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Chemoselective Additions of Chloromethyllithium Carbenoid to Cyclic Enones: A Direct Access to Chloromethyl Allylic Alcohols

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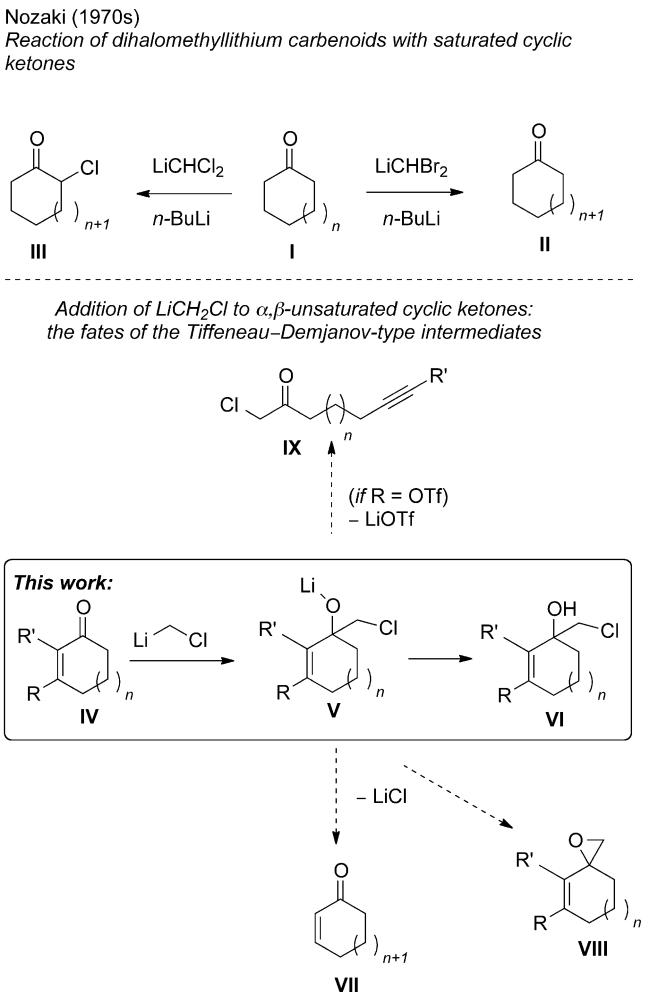
Abstract: Chloromethyllithium carbenoid has been chemoselectively added to cyclic enones (5-, 6- and 7-membered systems, including two natural products) to provide chloromethyl allylic alcohols. Under the optimized reaction conditions neither concomitant (*n*+*1*) homologation nor conjugate addition or Simmons–Smith-like cyclopropanation takes place. The presence of LiBr is estimated to play a dual role, namely as a carbenoid stabilizer and mild Lewis acid activator of the C=O group. Notably, the mesomeric effect caused by β-heteroatom-containing substituents promotes the attack of the reagent at the most activated position.

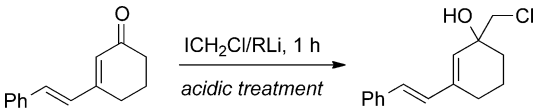
Keywords: allylic alcohols; chemoselectivity; chloro compounds; enones; lithium carbenoids

Cyclic ketones are ubiquitous motifs in nature and from a synthetic perspective they constitute versatile building blocks susceptible of multiple transformations.[1] In particular, the reaction with functionalized carbon nucleophiles (e.g., sulphur ylides,[2] diazo compounds[3]) has been frequently employed as a useful strategy to access homologated structures such as epoxides[4] or (*n*+*1*) cyclic units.[5] In this sense, such reactions constitute effective alternatives to the classic Tiffeneau–Demjanov reaction[6] which, despite its synthetic potential, is not straightforward provided that it is a multi-step route.[6d,7] Indeed, in this scenario a prominent position is occupied by lithium carbenoid reagents[8] pioneered by Nozaki and co-workers who developed in the 1970s a series of useful protocols to access the aforementioned homologated *saturated* structures.[9] In these seminal works, they showed that upon reaction of a cyclic ketone (**I**) with dihalomethyllithium reagents (i.e., $LiCHCl_2$ or $LiCHBr_2$) followed by the so-called β-oxido carbenoid rearrangement in the presence of a lithium base, it is possible to obtain a homologated α-chloro ketone (**III**) or a simple homologated ketone (**II**), respectively (Scheme 1, *top*).[8c,10] On the other hand, the employment of monohalomethyllithium carbenoids (e.g.,



Scheme 1. Context of the presented work.

