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## **Organic Synthesis with Lithium Carbenoids at the Helm: Mechanistic Aspects and Applications in Synthetic Medicinal Chemistry**

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## Organic Synthesis with Lithium Carbenoids at the Helm: Mechanistic Aspects and Applications in Synthetic Medicinal Chemistry

Homologation processes constitute established and highly versatile tools for synthetic chemists with focus on medicinal applications.

In this context, organometallic compounds presenting a metal and at least one electronegative group (*e.g.* halogen) at the same carbon usually referred as carbenoids, can be advantageously employed in such processes. Their chemistry is characterized by the intrinsic ambiphilicity between the nucleophilic and electrophilic behaviour, depending – *inter alia* – on the nature of the metal and thus, understanding mechanisms governing such transformations becomes crucial for designing highly reliable and chemocontrolled tactics.

Within this Thesis the preparation and the synthetic employment of unstable – but highly reactive - nucleophilic lithium halocarbenoids is presented: the introduction of a functionalized methylenic fragment into a given electrophile is the concept behind the whole work. The reactivity of these reagents – towards electrophiles such as Weinreb amides, heterocumulenes [*e.g.* iso(thio)cyanates] and unsaturated carbonyls is illustrated jointly with mechanistic rationale and discussion on the stability, isolation and characterization of the intermediates involved in the transformations.

We also document sequential transformations – run *via* a single synthetic operation – in which the carbenoid-mediated homologation represents the key step. As illustrated in the case of  $\alpha,\beta$ -unsaturated carbonyl compounds, the homologation *followed* by a Meinwald rearrangement and the trapping with an electrophile, enables the flash access to fully substituted aldehydes: *i.e.* the fine tuning of reactions with carbenoids are employed for the construction of densely functionalized molecular architectures.

A short, high-yielding synthesis of the HIV inhibitor Nelfinavir is achieved under full stereocontrol by merging a lithium carbenoid homologation followed by an enzymatic reduction.

Considering the chemical characteristics of carbenoids analogous to the prototypal homologating agent – diazomethane – whose use in synthesis is limited by the notorious safe issues it poses, an operationally simple and effective version of the classical Arndt-Eistert is proposed.

## **Organic Synthesis with Lithium Carbenoids at the Helm: Mechanistic Aspects and Applications in Synthetic Medicinal Chemistry**

Für den pharmazeutischen bzw. medizinischen Chemiker stellen Verfahren zur Homologisierung organischer Moleküle etablierte und vielseitige Werkzeuge für die Synthese dar. Bei solchen Verfahren kommt der Verbindungsklasse der Carbenoide – organometallische Verbindungen, welche am selben Kohlenstoffatom sowohl ein Metallatom als auch einen elektronegativen Substituenten (z.B. ein Halogenatom) aufweisen – eine besondere Bedeutung als Homologisierungsreagentien zu. Ihre komplexe Chemie ist durch die intrinsische Ambivalenz zwischen dem nucleophilen und elektrophilen Verhalten gekennzeichnet, welche unter anderem auch von der Art des Metalls abhängt. Aus diesem Grund ist das Verständnis jener Mechanismen, die solche Transformationen steuern, entscheidend für die Entwicklung von neuen, zuverlässigen und unter chemischer Kontrolle ablaufenden Synthesen.

Im Rahmen dieser Arbeit wird die Herstellung von instabilen, aber hoch reaktiven nucleophilen Lithiumhalogen-carbenoiden und ihre Anwendung als Synthesebausteine vorgestellt. Die Einführung eines funktionalisierten Methylenfragments in ein gegebenes Elektrophil ist das Konzept der gesamten Arbeit. Die Reaktivität dieser Reagenzien - gegenüber Elektrophilen wie Weinreb-Amiden, Heterocumulenen [z.B. Iso(thio)cyanaten] und ungesättigten Carbonylverbindungen - wird eingehend untersucht sowie mechanistische Überlegungen hinsichtlich Stabilität, Isolierung und Charakterisierung der an den Transformationen beteiligten Zwischenstufen diskutiert.

Weiters werden sequentielle Transformationen beschrieben, welche im Zuge einer ‚Eintopfreaktion‘ ablaufen, bei denen eine Carbenoid-vermittelte Homologisierung den Schlüsselschritt der Reaktionssequenz darstellt. So wird eine neue, effiziente Synthese von  $\beta,\gamma$ -ungesättigten Aldehyden mit quartären oder tertiären  $\alpha$ -Positionen vorgestellt, welche - ausgehend von  $\alpha,\beta$ -ungesättigten Carbonylverbindungen - nach  $C_1$ -Homologisierung, anschließender Meinwald-Umlagerung (Epoxid-Aldehyd-Isomerisierung) und dem Abfangen mit einem Elektrophil einen eleganten Zugang zu den Zielverbindungen gestattet, wobei die Feinabstimmung der Reaktivität des verwendeten Carbenoides eine entscheidende Rolle spielt.

Schließlich wird in der vorliegenden Arbeit auch ein kurzes, durch eine hohe Gesamtausbeute charakterisiertes Verfahren zur Herstellung des HIV-Inhibitors Nelfinavir beschrieben. Bei dieser Synthese, welche unter vollständiger Stereokontrolle abläuft, stellen eine Homologisierung mittels eines Lithiumcarbenoids, gefolgt von einer Enzym-katalysierten Reduktionreaktion, die Schlüsselschritte der Reaktionssequenz dar.

Die vorgestellten Reaktionen können als effektive, moderne Version der klassischen Arndt-Eistert Reaktion betrachtet werden, bei der das prototypische, jedoch problematische Homologisierungsreagenz Diazomethan durch geeignete, wesentlich ungefährlichere und besser handhabbare Carbenoide ersetzt wird.

## Abbreviation List

|         |                                   |                   |                                  |
|---------|-----------------------------------|-------------------|----------------------------------|
| 2-MeTHF | 2-Methyltetrahydrofuran           | LDA               | Lithium diisopropylamide         |
| Bn      | Benzyl                            | LiHDMS            | Lithium bis(trimethylsilyl)amide |
| Boc     | <i>tert</i> -Butyloxycarbonyl     | LNCy <sub>2</sub> | Lithium dicyclohexylamide        |
| Cbz     | Carboxybenzyl                     | LTMP              | Lithium tetramethylpiperidide    |
| CPME    | Cyclopentyl methyl ether          | NMR               | Nuclear magnetic resonance       |
| EDG     | Electron donating group           | PG                | Protecting group                 |
| EWG     | Electron withdrawing group        | THF               | Tetrahydrofuran                  |
| HIV     | Human immunodeficiency virus      | TMP               | Tetramethylpiperidine            |
| HMPA    | Hexamethylphosphoramide           | TMS               | Trimethylsilyl                   |
| HRMS    | High Resolution Mass Spectrometry | Ts                | Tosyl                            |
| IR      | Infrared                          |                   |                                  |



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- Publication 1* Pace, V.;\* **Castoldi, L.**; Monticelli, S.; Rui, M.; Collina S.  
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- Publication 11 Mamuye, A. D.; Monticelli, S.; **Castoldi, L.**; Holzer, W.; Pace, V. \*  
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*Merging lithium carbenoid homologation and enzymatic reductions: a*

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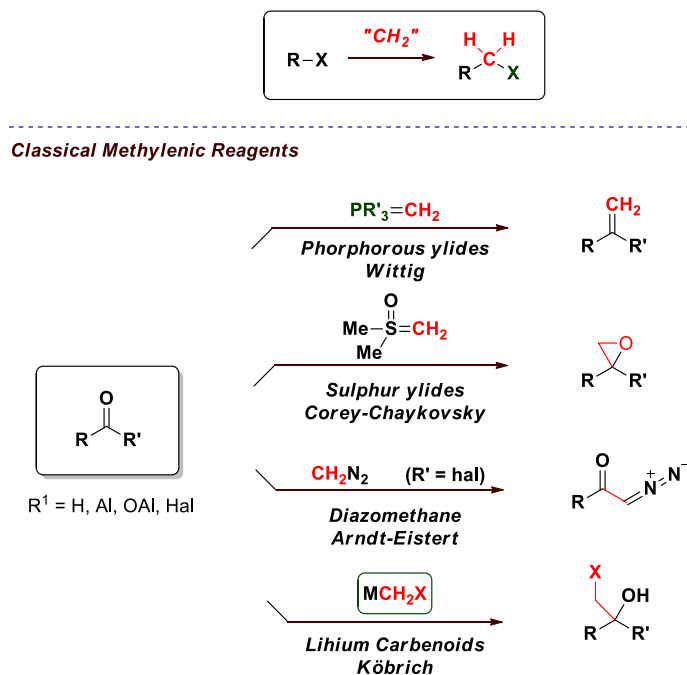
|                |                                                                                               |
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|                | <i>combinative approach to the HIV-protease inhibitor Nelfinavir</i>                          |
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| Publication 15 | <b>Castoldi, L.;</b> Ielo, L.; Holzer, W.; Giester, G.; Roller, A.; Pace, V.*                 |
|                | <i><math>\alpha</math>-arylamino diazoketones: diazomethane-loading controlled synthesis,</i> |
|                | <i>spectroscopic investigations and structural X-ray analysis.</i>                            |
|                | <i>J. Org. Chem</i> , Accepted (Manuscript ID: jo-2017-03134r).....                           |
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## 1. Introduction

### 1.1 Carbon Chain Homologation Reactions: Methylenating agents. An Overview

Methylenating agents are recognized as valuable synthetic tools in homologation reaction, allowing the formal insertion of a methylene unit (*i.e.* CH<sub>2</sub>) into a given preformed bond (Scheme 1).<sup>1</sup> Classical examples of homologation processes are represented by the carbon chain extension or the ring expansion of carbonyl compounds.<sup>2</sup>

In this context, the addition of a functionalized methylene unit (*e.g.* -CH<sub>2</sub>X, X = Halogen, CN, OR) to an electrophile is a versatile synthetic operation, which enables the addition of a fragment with the *exact* degree of derivatization.<sup>3</sup> As such, in just one synthetic operation it is possible to assemble a new carbon-carbon-heteroatom fragment susceptible of further functionalization in a direct and straightforward manner. Moreover, optimized reaction conditions favor high chemocontrol avoiding issues arising from the functionalization realized on the substituted precursor.<sup>4</sup> Classical methylenic reagents are considered the Wittig-type<sup>5</sup> phosphorous ylides, the Corey-Chaykovsky<sup>6</sup> sulphur ylides, diazomethane<sup>1c,7</sup> or, the Köbrich lithium carbenoids<sup>8</sup> (LiCH<sub>2</sub>X) which be discussed in-depth within this Doctoral Thesis (*Scheme 1*).



## 1.2 Homologation Reactions: Valuable Tools in Medicinal Chemistry

The importance of homologation across the chemical sciences is showcased by the alteration of the pharmacological profile of various biologically active substances featuring a different number of methylene units within a given carbon skeleton (*Figure 1*). For example, Enalaprilat-type derivatives **1** manifest a different pharmacokinetic behaviour depending on the ring size. Similarly, two bis-ammonium salts - namely Hexamethonium **2** and Decamethonium **3** do act in diverse mode towards the nicotinic receptor, being the former a *non* depolarising ganglionic blocker and, the latter a depolarising muscle relaxant.<sup>9</sup> In both examples, it appears evident how the different ring size or the length of the chain profoundly modulates the biological response.

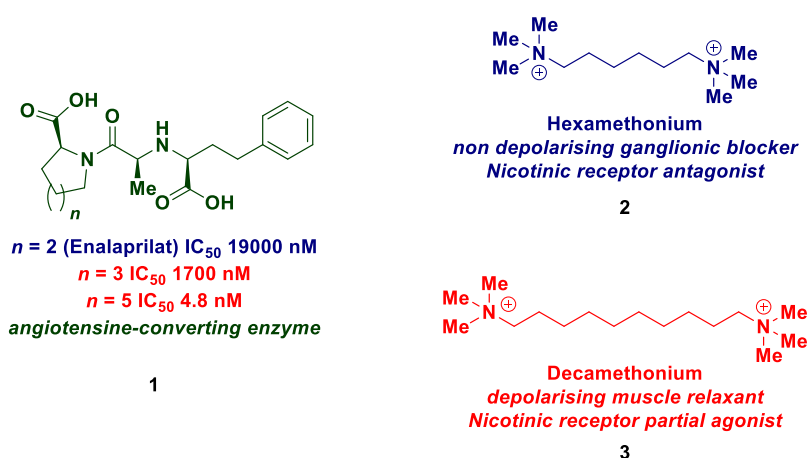
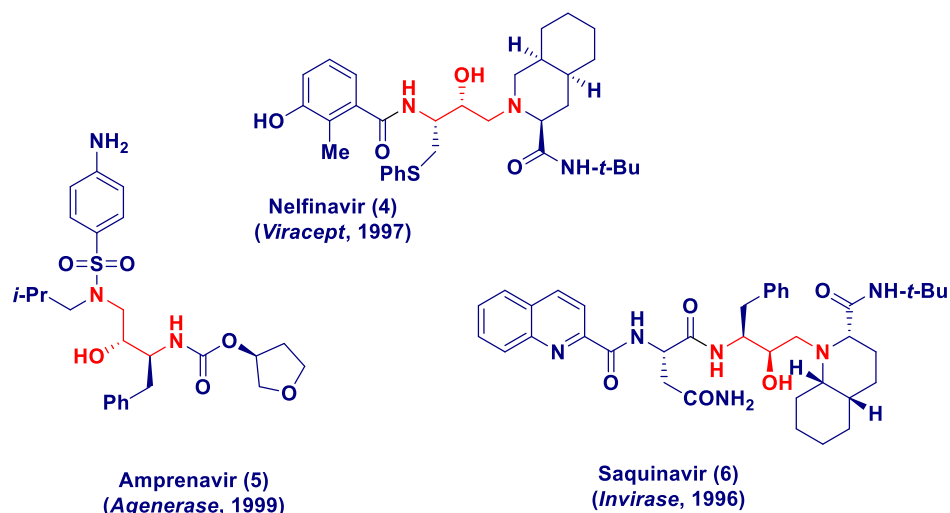
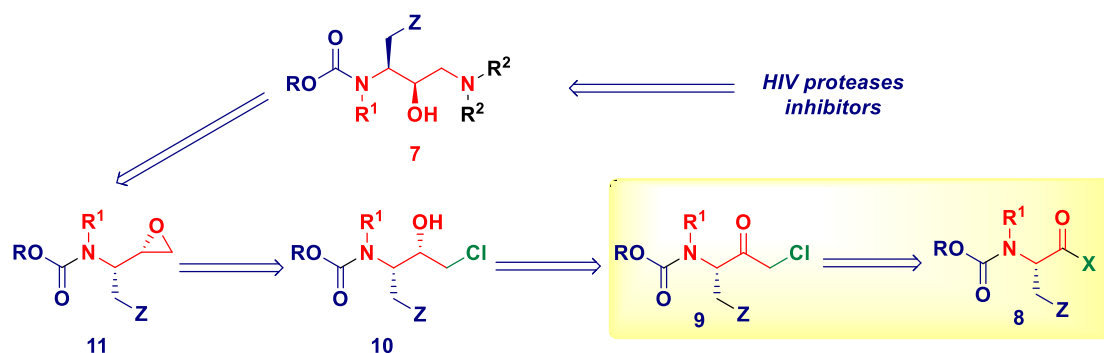


Figure 1. Concept of homologation in medicinal chemistry.

Noteworthy, homologation reactions are well established tools in the synthesis of biologically active intermediates, as well illustrated in the classical route towards the preparation of HIV proteases inhibitors (*e.g.* Saquinavir, Nelfinavir). In order to synthesize the enantiomerically pure 1,3-diamino-propan-2-ol **10**, the key synthon requested to access the pharmacophore **7**, an homologation pathway is followed (*Scheme 2*).<sup>10</sup>



### Retrosynthetic Analysis



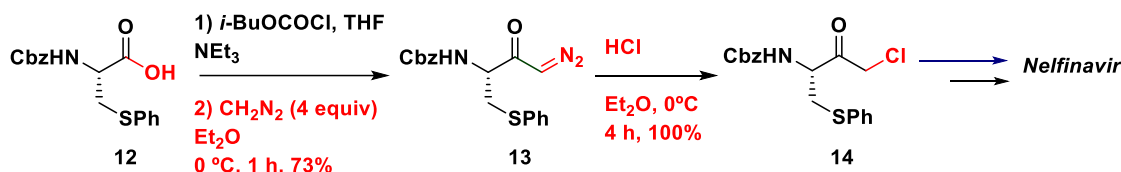
Scheme 2. Retrosynthetic analysis of the synthesis of HIV proteases inhibitors.

As represented in the retrosynthetic analysis (Scheme 2), the homologation of a given carboxylic acid derivative **8** provides the  $\alpha$ -haloketone **9**, which is stereoselectively reduced to the corresponding  $\beta$ -halohydrin **10**. The ensuing ring-closure to the epoxide **11**,<sup>11</sup> followed by the reaction with an amine affords the targeted scaffold **7**.<sup>10c</sup>

The critical step in the synthetic route is represented by the homologation, which historically has been accomplished through the preparation of a diazo intermediate.<sup>1c,7d-g,7i,12</sup> However, the well-known concerns related to the use of diazomethane (*i.e.* explosivity, mutagenicity) in pilot plant,<sup>13</sup> are in sharp disagreement with the strict requirements imposed to pharmaceutical industries.<sup>14</sup>

Initial studies on the preparation of Nelfinavir conducted by Kaldor and co-workers<sup>15</sup> relied on the classical Arndt-Eistert procedure:<sup>7b,7f</sup> carboxylic acid **12** was activated as a mixed anhydride and

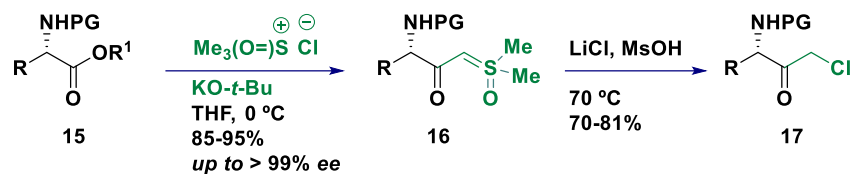
treated with an excess of diazomethane (4.0 equiv) to give the intermediate  $\alpha$ -diazoketone **13** (Scheme 3). The subsequent acidic treatment gave the desired  $\alpha$ -haloketone **14** with almost full retention of the optical purity. However, the requirement of such an excess of the toxic and explosive diazomethane narrows the application of the procedure in large scale preparations.<sup>7d,7e,13,16</sup>



Scheme 3. Kaldor's homologation via Arndt-Eistert-type synthesis of  $\alpha$ -haloketones.

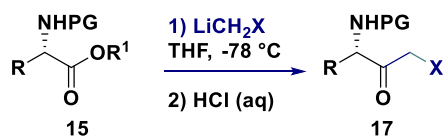
More recently, there has been a renewed interest towards diazomethane-based homologations with the aim to conjugate its undiscussed synthetic potential with the adoption of safer and more sustainable procedures. For instance, Morandi and Carreira described the *in situ* generation of diazomethane for cyclopropanation-type processes,<sup>17</sup> while Pace *et al.* carried out the Arndt-Eistert homologation by employing diazomethane in only stoichiometric amount in the presence of calcium oxide as an acid scavenger.<sup>7c,18</sup> Moreover, since nowadays microfluidic techniques constitute well established tools in modern organic synthesis,<sup>19</sup> significant benefits have been achieved also in the preparation of  $\alpha$ -diazoketones, as documented by a laboratory-scale synthesis of HIV-proteases inhibitors precursors by Kappe and co-workers.<sup>20</sup> Interestingly, the use of the safer – but considerably less reactive and more expensive - substitute trimethylsilyldiazomethane (TMSCHN<sub>2</sub>) introduced by Aoyama and Shioiri in 1980, did not find significant applications in the field.<sup>21</sup>

Nugent and co-workers proposed the replacement of diazomethane with the safer dimethylsulfoxonium methylide, which in the presence of a base converts the ester derivative **15** into the  $\beta$ -ketodimethylsulfoxonium ylide **16**, subsequently hydrolyzed to the desired  $\alpha$ -chloroketone **17** (Scheme 4).<sup>22</sup> Notably, this racemization-free technique has not been thoroughly applied to industrial processes, thus leaving its importance practically circumscribed to academia.



Scheme 4. Nugent's two-steps homologation of esters to  $\alpha$ -haloketones.

The most employed methodology reported in the literature to access  $\alpha$ -aminoalkyl- $\alpha'$ -halomethylketones **17** on a pilot plant is the homologation of amino ester **15** derivatives with monohalolithium reagents ( $\text{LiCH}_2\text{X}$ ,  $\text{X} = \text{Cl}, \text{Br}, \text{I}$ ) – usually referred as carbenoids (Scheme 5).<sup>10a,10c,23</sup> This approach offers clear advantages for preparing  $\alpha$ -aminoalkyl- $\alpha'$ -halomethylketones compared to the diazomethane-based methodologies mainly because of the tamed hazard of analogous reagents at pilot scale.<sup>10a</sup>

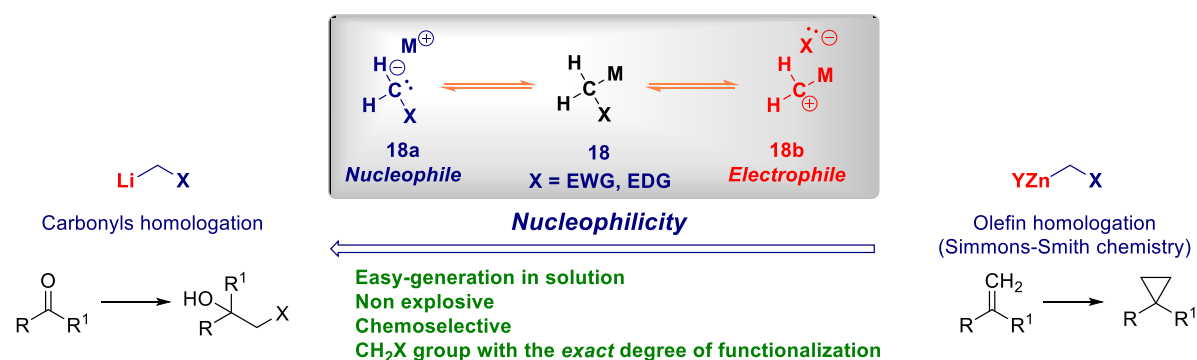


Scheme 5. Carbenoids homologation of  $\alpha$ -aminoesters to the corresponding  $\alpha$ -haloketone.



### 1.3 Halocarbenoids: General Features

Carbenoidic reagents play a prominent role within the plethora of homologating agents.<sup>24</sup> The term carbenoid was introduced by the pioneers in this field Closs<sup>25</sup> and Moss.<sup>26</sup> Carbenoids are defined as organometallics having a metal (*e.g.* Li, Mg) and, bonded at the same carbon atom, one electronegative atom (*Scheme 6*).<sup>27</sup>



*Scheme 6.* Ambiphilic reactivity of metal carbenoids and key features.

As first explained by Köbrich,<sup>26,28</sup> the presence of an electron-donating and electron-withdrawing substituent at the carbon center brings to ambiphilicity, which means that they can display nucleophilic or electrophilic behavior, in different experimental set up.<sup>24f,29</sup> It is accepted that the nucleophilic behavior results at low temperatures, while their electrophilicity comes into play at higher temperatures (*Scheme 6*). It is important to stress that carbenoids of lithium and magnesium, because of their excellent nucleophilicity, do react predominantly as carbanions.<sup>24b,29c-</sup>

<sup>f</sup> On the other hand, less nucleophilic carbenoids such as zinc or rhodium linked ones exhibit preferentially an electrophilic behavior.<sup>24a,30</sup>

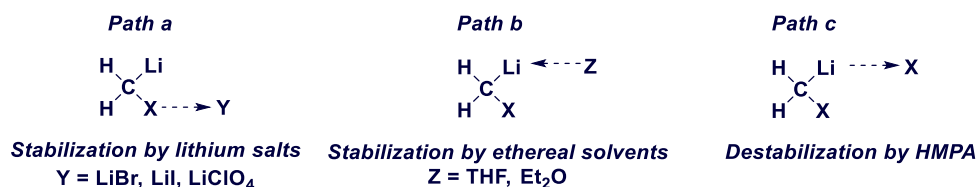
The difference in reactivity between carbenes and carbenoids has been firstly evidenced in the seminal studies by Closs,<sup>25,31</sup> who noticed a different capability to induce stereocontrol in the cyclopropanation carried out with diphenylcarbene or, with the carbenoid prepared from diphenyldibromomethane and methyllithium. The intermediate species formed upon the metal halogen exchange presented similar but not identical properties compared to free carbenes. In fact, the latter are achiral and their insertion leads to a racemic product while, carbenoids, depending on the substituents, can be chiral. In particular, Walborsky, introduced the concept of



can be regarded as the less stable ones in comparison with magnesium and zinc analogues, which are considered relatively more stable.<sup>34</sup>

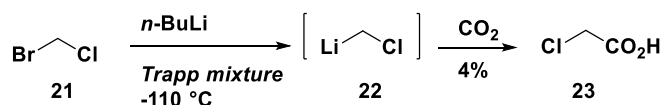
The nature of the leaving group can also affect the stability, being halogen- and oxy-species particularly unstable.<sup>8a</sup> Computational studies predicted the decreasing stability – and the concomitant increasing of the carbenoid character – in the series  $\text{LiCH}_2\text{F} < \text{LiCH}_2\text{Cl} < \text{LiCH}_2\text{Br} < \text{LiCH}_2\text{I}$ .<sup>29b</sup> The carbenoid character is also more pronounced when the metallated carbon is connected to less heavy groups.<sup>35</sup>

- 2) The addition of lithium halide salts, which can coordinate to the halogen atom of the carbenoid, results beneficial for the stability as a result of the disruption of the internal Li-X interaction responsible for  $\alpha$ -elimination. (*Scheme 9 – path a*).<sup>32b,36</sup> Moreover, according to Matteson,<sup>37</sup> the presence of LiBr not only stabilizes the carbenoid but also avoids the competing attack of MeLi to the electrophile present in the medium under Barbier condition.<sup>38</sup> This is a particularly important observation since the generation of the carbenoid must be kinetically favoured over the concomitant attack of the lithiating agent to the electrophile. Carbenoid can also be stabilized by ethereal solvents (*Scheme 9 – path b*) or destabilized by like hexamethylphosphoramide (HMPA) (*Scheme 9 – path c*).<sup>32b</sup>



*Scheme 9.* Coordinative factors influencing  $\alpha$ -elimination.

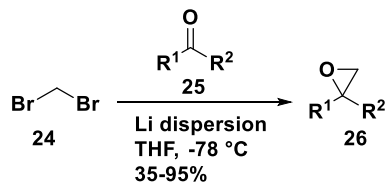
- 3) During the first studies by Köbrich, the generation of chloromethyl lithium from bromochloromethane and *n*-butyllithium had to be realized at  $-110^\circ \text{C}$ . However, the initial synthetic efficiency under non-Barbier conditions was quite limited as demonstrated by the extremely low yield (only 4%) observed in the carboxylation of  $\text{LiCH}_2\text{Cl}$  (*Scheme 10*).<sup>28,35a</sup>



*Trapp mixture* = THF-Et<sub>2</sub>O-*n*-pentane 75:15:10 v/v

*Scheme 10.* External quenching procedure proposed by Köbrich.

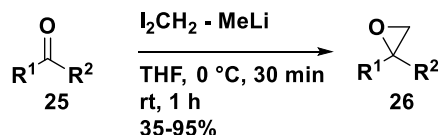
Later on, Cainelli showed that monohalo methyllithiums could be efficiently prepared at -78 °C if experiments are carried out under Barbier-type conditions.<sup>39</sup> In this case, generating the carbenoid in the presence of the electrophile in the reaction medium, allows the immediate homologation of the carbonyl to the epoxide thus, avoiding the decomposition of the carbenoidic species. Notably, lithium metal resulted more efficient than alkyllithium reagents for generating the carbenoid (*Scheme 11*).<sup>6a,40</sup>



*Scheme 11.* Internal quenching-Barbier conditions proposed by Cainelli.

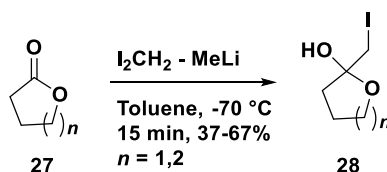
Although Cainelli's<sup>39</sup> study is important for establishing the correct generation of carbenoids through Barbier conditions, the temperature at which the carbenoidic species decomposed was not univocally defined. In 1984 Villieras<sup>32b</sup> agreed with the previous studies of Köbrich,<sup>8a</sup> corroborating the requirement of temperatures lower than -115 °C to avoid  $\alpha$ -elimination. Moreover, he also introduced the beneficial effects of adding lithium salts or employing Lewis-basic type solvents above mentioned.

Later studies in the 1980s and the 1990s by Matteson<sup>37,41</sup> and Barluenga<sup>42</sup> pointed out the feasibility of reactions at -78 °C. Although such thermal conditions are considered the optimal ones for generating both chloromethylithium and bromomethylithium, even slightly higher temperatures (-65 °C) can be used.<sup>43</sup> Surprisingly, the preparation of iodomethylithium can be accomplished in batch at 0 °C as noted by Concellón: however, this represents the only case of epoxydation of carbonyl compounds at such high temperature (*Scheme 12*).<sup>44</sup>



*Scheme 12.* Employment of iodomethylithium at 0 °C.

Morin, on the other hand, found out that a temperature of  $-70\text{ }^{\circ}\text{C}$  is mandatory in chemistry involving iodomethylithium.<sup>45</sup> He also underlined the possibility to employ of toluene as medium of reaction. In the course of investigations aimed at iodomethylate lactones **27** (Scheme 13).<sup>42a</sup>



Scheme 13. Employment of iodomethylithium  $-70\text{ }^{\circ}\text{C}$ .

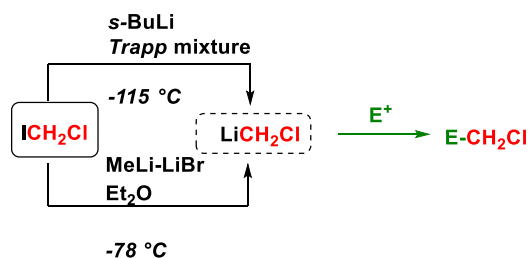
#### 1.4 Generation of monohalolithium carbenoids

According to the recent literature, the four following methods can be employed for the generation of monohalocarbenoids: *a*) halogen-metal exchange with organolithium reagents (with both RLi or Li metal);<sup>46</sup> *b*) lithium-hydrogen exchange (*i.e.* deprotonation); *c*) tin-lithium exchange;<sup>47</sup> *d*) sulfinyl-lithium exchange.<sup>48</sup> As a general rule, in order to minimize the degradation pathways in batch systems, the use of Barbier-type condition is strongly recommended.<sup>24c</sup>

##### 1.4.1 Lithiation *via* Lithium-halogen exchange

The lithium-halogen exchange on a given dihalomethane is regarded as the most common lithiation method for generating carbenoidic reagents.<sup>46</sup> Furthermore, dihalomethane precursors have the advantage to be widely available from common chemical suppliers.

Among the first methods of preparation of monohalolithiums, Villieras indicated *n*-BuLi as the lithiating agent and the Trapp mixture (THF-Et<sub>2</sub>O-*n*-pentane, 75:15:10 v/v)<sup>49</sup> as the solvent at  $-115\text{ }^{\circ}\text{C}$ . Nowadays MeLi or PhLi are considered more suitable bases for the lithium halogen exchange,<sup>42b</sup> while *n*-BuLi is more often employed in deprotonation reactions.<sup>50</sup> Moreover, Matteson<sup>37</sup> and Pace<sup>51</sup> employed the commercially available MeLi-LiBr complex in Et<sub>2</sub>O to prepare carbenoids (Scheme 14).



Scheme 14. First methods of preparation of chloromethyl lithium.

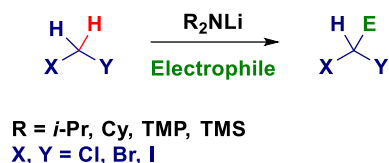
As described in the previous paragraph, the presence of lithium bromide in the reaction medium can induce the coordination of the carbenoid and, contemporaneously counteract the attack of MeLi to the electrophile. Additionally, this salt can act as a Lewis acid by increasing the electrophilicity of the carbon and, ultimately the attack of the carbenoid to the substrate.<sup>52</sup> In the formation of monohalo carbenoids, considering the iodo atom as the best exchangeable halogen, chloriodomethane constitutes the first choice,<sup>53</sup> though the cheaper bromochloromethane could be reputed a valid alternative for industrial processes.<sup>10a</sup> Taking into account that such a lithium-halogen exchange occurs quantitatively, a stoichiometric ratio between the dihalomethane and the lithiating agent should suffice for the purpose. However, it is wise to employ a small excess of dihalomethane in order to avoid the residual possibility of competing attack of the alkyllithium to the electrophile.<sup>24e</sup> In this way, the proper generation and reactivity of the sensitive halolithium is guaranteed.

Very recently, Luisi and coworkers showcased the effectiveness of microfluidic systems for generating  $\text{LiCH}_2\text{Cl}$  followed by *external* trapping with electrophiles at higher temperatures (up to -20 °C).<sup>54</sup> The system works good with a plethora of electrophiles ranging from carbonyl compounds, imines, Weinreb amides and isocyanates.

#### 1.4.2 Lithiation *via* Lithium-hydrogen exchange

Procedures involving the lithium exchange with halogen are suitable for the formation of dihalomethyl carbenoids (e.g.  $\text{LiCHCl}_2$ ,  $\text{LiCHBr}_2$  and  $\text{LiCHI}_2$ ) from the corresponding dihalomethane.<sup>46</sup> The most common strategy involves the employment of a lithium amide base such as LDA, LNCy<sub>2</sub>, LTMP, LiHDMS which can abstract the proton from the dihalomethane. The

treatment with the highly basic *s*-BuLi at very low temperatures (-115 °C) is not able to deprotonate, rather the corresponding halogen exchange occurs (*Scheme 15*).<sup>32b</sup>



*Scheme 15.* Lithiation via lithium-hydrogen exchange.

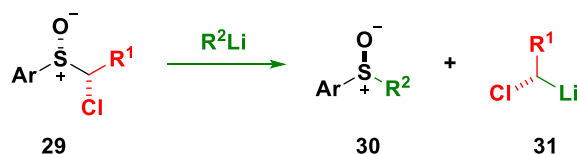
Noteworthy, LiCHl<sub>2</sub> can be easily formed prior to the reaction with the electrophile as recently documented by Bull.<sup>55</sup> Moreover, Molinski applied the deprotonation strategy for obtaining trichloromethylithium from chloroform and *n*-BuLi at -100 °C.<sup>56</sup>

In general, the choice of the amide base does not affect dramatically the chemocontrol of the reaction, except in the case of isocyanate as substrates (*vide infra* – *Publication 8*), in which the employment of a high sterically hindered base is required (*e.g.* LTMP) to avoid the concomitant attack of the base to the heterocumulene.

#### 1.4.3 Lithiation via Lithium-Sulfoxide Exchange

Hoffmann reported that magnesium carbenoids can be generated through magnesium-sulfinyl exchange, as an alternative to the classical metal-halogen one.<sup>57</sup> The protocol is accomplished treating the sulfoxide with a Grignard reagent, usually *i*-PrMgCl and, because of the higher stability of these species even at -60 °C, no significant decomposition takes places within (at least) 30 min. As a consequence of their known configurational stability,<sup>58</sup> such organometallics can be useful in asymmetric processes. However, the main limitation for using magnesium carbenoids deals with the significantly decreased nucleophilicity compared to lithium analogues.<sup>34a,34b,59</sup> In this context, Clososki highlighted their lack of reactivity towards ketones thus, leaving – among the series of carbon electrophiles – only aldehydes as substrates for these carbenoids.<sup>24g,60</sup>

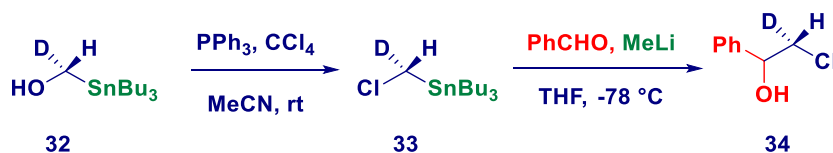
In the early 2000s, the lithium-sulfinyl exchange has been employed by Blackemore and coworkers for the preparation of lithium carbenoids, starting from a halogenated arylsulfoxide (*e.g.* *p*-tolyl).<sup>61</sup> Mechanistically, the reaction involves the attack of the lithium reagent to the electrophilic sulfur, followed by the collapsing to a thioether **30** and the carbenoid **31**. From a stereochemical perspective, the inversion of configuration at sulfur is observed (*Scheme 16*).<sup>61a-c</sup>



Scheme 15. Lithium carbenoids from halogenated arylsulfoxides.

#### 1.4.4 Lithiation via Lithium-Tin Exchange

Cognizant of the extremely easy tin/lithium exchange process for preparing organolithium compounds,<sup>53</sup> Hammerschmidt applied such a methodology for accessing lithium carbenoids (Scheme 17).<sup>47,62</sup> In detail, he reported the generation of the chiral deuterated stannane **33** using homochiral [ $D_1$ ]-chloromethyl-tri-(*n*-butyl)-stannane **32** as the precursor,<sup>63</sup> which upon reaction with MeLi provides the configurationally stable chloromethyl lithium (LiCHDCl). Such a chiral carbenoid has been exclusively employed in reactions with aldehydes as the electrophiles thus, leaving not full uncovered the innate synthetic potential. Notably, the formation of side-products is dependent on the nature of the organolithium used for realizing the exchange. Accordingly, MeLi furnishes highly satisfactory results compared to *n*-BuLi, which provides less clean reactions with considerable formation of undesired impurities. A possible explanation of this important aspect is paved on the lower basicity of MeLi compared to *n*-BuLi. However, this seminal work represents an outstanding contribution in chiral organolithium chemistry because of the proof of the configurational stability of halomethyl lithium species at very low temperature.



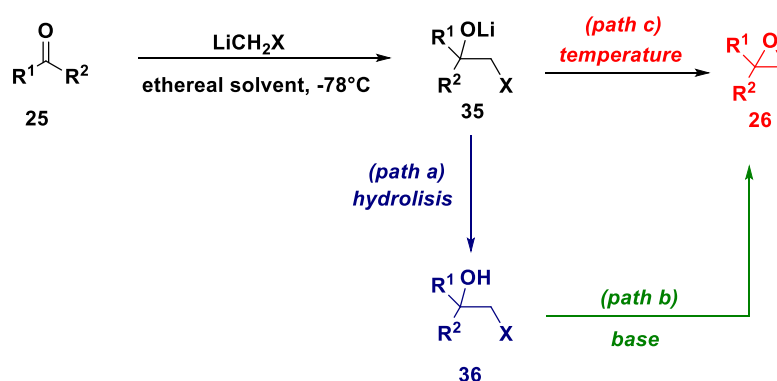
Scheme 17. Preparation of chiral chloromethyl lithium *via* tin-lithium exchange.



## 2 Electrophilic partners of Lithium Carbenoids

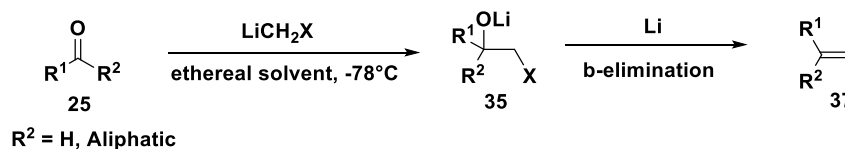
### 2.1 Carbonyl adducts

Carbonyl compounds have been extensively employed as electrophilic partners in reaction involving nucleophilic lithium carbenoids. As shown in early works by Cainelli,<sup>39,64</sup> Villieras,<sup>32b,65</sup> and Matteson,<sup>37,41</sup> followed by more recent contributions (Barluenga, Concellón,<sup>5b,42c,66</sup> Lautens<sup>67</sup>), the addition of a halomethyl lithium to an aldehyde or a ketone gives an isolable  $\beta$ -halohydrin **36** upon acidic quenching (*Scheme 18, path a*), which can be transformed into epoxides (*Scheme 18, path b*) by ring closure through a base-assisted process or, by simply increasing the temperature of the reaction (*Scheme 18, path c*).



*Scheme 18.* Reactivity of carbonyl compounds.

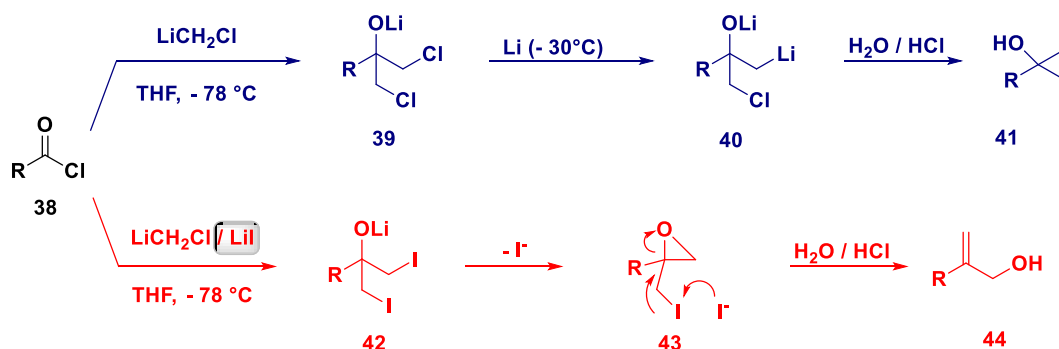
Cainelli's group<sup>64</sup> was interested in the evaluation of a synthetic method alternative to the Corey Chaykovsky epoxidation;<sup>6a,68</sup> in fact, the halolithium and the sulfur ylides can be considered carbanions stabilized by an electronegative group.<sup>1b</sup> In both cases, the electronegative moiety features also leaving group capability and, thus halomethyl lithiums lead to oxiranes through the formation of a halohydrin alkoxide intermediate, which then undergoes the 1,2-elimination. Alternatively, the subsequent treatment of the alkoxide with lithium metal conducts to an olefin *via* an intermediate  $\beta$ -dilithiated species (*Scheme 19*).<sup>5b</sup>



*Scheme 19.* Olefins from carbonyl compounds.

## 2.2 Carboxylic acid chlorides

Barluenga and co-workers<sup>66b,69</sup> investigated the reactivity of carboxylic acid chlorides towards chloromethylithium. A variation of their classic homologation conditions was applied to these substrates in order to obtain cyclopropanols (**41**) or allyl alcohols (**44**) (Scheme 20). Accordingly, chloromethylithium attacks the chloride twice (because of the instability of the intermediate ketone) giving **39**, which then is subjected to lithiation with Li metal yielding the dilithiated species **40**. The simple acidic quenching directly gives the 1,1-cyclopropanol in high yields. When lithium iodide is present in the reaction mixture, the corresponding elimination pathway is activated *via* the attack of the halide anion to the halogen of the intermediate epihalohydrin, finally furnishing an allylic alcohol.

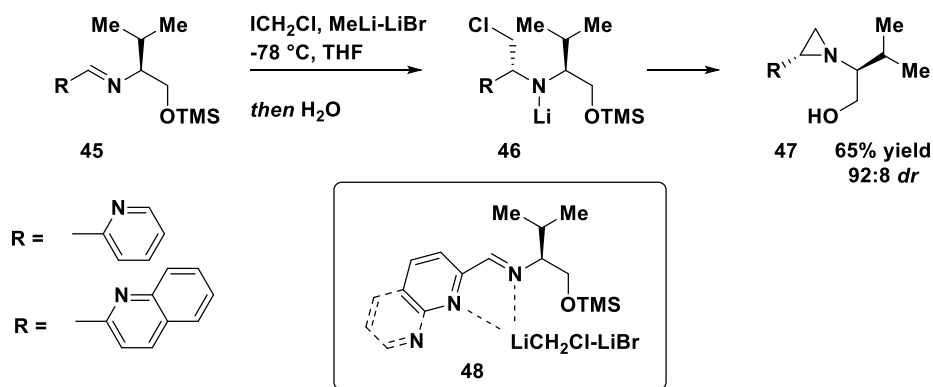


Scheme 20. Preparation of cyclopropanols and allyl alcohol.

