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Homologation of halostannanes with carbenoids: a convenient and straightforward one-step access to α-functionalized organotin reagents†

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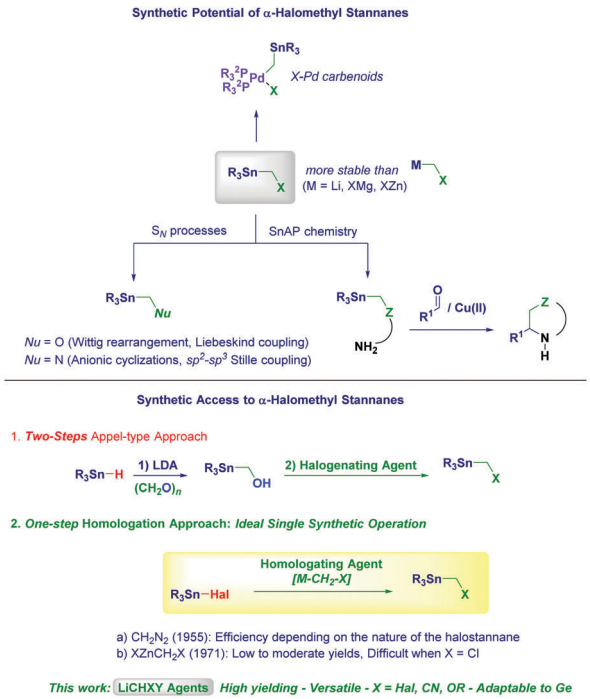
A direct, single synthetic homologative transformation of halostannanes into mono- or di-substituted methyl analogues is documented. Critical for the success of the operation is the excellent nucleophilicity of carbenoid-like methyllithium reagents (LiCHXY, X, Y = halogen, OR, and CN): by simply individuating the reagents' substitution pattern, the desired functionalized fragment is delivered to the electrophile. The wide scope of the protocol is evidenced also in the case of analogous halogermanium compounds. The tandem homologation–quenching with nucleophiles and the use of α-chloroallyllithium is also discussed.

The unique reactivity of the C-Sn bond together with the good stability makes organotin compounds highly versatile entities in chemistry.[1] Accordingly, their use in preparative processes is not limited to pivotal synthetic operations (*in primis* the Stille coupling)[2] but also encompasses fundamental organometallic techniques.[3] In this context, α-halomethyl stannanes (R_3Sn-CH_2-X) represent privileged tin-containing reagents because of the formal analogy with metal carbenoids (M–CH_2–X). In fact, their excellent stability overcomes important limitations of classical metal species (M = Li, MgY, and ZnY) such as α-elimination.[4] As a consequence of this significant advantage, the reactivity portfolio of these stannanes has been considerably exploited in a series of synthetic processes ranging from the equivalence with alkoxymethyl anions[5] to electrophilic carbon units suitable for the preparation of multifunctionalized organotin compounds *via* nucleophilic substitutions.[6] For example, the corresponding α-alkoxy derivatives serve as placeholders for triggering Wittig rearrangements[7] or Liebeskind-type couplings,[8] whereas α-amino analogues could be employed in anionic (or nucleophilic) cyclizations (Scheme 1).[9] Pd-catalyzed sp^2–sp^3 Stille cross-couplings with α-aminomethyl stannanes have been also recently developed by scientists at Merck for accessing anti-HIV molecules.[10] Undoubtedly, the introduction of SnAP (tin amino protocol) reagents by Bode in 2013 – as an elegant alternative to metal-catalyzed cross-couplings for preparing in one step saturated heterocycles from aldehydes – constitutes one of the most versatile uses of α-halomethyl stannanes as precursors of functionalized organometallics.[11] Additionally, the C-X bond of α-halomethyl stannanes can undergo Pd-insertion, thus enabling the access to halopalladio-carbenoids as showcased by Fillion.[12]



Scheme 1 General context of the presented work.

