A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition

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Accepted Article

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Authors: Laura Ielo, Saad Touqeer, Alexander Roller, Thierry Langer, Wolfgang Holzer, and Vittorio Pace

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201812525
Angew. Chem. 10.1002/ange.201812525

Link to VoR: http://dx.doi.org/10.1002/anie.201812525
http://dx.doi.org/10.1002/ange.201812525

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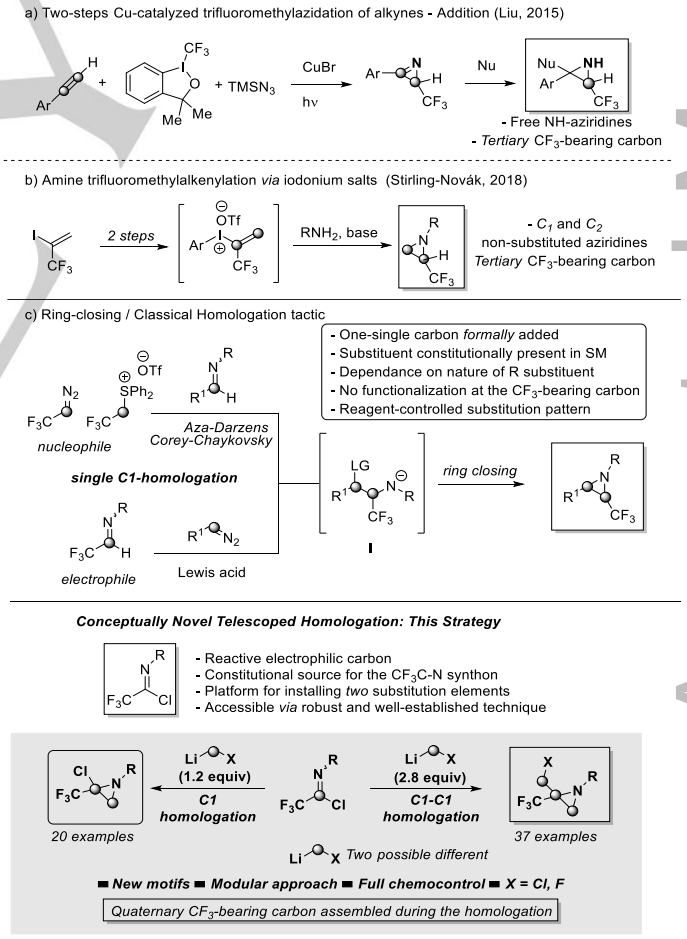
Telescoped, Divergent, Chemoselective *C1* and *C1-C1* Homologation of Imines Surrogates: A Straightforward Access to Quaternary Chloro- and Halomethyl-trifluoromethyl-aziridines

Laura Ielo, Saad Touqeer, Alexander Roller, Thierry Langer, Wolfgang Holzer and Vittorio Pace*

Abstract: A conceptually novel, high yielding, mono- or bis-homologation realized with lithium halocarbenoids enables the one-step, fully chemocontrolled assembling of a new class of quaternary trifluoromethyl-aziridines. Trifluoroacetimidoyl chlorides (TFAIC) act as convenient electrophilic platforms enabling the addition of one or two homologating elements by simply controlling the stoichiometry of the process. Mechanistic studies highlighted that the homologation event - carried out with *two* different carbenoids ($LiCH_2Cl$ and $LiCH_2F$) - conducts to fluoromethyl-analogues, in which the first nucleophile is employed for constructing the cycle and, the second for decorating the resulting molecular architecture.