## 2.3 Imines

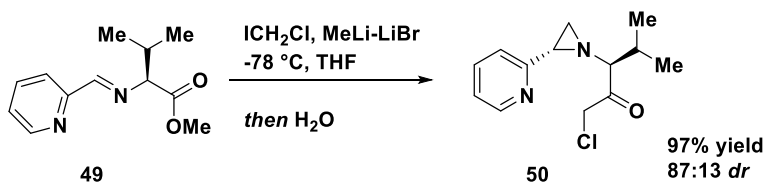
Imines are attractive substrates for halomethylating reagents as a consequence of the versatility the corresponding homologated structures - *i.e.*  $\beta$ -haloamines or aziridines – do present.<sup>70</sup> In fact, they constitute final compounds or intermediates for the synthesis of amino acids,  $\beta$ -lactams and alkaloids.<sup>70-71</sup> Different methylene transfer protocols have been established for the synthesis of aziridines starting from imines by employing diazomethane, sulfur ylides, dihalomethanes and diethylzinc.<sup>23</sup> With the aim to improve the scope and the efficiency of the transformation, Savoia and co-workers proposed the employment of chloromethylithium on a specific imine **45**, derived from *O*-TMS protected (*S*)-valinol, 2-pyridinecarboxaldehyde and 2-quinolinecarboxaldehyde

(Scheme 21).<sup>72</sup> This procedure allows the preparation of chiral substituted aziridines in high yield and stereocontrol. Chloromethyl lithium was selected as the reagent of choice compared to the much less nucleophilic zinc carbenoid (*i.e.*  $\text{ClCH}_2\text{ZnEt}$ ): by raising the temperature up to 20 °C a spontaneous ring closure takes place with the formation of the desired aziridines. Essential for the aziridination is the presence of a pyridyl type group, which chelate the incipient carbenoid **48**, thus enhancing its nucleophilic character for attacking the poorly electrophilic imine carbon.



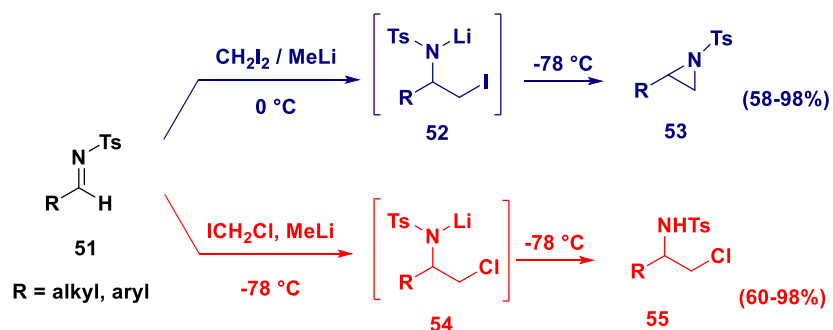
Scheme 21. Savoia's carbenoid-mediated aziridination.

Interestingly, no reactivity is observed whether the nitrogen of the pyridine is not located at the 2-position, as well as, in the case of highly sterically hindered substituents on the imine nitrogen. Preserving the chemocontrol is particularly difficult in imines presenting additional electrophilic sites: the reaction performed on the (*S*)-valine methyl ester derivative **49** occurs with the double addition to both sites (imine and ester), thus obtaining the aziridine bearing the  $\alpha$ -chloroketone motif **50** (Scheme 22).



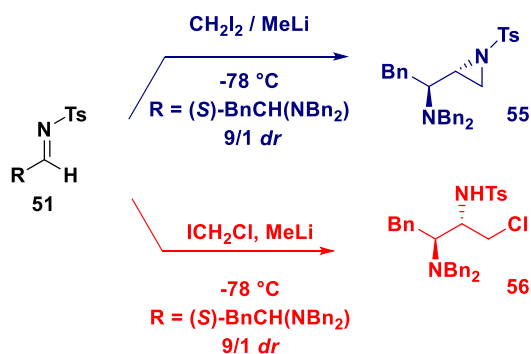
Scheme 22. Non-chemoselective addition to an imine bearing an ester moiety.

Considering that halomethylithium reagents generated *in situ* show a limited reactivity towards poorly electrophilic compounds, Concellón and co-workers<sup>73</sup> presented a strategy in which the electrophilicity of the azomethinic is enhanced by means of an electron-withdrawing group on the imine nitrogen. In particular, the addition of iodomethylithium at 0 °C (chloromethylithium gives analogous results) to sulfonyl-protected imine **51** was proposed as a simple and rapid experimental protocol to prepare *N*-tosylaziridines in one pot (*Scheme 23*). Unfortunately, the removal of tosyl-type protecting groups requires harsh conditions, thus limiting the appeal of the synthetic strategy. During further investigations, the same protocol has been applied to *N*-sulfonyl protected imines in the case of the addition of chloromethylithium.<sup>74</sup> The method afforded  $\beta$ -chloroamines **55** after acidic work-up at -78 °C, showing the possibility to isolate the intermediates and, thus to avoid the cyclization step to the aziridine. The main difference consists in the formation of a iodinated intermediate **52** (with iodomethylithium), which rapidly undergoes the heterocyclization to give the corresponding aziridines **53**; whereas, in the case of chloromethylithium, the corresponding  $\beta$ -chloro amide intermediate **54** does not lead to the immediate ring closure and, upon acidic quenching at -78 °C, directly furnishes the  $\beta$ -chloroamine **55**.



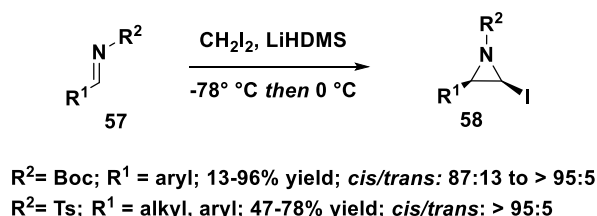
*Scheme 23.* Concellón's carbenoids additions to imines.

Notably, the bulky *N,N*-dibenzylamino group on nitrogen influences the stereochemical outcome of the whole addition. (*Scheme 24*).



Scheme 24. Divergent access to aziridines or  $\beta$ -chloroamines determined by the carbenoid nature.

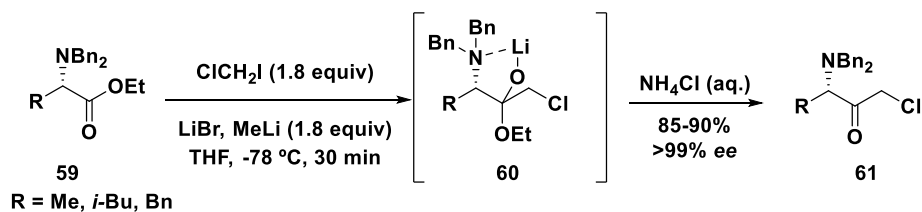
Recently, Bull and co-workers<sup>75</sup> reported the preparation of *N*-Boc and *N*-Ts protected  $\alpha$ -iodoaziridines **58** starting from the corresponding imines **57**. For this purpose, they employed diiodomethylithium, formed via deprotonation of diiodomethane with LiHDMS at  $-78\text{ }^\circ\text{C}$  to obtain in *one pot* disubstituted aziridines with high *cis*-selectivity (Scheme 25).



Scheme 25. Bull's synthesis of iodoaziridines.

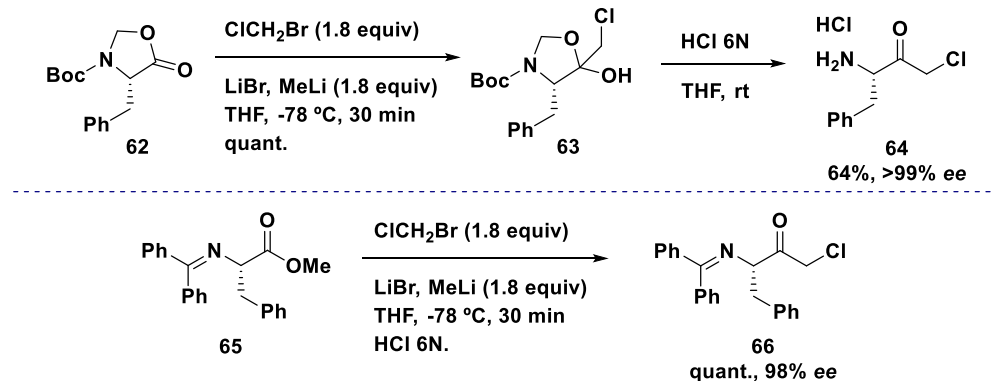
## 2.4 Esters and Weinreb amides

In the early 1990s, Barluenga<sup>42b</sup> documented the homologation of esters to access  $\alpha$ -haloketones **61** through the addition of lithium carbenoids at  $-78\text{ }^\circ\text{C}$  formed under classical Barbier-type conditions (Scheme 26). Regardless the organometallic reagent is or not employed in excess, esters mainly react giving carbinols *via* the double addition of the carbenoid. However, the presence of a disubstituted  $\alpha$ -amino group (*e.g.* **59**) enables the internal coordination of the corresponding tetrahedral intermediate **60** and, as such, the double addition is conveniently avoided.<sup>42c</sup> The unusual stability of this intermediate is guaranteed by the presence of the electronegative halogen and oxygen atoms, which prevents the elimination of the alkoxyde group.



Scheme 26. Barluenga's homologation of esters to  $\alpha$ -haloketones.

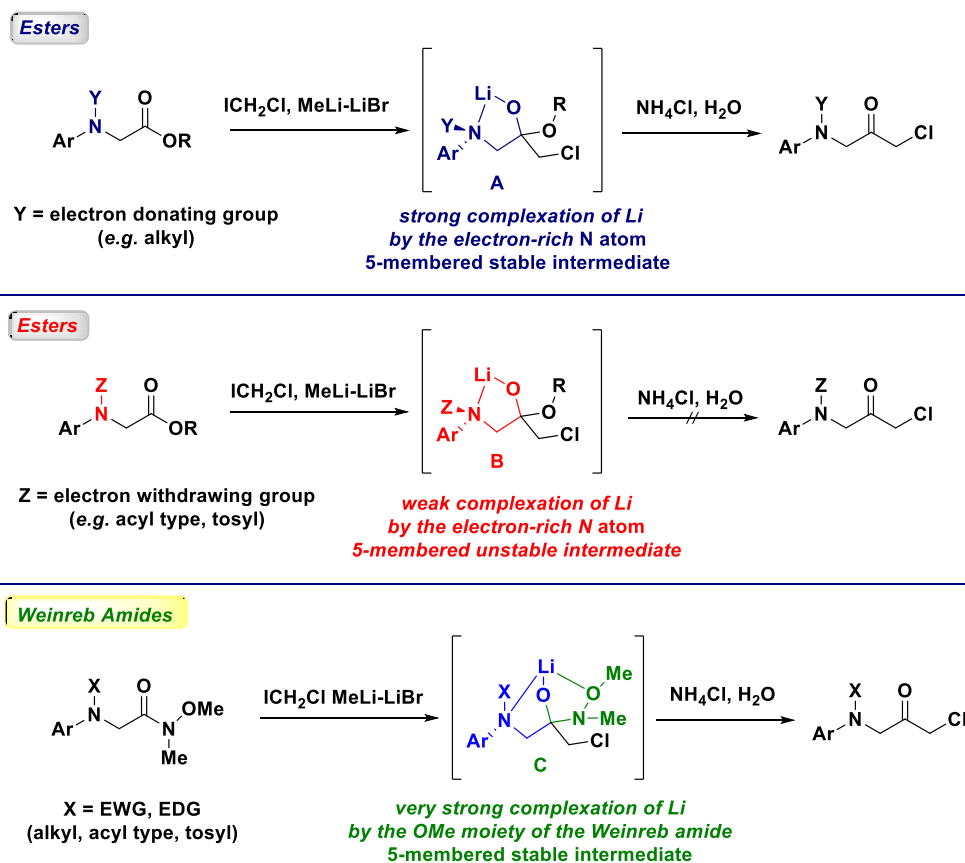
The group of Izawa studied the reactivity of esters and found that the presence of an amino or amido group presenting a hydrogen atom (*i.e.* non fully substituted) inhibits the homologation reaction.<sup>76</sup> In fact, the abstraction of the hydrogen by the basic carbenoid is favoured rather than its attack to the ester functionality. The solution to this drawback was represented by the formation of the corresponding *N*-protected 3-oxazolidin-5-ones **62** as suitable protecting groups, which can be easily chloromethylated to afford the intermediate **63** (Scheme 27). After acidic treatment, the latter is transformed into the desired chloroketone **64**. Furthermore, the Izawa's group reported the chemoselective chloromethylation of *N*-imine protected amino acids esters **65**. This is indeed one of the rare cases of chemoselectivity – due to the concurrence of two factors, namely the low electrophilicity of the imine's carbon and the steric hindrance – observed in the nucleophilic additions of carbenoids and, will be treated in detail within this thesis. Alternatively, Hilpert and co-workers introduced the *in situ* protection of the (secondary) amide moiety - as a labile *N*-trimethylsilyl amine - which is then easily removed during the work-up procedure.<sup>77</sup>



Scheme 27. Izawa's homologation of lactones and imino-esters to access  $\alpha$ -amino- $\alpha'$ -chloroketones.

Very recently, Pace rationalized the reactivity of carboxylic acid derivatives towards lithium carbenoids.<sup>51</sup> In fact, a direct comparative study between esters and Weinreb amides pointed out

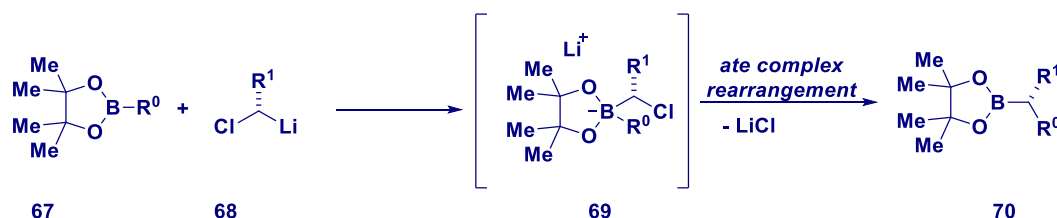
that the different reactivity of these starting materials has to be related to the formation of a more or less stable tetrahedral intermediate (*Scheme 28*). The experiments, conducted on *N*-arylamino acetic acid derivatives, suggest that in the case of esters the homologation proceeds only if an additional electron-donating group (EDG) is present on the nitrogen, which evidently increases its basicity and, as a consequence, the capability to coordinate with the lithium of the alkoxide (intermediate **A**). When an electron-withdrawing group (EWG) is present the intermediate **B** is not stabilized enough and thus, the homologative transformation does not take place. In the case of Weinreb amides,<sup>78</sup> the constitutive presence of the *N*-methoxy-*N*-methyl group allows the reaction to occur regardless the nature of the substituent on the nitrogen as a consequence of the exceptional stability of the intermediate **C**.



*Scheme 28.* Pace's mechanistic explanation of the different behaviour of esters and Weinreb amides towards lithium carbenoid-mediated homologation.

## 2.5 Homologation of Boron Electrophiles

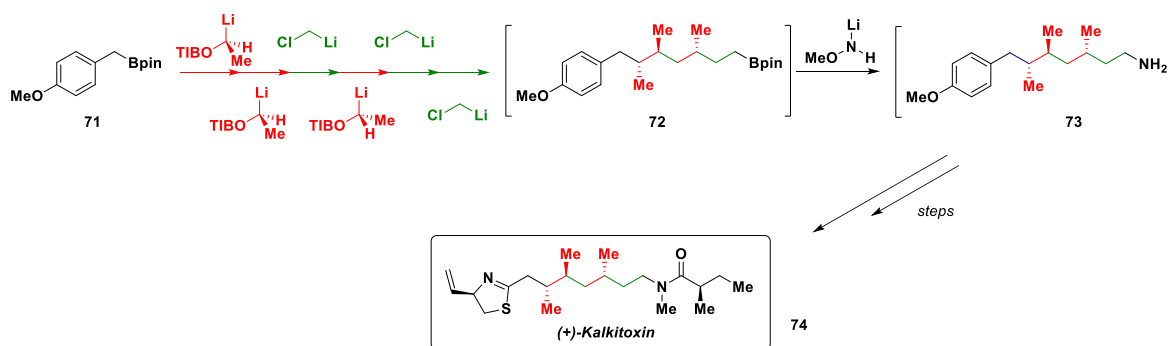
The homologation of non-carbon electrophiles has been reported as a strategy to realize transformations such as ring-enlargement in the cases of zirconium,<sup>79</sup> silicon or germanium.<sup>80</sup> In the 1980s, Matteson documented that boronic esters, showing slightly less reactivity towards alkillithiums compared to aldehydes and ketones, can be homologated with lithium halocarbonoids.<sup>81</sup> He demonstrated that boronic esters featuring a chiral diol are susceptible of homologation in a two-steps sequence consisting of: a) initial addition of  $\text{LiCHCl}_2$  to give an ( $\alpha$ -haloalkyl)boronic ester followed by, b) reaction with a Grignard reagent. These processes proceeded with exceptionally high levels of stereocontrol and, recently have been exploited in outstanding works by Blakemore.<sup>48,61a-c,82</sup> The authors describe the addition of the nucleophile to the electrophilic boron atom of **67** to give intermediate **69** thus forming the homologated **70** (Scheme 29).



Scheme 29. Blakemore's application of Matteson homologation with chiral lithium carbenoids.

Aggarwal extended the concept of the Matteson homologation to iterative homologation processes for the efficient stereocontrolled syntheses of two natural products, (+)-Kalkitoxin and (+)-Hydroxyphthioceranic acid<sup>44a,47</sup> using chiral lithiated benzoate esters and chloromethylithium (Scheme 30).<sup>83</sup>





Scheme 30. Aggarwal's assembly-line synthesis of (+)-Kalkitoxin.

Notably, the purification during the whole homologation cycle could be avoided, thus considerably improving the overall synthetic performance. In the case of (+)-kalkitoxin **74**, six iterative homologations were executed on the commercially available boronic ester **71** to build up the carbon array before the C-B bond was transformed into the required C-N bond (**73**) without purification of the intermediates. Such an approach developed by Aggarwal, comes close to the Hendrickson's<sup>84</sup> concept of the *ideal synthesis* aimed at avoiding unnecessary steps (e.g. purification of the intermediates).<sup>50a,83,85</sup>

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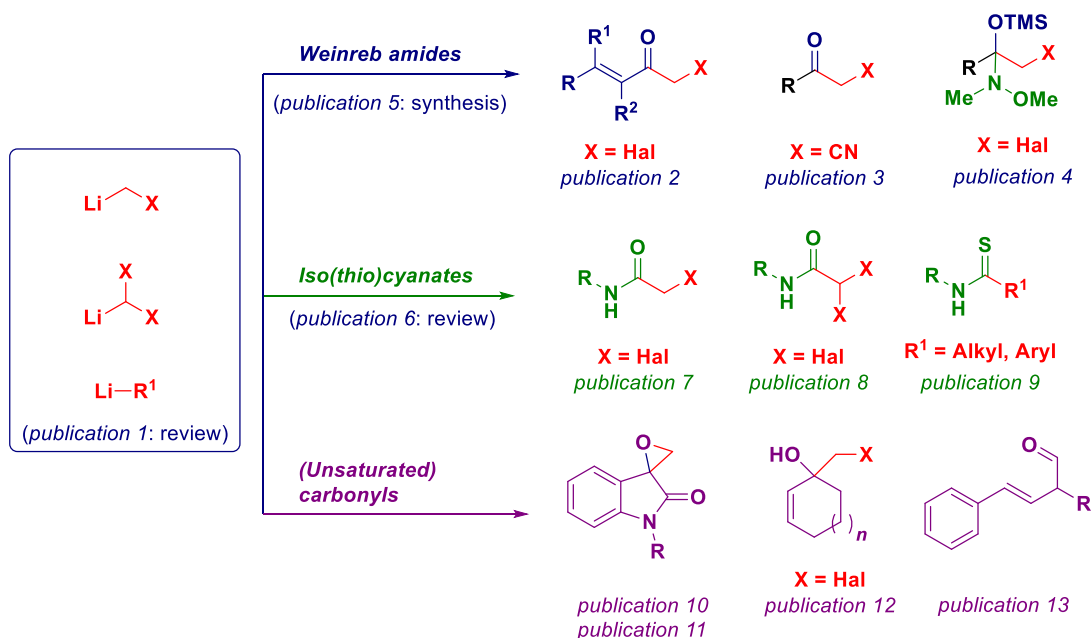
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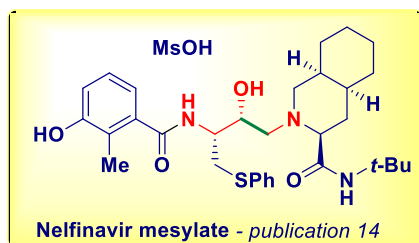
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#### 4. Results and Discussion

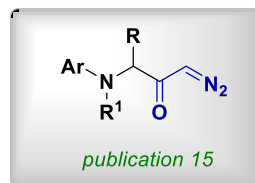
In this section, the research achievements obtained and published during the realization of this Doctoral Thesis are presented. The reactivity of lithium reagents - with particular emphasis - but not limited to - halocarbenoids has been thoroughly investigated in the cases of carbon electrophiles such as Weinreb amides, iso(thio)cyanates and unsaturated carbonyls (including isatins). The common concept behind the tactics object of study was achieving transformations with high control of chemoselectivity / regioselectivity which could, ultimately, provide robust and versatile tools to be exploited in synthetic chemistry. As such, we aimed at developing preparative strategies featuring conceptual simplicity for accessing the targeted scaffolds by minimizing the number of steps of a synthetic route. The employment of selected synthesized compounds in recently established chemistries is also presented with the aim to connect conceptually different fields. We also introduce novel tactics in which once the halomethylation is executed, the tunings of the reaction conditions could trigger unexpected outcomes, which finally lead to complex molecular architectures.



#### Application to Synthetic Medicinal Chemistry



#### Redesigning the Arndt-Eistert Synthesis



A general vista of the chemistry of halocarbenoids presented in the introduction of this Thesis is resumed in *Publication 1*.

The first topic deals with the addition of organometallic reagents to Weinreb amides, highlighting the versatility of these acylating agents in synthetic processes and, giving a perspective on the use of amide-type substrates as privileged material for accomplishing chemoselective additions of organometallic reagents. In particular, we use Weinreb amides for the synthesis of  $\alpha,\beta$ -unsaturated  $\alpha'$ -haloketones (*Publication 2*), highlighting the differences in chemoselectivity with usually employed esters. The homologation of Weinreb amides was further exploited in the cases of functionalized lithiated acetonitrile derivatives ( $\text{LiCR}^1\text{R}^2\text{CN}$ ) (*Publication 3*). Moreover, as a mechanistic proof, the tetrahedral intermediates generated upon the addition of halolithium carbenoids ( $\text{LiCH}_2\text{X}$  and  $\text{LiCHXY}$ ) to Weinreb amides have been intercepted for the first time and fully characterized as *O*-TMS heminals (*Publication 4*). Most of the Weinreb amides employed in

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this Thesis have been prepared according to a modified Schotten-Baumann protocol (*Publication 5*).

The study of homologation procedures continues with the employment of heterocumulenes (isocyanates and isothiocyanates), which, featuring a highly reactive carbon, do allow the easy installation of various C-nucleophiles (*Publication 6*). Accordingly, the addition of lithium monohalocarbenoids is presented as a straightforward method to access valuable  $\alpha$ -halomethylamides through a single synthetic operation (*Publication 7*). Moreover, the scope of the reaction has been further extended to the preparation of dihalocarbenoids (*Publication 8*). The tactic is further exploited for a simple, high-yielding synthesis of thioamides starting from isothiocyanates and a plethora of organolithium reagents, including sterically hindered and/or enantiopure ones (*Publication 9*).

Subsequently, the addition of halomethylolithiums to functionalized isatins (whose preparation is reported in *publication 11*), ensued by base mediated ring closure is reported as an effective methodology to access spiroepoxyoxindoles (*Publication 10*). Furthermore, the reactivity of cyclic enones with lithium carbenoids is discussed: high chemoselectivities were achieved for the obtainment of interesting chloromethyl allylic alcohols (*Publication 12*).

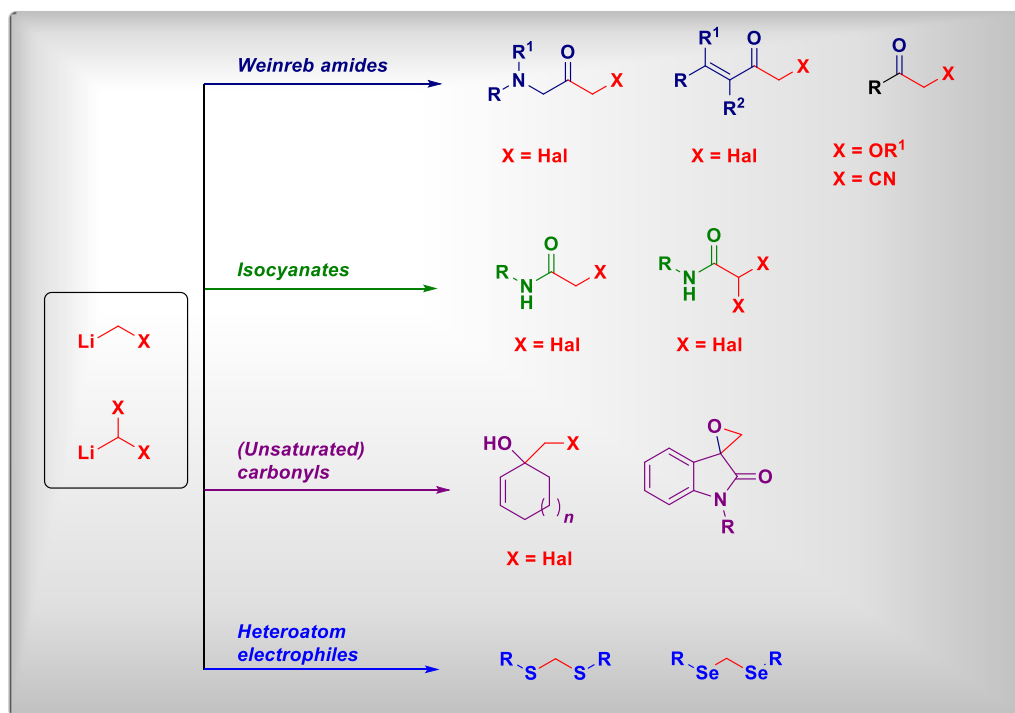
Following the research on cyclic enones, it has been developed a rapid and high-yielding synthesis of aldehydes with all-carbon  $\alpha$ -quaternary centers from  $\alpha,\beta$ -unsaturated acyclic and cyclic ketones. In a single operation step, we achieved the merging of three different transformations: the homologation, the epoxide–aldehyde isomerization and the  $\alpha$ -functionalization with an external or internal electrophile of the putative aldehyde enolate, whose intermediacy was confirmed by labeling experiments (*Publication 13*).

To highlight the versatility of the protocols studied herein, we documented an asymmetric protocol for preparing the HIV inhibitor Nelfinavir, whose critical steps are represented by an homologation procedure with lithium carbenoids and an enzymatic stereoselective reduction (*Publication 14*).

Finally, considering the Arndt-Eistert reaction as the prototypal homologation, we report a straightforward preparation of a series of  $\alpha$ -amino diazoketones *via* an unique diazotization procedure thus, restricting the use of diazomethane to the preparation of a common precursor which was properly modified according to the synthetic needs (*Publication 15*).



In this article we provide an overview of our ongoing research focused on the employment of halomethyl lithium carbenoids in synthetic chemistry. In particular, we discuss preparative and stability aspects, followed by a detailed discussion on the novel tactics developed so far. Noteworthy, carbenoids are introduced as homologating agents belonging to the class of C-1 building blocks and in that context analogies and differences with similar reagents (e.g. diazomethane, sulfur ylides, carbenoids of different metals) are presented. A detailed discussion on the homologation of carbon electrophiles is succinctly reported. This article constitutes the source of inspiration for the Introduction of this Doctoral Thesis.

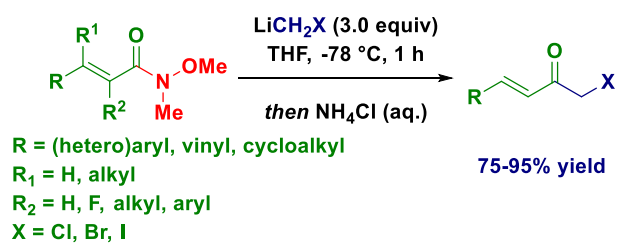


Vittorio Pace,\* **Laura Castoldi** and Wolfgang Holzer

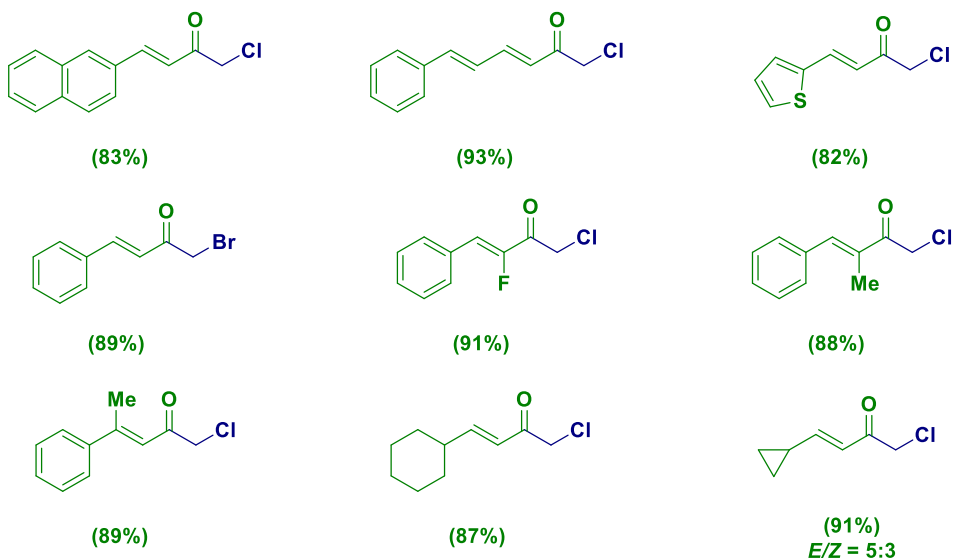
*Synthesis of  $\alpha,\beta$ -Unsaturated  $\alpha'$ -Haloketones through the Chemoselective Addition of Halomethylolithiums to Weinreb Amides*

*J. Org. Chem.* **2013**, *78*, 7764-7770

We demonstrated the efficient performance of Weinreb amides for obtaining  $\alpha,\beta$ -unsaturated- $\alpha'$ -haloketones under full chemocontrol.



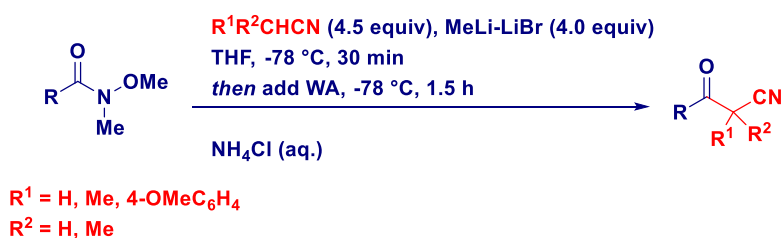
*Selected examples (out of 20)*



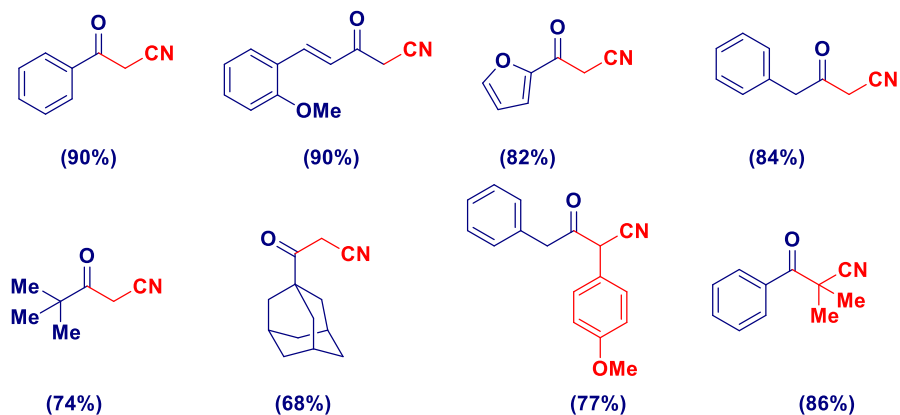
*Chemoselective efficient synthesis of functionalized  $\beta$ -oxonitriles through cyanomethylation of Weinreb amides*

*Org. Biomol. Chem.* **2015**, *13*, 1969-1973

Thanks to the high nucleophilicity of nitrile-type carbanions and the acylating properties of Weinreb amides, we describe an effective protocol for the preparation  $\beta$ -oxonitriles. Key points of the method are: a) high yields, avoiding purification *via* column chromatography; b) possibility to synthesize polysubstituted  $\alpha$ -cyanoketones by choosing the proper  $R^1R^2\text{LiCN}$  carbanion; c) excellent chemoselectivity found in particular systems such as  $\alpha,\beta$ -unsaturated Weinreb amides.



*Selected examples (out of 20)*

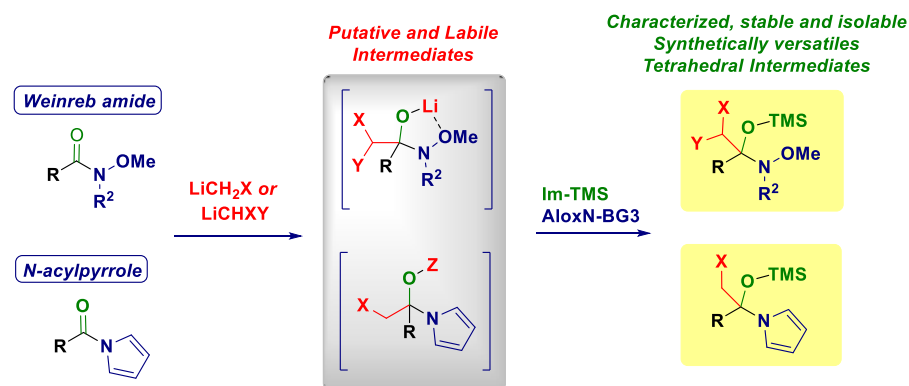


Laura Castoldi, Wolfgang Holzer, Thierry Langer and Vittorio Pace\*

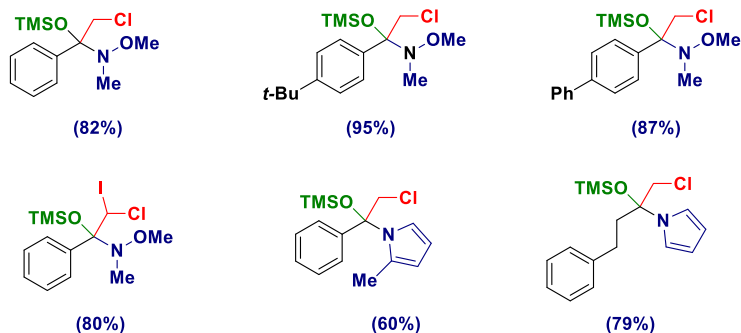
*Evidence and Isolation of Tetrahedral Intermediates Formed upon the Addition of Lithium Carbenoids to Weinreb Amides and N-acylpyrroles*

*Chem. Commun.* **2017**, 53, 9498-9501 - Highlighted in *Synfacts* **2017**, 13, 1185

Despite the widespread acceptance of the formation of a five-membered cycle in the tetrahedral intermediate generated upon the addition of an organometallic reagent to a Weinreb amide, no unambiguous proof has been disclosed in the > 35 years history of these highly valuable acylating agents. Herein, we isolated and fully characterized ( $^1\text{H}$ ,  $^{13}\text{C}$ ,  $^{15}\text{N}$ -NMRs, HRMS, IR) for the first time the tetrahedral intermediates – as *O*-TMS hemiaminals – obtained from the reaction of Weinreb amides with both mono- and dihalomethyl carbenoids. Pivotal for the success were: 1) use of TMS-imidazole as the silylating agent and, 2) chromatographic purification on deactivated neutral alumina (Brockmann grade 3). The methodology is completely adaptable for isolating analogous hemiaminals derived from *N*-acyl pyrroles.



Selected examples (out of > 25)

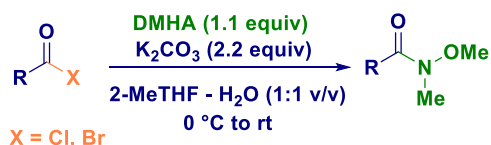


Vittorio Pace,\* **Laura Castoldi**, Andrés R. Alcántara and Wolfgang Holzer

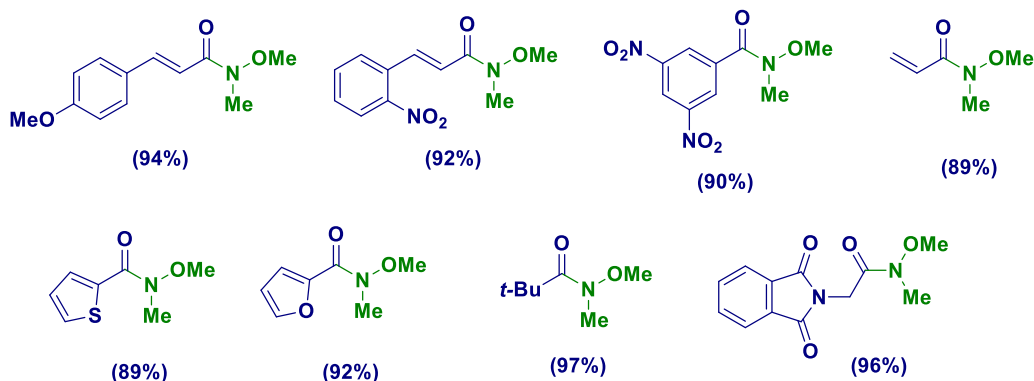
*Highly efficient and environmentally benign preparation of Weinreb amides in the biphasic system  
2-MeTHF/water*

*RSC Adv.* **2013**, 3, 10158-10162

We have developed a straightforward access to synthetically useful Weinreb amides starting from commercially available or readily obtainable acid halides in the biphasic medium (alkaline) water / 2-MeTHF. Due to the immiscibility of this biomass derived solvent with water, there is no necessity to use any noxious organic solvent within the whole preparative process. Pure compounds are obtained by simple removal of 2-MeTHF, thus avoiding purification steps which would complicate the efficiency of the sequence. The protocol is characterized by a wide applicability to variously functionalized acid halides and moreover, has been used for the preparation of a multi-electrophilic aldehyde of pharmacological relevance.



*Selected examples (out of 21)*

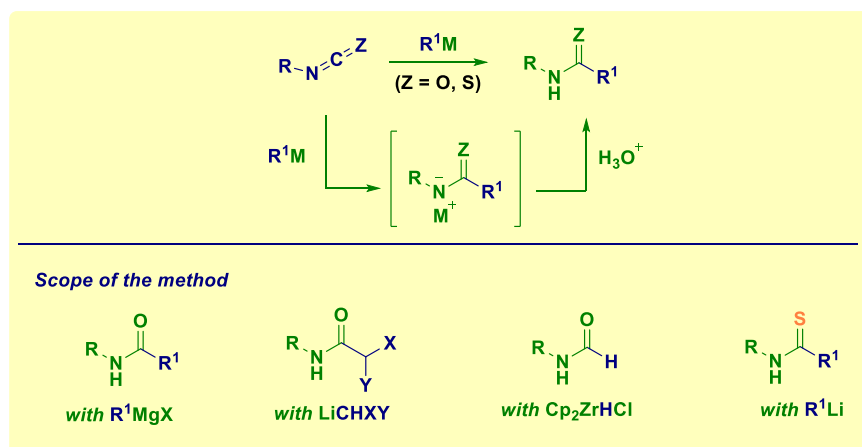


Vittorio Pace,\* Serena Monticelli, Karen de la Vega-Hernández and **Laura Castoldi**

*Isocyanates and isothiocyanates as versatile platforms for accessing (thio)amide-type compounds.*

*Org. Biomol. Chem.* **2016**, *14*, 7848-7854 – *Invited Perspective*

The amide bond is the chemical functionality most represented in Nature and synthesizing it is one of the most pursued topics in modern organic synthesis. In the 1920s Gilman introduced iso(thio)cyanates as valuable reagents for titrating organometallic reagents: the process entailed the acylation of the carbanion with the formation of a (thio)amide. It was quite surprising the almost lack of further preparative studies before Bode published an excellent method for preparing sterically hindered amides from Grignard reagents and isocyanates. In this perspective we present the factors which account for the high efficiency of heterocumulenes acylation: a) the excellent electrophilicity of the carbon; 2) the practically negligible deleterious effect (electronic and steric) displayed by the substituent on the nitrogen. Results from our own and other groups are succinctly presented in the case of the addition of carbanions and related agents (*i.e.* hydride).

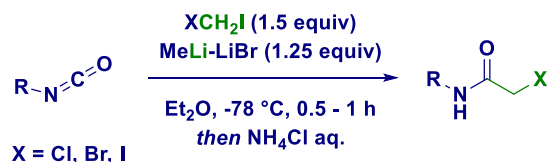


Vittorio Pace,\* **Laura Castoldi** and Wolfgang Holzer

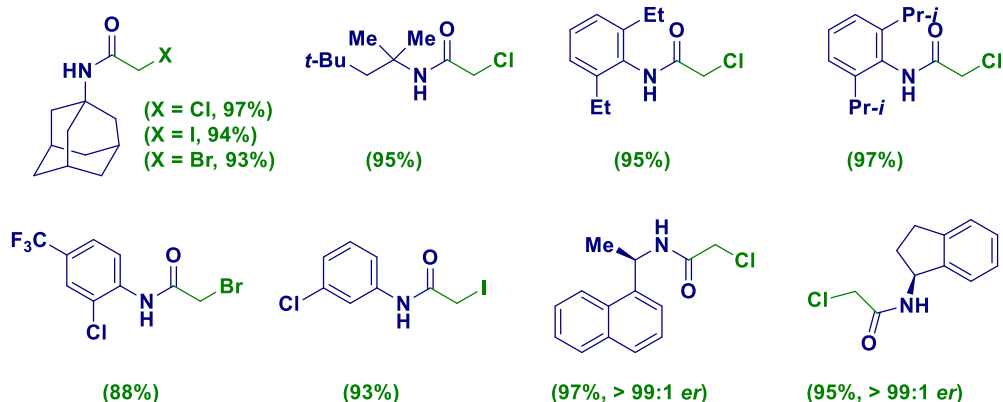
*Addition of lithium carbenoids to isocyanates: a direct access to synthetically useful N-substituted 2-haloacetamides.*

*Chem. Commun.* **2013**, 49, 8383-8385 - Highlighted in *Synfacts* **2013**, 9, 1218

We reported the synthesis of *N*-substituted 2-haloacetamides starting from widely available isocyanates. The reaction showcases an excellent substrate scope allowing the chemoselective addition of  $\text{LiCH}_2\text{X}$  to a wide range of isocyanates with different substitution pattern on nitrogen. No differences have been observed switching from aliphatic to aromatic materials. The protocol is amenable for the synthesis of highly sterically hindered  $\alpha$ -haloamides and importantly, chemoselectivity is preserved in the presence of additional. Additional points of interest are: a) The tactic provides haloamides in almost quantitative yields, without needing to perform chromatography purifications; b) the different monohalocarbenoids react equally; c) the stereochemical information contained in the starting isocyanate is fully transferred to the haloamide.