The synthetic potential of α-halomethyl stannanes is rather counterbalanced by the inherent difficulties in accessing them through simple and direct procedures. It seems nowadays that the two-step Appel-type protocol[13] starting from a tin hydride derivative and subsequent halogenation is the preferred technique for these α-halo analogues.[7,14] Cognizant of the strict safety

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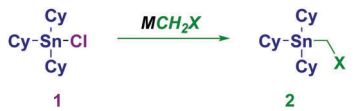
limitations dealing with the use of toxic Sn compounds in chemical processes,[15] we deemed a homologation process of a commercially available halostannane derivative (R_3Sn-X) with a M-CH_2-X reagent would be ideal for the purpose. Initial studies with diazomethane in the 1950s demonstrated the feasibility of the approach, although it was shown to be highly dependent on the substrate.[16] Seyferth also introduced in the early 1970s the use of zinc carbenoids, observing a strict dependence of the success of the transformation on the nature of the carbenoid (*i.e.* the halogen).[17] α-Iodo or α-bromo derivatives could be accessed in modest to moderate yields (30-66%), while α-chloro analogues could be prepared only *via* nucleophilic displacement (AgCl, seven days) starting from the corresponding iodinated compound.

In recent years, our group has documented a series of homologation techniques for introducing into a given carbon or heteroatom electrophile a CH_2X fragment through a single synthetic operation, thus compressing the synthetic sequence to the only required transformation.[18]

Herein, we report the effectiveness of the nucleophilic substitution on halostannanes with lithium carbenoids and related reagents ($LiCH_2X$, X = halogen, OR, and CN) for accomplishing a direct, one-step and straightforward formation of R_3Sn-CH_2-X type reagents. We anticipate the applicability of the protocol to the homologation of analogous organogermanium derivatives. Conceptually, the overall process can be regarded as a transmetallation of Li into Sn or Ge carbenoids, in which the products retain the α-halomethyl unit susceptible to late functionalization.

We selected the aliphatic tri-cyclohexyltin chloride **1** as the model substrate to rapidly evaluate the proposed homologation based strategy (Table 1). Moreover, the scarce commercial availability of the corresponding hydride required for applying the Appel-type protocol could be efficiently overcome. Generating chloromethyllithium ($LiCH_2Cl$) *via* lithium/iodine exchange on ICH_2Cl promoted by MeLi-LiBr under the usual Barbier-type conditions demonstrated the feasibility of the process. Although the reaction with 1.2 equiv. of $LiCH_2Cl$ reached 68% completion, as judged by GC-MS analysis of the crude, the subsequent chromatographic purification on silica gel was troublesome, finally leading to 56% isolated yield of the desired α-chloromethyl stannane **2** (entry 1). Switching to Et_2O was detrimental (entry 2), while by progressively increasing the carbenoid loading up to 2.8 equiv. a quantitative conversion could be reached, thus significantly simplifying the purification procedure to a simple fast column chromatography - 93% isolated yield (entry 4). Attempting the homologation with a more stable (but less nucleophilic) magnesium carbenoid ($ClMgCH_2Cl$-LiCl) resulted in no transformation (entry 5).[19] It is worth observing the chemoselectivity of the process: no deleterious effect originated from the competitive Sn-Li exchange was noticed. As expected, changing ICH_2Cl with ICH_2Br – *ceteris paribus* – generated $LiCH_2Br$,[20] which accomplished the homologation in comparable efficiency (entry 6).

Table 1 Reaction optimization[a]