The constitutive presence of a trifluoromethyl group (CF_3) within an organic framework deeply modulates its physico-chemical properties, thus rendering the scaffold a highly valuable entity across the chemical sciences.[1] Incorporating such a functionality within a 3-membered nitrogen cycle would result in unique motifs (CF_3-aziridines)[2] featuring interesting reactivity, synthetic versatility and pharmacological properties determined by the interaction of this lipophilic core with biological targets. This innate potential is reflected in intensive efforts towards the development of efficient tactics for preparing CF_3-aziridines. In 2015 Liu developed a two-steps Cu-catalyzed trifluoromethylazidation of alkynes followed by the addition of nucleophiles to the intermediate azirines (Scheme 1a),[3] while Stirling and Novák disclosed in 2018 the metal-free alkenylation/cyclization of amines with trifluoroalkenyl iodonium salts (Scheme 1b).[4] Each of these strategies leads to structurally different motifs – though in both cases tertiary CF_3-bearing carbons are obtained - presenting well defined relative placement of substituents: Liu's one conducts to α-aryl-α-substituted-trifluoromethylaziridines, whereas *via* the Stirling-Novák protocol unsubstituted trifluoromethylaziridines are formed.

Historically, the conceptual simplicity of ring closure operations (3-*exo*-*tet*) on formal β-substituted CF_3-containing amine derivatives emerged as a valuable tool for accessing the targeted scaffolds (Scheme 1c).[2a, 2c] Accordingly, the key intermediate **I** can be accessed *via* a C1-homologative transformation carried out with CF_3-nucleophilic synthons on properly activated imines as shown by Carreira,[5] Xiao[6] and Cahard[7] or, alternatively through the homologation of electrophilic CF_3-containing imines with standard diazo chemistry.[8] However, as a common feature, the homologation event is limited to the transfer of *one* single carbon unit *per* transformation.[9] We realized that accomplishing *two* consecutive C1-homologations *within* the same process would represent a highly significant challenge with the final goal of reaching *quaternary* functionalized aziridine derivatives through a single chemical operation. Our synthetic plan started by individuating the easily accessible trifluoroacetimidoyl chlorides (TFAIC)[10] as the proper electrophilic imine surrogate placeholders on which realizing the bis-functionalization. The intrinsic reactivity conferred by the chlorine not only would ensure the smooth addition of the homologating agent but, more importantly, would be the key to enable the incorporation of two nucleophilic elements on the sp^2 C-N double bond of the TFAIC.



Scheme 1. General context of the presented work.

Recently, our group documented that homologation processes mediated by lithium carbenoids ($LiCH_2X$)[11] might forge complex

[*] Dr. Laura Ielo, MSc. Saad Touqeer, Prof. Dr. Thierry Langer, Prof. Dr. Wolfgang Holzer, Prof. Dr. Vittorio Pace*
University of Vienna, Department of Pharmaceutical Chemistry, Althanstrasse, 14, A-1090, Vienna (Austria)
E-mail: vittorio.pace@univie.ac.at; web: drugsynthesis.univie.ac.at/
Ing. Alexander Roller
University of Vienna, X-Ray Structure Analysis Center, Waehringerstrasse 42, A-1090 Vienna (Austria)

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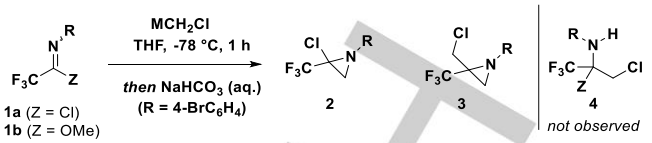
molecular architectures in an extremely convenient and effective way by simply selecting the reaction conditions,[12] thus making flexible and modular the strategy to a given target.[13] By introducing the unprecedented concept of C1-C1-double homologation – eventually realized with two distinct homologating agents - within a unique chemical event, herein we present a straightforward tactic enabling the construction of unkown α-halo-α-trifluoromethylaziridines and α-halomethyl-α-trifluoromethyl aziridines.[2c, 14]