Selected examples (out of 18)

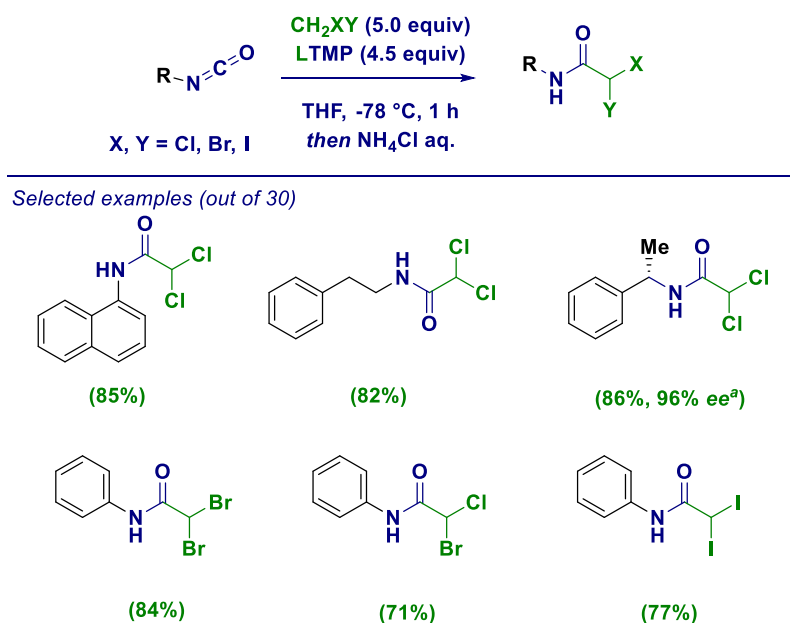


Vittorio Pace,\* **Laura Castoldi**, Ashenafi Damtew Mamuye and Wolfgang Holzer

*Homologation of Isocyanates with Lithium Carbenoids: A Straightforward Access to  $\alpha$ -Halomethyl- and  $\alpha,\alpha$ -Dihalomethylamides*

*Synthesis* **2014**, 46, 2897-2909 (Invited Feature Article)

The methodology could also be extended to the synthesis of  $\alpha,\alpha$ -dihaloamides, which is a demanding task because of the chemoselective difficulties associated with the use of halogenation procedures. The generation of dihalolithium carbenoids ( $\text{LiCHXY}$ ) through the deprotonation of a dihalomethane with a lithium amide base under Barbier conditions in the presence of the isocyanate gives the expected compounds in high yields and optical purity. We found LTMP as the optimal base able to selectively generate the dihalocarbenoids. Interestingly, lithium diiodomethane was prepared according to the Bull's protocol prior to the addition of the isocyanate thus, showing a superior stability compared to analogous monohalo and dihalo species. Again, the addition of dihalolithium carbenoids does not alter the enantiopurity of the starting isocyanates.



<sup>a</sup> 96% ee for the supplied starting material.

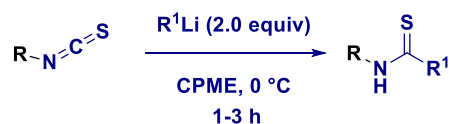


**Vittorio Pace**,\* Laura Castoldi, Serena Monticelli, Sandra Safranek, Alexander Roller, Thierry Langer and Wolfgang Holzer

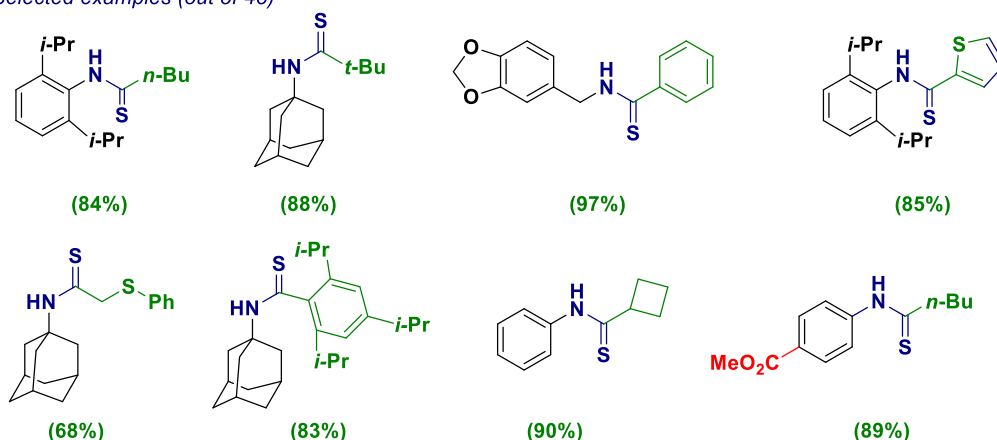
*A Robust, Eco-Friendly Access to Secondary Thioamides through the Addition of Organolithium Reagents to Isothiocyanates in Cyclopentyl Methyl Ether (CPME)*

*Chem. Eur. J.* **2015**, *21*, 18966-18970 - Highlighted in *Org. Process Res. Dev.* **2016**, *20*, 105

We next focused on investigating the reactivity of isothiocyanates considering that accessing thioamides through such a approach would have allowed to overcome the severe limitations related to the synthesis of these building blocks. The procedure is applicable to a set of different combinations of isothiocyanates and organolithiums giving the expected thioamides in excellent yields. We were delighted in expanding the protocol to the straightforward synthesis of complex thioamides including highly sterically demanding structures. It is important to note that by transmetalating the lithium carbanion to a Gilman reagent ( $R_2CuLi$ ) it is possible to chemoselectively obtain a functionalized thioamide presenting untouched an ester groups thus, directing the addition of the organometallic species exclusively at the isothiocyanate moiety.



*Selected examples (out of 45)*

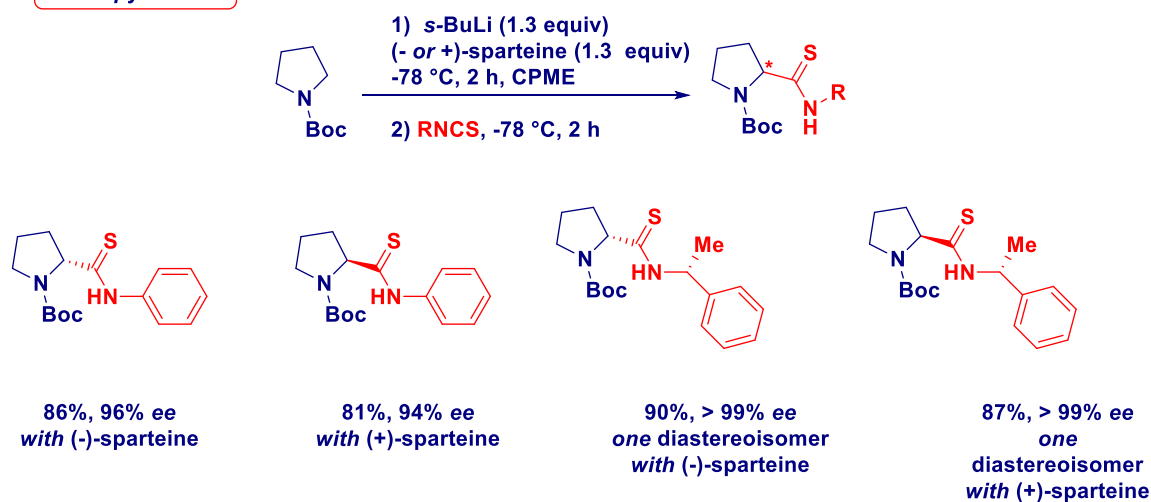


No racemization takes place upon the addition of various organolithium reagents to optically active isothiocyanates. The formation of enantiopure *N*-Boc-pyrrolidine or Hoppe's carbamate,

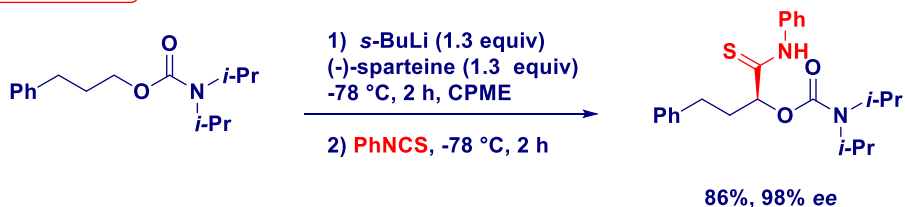
through the deprotonation in the presence of chiral ligands (-)- or (+)-sparteine affords the corresponding thioamides with full retention of stereochemistry and in excellent diastereomeric ratio. As expected, by switching from one enantiomer of sparteine to the other, it is possible to get both asymmetric forms of a given thioamide with comparable optical purity. The simplicity of the reaction conditions developed and the results in terms of enantiopurity allow to conclude that the present method showcases better performances compared with sulfurating protocols in which *ee*'s erosion can be problematic.

#### Chiral thioamides from enantiopure organolithium reagents

##### N-Boc-pyrrolidine



##### Hoppe's carbamate

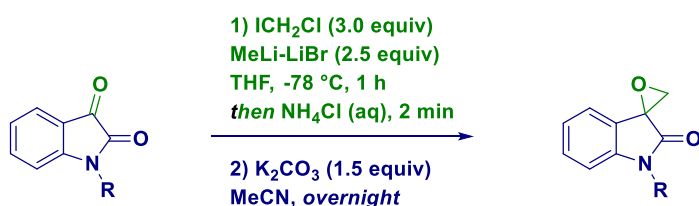


Vittorio Pace,\* **Laura Castoldi**, Ashenafi Damtew Mamuye, Thierry Langer and Wolfgang Holzer

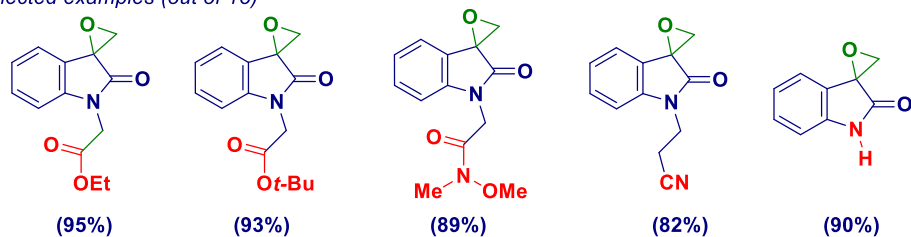
*Chemoselective Addition of Halomethylolithiums to Functionalized Isatins: A Straightforward Access to Spiro-Epoxyoxindoles*

*Adv. Synth. Catal.* **2016**, 358, 172-177 - Highlighted in *Synfacts* **2016**, 12, 302

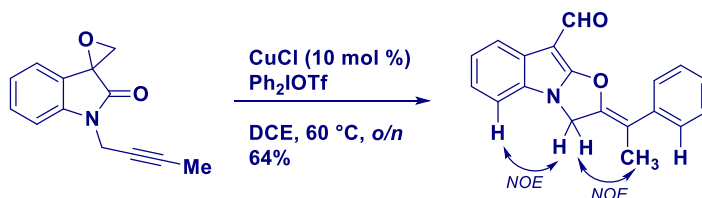
An efficient chemoselective access to rare spiro-epoxyoxindoles has been developed through the addition of the chloromethylolithium to *N*-functionalized isatins followed by the ring-closure. The protocol showcases an excellent scope and, chemoselectivity is fully maintained in the presence of additional electrophilic functionalities. The Gaunt's Cu-catalyzed intramolecular electrophilic oxyarylation of a *N*-propargyl-type spiroepoxyoxindole affords a complex tricyclic system.



Selected examples (out of 15)



Gaunt's oxyarylation

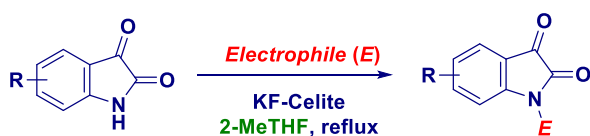


Ashenafi Damtew Mamuye, Serena Monticelli, **Laura Castoldi**, Wolfgang Holzer and Vittorio Pace\*

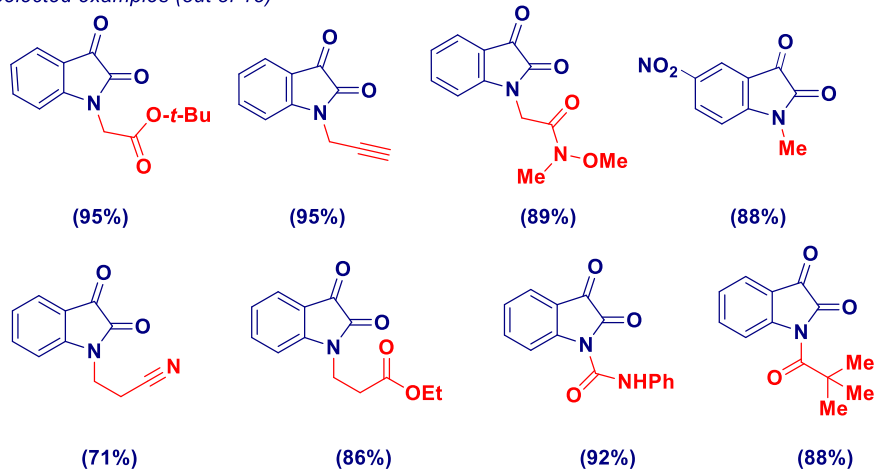
*Eco-friendly chemoselective N-functionalization of isatins mediated by supported KF in 2-MeTHF*

*Green Chem.* **2015**, *17*, 4194-4197

An efficient *N*-functionalization of isatin derivatives promoted by the combination of the coated base KF-Celite and the biomass derived solvent 2-MeTHF has been disclosed. The high yielding method shows excellent versatility and applicability to different electrophilic agents ranging from simple primary alkyl halides to isocyanates, acyl halides or Michael acceptors.



Selected examples (out of 15)

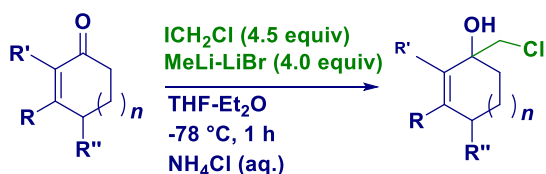


Vittorio Pace,\* **Laura Castoldi** and Wolfgang Holzer

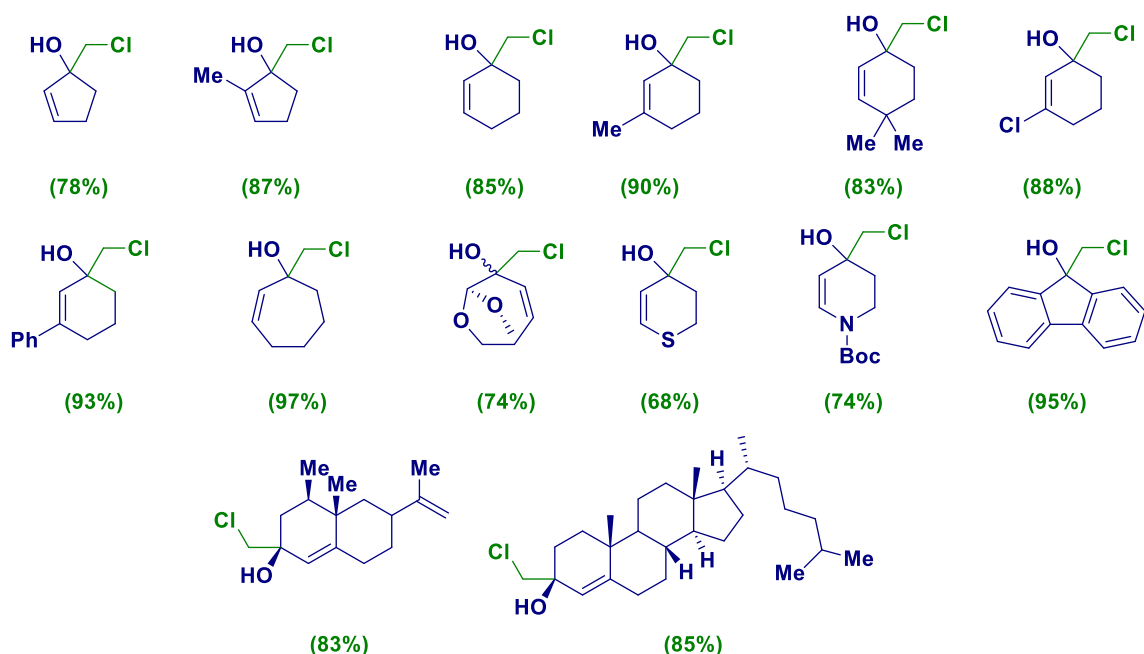
*Chemoselective Additions of Chloromethylithium Carbenoid to Cyclic Enones: A Direct Access to Chloromethyl Allylic Alcohols*

*Adv. Synth. Catal.* **2014**, 356, 1761-1766 - Highlighted in *Synfacts* **2014**, 10, 856

We have reported the reactivity of a lithium carbenoid ( $\text{LiCH}_2\text{Cl}$ ) with a series of cyclic  $\alpha,\beta$ -unsaturated enones. Key features disclosed within this study are: 1)  $\text{LiBr}$  not only acts as a carbenoid stabilizer but also as a mild Lewis acid activator of the  $\text{C}=\text{O}$  bond; 2) in the case of  $\beta$ -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; 3) the protocol is tolerant to various ring-sized enones (5, 6, 7 membered and also complex natural product structures) bearing eventually different substitution patterns.



*Selected examples*

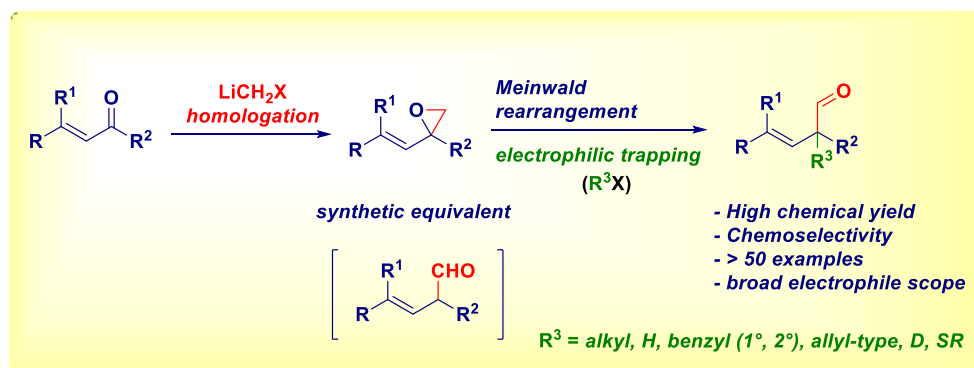


Vittorio Pace,\* **Laura Castoldi**, Eugenia Mazzeo, Marta Rui, Thierry Langer and Wolfgang Holzer

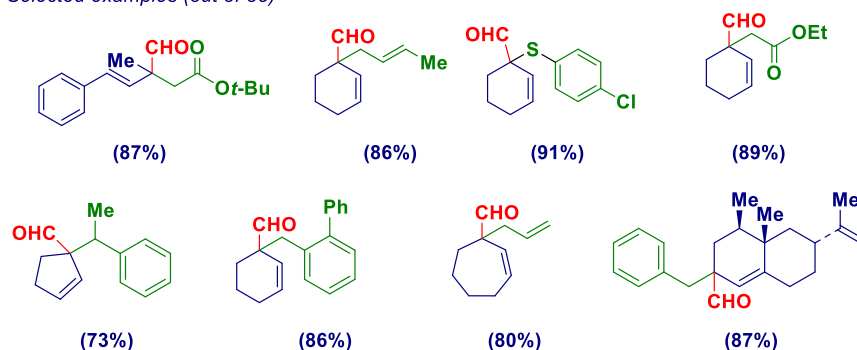
**Efficient Access to All-Carbon Quaternary and Tertiary  $\alpha$ -Functionalized Homoallyl Aldehydes from Ketones**

*Angew. Chem. Int. Ed.* **2017**, 56, 12677-12682 - Highlighted in *Synfacts* **2017**, 11, 1184

The homologation of an  $\alpha,\beta$ -unsaturated ketone with a lithium carbenoid – upon increasing of temperature – directly affords an  $\alpha$ -fully substituted aldehyde. Such a completely novel tactic – constituted by a *single* synthetic operation – is the result of *three* different processes whose fine tuning allows to document an extremely easy access to  $\beta,\gamma$ -unsaturated aldehydes. The overall strategy consists of: 1)  $C_1$ -homologation; 2) epoxide-aldehyde Lewis acid mediated isomerization and, 3) enolate electrophilic trapping. The synthetic equivalence between a vinyl oxirane and a  $\beta,\gamma$ -unsaturated aldehyde is the key concept governing the technique. Mechanistic studies and labeled experiments suggest the intervention of an aldehyde enolate as the crucial intermediate. Significantly, the homologating carbenoid formation event (carbenoid precursor and organolithium) plays a critical role in determining the chemoselectivity.



Selected examples (out of 35)

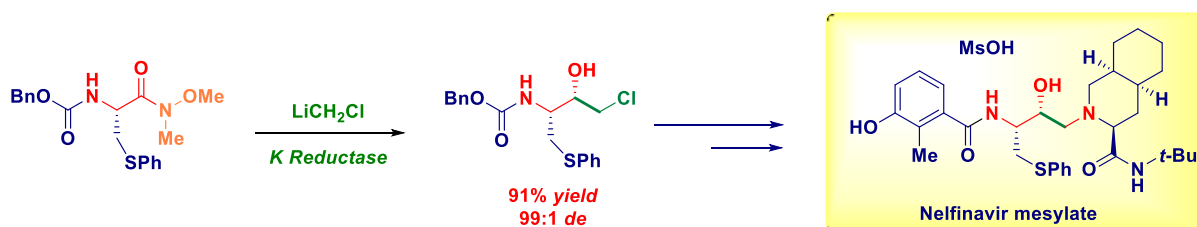


Laura Castoldi, Laura Ielo, Pilar Hoyos, María J. Hernáiz, Laura De Luca, Andrés R. Alcántara, Wolfgang Holzer and Vittorio Pace\*

**Merging Lithium Carbenoid Homologation and Enzymatic Reductions: A Combinative Approach to the HIV-Protease Inhibitor Nelfinavir**

*Manuscript submitted.*

From a medicinal chemistry perspective, the importance of  $\alpha$ -haloketones is clearly illustrated in the synthesis of HIV-protease inhibitors where they constitute highly valuable intermediates. Because of the lack of availability of safe strategies – *i.e.* diazomethane-free processes – we designed a highly efficient formal synthesis of Nelfinavir whose key steps were: a) the homologation of a Weinreb amide to the corresponding  $\alpha$ -haloketone and, b) its enzymatic reduction to a chiral enantiopure halohydrin (99:1 *de*), direct precursor of the biologically active drug.

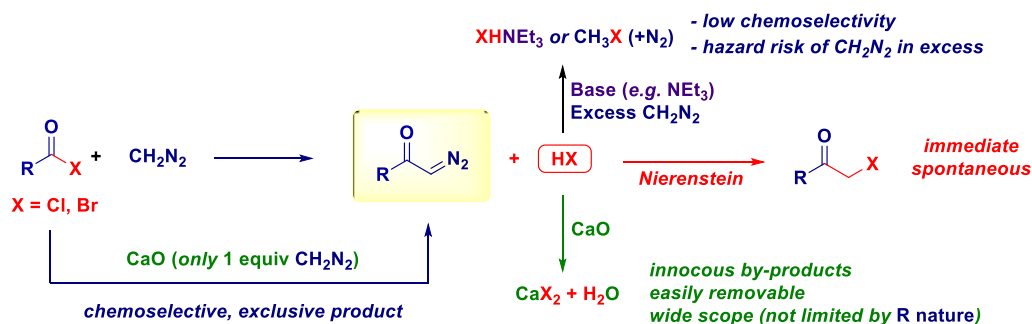


***α-Arylamino Diazoketones: Diazomethane-Loading Controlled Synthesis, Spectroscopic Investigations and Structural X-ray Analysis***

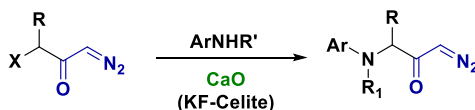
*J. Org. Chem.* **2018**, accepted (Manuscript ID: jo-2017-03134r.R1)

As summarized at the beginning of this Thesis, the first and probably most common C-1 homologating agent is diazomethane, whose use in synthesis dates back to 1920s. Despite the undiscussed potential and versatility, the proved mutagenicity, toxicity and explosion risks pose serious issues to the practicability of reactions involving diazomethane. Notwithstanding, diazoketones are valuable scaffolds in synthesis and, we conclude this Thesis, presenting a useful technique allowing the access to α-amino diazoketones (*i.e.* direct precursors of HIV inhibitors) in which *only* stoichiometric diazomethane is required. The key for the success is employing the inexpensive calcium oxide which acts as an acid scavenger thus, continuously removing from the reaction mixture the hydrohalic acid liberated during the diazomethane homologation and/or the subsequent nucleophilic displacement with an amine.

**Synthesis of α-diazoketones with stoichiometric diazomethane**



**Application to the synthesis of α-arylamino diazoketones**



**Advantages:**

- The common diazo precursors are easily obtained in high yields;
- The use of diazomethane is limited to the preparation of the alkylating agents;
- High yields and full control of chemoselectivity



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## 5. Conclusions and Outlook

Since the seminal studies by Köbrich, lithium halomethylcarbenoids emerged as synthetically versatile reagents for accomplishing homologation reactions on a plethora of electrophiles not limited to carbon species. They allow the formal incorporation of a (reactive) halomethylenic fragment into an electrophile thus, overcoming additional steps needed for the transformations of similar intermediates (*e.g.* diazoketones, sulfur ylides) into the desired adducts. We showed the effectiveness in performing highly chemocontrolled homologations in the presence of additional electrophilic substrates.

Nowadays, the recently developed Luisi's protocol for generating  $\text{LiCH}_2\text{X}$  reagents with microfluidic techniques - at temperatures up to  $-20\text{ }^\circ\text{C}$  without the requirement of Barbier-type conditions - would certainly allow to further exploit the synthetic potential of these reagents in broader contexts.

The employment of carbenoids in alkylation type processes still remains at its infancy and, in our opinion, would represent a formidable and challenging area for further investigations, which would allow to realize one-carbon elongations on  $\text{C-sp}^3$  systems.

Without any doubt, the important contributions by Hammerschmidt and coworkers on the configurational stability of halo-[ $\text{D}_1$ ]-methylolithium will open the field to the establishment of chiral carbenoid-mediated homologation techniques to access enantiomerically pure functionalized halomethyl-derivatives.

In this regard, the generation of chiral, fully substituted carbenoids (*i.e.*  $\text{LiCRR}^1\text{X}$ ) ensued by application to homologation processes is certainly a major challenge which will deserve in-depth studies to provide robust and versatile tools for organic transformations of medicinal interest.



*Publication n. 1*

**New Perspectives in Lithium Carbenoid Mediated Homologations.**

Pace, V.;;\* Castoldi, L.; Monticelli, S.; Rui, M.,; Collina S.

*Synlett* **2017**, 28, 879-888 (DOI: 10.1055/s-0036-1588139)



# New Perspectives in Lithium Carbenoid Mediated Homologations

Vittorio Pace<sup>\*a</sup>

Laura Castoldi<sup>a</sup>

Serena Monticelli<sup>a</sup>

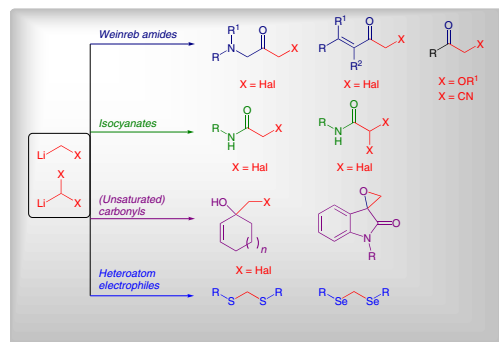
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Dedicated to Professor Friedrich Hammerschmidt on the occasion of his retirement



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**Abstract**  $\alpha$ -Functionalized organolithium reagents (e.g.,  $\text{LiCH}_2\text{X}$ ) are versatile reagents for accomplishing homologations of carbon- and heteroatom-type electrophiles. The proper selection of the reaction conditions allows one to direct their intrinsic ambiphilicity towards the nucleophilic character. Herein, the homologation of various electrophiles ranging from Weinreb amides to isocyanates, carbonyl derivatives, and chalcogenides – with a particular focus on the chemoselectivity of the processes – is summarized.

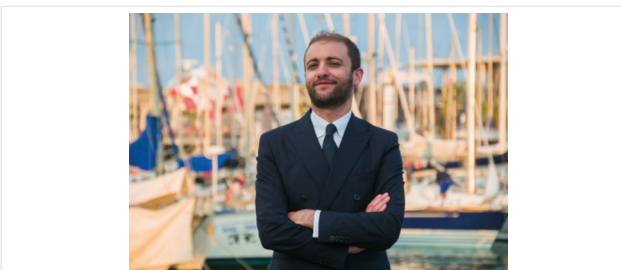
- 1 Introduction
- 2 Homologation of Weinreb Amides
- 3 Homologation of Cyclic Ketones
- 4 Homologation of Isocyanates
- 5 Homologation of Disulfides and Diselenides
- 6 Conclusions

**Key words** carbenoids, lithium, homologation, chemoselectivity, organometallic reagents

## 1 Introduction

The formal addition of a substituted methylene unit (e.g.,  $\text{CH}_2\text{X}$ ,  $\text{X}$  = halogen, CN, OR) to an electrophile is a fundamental synthetic operation enabling the delivery of a given fragment with the exact degree of derivatization.<sup>1</sup> As such, the formation of a new carbon–carbon or carbon–heteroatom bond is accomplished under high chemocontrol, and thus issues arising from the late-functionalization of an unsubstituted precursor could be advantageously overcome.<sup>2</sup>

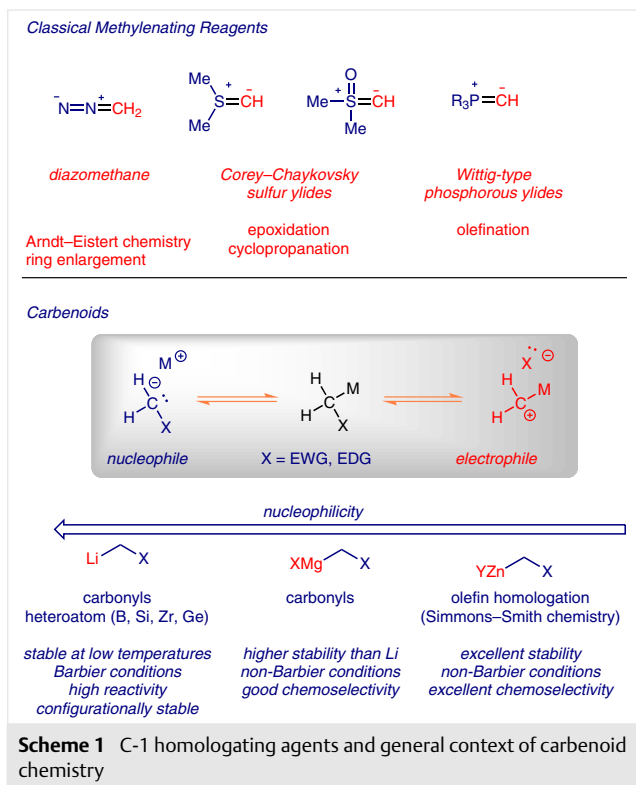
In this context, classical reagents versatile for this so-called homologation reactions<sup>3</sup> are halocarbenoids intro-



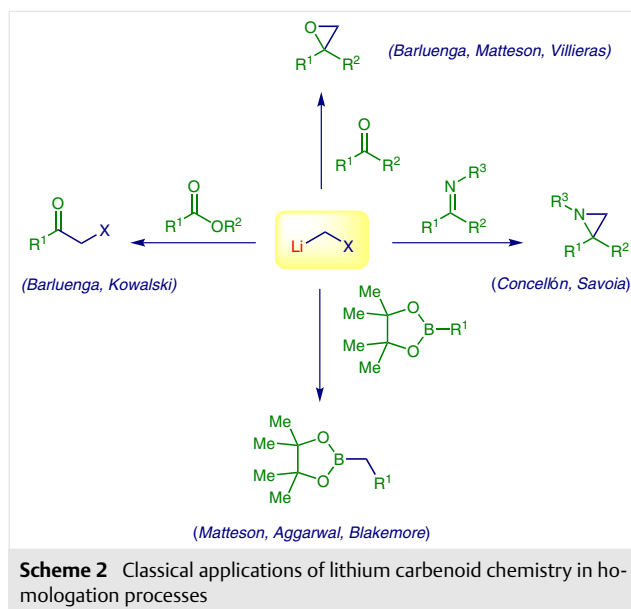
**Vittorio Pace** obtained the degree in Pharmacy from the University of Perugia (Italy), then he received a PhD in Chemical Sciences from the Complutense University of Madrid under the guidance of Prof. A. R. Alcántara and J. V. Sinisterra. In 2010 he moved to the University of Vienna to join the group of Prof. W. Holzer as a Mach postdoc fellow. Postdoctoral training continued with Prof. D. J. Procter at The University Manchester (2011–2013) and with Prof. B. Olofsson at Stockholm University (2013–2014). In August 2014 he came back to Vienna as a group leader in Synthetic Chemistry at the Department of Pharmaceutical Chemistry. In November 2014 he obtained the habilitation for Associate Professor of Organic Chemistry by the Italian Ministry of Education. In 2015 he was awarded with the Vincenzo Caglioti Prize by the Accademia Nazionale dei Lincei, the Ciamician Medal by the Division of Organic Chemistry of the Italian Chemical Society, and the Young Investigator Award by the Faculty of Life Sciences of the University of Vienna. In November 2016 he received the Habilitation (venia docendi) in Pharmaceutical Chemistry from the University of Vienna. His main research interest deals with the application of lithium carbenoids and organometallic reagents in organic synthesis

duced in organic synthesis during the 1960s by Köbrich.<sup>4</sup> Although at first sight they may be considered analogues of similar reagents such as diazomethane<sup>5</sup> or Corey–Chaykovsky ylides,<sup>6</sup> their capability to switch the reactivity from nucleophilic to electrophilic renders them unique species within the class of organometallic reagents (Scheme 1). Indeed, two main parameters are governing the equilibrium between the nucleophilic and the electrophilic reactivity: 1) the nature of the metal and 2) the temperature. Nowadays,

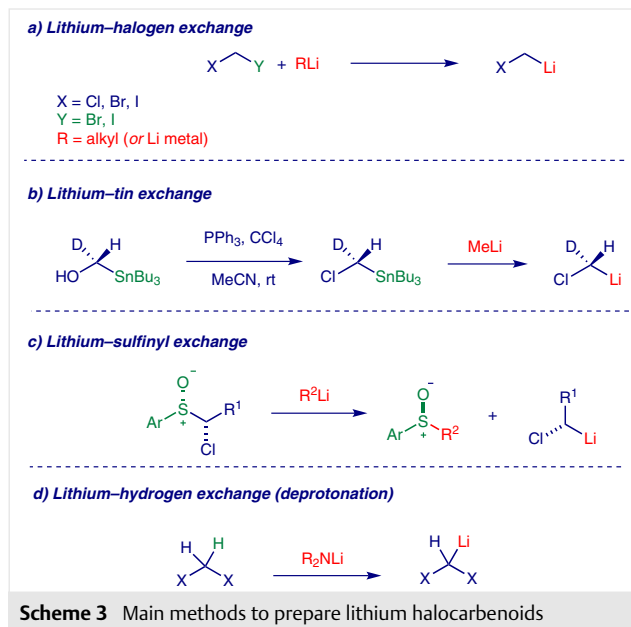
it is quite well recognized that the employment of lithium species (e.g.,  $\text{LiCH}_2\text{X}$ ) guarantees the predominance of the nucleophilic behavior,<sup>4d-g,4j,7</sup> while switching to carbenoids of less electropositive metals (e.g., Zn)<sup>8</sup> allows the electrophilic reactivity to come in to play, as for example exemplified by the powerful Simmons–Smith chemistry for the olefin homologation.<sup>9</sup> As a consequence of the tamed nucleophilicity of magnesium organometallics (compared to lithium counterparts), the corresponding carbenoids can be conveniently used for designing high chemoselective protocols.<sup>10</sup> Clososki and coworkers were able to selectively add  $\text{ClMgCH}_2\text{Cl} \cdot \text{LiCl}$  to an aldehyde even in the presence of concomitant electrophilic functionalities such as ketones, esters, nitriles, or amides.<sup>11</sup>



The introduction of a reactive halomethylene unit provides de facto the possibility to exploit the inherent reactivity of this motif. Since seminal contributions in the 1960s and 1970s by Köbrich,<sup>4a,12</sup> – followed by in depth studies by Matteson,<sup>13</sup> Barluenga,<sup>14</sup> Villieras,<sup>15</sup> Concellón,<sup>16</sup> and Savoia<sup>17</sup> – the addition of  $\text{LiCH}_2\text{Hal}$  to carbonyl-type compounds such as aldehydes, ketones, esters, or activated imines, followed by the easy ring-closure, has been regarded as an effective alternative to the Corey–Chaykovsky chemistry (Scheme 2).<sup>6</sup> Analogously, the elegant homologation of boron electrophiles introduced by Matteson in the 1980s<sup>18</sup> laid the cornerstone for outstanding transformations recently developed by Aggarwal<sup>19</sup> and Blakemore.<sup>20</sup>



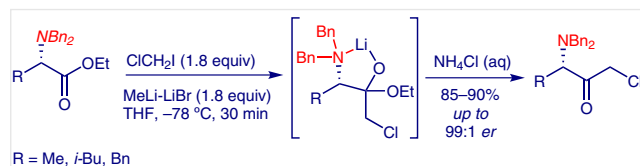
Despite the high potential of lithium halocarbenoids, the limited thermal stability has somewhat represented the Achilles heel because of the almost strict requirement of employing Barbier-type conditions.<sup>4f</sup> Accordingly, the three following methods can be employed for the generation of monohalocarbenoids (Scheme 3): a) halogen–metal exchange with organolithium reagents (with both  $\text{RLi}$  or  $\text{Li}$  metal);<sup>4f</sup> b) tin–lithium exchange;<sup>21</sup> c) sulfinyl–lithium exchange.<sup>20a</sup> The latter two methods allow to access configurationally stable carbenoids and, notably the tin–lithium exchange could be used for the generation of the high chemically (but not configurationally) unstable fluoro-



methyllithium.<sup>22</sup> A breakthrough in the area has been recently introduced by Luisi and coworkers who documented the formation of  $\text{LiCH}_2\text{Cl}$  under non-Barbier conditions (i.e., a wide range of electrophiles could be added after the generation of the carbenoid) by using in flow-chemistry technology.<sup>23</sup> This approach is highly promising since the Kirmse  $\alpha$ -elimination<sup>24</sup> to a free carbene and  $\text{LiCl}$  can be conveniently inhibited through this method thus providing an additional tool to classically employed coordinative strategies (i.e., addition of lithium salts or use of Lewis base solvents).<sup>15,25</sup> Finally, d) the relative high acidity of dihalomethanes enables the selective deprotonation with lithium amide bases thus constituting an efficient way to dihalocarbenoids.<sup>4f</sup> Alternatively, deprotonation with lithium amide bases or simple organolithium reagents can be accomplished in the presence of different electron-withdrawing groups (e.g.,  $\text{CN}$ ).<sup>26</sup>

## 2 Homologation of Weinreb Amides

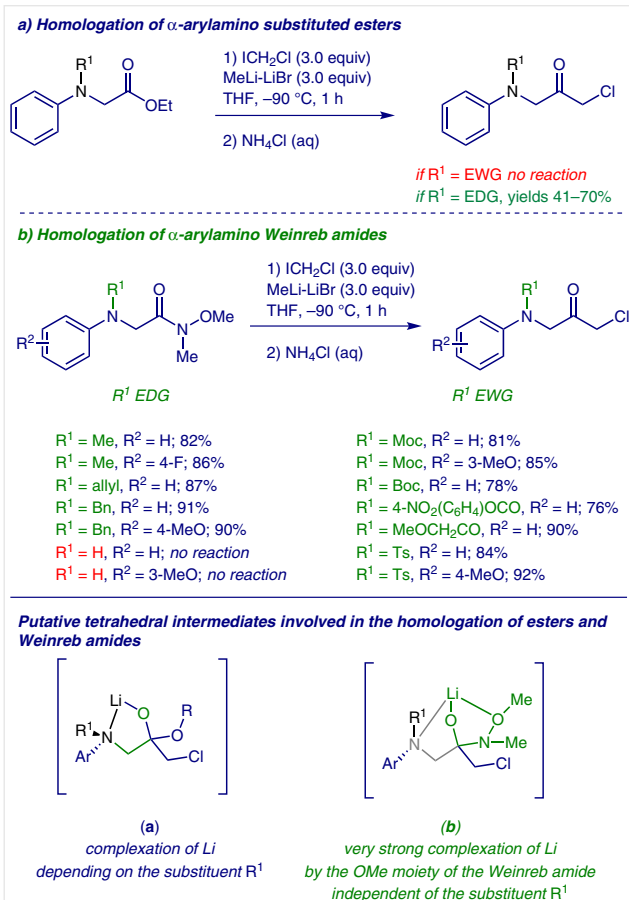
In 2013 our group launched a research program focused on the halomethylation of suitable acylating agents such as esters introduced by Barluenga during the 1990s.<sup>14b,c</sup> This chemistry proved to be successful – also because of the almost full retention of the stereochemical information during the process – as demonstrated by various applications in the synthesis of highly valuable building blocks required for obtaining HIV protease inhibitors.<sup>27</sup> Applications of the Barluenga's ester homologation strategy to industrial processes pointed out the dramatic effect displayed by the substituent at the  $\alpha$ -nitrogen (Scheme 4).<sup>28</sup> The presence of free N–H moieties was not tolerated due to the competing deprotonation by the carbenoid.



**Scheme 4** Barluenga's homologation of  $\alpha$ -amino esters

Motivated by the request of designing a versatile protocol for accessing 3-arylamino-1-chloroacetones<sup>5e,29</sup> featuring an electron-withdrawing group (EWG) at nitrogen, we were surprised by the impossibility of transforming esters into the desired  $\alpha$ -haloketones according to the aforementioned Barluenga's conditions (Scheme 5 – path a).<sup>30</sup> These particular – fully functionalized at nitrogen – acyl placeholders could not evidently be considered belonging to the secondary amine type category discussed above and the experimentally observed chemical inertness should be caused by different factor(s). Additionally, the good reactivity displayed by  $\alpha$ -arylamino esters presenting an alkyl-

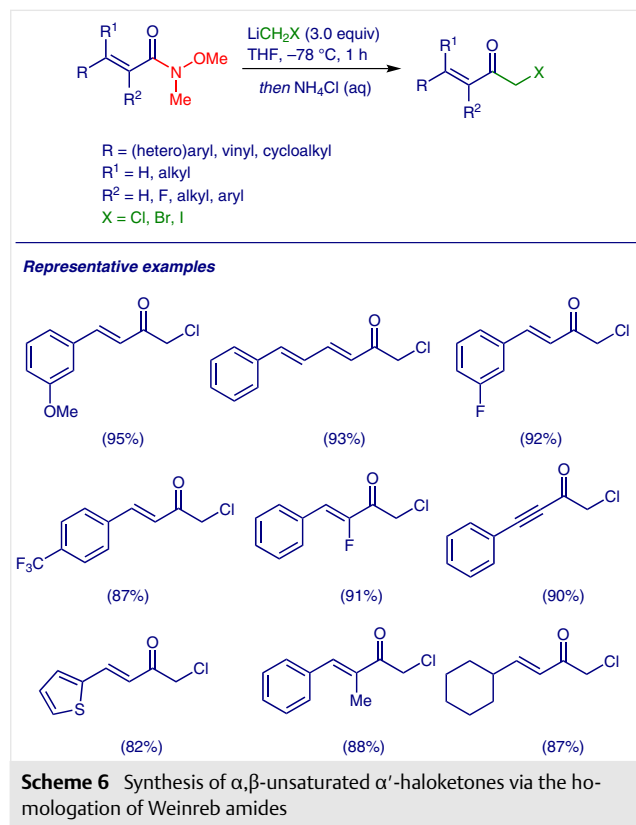
type (i.e., with electron-donating properties, Scheme 5 – path b) moiety, suggested us to consider the stability of the putative tetrahedral intermediate<sup>31</sup> – formed upon the addition of the carbenoid to the ester – as the key parameter governing the process. The simple switching to Weinreb amides<sup>32</sup> – well-known as exceptional substrates for the acylation of organometallic reagents – allowed us to realize the desired chloromethylation in high yield (Scheme 5 – path b). Consistent with the proposed cyclic intermediate, the methoxy group in Weinreb amide provides an additional coordination side arm and thus an increased stability of the intermediate.<sup>30</sup>



**Scheme 5** Homologation of  $\alpha$ -arylamino substituted esters and Weinreb amides

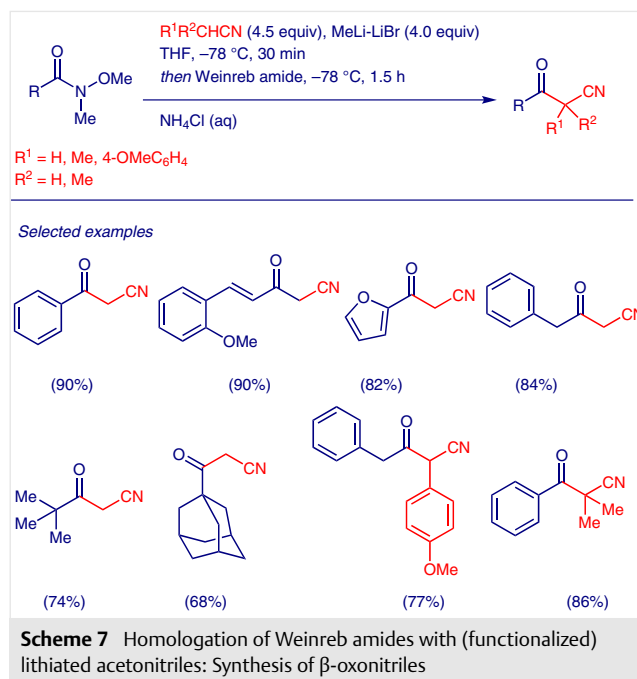
The excellent performance of Weinreb amides in reactions with halocarbenoid reagents is even more evident in the case of more complex targets as  $\alpha,\beta$ -unsaturated  $\alpha'$ -haloketones (Scheme 6).<sup>33</sup> Indeed, the employment of esters posed serious chemoselective issues because of the preferential double addition of the carbenoid to give carbinols instead of the required  $\alpha$ -haloketones. In this case, the halomethylation of Weinreb amides proceeds with full chemocontrol. The outstanding chemoselectivity of the

method is further highlighted by the lack of carbenoid-mediated cyclopropanation-type phenomena.<sup>34</sup> The protocol is quite general and is not dependent on the particular halomethyl fragment employed ( $\text{CH}_2\text{X}$ ,  $\text{X} = \text{Cl}$ ,  $\text{Br}$ , or  $\text{I}$ ).



