

# SYNLETT Spotlight

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

## Chloromethylithium

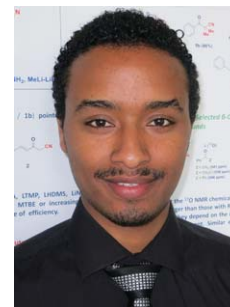
Compiled by Ashenafi Damtew Mamuye<sup>a,b</sup>

Ashenafi Damtew Mamuye was born in Alem-Ketema, Ethiopia in 1984. He completed his B.Sc. in Applied Chemistry at the University of Gondar (2006) and received his M.Sc. in Medicinal Chemistry from Addis Ababa University (2009). He worked as teaching assistant from 2009 to 2011 in Ethiopia. In 2012 he joined the University of Sassari to undertake doctoral studies in Chemical Science and Technology under the supervision of Prof. Ugo Azzena. Starting from October 2013, he is a visiting PhD student at the University of Vienna under the supervision of Dr. Vittorio Pace and Prof. Wolfgang Holzer. His research focuses on  $\alpha$ -substituted organolithiums (e.g. carbenoids), arene-catalyzed lithiation, and pyrazole chemistry.

<sup>a</sup> Department of Pharmaceutical Chemistry - Division of Drug Synthesis, University of Vienna, Althanstrasse 14, 1090 Vienna, Austria

<sup>b</sup> Dipartimento di Chimica, Università di Sassari, I-07100-Sassari, Italy

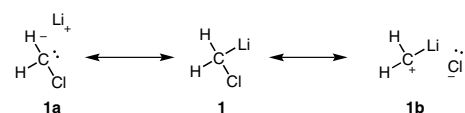
E-mail: ashenafi.mamuye@univie.ac.at



### Introduction

Chloromethylithium ( $\text{LiCH}_2\text{Cl}$ ) 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.<sup>1</sup> Chloromethylithium can be prepared via a halogen–lithium exchange reaction on a given dihalomethane. Iodo- and bromo-chloromethane ( $\text{ICH}_2\text{Cl}$  and  $\text{BrCH}_2\text{Cl}$ ) are the ideal precursors jointly with methylithium–lithium bromide complex or *n*-butyllithium.<sup>2</sup> It is highly unstable except at very low temperatures ( $-78\text{ }^\circ\text{C}$

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 etheral-type solvents (THF or diethyl ether) had beneficial effects on its stability.<sup>3</sup>

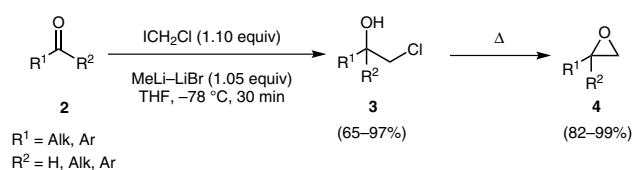


Scheme 1 Ambiphilicity of chloromethylithium

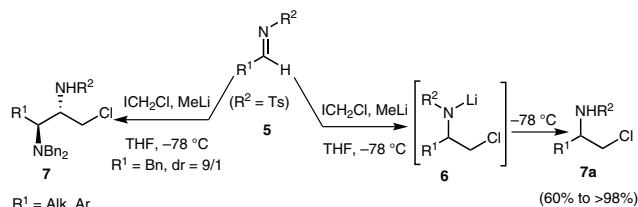
Interestingly, Le Floch and co-workers showed that by replacing the two hydrogens with electron-withdrawing groups, it is possible to dramatically improve the stability of the corresponding carbenoid.<sup>4</sup>

### Abstracts

(A) Carbonyl-type compounds have been homologated with lithium carbenoids. The addition of  $\text{LiCH}_2\text{Cl}$  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**.<sup>5</sup> The strategy has very recently been applied to cyclic  $\alpha,\beta$ -unsaturated enones to access chloromethyl allylic alcohols in high yield.<sup>6</sup>



(B) Concellón and co-workers conveniently used a strategy for the preparation of  $\beta$ -chloro amines (**7,7a**) starting from activated *N*-arylsulfonamido imines **5**.<sup>7</sup>



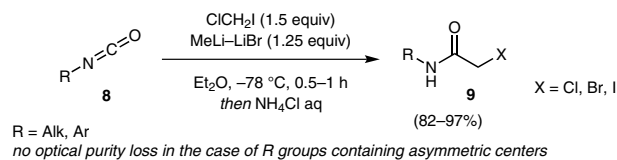
SYNLETT 2014, 25, 2814–2815

Advanced online publication: 05.11.2014

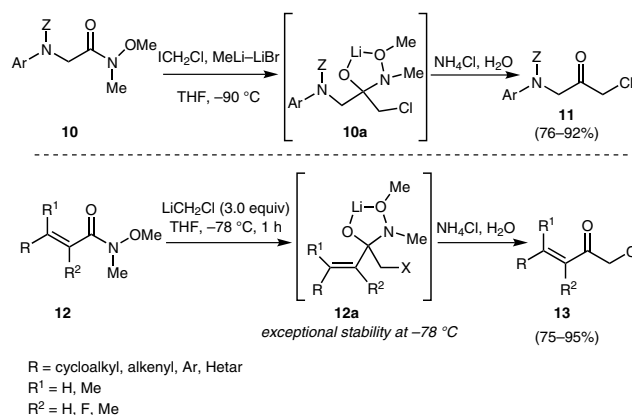
DOI: 10.1055/s-0034-1379442; Art ID: st-2014-v0496-v