Table 1. Reaction optimization.[a]



1 **2**

Entry	ICH_2Cl (equiv.)	RLi (equiv.)	Solvent	Temp. [°C]	Yield of **2** [%][b]
1	2.0	MeLi-LiBr (1.5)	THF	−78	62
2	3.0	MeLi-LiBr (2.5)	THF	−78	79
3	4.5	MeLi-LiBr (4.0)	THF	−78	88
4	4.5	MeLi-LiBr (4.0)	THF	−70	71
5	4.5	MeLi-LiBr (4.0)	THF	−60	49
6	4.5	MeLi-LiBr (4.0)	THF	−95	91
7	4.5	MeLi-LiBr (4.0)	Et_2O	−78	84
8	4.5	MeLi-LiBr (4.0)	MTHF	−78	70
9	4.5	MeLi-LiBr (4.0)	CPME	−78	66
10	4.5	MeLi-LiBr (4.0)	Trapp mixture	−78	80
11	4.5	MeLi-LiBr (4.0)	THF:Et_2O	−78	93
12	4.5	MeLi (4.0)	THF	−78	35

[a] Reactions time: 1 h.
[b] Isolated yields.

$LiCH_2X$)[11] in analogous processes has been practically limited to the formation of epoxides starting from *saturated* cyclic ketones,[12] leaving almost unexplored in-depth investigations on their reactivity with multifunctionalized structures such as α,β-unsaturated (cyclic) ketones.[13] In the course of a currently ongoing project in our group focused on the use of such reagents for the homologation of electrophilic substrates such as carboxylic acid derivatives (Weinreb amides/esters)[14] and isocyanates,[15] we have been attracted by the possibility to access cyclic allylic alcohols incorporating at the quaternary carbon a reactive chloromethylenic group. Although conceptually simple, the envisaged synthetic operation had to consider the possible decomposition pathways which can occur on the Tiffeneau–Demjanov-type tetrahedral intermediate (**V**, Scheme 1, *bottom*): a) the transformation into the homologated ketone of type **VII** by expulsion of the halogen atom and transposition – in analogy to diazomethane-based ring enlargement operations;[16] b) the ring closure *via* an internal displacement of the chlorine atom carried out by the highly nucleophilic lithium alkoxide to give the corresponding epoxide (**VIII**), similarly to Corey–Chaykovsky processes.[2a,5b,17] In addition, c) in the case of enones like vinylogous carboxylic acid triflates (**IV** with R = OTf), the possibility exists to promote highly efficient tandem nucleophilic addition–fragmentation reactions to provide alkynyl ketones **IX**, as recently exploited by Dudley and co-workers[18] as an alternative to Eschenmoser–Tanabe processes.[19] Finally, we considered as another possible shortcoming the inherent known tendency of lithium carbenoids to promote cyclopropanation-type reactions with olefins.[20]

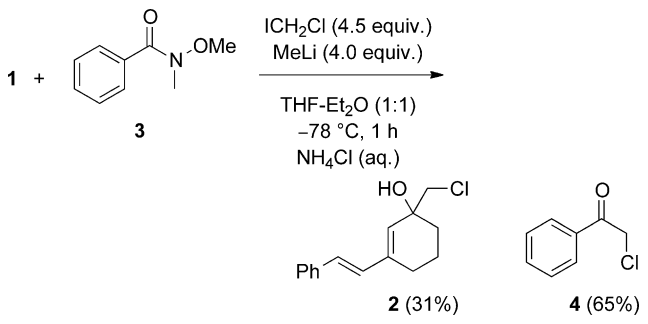
In this work, we disclose a chemoselective 1,2-addition of $LiCH_2Cl$ to cyclic enones. Significantly, under the optimized reaction conditions, it is possible to access exclusively the adduct arising from the addition of the carbenoid to the *most* activated carbon atom of the cycle thus, providing an easy access to tertiary cyclic allylic alcohols without any contaminating side-product such as epoxides or homologated ketones. This procedure has been applied to five-, six- and seven-membered enones including fused natural products structures. The reaction is tolerant to sensitive olefins and/or other functionalities susceptible to carbenoids. A mechanistic explanation of the different behaviors towards the reagents displayed by β-oxo-, β-thio- and β-aza-type substituted cyclic enones is provided.

