Carbenoids

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Telescoped, Divergent, Chemoselective C1 and C1-C1 Homologation of Imine Surrogates: Access to Quaternary Chloro- and Halomethyl-Trifluoromethyl Aziridines

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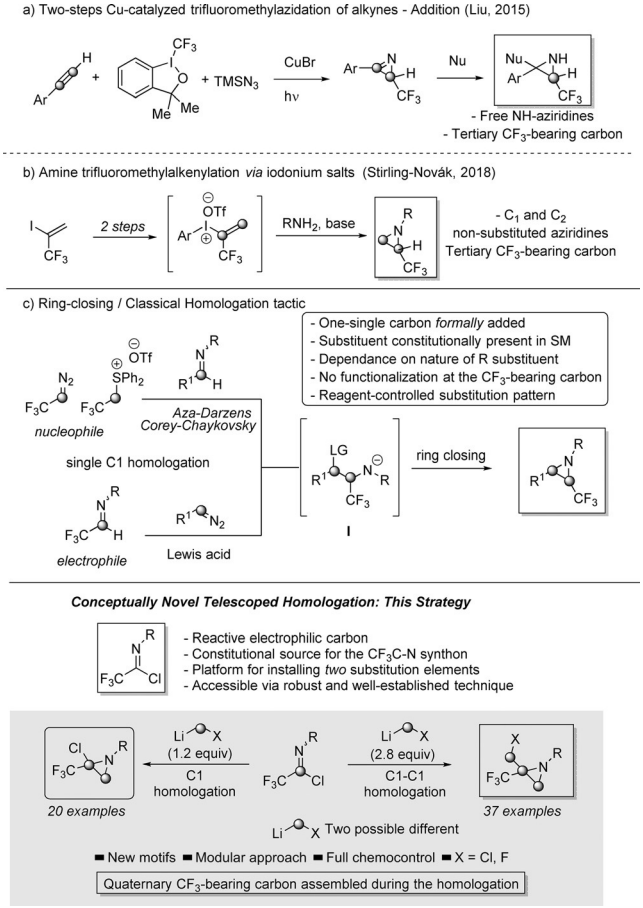
Abstract: *A conceptually novel, high-yielding, mono- or bis-homologation was realized with lithium halocarbenoids and enables the one-step, fully chemocontrolled assembly of a new class of quaternary trifluoromethyl aziridines. Trifluoroacetimidoyl chlorides (TFAICs) act as convenient electrophilic platforms, enabling the addition of either 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 $LiCH_2F$), leads 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 physicochemical properties, thus rendering the scaffold a highly valuable entity across the chemical sciences.[1] Incorporating such a functionality within a three-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-step Cu-catalyzed trifluoromethylazidation of alkynes followed by the addition of nucleophiles to the intermediate azirines (Scheme 1 a),[3] while Stirling and Novák disclosed in 2018 the metal-free alkenylation/cyclization of amines with trifluoroalkenyl iodonium salts (Scheme 1 b).[4] Each of these strategies leads to structurally different motifs, though in both cases tertiary CF_3-bearing carbon atoms are obtained, presenting well-defined relative placement of substituents: Liu's work delivers α-aryl-α-substituted-trifluoromethylaziridines, whereas the Stirling–Novák protocol delivers unsubstituted trifluoromethylaziridines.



Scheme 1. General context of the presented work. LG = leaving group, Tf = trifluoromethanesulfanyl, TMS = trimethylsilyl.