Weinreb amides could serve as acylating agents also for lithiated acetonitriles species ( $\text{LiR}^1\text{R}^2\text{CCN}$ ), which, remarkably, due to higher intrinsic stability (compared to halocarbenoids), did not require the employment of Barbier-type conditions (Scheme 7).<sup>26b</sup> Again, the protocol manifests a large scope allowing the direct, high yielding synthesis not only of  $\alpha$ -cyanomethylketones (i.e.,  $\beta$ -oxonitriles) but also of  $\alpha$ -mono and  $\alpha,\alpha$ -disubstituted analogues. This is quite interesting since functionalization procedures dealing with the alkylation or arylation of unsubstituted  $\alpha$ -cyanomethylketones are often complicated by electronic and sterical effects.<sup>35</sup>

Our investigations in the area continued with the development of a strategy enabling the homologation with  $\alpha$ -oxy substituted methyl lithium carbanions – prepared according to the Yus arene-catalyzed reductive lithiation of chloromethyl ethers<sup>36</sup> – in order to prepare  $\alpha$ -oxygenated ketones (Scheme 8).<sup>37</sup> Key features of the method are: 1) broad substrate scope in terms of both Weinreb amides and halo-functionalized ether (primary, secondary (cyclo)alkyl-, aryl-); 2) high yields regardless the electronic and steric factors present on the starting materials; 3) full preserva-



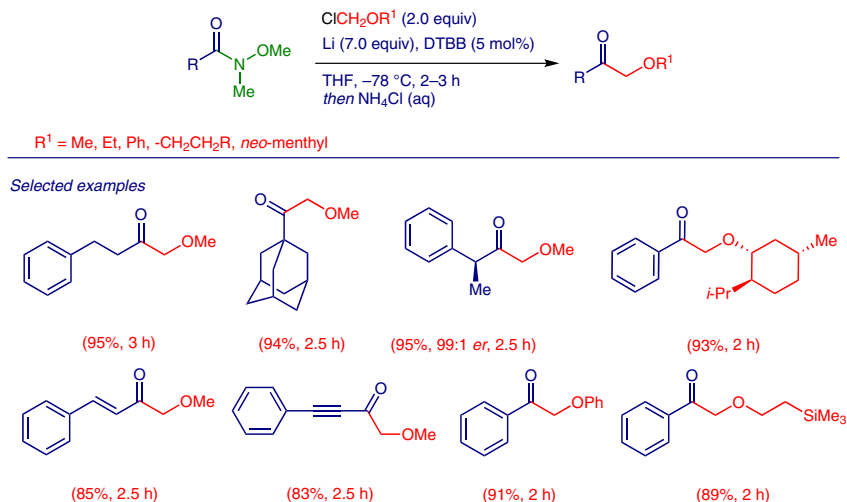
tion of the optical purity of the starting materials during the process (through both the employment of enantioenriched Weinreb amides and optically active organolithium species) thus accounting for a rapid, highly efficient access to enantiopure substituted  $\alpha$ -oxygenated ketones.

### 3 Homologation of Cyclic Ketones

Considering the feasibility of lithium  $\alpha$ -halocarbenoid mediated epoxidations of carbonyl-type functionalities,<sup>13,15,38</sup> we wondered if these reagents could be added to more challenging substrates such as  $\alpha,\beta$ -unsaturated cyclic ketones. In principle, the addition of  $\text{CH}_2\text{X}$  units to the  $\text{C}=\text{O}$  group of ketones could yield the following products (Scheme 9): a) halohydrin upon acidic quenching; b) epoxide through temperature-triggered ring closure; c) homologation of the cyclic system to the  $(n + 1)$  cycle. Moreover, d) the conjugated  $\text{C}=\text{C}$  bond can also be involved in Simmons-Smith-type chemistry. Chloromethyl lithium has been found to add in a 1,2-fashion with almost full selectivity, thus enabling the easy formation of quaternary allylic chlorohydrins.<sup>39</sup> Key features disclosed are: 1) LiBr not only acts as a carbenoid stabilizer, but also as a mild Lewis acid activator of the  $\text{C}=\text{O}$  bond;<sup>40</sup> 2) the protocol is tolerant to various ring-sized enones (five-, six-, seven-membered and also complex natural product structures) bearing eventually different substitution patterns.

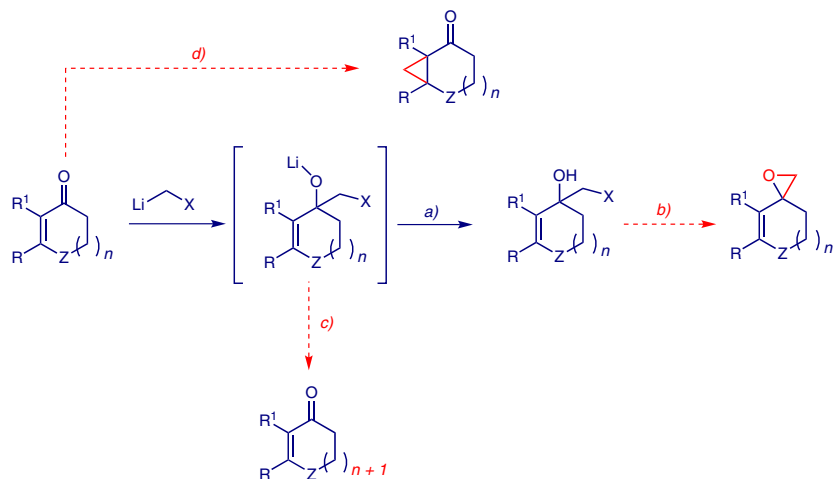
Cognizant of the good performance of the ring-closure strategy of  $\beta$ -halohydrins to access important targets such as spiro-epoxyoxindoles recently shown by Zhu et al.,<sup>41</sup> we



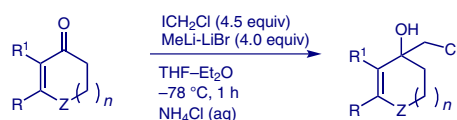


**Scheme 8** Employment of  $\alpha$ -oxy substituted methyllithiums in the homologation of Weinreb amides

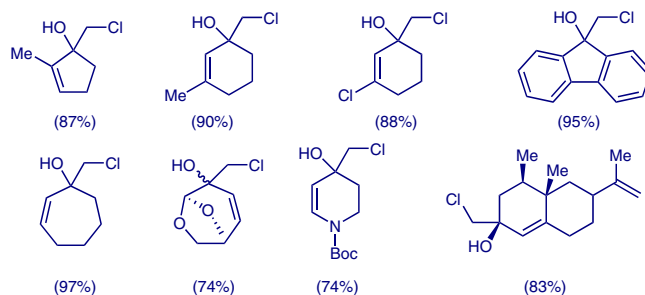
**Chemoselectivity issues arising from the addition of  $\text{LiCH}_2\text{Cl}$  to  $\alpha,\beta$ -unsaturated cyclic ketones**



**Developed method**

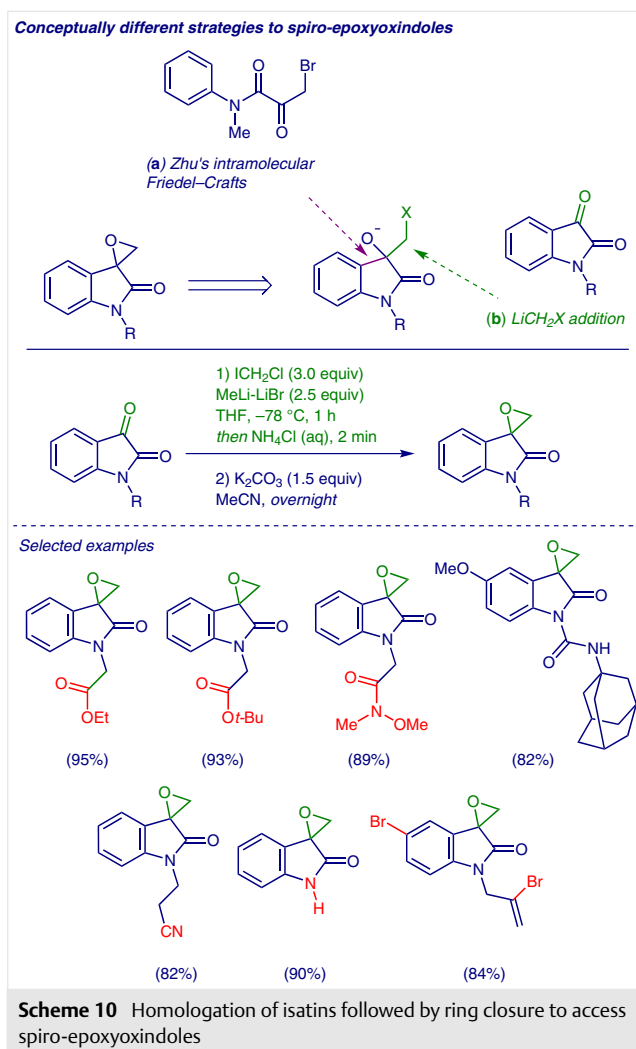


**Selected examples**



**Scheme 9** General context of the addition of a lithium carbenoid to cyclic unsaturated  $\alpha,\beta$ -ketones and development of a chemoselective strategy

designed a different retrosynthetic approach based on the homologation of widely available functionalized isatins (Scheme 10).<sup>42</sup> Conceptually, our protocol, which differs from Zhu's intramolecular Friedel–Crafts strategy, is paved on the straightforward addition of the  $\text{LiCH}_2\text{Cl}$  carbenoid to the extremely highly electrophilic isatin carbonyl.<sup>43</sup> The high chemoselectivity of the process is quite remarkable: the addition of the carbenoid takes place exclusively to the isatin carbonyl even in the presence of additional electrophilic functionalities [e.g., (Weinreb) amides, esters, nitriles] at the isatin core. Significantly, exchangeable C-sp<sup>2</sup> bromine atoms did not influence the proper generation of the carbenoid from  $\text{ICH}_2\text{Cl}$  during the lithiation step.



## 4 Homologation of Isocyanates

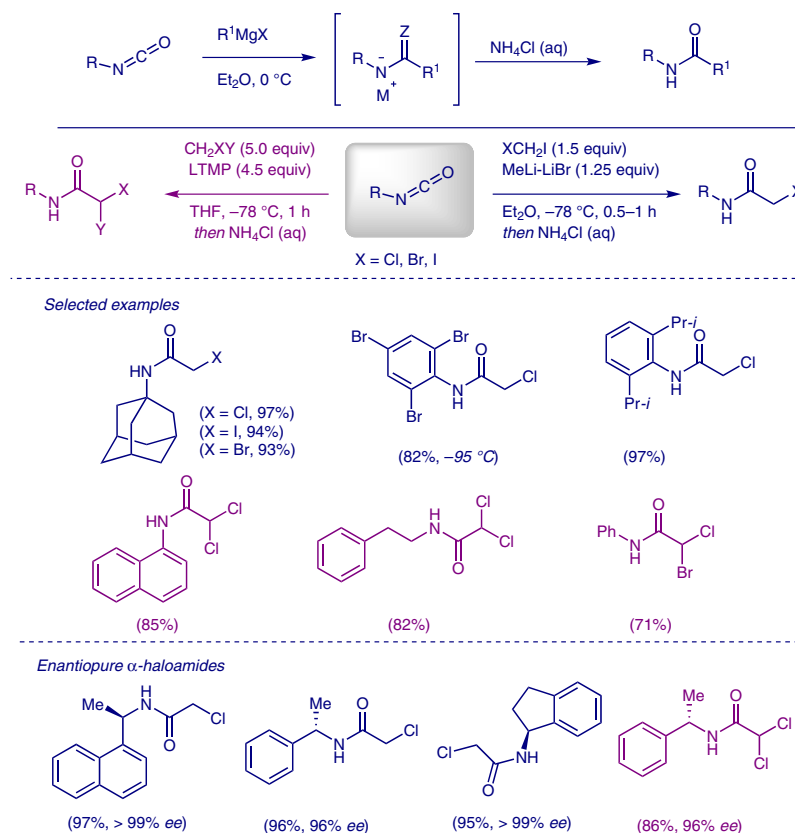
The intrinsic potentiality of delivering a  $\text{CH}_2\text{X}$  fragment through a unique, chemoselective synthetic operation – which would have overcome the chemo- and regioselectivity issues arising from the introduction of halogens via clas-

sical mechanistically based approaches (e.g., electrophilic or radical halogenations) – motivated us to investigate the reaction of carbenoids with isocyanates.<sup>2</sup> This class of highly electrophilic heterocumulene compounds<sup>44</sup> have been recognized as excellent partners in reactions with carbanions since the 1920s when Gilman<sup>45</sup> proposed the use of these species for the titration of organometallic reagents. Surprisingly, applications of this approach to thioamides at preparative scale were scarce<sup>46</sup> until Bode demonstrated its usefulness in the synthesis of sterically hindered amides, which are difficult to synthesize via alternative.<sup>47</sup>

We documented the applicability of the technique to the chemoselective, high-yielding synthesis of  $\alpha$ -halomethyl amides (Scheme 11).<sup>48</sup> The reaction showcases an excellent substrate scope allowing the chemoselective addition of  $\text{LiCH}_2\text{X}$  to a wide range of isocyanates with different substitution pattern at nitrogen. No differences have been observed switching from aliphatic to aromatic materials. The protocol is amenable for the synthesis of highly sterically hindered and functionalized  $\alpha$ -haloamides. Further points of interest are: a) The tactic provides haloamides in almost quantitative yields, without needing to perform chromatography purifications; b) the different monohalocarbenoids react equally; c) the stereochemical information contained in the starting isocyanate is fully transferred to the  $\alpha$ -haloamide. The methodology could also be extended to the synthesis of  $\alpha,\alpha$ -dihaloamides, which is a challenging task because of the chemoselective difficulties associated with the use of halogenation procedures.<sup>49</sup> The generation of dihalolithium carbenoids ( $\text{LiCHXY}$ ) through the deprotonation of a dihalomethane with a lithium amide base under Barbier conditions in the presence of the isocyanate gives the expected compounds in high yields and optical purity. Lithium 2,2,6,6-tetramethylpiperide (LTMP) was found to be the optimal base for the selective generation of the dihalocarbenoids. Again, the addition of dihalolithium carbenoids does not alter the enantiopurity of the starting isocyanates.<sup>49</sup>

The scope of the nucleophilic addition to isocyanates worked out also with hydride species.<sup>50</sup> This long-standing issue – affected by the overreduction of formamides to amines – could be easily solved by selecting the highly chemoselective Schwartz reagent as the hydride donor. We were delighted in observing full chemoselectivity during the  $\text{LiCH}_2\text{I}$ -mediated Matteson homologation of the boronic ester featuring a formamido substituent. Isothiocyanates reacted extremely well with  $\alpha$ -oxygenated (Hoppe carbamate)<sup>51</sup> or  $\alpha$ -nitrogenated (*N*-Boc-pyrrolidine)<sup>52</sup> chiral organolithium reagents (generated in the presence of asymmetric ligands, that is, (–)- or (+)-sparteine.<sup>53</sup> On the other hand, the synthesis of analogous  $\alpha$ -halothioamides resulted non feasible probably because of the alkylating effect displayed by the isothiocyanate sulfur on the carbenoid precursor ( $\text{ICH}_2\text{Cl}$ ).

## Bode's synthesis of amides from isocyanates



Scheme 11 Homologation of isocyanates with lithium carbenoids to access α-halo- and α,α-dihaloacetamide derivatives

## 5 Homologation of Disulfides and Diselenides

With the aim of designing new homologation protocols for heteroatom-type electrophiles,<sup>26a,54</sup> we focused our attention on disulfides which, as evidenced in prior studies by Field<sup>55</sup> and Schill,<sup>56</sup> resulted reluctant towards methylenating agents such as zinc carbenoids, diazomethane, or sulfur ylides. The homologation to the corresponding dithioacetal could be nicely performed by employing  $\text{LiCH}_2\text{Br}$  (Scheme 12).<sup>57</sup> Mechanistically, the attack of the latter to the disulfide to form the (isolable) intermediate α-halomethyl sulfide releases a mercapto anion able to displace the halogen upon increasing of temperature. The methodology features a wide substrate scope, and functionalized disulfides reacted efficiently regardless the substitution pattern. It is worth highlighting the success in the case of an asymmetric disulfide and in the homologation of diselenides to the corresponding diselenoacetals. The synthetic applicability of bromo-containing dithioacetals is well demonstrated by the palladium-catalyzed Feringa-Fañanás-Martín cross-coupling with an heteroaromatic or-

ganolithium, thus consisting in a valid alternative to commonly employed Suzuki-type chemistry for accessing polyaromatic structures.<sup>58</sup>

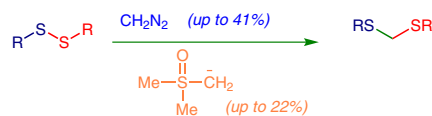
## 6 Conclusions

Since the seminal studies by Köbrich, lithium halomethyl carbenoids emerged as synthetically versatile reagents for accomplishing homologation reactions on a plethora of electrophiles not limited to carbon species. They allow the formal incorporation of a (reactive) halomethylenic fragment into an electrophile thus overcoming additional steps needed for the transformations of similar intermediates (e.g., diazoketones, sulfur ylides) into the desired adducts. We showed the effectiveness in performing highly chemocontrolled homologations in the presence of additional electrophilic substrates.

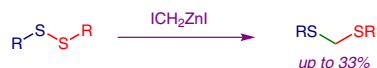
Nowadays, the recently developed Luisi's protocol for generating  $\text{LiCH}_2\text{X}$  reagents with microfluidic techniques – at temperatures up to -20 °C without the requirement of

## Precedent Homologies

Schill, 1970: Diazomethane (nucleophilic)  
Field, 1977: Sulfur ylide (nucleophilic)



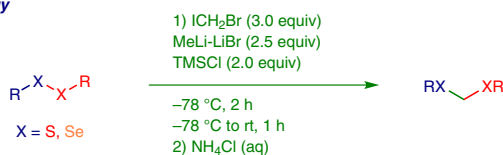
Field, 1975: Zinc carbenoid (electrophilic)



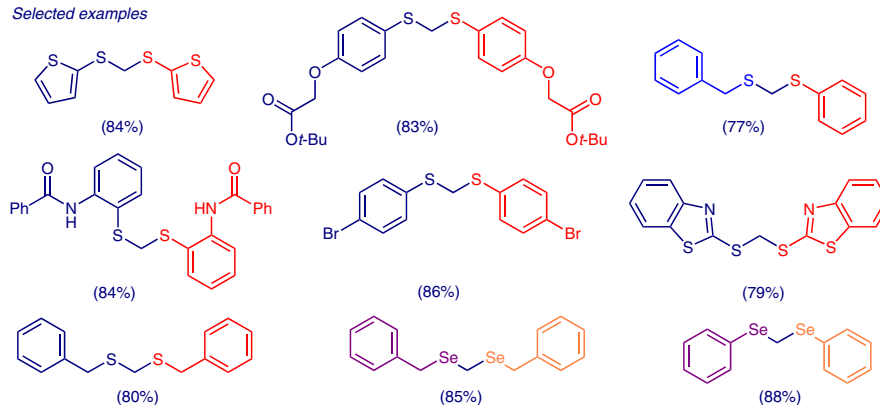
## Lithium carbenoid based tactic



## Methodology



## Selected examples



**Scheme 12** LiCH<sub>2</sub>Br-based homologation of disulfides and diselenides

Barbier-type conditions – would certainly allow to further exploit the synthetic potential of these reagents in broader contexts.

Without any doubt, the important contributions by Hammerschmidt and coworkers on the configurational stability of halo-[D<sub>1</sub>]-methyl lithium will open the field to the establishment of chiral carbenoid-mediated homologation techniques to access enantiomerically pure functionalized halomethyl derivatives.

In this regard, the generation of chiral, fully substituted carbenoids (i.e., LiCRR<sup>1</sup>X) ensued by application to homologation processes is certainly a major challenge which will deserve in-depth studies to provide robust and versatile tools for organic transformations.

## Acknowledgment

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*Publication n. 2*

**Synthesis of  $\alpha,\beta$ -unsaturated  $\alpha'$ -haloketones through the chemoselective addition of halomethylolithiums to Weinreb amides.**

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Details on experimental procedures, characterization data and copies of NMR spectra of all compounds are reported.





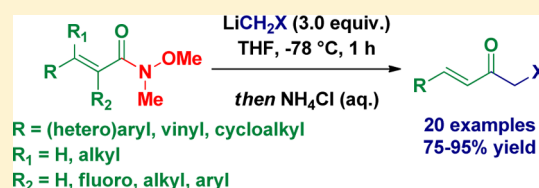
Synthesis of  $\alpha,\beta$ -Unsaturated  $\alpha'$ -Haloketones through the Chemoselective Addition of Halomethylolithiums to Weinreb Amides

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## S Supporting Information

**ABSTRACT:** A straightforward synthesis of variously functionalized  $\alpha,\beta$ -unsaturated  $\alpha'$ -haloketones has been achieved through the chemoselective addition of halomethylolithium carbenoids to Weinreb amides at  $-78^\circ\text{C}$ . A comparative study employing the corresponding esters under the same reaction conditions pointed out that the instability of the tetrahedral intermediate formed from the latter is responsible for the observed formation of carbinols instead of the desired haloketones.



$\alpha$ -Haloketones are invaluable versatile intermediates in organic synthesis as a consequence of the high reactivity displayed toward nucleophiles by both the electrophilic methylene and the carbonyl carbon atom.<sup>1</sup> The conjugation of the carbonyl group with a vinyl fragment introduces a third electrophilic site within this short carbon array; thus, the complex  $\alpha,\beta$ -unsaturated  $\alpha'$ -haloketone additionally becomes a Michael acceptor.<sup>2</sup> Indeed, in organic synthesis this motif has been employed in a plethora of transformations ranging from the synthesis of (bioactive) heterocycles<sup>2,3</sup> and natural products analogues (e.g., coruscanones)<sup>4</sup> to the preparation of silyloxy-1,3-dien-7-ynes.<sup>5</sup> Some known synthetic routes to  $\alpha,\beta$ -unsaturated  $\alpha'$ -haloketones are displayed in Scheme 1. A common route is the halogenation protocol (via *a*), where an  $\alpha,\beta$ -unsaturated  $\alpha'$ -methylketone is transformed into a kinetically unstable (silyl)enol ether, which is subsequently trapped with a halonium source.<sup>2a,3b</sup> Alternatively, Wittig-type condensation between an aldehyde and a phosphorane derived from 1,3-dichloroacetone has been used (via *b*).<sup>3a,6</sup> Moreover, an approach employing a Cu(I)-mediated 1,2-H shift of copper chlorocarbene, generated from noneasily accessible trichloromethyl carbinols (via *c*) has been employed.<sup>7</sup> Unfortunately, these strategies suffer from a series of drawbacks ranging from chemo- and regioselective issues (i.e., overhalogenations, sensitivity of the conjugated C–C double bond to electrophilic haloniums) to low efficiency and lack of generality, for instance, in the case of Wittig-type reactions with EDG-substituted aldehydes or with Cu(I)-mediated processes.

Alternatively, the homologation of an  $\alpha,\beta$ -unsaturated aldehyde to the corresponding halohydrin through the addition of a carbenoid followed by an oxidation step (Scheme 1, bottom, via *d*) has proven to be a moderately efficient two-pot procedure to access the target compounds.<sup>8</sup> In this sense, we argued that a homologation protocol of an adequate carboxylic acid derivative would satisfy the demand of an economic and direct access to the desired haloketones. To the best of our knowledge, the only example for the transformation of an  $\alpha,\beta$ -unsaturated ester into an  $\alpha,\beta$ -unsaturated  $\alpha'$ -haloketone has been reported by Kowalski through a complex sequential

bromomethylation reaction with  $\text{LiCH}_2\text{Br}_2$  and *n*-BuLi at  $-90^\circ\text{C}$  (Scheme 1, bottom, via *e*).<sup>9</sup> Thus, we considered the use of simpler monohalomethylolithium carbenoids ( $\text{LiCH}_2\text{X}$ )<sup>10</sup> appropriate for the direct functionalization of a carboxylic surrogate.

Therefore, herein we present a chemoselective protocol to achieve  $\alpha,\beta$ -unsaturated  $\alpha'$ -haloketones via the lithium carbenoids homologation of suitable Weinreb amides (Scheme 1, bottom central). We also highlight why esters are not optimal substrates for such transformations at  $-78^\circ\text{C}$  because of double addition of the carbenoids, thus giving carbinols instead of the desired haloketones. To this end, we initially investigated the reaction of commercially available ethyl cinnamate (**1a**) with in situ formed chloromethylolithium (Table 1). By performing the reaction at  $-78^\circ\text{C}$  with an excess of  $\text{LiCH}_2\text{Cl}$ , only carbinol **2** resulting from double addition of the carbenoid to the ester could be isolated in 79% yield (entry 1). Analogously, also in the case of stoichiometric addition, carbinol **2** was the only reaction product (entry 2). On the other hand, when the reaction mixture was kept at  $-115^\circ\text{C}$  (Villieras conditions<sup>11</sup>) the desired chloroketone **3a** was the major reaction product (51%) along with 15% of the carbinol **2** (entry 3). An analogous outcome was observed when other cinnamate esters **1b–d** (methyl, benzyl, isopropyl) were used instead of **1a** (entries 4–9). These preliminary results indicated that esters are prone to undergo a double addition of the carbenoid at  $-78^\circ\text{C}$ , because of the instability of the tetrahedral intermediate at that temperature (vide infra). Thus, we turned our attention to the corresponding Weinreb amide **1e** because of the well-known stability of the tetrahedral intermediate formed upon addition of organometallic species to this carboxylic derivative.<sup>12</sup> Pleasingly, the addition of  $\text{LiCH}_2\text{Cl}$  to such a substrate (**1e**) provided exclusively the desired chloroketone **3a** in excellent yield (88%, entry 10) without any trace of the corresponding carbinol. By lowering temperature to

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Scheme 1. Context of Presented Work

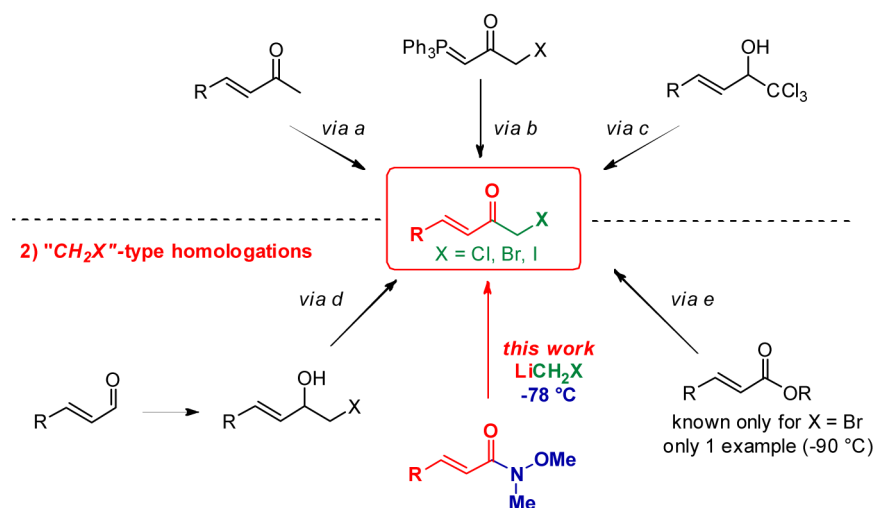
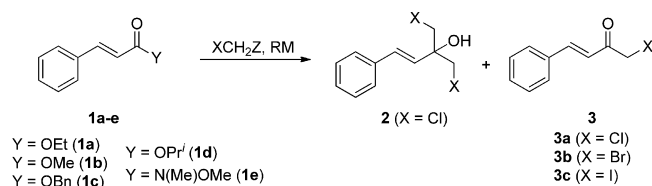
1) Classical routes to  $\alpha,\beta$ -unsaturated- $\alpha'$ -haloketones

Table 1. Halomethylation of Esters and Weinreb Amides



| entry | substrate | $\text{MCH}_2\text{X}$ (equiv)                         | temp ( $^\circ\text{C}$ ) | yield of 2 <sup>b</sup> (%) | yield of 3 <sup>b</sup> (%) |
|-------|-----------|--------------------------------------------------------|---------------------------|-----------------------------|-----------------------------|
| 1     | 1a        | $\text{LiCH}_2\text{Cl}$ (1.8)                         | -78                       | 79                          |                             |
| 2     | 1a        | $\text{LiCH}_2\text{Cl}$ (1.0)                         | -78                       | 48                          |                             |
| 3     | 1a        | $\text{LiCH}_2\text{Cl}$ (1.8)                         | -115                      | 15                          | 51                          |
| 4     | 1b        | $\text{LiCH}_2\text{Cl}$ (1.8)                         | -78                       | 80                          |                             |
| 5     | 1c        | $\text{LiCH}_2\text{Cl}$ (1.8)                         | -78                       | 73                          |                             |
| 6     | 1d        | $\text{LiCH}_2\text{Cl}$ (1.8)                         | -78                       | 52                          |                             |
| 7     | 1d        | $\text{LiCH}_2\text{Cl}$ (1.8)                         | -115                      | 11                          | 33                          |
| 8     | 1e        | $\text{LiCH}_2\text{Cl}$ (1.8)                         | -115                      | 18                          | 47                          |
| 9     | 1a        | $\text{LiCH}_2\text{Cl}$ (1.8)                         | -115                      | 21                          | 56                          |
| 10    | 1e        | $\text{LiCH}_2\text{Cl}$ (1.8)                         | -78                       |                             | 88                          |
| 11    | 1e        | $\text{LiCH}_2\text{Cl}$ (1.8)                         | -90                       |                             | 96                          |
| 12    | 1e        | $\text{LiCH}_2\text{Cl}$ (3.0) <sup>c</sup>            | -78                       |                             | 94                          |
| 13    | 1e        | $\text{LiCH}_2\text{Cl}$ (3.0) <sup>c</sup>            | -60                       |                             | 63                          |
| 14    | 1e        | $\text{Mg}(\text{CH}_2\text{Cl})_2$ (3.0) <sup>c</sup> | -78                       |                             |                             |
| 15    | 1e        | $\text{LiCH}_2\text{Br}$ (3.0) <sup>c</sup>            | -78                       |                             | 89 <sup>d</sup>             |
| 16    | 1e        | $\text{LiCH}_2\text{I}$ (3.0) <sup>c</sup>             | -78                       |                             | 92 <sup>e</sup>             |

<sup>a</sup>Unless otherwise indicated,  $\text{MCH}_2\text{X}$  were generated from  $\text{ICH}_2\text{Cl}$  and  $\text{MeLi-LiBr}$  in equimolar amounts. <sup>b</sup>Isolated yields. <sup>c</sup>Generated from 4.0 equiv of dihalomethane and 3.0 equiv of  $\text{MeLi-LiBr}$  or  $i\text{-PrMgCl-LiCl}$  (entry 14). <sup>d</sup>3b. <sup>e</sup>3c.

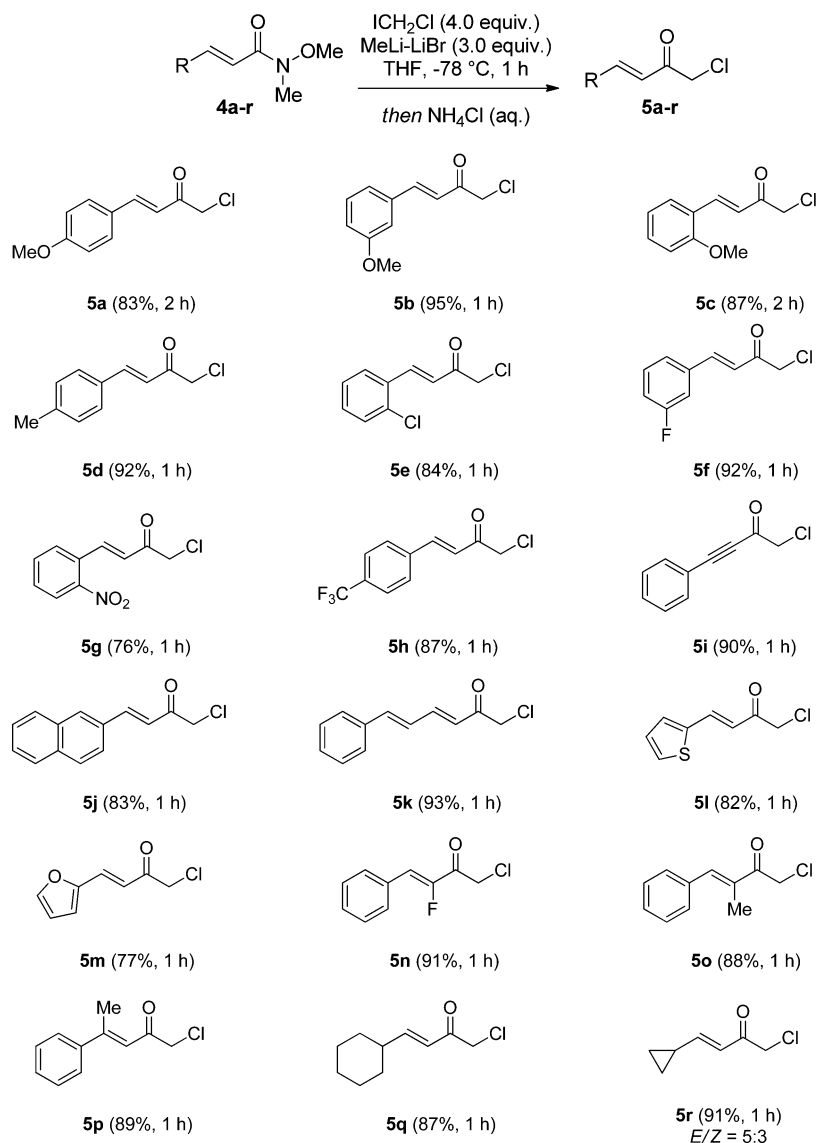
$-90^\circ\text{C}$ , a further increase in the yield of 3a was noticed (96%, entry 11), thus confirming the influence of this parameter on the stability of the carbenoid. A further improvement was the use of an excess of iodochloromethane (4.0 equiv) and  $\text{MeLi-LiBr}$  (3.0 equiv) which overcame this deleterious effect of temperature, and by running the reaction at  $-78^\circ\text{C}$ , chloroketone 3a was obtained in an excellent 94% yield without needing to perform any chromatographic purification (entry 12). Attempts to increase the temperature up to  $-60^\circ\text{C}$  significantly decreased the yield (entry 13) and, remarkably, the

use of a more stable but less nucleophilic magnesium carbenoid<sup>13</sup> did not provide any reaction product (entry 14). Analogously, the established reaction conditions allowed the efficient preparation of the corresponding  $\alpha$ -bromo and  $\alpha$ -iodoketones 3b and 3c, respectively, starting from  $\text{CH}_2\text{Br}_2$  and  $\text{CH}_2\text{I}_2$  as the carbenoid precursors (entries 15 and 16). Remarkably, under the reaction conditions applied the C-C double bond was not affected (i.e., cyclopropanation which is known to be accomplished by using Li carbenoids<sup>14</sup>), as reported for analogous substrates under Corey-Chaykovsky conditions.<sup>15</sup>

Once the optimal conditions had been established, we next examined the scope of the reaction. Various substituted cinnamoyl-type Weinreb amides afforded the corresponding  $\alpha$ -haloketones of type 5 in high yields (Table 2). Some points merit mention: (a) a strong electron-releasing group (i.e., OMe) in activating position on the aromatic ring determines a considerable increase of the reaction time; however efficiency was not altered (to ensure non-degradation of the carbenoids,  $\text{ICH}_2\text{Cl}$ , and  $\text{MeLi-LiBr}$  were added portionwise); (b) substituents susceptible to reduction, such as halogens (5e, 5f, 5h) or even a nitro group (5g) are well tolerated; (c) an extended cinnamoyl system (5k), substituents across the olefinic double bond (5o-p), and also switching to the accordant alkyne system (5i), do not affect the reaction. Importantly,  $\alpha$ -chloro- $\alpha'$ -fluoro ketone 5n could be obtained in higher efficiency compared to previous procedures involving sulfur ylides.<sup>16</sup> Interestingly, the protocol is also applicable to naphthalenic (5j) and heteroaromatic substrates (5l, m): in the latter cases, no concomitant lithiations at the ortho positions to the heteroatoms are observed at all.

Remarkably, the procedure could also be applied to the synthesis of  $\alpha,\beta$ -unsaturated ketones presenting cycloalkyl type substituents on the  $\beta$ -carbon such as a cyclohexyl (5q) or a cyclopropyl group (5r). However, in this latter case an inseparable mixture of *E/Z* isomers was obtained.

To rationalize the observed chemoselectivity, we considered the exceptional stability at  $-78^\circ\text{C}$  of the intermediate II furnished by the *N*-methoxy group of the Weinreb amide I, which evidently does not allow a second addition of  $\text{LiCH}_2\text{X}$  (Scheme 2, path a). As a consequence of this high stability of II, the desired  $\alpha$ -haloketone III is formed only after acidic

Table 2. Chloromethylation of Various Functionalized  $\alpha,\beta$ -Unsaturated Weinreb Amides<sup>a</sup>

<sup>a</sup>Yields are referred to isolated products; otherwise indicated E/Z > 99:1 (<sup>1</sup>H NMR).

hydrolysis of the tetrahedral intermediate **II**. By contrast, the addition of the carbenoid to an ester **IV** results in the formation of a tetrahedral intermediate **V** (not stable at  $-78\text{ }^{\circ}\text{C}$ ), which is in equilibrium with the transient  $\alpha$ -haloketone **III**, the latter more susceptible to a second attack of the carbenoid (compared to the starting ester), and thus furnishing the carbinol **VI** (Scheme 2, path *b*). This explanation is in agreement with the finding that by running the halomethylation of esters at  $-115\text{ }^{\circ}\text{C}$  the major product is the  $\alpha$ -haloketone. Thus, it is conceivable that the tetrahedral intermediate **V** formed through monoaddition to an ester, is only stable (thus, hindering the second addition) at that very low temperature but not at  $-78\text{ }^{\circ}\text{C}$ .

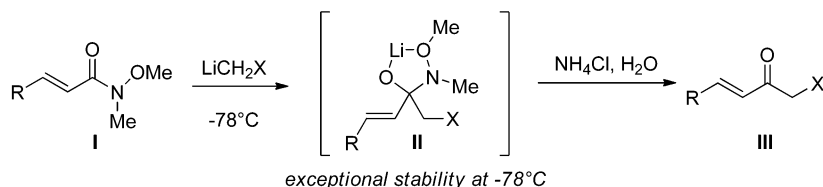
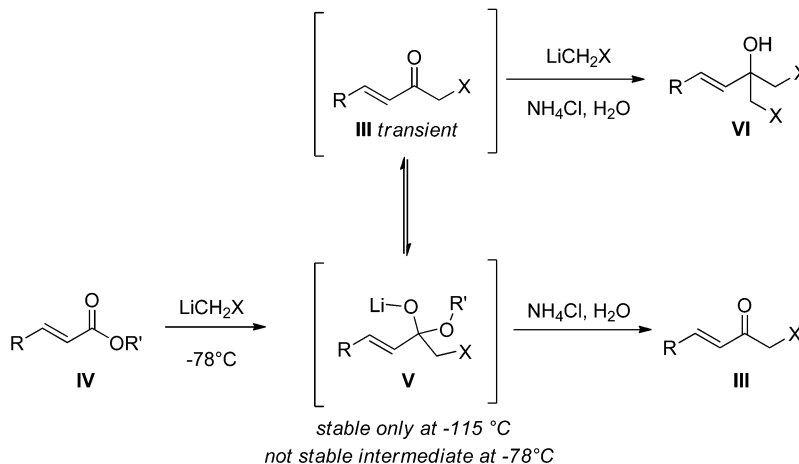
To conclude, we have disclosed a direct and straightforward access to synthetically useful  $\alpha,\beta$ -unsaturated  $\alpha'$ -haloketones through the addition of halomethyl lithium carbenoids to Weinreb amides. Remarkably, the use of these starting materials allows the chemoselective addition of only one equivalent of the carbenoids without any trace of side products such as carbinol or 1,4-addition products neither cyclopropanes

generated through Simmons–Smith-type processes. Interestingly, the observed experimental results fit with the theoretical explanation based on the temperature-dependent stability of the tetrahedral intermediate formed upon addition of the carbenoids to esters, which at  $-78\text{ }^{\circ}\text{C}$  undergo double addition to provide carbinols instead of the desired  $\alpha$ -haloketones.

## EXPERIMENTAL SECTION

**General Experimental Methods.** All <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on spectrometers operating at 200, 300, 400, or 500 MHz and at 50, 75, 100, or 125 MHz. The <sup>15</sup>N and <sup>19</sup>F NMR experiments were conducted on a 400 MHz spectrometer (40 and 377 MHz, respectively). The <sup>15</sup>N NMR spectra were referenced against external nitromethane; for the <sup>19</sup>F NMR spectra absolute referencing via the  $\Xi$  ratio was used. All melting points are uncorrected. Column chromatography purifications were conducted on silica gel 60 (40–63  $\mu\text{m}$ ). TLC was carried out on aluminum sheets precoated with silica gel 60F254; the spots were visualized under UV light ( $\lambda = 254\text{ nm}$ ) and/or  $\text{KMnO}_4$  (aq) was used as revealing system. All nonaqueous reactions were run under an inert atmosphere (argon) with flame-dried glassware using standard techniques. THF was distilled over Na using benzophenone as an indicator. Dynamic esters, chloriodo-

Scheme 2. Temperature-Based Mechanistic Explanation of the Different Behavior toward Halomethylithium Reagents of Weinreb Amides (Path a) and Esters (Path b)

a) Chemoselective monoaddition of  $\text{LiCH}_2\text{X}$  to Weinreb amides at  $-78^\circ\text{C}$ b) Temperature depending addition of  $\text{LiCH}_2\text{X}$  to esters

methane, dibromomethane, diiodomethane, and  $\text{MeLi-LiBr}$  complex (1.5 M in diethyl ether) are commercially available. Weinreb amides **1e**,<sup>17</sup> **4a**,<sup>17</sup> **4b**,<sup>18</sup> **4c**,<sup>19</sup> **4d**,<sup>20</sup> **4e**,<sup>21</sup> **4f**,<sup>18</sup> **4g**,<sup>17</sup> **4h**,<sup>22</sup> **4i**,<sup>23</sup> **4j**,<sup>24</sup> **4k**,<sup>17</sup> **4l**,<sup>21</sup> **4m**,<sup>25</sup> **4n**,<sup>26</sup> **4o**,<sup>27</sup> **4p**,<sup>27</sup> and **4r**<sup>28</sup> are known compounds prepared as previously reported. However, copies of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are provided in the Supporting Information.