As the model reaction we selected the challenging enone **1** bearing two conjugated olefinic moieties and thus, susceptible not only to cyclopropanation but also to 1,4- or 1,6-conjugate additions, which have been previously observed with carbenoid reagents.[21] Upon generation of the $LiCH_2Cl$ carbenoid in the presence of **1** through the reaction of MeLi-LiBr (1.5 equiv.) with ICH_2Cl (2.0 equiv.) it was possible to obtain the chlorohydrin **2** in a satisfactory 62% yield after 1 h (Table 1, entry 1). By increasing the amount of carbenoid up to 4 equiv., the desired product could be obtained in an excellent 88% yield without needing to perform any additional purification (entry 3). Raising the temperature up to −60 °C resulted in decreased yields (entries 4 and 5), whereas at −95 °C only a minimal gain was observed (entry 6). Thus, performing the reaction at −78 °C constitutes a good compromise between an easy experimental feasibility

and reaction efficiency. The solvent effect was also noticeable: we observed that a 1:1 v/v mixture of THF and diethyl ether maximizes the yield (entry 11) compared to media constituted by these solvents not mixed (entries 3 and 7) or by the use of the Trapp mixture[22] (THF:Et_2O:*n*-pentane, 2:2:1, v/v) which is frequently employed in organometallic reactions (entry 10). Analogously, the formation of the highly sensitive carbenoid species is significantly decreased in non-optimal coordinating solvents such as 2-methyltetrahydrofuran[23] (MTHF, entry 8) and cyclopentyl methyl ether (CPME, entry 9).

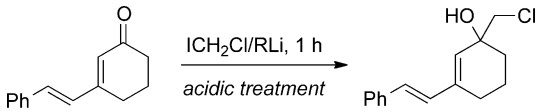
Notably, the presence of a mild Lewis acid such as LiBr is crucial for the successful outcome of the reaction. Indeed, it is now well established that such a salt stabilizes the carbenoid species by preventing its decomposition into a carbene through a coordinative effect with $LiCH_2Cl$.[12a,24] However, by generating the latter (4 equiv.) in the absence of LiBr (i.e., use of simple MeLi ethereal solution), compound **2** could be obtained in only 35% yield after 1 h (entry 12). This somewhat surprising result prompted us to run a control experiment in the presence of a Weinreb amide (**3**) which, as we reported recently,[14] is known to react with this carbenoid (Scheme 2). Thus, by treating an equimolar mixture of **1** and **3** with $LiCH_2Cl$ we could isolate chlorohydrin **2** and chloro ketone **5** in 31% and 65% yields, respectively. Based on this result, we concluded that although the generation of the carbenoid is not maximized (for the lack of the coordinating effect of LiBr) its formation is still effective and thus, the beneficial activity of the bromide should be found predominantly in its mild Lewis acidic activating effect towards the carbonyl of the enone.

Subsequently, we observed that the generation of the carbenoid through the slow addition (5 min) of MeLi-LiBr complex to the solution of ICH_2Cl performs better than the addition of simple MeLi solution to a mixture of ICH_2Cl and LiBr (Table 2, entries 1 and 2). As a further confirmation of the pivotal double role of LiBr (carbenoid stabilizer and carbonyl activator), the use of a substoichiometric amount



Scheme 2. Control experiment in the presence of a Weinreb amide: study of the effect of LiBr.