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 1 c).[2a,c] Accordingly, the key intermediate **I** can be accessed by either a C1-homologative transformation carried out with CF_3-nucleophilic synthons on properly activated imines as shown by the groups Carreira,[5]

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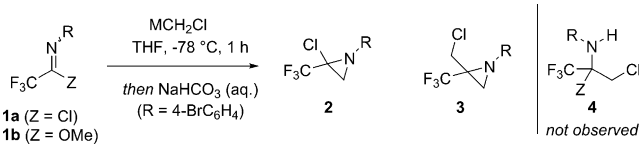
Xiao,[6] and Cahard,[7] or alternatively through the homologation of electrophilic CF_3-containing imines with standard diazo chemistry.[8] However, as a common feature, the homologation event is limited to the transfer of one single-carbon unit per transformation.[9] We realized that accomplishing two 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 using the easily accessible trifluoroacetimidoyl chloride (TFAIC)[10] as the proper electrophilic imine surrogate placeholders for 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.

Recently, our group documented that homologation processes mediated by lithium carbenoids ($LiCH_2X$)[11] might forge complex molecular architectures in an extremely convenient and effective way by simply selecting the reaction conditions,[12] thus making the strategy to a given target flexible and modular.[13] By introducing the unprecedented concept of C1-C1 double homologation, eventually realized with two distinct homologating agents, within a unique chemical event, we present herein a straightforward protocol enabling the construction of unknown α-halo-α-trifluoromethylaziridines and α-halomethyl-α-trifluoromethyl aziridines.[2c,14]

We commenced our investigations by 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 the carbenoid loading to 1.5 and 2.3 equivalents showed the contemporaneous formation of the bis-homologated adduct chloromethylaziridine **3**, though as the minor product (entries 2 and 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 a placeholder for two simultaneous functionalizations, the desired compound **3** was the exclusive reaction product in 91% yield when 2.8 equivalents of the 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 (see mechanistic details). Some additional points merit mention: a) The reaction reaches completion within 1 hour, thus allowing selective access to either 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 and 6); d) Running the reaction in Et_2O led to a reduced yield (entry 7), confirming the preference for the more polar THF; e) Replacing **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.

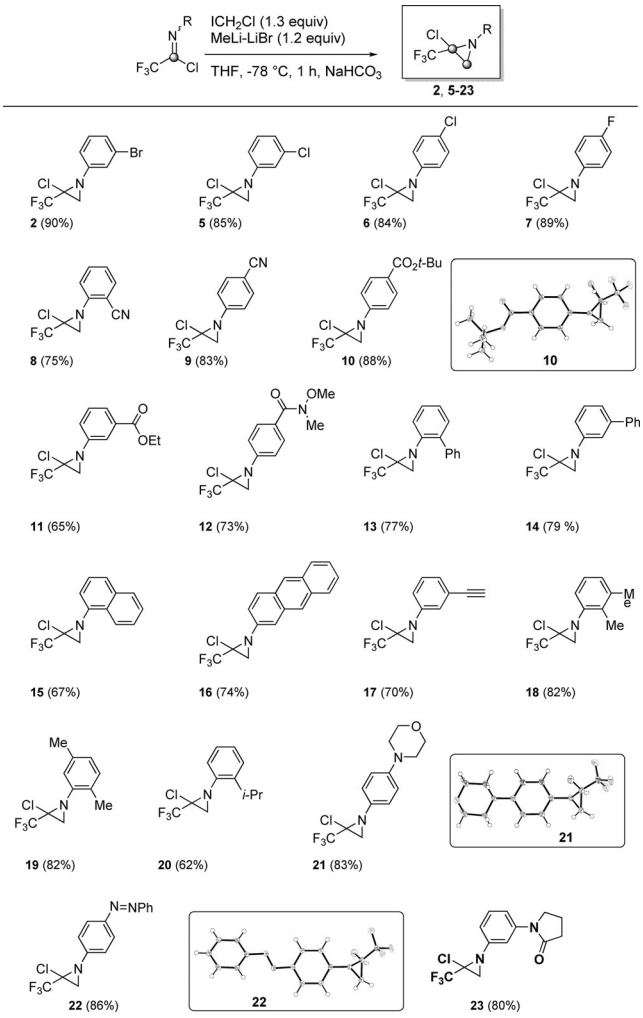


Entry	Homologating agent	Equiv	Yield [%][a]	
			2	**3**
1	$LiCH_2Cl$	1.2	90	<2
2	$LICH_2Cl$	1.5	57	23
3	$LICH_2Cl$	2.3	22	73
4	$LICH_2Cl$	2.8	–	91
5[b]	$ClMgCH_2Cl$	2.8	–	–
6[b,c]	$ClMgCH_2Cl$	2.8	–	–
7[d]	$LICH_2Cl$	2.8	–	82
8[e]	$LiCH_2Cl$	2.8	–	–

