsynthesis.univie.ac.at/
[b] University of Milano - Department of Pharmaceutical Sciences. Via Golgi 19, 20133 Milano, Italy.
[c] University of Torino - Department of Chemistry. Via Giuria 7, 10125 Torino, Italy.

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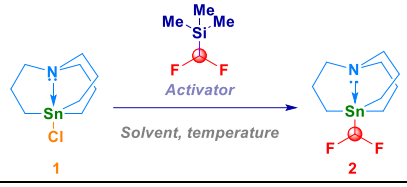
We selected the commercially available chloro-stannatrane **1** as the model substrate for evaluating the strategy proposed (Table 1). This choice was motivated by the following reasons: a) the stannatrane backbone – introduced in synthesis by Vedejs[16] - due to the constitutive apical nitrogen atom which enlarges the Sn-C bond, manifest a higher tendency to transmetallate and thus, to be engaged in nucleophilic transfer operations;[17] b) as showcased in illuminating works by Biscoe,[18] stannatranes are particularly suited for coupling (enantioenriched) secondary systems; c) the expected difluoromethyl analogue **2** is, to the best of our knowledge, an unknown reagent, potentially useful in fluorination chemistry, thus substituting inherently less reactive "dummy"-based species (*e.g.* R_3SnCHF_2).[19]
Activating the pronucleophile with CsF (in toluene or DMF) or with TBAT (tetrabutylammonium difluorodiphenylsilicate) was not effective and, the starting chloro-stannatrane **1** was fully recovered (entries 1-3). The adoption of a Lewis base activation protocol with a commercially available solution of potassium *tert*-pentoxide (amylate) in toluene enabled a clean transformation in THF at -50 °C, thus giving **2** in 79% isolated yield (entry 4). Temperature increasing – *coeteris paribus* – to -20 °C and 0 °C, respectively, was beneficial (entries 5-6). The stoichiometric ratio between $TMSCHF_2$ and *t*-PentOK could be dwindled to 1.5:1.4 without affecting the transformation efficiency (entry 7), whereas the further decrease was detrimental (entry 8). Some additional aspects merit mention: a) a slight excess (0.1 equiv) of the pronucleophile compared to the alkoxide was essential for the complete genesis of the difluoromethyl carbanion-like species and thus, for suppressing the (non isolable) stannatrane nucleophilic substitution adduct [Sn-O(*t*-Pent), entry 9]; b) using Barbier-type conditions was crucial for observing reactivity, thus remarking the limited chemical integrity of this carbanion (entry 10).

Table 1. Reaction optimization.