We commenced our investigations reacting the electrophilic TFAIC **1a** – featuring a potentially exchangeable bromine - with $LiCH_2Cl$ (1.2 equiv) under standard homologation conditions: the α-chloroaziridine **2** was formed as the unique product in an excellent 90% yield (Table 1 – entry 1). The increase of carbenoid loading to 1.5 and 2.3 equiv respectively, evidenced the contemporaneous formation of the bis-homologated adduct chloromethylaziridine **3**, though as the minor product (entries 2-3). The indicative decrease of the formation of **2** at progressively higher amounts of $LiCH_2Cl$ was symptomatic of the strict dependence on the stoichiometry of the process. Thus, having ascertained the initial hypothesis of employing **1** as placeholder for two simultaneous functionalizations, the desired compound **3** was the exclusive reaction product – 91% isolated yield - when 2.8 equiv of carbenoid were used (entry 4). Significantly, the putative intermediate compound **4** formed upon homologation of **1** followed by acidic quenching could not be observed, thus suggesting an extremely high reactivity for this species (*vide infra* for mechanistic details). Some additional points merit mention: a) The reaction reach completion within 1 h, thus allowing to selectively obtain the mono- or the bis-homologated product by simply selecting the stoichiometry; b) Chemoselectivity is fully preserved in the presence of the reactive bromine, suggesting high versatility and flexibility; c) a tamed nucleophilic but more stable carbenoid (*i.e.* $ClMgCH_2Cl$-LiCl)[15] does not induce the transformation even at higher temperature (entries 5-6); d) Running the reaction in Et_2O sensitively dropped the yield (entry 7), confirming the preference for the more polar THF; e) Replacing TFAIC **1a** with the corresponding imidate **1b** was not possible (entry 8), suggesting the process requires an activated imine surrogate to proceed.

Table 1. Optimization of the reaction



Entry	Homologating agent	Equiv	**2** Yield (%)[a]	**3** Yield (%)[a]
1	$LiCH_2Cl$	1.2	90	< 2
2	$LICH_2Cl$	1.5	57	23
3	$LICH_2Cl$	2.3	22	73
4	$LICH_2Cl$	2.8	-	91
5[b]	$ClMgCH_2Cl$	2.8	-	-
6[b,c]	$ClMgCH_2Cl$	2.8	-	-
7[d]	$LICH_2Cl$	2.8	-	82
8[e]	$LiCH_2Cl$	2.8	-	-

Otherwise indicated $LiCH_2Cl$ was generated under Barbier conditions in THF at -78 °C starting from ICH_2Cl and MeLi-LiBr 1.5 M and compound **1a** was used as the starting agent. [a] Isolated yield. [b] Formed from ICH_2Cl and *i*-PrMgCl-LiCl (ref. 15). [c] Run at -30 °C. [d] Et_2O was used as the solvent. [e] Compound **1b** was used.

Having determined the conditions for achieving full chemocontrol, the scope of the mono-homologation technique *en route* to valuable α-chloroaziridines was evaluated (Scheme 2). The protocol turned to be highly versatile, chemoselective and of general applicability, as documented by the structural diversity of the synthesized compounds. The following points underline the potential of the methodology: 1) neither the substituents' electronic behaviour and their position across the aromatic ring influence the outcome; 2) no concomitant halogen-lithium exchange occurs in systems featuring these substituents, including bromine, chlorine and fluorine (**2**, **5**-**7**) The superb chemocontrol is clearly evidenced in reactions carried out with substrates presenting functionalities notoriously highly sensitive to organolithium reagents such as nitrile (**8**-**9**), ester (**10**-**11**) or even a Weinreb amide (**12**). Taken together these examples showcase the formidable electrophilicity of TFAICs, enabling the selective homologation exactly on the targeted carbon. Aromatic (**13**-**16**), as well as unsaturated (**17**) and aliphatic (**18**-**19**) groups on the aromatic ring were perfectly tolerated including in the presence of sterically relevant elements (**20**). Nitrogen-featuring substituents on the aromatic ring such as morpholine (**21**), a diazo moiety (**22**) and a lactam (**23**) further demonstrate the potential of the tactic.