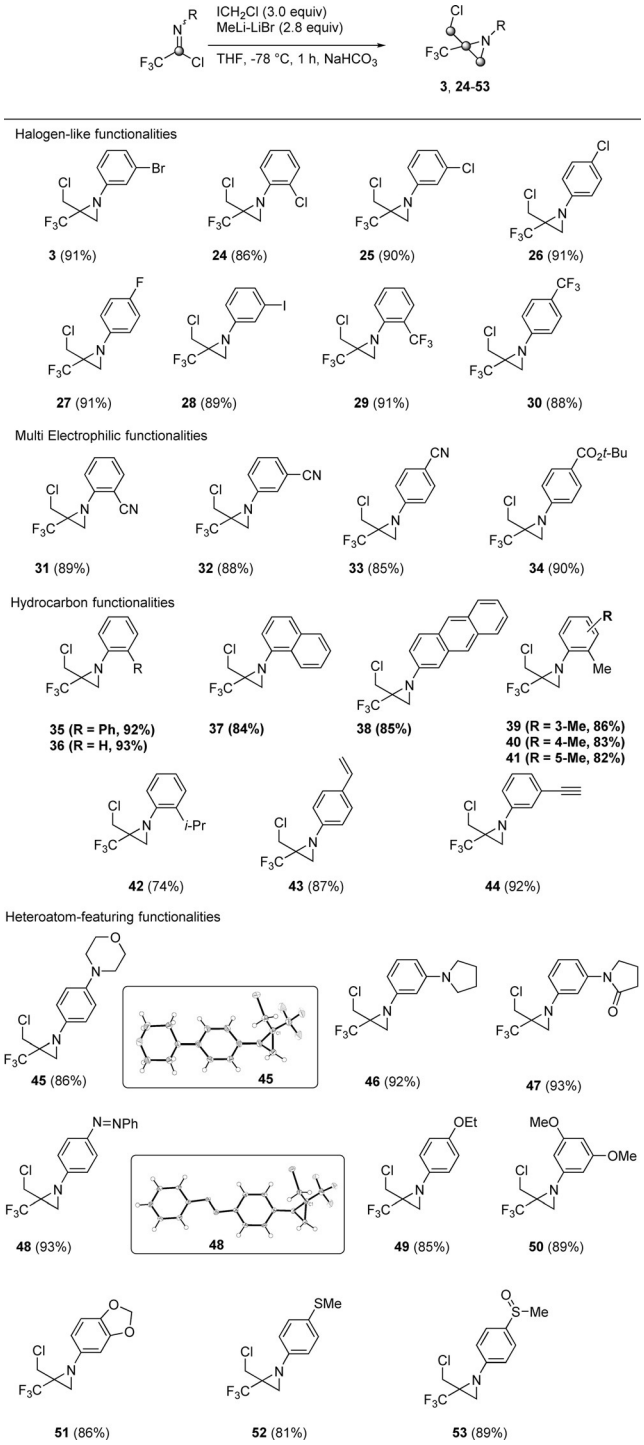
Unless otherwise indicated $LiCH_2Cl$ was generated under Barbier conditions in THF at −78 °C starting from ICH_2Cl and MeLi–LiBr (1.5 M) and **1a** was used as the starting agent. [a] Yield of isolated product. [b] Formed from ICH_2Cl and *i*PrMgCl–LiCl (Ref. [15]). [c] Run at −30 °C. [d] Et_2O was used as the solvent. [e] The compound **1b** was used.