**Preparation of (2E)-3-Cyclohexyl-N-methoxy-N-methylacrylamide (4q).** To a dry THF (9 mL) solution of (E)-methyl 3-cyclohexylacrylate<sup>29</sup> (575 mg, 3.42 mmol, 1 equiv) cooled at  $-10^\circ\text{C}$  was added *N,O*-dimethylhydroxylamine hydrochloride (500 mg, 5.13 mmol, 1.5 equiv), and after 2 min, *i*-PrMgCl (2 M THF solution) (1.06 g, 5.13 mL, 10.26 mmol, 3.0 equiv) was added dropwise during 5 min. The solution was allowed to reach rt during 3 h and then was quenched with satd  $\text{NH}_4\text{Cl}$ . The organic phase was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 15$  mL), dried, and filtered. After removal of the solvent in vacuo, Weinreb amide **4q** was obtained in 94% yield (634 mg) as a light yellow oil.  $^1\text{H}$  NMR (300 MHz  $\text{CDCl}_3$ )  $\delta$ : 6.93 (dd,  $J = 15.6$ ,  $J = 7.0$  Hz, 1H), 6.34 (dd,  $J = 15.6$ ,  $J = 1.4$  Hz, 1H), 3.70 (s, 3H), 3.23 (s, 3H), 2.22–2.09 (m, 1H), 1.79–1.65 (m, 5H), 1.29–1.14 (m, 5H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 167.1, 152.6, 115.9, 61.3, 40.4, 32.1, 31.7, 31.3, 25.6, 25.4, 25.4. IR (NaCl,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 2964, 1685, 1620, 1419, 1390, 1297, 1171, 1012, 706. Anal. Calcd for  $\text{C}_{11}\text{H}_{19}\text{NO}_2$ : C, 66.97; H, 9.71; N, 7.10. Found: C, 67.09; H, 9.59; N, 7.23.

**General Procedure for the Halomethylation of Weinreb Amides with Li Carbenoids.** To a solution of Weinreb amide (1.0 equiv) in THF cooled at  $-78^\circ\text{C}$  was added the dihalomethane (4.0 equiv), and subsequently,  $\text{MeLi-LiBr}$  complex (1.5 M solution in diethyl ether, 3.0 equiv) was added dropwise during 5 min. The resulting solution was stirred at that temperature for 1–2 h (see text), and then  $\text{NH}_4\text{Cl}$  saturated aqueous solution was added at  $-78^\circ\text{C}$ . After removal of the cooling bath, the mixture was allowed to reach rt and washed with  $\text{Et}_2\text{O}$  and brine. The two resulting phases were separated, and the organic phase was dried over anhydrous  $\text{MgSO}_4$ , filtered, and removed in vacuo to give the desired haloketones in a pure form without needing to perform further purifications.

**(3E)-1-Chloro-4-phenyl-3-buten-2-one (3a).**<sup>7</sup> Following the general procedure, starting from (2E)-*N*-methoxy-*N*-methyl-3-phenylacrylamide (**1e**) (0.27 g, 1.43 mmol),  $\text{ICH}_2\text{Cl}$  (1.0 g, 0.41 mL, 5.7 mmol), and  $\text{MeLi-LiBr}$  (2.85 mL, 4.28 mmol) in THF,  $\alpha$ -chloroketone **3a** was obtained in 95% yield (0.23 g) as a pale yellow solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.71 (d,  $J = 16.1$  Hz, 1H,  $\text{PhCH=}$ ), 7.59 (m, 2H, Ph H-2, H-6), 7.43 (m, 1H, Ph H-4), 7.42 (m, 2H, Ph H), 6.98 (d, 1H,  $J = 16.1$  Hz), 4.30 (s, 2H,  $\text{CH}_2\text{Cl}$ ).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 191.1 ( $\text{C=O}$ ), 145.2 (Ph-CH=), 133.9 (Ph C-1), 131.1 (Ph C-4), 129.0 (Ph C-3), 129.0 (Ph C-5), 128.6 (Ph C-2), 128.6 (Ph C-6), 121.6 ( $=\text{CHCO}$ ), 47.4 ( $\text{CH}_2\text{Cl}$ ). IR (NaCl,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3080, 1682, 1594, 1511, 1255, 904. Mp:  $56^\circ\text{C}$  (lit.<sup>7</sup> mp  $55^\circ\text{C}$ ). Anal. Calcd for  $\text{C}_{10}\text{H}_9\text{ClO}$ : C, 66.49; H, 5.02. Found: C, 66.35; H, 4.89.

**(3E)-1-Bromo-4-phenyl-3-buten-2-one (3b).**<sup>30</sup> Following the general procedure, starting from (2E)-*N*-methoxy-*N*-methyl-3-phenylacrylamide (**1e**) (0.27 g, 1.43 mmol),  $\text{CH}_2\text{Br}_2$  (990 mg, 0.40 mL, 5.7 mmol), and  $\text{MeLi-LiBr}$  (2.85 mL, 4.28 mmol) in THF,  $\alpha$ -bromoketone **3b** was obtained in 89% yield (0.29 g) as a pale yellow solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.70 (d,  $J = 16.1$  Hz, 1H,  $\text{ArCH=}$ ), 7.59 (m, 2H Ph H-2, 6), 7.42 (m, 1H; Ph H-4), 7.41 (m, 2H, Ph H-3, Ph), 6.95 (d,  $J = 16.1$  Hz,  $=\text{CHCO}$ ), 4.09 (s, 2H,  $\text{CH}_2\text{Br}$ ).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 191.0 ( $\text{C=O}$ ), 145.4 ( $\text{ArCH=}$ ), 133.9 (Ph C-1), 131.1 (Ph C-4), 129.0 (Ph C-3), 129.0 (Ph C-5), 128.6 (Ph C-6), 128.6 (Ph C-6), 122.2 ( $=\text{CHCO}$ ), 33.1 ( $\text{CH}_2\text{Br}$ ). IR (NaCl,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 1693, 1611, 1498, 1450, 1390, 1069, 990, 890, 749. Mp:  $45^\circ\text{C}$  (lit.<sup>30</sup> mp  $44$ – $45^\circ\text{C}$ ). Anal. Calcd for  $\text{C}_{10}\text{H}_9\text{BrO}$ : C, 53.36; H, 4.03. Found: C, 53.48; H, 4.17.

**(3E)-1-Iodo-4-phenyl-3-buten-2-one (3c).**<sup>31</sup> Following the general procedure, starting from (2E)-*N*-methoxy-*N*-methyl-3-phenylacrylamide (**1e**) (0.27 g, 1.43 mmol),  $\text{CH}_2\text{I}_2$  (1.53 g, 0.46 mL, 5.7 mmol), and  $\text{MeLi-LiBr}$  (2.85 mL, 4.28 mmol) in THF,  $\alpha$ -iodoketone **3c** was obtained in 92% yield (0.36 g) as a pale yellow solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.69 (d,  $J = 16.4$  Hz, 1H), 7.59–7.57 (m, 2H), 7.43–7.41 (m, 3H), 6.89 (d,  $J = 16.4$  Hz, 1H), 4.02 (s, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 192.1, 144.8, 133.8, 130.9, 128.9, 128.4, 122.2,



5.0. IR (NaCl,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 1640, 1573, 1438, 1270, 1072, 990, 874, 803, 764, 704. Mp: 57 °C (lit.<sup>31</sup> mp 56.5–58.5 °C). Anal. Calcd for  $\text{C}_{10}\text{H}_9\text{IO}$ : C, 44.14; H, 3.33. Found: C, 44.32; H, 3.50.

**(3E)-1-Chloro-2-(chloromethyl)-4-phenyl-3-buten-2-ol (2).**<sup>32</sup> To a solution of ethyl cinnamate (176 mg, 1.0 mmol) in THF (3 mL) cooled at –78 °C was added chloriodomethane (317 mg, 1.8 mmol, 0.13 mL) and, after 2 min, MeLi–LiBr ethereal solution (1.5 M, 1.8 mmol, 1.20 mL). The resulting solution was stirred at that temperature for 1 h, and then  $\text{NH}_4\text{Cl}$  saturated aqueous solution was added at –78 °C. After removal of the cooling bath the mixture was allowed to reach rt and washed with  $\text{Et}_2\text{O}$  and brine. The two resulting phases were separated, and the organic phase was dried over anhydrous  $\text{MgSO}_4$ , filtered, and removed in vacuo to give **2** after flash chromatography on silica gel (hexanes–AcOEt, 9:1) as a light yellow oil (182 mg, 79% yield).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.35–7.17 (m, 5H), 6.83 (d,  $J$  = 15.9 Hz, 1H), 6.24 (d,  $J$  = 15.9 Hz, 1H), 3.71 (d,  $J$  = 9.9 Hz, 1H), 3.24 (d,  $J$  = 9.9 Hz, 1H), 2.59 (s, 1H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 135.8, 132.5, 128.6, 128.2, 127.1, 126.7, 74.2, 49.3 ( $\times 2$ ). IR (NaCl,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3502, 2993, 712, 961, 903. Anal. Calcd for  $\text{C}_{11}\text{H}_{12}\text{Cl}_2\text{O}$ : C, 57.16; H, 5.23. Found: C, 57.33; H, 5.38.

**(3E)-1-Chloro-4-(4-methoxyphenyl)-3-buten-2-one<sup>3a</sup> (5a).** Following the general procedure, starting from (*E*)-*N*-methoxy-3-(4-methoxyphenyl)-*N*-methylacrylamide (**4a**) (0.32 g, 1.43 mmol),  $\text{ICH}_2\text{Cl}$  (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (2.85 mL, 4.28 mmol) in THF,  $\alpha$ -chloroketone **5a** was obtained in 83% yield (0.25 g) as a colorless solid.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.68 (d,  $J$  = 15.9 Hz, 1H), 7.54 (d,  $J$  = 8.8 Hz, 2H), 6.93 (d,  $J$  = 8.8 Hz, 2H), 6.86 (d,  $J$  = 16.0 Hz, 1H), 4.28 (s, 2H), 3.85 (s, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$ : 191.4, 162.3, 145.2, 130.7, 130.7, 126.8, 119.4, 114.7, 144.7, 55.6, 47.6. IR (NaCl,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 1681, 1594, 1571, 1511, 1302, 1255, 1172, 905, 727. Mp: 98 °C (lit.<sup>3a</sup> mp 98 °C). Anal. Calcd for  $\text{C}_{11}\text{H}_{11}\text{ClO}_2$ : C, 62.72; H, 5.26. Found: C, 62.61; H, 5.15.

**(3E)-1-Chloro-4-(3-methoxyphenyl)-3-buten-2-one (5b).** Following the general procedure, starting from (*E*)-*N*-methoxy-3-(3-methoxyphenyl)-*N*-methylacrylamide (**4b**) (0.32 g, 1.43 mmol),  $\text{ICH}_2\text{Cl}$  (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (2.85 mL, 4.28 mmol) in THF,  $\alpha$ -chloroketone **5b** was obtained in 95% yield (0.29 g) as a thick oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.67 (d,  $J$  = 16.0 Hz, 1H), 7.33 (m, 1H), 7.18 (m, 1H), 7.08 (m, 1H), 6.95 (d,  $J$  = 16.0 Hz, 1H), 4.36 (s, 2H), 3.85 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 191.2, 158.8, 145.1, 135.2, 130.0, 121.9, 121.3, 116.9, 113.4, 55.3, 47.4. IR (NaCl,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 1684, 1608, 1579, 1246, 905, 727. Anal. Calcd for  $\text{C}_{11}\text{H}_{11}\text{ClO}_2$ : C, 62.72; H, 5.26. Found: C, 62.85; H, 4.99.

**(3E)-1-Chloro-4-(2-methoxyphenyl)-3-buten-2-one (5c).** Following the general procedure, starting from (*E*)-*N*-methoxy-3-(2-methoxyphenyl)-*N*-methylacrylamide (**4c**) (0.32 g, 1.43 mmol),  $\text{ICH}_2\text{Cl}$  (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (2.85 mL, 4.28 mmol) in THF,  $\alpha$ -chloroketone **5c** was obtained in 87% yield (0.26 g) as a light yellow thick oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.02 (d,  $J$  = 16.3 Hz, 1H, ArCH=), 7.56 (m, 1H, Ph H-6), 7.39 (m, 1H, Ph H-4), 7.02 (d,  $J$  = 16.3 Hz, =CHCO), 6.98 (m, 1H, Ph H-5), 6.93 (m, 1H, Ph H-3), 4.33 (s, 2H,  $\text{CH}_2\text{Cl}$ ), 3.90 (s, 3H, ArOCH<sub>3</sub>).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 191.6 (C=O), 158.8 (Ph C-2), 140.4 (ArCH=), 132.4 (Ph C-4), 129.1 (Ph C-6), 122.8 (Ph C-6), 122.4 (=CHCO), 120.8 (Ph C-5), 111.2 (Ph C-3), 55.5 (ArOCH<sub>3</sub>), 47.3 ( $\text{CH}_2\text{Cl}$ ). IR (NaCl,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3075, 1682, 1613, 1583, 1242, 902, 708. Anal. Calcd for  $\text{C}_{11}\text{H}_{11}\text{ClO}_2$ : C, 62.72; H, 5.26. Found: C, 62.64; H, 5.13.

**(3E)-1-Chloro-4-(4-methylphenyl)-3-buten-2-one<sup>6b</sup> (5d).** Following the general procedure, starting from (*E*)-*N*-methoxy-*N*-methyl-3-(4-methylphenyl)acrylamide (**4d**) (0.29 g, 1.43 mmol),  $\text{ICH}_2\text{Cl}$  (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (2.85 mL, 4.28 mmol) in THF,  $\alpha$ -chloroketone **5d** was obtained in 92% yield (0.26 g) as a yellowish solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.69 (d,  $J$  = 16.1 Hz, 1H, ArCH=), 7.48 (m, 2H, Ph H-2,6), 7.22 (m, 2H, Ph H-3,5), 6.93 (d,  $J$  = 16.1 Hz, 1H, =CHCO), 4.29 (s, 2H,  $\text{CH}_2\text{Cl}$ ), 2.39 (s, 3H, ArCH<sub>3</sub>).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 191.3 (C=O), 145.3 (ArCH=), 141.8 (Ph C-4), 131.2 (Ph C-1), 129.8 (Ph C-3), 129.8 (Ph C-5), 128.7 (Ph C-2), 128.7 (Ph C-6), 120.6 (=CHCO), 47.4 ( $\text{CH}_2\text{Cl}$ ), 21.6 (ArCH<sub>3</sub>). IR (NaCl,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 1690, 1662, 1618,

1601, 801, 782. Mp: 100 °C (lit.<sup>6b</sup> mp 99–101 °C). Anal. Calcd for  $\text{C}_{11}\text{H}_{11}\text{ClO}$ : C, 67.87; H, 5.70. Found: C, 67.74; H, 5.84.

**(3E)-1-Chloro-4-(2-chlorophenyl)-3-buten-2-one (5e).** Following the general procedure, starting from (*E*)-3-(2-chlorophenyl)-*N*-methoxy-*N*-methylacrylamide (**4e**) (0.32 g, 1.43 mmol),  $\text{ICH}_2\text{Cl}$  (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (2.85 mL, 4.28 mmol) in THF,  $\alpha$ -chloroketone **5e** was obtained in 84% yield (0.26 g) as an orange, thick oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.11 (d,  $J$  = 16.1 Hz, 1H, ArCH=), 7.68 (1H, dd,  $J$  = 7.6 Hz, 1.9 Hz, Ph H-6), 7.44 (m, 1H, Ph H-3), 7.35 (m, 1H, Ph H-4), 7.30 (m, 1H, Ph H-5), 6.95 (d,  $J$  = 16.1 Hz, =CHCO), 4.33 (s, 2H,  $\text{CH}_2\text{Cl}$ ).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 191.1 (C=O), 140.9 (ArCH=), 135.7 (Ph C-2), 132.2 (Ph C-1), 131.8 (Ph C-4), 130.4 (Ph C-3), 127.7 (Ph C-6), 127.2 (Ph C-5), 124.2 (=CHCO), 47.2 ( $^1J(\text{CH}_2)$  = 148.5 Hz,  $^3J(\text{CH}_2, \text{=CH})$  = 1.2 Hz,  $\text{CH}_2\text{Cl}$ ). IR (NaCl,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 1684, 1605, 1594, 1362, 805. Anal. Calcd for  $\text{C}_{10}\text{H}_8\text{Cl}_2\text{O}$ : C, 55.84; H, 3.75. Found: C, 55.91; H, 3.61.

**(3E)-1-Chloro-4-(3-fluorophenyl)-3-buten-2-one (5f).** Following the general procedure, starting from (*E*)-3-(3-fluorophenyl)-*N*-methoxy-*N*-methylmethylacrylamide (**4f**) (0.30 g, 1.43 mmol),  $\text{ICH}_2\text{Cl}$  (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (2.85 mL, 4.28 mmol) in THF,  $\alpha$ -chloroketone **5f** was obtained in 92% yield (0.26 g) as a yellow thick oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.66 (d,  $J$  = 16.1 Hz, 1H, Ph–CH=), 7.38 (m, 1H, Ph H-5), 7.36 (m, 1H, Ph H-6), 7.28 (m, 1H, Ph H-2), 7.13 (m, 1H, Ph H-4), 6.97 (d,  $J$  = 16.1 Hz, 1H, =CHCO), 4.29 (s, 2H,  $\text{CH}_2\text{Cl}$ ).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 191.1 (C=O), 163.0 (d,  $^1J(\text{C,F})$  = 247.4 Hz, Ph C-3), 143.7 (d,  $^4J(\text{C,F})$  = 2.8 Hz, Ph–CH=), 136.2 (d,  $^3J(\text{C,F})$  = 7.7 Hz, Ph C-1), 130.6 (d,  $^3J(\text{C,F})$  = 8.3 Hz, Ph C-5), 124.7 (d,  $^4J(\text{C,F})$  = 2.9 Hz, Ph C-6), 122.7 (=CHCO), 118.0 (d,  $^2J$  = 21.5 Hz, Ph C-4), 114.7 (d,  $^2J$  = 22.0 Hz, Ph C-2), 47.4 ( $\text{CH}_2\text{Cl}$ ).  $^{19}\text{F}$  NMR (377 MHz,  $\text{CDCl}_3$ )  $\delta$ : –112.1. IR (NaCl,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 1681, 1602, 1591, 1362, 1297, 1078, 905, 727. Anal. Calcd for  $\text{C}_{10}\text{H}_8\text{ClFO}$ : C, 60.47; H, 4.06. Found: C, 60.34; H, 4.19.

**(3E)-1-Chloro-4-(2-nitrophenyl)-3-buten-2-one (5g).** Following the general procedure, starting from (*E*)-*N*-methoxy-*N*-methyl-3-(2-nitrophenyl)acrylamide (**4g**) (0.34 g, 1.43 mmol),  $\text{ICH}_2\text{Cl}$  (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (2.85 mL, 4.28 mmol) in THF,  $\alpha$ -chloroketone **5g** was obtained in 76% yield (0.24 g) as a yellow thick oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.14 (d,  $J$  = 16.0 Hz, 1H), 7.72–7.58 (m, 4H), 6.87 (d,  $J$  = 16.0 Hz, 1H), 4.38 (s, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$ : 190.8, 148.5, 133.7, 131.9, 130.9, 130.4, 129.2, 126.6, 125.2, 46.9. IR (NaCl,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 1684, 1605, 1592, 1360, 1273, 1128, 904, 807. Anal. Calcd for  $\text{C}_{10}\text{H}_8\text{ClNO}_3$ : C, 53.23; H, 3.57; N, 6.21. Found: C, 53.35; H, 3.44; N, 6.08.

**(3E)-1-Chloro-4-[4-(trifluoromethyl)phenyl]-3-buten-2-one (5h).** Following the general procedure, starting from (*E*)-*N*-methoxy-*N*-methyl-3-[4-(trifluoromethyl)phenyl]acrylamide (**4h**) (0.37 g, 1.43 mmol),  $\text{ICH}_2\text{Cl}$  (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (2.85 mL, 4.28 mmol) in THF,  $\alpha$ -chloroketone **5h** was obtained in 87% yield (0.31 g) as a yellow thick oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.72 (d,  $J$  = 16.0 Hz, 1H, COCH=CH), 7.65–7.70 (m, 4H, Ph–H), 7.06 (d,  $J$  = 16.0 Hz, 1H, COCH), 4.31 (s, 2H,  $\text{CH}_2$ ).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$ : 191.0 (C=O), 143.2 (COCH=CH), 137.3 (Ph C-1), 132.4 (q,  $J$  = 32.8 Hz, Ph C-4), 128.7 (Ph C-2,6), 126.0 (q,  $J$  = 3.9 Hz, Ph C-3,5), 123.7 (q,  $J$  = 272.5 Hz,  $\text{CF}_3$ ), 123.6 (COCH=), 47.5 ( $\text{CH}_2$ ).  $^{19}\text{F}$  NMR (471 MHz,  $\text{CDCl}_3$ )  $\delta$ : –62.93. IR (NaCl,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 1684, 1604, 1593, 1362, 1173, 1077, 905, 728. Anal. Calcd for  $\text{C}_{11}\text{H}_8\text{ClF}_3\text{O}$ : C, 53.14; H, 3.24. Found: C, 53.00; H, 3.36.

**1-Chloro-4-phenyl-3-buten-2-one<sup>33</sup> (5i).** Following the general procedure, starting from *N*-methoxy-*N*-methyl-3-phenylpropionamide (**4i**) (0.27 g, 1.43 mmol),  $\text{ICH}_2\text{Cl}$  (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (2.85 mL, 4.28 mmol) in THF,  $\alpha$ -chloroketone **5i** was obtained in 90% yield (0.23 g) as a yellow thick oil.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.64–7.54 (m, 2H), 7.51–7.37 (m, 3H), 4.33 (s, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$ : 179.0, 133.5, 131.6, 128.9, 128.9, 119.3, 95.5, 85.7, 49.6. IR (NaCl,  $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 2201, 1671, 758, 689. Anal. Calcd for  $\text{C}_{10}\text{H}_7\text{ClO}$ : C, 67.24; H, 3.95. Found: C, 67.09; H, 4.06.

**(3E)-1-Chloro-4-(2-naphthyl)-3-buten-2-one (5j).** Following the general procedure, starting from (*E*)-*N*-methoxy-*N*-methyl-3-(naphthalen-2-yl)acrylamide (**4j**) (0.35 g, 1.43 mmol), ICH<sub>2</sub>Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (2.85 mL, 4.28 mmol) in THF,  $\alpha$ -chloroketone **5j** was obtained in 83% yield (0.27 g) as a pale yellow thick oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.02–7.97 (m, 1H), 7.87 (ddd, *J* = 14.9, 10.2, 4.7 Hz, 4H), 7.71 (dt, *J* = 8.7, 2.1 Hz, 1H), 7.60–7.50 (m, 2H), 7.04 (dd, *J* = 47.7, 15.9 Hz, 1H), 4.34 (s, 2H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$ : 191.6, 145.7, 135.0, 133.6, 131.8, 131.7, 129.3, 129.1, 128.2, 128.1, 127.3, 123.8, 122.6, 122.0, 47.9. IR (NaCl,  $\nu_{\text{max}}$  cm<sup>−1</sup>): 3083, 1683, 1591, 901. Anal. Calcd for C<sub>14</sub>H<sub>11</sub>ClO: C, 72.89; H, 4.81. Found: C, 73.01; H, 4.71.

**(3E,5E)-1-Chloro-6-phenyl-3,5-hexadien-2-one (5k).** Following the general procedure, starting from (*E*)-*N*-methoxy-*N*-methyl-3-(naphthalen-2-yl)acrylamide (**4k**) (0.31 g, 1.43 mmol), ICH<sub>2</sub>Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (2.85 mL, 4.28 mmol) in THF,  $\alpha$ -chloroketone **5k** was obtained in 93% yield (0.27 g) as a brown thick oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.48 (m, *J* = 15.3 Hz, 10.7 Hz, 1H, CH=CHCO), 7.48 (m, 2H, Ph H-2, H-6), 7.38 (m, 2H, Ph H-3, H-5), 7.35 (m, 1H, Ph H-4), 7.02 (d, *J* = 15.5 Hz, 1H, ArCH=), 6.92 (dd, *J* = 15.5 Hz, 10.7 Hz, 0.6 Hz, 1H, ArCH=CH), 6.52 (d, *J* = 15.3 Hz, 1H, CH=CHCO), 4.23 (s, 2H, CH<sub>2</sub>Cl). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 191.1 (C=O), 145.2 (CH=CHCO), 143.2 (ArCH=), 135.7 (Ph C-1), 129.6 (Ph C-6), 128.9 (Ph C-3), 128.9 (Ph C-5), 127.4 (Ph C-2), 127.4 (Ph C-6), 126.2 (ArCH=CH), 124.8 (CH=CHCO), 47.2 (CH<sub>2</sub>Cl). IR (NaCl,  $\nu_{\text{max}}$  cm<sup>−1</sup>): 3081, 1685, 1590, 1275, 905, 788. Anal. Calcd for C<sub>12</sub>H<sub>11</sub>ClO: C, 69.74; H, 5.36. Found: C, 69.91; H, 5.21.

**(3E)-1-Chloro-4-(2-thienyl)-3-buten-2-one (5l).** Following the general procedure, starting from (*E*)-*N*-methoxy-*N*-methyl-3-(2-thienyl)acrylamide (**4l**) (0.28 g, 1.43 mmol), ICH<sub>2</sub>Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (2.85 mL, 4.28 mmol) in THF,  $\alpha$ -chloroketone **5l** was obtained in 82% yield (0.22 g) as a brown thick oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.83 (d, *J* = 15.6, 1H, ArCH=), 7.45 (dd, <sup>3</sup>*J* = 5.1, 1H, Th H-5), 7.36 (d, <sup>3</sup>*J* = 3.6 Hz, 1H, Th H-3), 7.09 (dd, <sup>3</sup>*J* = 5.1 Hz, <sup>3</sup>*J* = 3.6 Hz, 1H, Th H-4), 6.76 (d, *J* = 15.6 Hz, 1H, =CHCO), 4.24 (s, 2H, CH<sub>2</sub>Cl). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 190.9 (C=O), 139.4 (Th C-2), 137.5 (<sup>1</sup>*J* = 158.1 Hz, ArCH=), 132.8 (<sup>1</sup>*J* (ThC3,H3) = 167.5 Hz, Th C-3), 129.8 (<sup>1</sup>*J* (ThC5,H5) = 186.8 Hz, <sup>2</sup>*J* (ThC5,H4) = 7.3 Hz, <sup>3</sup>*J* (ThC5,H3) = 10.9 Hz, Th C-5), 128.5 (<sup>1</sup>*J* (ThC4,H4) = 169.5 Hz, <sup>2</sup>*J* (ThC4,H3) = 5.2 Hz, <sup>3</sup>*J* (ThC4,H5) = 4.0 Hz, Th C-4), 120.1 (<sup>1</sup>*J* = 159.3 Hz, <sup>3</sup>*J* = 2.8 Hz, =CHCO), 47.4 (<sup>1</sup>*J*(CH<sub>2</sub>) = 149.4 Hz, <sup>3</sup>*J*(CH<sub>2</sub>, =CH) = 2.8 Hz, CH<sub>2</sub>Cl). IR (NaCl,  $\nu_{\text{max}}$  cm<sup>−1</sup>): 3078, 1681, 1587, 1279. Anal. Calcd for C<sub>8</sub>H<sub>7</sub>ClOS: C, 51.48; H, 3.78; S, 17.18. Found: C, 51.48; H, 3.63; S, 17.32.

**(3E)-1-Chloro-4-(2-furyl)-3-buten-2-one<sup>6a</sup> (5m).** Following the general procedure, starting from (*E*)-3-(furan-2-yl)-*N*-methoxy-*N*-methylacrylamide (**4m**) (0.26 g, 1.43 mmol), ICH<sub>2</sub>Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (2.85 mL, 4.28 mmol) in THF,  $\alpha$ -chloroketone **5m** was obtained in 77% yield (0.19 g) as a colorless thick oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.53 (d, *J* = 1.8 Hz, 1H), 7.47 (d, *J* = 15.6 Hz, 1H), 6.86 (d, *J* = 15.6 Hz, 1H), 6.74 (d, *J* = 3.5 Hz, 1H), 6.51 (dd, *J* = 3.5, 1.8 Hz, 1H), 4.24 (s, 2H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$ : 191.6, 151.3, 146.2, 131.5, 119.3, 117.9, 113.4, 48.2. IR (NaCl,  $\nu_{\text{max}}$  cm<sup>−1</sup>): 3087, 1691, 1606, 1590, 1232, 908, 809. Anal. Calcd for C<sub>8</sub>H<sub>7</sub>ClO<sub>2</sub>: C, 56.32; H, 4.14. Found: C, 56.44; H, 4.26.

**(3Z)-1-Chloro-3-fluoro-4-phenyl-3-buten-2-one<sup>16</sup> (5n).** Following the general procedure, starting from (2Z)-2-fluoro-*N*-methoxy-*N*-methyl-3-phenylacrylamide (**4n**) (0.29 g, 1.43 mmol), ICH<sub>2</sub>Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (2.85 mL, 4.28 mmol) in THF,  $\alpha$ -chloroketone **5n** was obtained in 91% yield (0.26 g) as a light yellow thick oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.68 (m, 2H, Ph H-2,6), 7.43 (m, 3H, Ph H-3,4,5), 6.95 (d, *J* = 37.2 Hz, 1H, ArCH=), 4.51 (d, *J* = 2.3 Hz, CH<sub>2</sub>Cl). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 185.8 (d, <sup>2</sup>*J* = 34.6 Hz, C=O), 152.4 (d, <sup>1</sup>*J* = 270.4, <sup>1</sup>*J*(CF, =CH) = 6.0 Hz, =CF), 131.0 (d, <sup>4</sup>*J* = 8.2, Ph C-2), 131.0 (d, <sup>4</sup>*J* = 8.2, Ph C-6), 130.5 (d, <sup>6</sup>*J* = 2.8 Hz, Ph C-4), 130.4 (Ph C-1), 129.0 (Ph C-3), 129.0 (Ph C-5), 117.3 (d, <sup>2</sup>*J* = 4.2 Hz, ArCH=), 45.6 (<sup>1</sup>*J*(CH<sub>2</sub>) = 150.0 Hz, CH<sub>2</sub>Cl). <sup>19</sup>F NMR (377 MHz, CDCl<sub>3</sub>)  $\delta$ : −127.6 (d, *J* =

37.2 Hz, t, *J* = 2.2 Hz). IR (NaCl,  $\nu_{\text{max}}$  cm<sup>−1</sup>): 1685, 1605, 1594, 1362, 1174, 907, 724. Anal. Calcd for C<sub>10</sub>H<sub>8</sub>ClFO: C, 60.47; H, 4.06. Found: C, 60.34; H, 3.93.

**(3E)-1-Chloro-3-methyl-4-phenyl-3-buten-2-one (5o).** Following the general procedure, starting from (*E*)-*N*-methoxy-*N*-2-dimethyl-3-phenylacrylamide (**4o**) (0.29 g, 1.43 mmol), ICH<sub>2</sub>Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (2.85 mL, 4.28 mmol) in THF,  $\alpha$ -chloroketone **5o** was obtained in 88% yield (0.24 g) as a brown thick oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.52 (d, *J* = 1.5 Hz, 1H), 7.46–7.37 (m, 5H), 4.59 (s, 2H), 2.13 (d, *J* = 1.4 Hz, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$ : 193.3, 140.8, 135.3, 135.1, 130.0, 130.0, 129.3, 128.7, 128.7, 45.4, 13.6. IR (NaCl,  $\nu_{\text{max}}$  cm<sup>−1</sup>): 1677, 1598, 1574, 1378, 1093, 904, 728. Anal. Calcd for C<sub>11</sub>H<sub>11</sub>ClO: C, 67.87; H, 5.70. Found: C, 67.72; H, 5.83.

**(3E)-1-Chloro-4-phenyl-3-penten-2-one<sup>34</sup> (5p).** Following the general procedure, starting from (*E*)-*N*-methoxy-*N*-methyl-3-phenylbut-2-enamide (**4p**) (0.29 g, 1.43 mmol), ICH<sub>2</sub>Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (2.85 mL, 4.28 mmol) in THF,  $\alpha$ -chloroketone **5p** was obtained in 89% yield (0.25 g) as a pale yellow solid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.56–7.52 (m, 2H), 7.44–7.42 (m, 3H), 6.71 (d, *J* = 1.2 Hz, 1H), 4.20 (s, 2H), 2.61 (d, *J* = 1.3 Hz, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$ : 191.9, 158.5, 142.1, 129.8, 128.8, 128.8, 126.7, 126.7, 120.1, 49.6, 19.0. IR (NaCl,  $\nu_{\text{max}}$  cm<sup>−1</sup>): 1677, 1597, 1446, 1378, 1093, 905. Mp: 71 °C (lit.<sup>34</sup> mp 71–71.5 °C). Anal. Calcd for C<sub>11</sub>H<sub>11</sub>ClO: C, 67.87; H, 5.70. Found: C, 67.99; H, 5.59.

**(3E)-1-Chloro-4-cyclohexyl-3-buten-2-one (5q).** Following the general procedure, starting from (*E*)-3-cyclohexyl-*N*-methoxy-*N*-methylacrylamide (**4q**) (0.28 g, 1.43 mmol), ICH<sub>2</sub>Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (2.85 mL, 4.28 mmol) in THF,  $\alpha$ -chloroketone **5q** was obtained in 87% yield (0.23 g) as a pale yellow oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  6.92 (dd, *J* = 16.0, 6.8 Hz, 1H), 6.24 (dd, *J* = 16.0, 1.4 Hz, 1H), 4.21 (s, 2H), 2.22–2.11 (m, 1H), 1.80–1.71 (m, 5H), 1.32–1.09 (m, 5H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  191.6, 155.5, 123.8, 47.2, 40.9, 32.1, 31.7, 25.9, 25.9, 25.7. IR (NaCl,  $\nu_{\text{max}}$  cm<sup>−1</sup>): 1684, 1615, 1380, 1280, 1051, 901. Anal. Calcd for C<sub>10</sub>H<sub>15</sub>ClO: C, 64.34; H, 8.10. Found: C, 64.47; H, 8.22.

**(3E/Z)-1-Chloro-4-cyclopropyl-3-buten-2-one (5r).** Following the general procedure, starting from (*E*)-3-cyclopropyl-*N*-methoxy-*N*-methylacrylamide (**4r**) (0.22 g, 1.43 mmol), ICH<sub>2</sub>Cl (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (2.85 mL, 4.28 mmol) in THF,  $\alpha$ -chloroketone **5r** was obtained in 91% yield (0.19 g) as a pale yellow oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ : 6.48–6.38 (m, 3.4H, major + minor), 4.16 (s, 2H, major), 3.86 (s, 1.1H, minor), 1.65–1.59 (m, 2H, major + minor), 1.05–1.02 (m, 3.5H, major + minor), 0.75–0.69 (m, 3.5H, major + minor). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$ : 191.4, 190.3, 156.0, 155.8, 123.0, 122.7, 47.0, 15.2, 15.0, 9.5, 9.4, 4.6. IR (NaCl,  $\nu_{\text{max}}$  cm<sup>−1</sup>): 1686, 1681, 1597, 1381, 903. Anal. Calcd for C<sub>7</sub>H<sub>9</sub>ClO: C, 58.14; H, 6.27. Found: C, 58.28; H, 6.42.

## ■ ASSOCIATED CONTENT

### Supporting Information

Copies of <sup>1</sup>H NMR and <sup>13</sup>C NMR for all compounds (Weinreb amides and  $\alpha$ -haloketones). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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*Publication n. 3*

**Chemoselective efficient synthesis of functionalized  $\beta$ -oxonitriles through cyanomethylation of Weinreb amides.**

Mamuye, A. D.; Castoldi, L.; Azzena, U.; Holzer, W.; Pace, V.\*

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The Supporting Information is available on the website at:

[www.rsc.org/suppdata/ob/c4/c4ob02398f/c4ob02398f1.pdf](http://www.rsc.org/suppdata/ob/c4/c4ob02398f/c4ob02398f1.pdf).

Details on experimental procedures, characterization data and copies of NMR spectra of all compounds are reported.





*Publication n. 4*

**Evidence and isolation of tetrahedral intermediates formed upon the addition of lithium carbenoids to Weinreb amides.**

Castoldi, L.; Holzer, W.; Langer, T.; Pace, V.\*

*Chem. Commun.* **2017**, 53, 9498-95012 (DOI:10.1039/C7CC05215D)

The Supporting Information is available on the website at  
[www.rsc.org/suppdata/c7/cc/c7cc05215d/c7cc05215d1.pdf](http://www.rsc.org/suppdata/c7/cc/c7cc05215d/c7cc05215d1.pdf).

Details on experimental procedures, characterization data and copies of NMR spectra of all compounds are reported.





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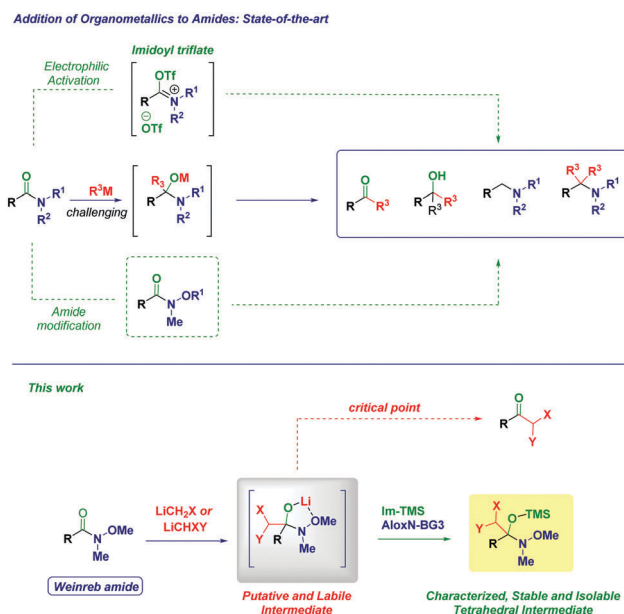
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# Evidence and isolation of tetrahedral intermediates formed upon the addition of lithium carbenoids to Weinreb amides and *N*-acylpyrroles†

Laura Castoldi, Wolfgang Holzer, Thierry Langer and Vittorio Pace \*

The tetrahedral intermediates generated upon the addition of halolithium carbenoids ( $\text{LiCH}_2\text{X}$  and  $\text{LiCHXY}$ ) to Weinreb amides have been intercepted and fully characterized as *O*-TMS heminals. The commercially available *N*-trimethylsilyl imidazole is the ideal trapping agent whose employment, combined with a straightforward neutral Alox chromatographic purification, enables the isolation of such labile species. The procedure could be advantageously extended also for obtaining *O*-TMS heminals from *N*-acylpyrroles. These intermediates manifest interesting reactivity including as precursors of more complex carbenoids.

The addition reactions of nucleophiles to the amide carbonyl constitute extremely important chemical transformations governing key cascades in biological systems and fundamental synthetic operations.<sup>1</sup> Mechanistically, a given nucleophile adds to a  $\text{C}=\text{O}$  functionality affording a tetrahedral intermediate which, depending on the reaction conditions, could restore the carbonyl group (*via* the exclusion of a suitable leaving group, *i.e.* addition-elimination pathway). Conversely – whenever the leaving group could not be eliminated – the overall process upon simple acidolysis affords an hydroxyl-type final product.<sup>2</sup> For a long time, the tamed reactivity of amides towards carbon nucleophiles compared to other carboxylic acid derivatives has been rewarded as a limitation, thus considering them reluctant species in analogous processes (Scheme 1).<sup>3</sup> Nowadays, the opportune activation of the amide bond with electrophilic reagents represents an excellent and robust tool for enabling the chemoselective addition of organometallic reagents *en route* to the synthesis of ketones, alcohols, or amines as documented in illuminating recent works by Charette,<sup>4</sup> Huang<sup>5</sup> and Movassaghi.<sup>6</sup> Undoubtedly, the introduction by Nahm and Weinreb of *N*-methoxy-*N*-methyl amides in 1981<sup>7</sup> represented a breakthrough in the field and currently they are routinely employed for accessing carbonyls with high chemocontrol.<sup>8</sup> The complexation of the metal of the putative tetrahedral intermediate



Scheme 1 General context of the presented work.

to form a five-membered cycle is the critical factor justifying the effectiveness in hampering common undesired drawbacks such as overaddition phenomena or low reactivity. Further advancements on *N*-alkoxy amides pointed out the feasibility of the addition of two different organometallics as showcased recently in elegant works by Chida-Sato,<sup>9</sup> Sarpong,<sup>10</sup> Helmchen,<sup>11</sup> Feringa,<sup>12</sup> Schwartz<sup>13</sup> and Vincent-Kouklovsky,<sup>14</sup> thus, disclosing new concepts for carbonyl and amine synthesis. Additionally, the recent development of impressive catalytic tactics for enabling the reactivity of amide carbonyls with organometallic reagents by the group of Garg<sup>15</sup> and Szostak<sup>16</sup> opened new avenues for the use of amide as feedstocks in analogous processes.

Recently, we recognized the excellent performance of Weinreb amides as privileged acylating agents for chemoselective homologations with  $\alpha$ -substituted methyllithium reagents ( $\text{LiCH}_2\text{X}$ ).<sup>17</sup> Compared to more classical substrates for similar reactions

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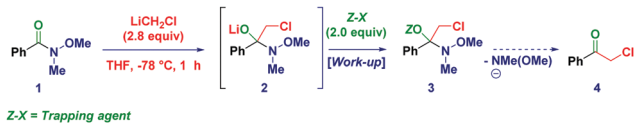
(e.g. esters), Weinreb amides showed an impressive superiority, which we attributed to the chelating effect typical of these species. However, the inherent transient nature of the tetrahedral intermediate<sup>18</sup> formed through the addition of a strongly nucleophilic organometallic reagent implies severe difficulties in isolating and identifying *via* spectroscopic methods these species and, ultimately to fully uncover their synthetic potential.<sup>19</sup> With the aim to support these hypotheses, we document herein the isolation and the structural elucidation of *O*-trimethylsilyl protected hemiaminals obtained *via* the addition of lithium halocarbenoids (LiCH<sub>2</sub>X and LiCHXY)<sup>20</sup> to variously functionalized Weinreb amides and analogous *N*-acylpyrroles.<sup>21</sup>

At the outset of our investigations, we easily recognized the importance of finding suitable reaction conditions and work-up operations enabling not only the safe capture but, more importantly, also preserving the chemical integrity of the labile tetrahedral intermediate. The ideal trapping agent should present a remarkable oxophilicity and contemporaneously provide the sufficient stability to avoid the undesired elimination of the *N*-methyl-*N*-methoxy fragment, which would have afforded the corresponding ketone. Cognizant of these critical requirements, Weinreb amide **1** was selected as the model substrate and reacted with LiCH<sub>2</sub>Cl (Table 1) under our usual Barbier-type conditions.<sup>17c,22</sup> Neither through basic aqueous or methanolic work-up could the free hemiaminal be isolated. TMSCl in the presence of pyridine (entry 1) served as an effective trapping agent (**3**) as deduced from the diagnostic hemiaminal (carbon) <sup>13</sup>C (96.0 ppm) and (nitrogen) <sup>15</sup>N-NMR (−207.3 ppm) resonances. The employment of imidazole as the base was particularly convenient since the conversion could be increased up to 90% (entry 2). Pleasingly, the commercially available *N*-TMS-imidazole (Im-TMS) allowed to maximize the conversion up to 95% (entry 3), whereas the more bulky TBDMS and TPS

reagents afforded exclusively the corresponding α-chloroketone (entries 4–5), presumably due to steric factors affecting negatively the stability of the intermediate. The work-up and purification technique followed for getting analytically pure **3** deserve particular mention. After basic aqueous treatment (NaHCO<sub>3</sub> 5%) and extraction of the organic phase with Et<sub>2</sub>O, we noticed a substantial transformation of the product into ketone **4** during recording of NMR spectra in CDCl<sub>3</sub>, presumably because of the acidity of this deuterated solvent. Analogously, attempts to purify the crude mixture through silica gel were unsuccessful, even upon prior neutralizing treatment with TEA (10% or neat) or TMSCl (entries 6–8). Excellent purification was achieved by using Brockmann 3 grade neutral alumina (AloxN-BG3), which allowed us to finally isolate **3** in 91% yield (entry 9). Different deactivation grades of Alox were less effective (entries 10–11), while different alumina type phases (acidic or basic) were not suitable for the purpose (not shown).