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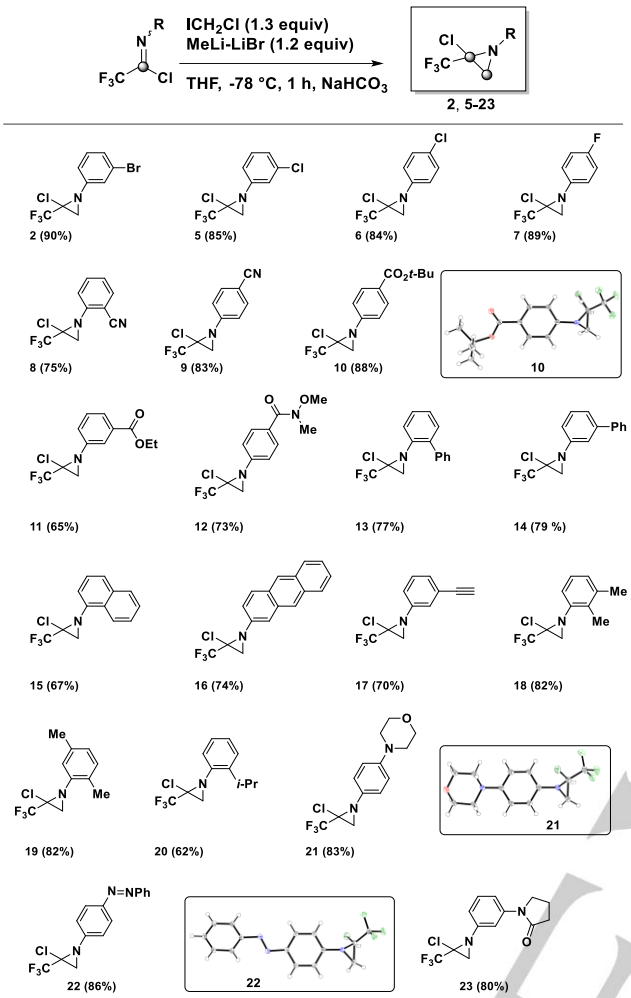
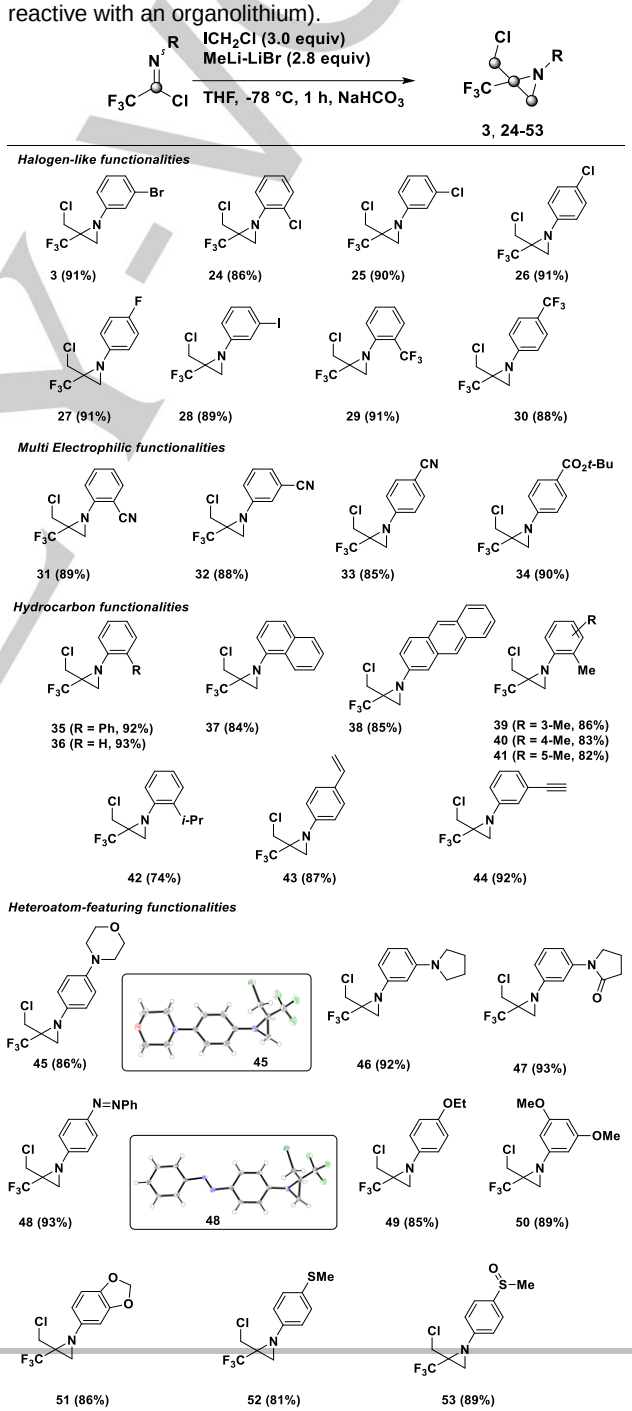