© Georg Thieme Verlag Stuttgart · New York

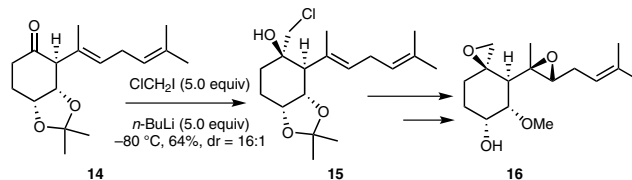
(C) Very recently Pace and co-workers reported the treatment of isocyanates **8** with  $\text{LiCH}_2\text{Cl}$  to access versatile *N*-chloro acetamides **9** in high yields even in the presence of optically active starting materials which did not racemize during the process.<sup>8</sup>



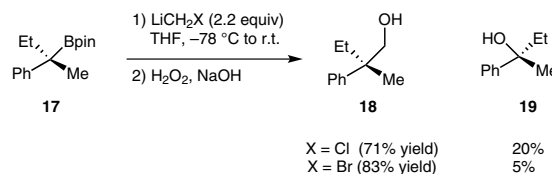
(D) A general method for the synthesis of  $\alpha$ -arylamino- $\alpha'$ -chloro ketones in the presence of various substituents on the nitrogen atom has been developed by Pace et al. who employed Weinreb amides **10** as electrophilic starting materials for the chloromethylation.<sup>3</sup> Remarkably, the use of such amides could be successfully extended to the synthesis of  $\alpha'$ -halo- $\alpha,\beta$ -unsaturated ketones **13** for which the use of esters provided exclusively the double addition products (i.e. carbinols).<sup>10</sup> In this regard, the high stability under the reaction conditions of tetrahedral intermediate **12a**, formed upon the addition of chloromethyl lithium 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**. Interestingly, the chloromethylation of the complex ketone **14** proceeded in good yield and dr.<sup>11</sup>



(F) Matteson pioneered the chemistry of monohalolithium carbenoids with boronic esters.<sup>2c</sup> Recently, Aggarwal reported the homologation of tertiary boronic esters **17** with chloromethyl lithium followed by oxidation to produce the corresponding enantiopure alcohols **18**. In addition, they rationalized that the formation of **18** or **19** depends on the intermediate complex formed from **17** and chloromethyl lithium, which can undergo O-migration (giving **19**) or C-migration.<sup>12</sup> By switching to  $\text{LiCH}_2\text{Br}$  the undesired O-migration can be minimized.



## References

- (1) For seminal studies, see: (a) Köbrich, G.; Akhtar, A.; Ansari, F.; Breckoff, W. E.; Büttner, H.; Drischel, W.; Fischer, R. H.; Flory, K.; Fröhlich, H.; Goyert, W.; Heinemann, H.; Hornke, I.; Merkle, H. R.; Trapp, H.; Zündorf, W. *Angew. Chem. Int. Ed.* **1967**, *6*, 41. For recent reviews, see: (b) Pace, V. *Aust. J. Chem.* **2014**, *67*, 311. (c) Capriati, V.; Florio, S. *Chem. Eur. J.* **2010**, *16*, 4152. (d) Boche, G.; Lohrenz, J. C. W. *Chem. Rev.* **2001**, *101*, 697.
- (2) (a) Sadhu, K. M.; Matteson, D. S. *Tetrahedron Lett.* **1986**, *27*, 795. (b) Tarhouni, R.; Kirschleger, B.; Rambaud, M.; Villieras, J. *Tetrahedron Lett.* **1984**, *25*, 835. (c) Matteson, D. S.; Majumdar, D. *J. Am. Chem. Soc.* **1980**, *102*, 7588.
- (3) Pace, V.; Holzer, W.; Verniest, G.; Alcántara, A. R.; De Kimpe, N. *Adv. Synth. Catal.* **2013**, *355*, 919. See also ref. 2b.
- (4) Cantat, T.; Jacques, X.; Ricard, L.; Le Goff, X. F.; Mézailles, N.; Le Floch, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 5947.
- (5) Sadhu, K. M.; Matteson, D. S. *Tetrahedron Lett.* **1986**, *27*, 795.
- (6) Pace, V.; Castoldi, L.; Holzer, W. *Adv. Synth. Catal.* **2014**, *356*, 1761.
- (7) (a) Concellón, J. M.; Rodríguez-Solla, H.; Simal, C. *Org. Lett.* **2008**, *10*, 4457. (b) Concellón, J. M.; Rodríguez-Solla, H.; Bernad, P. L.; Simal, C. *J. Org. Chem.* **2009**, *74*, 2452.
- (8) (a) Pace, V.; Castoldi, L.; Holzer, W. *Chem. Commun.* **2013**, *49*, 8383. (b) Pace, V.; Castoldi, L.; Mamuye, A. D.; Holzer, W. *Synthesis* **2014**, *46*, 2897.
- (9) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. (b) Balasubramaniam, S.; Aidhen, I. S. *Synthesis* **2008**, 3707. (c) Pace, V.; Castoldi, L.; Alcántara, A. R.; Holzer, W. *RSC Adv.* **2013**, *3*, 10158. For a highlight on the activation strategies of amides towards organometallics, see: (d) Pace, V.; Holzer, W.; Olofsson, B. *Adv. Synth. Catal.* **2014**, in press (DOI: 10.1002/adsc.201400630). (e) Pace, V.; Holzer, W. *Aust. J. Chem.* **2013**, *66*, 507.
- (10) Pace, V.; Castoldi, L.; Holzer, W. *J. Org. Chem.* **2013**, *78*, 7764.
- (11) Hutchings, M.; Moffat, D.; Simpkins, N. S. *Synlett* **2001**, 661.
- (12) Sonawane, R. P.; Jheengut, V.; Rabalakos, C.; Larouche-Gauthier, R.; Scott, H. K.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2011**, *50*, 3760.