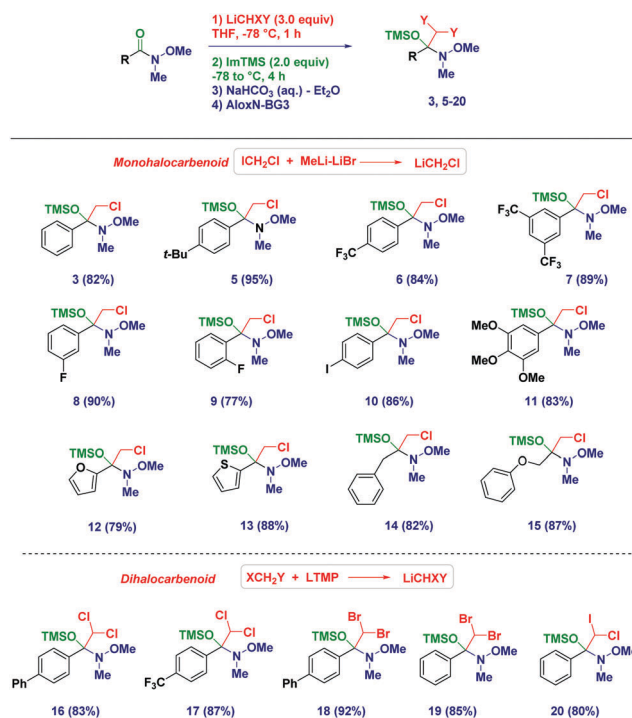
With the optimized conditions in hand, we then applied the methodology to different Weinreb amides (Scheme 2). The corresponding tetrahedral intermediates could be easily isolated and characterized in high to excellent chemical yields. Accordingly, aromatic (**3–11**) and heteroaromatic (**12–13**) Weinreb amides provided the *O*-TMS protected hemiaminals regardless of the electronic behavior of the substituents across the ring. Notably, the presence of an exchangeable iodine atom on the aromatic ring did not have a detrimental effect (**10**), thus highlighting an excellent chemoselectivity during the carbenoid generation event starting from ICH<sub>2</sub>Cl. Switching to aliphatic analogues (**14–15**), no alteration was observed during the trapping–isolation sequence even in the presence of a α-heteroatom (**15**). Tetrahedral intermediates

Table 1 Reaction and isolation procedure optimization<sup>a</sup>



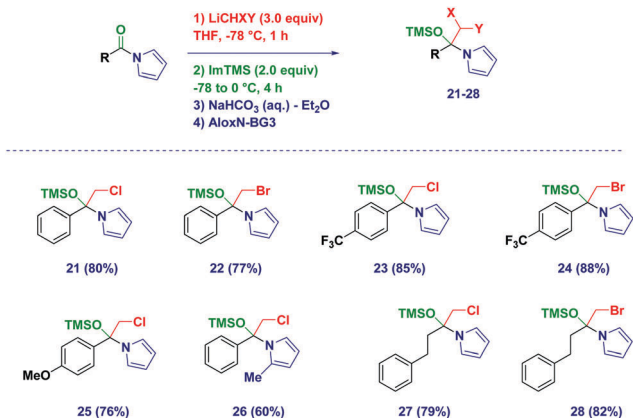
| Entry <sup>a</sup> | Trapping agent (2.0 equiv.) | Conversion/ratio 3:4 <sup>b</sup> (%) | Chromatographic system       | Yield of 3 <sup>c,d</sup> (%) |
|--------------------|-----------------------------|---------------------------------------|------------------------------|-------------------------------|
| 1                  | TMSCl-Py                    | 87/5:1                                | AloxN-BG3                    | 71                            |
| 2                  | TMSCl-Im                    | 90/20:1                               | AloxN-BG3                    | 70                            |
| 3                  | Im-TMS                      | 95/25:1                               | AloxN-BG3                    | 86                            |
| 4                  | Im-TBDMS                    | 86/0:1                                | —                            | —                             |
| 5                  | Im-TPS                      | 89/0:1                                | —                            | —                             |
| 6                  | Im-TMS                      | 95/25:1                               | SiO <sub>2</sub>             | 0                             |
| 7                  | Im-TMS                      | 95/25:1                               | SiO <sub>2</sub> -TEA (10%)  | 6                             |
| 8                  | Im-TMS                      | 95/25:1                               | SiO <sub>2</sub> -TMSCl (5%) | 12                            |
| 9                  | Im-TMS                      | 95/25:1                               | AloxN-BG3                    | 91                            |
| 10                 | Im-TMS                      | 95/25:1                               | AloxN-BG4                    | 78                            |
| 11                 | Im-TMS                      | 95/25:1                               | AloxN-BG2                    | 70                            |

<sup>a</sup> LiCH<sub>2</sub>Cl was generated from ICH<sub>2</sub>Cl (3.0 equiv.) and MeLi-LiBr (2.8 equiv.) in THF at −78 °C. <sup>b</sup> <sup>1</sup>H-NMR calculated conversion. <sup>c</sup> Otherwise stated, yields refer to isolated and purified compounds according to conditions in entry 9 (AloxN-BG3). <sup>d</sup> For the preparation of AloxN-BG3, see the ESI.



Scheme 2 Trapping–isolation sequence of *O*-TMS protected aminals from Weinreb amides with monohalo- and dihalomethyl lithium carbenoids.





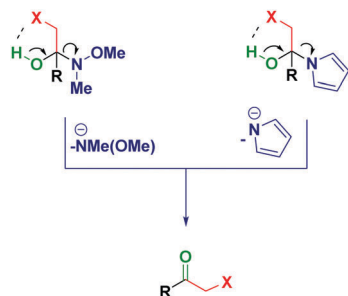
Scheme 3 O-TMS protected hemiaminals from *N*-acylpyrroles and carbenoids.

generated upon the addition of (mixed) dihalocarbenoids<sup>23</sup> could be easily accessed (**16–20**) and could serve as excellent placeholders for forming more complex, synthetically versatile carbenoids (*vide infra*). Remarkably, C<sub>6</sub>D<sub>6</sub> solutions of the intermediates showed an excellent stability up to 6 months (kept at  $-20\text{ }^{\circ}\text{C}$ ), thus further showcasing the convenience of this solvent for NMR analyses.

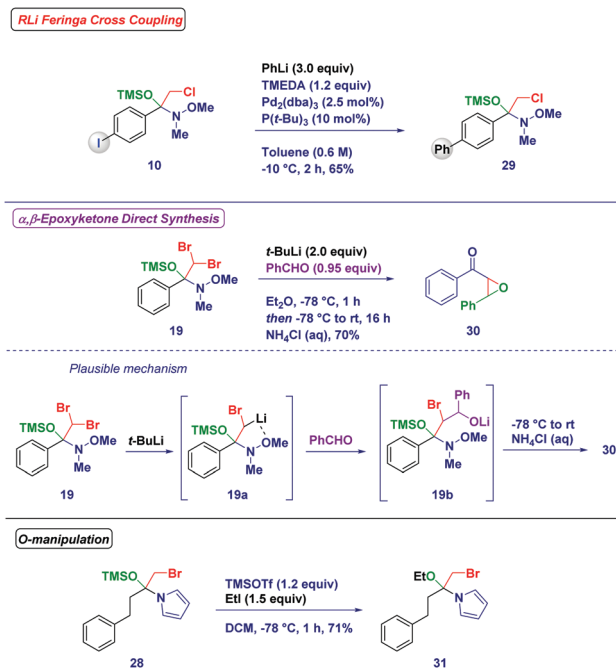
The protocol was also amenable for forming the tetrahedral intermediates – under analogous reaction conditions – starting from *N*-acylpyrroles (Scheme 3). Again the aromatic (**21–26**) vs. aliphatic (**27–28**) nature of the materials did not influence the positive outcome of the process, which significantly also proved to be applicable to intermediates that formed upon the addition of LiCH<sub>2</sub>Br.<sup>24</sup> However, the increase of sterical demand on the pyrrole core slightly decreases the isolated yield of the protected hemiaminal (**26**).

Previous reports from Evans<sup>25</sup> and Brandänge<sup>26</sup> entailed the formation and isolation of hemiaminals from *N*-acylpyrroles and RLi or RMgX in the native form (*i.e.* presenting a free OH functionality).<sup>27</sup> However, in the cases discussed herein, the plausible intramolecular formation of a halogen bond<sup>28</sup> between the putative OH and the halogen would trigger the elimination and, as such, it renders it impossible to obtain analogous hemiaminals (Scheme 4).

The reactivity of the synthesized tetrahedral intermediates was then tested with the aim of investigating the synthetic utility of these species (Scheme 5). The iodo-containing intermediate **10** resulted in an excellent substrate for the Feringa/Fañanas-Mastral



Scheme 4 Plausible halogen-bond formation on putative hemiaminals.



Scheme 5 Derivatization of O-TMS protected hemiaminals.

Pd-catalyzed coupling of an organolithium.<sup>29</sup> Significantly, under the reaction conditions the tetrahedral intermediate could be completely preserved from degradation (**29**). An O-TMS protected hemiaminal (**19**) featuring two bromine atoms was amenable to subsequent Li/Br exchange to generate a new, more complex carbenoid (**19a**) whose stability was increased by the chelating effect of the *N*-methoxy group. The attack of this carbenoid to benzaldehyde generated an O-lithiated bromohydrin (**19b**), which upon spontaneous ring-closure and acidic treatment resulted in the formation of the highly valuable and challenging  $\alpha,\beta$ -epoxyketone **30**.<sup>30</sup> Moreover, Lewis acid treatment (TMSOTf) of the *N*-acylpyrrole derivative hemiaminal **28** followed by trapping with ethyl iodide afforded the O-ethyl product **31**.

In summary, we have disclosed an effective strategy for obtaining O-trimethylsilyl protected hemiaminals formed through the addition of lithium monohalo- and dihalo-carbenoids to Weinreb amides. The proper combination of Im-TMS (as the trapping agent) and Brockmann grade 3 neutral alumina (as the stationary phase for chromatography) was found to be – together with recording NMR analyses in benzene-*d*<sub>6</sub> – the critical factor for enabling the isolation of such labile tetrahedral intermediates. The method is also amenable for forming analogous protected hemiaminals from *N*-acylpyrroles. A concise examination of the manipulation these species may undergo is also discussed.

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*Publication n. 5*

**Highly efficient and environmentally benign preparation of Weinreb amides in the biphasic system 2-MeTHF/water.**

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The Supporting Information is available on the website at

<http://www.rsc.org/suppdata/ra/c3/c3ra41262h/c3ra41262h.pdf>

Details on experimental procedures, characterization data and copies of NMR spectra of all compounds are reported.



## COMMUNICATION

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# Highly efficient and environmentally benign preparation of Weinreb amides in the biphasic system 2-MeTHF/water†

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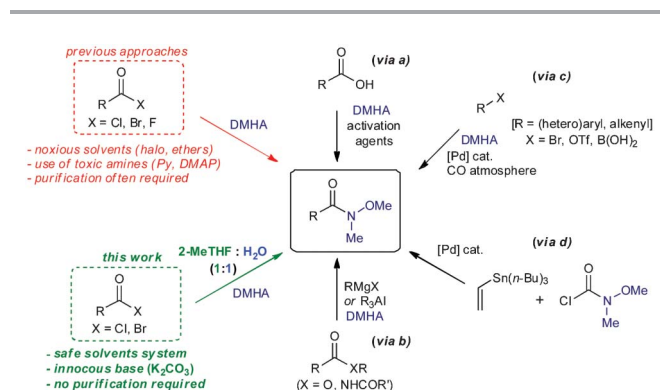
[www.rsc.org/advances](http://www.rsc.org/advances)Vittorio Pace,<sup>\*a</sup> Laura Castoldi,<sup>a</sup> Andrés R. Alcántara<sup>b</sup> and Wolfgang Holzer<sup>a</sup>

**A straightforward chromatography-free preparation of Weinreb amides starting from acid halides has been achieved in the biphasic medium 2-MeTHF/water. Analytically pure compounds were isolated in excellent yields simply after removal of 2-MeTHF, which absolutely avoids the use of any contaminant organic solvent within the whole process due to its (practically) immiscibility with water.**

*N*-methoxy-*N*-methylamides, commonly known as Weinreb amides, are highly versatile scaffolds in organic synthesis.<sup>1,2</sup> Since their introduction in early 1980s, their usefulness as acylating agents upon reaction with organometallic species or hydride donors has been continuously increased.<sup>3,4</sup> In particular, this motif continues to represent the ideal starting material for the preparation of ketones and aldehydes with the above mentioned reactants. Indeed, the formation of a strongly stabilized metal-chelated intermediate accounts for the (almost) complete elimination of any undesired product resulting from the overaddition of these reagents to the resulting carbonyl-type carbon atom.<sup>5</sup> Effectively, Weinreb amides allow to shorten synthetic processes by avoiding unnecessary protecting-deprotecting steps, thus maximizing the chemical economy in agreement with the 2nd and 8th Anastas' Principles of Green Chemistry.<sup>6</sup>

Due to this paramount importance in synthesis, different protocols have been established for their preparation. The classical approach employs a carboxylic acid which, however needs to be activated prior to its reaction with the commercially available *N*,*O*-dimethylhydroxylamine hydrochloride (DMHA).<sup>3</sup> Unfortunately, the activation requires the use of an excess of hazardous reagents (*e.g.* DCC,<sup>7</sup> HOBT,<sup>8</sup> deoxo-fluor,<sup>9</sup> PPh<sub>3</sub>-I<sub>2</sub>,<sup>10</sup> P[NCH<sub>3</sub>(OCH<sub>3</sub>)])<sup>11</sup> which maybe pyrophoric or even explosive (Scheme 1, path a). Alternatively, carboxylic esters or imides maybe activated with organoaluminium<sup>1</sup> or Grignard reagents<sup>12</sup>

(Scheme 1, path b); however, the use of such reagents at pilot plant scale is limited by safety concerns against the 12th Principle.<sup>6</sup> Moreover, these expensive activators are not always effective in promoting the formation of Weinreb amides starting from hindered carboxylic acid derivatives,<sup>13</sup> so that more sophisticated routes have been reported, such as the palladium-catalyzed aminocarbonylation<sup>14</sup> of aryl bromides,<sup>15</sup> arylboronic acids and lactam/lactone-derived vinyl triflates in a carbon monoxide atmosphere (Scheme 1, path c),<sup>16</sup> and the Stille-type cross-coupling reaction between aryl and vinyl stannanes and *N*-methoxy-*N*-methylcarbamoyl chloride (Scheme 1, path d).<sup>17</sup> Although in general effective in promoting the amidation-type reactions, the attractiveness of the procedures involving the activation of a carboxylic acid is limited by the concomitant production of undesired products derived from the active intermediate species. As a consequence, they often require tedious and somewhat complicated chromatographic separations<sup>13</sup> with contaminant solvents, thus lengthening the synthetic sequence and producing toxic and unnecessary organic wastes, contravening the 1st Principle of Green Chemistry.<sup>6</sup> Evidently, the development of general and efficient protocols for the synthesis of Weinreb amides under more sustainable conditions is a formidable challenge to be pursued. Thus, herein we disclose our findings on an environmentally benign and cost-effective preparation of



Scheme 1 Synthetic approaches to Weinreb amides.

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these valuable scaffolds without performing any purification (*i.e.* chromatography, recrystallization, distillation) by means of a Schotten–Baumann-type reaction<sup>18</sup> in a biphasic medium water-2-methyltetrahydrofuran (2-MeTHF)<sup>19–22</sup> without the necessity to use any additional organic solvent during the overall process.

At first sight, the reaction of an acid halide and DMHA represents the conceptually simplest approach to the targets: in this context, it should be argued that such a methodology is much more atom efficient<sup>23</sup> compared to those protocols using carboxylic derivatives not always commercially available (*e.g.* esters, anhydrides, imides, *etc.*). Unfortunately, acid halide-mediated synthesis of Weinreb amides previously reported are performed in halogenated or ethereal solvents in the presence of amines such as pyridine.<sup>1,5,24</sup> It is clear that a chemical synthesis carried out under these conditions presents serious issues from an environmental perspective and for the safety of the operators both in laboratory and industrial scale. Furthermore, these methods do not allow a straightforward approach to Weinreb amides because purifications are often necessary. In this context, due to our commitment to carry out chemical synthesis under more sustainable conditions,<sup>25–30</sup> we decided to test a biosolvent, 2-MeTHF, derived from renewable sources (corncoobs and bagasse) and whose use, as documented in the literature, fulfils 3rd, 5th and 7th Principles.<sup>6</sup> In fact, the search for more sustainable solvents is a major task inside Green Chemistry,<sup>31,32</sup> and inside this area, the use of biosolvents is a growing tendency, especially in Pharma Industry.<sup>33–35</sup>

As the model reaction, we selected the challenging substrate cinnamoyl chloride **1**, in which the presence of a conjugated olefinic system renders it susceptible to the possible attack of the nucleophilic amine also at the  $\beta$ -position to the carbonyl moiety.

As reported in Table 1, the use of a series of common organic solvents (dichloromethane, diethyl ether, acetonitrile, DMF, AcOEt, THF, 2-MeTHF) in the presence of potassium carbonate as the base, affords the desired Weinreb amide **1a** in moderate yields (entries 1–7). Interestingly, with less than 2 equiv. of base yields of **1a** diminished sensitively (entry 8), while no reaction was observed at all in its absence (entry 9). This behaviour may be understood as a consequence of the deprotonating action displayed by the bases on the hydrochloride salt of DMHA. Interestingly, inorganic bases performed better than organic ones (entries 11–12), while the use of a supported inorganic base (KF-Celite)<sup>37–40</sup> reduced remarkably the yields due to its insolubility in both aqueous and organic phases (entry 13). Remarkably, switching to the biphasic system organic solvent–water compound **1a** could be obtained in higher yields (entries 14–17): evidently, the use of the so-called Schotten–Baumann conditions<sup>18</sup> allows not only to deprotonate DMHA but, also to neutralize the hydrochloric acid formed upon the amidation and thus, driving the reaction to completion. In this context, the employment of immiscible solvent systems provide the optimum results due to the fact that the so-obtained Weinreb amide remains in the organic phase, while the inorganic by-products move to the aqueous phase. Among the various solvents screened, ethereal ones provided better results compared to toxic chlorinated and hydrocarbon ones (entries 16, 17), being 2-MeTHF–water the ideal combination (entry 14). Some

Table 1 Optimization of the reaction conditions<sup>a</sup>



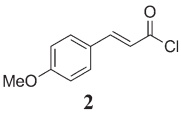
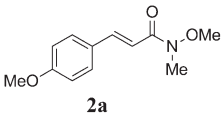
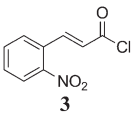
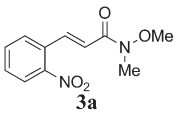
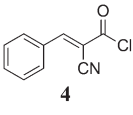
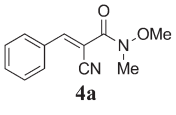
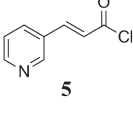
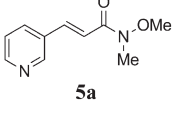
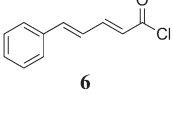
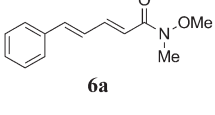
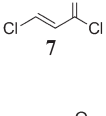
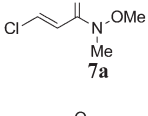
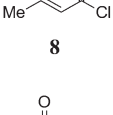
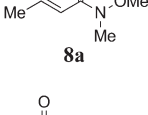
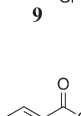
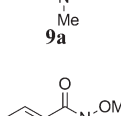
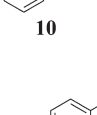
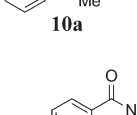
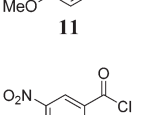
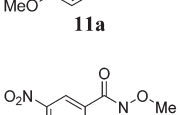
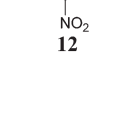
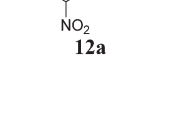
| Entry           | Solvent                                                        | Base                           | Base equiv. | Isolated Yield of <b>1a</b> [%] |
|-----------------|----------------------------------------------------------------|--------------------------------|-------------|---------------------------------|
| 1               | CH <sub>2</sub> Cl <sub>2</sub>                                | K <sub>2</sub> CO <sub>3</sub> | 2.2         | 42                              |
| 2               | Et <sub>2</sub> O                                              | K <sub>2</sub> CO <sub>3</sub> | 2.2         | 47                              |
| 3               | MeCN                                                           | K <sub>2</sub> CO <sub>3</sub> | 2.2         | 39                              |
| 4               | Toluene                                                        | K <sub>2</sub> CO <sub>3</sub> | 2.2         | 28                              |
| 5               | AcOEt                                                          | K <sub>2</sub> CO <sub>3</sub> | 2.2         | 37                              |
| 6               | THF                                                            | K <sub>2</sub> CO <sub>3</sub> | 2.2         | 44                              |
| 7               | 2-MeTHF                                                        | K <sub>2</sub> CO <sub>3</sub> | 2.2         | 51                              |
| 8               | 2-MeTHF                                                        | K <sub>2</sub> CO <sub>3</sub> | 1.1         | 37                              |
| 9               | 2-MeTHF                                                        | —                              | —           | <i>n.r.</i>                     |
| 10              | 2-MeTHF                                                        | NaHCO <sub>3</sub>             | 2.2         | 43                              |
| 11              | 2-MeTHF                                                        | NEt <sub>3</sub>               | 2.2         | 35                              |
| 12              | 2-MeTHF                                                        | DIPEA                          | 2.2         | 33                              |
| 13              | 2-MeTHF                                                        | KF-Celite <sup>36</sup>        | 2.2         | 20                              |
| 14 <sup>a</sup> | 2-MeTHF–H <sub>2</sub> O <sup>b</sup>                          | K <sub>2</sub> CO <sub>3</sub> | 2.2         | 97                              |
| 15              | Et <sub>2</sub> O–H <sub>2</sub> O <sup>b</sup>                | K <sub>2</sub> CO <sub>3</sub> | 2.2         | 86                              |
| 16              | CH <sub>2</sub> Cl <sub>2</sub> –H <sub>2</sub> O <sup>b</sup> | K <sub>2</sub> CO <sub>3</sub> | 2.2         | 81                              |
| 17              | Toluene–H <sub>2</sub> O <sup>b</sup>                          | K <sub>2</sub> CO <sub>3</sub> | 2.2         | 72                              |

<sup>a</sup> Unless otherwise specified reactions were carried out during 1 h from 0 °C to rt. <sup>b</sup> 1 : 1 v/v mixture. (*n.r.* no reaction).

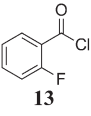
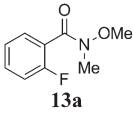
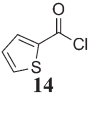
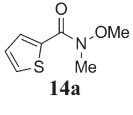
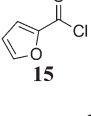
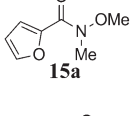
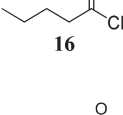
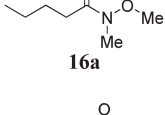
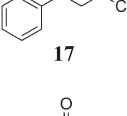
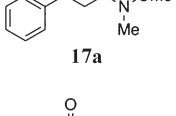
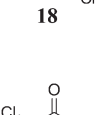
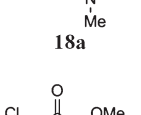
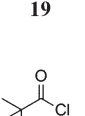
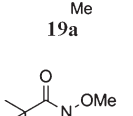
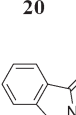
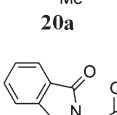
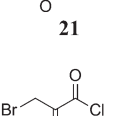
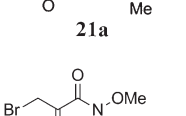
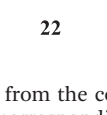
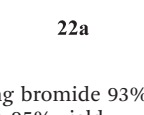
point merits mention: a) to minimize the possible hydrolysis of the acyl halide, it was initially dissolved in 2-MeTHF jointly with DMHA and subsequently the basic solution was added; otherwise a slight decrease of the yield (*ca.* 10%, as a consequence of the rapid hydrolysis to the acid) was noticed; b) reaction reached to completion within 1 h and the isolation of the product is simply performed after acidic wash (1 M HCl) and separation of the phases. In this sense, the low solubility of 2-MeTHF in water (4 g 100 mL<sup>−1</sup>)<sup>41</sup> allows an extremely easy isolation without needing to add any other solvent (*e.g.* diethyl ether, ethyl acetate, dichloromethane, *etc.*), and in the absence of any additional purification steps. Thus, analytically pure Weinreb amide **1a** was simply isolated after evaporation of the non-carcinogenic 2-MeTHF<sup>42</sup> under reduced pressure.

Inspired by this success, we turned our attention towards different acyl halides. As shown in Table 2 the protocol results of broad application, allowing an easy preparation of these amides in a straightforward manner. Interestingly  $\alpha,\beta$ -unsaturated systems react smoothly without any side reaction (*i.e.* attack of the amine on the  $\beta$ -carbon), affording the Weinreb amides in high yields, regardless of the nature of the substituents across the C–C double bond or on the aryl systems directly connected to it (entries 1–8). Significantly, the extended conjugation in case of chloride **6** did not affect the outcome of the reaction (entry 5). It should be highlighted that this protocol represents a versatile alternative for the preparation of these particular Weinreb amides compared to previous described ones involving Wittig-type reactions between an unsaturated aldehyde and a phosphorane.<sup>43–45</sup> Analogously, both functionalized aromatic and heteroaromatic acid halides react very well, giving the desired Weinreb amides in excellent yields (entries 9–14). It has been reported that more reactive

**Table 2** Substrate scope of the reaction

| $  \begin{array}{c}  \text{R}-\text{C}(=\text{O})-\text{X} \\  \text{X} = \text{Cl, Br}  \end{array}  \xrightarrow[\text{2-MeTHF - H}_2\text{O (1:1 v/v), 0}^\circ\text{C to rt}]{\text{DMHA (1.1 equiv.), K}_2\text{CO}_3 \text{ (2.2 equiv.)}}  \begin{array}{c}  \text{R}-\text{C}(=\text{O})-\text{N}(\text{Me})_2  \end{array}  $ |                                                                                     |                                                                                     |                    |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------|
| Entry                                                                                                                                                                                                                                                                                                                                  | Substrate                                                                           | Product                                                                             | Isolated Yield (%) |
| 1                                                                                                                                                                                                                                                                                                                                      |    |    | 94                 |
| 2                                                                                                                                                                                                                                                                                                                                      |    |    | 92                 |
| 3                                                                                                                                                                                                                                                                                                                                      |    |    | 83                 |
| 4                                                                                                                                                                                                                                                                                                                                      |    |    | 86                 |
| 5                                                                                                                                                                                                                                                                                                                                      |   |   | 97                 |
| 6                                                                                                                                                                                                                                                                                                                                      |  |  | 92                 |
| 7                                                                                                                                                                                                                                                                                                                                      |  |  | 91                 |
| 8                                                                                                                                                                                                                                                                                                                                      |  |  | 89                 |
| 9 <sup>a</sup>                                                                                                                                                                                                                                                                                                                         |  |  | 96 <sup>a</sup>    |
| 10                                                                                                                                                                                                                                                                                                                                     |  |  | 94                 |
| 11                                                                                                                                                                                                                                                                                                                                     |  |  | 90                 |

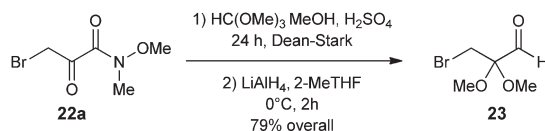
**Table 2** (Continued)

| Entry | Substrate                                                                            | Product                                                                               | Isolated Yield (%) |
|-------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|--------------------|
| 12    |    |    | 96                 |
| 13    |    |    | 89                 |
| 14    |    |    | 92                 |
| 15    |    |    | 93 <sup>b</sup>    |
| 16    |    |    | 90                 |
| 17    |   |   | 88                 |
| 18    |   |  | 95                 |
| 19    |   |  | 97                 |
| 20    |  |  | 96                 |
| 21    |  |  | 89                 |

<sup>a</sup> Starting from the corresponding bromide 93% yield. <sup>b</sup> starting from the corresponding bromide 95% yield.

halides (*i.e.* aromatic) are substrates leading to lower yields in Schotten–Baumann type amidations compared to aliphatic ones;<sup>46</sup> however, in our hands we did not observe this pattern, probably because the alkaline aqueous solution (responsible of the hydrolysis) is added to the mixture of DMHA and acid halide in 2-MeTHF. Similarly, aliphatic acid halides afforded the corresponding Weinreb amides regardless the presence of distinct





**Scheme 2** Synthetic versatility of a Weinreb amide.

groups including a halide or an ester sensitive to hydrolysis within the core of the acid (entries 15–21). Of particular significance is the excellent yield obtained for the bulky pivaloyl chloride (entry 19), which, as previously reported, proved to be a problematic substrate.<sup>13</sup> Although reactions carried out on acid chlorides reached to completion within 1 h, a dramatic decrease of the reaction times was noticed for the corresponding bromides that provided the desired Weinreb amides within only 20 min.

Finally, we employed Weinreb amide **22a** for the preparation of the aldehyde **23**, which is a key synthon for the preparation of pharmacologically relevant targets such as glyoxalase I inhibitors<sup>47</sup> or cardiotoxic biimidazoles.<sup>48</sup> As previously reported by Chari and Kozarich,<sup>47</sup> it has been obtained in low overall yield after a long reduction-oxidation sequence starting from the corresponding ester. Moreover, also when the reduction of the ester was attempted with DIBAL-H, the yield did not increase significantly.<sup>49</sup> Thus, we could selectively prepare **23** in 79% yield by simply reducing the protected Weinreb amide derived from **22a** with  $\text{LiAlH}_4$  in 2-MeTHF (Scheme 2). In such a way, the access to **23** is facilitated compared to the above mentioned procedures: 1) on one hand the Weinreb amide could be directly reduced to the aldehyde and 2) the reduction of the Weinreb amide with  $\text{LiAlH}_4$  is evidently more convenient than the reduction of the ester with DIBAL-H.

## Conclusions

In conclusion, we have developed a straightforward access to synthetically useful Weinreb amides starting from commercially available or readily obtainable acid halides in the biphasic medium (alkaline) water/2-MeTHF. Due to the immiscibility of this biomass derived solvent with water, there is no necessity to use any noxious organic solvent within the whole preparative process. Pure compounds are obtained by simple removal of 2-MeTHF, thus avoiding purification steps which would complicate the efficiency of the sequence. The protocol is characterized by a wide applicability to variously functionalized acid halides and moreover, has been used for the preparation of a multielectrophilic aldehyde of pharmacological relevance. Further studies on the topic are currently in progress in our laboratory and will be presented in due course.

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*Publication n. 6*

**Isocyanates and isothiocyanates as versatile platforms for accessing (thio)amide-type compounds.**

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## Isocyanates and isothiocyanates as versatile platforms for accessing (thio)amide-type compounds

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The addition of carbon (Grignard and organolithium reagents) and hydride nucleophiles (Schwartz reagent) to isocyanates and isothiocyanates constitutes a versatile, direct and high yielding approach to the synthesis of functionalized (thio)amide derivatives including haloamides and formamides. The chemo-selective delivery of a nucleophilic (eventually configurationally stable) organometallic species to a given iso(thio)cyanate is the crucial parameter for the success of the strategy. Thus, the influence of the factors governing classical methodologies (e.g. dehydrative condensation) such as steric hindrance and electronic properties of the reactants become practically negligible.

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### 1. Introduction

The construction of amide-type bonds constitutes one of the fundamental operations in synthetic chemistry because of the



**Vittorio Pace**

Vittorio Pace obtained a degree in Pharmacy from the University of Perugia (Italy) and then received a PhD in Chemical Sciences from the Complutense University of Madrid under the guidance of Prof. A. R. Alcántara and J. V. Sinisterra. In 2010 he moved to the University of Vienna to join the group of Prof. W. Holzer as a Mach postdoc fellow. Postdoctoral training continued with Prof. D. J. Procter at the Univer-

sity of Manchester (2011–2013) and with Prof. B. Olofsson at Stockholm University (2013–2014). In August 2014 he came back to Vienna as a group leader in Synthetic Chemistry at the Department of Pharmaceutical Chemistry. In November 2014 he obtained the habilitation for Associate Professor of Organic Chemistry from the Italian Ministry of Education. In 2015 he was awarded the Vincenzo Caglioti Prize by the Accademia Nazionale dei Lincei, the Ciamician Medal by the Division of Organic Chemistry of the Italian Chemical Society and the Young Investigator Award by the Faculty of Life Sciences of the University of Vienna. His main research interest deals with the application of lithium carbenoids and organometallic reagents in organic synthesis.



**Serena Monticelli**

Serena Monticelli was born in Taranto (Italy) in 1988 and received a MSc degree cum laude in Pharmacy in 2013 from the University of Bari. In 2015, she obtained a postgraduate MSc in “Drug Design and Development” from the University of Pavia (Italy) and later on, she started doctoral studies at the University of Vienna (Austria) under the supervision of Dr V. Pace and Prof. T. Langer working on organometallic

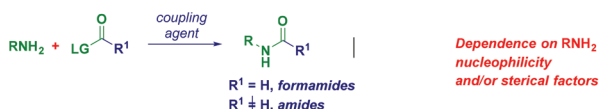
chemistry in the form of a Uni:docs grant funded by the University of Vienna. Her current research interests include the use of organolithium methods (mainly halocarbenoids) and their application in synthetic medicinal chemistry.

widespread presence of this motif in natural products, peptides, biologically active compounds, *inter alia*.<sup>1</sup> Although conceptually intuitive and efficient for accessing simple amides, the dehydrative condensation of a carboxylic acid with an amine triggered by a coupling reagent (usually needed in stoichiometric amounts) presents significant drawbacks in the case of highly sterically hindered and electron-deficient (form)-amides (Scheme 1, path A).<sup>2</sup> These issues are equally evident also in the preparation of  $\alpha$ -halomethylamides – a versatile class of building blocks<sup>3</sup> – generated *via* the reaction of a given  $\alpha$ -haloacetyl halide and an amine.<sup>4</sup> Moreover, electrophilic halogenation procedures of methylamides show limited

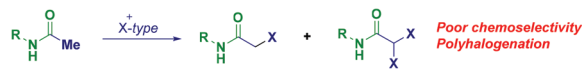
chemoselectivity (*i.e.* polyhalogenations may occur – path B).<sup>5</sup> Similarly, the synthesis of thioamides – which differ significantly from the corresponding oxoamides in terms of reactivity and properties<sup>6</sup> – still represents a formidable challenge since it has been plagued by inherent difficulties including, but not limited to, the use of highly contaminating, toxic and stinking sulfurating agents (*e.g.* Lawesson reagent – path C).<sup>7</sup> Additionally, thionation procedures may not be straightforward and direct towards the formal replacement of oxygen with sulfur, an operation which *per se* requires harsh reaction conditions (high temperatures, prolonged reaction times, tedious work-up).<sup>8</sup> As a consequence, the electrophilic activation of the oxoamide functionality is often necessary prior to the treatment with sulfurating agents.<sup>9</sup>

Despite these difficulties encompassing the syntheses of both oxoamides and thioamides, remarkable advancements have been made in the last few years recalling the seminal work of Gilman<sup>10</sup> and Worrall<sup>11</sup> who reported the addition of Grignard and organolithium reagents to iso(thio)cyanates as a precise titration method for these organometallic species. Unfortunately, applications of this tactic for preparative purposes have been underestimated for a long time<sup>12</sup> and, only in 2012 Bode and coworkers fully recognized its potentiality and effectiveness (Scheme 2).<sup>13</sup> In fact, these authors could solve a long-standing issue in organic synthesis dealing with efficient access to highly sterically hindered and electron-deficient secondary amides. Some interesting features that merit mention are: (a) bulky substituents could be accommodated on both the Grignard reagents and the isocyanate; (b) no substantial difference between the aromatic and aliphatic partners were noticed; (c) scale-up of the reaction and replacing diethyl ether with the more attractive and more environmentally benign 2-methyltetrahydrofuran (2-MeTHF)<sup>14</sup> were possible; (d) in no

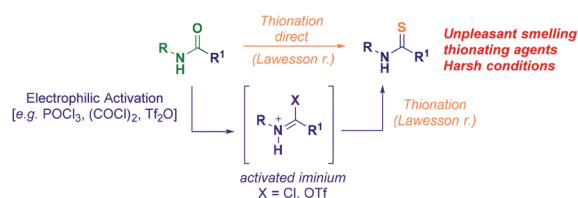
**A) Synthesis of (Form)-Amides through Amine / Carboxylic Acid Derivative Condensation**



**B) Synthesis of (Halo)-Amides through Electrophilic Halogenation**



**C) Synthesis of Thioamides through Thionation of Oxoamides**



**Scheme 1** Classical approaches to the synthesis of (form)amides, haloamides and thioamides.



**Karen de la Vega-Hernández**

Karen de la Vega-Hernández was born in Havana, Cuba in 1990. She received her B.Sc. degree in Pharmaceutical Sciences from the University of Havana (2013) (advisor: Prof. O. Cuesta) and her M.Sc. in Pharmacology from the same university (2015). Since 2013, she has worked as an instructor professor in the Institute of Pharmacy and Foods, University of Havana. In November 2015, she joined the group of Dr Vittorio Pace as an Ernst Mach fellow where she has been working on organometallic synthesis. Her main research interests are organozirconium and organolithium chemistry, as well as bidimensional NMR spectroscopic techniques.

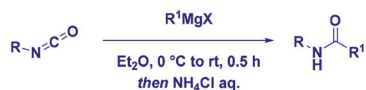
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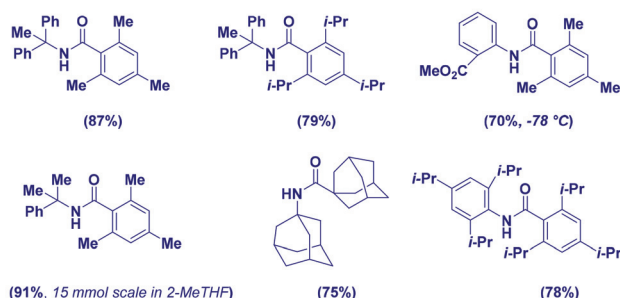
**Laura Castoldi**

Laura Castoldi received a MSc in Chemistry and Pharmaceutical Technology from the University of Pavia in 2011. After being awarded with an Ernst Mach grant she joined the Pace-Holzer group in Vienna where she is actually completing her PhD in the form of the Uni:docs program. From 2015–2016 she spent a visiting period in the group of Prof. Alcántara at the Complutense University of Madrid as a Marietta Blau fellow (OEAD). Her thesis is focused on the development of homologation procedures with lithium carbenoid reagents, resulting until now in >15 publications.

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## Selected examples

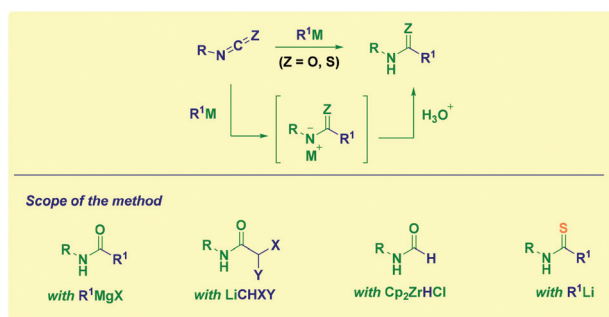


**Scheme 2** Bode's synthesis of amides from isocyanates and Grignard reagents.

case overaddition of the Grignard reagent to the formed amide was observed; and (e) by lowering temperature the chemoselective addition of the organomagnesium reagent to the isocyanate was achieved in the presence of concomitant electrophilic sites.

The success of this tactic stems from the straightforward formation of the C–C bond through the attack of the nucleophilic organometallic reagent ( $\text{R}^1\text{M}$ ) to the highly electrophilic carbon of the iso(thio)cyanate (Scheme 3).<sup>15</sup> Conceptually, it relies on a different disconnection approach compared to the C–N ligation governing classical couplings between carboxylic derivatives and amines. As a consequence, the iso(thio)cyanate/ $\text{R}^1\text{M}$  is *per se* free from the above indicated drawbacks associated with the C–N approach, thus constituting a reliable, effective and versatile tool for (thio)amide-type bond formations.

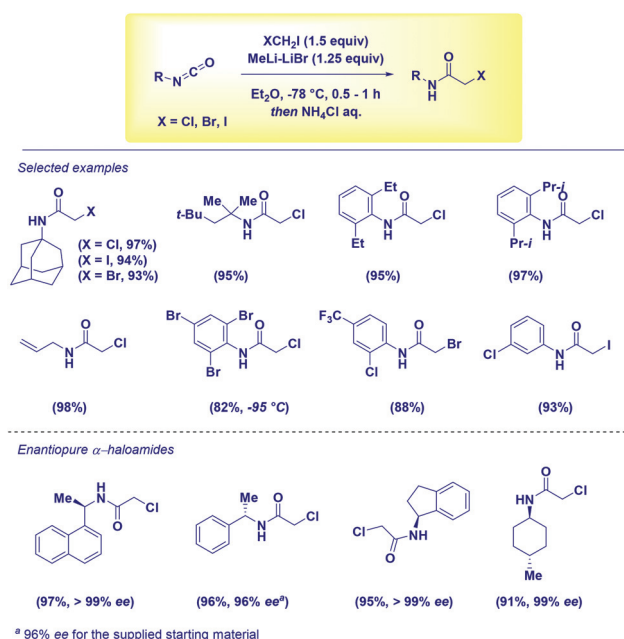
In this Perspective, our investigations on the use of isocyanates and isothiocyanates as powerful precursors of formamides,  $\alpha$ - (or  $\alpha,\alpha$ -di)haloamide and thioamides upon reactions with organolithium reagents (unfunctionalized or functionalized such as carbenoids) are contextualized.



**Scheme 3** Iso(thio)cyanates in nucleophilic additions of C- and H-nucleophiles: a general concept.

## 2. Synthesis of $\alpha$ -haloamide and $\alpha,\alpha$ -dihaloamides from isocyanates and lithium carbenoids

In recent years, our research group has been designing synthetic methods based on the use of nucleophilic lithium halo-carbenoids (Köbrich reagents).<sup>16</sup> In particular, we explored homologation procedures (*e.g.* halomethylations) of a series of carbonyl derivatives such as Weinreb amides,<sup>17</sup>  $\alpha,\beta$ -unsaturated cyclic ketones,<sup>18</sup> isatins<sup>19</sup> or heteroatoms containing electrophiles such as disulfides.<sup>20</sup> The formal insertion into a given carbon or heteroatom array of a halomethylene fragment allows one to overcome *de facto* the limitations related to the use of halogenation-type procedures based on radical or electrophilic mechanisms since the desired  $\text{CH}_2\text{X}$  or  $\text{CHXY}$  (with the exact halogenation degree) units are simply delivered to a given electrophile. In 2013 we reported the synthesis of *N*-substituted 2-haloacetamides starting from widely available isocyanates (Scheme 3).<sup>21</sup> The reaction showcases an excellent substrate scope allowing the chemoselective addition of  $\text{LiCH}_2\text{X}$  to a wide range of isocyanates with different substitution patterns on nitrogen. Thus, no differences have been observed on switching from aliphatic to aromatic materials. The protocol is amenable to the synthesis of highly sterically hindered  $\alpha$ -haloamides, and importantly, chemoselectivity is fully maintained in the presence of additional (sensitive to organolithium reagents) functionalities such as halogenated arenes or an olefin (Scheme 4). Additional points of interest are: (a) the reactions reach completion within 1 h providing haloamides in almost quantitative yields, without needing to perform chromatographic purifications;



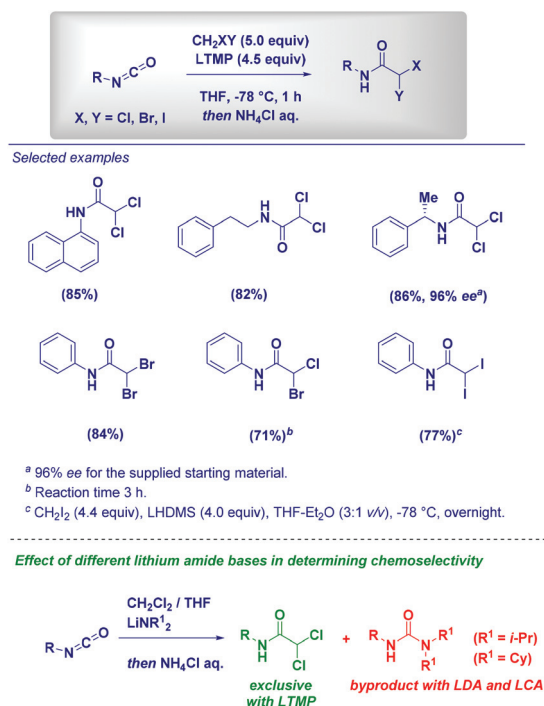
\* 96% ee for the supplied starting material

**Scheme 4** Scope of the monohalomethylation with isocyanates: synthesis of  $\alpha$ -haloamides.



(b) amongst the different monohalocarbenoids chloro-, bromo- and iodo-methylolithiums react equally; and (c) the stereochemical information contained in the starting isocyanate is fully transferred to the haloamide (*i.e.* no racemization processes take place).