Scheme 2. C1-homologation for preparing chloro-trifluoromethylaziridines. Crystal structures are deposited at CCDC ([**10**] 186913; [**21**] 186914; [**22**] 186911).

The conceptually novel C1-C1 double homologation was then applied for the synthesis of α-chloromethyl-α-trifluoromethyl aziridines (Scheme 3). Pleasingly, the optimized conditions found in Table 1 were of general applicability, thus allowing the straightforward preparation of these unknown scaffolds featuring a quaternary all-substituted carbon through a single synthetic operation. TFAICs reacted extremely well with independence from the electronic or sterical properties of substituents. Accordingly, all halogens (**3**, **24**-**27**) – including the reactive iodine (**28**) or the trifluoromethyl group (**29**-**30**) – furnished the bis-homologated adducts in high yields after short reaction times. Chloromethyllithium proved to be highly selective, as observed in the cases of nitriles regardless their relative position (**31**-**33**) - and an ester (**34**). This is quite noteworthy since these functionalities are known to be highly susceptible to the attack of carbanions. Embodying hydrocarbon functionalities such as aryl (**35**, **37**-**38**), or aliphatic groups (**39**-**41**) does not alter the efficiency including in case of significant steric hindrance (**42**). Unsaturated motifs such as an olefin (**43**) or alkyne (**44**) were perfectly tolerated. Neither the carbenoid-mediated Simmons-Smith-type cyclopropanation on the olefin[16] and abstraction of the acidic proton of the terminal alkyne were observed. A series of nitrogen-containing groups – *e.g.* morpholine (**45**), pyrrolidine (**46**), lactam (**47**), diazo (**48**) - could be placed on the ring, further expanding the scope of the protocol. Remarkably, recrystallization of compound **48** provided enantiomerically pure (*S*)-**48** as unambiguously ascertained by X-ray structural analysis. Ethers (**49**-**50**) or cyclic acetal (**51**) are compatible with the reaction conditions, as well as, diversely oxidized sulfur substituents of opposite electronic characteristics such as sulfide (**52**, electron-donating) and sulfoxide (**53**, electron-withdrawing and potentially reactive with an organolithium).



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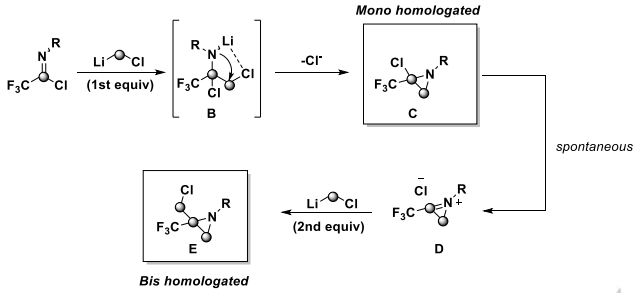
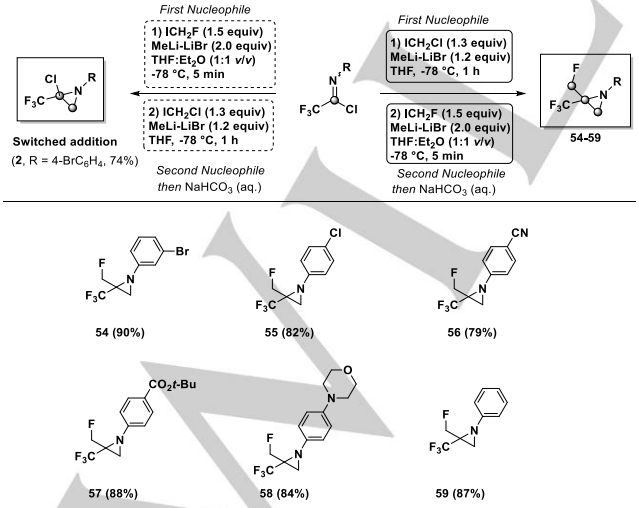
Scheme 3. C1-C1 bis-homologation for preparing chloromethyl-trifluoromethylaziridines. Crystal structures are deposited at CCDC ([**45**] 186915; [**48**] 186912.