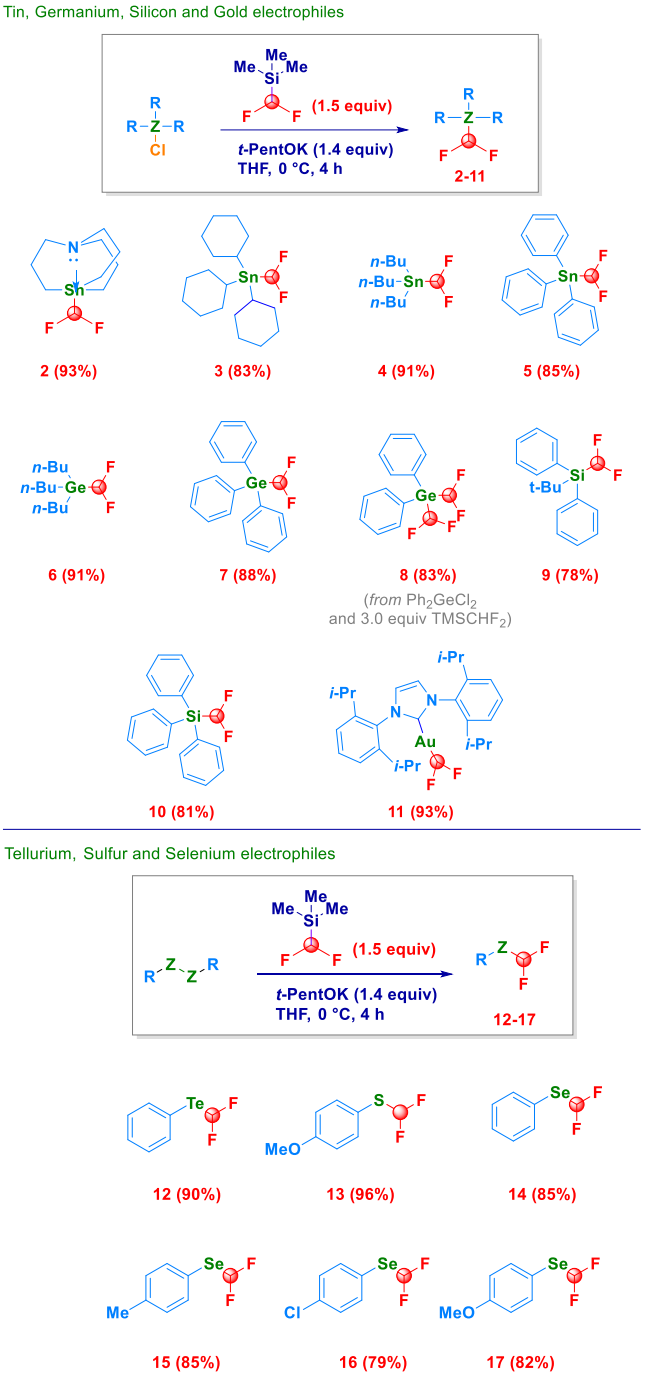


1 2

Entry	Activator (equiv)	$TMSCHF_2$ (equiv)	Solvent / Temp. (° C)	Yield of **2** (%)[a]
1	CsF (1.8)	2.0	Toluene / 90	-
2	CsF (1.8)	2.0	DMF / 90	-
3	TBAT (1.8)	2.0	DMF / 90	-
4	*t*-PentOK (1.8)	2.0	THF / -50	79
5	*t*-PentOK (1.8)	2.0	THF / -20	87
6	*t*-PentOK (1.8)	2.0	THF / 0	94
7	*t*-PentOK (1.4)	1.5	THF / 0	93
8	*t*-PentOK (1.2)	1.1	THF / 0	83
9[b]	*t*-PentOK (1.5)	1.5	THF / 0	85
10[c]	*t*-PentOK (1.4)	1.5	THF / 0	-

[a] Yields refer to isolated and purified compounds. [b] ^{1}H-NMR and GCMS analyses of the reaction crude indicate the presence of stannatrane-O-*t*-Pent adduct whose purification was unfortunately not effective. [c] Reaction carried out under *non* Barbier-type conditions. Entries 1-3 run for 6 h. Entries 4-10 run for 1 h.

With the optimal conditions for the direct homologative transfer of the CHF_2 unit to a halostannane-type derivative, we then investigated the scope of the reaction (Scheme 2). Pleasingly, tricyclohexyl- and tri(*n*-butyl)- stannanes smoothly underwent the transformation, furnishing analogues **3** and **4** in comparable high yield. Switching to aromatic substituents (**5**) on tin did not affect the effectiveness. Previously undisclosed difluoromethyl derivatives of organogermanium compounds could also be prepared under our conditions in case of both trialkyl- (**6**) and triphenyl- (**7**) systems.[20] This is particularly intriguing since organogermaniums recently emerged as more sustainable and attractive alternatives to the more common organotin compounds.[21] Notably, dichlorodiphenylgermanium was a competent electrophile for the double functionalization, conducting to the bis-(difluoromethyl) derivative **8** in a very good 83% isolated yield. The difluoromethyl fragment released by the silicon atom of $TMSCHF_2$ could be efficiently transferred to a different silicon center by reacting with a halo-silane, thus conducting to the unprecedented difluoromethylsilanes **9** (*t*-butyldiphenyl, 78%) and **10** (triphenyl, 81%). The combined electronic and steric factors imparted by these substituents may be advantageously employed for modulating the reactivity of difluoromethylsilane (*vide infra*). Furthermore, the NHC-Au(I)-Cl complex could be engaged in the transformation, giving the corresponding -CHF_2 adduct **11** in high yield. The scalability of the transformation (15 mmol) was deducted by high-yielding processes for compounds **2** (xx%) and **10** (85%)
The formal nucleophilic substitution process was not only achieved on heteroatom-halide functionalities but, was also effective in the case of symmetrical RZ-ZR moieties acting as convenient starting materials. Accordingly, organotellurium (**12**), organosulfur (**13**) and organoseleniums (**14**-**17**) were easily prepared. The proposed strategy favourably compares with reported protocols, as for example the use of the non-commercially available PhSeCN with the same $TMSCHF_2$[22] or, the use of the gaseous species chlorodifluoromethane.[23]



Scheme 2. Difluoromethyl-group transfer under nucleopilic regime from $TMSCH_2$ to different heteroatom-based electrophiles.

With the aim to gain insights into structural features of difluoromethyl-tin analogues **2** and **5**, their crystallographic X-ray analysis revealed some important aspect (Figure 1). In the case of stannatrane, the Sn1-C1 bond has a length of 2.233 Å, significantly longer compared to classical organotins (R_3SnR^1).[24] This element is in agreement with the reasons accounting for the chemical profile of the stannatrane backbone: the enlarged Sn-C bond makes it more labile and thus, confers a high reactivity. In fact, the analogous bond Sn1-C1 in the triphenyltin analogue **5** is 2.197 Å. Moreover, the Sn1-N1 distance in the stannatrane is 2.478 Å, whereas the two carbon-fluorine bonds in both structures are comparable (1.313 Å and 1.317 Å in stannatrane **2** and, 1.225 Å and 1.338 Å in triphenyltin- **5**). The angle C1-Sn1-C2 (102.66°) matches with the analogous C1-Sn1-C5 (103.77°) and C1-Sn1-C8 (102.27°) in the stannatrane which also shows a characteristic planar orientation N1-Sn1-C6 (178.61°). The absence of the rigidifying backbone in **5** is evident from the values of the angles C1-Sn1-C8 (107.36°), C1-Sn1-C14 (110.30°) and C1-Sn1-C2 (103.13°).

