SYNLETT
Spotlight

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research
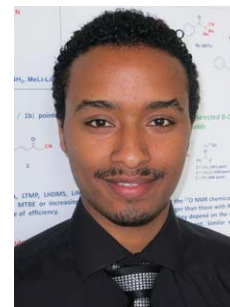
Chloromethyllithium

Compiled by Ashenafi Damtew Mamuye[a,b]

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Introduction

Chloromethyllithium ($LiCH_2Cl$) is a synthetically useful reagent belonging to the category of carbenoids, which are known to exhibit an ambiphilic behavior ranging from nucleophilic (at low temperatures) to electrophilic (at higher temperatures). This fact can be deduced by the resonance structures represented in Scheme 1, in which the extreme ionization of the polar bonds could lead, in principle, to the carbanionic (1a) or carbocationic (1b) species.[1] Chloromethyllithium can be prepared via a halogen–lithium exchange reaction on a given dihalomethane. Iodo- and bromo-chloromethane (ICH_2Cl and $BrCH_2Cl$) are the ideal precursors jointly with methyllithium–lithium bromide complex or n-butyllithium.[2] It is highly unstable except at very low temperatures (–78 °C or below); however, performing the reaction in the presence of the electrophile (i.e. Barbier-type conditions) allows to realize efficient processes. The presence of lithium halides and the use of ethereal-type solvents (THF or diethyl ether) had beneficial effects on its stability.[3]
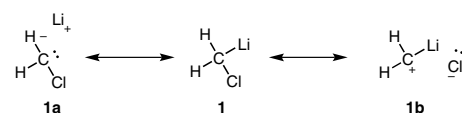

Scheme 1 Ambiphilicity of chloromethyllithium

Interestingly, Le Floch and co-workers showed that by replacing the two hydrogens with electron-withdrawing groups, it is possible to dramatically improve the stability of the corresponding carbenoid.[4]

Abstracts

(A) Carbonyl-type compounds have been homologated with lithium carbenoids. The addition of $LiCH_2Cl$ to an aldehyde or a ketone (2) after mild acidic treatment provides the corresponding halohydrin (3) in high yields. Interestingly, when the reaction is allowed to reach room temperature, an intramolecular nucleophilic displacement takes place, thus affording directly the epoxide 4.[5] The strategy has very recently been applied to cyclic α,β-unsaturated enones to access chloromethyl allylic alcohols in high yield.[6]
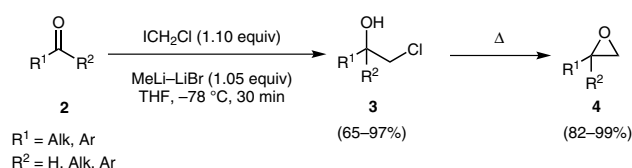
(B) Concellón and co-workers conveniently used a strategy for the preparation of β-chloro amines (7,7a) starting from activated N-arylsulfonamido imines 5.[7]
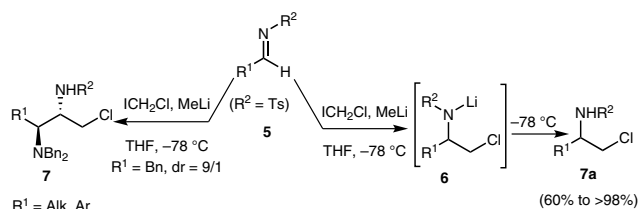
(C) Very recently Pace and co-workers reported the treatment of iso-cyanates **8** with LiCH₂Cl to access versatile *N*-chloro acetamides **9** in high yields even in the presence of optically active starting materials which did not racemize during the process.[8]
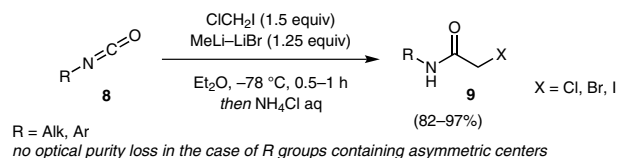

(D) A general method for the synthesis of α-arylamino-α′-chloro ke-tones in the presence of various substituents on the nitrogen atom has been developed by Pace et al. who employed Weinreb amides[9] **10** as electrophilic starting materials for the chloromethylation.[3] Remark-ably, the use of such amides could be successfully extended to the synthesis of α′-halo-α,β-unsaturated ketones **13** for which the use of esters provided exclusively the double addition products (i.e. carbi-nols).[10] In this regard, the high stability under the reaction conditions of tetrahedral intermediate **12a**, formed upon the addition of chloro-methyllithium to Weinreb amide **12**, prevents the deleterious double addition of the reagent.
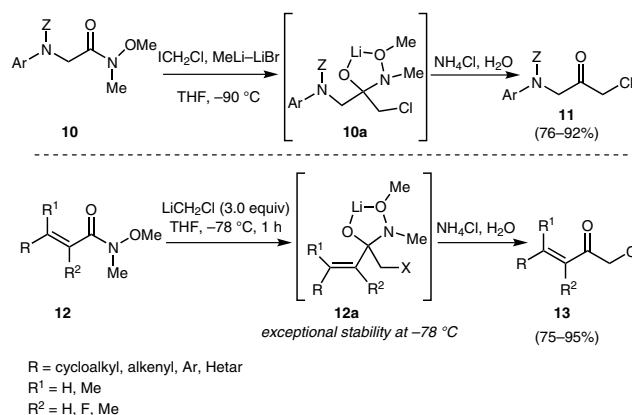
(E) Simpkins and co-workers realized an efficient synthesis of the key intermediate **15** needed for the total synthesis of fumagillol **16**. Inter-estingly, the chloromethylation of the complex ketone **14** proceeded in good yield and dr.[11]
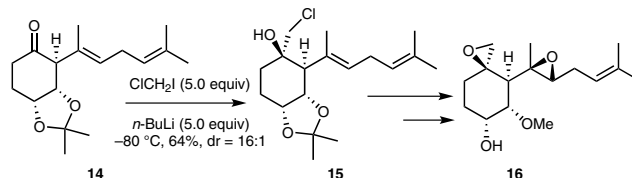
(F) Matteson pioneered the chemistry of monohalolithium carbenoids with boronic esters.[2c] Recently, Aggarwal reported the homologation of tertiary boronic esters **17** with chloromethyllithium followed by ox-idation to produce the corresponding enantiopure alcohols **18**. In ad-dition, they rationalized that the formation of **18** or **19** depends on the intermediate complex formed from **17** and chloromethyllithium, which can undergo O-migration (giving **19**) or C-migration.[12] By switching to LiCH₂Br the undesired O-migration can be minimized.
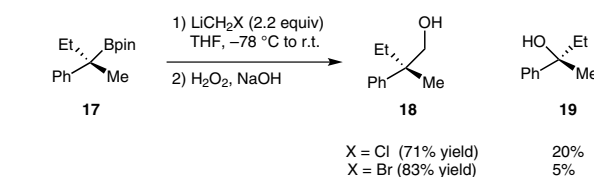
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