Mechanistically, the telescoped homologation can be rationalized *via* the expected addition of the 1st equiv of $LiCH_2Cl$ to form the tetrahedral intermediate **B** (Scheme 4). Presumably, the internal coordination between the lithium cation of the amidic functionality and the chlorine[2c, 8c] introduced during the homologation event would then trigger an internal nucleophilic displacement leading to the mono-homologated chloroaziridine **C**. Whenever an excess of homologating agent is present (2.8 equiv) and no quenching is realized, the intermediate chloroaziridine spontaneously evolves[8c, 17] to the highly electrophilic azirinium ion **D** which then undergoes the second homologation to finally yield chloromethylaziridine **E**.



Scheme 4. Plausible mechanism for the C1 and C1-C1 homologations.

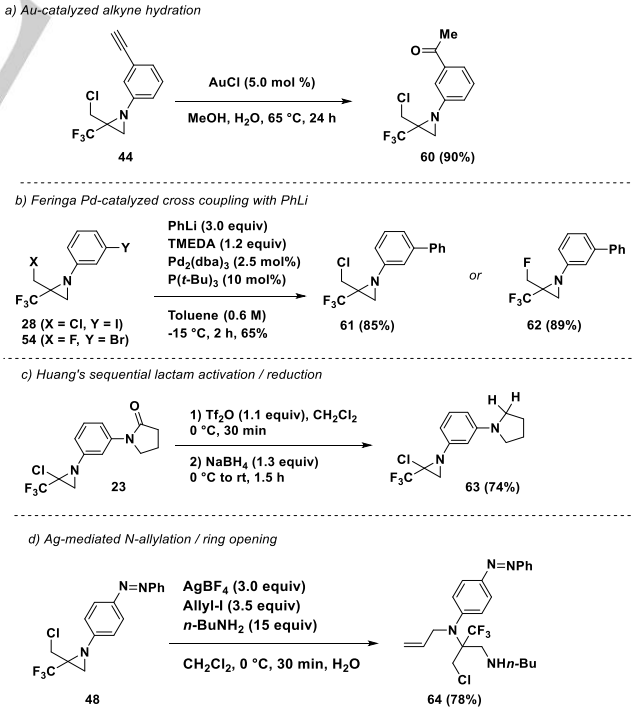
In order to provide evidence for the mechanistic rationale, a telescoped homologation accomplished with two different agents, - $LiCH_2Cl$ and $LiCH_2F$[18] – was designed (Scheme 5). The first carbenoid was used as a C1 source for constructing the aziridinyl ring, while the fluorinated carbenoid was conveniently used to install the functionalizing CH_2F motif. With much of our delight a series of fluoromethyl-trifluoromethylaziridines (**54**-**59**) could be easily accessed in a modular and divergent way *via* a single synthetic operation consisting in the controlled generation and employment of these two carbenoids during the same sequence.



Scheme 5. Synthesis of fluoromethyl-trifluoromethylaziridines *via* the homologation with two different carbenoids.