Table 2. Effect of additives on the chloromethylation of cyclic enone **1**.[a]

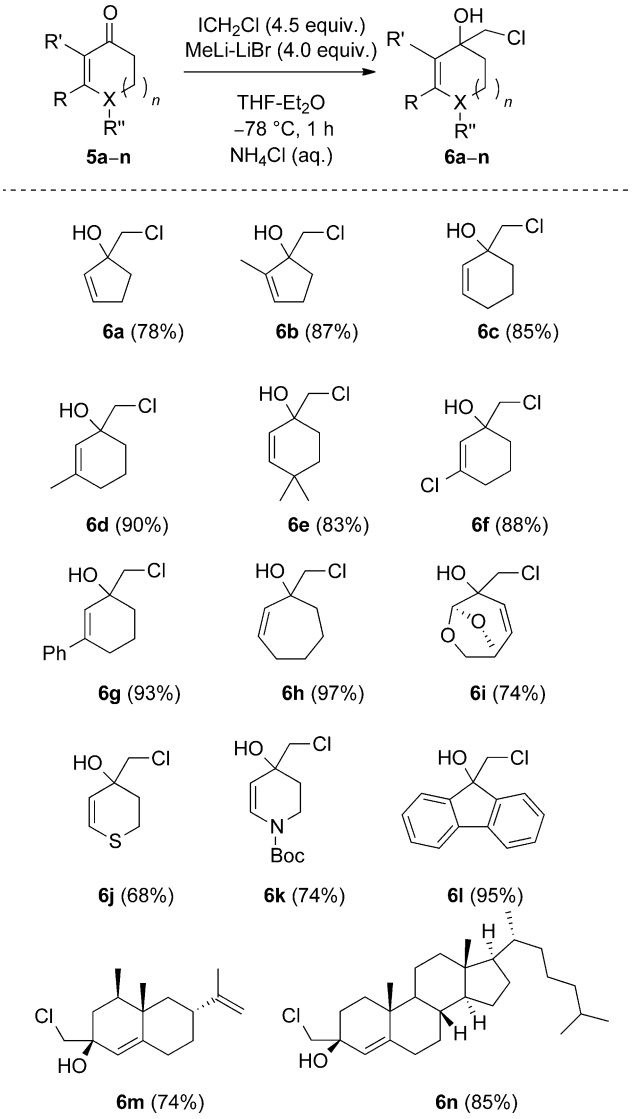


Entry	Additive	Equiv.	Yield of **2** [%][b]
1	LiBr[c]	4.0	93
2	LiBr[d]	4.0	82
3	LiBr[c]	0.2	74
4	$MgBr_2$	4.0	68
5	$MgBr_2$-etherate	4.0	75
6	MgI_2	4.0	72
7	$Mg(ClO_4)_2$	4.0	77
8	$Mg(OTf)_2$	4.0	74
9	$ZnBr_2$	4.0	66
10	ZnI_2	4.0	69
11	$Zn(OTf)_2$	4.0	64

[a] Reaction time: 1 h.
[b] Isolated yields.
[c] From MeLi-LiBr ethereal solution.
[d] Added as a powder.

(20 mol%, entry 3) resulted in a lower yield. Subsequently, we screened other known Lewis acids such as $MgBr_2$, $MgBr_2$-etherate, MgI_2, $Mg(ClO_4)_2$, $Mg(OTf)_2$, $ZnBr_2$, ZnI_2, $Zn(OTf)_2$ (entries 4–11) and confirmed that LiBr is the best one for the purpose. Presumably these salts can also act by generating Mg or Zn carbenoids[25] through *in situ* transmetallations and thus, lowering the nucleophilicity of the carbenoid-type species.