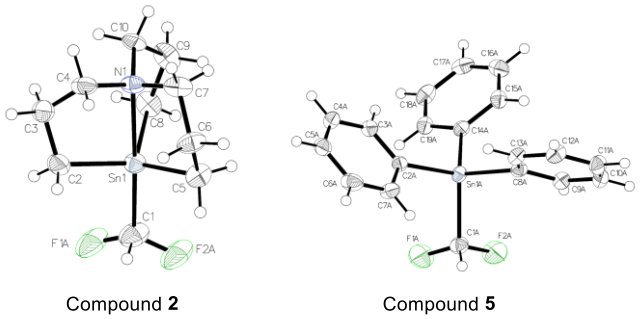
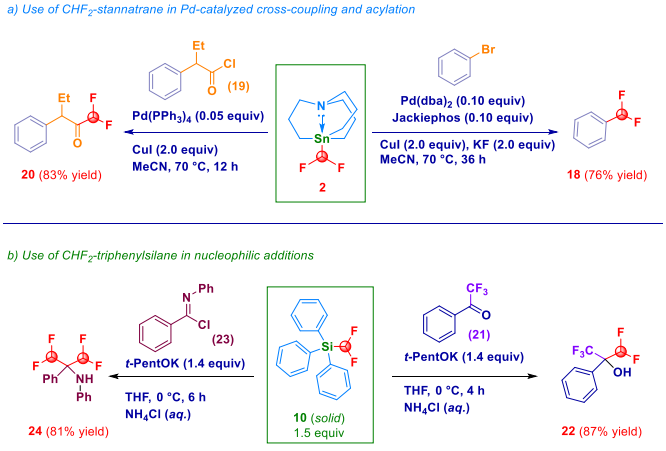


Figure 1. X-rays structures of selected difluoromethyltin derivatives (**2** CCDC 2150362 and, **5** CCDC 2150363).

The synthetic potential of selected prepared compounds was then evaluated (Scheme 3). Difluoromethyl stannatrane **2** acted as a versatile coupling agent in two recently developed protocols by Biscoe,[18a,18d] namely: a) the Pd-catalyzed cross-coupling with bromobenzene furnishing **18** in 76% yield and, b) the Pd-catalyzed acylation with an acyl choride **19** which resulted in the clean formation of difluorometylketone **20** in 83% yield (*path a*). As an additional proof of the enhanced reactivity conferred by the stannatrane backbone, it is worth noting that Sn-CHF_2 analogues **3**, **4** and **5** did not promote at any extent both transformations. Intrigued by the solid physical state of the triphenylsilane derivative **10**, upon the usual activation with potassium *tert*-pentoxide and reaction with α,α,α-trifluroacetophenone **21**, we were delighted in observing the preparation of the *gem*-difluoromethyl-trifluoromethyl carbinol **22** in 87% yield (*path b*).[25] Although reactive, the process carried out with the *tert*-butyldiphenyl analogue **9**, gave **22** in 54% yield, probably as consequence of the increased steric hindrance on the *Si*-atom. The same activated form of the triphenylsilane derivative **10** accomplished also a double nucleophilic attack on the azomethinic carbon of *N*-phenylbenzimidoyl choride **23** *en route* to bis(difluoromethyl) amine **24** (81% yield). Collectively, these experiments indicate derivative **10** as a valuable difluoromethylating agent form whose solid state – although not suitable for X-ray analysis - may have advantages on the liquid $TMSCHF_2$.



Scheme 3. Synthetic uses of CHF_2- stannatrane and triphenylsilane.

In summary, we reported the direct nucleophilic transfer of a difluoromethyl unit to a series of heteroatom-centered electrophiles (Sn, Ge, Si, Au, Se, S, Te) for forging bench stable analogues. The procedure is levered on the Lewis base mediated activation (potassium *tert*-pentoxide) of the commercially available and experimentally convenient $TMSCHF_2$. Not only chlorinated starting materials could be employed but, also chalcogenides of general structure RZ-ZR, thus giving a straightforward access to the title compounds through a flexible and intuitive logic. Among the prepared motifs, particular mention deserves: *i)* the stannatrane analogue for which structural aspects deducted by the X-ray crystallographic analysis support a unique reactivity in Pd-catalyzed cross-coupling or acylation processes and, *ii*) the triphenylsilyl-derivative which can be regarded as a valuable alternative to the starting $TMSCHF_2$ for the delivery of the CHF_2 unit to electrophilic linchpins (ketone and imidoyl chloride).

Acknowledgements

The Authors thank the University of Vienna and the University of Torino for financial support.
Dedicated to Professor Helmut Spreitzer in the occasion of his retirement.

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Direct and straightforward transfer of C1 functionalized synthons to phosphorous electrophiles for accessing gem-P-containing methanes.

Touqeer, S.; Ielo, L.; **Miele, M**.; Urban, E.; Holzer, W.; Pace, V. *

Org. Biomol. Chem. **2021**, *19,* 2425-2429. (DOI: 0.1039/D1OB00273B)