1 2

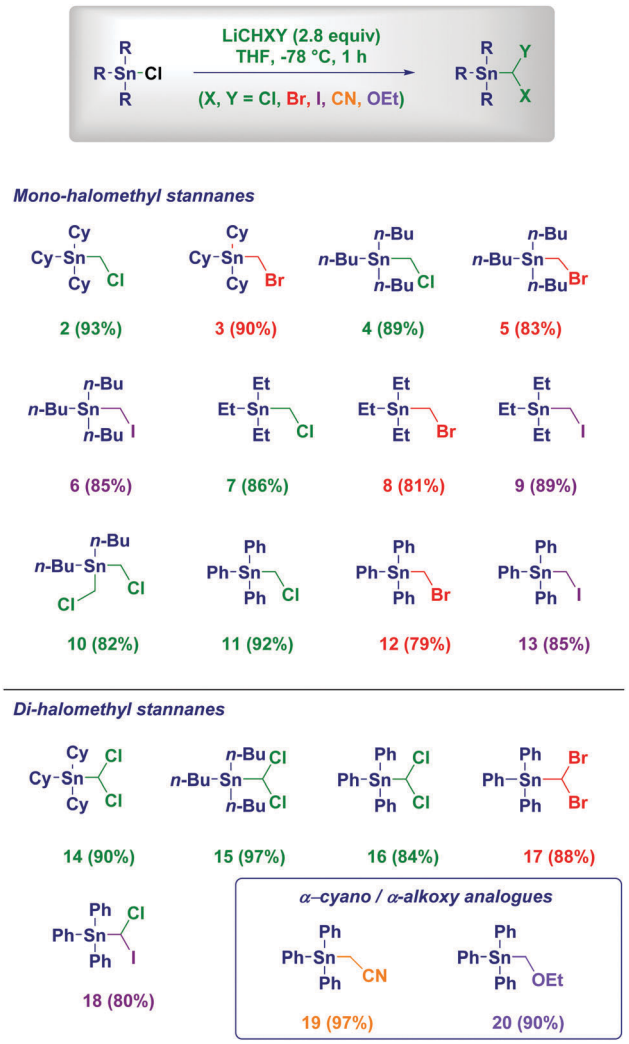
Entry	Carbenoid (equiv.)	Solvent	Conversion[b] (%)	Yield of 2[c] (%)
1	$LiCH_2Cl$ (1.2)	THF	68	56
2	$LiCH_2Cl$ (1.2)	Et_2O	55	31
3	$LiCH_2Cl$ (2.2)	THF	95	83
4	$LiCH_2Cl$ (2.8)	THF	>99	93
5[d]	$ClMgCH_2Cl$-LiCl (2.8)	THF	—	—
6[e]	$LiCH_2Br$ (2.8)	THF	95	90

[a] Otherwise stated, $LiCH_2Cl$ was generated from ICH_2Cl (3.0 equiv.) and MeLi-LiBr (2.8 equiv.) in THF at −78 °C. [b] GC-MS calculated conversion. [c] Yields refer to isolated and purified compounds. [d] Formed from ICH_2Cl (3.0 equiv.) and i-PrMgCl-LiCl (2.8 equiv.) in THF at −78 °C under non-Barbier conditions. [e] Formed from ICH_2Br (3.0 equiv.) and MeLi-LiBr (2.8 equiv.) in THF at −78 °C under Barbier conditions.

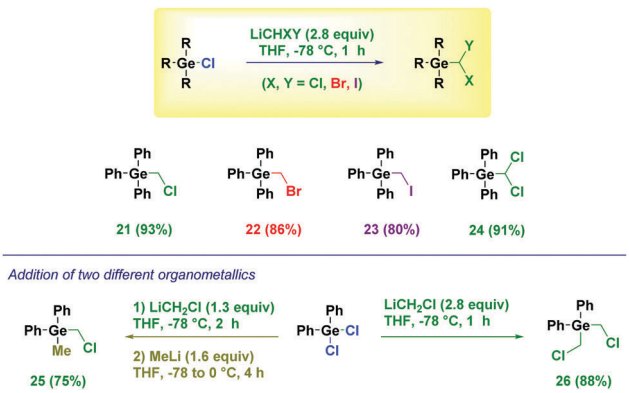
Having disclosed the optimal conditions for the one-step homologation of halostannanes into α-halomethyl stannanes, we then investigated the scope of the reaction (Scheme 2). Aliphatic halostannanes proved to be excellent substrates for the transformation, enabling the formation of all the targeted α-chloro, α-bromo and α-iodo analogues in excellent yields through a single synthetic operation (**2–9**). Notably, a dihalostannane smoothly undergoes the substitution of both halogens, affording the bis-(chloromethyl) derivative **10** in 82% yield, previously obtained in 40% yield with the Appel method.[21] Switching to aryl-stannanes was possible without compromising the efficiency of the process, as indicated by the reactions with $LiCH_2Cl$, $LiCH_2Br$ and $LiCH_2I$, respectively (**11–13**). It is worth mentioning the higher performance of the Li carbenoid approach compared to the Zn species which afforded **12** in 30% yield.[22] By adopting a deprotonation strategy on dihalomethanes of type XCH_2Y, the corresponding dihalolithium carbenoids were easily prepared[23] and then reacted with the halostannanes giving the corresponding dihalomethyl tin compounds (**14–18**) whose synthesis proved to be challenging with other methodologies.[24] The precise control of the chemoselectivity of the process is further documented by the one-step preparation of the not previously reported analogue **18** featuring two different halogens on the attacking carbon. Carbenoid-like reagents such as $LiCH_2CN$ (generated *via* MeCN deprotonation, **19**)[25] and $LiCH_2OEt$ (generated *via* the Yus' reductive lithiation of $ClCH_2OEt$, **20**)[26] could be advantageously employed in the process, thus expanding the synthetic potential of the methodology.