With the optimized conditions in hand, we next turned our attention to the scope of the reaction (Scheme 3). Interestingly, it could be applied to differently sized ring systems, thus providing cyclopentene (**6a**, **b**), cyclohexene (**6c–g)** and cycloheptene (**6h**) derivatives bearing different substituents across the cyclic core. Pleasingly, the protocol tolerates functionalities sensitive to organolithiums such as a chlorine atom (**5f**→**6f**) or even the bicyclic acetal-type system of levoglucosenone (**5i**→**6i**), a cellulose-derived cyclic enone, which is frequently employed as versatile scaffold in synthetic medicinal chemistry.[26] Unfortunately, although compound **6i** was obtained as a single diastereoisomer, no stereochemical proof could be deduced by NOE experiments (see the Supporting Information). The presence of heteroatoms in the starting enones is permitted, thus providing chlorohydrins **6j** and **6k** in high yields. The reactive olefinic moiety can also be included into an aromatic system as evidenced in the case of compound **6l** resulting from fluorenone **5l**: it should be noted that the carbenoid, under the reaction conditions, does not display any electrophilic reactivity towards the aromatic rings of



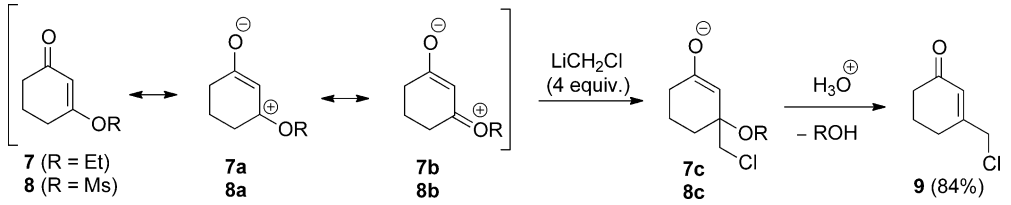
Scheme 3. Scope of the reaction[28].

this latter substrate. Remarkably, the methodology could be efficiently applied to complex enone systems incorporated into natural products such as nootkatone (**5m**), a sesquiterpene derived from grapefruit with insecticide-repellent properties towards deer ticks.[27] With much of our delight we prepared the medicinally relevant scaffold **6n** from cholest-4-en-3-one (**5n**) in high yield, thus showcasing the possibility to expand the use of such chemistry to non-academic audiences. Pleasingly, both these products were obtained as single diastereoisomers showing a stereochemistry at the newly formed quaternary center as depicted in Scheme 3 (**6m**, **6n**).

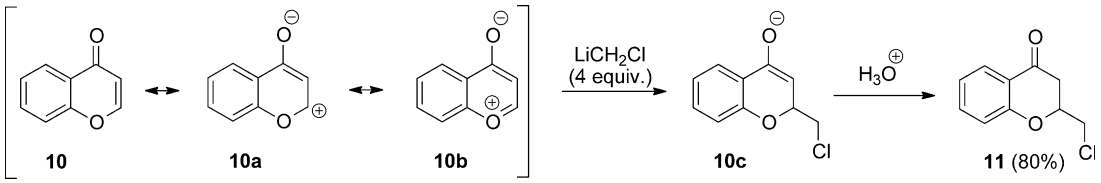
Of particular significance is the presence of an electron-releasing oxygen atom at the β-position of the olefinic bond which, formally transforms the enone systems **7** and **8** into masked 1,3-dicarbonyl derivatives (Scheme 4).[29] The resulting mesomeric effect, as showed by the canonic forms **7a/7b** and **8a/8b**, evidently allows the attack of the carbenoid at such (activated) positions with formation of intermediates **7c** and **8c**, respectively. The nature of the group linked to the enol-type oxygen atom plays a pivotal role in determining the mechanism for the collapse of the addition intermediates of type **c**. Thus, in the presence of nucleofugal leaving groups (e.g., EtO or MsO) which could be easily eliminated, upon quenching the enone system is re-established providing compound **9** as the sole reaction product in 84% isolated yield.

On the other hand, in the case of chromone **10** the carbenoid addition takes place *simili modo* on the (activated) β-C-atom of the enone system, thus affording the intermediate **10c**. The latter evidently does not possess any (nucleofugal) leaving group and, as a consequence, the acidic treatment of this enolate could only restore the ketone form thus, giving the substituted chromanone **11** in 80% yield. It is worth observing the difference in reactivity between the masked 1,3-dicarbonyl compounds and β-chloroenone **5f**: in this latter case, the impossibility to conjugate the lone-pair of chlorine with the enone system, accounts for the direct 1,2-addition.