No variation of the reactivity profile of the starting TFAICs was noticed, thus confirming the general outcome discussed for chloromethyl analogues. Importantly and, as a further evidence of the mechanism, exchanging the order of addition of the two carbenoids resulted in the formation of the sole mono-homologated aziridine. The tamed nucleophilicity of $LiCH_2F$[18] compared to $LiCH_2Cl$ results in no attack to TFAIC, thus demonstrating that the monohomologated chloroaziridine obtained (**2**) is formed in 74% yield during the second homologation event with $LiCH_2Cl$. Notably, such a second homologation is limited at the insertion of only one carbon unit because of the stoichiometry employed.

The conceptual novelty of the strategy elaborated was then complemented with a survey on the chemical behaviour of these non-previously reported scaffolds (Scheme 6). The substituents on the aromatic rings act as versatile platforms for selective functionalizations. The alkyne **44** serves as an expeditious naked source of the corresponding methyl ketone **60** generated upon Au(I)-catalyzed Wacker-type hydration (path *a*).[19] The Pd-catalyzed Feringa cross-coupling of PhLi with iodo- (**28**) or bromoarenes (**54**) was suitable for both chloromethyl- (**61**) and fluoromethyl-aziridines (**62**) with comparable yields (path *b*).[20] The electrophilic activation of the lactam moiety of compound **23**,[21] followed by *in situ* reduction under Huang's conditions[22] delivered the corresponding reduced pyrrolidinyl system **63** (path *c*). Finally, the aziridine Ag-mediated ring-opening with an amine in the presence of an allylating agent gave with excellent regioselectivity the 1,2-diamine scaffold **64** featuring full substitution at the initial aziridine carbon (path *d*).[23]



Scheme 6. Manipulation of synthesized compounds.

In summary, we have documented the assembling of quaternary all-substituted trifluoromethylaziridines *via* a single synthetic operation consisting in the lithium halocarbenoids-mediated mono- or bis-homologation of trifluoroacetimidoyl chlorides. These easily accessible electrophilic substrates act as convenient placeholders for installing up to *two* nucleophilic elements: the fine tuning of the reaction stoichiometry accounts for excellent levels of chemocontrol. As such, the use of an excess of homologating agent enables to formally install *two* carbon units, namely the methylene fragment of the aziridinyl ring and, the functionalizing exocyclic halomethylenic moiety. Based on mechanistic – experimental evidences two different carbenoids can be advantageously used for the process. Uniformly high yields, superb chemoselectivity and efficiency make the overall sequence a straightforward and modular route towards a new class of chemical entities assembled and functionalized within a unique synthetic event.

Acknowledgements

The University of Vienna is gratefully acknowledged for financial support. L. Ielo and S. Touqeer thank OEAD for postdoctoral and predoctoral grants, respectively. The Authors are indebted to Albemarle Corporation and ABCR Germany for generous gifts of organolithiums and fluoroiodomethane, respectively.

Keywords: Homologation • Aziridines • Carbenoid • Trifluoromethylation • Chemoselectivity.

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Layout 2:

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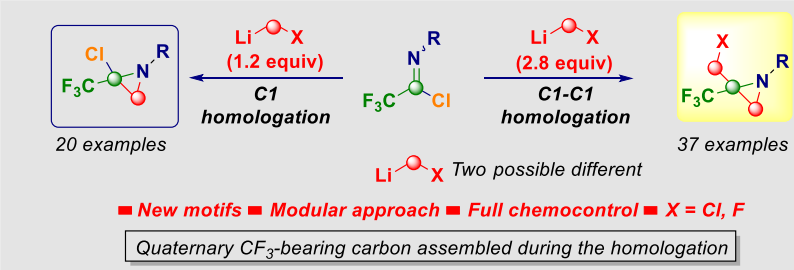

*Laura Ielo, Saad Touqeer, Alexander Roller, Thierry Langer, Wolfgang Holzer and Vittorio Pace**

Telescoped, Divergent, Chemoselective *C1* and *C1-C1* Homologation of Activated Imines Surrogates: A Straightforward Access to Quaternary Chloro- and Halomethyl-trifluoromethyl-aziridines