The methodology could also be extended to the synthesis of  $\alpha,\alpha$ -dihaloamides, which as highlighted above is a demanding task because of the chemoselective difficulties associated with the use of halogenation procedures. Pleasingly, the generation of dihalolithium carbenoids ( $\text{LiCHXY}$ ) through the deprotonation of a dihalomethane with a lithium amide base under Barbier conditions in the presence of the isocyanate gives the expected compounds in high yields and optical purity (Scheme 5).<sup>22</sup> To suppress the concomitant addition of the lithium amide to the isocyanate, we found LTMP (lithium 2,2,6,6-tetramethylpiperidide) as the optimal base able to selectively generate the dihalocarbenoids rather than furnishing mixtures contaminated by urea derivatives formed upon the direct addition of the lithium amide to the isocyanate. The formation of urea compounds should be attributed to the different kinetic behavior that lithium amides feature towards the deprotonation of a dihalomethane (to form the dihalocarbenoid). Interestingly, lithium diiodomethane was prepared according to Bull's protocol<sup>23</sup> prior to the addition of the isocyanate, thus showing superior stability compared to analogous monohalo and dihalospecies. Again, the addition of dihalolithium carbenoids does not alter the enantiopurity of the starting isocyanates.



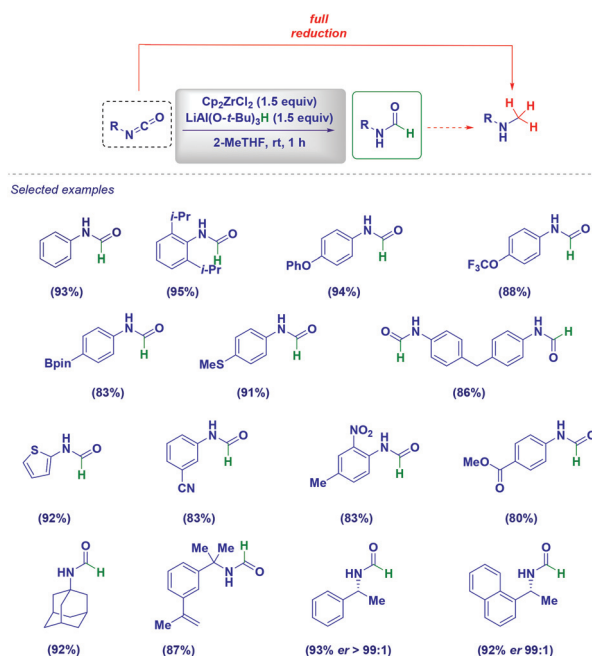
Scheme 5 Addition of lithium dihalomethylcarbenoids to isocyanates.

### 3. Synthesis of formamides from isocyanates

Very recently, our group documented a protocol for chemoselectively reducing isocyanates to synthetically versatile formamides (Scheme 6) through the use of the *in situ* generated Schwartz reagent.<sup>24</sup> Although known since the 1950s,<sup>25</sup> the partial reduction of such heterocumulenes has represented a significant challenge because of the observed full reduction to the corresponding *N*-methylamines in the presence of powerful reducing agents. The reaction showed a significant substrate scope, thus allowing decoration of the starting isocyanates with sensitive functionalities to the reductive conditions including nitro, cyano, ester and alkene groups, *inter alia*. In agreement with the general reactivity profile of these substrates towards nucleophiles, both the steric hindrance on the nitrogen and the nature of the isocyanate (aromatic vs. aliphatic) did not affect the efficiency of the reaction. Again, no alteration of the optical purity of the starting materials was evidenced during the reaction.

### 4. Synthesis of thioamides from isothiocyanates

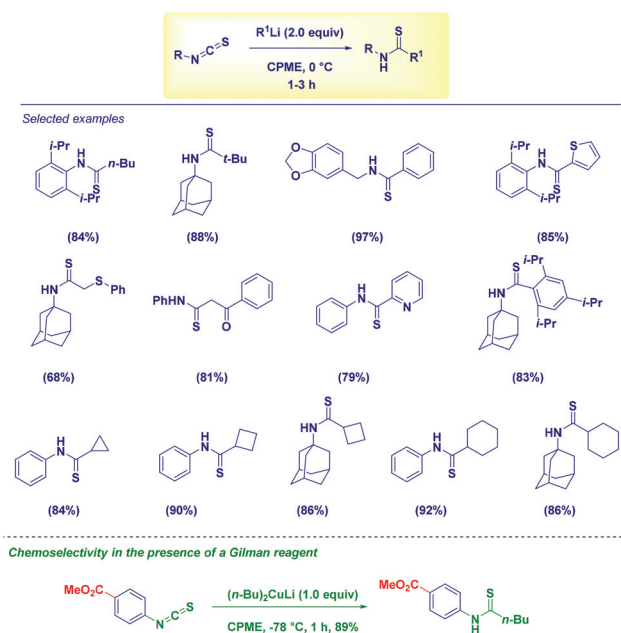
The reactivity of the sulfur counterparts – isothiocyanates – was also investigated with the aim of synthesizing valuable thioamides.<sup>26</sup> We were aware of the fact that accessing thioamides through such a conceptually simple and direct approach would have allowed one to overcome the severe limitations related to the synthesis of these important building blocks. Optimization studies carried out on the congested 1-adaman-



Scheme 6 Chemoselective Schwartz reagent mediated reduction of isocyanates to formamides.

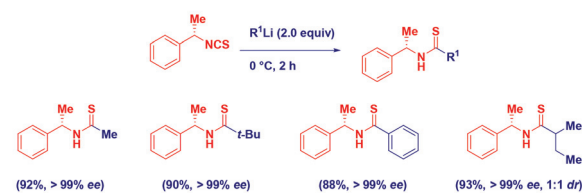
thioisothiocyanate revealed the feasibility of the method, and among the solvents tested cyclopentyl methyl ether (CPME)<sup>27</sup> proved to be the ideal one (Scheme 7). The procedure is applicable to a set of different combinations of isothiocyanates and organolithiums commercially available, giving the expected analytically pure thioamides in excellent yields after simple recrystallization from the same solvent. Because of the wide access to functionalized organolithiums *via* deprotonation or lithium halogen exchange techniques,<sup>28</sup> we were delighted in expanding the protocol to the straightforward synthesis of complex thioamides including highly sterically demanding structures. It is important to note that by transmetalating the lithium carbanion to a Gilman reagent ( $R_2CuLi$ )<sup>29</sup> it is possible to chemoselectively obtain a functionalized thioamide bearing an ester group, thus directing the addition of the organometallic species exclusively at the isothiocyanate moiety.

No racemization takes place upon the addition of various organolithium reagents to optically active isothiocyanates (Scheme 8), in agreement with the results observed in the cases of less basic (di)halocarbenoids and isocyanates. More importantly, the formation of enantiopure reagents such as lithiated *N*-Boc-pyrrolidine<sup>30</sup> or Hoppe's carbamate,<sup>31</sup> through the deprotonation in the presence of chiral ligands (–) or (+)-sparteine affords the corresponding thioamides with (almost) full retention of stereochemistry and in excellent diastereomeric ratio. As expected, by switching from one enantiomer of sparteine to the other, it is possible to obtain both asymmetric forms of a given thioamide with comparable optical purity. The simplicity of the reaction conditions developed and the results in terms of enantiopurity allow one to conclude that the present method showcases better performances compared with sulfuring protocols in which ee erosion can be problematic.

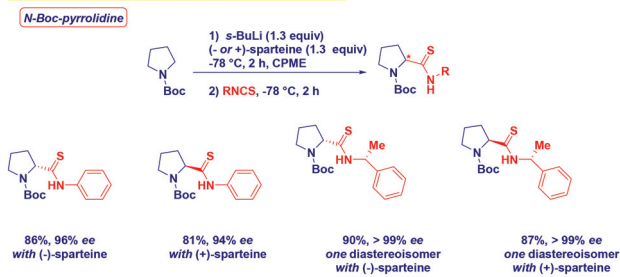


**Scheme 7** Addition of organolithium to isothiocyanates: access to thioamides.

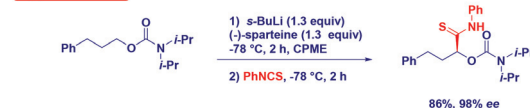
#### Chiral thioamides from enantiopure isothiocyanates



#### Chiral thioamides from enantiopure organolithium reagents



#### Hoppe's carbamate



**Scheme 8** Preparation of asymmetric thioamides *via* the addition of (chiral) organolithium reagents to (enantiopure) isothiocyanates.

## 5. Conclusions

The nucleophilic addition of functionalized organometallic reagents (Grignard and organolithium) to iso(thio)cyanates represents an attractive tool for the preparation of amide-type compounds not always efficiently reachable *via* classical chemistry. Analogously, by switching to a hydride nucleophile (Schwartz reagent), a highly chemoselective reduction of variously functionalized isocyanates to formamides takes place.

The tactic can be exploited also for preparing thioamides in excellent yields and optical purities. A number of lithium nucleophiles both commercially available or generated prior to the reaction – eventually in the enantiopure form – can be employed for the addition to isothiocyanates. Significantly, nowadays extensive series of both isocyanates<sup>15b</sup> and isothiocyanates<sup>32</sup> are available from common chemical suppliers, or alternatively can be prepared through standard methods.<sup>33</sup> The development of this highly efficient method should increasingly become a crucial tool in modern synthetic chemistry.

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*Publication n. 7*

**Addition of lithium carbenoids to isocyanates: a direct access to synthetically useful *N*-substituted 2-haloacetamides.**

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<http://www.rsc.org/suppdata/cc/c3/c3cc44255a/c3cc44255a.pdf>

Details on experimental procedures, characterization data and copies of NMR spectra of all compounds are reported.



## Addition of lithium carbenoids to isocyanates: a direct access to synthetically useful *N*-substituted 2-haloacetamides†

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**The addition of lithium carbenoids to isocyanates provides a versatile access to *N*-substituted 2-haloacetamides: the reaction tolerates the presence of variously functionalized substituents on the nitrogen atom, including sterically demanding ones and reactive halogens. No erosion of the enantiopurity was observed in the case of optically active isocyanates. One of the substrates prepared has been employed in Charette's type chemoselective addition of a Grignard reagent to access an  $\alpha$ -chloroketone.**

Lithium carbenoids ( $\text{LiCH}_2\text{X}$ ) are versatile chemical species,<sup>1</sup> first described by Köbrich during the 1960s,<sup>2</sup> which are able to install a reactive halomethylenic functionality susceptible to further modification (*i.e.* reaction with nucleophiles) in a one-pot procedure. They exhibit a particular ambiphilic behaviour depending on the temperature at which a given transformation is run: in fact, they can switch from a nucleophilic reactivity (lower temperatures) to an electrophilic one (higher temperatures).<sup>1a-c</sup> In particular, their nucleophilic properties have been used for performing  $-\text{CH}_2$ -type homologation on a wide range of electrophiles such as aldehydes,<sup>3</sup> ketones,<sup>3b,c,4</sup> esters,<sup>5</sup> Weinreb amides,<sup>6</sup> acyl halides,<sup>7</sup> imines<sup>8</sup> and boronic esters.<sup>9</sup> Unfortunately, despite the invaluable synthetic usefulness, their application in organic synthesis has been somewhat limited by their inherent thermal instability and thus, comprehensive studies on their reactivity with other electrophiles have not been realized. Due to our interest in preparing  $\alpha$ -halocarbonyl derivatives as prochiral materials<sup>10</sup> we were attracted by the possibility of preparing  $\alpha$ -haloacetamides directly from an isocyanate and a lithium carbenoid. This approach would constitute a significant advancement compared to the more common protocol which involves the nucleophilic substitution of an  $\alpha$ -haloacetyl halide with an amine.<sup>11</sup> Apart from the safety issues involving the use of such highly reactive building blocks (strong acylating and alkylating

agents), the main reason which renders them non-attractive is the low reactivity displayed in such processes by sterically hindered or electron-poor amines.<sup>12</sup>

Surprisingly, only a few examples of additions of classical organolithium reagents to isocyanates have been described.<sup>13</sup> On the other side, other organometallics such as stannanes,<sup>14</sup> copper species<sup>15</sup> or (mixed) Grignard reagents<sup>16</sup> received more attention in synthetic applications. In this context, renewed interest in this chemistry has been exploited by Bode and co-workers who reported the successful preparation of sterically hindered secondary amides by the addition of Grignard reagents to isocyanates.<sup>17</sup> Thus, herein we detail our investigations of the first addition of lithium carbenoids ( $\text{LiCH}_2\text{X}$ , X = Cl, Br, I) to variously *N*-functionalized isocyanates underlying also the effectiveness of the procedure in preserving the optical purity of enantioenriched starting materials.

We selected the reaction between the highly sterically hindered *N*-adamantyl isocyanate **1** and  $\text{LiCH}_2\text{X}$  generated *in situ* from a dihalomethane and  $\text{MeLi-LiBr}$  as the model (Table 1). By running the reaction at  $-78^\circ\text{C}$  in THF we were pleased to recover **2a** in 87% yield as the unique product without any additional purification needed. Further optimization showed that this electrophile could be efficiently chloromethylated also by using a minimal loading of carbenoids (1.25 equiv., entry 3) compared to our previous findings involving less electrophilic Weinreb amide substrates.<sup>6</sup> As a consequence of the stabilization of carbenoids through a Lewis-basic effect of the solvent, employment of less coordinating media such as methyl *t*-butyl ether (MTBE), cyclopentyl methyl ether (CPME) and 2-methyltetrahydrofuran (MTHF) – frequently used as alternatives to classic ethers<sup>18</sup> – lowers to some extent reaction yields (Table 1, entries 5–7). Significantly, by running the reaction in diethyl ether compound **2a** could be isolated in a very satisfactory 97% yield after 1 h (entry 8). When the reaction time was prolonged up to 2 h unidentified side products (*ca.* 10%) contaminated **2a** (entry 9). As it could be expected with reactions involving carbenoid species, attempts to increase the temperature up to  $-50^\circ\text{C}$  had a deleterious effect on the formation of the chloroacetamide (entries 10 and 11). Analogously, the corresponding iodomethylation worked very well allowing us to obtain **2b** in 94% yield (entry 12), while the efficiency of the

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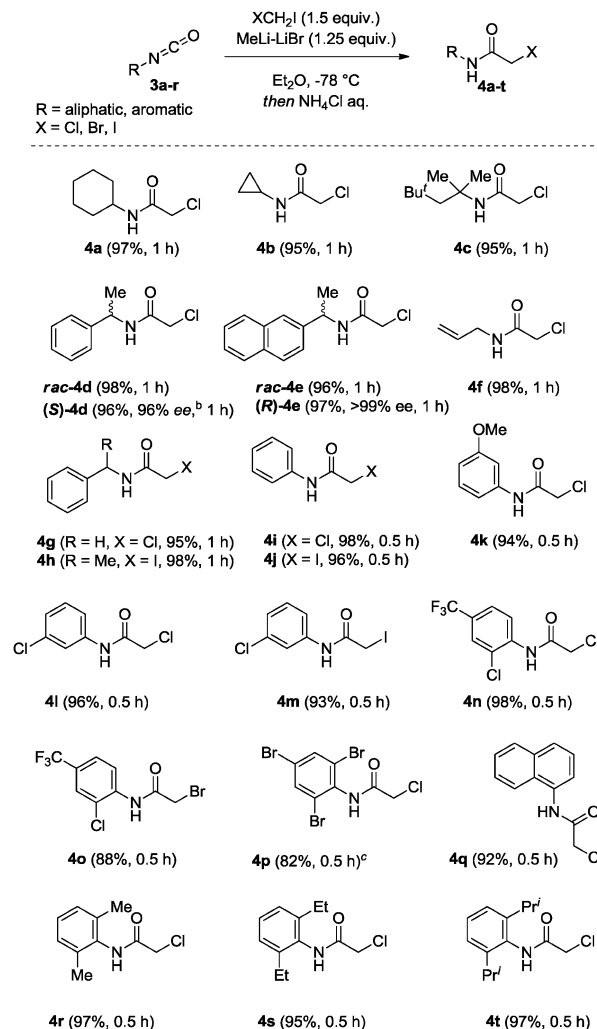
Table 1 Reaction optimization

| Entry | MCH <sub>2</sub> X <sup>a</sup><br>(equiv.) | Solvent           | Reaction<br>time (h) | Temp. (°C) | Yield<br>of 2 <sup>b</sup> (%) |
|-------|---------------------------------------------|-------------------|----------------------|------------|--------------------------------|
| 1     | LiCH <sub>2</sub> Cl (1.8)                  | THF               | 1                    | -78        | (2a) 87                        |
| 2     | LiCH <sub>2</sub> Cl (1.5)                  | THF               | 1                    | -78        | (2a) 86                        |
| 3     | LiCH <sub>2</sub> Cl (1.25)                 | THF               | 1                    | -78        | (2a) 87                        |
| 4     | LiCH <sub>2</sub> Cl (1.0)                  | THF               | 1                    | -78        | (2a) 82                        |
| 5     | LiCH <sub>2</sub> Cl (1.25)                 | MTBE              | 1                    | -78        | (2a) 65                        |
| 6     | LiCH <sub>2</sub> Cl (1.25)                 | CPME              | 1                    | -78        | (2a) 71                        |
| 7     | LiCH <sub>2</sub> Cl (1.25)                 | MTHF              | 1                    | -78        | (2a) 76                        |
| 8     | LiCH <sub>2</sub> Cl (1.25)                 | Et <sub>2</sub> O | 1                    | -78        | (2a) 97                        |
| 9     | LiCH <sub>2</sub> Cl (1.25)                 | Et <sub>2</sub> O | 2                    | -78        | (2a) 85                        |
| 10    | LiCH <sub>2</sub> Cl (1.25)                 | Et <sub>2</sub> O | 1                    | -60        | (2a) 69                        |
| 11    | LiCH <sub>2</sub> Cl (1.25)                 | Et <sub>2</sub> O | 1                    | -50        | (2a) 48                        |
| 12    | LiCH <sub>2</sub> I (1.25)                  | Et <sub>2</sub> O | 1                    | -78        | (2b) 94                        |
| 13    | LiCH <sub>2</sub> Br (1.25) <sup>c</sup>    | Et <sub>2</sub> O | 1                    | -78        | (2c) 79                        |
| 14    | LiCH <sub>2</sub> Br (1.25) <sup>d</sup>    | Et <sub>2</sub> O | 1                    | -78        | (2c) 93                        |

<sup>a</sup> MCH<sub>2</sub>X generated by using 25 mol% excess of XCH<sub>2</sub>Z compared to MeLi-LiBr (1.0 equiv.). <sup>b</sup> Isolated yields. <sup>c</sup> Generated from CH<sub>2</sub>Br<sub>2</sub>. <sup>d</sup> Generated from ICH<sub>2</sub>Br. Reactions run at the 3.8 mmol scale.

bromomethylation proved to be dependent on the nature of the dihalomethane employed for generating the carbenoid species. Thus, when LiCH<sub>2</sub>Br was generated from CH<sub>2</sub>Br<sub>2</sub> **2c** was recovered in 79% yield along with ca. 15% of unreacted starting material, while by using ICH<sub>2</sub>Br, which is evidently more prone to undergo the Li-halogen (I) exchange, the yield could be maximized up to 93% (entries 13 and 14). Once the optimal conditions had been established, we next examined the scope of the reaction (Scheme 1).

The protocol is of general applicability without significant differences in the reactivity of both aliphatic (less reactive) and aromatic (more reactive) isocyanates,<sup>19</sup> except for the reaction times needed to reach completion. In analogy to the above presented case of adamantyl isocyanate **1**, linearly branched chloroacetamide **4c** could be obtained with high efficiency. Remarkably, as evidenced by the excellent ees measured for compounds (*S*)-**4d** and (*R*)-**4e**, the basic conditions generated by the use of carbenoids do not alter the enantiopurity of the starting isocyanates. Significantly, no concomitant Simmons-Smith cyclopropanation-type<sup>20</sup> reaction (which is known to be accomplished with Li carbenoids)<sup>21</sup> could be observed in the presence of an alkene-containing substrate (**4f**). Different substituents attached at the ring of aromatic isocyanates are widely tolerated, thus, both electron-donating and electron-withdrawing groups could be placed without detecting any loss of efficiency (**4i–4t**). In particular, halogen containing functionalities, including relevant fluorine compounds<sup>22</sup> (**4n–4o**), which are interesting for medicinal chemists, could be prepared in high yields. It is worth mentioning that no side Li-Br exchange was noticed for the tribromo derivative **4p** when the reaction was run at -95 °C in the presence of an excess of ICH<sub>2</sub>Cl (4.0 equiv.); evidently, under these conditions the Li-alkyl iodide



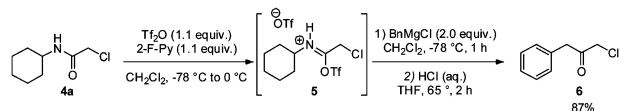
<sup>a</sup> Isolated yields and reaction times in parentheses – reactions run at 3.8 mmol scale; <sup>b</sup> 96% ee for the supplied starting material; <sup>c</sup> Reaction run at -95 °C by using 4.0 equiv. ICH<sub>2</sub>Cl and 1.2 equiv. MeLi-LiBr.

Scheme 1 Scope of the reaction.<sup>a</sup>

exchange occurs at a faster rate than the possible Li-bromoaryl one. The progressive increase in steric hindrance in a series of 2,6-dialkylphenyl isocyanates does not modify – to any extent – the outcome of the process (**4r–4t**). In all, we can assume that the divergent approach established towards the synthesis of this series of  $\alpha$ -haloacetamides may be explained by the fact that the reacting homologating reagent (LiCH<sub>2</sub>X) attaches the isocyanate carbon, which evidently is not affected by the steric factors present on the nitrogen. Thus, the issues arising from the limited availability of the nitrogen lone-pair in processes involving the acylation of  $\alpha$ -haloacetyl halide-type substrates are overcome.

We next turned our attention to the synthetic usefulness of the so-prepared  $\alpha$ -haloacetamides in organic synthesis. Interestingly, we employed cyclohexylamide **4a** for the generation of a highly electrophilic imidoyl triflate (**5**)<sup>23</sup> by applying the recently described Charette's<sup>24</sup> method to activate the inert amidic bond,<sup>25</sup> which afforded 1-chloro-3-phenylacetone **6** in an excellent 87% yield upon the addition of benzylmagnesium chloride followed by





**Scheme 2** Chemoselective addition of a Grignard reagent to an activated amidic bond.

acidic hydrolysis. To the best of our knowledge, no previous examples of analogous additions of Grignard reagents to  $\alpha$ -chloroacetamides in order to obtain  $\alpha$ -haloketones have been described. Significantly, it should be highlighted that the direct addition of  $\text{LiCH}_2\text{Cl}$  to an ester at  $-115^\circ\text{C}$  as described by Villieras provided **6** in a modest 55% yield.<sup>3c</sup> Thus, this first application of Charette's chemistry to an  $\alpha$ -chloroacetamide for the synthesis of  $\alpha$ -haloketones contributes to the development of a new method to prepare such important building blocks<sup>26</sup> through a different mechanistic pathway (Scheme 2).

In conclusion, we have presented the first addition of unstable lithium carbenoids to variously substituted isocyanates to access *N*-(2-haloacetamides). The protocol is of wide versatility since the homologation allows us to place chloro-, bromo- and iodo-methylene fragments *via* a one pot procedure in a chemoselective fashion. Remarkably, optically active isocyanates also react with full retention of stereochemistry at the chiral center. The reactivity of one of the so-prepared 2-haloacetamides has been successfully tested in the first synthesis of an  $\alpha$ -chloroketone through the chemoselective addition of a Grignard reagent to an imido-yl triflate species generated according to Charette's procedure. Further studies on the application of the protocol to multi-functionalized isocyanates are underway in our laboratory and the results will be reported in due course.

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*Publication n. 8*

**Homologation of isocyanates with lithium carbenoids: a straightforward access to  $\alpha$ -halomethyl- and  $\alpha,\alpha$ -dihalomethylamides.**

Pace, V.;\* Castoldi, L.; Mamuye, A.D.; Holzer, W.

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The Supporting Information is available on the website at:

[https://www.thieme-connect.de/media/synthesis/201421/supmat/sup\\_ss-2014-z0416-fa\\_10-1055\\_s-0034-1379209.pdf](https://www.thieme-connect.de/media/synthesis/201421/supmat/sup_ss-2014-z0416-fa_10-1055_s-0034-1379209.pdf)

Details on experimental procedures, characterization data and copies of NMR spectra of all compounds are reported.



# Homologation of Isocyanates with Lithium Carbenoids: A Straightforward Access to $\alpha$ -Halomethyl- and $\alpha,\alpha$ -Dihalomethylamides

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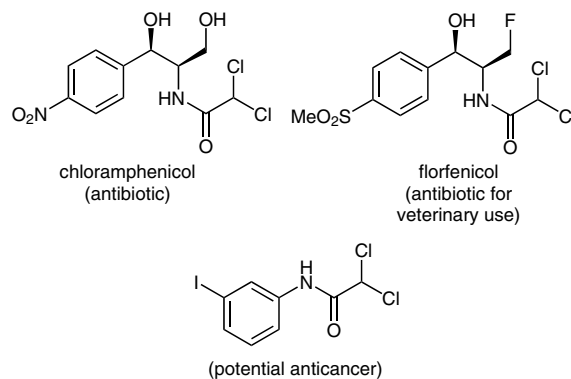
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**Abstract:** Treatment of widely available isocyanates with monohalolithium and dihalolithium carbenoids provides a valuable protocol for the one-pot preparation of  $\alpha$ -halo- and  $\alpha,\alpha$ -dihaloacetamide derivatives. While monohalolithium carbenoids can be prepared by a smooth lithium–halogen exchange, the preparation of the corresponding dihalo compounds proved to be highly dependent on the base used to realize the deprotonation, with lithium 2,2,6,6-tetramethylpiperidine emerging as optimal. The clear advantages of the procedure are: (a) broad scope of isocyanates that can be employed; (b) preservation of the optical purity when chiral materials are used; (c) divergent access to different haloamides by simply selecting the homologating agents. We also report an application of Charette's imido triflate activation of a secondary amide to the synthesis of an  $\alpha$ -chloro ketone and <sup>15</sup>N NMR data for selected compounds.

**Key words:** amides, carbenoids, lithiation, halides, nucleophilic addition

$\alpha$ -Haloamides and  $\alpha,\alpha$ -dihaloamides are versatile scaffolds in organic synthesis. In particular, the presence of the halogen atom(s) renders these structures valuable as alkylating units for a wide range of organic transformations such as the preparation of lactams or  $\alpha,\beta$ -unsaturated amides.<sup>2</sup> Moreover, they constitute useful synthons for accessing lanthanide-based macrocycles of biological interest used as contrast agents.<sup>3</sup> Analogously, the corresponding  $\alpha,\alpha$ -dihaloamides have found various applications in synthesis,<sup>4</sup> e.g. as materials to obtain  $\alpha$ -halogenated lactams.<sup>5</sup> Importantly, the  $\alpha,\alpha$ -dihaloamide moiety is found in biologically active compounds such as the broad-spectrum bacteriostatics analogues of chloramphenicol<sup>6</sup> or anticancer agents related to 2,2-dichloro-*N*-phenylacetamide<sup>7</sup> (Figure 1).

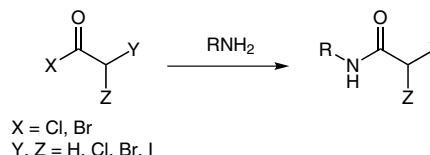
The classical approach to the synthesis of the aforementioned structures involves the reaction of an  $\alpha$ -halo- or  $\alpha,\alpha$ -dihalocarboxylic acid derivative (acyl halide or ester) with an amine.<sup>3b,8</sup> Unfortunately, the efficiency of the procedure depends on the nucleophilicity of the amine and thus sterically hindered or less nucleophilic amines still remain challenging materials.<sup>9</sup> It should be observed that this tactic requires the use of substrates that are not always commercially available such as  $\alpha$ -iodoacetyl,  $\alpha,\alpha$ -dibromoacetyl or  $\alpha,\alpha$ -diiodoacetyl halides. Thus, further halo-



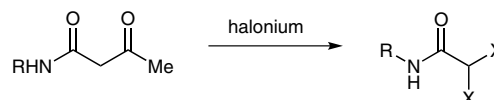
**Figure 1** Versatility of haloamides in medicinal chemistry

gen substitutions should be performed in order to reach the desired target.<sup>10</sup> Moreover, more complex routes involving tandem electrophilic  $\alpha,\alpha$ -dihalogenations–deacylations of acetoacetanilide derivatives have been reported (e.g., Reinshagen,<sup>11</sup> Liu–Zhu<sup>12</sup> and Li–Zhang<sup>13</sup>) (Scheme 1).

classical synthesis of  $\alpha$ -halo and  $\alpha,\alpha$ -dihaloacetamides

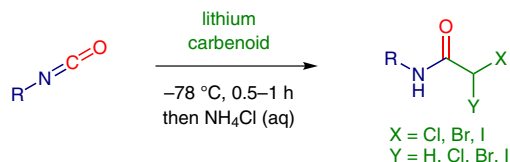


alternative approaches to  $\alpha,\alpha$ -dihaloacetamides



Reinshagen, 1974 (X = I): NaOI  
Liu–Zhu, 2012 (X = Cl, Br): (diacetoxyiodo)benzene - ZnCl<sub>2</sub>/ZnBr<sub>2</sub>  
Li–Zhang, 2013 (X = Cl, Br): NXs,  $\Delta$

this work:



**Scheme 1** Context of the presented work

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As a common feature, the introduction of the halogen through one of these methodologies takes places on a carbon atom already connected to a given array.

A distinct approach would rely on the addition of  $\alpha$ -halomethyl or  $\alpha,\alpha$ -dihalomethyl carbanion-type units<sup>14</sup> to a

proper electrophilic carbon source. Köbrich and co-workers in the late 1960s pioneered the use of halomethylithium reagents (carbenoids);<sup>15</sup> these species have been thoroughly employed for homologation-type reactions of various carbonyl derivatives such as aldehydes,<sup>16</sup> ke-

## Biographical Sketches



**Vittorio Pace** obtained a degree in pharmacy from the University of Perugia in 2005 working with Prof. M. Curini and Dr. O. Rosati. He then undertook Ph.D. studies (2006–2010) at the Complutense University of Madrid under the guidance of Prof. A. R. Alcántara. He realized placements at the Universities of Ghent (Belgium, Prof. N. De Kimpe), Trieste (Italy, Prof. L. Gardossi), and Graz (Austria,

Prof. W. Kroutil). In 2009 he also obtained a postgraduate M.Sc. in Drug Design and Development from the University of Pavia. In 2010 he moved to the University of Vienna to join the group of Prof. W. Holzer as an Ernst Mach postdoc fellow. Postdoctoral training continued with Prof. D. J. Procter at The University of Manchester (2011–2013) and with Prof. B. Olofsson at the University of Stock-

holm (2013–2014). In August 2014 he returned to Vienna as a group leader in Synthetic Chemistry (habilitation) at the Department of Pharmaceutical Chemistry headed by Prof. T. Langer and Prof. E. Urban. His main research interest deals with the application of lithium carbenoids and organometallic reagents in organic synthesis.



**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 a teaching as-

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**Laura Castoldi** was born in 1986 in Pavia (Northern Italy): after an Erasmus placement at the Complutense University of Madrid in the group of Profs. Alcántara and Sinisterra, she graduated in Chemistry and Pharmaceutical Technology in

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**Wolfgang Holzer** studied organic chemistry at the Technical University of Vienna (Austria) where he obtained his Ph.D. in 1982. After joining the Institute of Pharmaceutical Chemistry at the University of Vienna

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von Philipsborn. His main research interests are the chemistry of azoles, heterocyclic tautomerism, and the application of NMR spectroscopy for structural and conformational studies.

tones,<sup>16a-c,17</sup> N-electron-withdrawing-group substituted imines,<sup>18</sup> acid halides,<sup>19</sup> esters,<sup>16a,20</sup> and Weinreb amides.<sup>9b,21</sup> Conceptually, they are able to add a halomethylenic fragment to a reactive electrophile, thus they can be considered as functionalized organometallic reagents. Though they are regarded as ambiphilic reagents, nowadays, it is widely accepted that at low temperatures these lithium species display nucleophilic behavior.<sup>14d,22</sup> The main disadvantage that they possess is their well-known thermal instability. As such, three main precautions should be taken for their efficient use in synthesis: 1. generation under Barbier-type conditions (i.e., the electrophile must be present when the carbenoid is generated); 2. the use of low temperatures ( $-78^{\circ}\text{C}$  is adequate) to minimize  $\alpha$ -elimination processes responsible for the possible degradation to a free carbene and a lithium halide salt; 3. the presence of lithium halide salts and the employment of ethereal solvents aids the preservation of the aforementioned  $\alpha$ -elimination through a coordinative effect.<sup>14d</sup>

Very recently Bode and co-workers re-explored the potential of the underestimated reaction of isocyanates with Grignard reagents to access sterically hindered and electron-deficient secondary amides with high efficiency.<sup>23</sup> Though there are precedents in the literature using various organometallic reagents such as organolithiums,<sup>24</sup> organomagnesiums,<sup>25</sup> organocopper species,<sup>26</sup> organomanganese,<sup>27</sup> or organostannanes,<sup>28</sup> it seems that this tactic has not been fully exploited as a versatile tool for amides synthesis. Inspired by this precedent<sup>29</sup> and by our own interest in designing transformations involving the use of lithium carbenoid reagents (e.g.,  $\text{LiCH}_2\text{X}$ ,  $\text{LiCHXY}$ ),<sup>9b,17b,21</sup> we wondered if isocyanates could be valuable as electrophilic reagents that are susceptible to homologation with such nucleophilic lithium species. The successful method could be applied to the one-pot preparation of  $\alpha$ -haloacetamides or  $\alpha,\alpha$ -dihaloacetamides starting from widely available materials such as isocyanates.

In this work we present a full account of our investigations on the halomethylation<sup>30</sup> and dihalomethylation of different substituted isocyanates. Pivotal for the efficiency of the reaction is the fine tuning of the generation of the carbenoids, in particular in the case of dihalomethylation. We also show the effectiveness of the procedure in homologating optically active isocyanates (without erosion of the enantiopurity) and an application of one of the so-obtained haloacetamides in the synthesis of a ketone through its transformation into an imidoyl triflate followed by the addition of a Grignard reagent.

The high sterically hindered *N*-adamantyl isocyanate **1** was identified as a model substrate for the homologation with chloromethyl lithium (Table 1). According to our previously reported procedures, chloromethyl lithium was generated by lithium–iodine exchange on chloriodomethane ( $\text{ICH}_2\text{Cl}$ ) performed with methyl lithium–lithium bromide (entry 1). Significantly, the use of 25 mol% excess of chloriodomethane with respect to methyl lithium–lithium bromide ensures maximized formation of the carbenoid. The selection of the complex methyl lithium–lithium

ium bromide was found to be important in order to minimize degradative  $\alpha$ -elimination on the so-formed carbenoid in agreement with pioneering studies by Villieras,<sup>16a</sup> confirmed more recently by our group.<sup>9b,17b,21</sup> An initial trial with tetrahydrofuran as the solvent and using 1.8 equivalents of chloromethyl lithium afforded the desired chloroamide in 87% isolated yield (entry 1); significantly, the transformation could be efficiently accomplished also with a lower amount of carbenoid. In this sense, the use of 1.25 equivalents proved to be ideal, leaving the conversion unaffected. This observation can be explained taking into account the presumed higher reactivity of isocyanates compared to other carbon electrophiles such as Weinreb amides,<sup>31</sup> which required higher loading of carbenoids to maximize conversion. The coordinating

**Table 1** Reaction Optimization for Monohalolithium Carbenoids

| Entry          | $\text{LiCH}_2\text{X}$<br>(equiv) <sup>a</sup> | Solvent               | Temp<br>( $^{\circ}\text{C}$ ) | Yield <sup>b</sup><br>(%) of <b>2</b> |
|----------------|-------------------------------------------------|-----------------------|--------------------------------|---------------------------------------|
| 1              | $\text{LiCH}_2\text{Cl}$ (1.8)                  | THF                   | $-78$                          | ( <b>2a</b> ) 87                      |
| 2              | $\text{LiCH}_2\text{Cl}$ (1.5)                  | THF                   | $-78$                          | ( <b>2a</b> ) 86                      |
| 3              | $\text{LiCH}_2\text{Cl}$ (1.25)                 | THF                   | $-78$                          | ( <b>2a</b> ) 87                      |
| 4              | $\text{LiCH}_2\text{Cl}$ (1.0)                  | THF                   | $-78$                          | ( <b>2a</b> ) 82                      |
| 5              | $\text{LiCH}_2\text{Cl}$ (1.25)                 | MTBE                  | $-78$                          | ( <b>2a</b> ) 65                      |
| 6              | $\text{LiCH}_2\text{Cl}$ (1.25)                 | CPME                  | $-78$                          | ( <b>2a</b> ) 71                      |
| 7              | $\text{LiCH}_2\text{Cl}$ (1.25)                 | MTHF                  | $-78$                          | ( <b>2a</b> ) 76                      |
| 8              | $\text{LiCH}_2\text{Cl}$ (1.25)                 | $\text{Et}_2\text{O}$ | $-78$                          | ( <b>2a</b> ) 97                      |
| 9 <sup>c</sup> | $\text{LiCH}_2\text{Cl}$ (1.25)                 | $\text{Et}_2\text{O}$ | $-78$                          | ( <b>2a</b> ) 85                      |
| 10             | $\text{LiCH}_2\text{Cl}$ (1.25) <sup>d</sup>    | $\text{Et}_2\text{O}$ | $-78$                          | ( <b>2a</b> ) 82                      |
| 11             | $\text{LiCH}_2\text{Cl}$ (1.25) <sup>e</sup>    | $\text{Et}_2\text{O}$ | $-78$                          | ( <b>2a</b> ) 79                      |
| 12             | $\text{LiCH}_2\text{Cl}$ (1.25)                 | $\text{Et}_2\text{O}$ | $-60$                          | ( <b>2a</b> ) 69                      |
| 13             | $\text{LiCH}_2\text{Cl}$ (1.25)                 | $\text{Et}_2\text{O}$ | $-50$                          | ( <b>2a</b> ) 48                      |
| 14             | $\text{LiCH}_2\text{I}$ (1.25)                  | $\text{Et}_2\text{O}$ | $-78$                          | ( <b>2b</b> ) 94                      |
| 15             | $\text{LiCH}_2\text{Br}$ (1.25) <sup>f</sup>    | $\text{Et}_2\text{O}$ | $-78$                          | ( <b>2c</b> ) 79                      |
| 16             | $\text{LiCH}_2\text{Br}$ (1.25) <sup>g</sup>    | $\text{Et}_2\text{O}$ | $-78$                          | ( <b>2c</b> ) 93                      |

<sup>a</sup> Generation of  $\text{LiCH}_2\text{X}$ : dihalomethane (25 mol% excess),  $\text{MeLi}$ – $\text{LiBr}$  (1.0 equiv), 1 h.

<sup>b</sup> Isolated yields.

<sup>c</sup> Reaction time 2 h.

<sup>d</sup>  $\text{MeLi}$  was employed as lithiating reagent.

<sup>e</sup>  $\text{BuLi}$  was employed as lithiating reagent.

<sup>f</sup> Generated from  $\text{CH}_2\text{Br}_2$ .

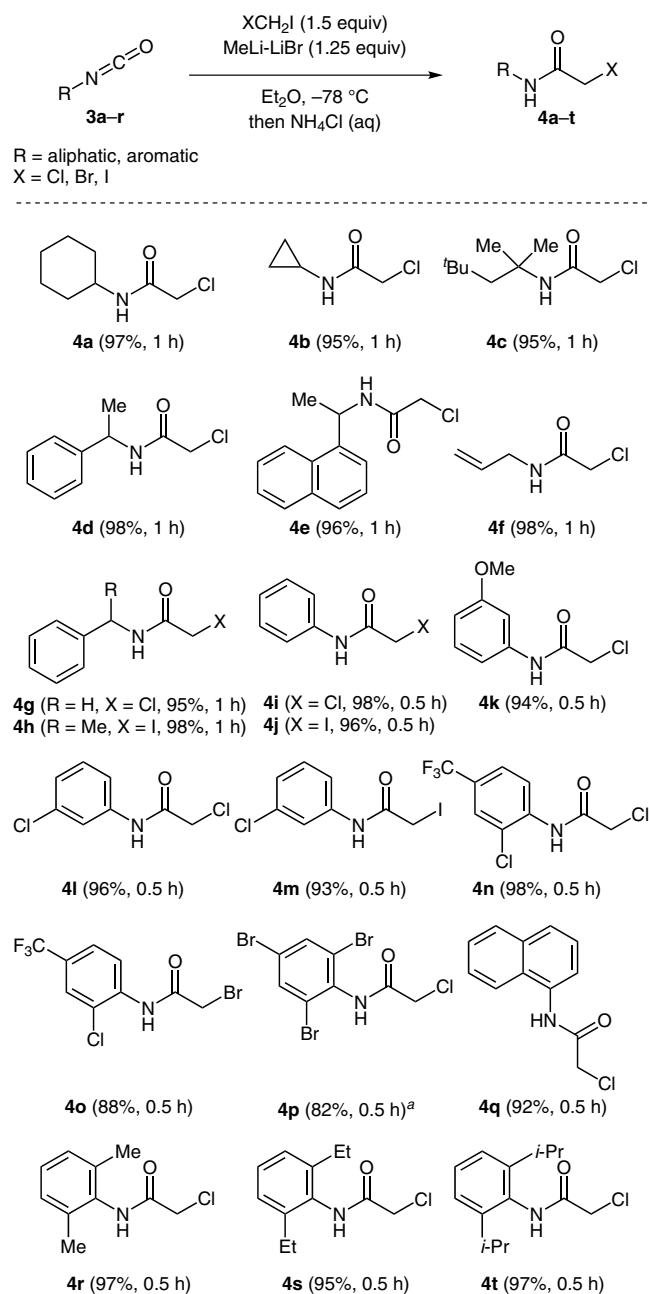
<sup>g</sup> Generated from  $\text{ICH}_2\text{Br}$ .

ability of the reaction solvent was pivotal in order to preserve its decomposition; methyl *tert*-butyl ether (MTBE), cyclopentyl methyl ether (CPME), and 2-methyltetrahydrofuran (MTHF),<sup>31c,32</sup> which are considered as ecofriendly alternatives of classic ethereal solvents, provided the desired product in substantially decreased yield (entries 5–7). Switching to diethyl ether was fundamental to maximize the reactivity, giving compound **2a** in an excellent 97% yield without the need to perform additional purification (entry 8). A final remark on the generation of chloromethyl lithium; using simple methyl lithium or butyllithium as lithiating agents results in a decrease of in the conversion, probably because the absent lithium bromide inhibits  $\alpha$ -elimination. By running reactions at higher temperatures a predictable decrease of the formation of **2a** was evident as a consequence of the well-known thermal instability of such species (entries 12 and 13).<sup>14d</sup> Reactions occurred rapidly and reached completion within a maximum of one hour; continued stirring for additional time resulted deleterious effects since unidentified materials were observed in the crude reaction mixture by <sup>1</sup>H NMR.

The process could be smoothly adapted to the preparation of the corresponding  $\alpha$ -iodo and  $\alpha$ -bromo derivatives **2b** and **2c**. Interestingly, we found that the optimal source of bromomethyl lithium was commercially available bromiodomethane instead of the commonly used dibromomethane due to the easier capability of the former to undergo lithium–halogen exchange compared to the latter.