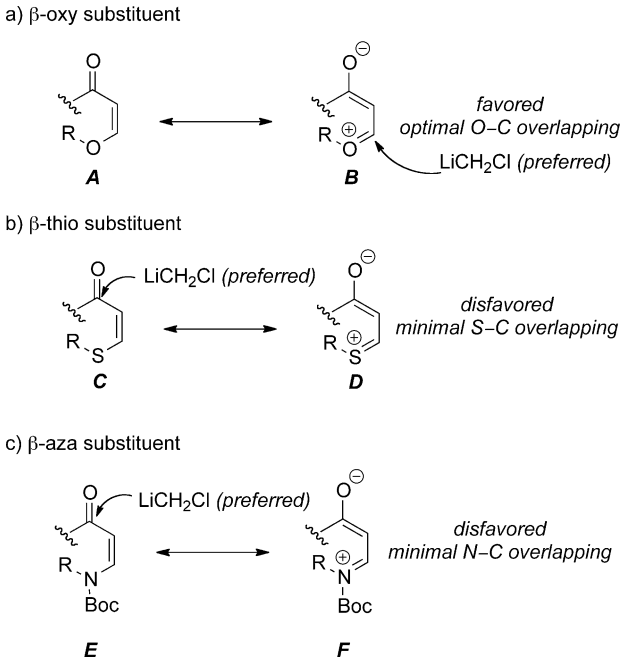
It is worth noting the different outcome of the reaction involving a β-oxo species (compounds **7**, **8, 10**, Scheme 4 and Scheme 5) and the corresponding β-thio analoge **5j** (Scheme 3). As shown in Scheme 6, we explain this behavior based on the lower ability (compared to oxygen) of the molecular orbital of the sulphur atom to overlap with the adjacent carbon. As a consequence, in the case of oxygen the attack of the carbenoid can be explained considering the larger contribution of canonic form **B**, while in the case of sulphur the correspondent form **D** is less favored. Similarly, the electron-withdrawing effect of a Boc group on the nitrogen atom of a 4-piperidone (i.e., compound **5k**) also reduces the extent of overlapping in structure **F**, thus favoring the attack *via* an 1,2-fashion.



Scheme 4. β-Activating effect of an RO group: the case of 3-alkoxy systems.



Scheme 5. β-Activating effect of an RO group: the case of chromone.



Scheme 6. Mechanistic explanation of the different behavior of β-oxo, β-thio and β-aza (protected) substituents.

In conclusion, we have reported the reactivity of a lithium carbenoid ($LiCH_2Cl$) with a series of cyclic α,β-unsaturated enones. Key features disclosed within this study are: (i) LiBr not only acts as a carbenoid stabilizer but also as a mild Lewis acid activator of the C=O bond; (ii) in the case of β-heteroatom (O, S, N) substituted enones the regioselectivity of the carbenoid addition can be rationalized considering the different relative stability of the relevant mesomeric forms; (iii) the protocol is tolerant to various ring-sized enones (5-, 6-, 7-membered and also complex natural product structures) bearing eventually different substitution patterns.

Experimental Section

Representative Procedure: Synthesis of 2

To a solution of enone **1** (198 mg, 1.00 mmol, 1.0 equiv.) in THF-Et_2O (2 mL, 1:1, v/v) cooled at −78 °C was added freshly distilled chloroiodomethane (794 mg, 0.33 mL, 4.5 mmol, 4.5 equiv.), followed by the dropwise addition of a solution of MeLi-LiBr complex (1.5 M, 2.67 mL, 4.0 mmol, 4.0 equiv.) during 5 min. The mixture was stirred for 1 additional hour before it was quenched with saturated aqueous NH_4Cl (2 mL) and extracted with Et_2O (3×5 mL). The organic layer was washed with brine (5 mL), dried over Na_2SO_4, filtered and after removing the solvent under reduced pressure, analytically pure chlorohydrin **2** was obtained as a colorless oil; yield: 231 mg (93%). Full experimental details including characterization of the compounds and copies of ^1H NMR and ^{13}C NMR spectra are available in the Supporting Information.

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