Having determined the reaction conditions for achieving full chemocontrol, the scope of the mono-homologation technique en route to valuable α-chloroaziridines was evaluated (Scheme 2). The protocol is 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 behavior nor their position across the aromatic ring influence the outcome; 2) no concomitant halogen–lithium exchange occurs in systems featuring bromine, chlorine, and fluorine (**2**, **5**–**7**). The superb chemocontrol is clearly evidenced in reactions carried out with substrates presenting functionalities that are 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 at the targeted carbon center. 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.

The conceptually novel C1-C1 double homologation was then applied to the synthesis of α-chloromethyl-α-trifluoromethyl aziridines (Scheme 3). Pleasingly, the optimized reaction conditions found in Table 1 were of general applicability, and thus allowed the straightforward preparation of unknown scaffolds, featuring a quaternary all-substituted carbon center, through a single synthetic operation. TFAICs reacted extremely well, independent of either the electronic or steric properties of the substituents (Scheme 3). Accordingly, all halogens (**3**, **24**–**27**), including the reactive iodine



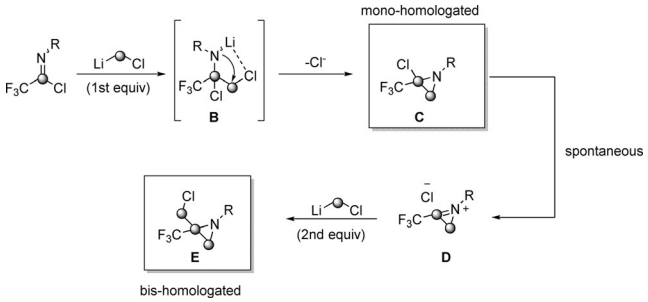
Scheme 2. C1 homologation for preparing chloro-trifluoromethylaziridines. Crystal structures[24] are shown with thermal ellipsoids at 50% probability.



Scheme 3. C1-C1 bis-homologation for preparing chloromethyl trifluoromethylaziridines. Crystal structures[24] are shown with thermal ellipsoids at 50% probability.

(**28**) or the trifluoromethyl group (**29** and **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 selectivity is quite noteworthy since these functionalities are known to be highly susceptible to attack by carbanions. Embodying hydrocarbon functionalities such as aryl (**35**, **37**, and **38**) or aliphatic groups (**39**–**41**) does not alter the efficiency, including a 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] nor abstraction of the acidic proton of the terminal alkyne were observed. A series of nitrogen-containing groups, for example, morpholine (**45**), pyrrolidine (**46**), lactam (**47**), and diazo (**48**), could be placed on the ring, further expanding the scope of the protocol. Remarkably, recrystallization of **48** provided enantiomerically pure (*S*)-**48** as unambiguously ascertained by X-ray structural analysis. Ethers (**49** and **50**) and a 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).

Mechanistically, the telescoped homologation can be rationalized by the expected addition of the first equivalent of $LiCH_2Cl$ to form the tetrahedral intermediate **B** (Scheme 4). Presumably, the internal coordination between

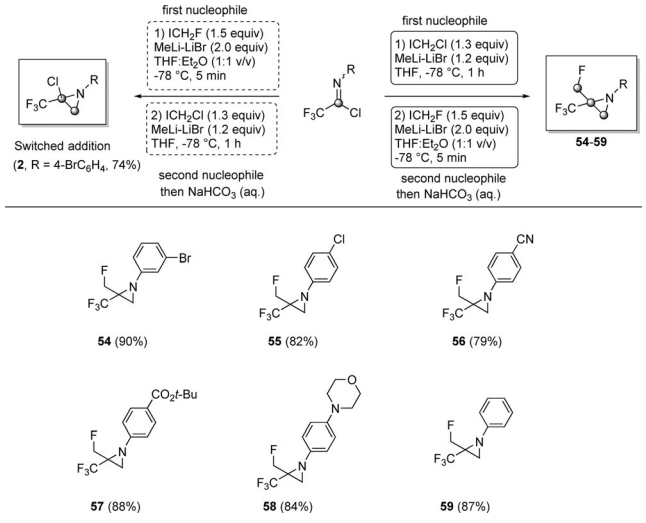


Scheme 4. Plausible mechanism for the C1 and C1-C1 homologations.