We were pleased to find that the protocol showcased its versatility in the homologation of halogermanium derivatives, as well (Scheme 3).[27] Indeed, these starting materials afforded the corresponding halo- (**21–23**) or dihalo- (**24**) methyl derivatives in high yields. The fine tuning of the stoichiometry enables the addition of two different lithium reagents ($LiCH_2Cl$ and MeLi) giving the mixed aromatic–aliphatic halogermanium **25**. Otherwise, double substitution with the same $LiCH_2Cl$ was noticed (**26**) in analogy to the above observed tin analogue.

With the aim to gain full insight into the potential of these easily synthesized building blocks featuring a reactive electrophilic carbon, we designed an effective *in situ* functionalization (Scheme 4). Upon quenching the homologation reaction with acidic water, a solution of *N*-, *O*- or *S*-nucleophilic species was

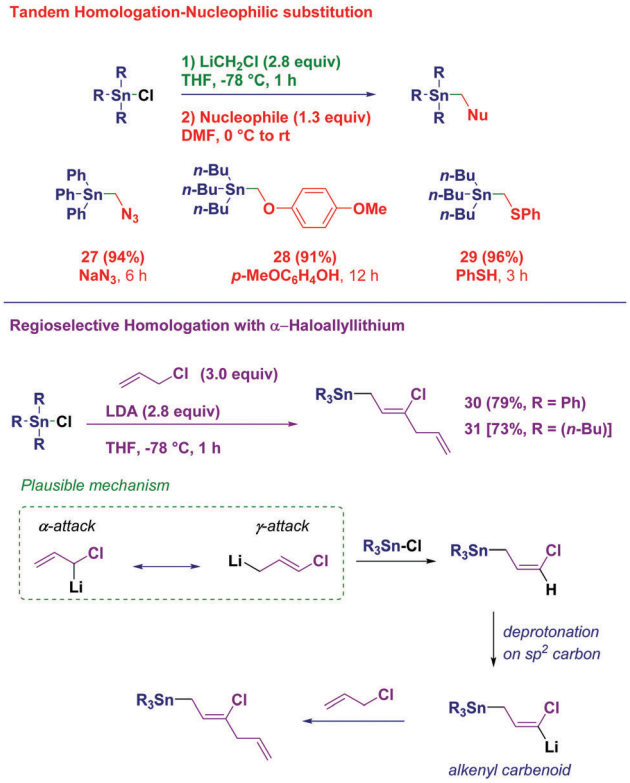


Scheme 2 Chemoselective homologative α- and α,α-difunctionalization of halostannanes.



Scheme 3 Chemoselective homologative α- and α,α-difunctionalization of halogermanes.

added to the reaction mixture directly leading to α-azidomethyl (**27**), α-aryloxymethyl (**28**) and α-arylthiomethyl stannanes, respectively (**29**). Finally, we were intrigued by the use of the more complex α-chloroallyl lithium as the homologating reagent.[28]



Scheme 4 Immediate derivatization with added nucleophiles and use of α-chloroallyllithium as the homologation reagent.

This nucleophilic reagent prepared *via* the deprotonation of allyl chloride with LDA may in principle display a dual reactivity towards a given electrophilic partner (α- or γ-attack). The homologation process occurring in a genuine regioselective γ-fashion did not stop at the expected chlorovinyl product. It further underwent lithiation giving an alkenyl-type carbenoid,[29] which could realize an S_N process on the allyl chloride, finally affording the bis-olefinic structures **30** and **31**. Overall, through a single synthetic operation the full control of the inserting *six* carbon units can be achieved.

In summary, we report a direct nucleophilic substitution of halostannanes and halogermanes with lithium carbenoid-like reagents including $LiCH_2Hal$, LiCHHalHal', $LiCH_2OR$ and $LiCH_2CN$ to obtain through a single operation highly valuable α- and α,α-disubstituted methyl derivatives. The method represents a significant advancement compared to the commonly used two-step Appel-type protocol or the previously known low efficient homologation strategies dealing with the use of diazomethane or zinc carbenoids. The derivatization of the formed products and the use of a more challenging carbenoid further highlight the synthetic potential.

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Conflicts of interest

There are no conflicts to declare.

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