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**.

To provide evidence for the mechanistic rationale, a telescoped homologation was accomplished with two different agents, $LiCH_2Cl$ and $LiCH_2F$[18] (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 by a single synthetic operation consisting of the controlled generation and employment of these two carbenoids during the same sequence.

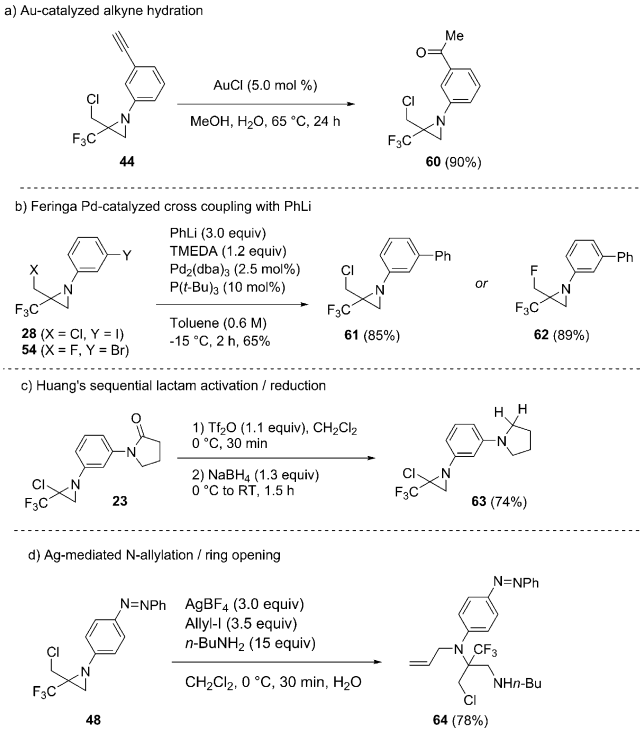
No variation of the reactivity profile of the starting TFAICs was noticed, thus confirming the general outcome discussed for chloromethyl analogues. Importantly and, as a further evidence of the mechanism, exchanging the order of addition of the two carbenoids resulted in the formation of



Scheme 5. Synthesis of fluoromethyl trifluoromethylaziridines by homologation with two different carbenoids. THF = tetrahydrofuran.

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 mono-homologated 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 behavior of these non-previously reported scaffolds (Scheme 6). The



Scheme 6. Manipulation of synthesized compounds. TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

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 (Scheme 6a).[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 (Scheme 6b).[20] The electrophilic activation of the lactam moiety of **23**,[21] followed by in situ reduction under Huang's conditions[22] delivered the corresponding reduced pyrrolidinyl system **63** (Scheme 6c). Finally, the aziridine Ag-mediated ring-opening with an amine in the presence of an allylating agent gave excellent regioselectivity for the 1,2-diamine scaffold **64**, featuring full substitution at the initial aziridine carbon center (Scheme 6d).[23]

In summary, we have documented the assembly of quaternary all-substituted trifluoromethylaziridines by a single synthetic operation consisting of a lithium-halocarbenoid-mediated mono- or bis-homologation of trifluoroace-

timidoyl 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 formal installation of two carbon units, namely the methylene fragment of the aziridinyl ring and the functionalizing exocyclic halomethylenic moiety. Based on mechanistic and experimental evidence two different carbenoids can be advantageously used for the process. Uniformly high yields and 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.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: aziridines · carbenoids · chemoselectivity · homologation · lithium

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[24] CCDC 186913 (**10**), 186914 (**21**), 186911 (**22**), 186915 (**45**), and 186912 (**48**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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