After determining the ideal reaction conditions, the scope of the methodology was investigated (Scheme 2). Various (eventually highly sterically demanding) aliphatic isocyanates reacted very well providing the corresponding chloroacetamides or iodoacetamides in high yields within one hour. Interestingly, no concomitant carbenoid-mediated cyclopropanation on the olefinic fragment of an allylic substrate was observed.<sup>33</sup> Aromatic isocyanates worked in a similar efficient manner despite the substitution pattern on the aromatic ring. In general, they reach completion in shorter times compared to their aliphatic counterparts.<sup>34</sup> It is worth underlining the possibility to perform this reaction on the tribromo derivative **3p** without observing competing aryl bromide–lithium exchange. In this case, the reaction required two precautions to minimize such a collateral reaction: (a) very low temperature (–95 °C) and (b) the use of 4.0 equivalents of chloriodomethane to generate the carbenoid. Pleasingly, the progressive increase of the steric hindrance at the *ortho* positions of 2,6-disubstituted isocyanates did not affect the efficiency of the protocol thus, permitting an easy access to chloroamides **4r–t**.

With the aim to expand the usefulness of the procedure, we turned our attention towards the addition of lithium dihalocarbenoids. According to the literature, the most common method to form these species is based on the deprotonation of a dihalomethane with a lithium amide base.<sup>35</sup> The reaction between phenyl isocyanate (**3i**) and the putative dihalomethyl lithium was selected as a model



**Scheme 2** Scope of the  $\alpha$ -halomethylation reaction. Isolated yields and reaction times in parentheses. <sup>a</sup> ICH<sub>2</sub>Cl (4.0 equiv), MeLi–LiBr (1.2 equiv), –95 °C.

reaction for screening (Table 2). By using the conditions developed for the corresponding  $\alpha$ -halomethylation [CH<sub>2</sub>Cl<sub>2</sub> (1.5 equiv), lithium reagent (1.25 equiv)] in the presence of lithium diisopropylamide, only urea **6a** was obtained in 84% yield with only a minimal amount (6%) of the desired  $\alpha,\alpha$ -dichloroamide **5** (entry 1). Modifications of the stoichiometry, reaction time, or the solvent did not have beneficial effects (entries 2–4). When the formation of the carbenoid was attempted in the absence of the electrophile, no reaction was observed at all, suggesting that its decomposition took place (entry 5). By switching to lithium dicyclohexylamide, introduced by Nozaki for

the generation of dihalocarbenoids,<sup>35c,d</sup> a similar competing attack of the base to the isocyanate to give urea **6b** was observed (entry 6). Because the formation of ureas through the addition of lithium amide bases is known in the literature,<sup>36</sup> we consider that their attack on the isocyanate is faster than the deprotonation of dichloromethane and thus the formation and reaction of dichloromethylithium with the electrophile. Running the reaction at lower temperatures (−100 °C) did not modify the reactivity profile (entry 7). Attempts to dichloromethylate **3i** adapting Izawa's procedure<sup>37</sup> for esters in the presence of methyl-lithium–lithium bromide, resulted equally in the formation of amide **7** (entry 8). Pleasingly, the use of the more sterically hindered base lithium 2,2,6,6-tetramethylpiperidide proved to be effective in avoiding the formation of urea compounds, thus allowing the chemoselective obtainment of dichloroacetamide **5** as indicated by <sup>1</sup>H NMR analysis of the crude (entry 9). Because of the lower nucleophilicity of dichloromethylithium compared to the corresponding monochloromethylithiums, we found the use of an excess of base [CH<sub>2</sub>Cl<sub>2</sub> (5 equiv), LTMP (4.5 equiv)] beneficial to maximize the yield up to 87% (entries 9–12).

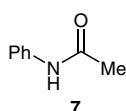


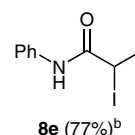
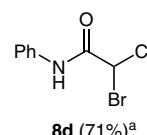
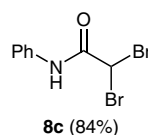
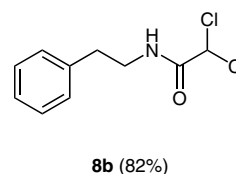
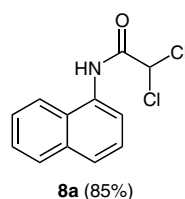
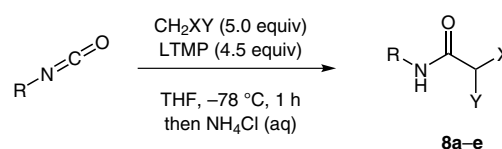
Figure 2

The dichloromethylation could be efficiently applied to various isocyanates (aromatic and aliphatic) providing compound **8a** and **8b** in very good yields (Scheme 3). Analogously, the lithium 2,2,6,6-tetramethylpiperidide assisted procedure could be employed to generate dibromo compound **8c** from dibromomethane and, the particularly challenging bromochloro derivative **8d** from bromochloromethane albeit in somewhat lower yield. Finally, by employing Bull's protocol<sup>18c,d</sup> for the generation of diiodomethylithium from diiodomethane and lithium hexamethyldisilazane we were able to prepare diiodoacetamide **8e**. It should be observed that diiodomethylithium could be preformed prior to the addition of the isocyanate, thus indicating the higher stability of this carbenoid compared to others employed in this study that require the isocyanate to be present when the carbenoid is generated. It should be stressed that compound **8e** has been previously synthesized by Reinshagen through a complex procedure involving the degradation of acetanilide with sodium hypiodite.<sup>11</sup>

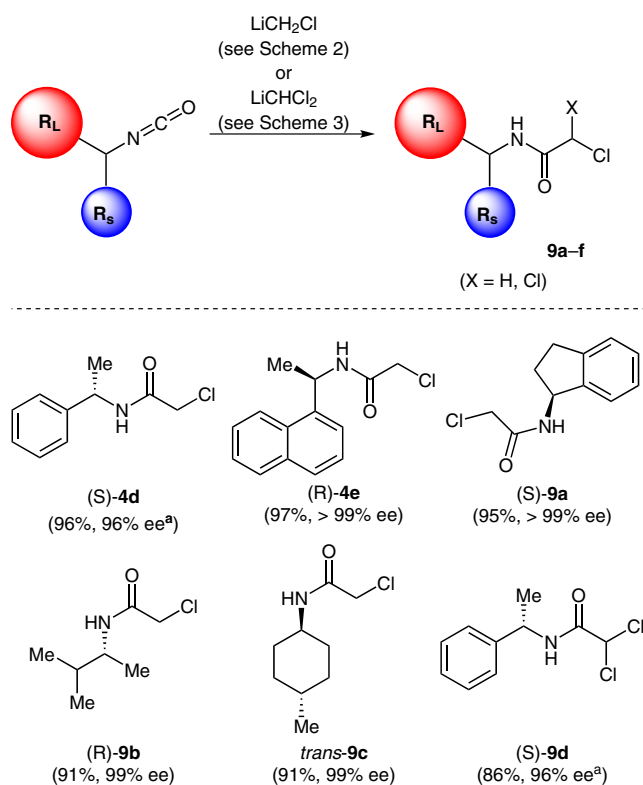
In order to gain a full insight into the studied transformation, we finally studied its adaptability to optically active isocyanates. Full preservation of the chiral information was evidenced both in the case of the addition of chloromethylithium to give (*S*)-**4d**, (*R*)-**4e**, (*S*)-**9a**, (*R*)-**9b**, and *trans*-**9c** and dichloromethylithium to give (*S*)-**9d** (Scheme 4).

**Table 2** Reaction Optimization for the Dichloromethylation of Phenyl Isocyanate<sup>a</sup>

| Entry          | Li reagent (equiv)       | CH <sub>2</sub> Cl <sub>2</sub> (equiv) | Time (h) | Yield <sup>b</sup> (%) |                  |
|----------------|--------------------------|-----------------------------------------|----------|------------------------|------------------|
|                |                          |                                         |          | <b>5</b>               | <b>6</b>         |
| 1              | LDA (1.25)               | 1.5                                     | 1        | 6                      | ( <b>6a</b> ) 84 |
| 2              | LDA (4.5)                | 5.0                                     | 1        | 9                      | ( <b>6a</b> ) 82 |
| 3              | LDA (4.5)                | 5.0                                     | 3        | 11                     | ( <b>6a</b> ) 79 |
| 4 <sup>c</sup> | LDA (4.5)                | 5.0                                     | 1        | 8                      | ( <b>6a</b> ) 86 |
| 5 <sup>d</sup> | LDA (4.5)                | 5.0                                     | 1        | –                      | –                |
| 6              | LiNCy <sub>2</sub> (4.5) | 5.0                                     | 1        | 12                     | ( <b>6b</b> ) 78 |
| 7 <sup>e</sup> | LiNCy <sub>2</sub> (4.5) | 5.0                                     | 1        | 14                     | ( <b>6b</b> ) 75 |
| 8 <sup>f</sup> | MeLi–LiBr (4.5)          | 5.0                                     | 1        | –                      | –                |
| 9              | LTMP (4.5)               | 5.0                                     | 1        | 87                     | –                |
| 10             | LTMP (3.0)               | 5.0                                     | 1        | 76                     | –                |
| 11             | LTMP (2.0)               | 5.0                                     | 1        | 71                     | –                |
| 12             | LTMP (6.0)               | 8.0                                     | 1        | 84                     | –                |

<sup>a</sup> Reactions were performed at −78 °C otherwise indicated.<sup>b</sup> Isolated yield.<sup>c</sup> Reaction run in Et<sub>2</sub>O.<sup>d</sup> **3i** was added after 1 min from the end of the addition of LDA.<sup>e</sup> Reaction run at −100 °C.<sup>f</sup> Amide **7** (Figure 2) was obtained in 86% yield.**Scheme 3** Synthesis of α,α-dihaloamides. <sup>a</sup> Reaction time 3 h. <sup>b</sup> CH<sub>2</sub>I<sub>2</sub> (4.4 equiv), LHDMS (4.0 equiv), THF–Et<sub>2</sub>O (3:1), −78 °C, overnight.

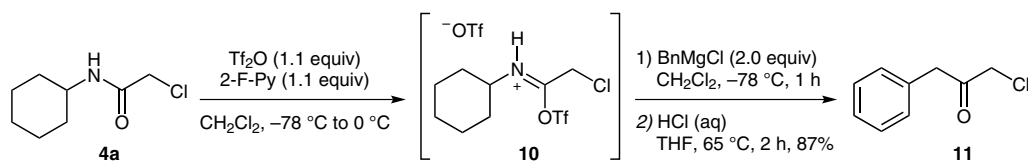




**Scheme 4** Application of the method to optically active isocyanates.  
<sup>a</sup> 96% ee for the supplied starting material.

Because of our interest in the synthesis of  $\alpha$ -halo ketone compounds,<sup>9b,21,32h,38</sup> we were attracted by a recent report by Charette and co-workers<sup>39</sup> dealing with the full chemoselective access to ketones from secondary amides via the formation of a highly electrophilic imidoyl triflate ion.<sup>40</sup> Pleasingly, upon activation of inert amide **4a** under such conditions, followed by the addition of benzylmagnesium chloride and acidic hydrolysis,  $\alpha$ -halo ketone **11** was obtained in an excellent 87% yield (Scheme 5). This example broadens the scope of such a powerful strategy in allowing the addition of organometallics also to substrates bearing reactive chloromethyl functionalities. Interestingly, such a tactic allows considerable simplification of the access to ketone **11** compared to former techniques such as the Villieras' direct addition of chloromethyl lithium to an ester, which had to be performed at  $-115^\circ\text{C}$ .<sup>16a</sup>

Finally, due to the lack of available information regarding  $^{15}\text{N}$  NMR data of  $\alpha$ -chloroamides synthesized in the course of this work, we report in Table 3 the  $^{15}\text{N}$  chemical shifts of the amidic nitrogen for selected examples.



**Scheme 5** Addition of benzylmagnesium chloride to an  $\alpha$ -chloroamide via activation as imidoyl triflate

**Table 3**  $^{15}\text{N}$  NMR Data for Selected Synthesized Compounds<sup>a</sup>

| Compound              | $^{15}\text{N}$ NMR ( $\delta$ ) |
|-----------------------|----------------------------------|
| <b>4b</b>             | −262.5                           |
| <b>4n</b>             | −259.3                           |
| <b>4o</b>             | −257.3                           |
| <b>5</b>              | −259.3                           |
| <b>6b</b>             | −276.1                           |
| <b>8a</b>             | −266.4                           |
| <b>8b</b>             | −273.5                           |
| <b>8c</b>             | −258.3                           |
| <b>8d</b>             | −259.2                           |
| <b>8e<sup>b</sup></b> | −260.3                           |
| <b>(S)-9a</b>         | −253.9                           |
| <b>(R)-9b</b>         | −256.0                           |
| <b>trans-9c</b>       | −252.7                           |
| <b>(S)-9d</b>         | −257.3                           |

<sup>a</sup> Measurements were realized in  $\text{CDCl}_3$  referencing against external  $\text{MeNO}_2$ .

<sup>b</sup>  $\text{DMSO}-d_6$  was used as the solvent.

In conclusion, we have demonstrated the effectiveness of the homologation of readily available isocyanates with lithium carbenoid (monohalo and dihalo) reagents to produce the corresponding secondary amide adducts through a simple nucleophilic addition. The method is particularly attractive compared to the usual procedures used to prepare these substrates because: 1. it does not rely on the nucleophilicity of the amine as occurs in the case of condensation with haloacetyl halides; 2. steric hindrance on the isocyanate does not affect the overall transformation; 3. the protocol can be smoothly adapted to the synthesis of the desired haloamides by correct selection of the isocyanate and the carbenoid; 4. with chiral isocyanates no erosion of the optical purity of reaction products was observed.

$^1\text{H}$ ,  $^{13}\text{C}$ ,  $^{15}\text{N}$ , and  $^{19}\text{F}$  NMR spectra were recorded on a Bruker AC-250 spectrometer (250 MHz for  $^1\text{H}$ , 62.5 MHz for  $^{13}\text{C}$ , and 235 MHz for  $^{19}\text{F}$ ) or on a Bruker Avance III 400 spectrometer (400 MHz for  $^1\text{H}$ , 100 MHz for  $^{13}\text{C}$ , 376 MHz for  $^{19}\text{F}$ , and 40 MHz for  $^{15}\text{N}$ ) or a Bruker Avance 500 spectrometer (500 MHz for  $^1\text{H}$ , 126 MHz for  $^{13}\text{C}$ ) from  $\text{CDCl}_3$  solutions at  $25^\circ\text{C}$ . The center of the (residual) sol-

vent signal was used as an internal standard which was related to TMS with  $\delta = 7.26$  ( $^1\text{H}$ ,  $\text{CDCl}_3$ ),  $\delta = 77.0$  ( $^{13}\text{C}$ ,  $\text{CDCl}_3$ ),  $\delta = 2.49$  ( $^1\text{H}$ ,  $\text{DMSO}-d_6$ ),  $\delta = 39.5$  ( $^{13}\text{C}$ ,  $\text{DMSO}-d_6$ ),  $\delta = 2.05$  ( $^1\text{H}$ ,  $\text{acetone}-d_6$ ), and  $\delta = 29.8$  ( $^{13}\text{C}$ ,  $\text{acetone}-d_6$ ). With the  $^{19}\text{F}$  NMR spectra absolute referencing via  $\Xi$  ratio was performed.  $^{15}\text{N}$  NMR spectra were referenced against external  $\text{MeNO}_2$ . Chiral HPLC was carried out with Chiralcel OD-H, or Chiralpak IA columns, as indicated. IR absorption spectra were recorded as NaCl pellets on a Shimadzu FT-IR 8400S (E41107) instrument. Spectra analyses were performed with the software Shimadzu IRsolution (Version 1.21, 2005). Elementary microanalyses were carried out using a Leco CHNS 932 equipment. Column chromatography purifications were conducted on silica gel 60 (40–63  $\mu\text{m}$ ). Melting points are uncorrected. Solutions were evaporated under reduced pressure with a rotary evaporator and the residue was chromatographed on a silica gel column ( $\text{EtOAc}$ –hexane, unless otherwise specified). TLC was carried out on aluminum sheets precoated with silica gel 60F<sub>254</sub> (Macherey-Nagel, Merk); the spots were visualized under UV light ( $\lambda = 254$  nm) and/or aq  $\text{KMnO}_4$  was used as the developing system. All chemicals were purchased from Sigma Aldrich, Acros, Alfa Aesar, and TCI and solvents were purified by distillation immediately before use according to standard procedures. Dihalomethanes used as carbenoids precursors and amine bases (*i*-Pr<sub>2</sub>NH and 2,2,6,6-tetramethylpiperidine) were distilled immediately before use.

#### Chemoselective Addition of Lithium Carbenoids to Isocyanates; General Procedure 1 (GP1)

To a cooled ( $-78^\circ\text{C}$ ) solution of isocyanate (1.0 equiv) in dry  $\text{Et}_2\text{O}$  (1 M concentration) was added the dihalomethane derivative (1.5 equiv). After 2 min, an ethereal solution of 1.5 M  $\text{MeLi}$ – $\text{LiBr}$  (1.25 equiv) was added dropwise over 5 min. The resulting solution was stirred for the appropriate time (see Table 1 and Scheme 2) at that temperature. Sat. aq  $\text{NH}_4\text{Cl}$  was added (2 mL/mmol substrate) and the cooling bath was removed, the mixture was stirred till it reached r.t., and then it was extracted with additional  $\text{Et}_2\text{O}$  ( $2 \times 5$  mL) and washed with water (5 mL) and brine (10 mL). The organic phase was dried (anhyd  $\text{Na}_2\text{SO}_4$ ), filtered, and the solvent removed under reduced pressure to give pure samples of haloacetamides.

#### *N*-(Chloroacetyl)adamantan-1-amine (**2a**)<sup>30</sup>

By following GP1, starting from 1-adamantyl isocyanate (0.67 g, 3.8 mmol),  $\text{ICH}_2\text{Cl}$  (1.0 g, 0.41 mL, 5.7 mmol), and  $\text{MeLi}$ – $\text{LiBr}$  (3.04 mL, 4.56 mmol) in  $\text{Et}_2\text{O}$  gave **2a** (839 mg, 97%) as a white solid; mp  $119^\circ\text{C}$ .

IR (NaCl): 3239, 3080, 2108, 1662, 1569, 1234  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.22$  (br s, 1 H), 3.90 (s, 2 H), 2.12–2.03 (m, 3 H), 2.03–1.95 (m, 6 H), 1.66 (t,  $J = 2.8$  Hz, 6 H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta = 164.5$ , 52.3, 42.8, 41.1, 36.1, 29.3.

Anal. Calcd for  $\text{C}_{12}\text{H}_{18}\text{ClNO}$ : C, 63.29; H, 7.97; N, 6.15. Found: C, 63.42; H, 8.09; N, 6.27.

#### *N*-(Iodoacetyl)adamantan-1-amine (**2b**)<sup>30</sup>

By following GP1, starting from 1-adamantyl isocyanate (0.67 g, 3.8 mmol),  $\text{CH}_2\text{I}_2$  (1.53 g, 0.46 mL, 5.7 mmol), and  $\text{MeLi}$ – $\text{LiBr}$  (3.04 mL, 4.56 mmol) in  $\text{Et}_2\text{O}$  gave **2b** (1140 mg, 94%) as a yellow solid; mp  $121$ – $123^\circ\text{C}$ .

IR (NaCl): 3250, 1664, 1570, 1230, 996  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.17$  (s, 1 H), 3.60 (s, 2 H), 2.22–1.81 (m, 9 H), 1.77–1.57 (m, 6 H).

$^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta = 165.9$ , 52.7, 41.2, 36.4, 29.4, 1.6.

Anal. Calcd for  $\text{C}_{12}\text{H}_{18}\text{INO}$ : C, 45.16; H, 5.68; N, 4.39. Found: C, 45.31; H, 5.75; N, 4.52.

#### *N*-(Bromoacetyl)adamantan-1-amine (**2c**)<sup>30</sup>

By following GP1, starting from 1-adamantyl isocyanate (0.67 g, 3.8 mmol),  $\text{ICH}_2\text{Br}$  (1.26 g, 0.43 mL, 5.7 mmol), and  $\text{MeLi}$ – $\text{LiBr}$

(3.04 mL, 4.56 mmol) in  $\text{Et}_2\text{O}$  gave **2b** (962 mg, 93%) as a white solid; mp  $124^\circ\text{C}$ .

IR (NaCl): 3243, 2105, 1661, 1572, 1232  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.12$  (br s, 1 H), 3.77 (s, 2 H), 2.10 (s, 3 H), 2.01 (d,  $J = 3.0$  Hz, 6 H), 1.69 (t,  $J = 6.3$  Hz, 6 H).

$^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta = 164.1$ , 52.5, 41.1, 36.2, 29.9, 29.3.

Anal. Calcd for  $\text{C}_{12}\text{H}_{18}\text{BrNO}$ : C, 52.95; H, 6.67; N, 5.15. Found: C, 53.09; H, 6.82; N, 5.30.

#### 2-Chloro-*N*-cyclohexylacetamide (**4a**)<sup>30</sup>

By following GP1, starting from cyclohexyl isocyanate (0.47 g, 3.8 mmol),  $\text{ICH}_2\text{Cl}$  (1.0 g, 0.41 mL, 5.7 mmol), and  $\text{MeLi}$ – $\text{LiBr}$  (3.04 mL, 4.56 mmol) in  $\text{Et}_2\text{O}$  gave **4a** (647 mg, 97%) as a white solid; mp  $113^\circ\text{C}$ .

IR (NaCl): 3241, 1651, 1567, 1223  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.40$  (br s, 1 H), 3.96 (s, 2 H), 3.73–3.69 (m, 1 H), 1.87–1.84 (m, 2 H), 1.65–1.63 (m, 2 H), 1.5–1.53 (m, 1 H), 1.33–1.29 (m, 2 H), 1.16–1.13 (m, 3 H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta = 164.8$ , 48.6, 42.7, 32.8, 25.4, 24.7.

Anal. Calcd for  $\text{C}_8\text{H}_{14}\text{ClNO}$ : C, 54.70; H, 8.03; N, 7.97. Found: C, 54.83; H, 8.14; N, 8.12.

#### 2-Chloro-*N*-cyclopropylacetamide (**4b**)<sup>30</sup>

By following GP1, starting from cyclopropyl isocyanate (0.32 g, 3.8 mmol),  $\text{ICH}_2\text{Cl}$  (1.0 g, 0.41 mL, 5.7 mmol), and  $\text{MeLi}$ – $\text{LiBr}$  (3.04 mL, 4.56 mmol) in  $\text{Et}_2\text{O}$  gave **4b** (480 mg, 95%) as a white solid; mp  $77^\circ\text{C}$ .

IR (NaCl): 3246, 1648, 1230, 990  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.64$  (br s, 1 H, NH), 4.01 (s, 2 H,  $\text{CH}_2\text{Cl}$ ), 2.74 (m, 1 H, NCH), 0.82 (m, 2 H,  $\text{CH}_2\text{CH}_2$ ), 0.57 (m, 2 H,  $\text{CH}_2\text{CH}_2$ ).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 167.2$  (C=O), 42.5 ( $\text{CH}_2\text{Cl}$ ), 22.8 (NCH), 6.4 ( $\text{CH}_2\text{CH}_2$ ).

$^{15}\text{N}$  NMR (40 MHz,  $\text{CDCl}_3$ ):  $\delta = -262.5$  (amide).

Anal. Calcd for  $\text{C}_5\text{H}_8\text{ClNO}$ : C, 44.96; H, 6.04; N, 10.49. Found: C, 45.15; H, 6.23; N, 10.24.

#### 2-Chloro-*N*-(2,4,4-trimethylpentan-2-yl)acetamide (**4c**)<sup>30</sup>

By following GP1, starting from 2-isocyanato-2,4,4-trimethylpentane (0.59 g, 3.8 mmol),  $\text{ICH}_2\text{Cl}$  (1.0 g, 0.41 mL, 5.7 mmol), and  $\text{MeLi}$ – $\text{LiBr}$  (3.04 mL, 4.56 mmol) in  $\text{Et}_2\text{O}$  gave **4c** (740 mg, 95%) as a white solid; mp  $38$ – $40^\circ\text{C}$ .

IR (NaCl): 3251, 1656, 1236, 907  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.43$  (s, 1 H), 3.90 (s, 2 H), 1.50–1.29 (m, 7 H), 1.06–0.92 (m, 10 H).

$^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta = 164.6$ , 55.8, 51.9, 43.1, 32.9, 31.8, 31.5, 31.2, 29.4, 28.8.

Anal. Calcd for  $\text{C}_{10}\text{H}_{20}\text{ClNO}$ : C, 58.38; H, 9.80; N, 6.81. Found: C, 58.19; H, 9.95; N, 6.68.

#### 2-Chloro-*N*-(1-phenylethyl)acetamide (**4d**)<sup>30</sup>

By following GP1, starting from  $\alpha$ -methylbenzyl isocyanate (0.56 g, 3.8 mmol),  $\text{ICH}_2\text{Cl}$  (1.0 g, 0.41 mL, 5.7 mmol), and  $\text{MeLi}$ – $\text{LiBr}$  (3.04 mL, 4.56 mmol) in  $\text{Et}_2\text{O}$  gave **4d** (736 mg, 98%) as a white solid; mp  $100^\circ\text{C}$ .

IR (NaCl): 3260, 2974, 1652, 1542, 1230, 907  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.30$ – $7.18$  (m, 5 H), 6.74 (s, 1 H), 5.05 (quint.,  $J = 7.0$  Hz, 1 H), 3.98 (m, 2 H), 1.46 (d,  $J = 6.9$  Hz, 3 H).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta = 165.0$ , 144.2, 128.8, 127.3, 125.8, 49.3, 42.7, 21.7.

Anal. Calcd for  $C_{10}H_{12}ClNO$ : C, 60.76; H, 6.12; N, 7.09. Found: C, 60.89; H, 6.29; N, 7.24.

### 2-Chloro-*N*-[1-(1-naphthyl)ethyl]acetamide (**4e**)<sup>30</sup>

By following GP1, starting from 1-(1-naphthyl)ethyl isocyanate (0.75 g, 3.8 mmol),  $ICH_2Cl$  (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in  $Et_2O$  gave **4e** (913 mg, 96%) as a white solid; mp 140 °C.

IR (NaCl): 3284, 1649, 1537, 1231  $cm^{-1}$ .

$^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  = 8.11 (d,  $J$  = 8.5 Hz, 1 H), 7.92 (d,  $J$  = 8.6 Hz, 1 H), 7.86 (d,  $J$  = 7.6 Hz, 1 H), 7.56 (m, 4 H), 6.81 (s, 1 H), 4.15 (s, 2 H), 1.74 (d,  $J$  = 7.0 Hz, 3 H).

$^{13}C$  NMR (126 MHz,  $CDCl_3$ ):  $\delta$  = 164.4, 137.0, 133.5, 130.5, 128.5, 128.2, 126.2, 125.5, 124.8, 122.6, 122.1, 44.8, 42.2, 20.4.

Anal. Calcd for  $C_{14}H_{14}ClNO$ : C, 67.88; H, 5.70; N, 5.65. Found: C, 67.99; H, 5.87; N, 5.82.

### *N*-Allyl-2-chloroacetamide (**4f**)<sup>30</sup>

By following GP1, starting from allyl isocyanate (0.32 g, 3.8 mmol),  $ICH_2Cl$  (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in  $Et_2O$  gave **4f** (508 mg, 98%) as a light orange oil.

IR (NaCl): 3294, 1662, 1542, 1419, 1261, 992  $cm^{-1}$ .

$^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  = 6.69 (br s, 1 H), 5.82–5.74 (m, 1 H), 5.18–5.10 (m, 2 H), 4.00 (s, 2 H), 3.88–3.86 (m, 2 H).

$^{13}C$  NMR (126 MHz,  $CDCl_3$ ):  $\delta$  = 164.8, 133.2, 115.7, 42.0, 41.1.

Anal. Calcd for  $C_5H_8ClNO$ : C, 44.96; H, 6.04; N, 10.49. Found: C, 45.11; H, 6.21; N, 10.68.

### *N*-Benzyl-2-chloroacetamide (**4g**)<sup>30</sup>

By following GP1, starting from benzyl isocyanate (0.50 g, 3.8 mmol),  $ICH_2Cl$  (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in  $Et_2O$  gave **4g** (663 mg, 95%) as a white solid; mp 95 °C.

IR (NaCl): 3286, 1658, 1535, 994  $cm^{-1}$ .

$^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  = 7.31–7.16 (m, 5 H), 6.81 (br s, 1 H), 4.42 (d,  $J$  = 6.1 Hz, 2 H), 4.02 (s, 2 H).

$^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$  = 165.9, 137.3, 128.8, 127.9, 127.8, 43.9, 42.6.

Anal. Calcd for  $C_9H_{10}ClNO$ : C, 58.86; H, 5.49; N, 7.63. Found: C, 59.11; H, 5.65; N, 7.84.

### 2-Iodo-*N*-(1-phenylethyl)acetamide (**4h**)

By following the general procedure, starting from  $\alpha$ -methylbenzyl isocyanate (0.56 g, 3.8 mmol),  $CH_2I_2$  (1.53 g, 0.46 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in  $Et_2O$  gave **4h** (1099 mg, 98%) as a light yellow solid; mp 118 °C.

IR (NaCl): 3298, 1655, 1551, 994  $cm^{-1}$ .

$^1H$  NMR (300 MHz, acetone- $d_6$ ):  $\delta$  = 7.93 (br s, 1 H), 7.33–7.13 (m, 5 H), 4.99–4.93 (m, 1 H), 3.71 (m, 2 H), 1.37 (m, 3 H).

$^{13}C$  NMR (75 MHz, acetone- $d_6$ ):  $\delta$  = 167.0, 144.6, 128.8, 127.3, 126.6, 49.5, 22.0, 0.0.

Anal. Calcd for  $C_{10}H_{12}INO$ : C, 41.54; H, 4.18; N, 4.84. Found: C, 41.63; H, 4.32; N, 5.01.

### 2-Chloro-*N*-phenylacetamide (**4i**)

By following GP1, starting from phenyl isocyanate (0.45 g, 3.8 mmol),  $ICH_2Cl$  (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in  $Et_2O$  gave **4i** (632 mg, 98%) as a white solid; mp 134 °C (Lit.<sup>8</sup> 134–135 °C).

IR (NaCl): 3262, 1651, 1546, 1235, 990, 907  $cm^{-1}$ .

$^1H$  NMR (200 MHz,  $CDCl_3$ ):  $\delta$  = 8.27 (br s, 1 H), 7.63–7.49 (m, 2 H), 7.47–7.30 (m, 2 H), 7.24–7.02 (m, 1 H), 4.18 (s, 2 H).

$^{13}C$  NMR (50 MHz,  $CDCl_3$ ):  $\delta$  = 164.0, 136.8, 129.2, 125.4, 120.3, 43.0.

Anal. Calcd for  $C_8H_8ClNO$ : C, 56.65; H, 4.75; N, 8.26. Found: C, 56.81; H, 4.93; N, 8.12.

### 2-Iodo-*N*-phenylacetamide (**4j**)<sup>30</sup>

By following GP1, starting from phenyl isocyanate (0.45 g, 3.8 mmol),  $CH_2I_2$  (1.53 g, 0.46 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in  $Et_2O$  gave **4j** (952 mg, 96%) as a white solid; mp 145 °C.

IR (NaCl): 3271, 1647, 1241, 992  $cm^{-1}$ .

$^1H$  NMR (200 MHz,  $CDCl_3$ ):  $\delta$  = 7.86 (br s, 1 H), 7.62–7.43 (m, 2 H), 7.43–7.28 (m, 2 H), 7.21–7.05 (m, 1 H), 3.86 (s, 2 H).

$^{13}C$  NMR (50 MHz,  $CDCl_3$ ):  $\delta$  = 165.3, 129.2, 125.2, 120.1, 0.1.

Anal. Calcd for  $C_8H_8INO$ : C, 36.81; H, 3.09; N, 5.37. Found: C, 36.81; H, 3.09; N, 5.37.

### 2-Chloro-*N*-(3-methoxyphenyl)acetamide (**4k**)<sup>30</sup>

By following GP1, starting from 3-methoxyphenyl isocyanate (0.57 g, 3.8 mmol),  $ICH_2Cl$  (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in  $Et_2O$  gave **4k** (713 mg, 94%) as a white solid; mp 93 °C.

IR (NaCl): 3291, 1661, 1543, 1376, 1254  $cm^{-1}$ .

$^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  = 8.14 (br s, 1 H), 7.21–7.15 (m, 2 H), 6.94 (m, 1 H), 6.67–6.64 (m, 1 H), 4.11 (s, 2 H), 3.74 (s, 3 H).

$^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$  = 163.7, 160.3, 137.8, 129.9, 112.2, 111.0, 105.9, 55.4, 42.9.

Anal. Calcd for  $C_9H_{10}ClNO_2$ : C, 54.15; H, 5.05; N, 7.02. Found: C, 54.33; H, 5.23; N, 7.27.

### 2-Chloro-*N*-(3-chlorophenyl)acetamide (**4l**)<sup>30</sup>

By following GP1, starting from 3-chlorophenyl isocyanate (0.58 g, 3.8 mmol),  $ICH_2Cl$  (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in  $Et_2O$  gave **4l** (744 mg, 96%) as a white solid; mp 100 °C.

IR (NaCl): 3278, 1661, 1267, 990  $cm^{-1}$ .

$^1H$  NMR (200 MHz,  $CDCl_3$ ):  $\delta$  = 8.29 (br s, 1 H), 7.69 (t,  $J$  = 2.0 Hz, 1 H), 7.51–7.28 (m, 2 H), 7.25–7.10 (m, 1 H), 4.21 (s, 2 H).

$^{13}C$  NMR (50 MHz,  $CDCl_3$ ):  $\delta$  = 164.3, 138.2, 135.3, 130.6, 125.8, 120.6, 118.5, 43.2.

Anal. Calcd for  $C_8H_7Cl_2NO$ : C, 47.09; H, 3.46; Cl, 34.75; N, 6.86; O, 7.84.

### *N*-(3-Chlorophenyl)-2-iodoacetamide (**4m**)<sup>30</sup>

By following GP1, starting from 3-chlorophenyl isocyanate (0.58 g, 3.8 mmol),  $CH_2I_2$  (1.53 g, 0.46 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in  $Et_2O$  gave **4m** (1.044 g, 93%) as a white solid; mp 84–85 °C.

IR (NaCl): 3289, 1659, 909  $cm^{-1}$ .

$^1H$  NMR (200 MHz,  $CDCl_3$ ):  $\delta$  = 7.99 (br s, 1 H), 7.66 (t,  $J$  = 1.9 Hz, 1 H), 7.46–7.28 (m, 2 H), 7.16 (dt,  $J$  = 7.8, 1.6 Hz, 1 H), 3.90 (s, 2 H).

$^{13}C$  NMR (50 MHz,  $CDCl_3$ ):  $\delta$  = 165.9, 138.8, 135.2, 130.5, 125.5, 120.5, 118.4, 0.0.

Anal. Calcd for  $C_8H_7ClINO$ : C, 32.52; H, 2.39; N, 4.74. Found: C, 32.39; H, 2.21; N, 4.88.

### 2-Chloro-*N*-[2-chloro-4-(trifluoromethyl)phenyl]acetamide (**4n**)

By following GP1, starting from 2-chloro-4-(trifluoromethyl)phenyl isocyanate (0.80 g, 3.8 mmol),  $ICH_2Cl$  (1.0 g, 0.41 mL, 5.7 mmol), and MeLi–LiBr (3.04 mL, 4.56 mmol) in  $Et_2O$  gave **4n** (1.013 g, 98%) as a white solid; mp 64–65 °C.

IR (NaCl): 3293, 1664, 1242, 990  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 9.01 (br s, 1 H, NH), 8.73 (d,  $J$  = 2.0 Hz, 1 H,  $\text{H}_{6\text{ph}}$ ), 7.51 (m, 1 H,  $\text{H}_{3\text{ph}}$ ), 7.34 (m, 1 H,  $\text{H}_{4\text{ph}}$ ), 4.25 (s, 2 H,  $\text{CH}_2\text{Cl}$ ).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 164.1 (C=O), 134.2 ( $\text{C}_{1\text{ph}}$ ), 130.3 (q,  $J$  = 33.2 Hz,  $\text{C}_{5\text{ph}}$ ), 129.6 ( $\text{C}_{3\text{ph}}$ ), 123.4 (q,  $J$  = 272.6 Hz,  $\text{CF}_3$ ), 121.9 (q,  $J$  = 3.8 Hz,  $\text{C}_{4\text{ph}}$ ), 117.9 (q,  $J$  = 4.0 Hz,  $\text{C}_{6\text{ph}}$ ), 44.0 ( $\text{CH}_2\text{Cl}$ ).

$^{15}\text{N}$  NMR (40 MHz,  $\text{CDCl}_3$ ):  $\delta$  = -259.3 (amide).

$^{19}\text{F}$  NMR (235 MHz,  $\text{CDCl}_3$ ):  $\delta$  = -62.4 (q,  $J$  = 0.7 Hz,  $\text{CF}_3$ ).

Anal. Calcd for  $\text{C}_9\text{H}_6\text{Cl}_2\text{F}_3\text{NO}$ : C, 39.73; H, 2.22; N, 5.15. Found: C, 39.56; H, 2.07; N, 5.29.

### 2-Bromo-*N*-[2-chloro-4-(trifluoromethyl)phenyl]acetamide (**4o**)<sup>30</sup>

By following GP1, starting from 2-chloro-4-(trifluoromethyl)phenyl isocyanate (0.80 g, 3.8 mmol),  $\text{ICH}_2\text{Br}$  (1.26 g, 0.43 mL, 5.7 mmol), and  $\text{MeLi-LiBr}$  (3.04 mL, 4.56 mmol) in  $\text{Et}_2\text{O}$  gave **4o** (1.21 g, 88%) as a white solid; mp 87–88  $^\circ\text{C}$ .

IR (NaCl): 3288, 1662, 1246, 996, 910  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.89 (br s, 1 H, NH), 8.71 (d,  $J$  = 1.8 Hz, 1 H,  $\text{H}_{6\text{ph}}$ ), 7.52 (d,  $J$  = 8.4 Hz, 1 H,  $\text{H}_{3\text{ph}}$ ), 7.35 (dd,  $J$  = 8.4, 2.0 Hz, 1 H,  $\text{H}_{4\text{ph}}$ ), 4.09 (s, 2 H,  $\text{CH}_2\text{Cl}$ ).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 163.6 (C=O), 134.5 ( $\text{C}_{1\text{ph}}$ ), 130.3 (q,  $J$  = 33.2 Hz,  $\text{C}_{5\text{ph}}$ ), 129.6 ( $\text{C}_{3\text{ph}}$ ), 126.6 ( $\text{C}_{2\text{ph}}$ ), 123.4 (q,  $J$  = 272.5 Hz,  $\text{CF}_3$ ), 121.9 (q,  $J$  = 3.8 Hz,  $\text{C}_{4\text{ph}}$ ), 117.9 (q,  $J$  = 4.0 Hz,  $\text{C}_{6\text{ph}}$ ), 29.4 ( $\text{CH}_2\text{Br}$ ).

$^{15}\text{N}$  NMR (40 MHz,  $\text{CDCl}_3$ ):  $\delta$  = -257.3 (amide).

$^{19}\text{F}$  NMR (235 MHz,  $\text{CDCl}_3$ ):  $\delta$  = -62.7 (s,  $\text{CF}_3$ ).

Anal. Calcd for  $\text{C}_9\text{H}_6\text{BrClF}_3\text{NO}$ : C, 34.15; H, 1.91; N, 4.43. Found: C, 34.27; H, 2.00; N, 4.51.

### 2-Chloro-*N*-(2,4,6-tribromophenyl)acetamide (**4p**)<sup>30</sup>

By following GP1, starting from 2,4,6-tribromophenyl isocyanate (1.46 g, 3.8 mmol),  $\text{ICH}_2\text{Cl}$  (2.68 g, 1.11 mL, 15.2 mmol), and  $\text{MeLi-LiBr}$  (3.04 mL, 4.56 mmol) in  $\text{Et}_2\text{O}$  (at -95  $^\circ\text{C}$ ) gave **4p** (1.27 g, 82%) as a white solid; mp 221–222  $^\circ\text{C}$ .

IR (NaCl): 3287, 1660, 998  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.01 (br s, 1 H, NH), 7.78 (s, 2 H), 4.26 (s, 2 H,  $\text{CH}_2\text{Cl}$ ).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 164.1 (C=O), 134.9 ( $\text{C}_{3\text{ph}}$ ,  $\text{C}_{5\text{ph}}$ ), 133.0 ( $\text{C}_{1\text{ph}}$ ), 124.1 ( $\text{C}_{2\text{ph}}$ ,  $\text{C}_{6\text{ph}}$ ), 122.4 ( $\text{C}_{4\text{ph}}$ ), 42.7 ( $\text{CH}_2\text{Cl}$ ).

$^{15}\text{N}$  NMR (40 MHz,  $\text{CDCl}_3$ ):  $\delta$  = -257.8 (amide).

Anal. Calcd for  $\text{C}_8\text{H}_3\text{Br}_3\text{ClNO}$ : C, 23.65; H, 1.24; N, 3.45. Found: C, 23.72; H, 1.30; N, 3.60.

### 2-Chloro-*N*-(1-naphthyl)acetamide (**4q**)<sup>30</sup>

By following GP1, starting from 1-naphthyl isocyanate (0.64 g, 3.8 mmol),  $\text{ICH}_2\text{Cl}$  (1.0 g, 0.41 mL, 5.7 mmol), and  $\text{MeLi-LiBr}$  (3.04 mL, 4.56 mmol) in  $\text{Et}_2\text{O}$  gave **4q** (768 mg, 92%) as a white solid; mp 154  $^\circ\text{C}$ .

IR (NaCl): 3273, 2963, 1663, 1552, 1509, 1399, 1270, 1251  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.78 (br s, 1 H), 7.98 (d,  $J$  = 7.5 Hz, 1 H), 7.88 (m, 2 H), 7.75 (d,  $J$  = 7.6 Hz, 1 H), 7.58–7.51 (m, 3 H), 4.36 (s, 2 H).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 164.3, 134.1, 131.2, 128.9, 126.9, 126.7, 126.5, 126.2, 125.7, 120.6, 120.2, 43.3.

Anal. Calcd for  $\text{C}_{12}\text{H}_{10}\text{ClNO}$ : C, 65.61; H, 4.59; N, 6.38. Found: C, 65.80; H, 4.77; N, 6.59.

### 2-Chloro-*N*-(2,6-dimethylphenyl)acetamide (**4r**)<sup>30</sup>

By following GP1, starting from 2,6-dimethylphenyl isocyanate (0.56 g, 3.8 mmol),  $\text{ICH}_2\text{Cl}$  (1.0 g, 0.41 mL, 5.7 mmol), and  $\text{MeLi-LiBr}$  (3.04 mL, 4.56 mmol) in  $\text{Et}_2\text{O}$  gave **4r** (729 mg, 97%) as a white solid; mp 140  $^\circ\text{C}$ .

IR (NaCl): 3266, 2975, 1655, 1588, 1331, 1251, 997  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.87 (br s, 1 H), 7.15–7.10 (m, 3 H), 4.26 (s, 2 H), 2.25 (s, 6 H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 164.3, 135.4, 132.7, 128.4, 127.9, 42.8, 18.3.

Anal. Calcd for  $\text{C}_{10}\text{H}_{12}\text{ClNO}$ : C, 60.76; H, 6.12; N, 7.09. Found: C, 60.91; H, 6.31; N, 7.22.

### 2-Chloro-*N*-(2,6-diethylphenyl)acetamide (**4s**)<sup>30</sup>

By following GP1, starting from 2,6-diethylphenyl isocyanate (0.66 g, 3.8 mmol),  $\text{ICH}_2\text{Cl}$  (1.0 g, 0.41 mL, 5.7 mmol), and  $\text{MeLi-LiBr}$  (3.04 mL, 4.56 mmol) in  $\text{Et}_2\text{O}$  gave **4s** (815 mg, 95%) as a white solid; mp 201  $^\circ\text{C}$ .

IR (NaCl): 3259, 2970, 2873, 1657, 1592, 1470, 1330, 1247  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.82 (br s, 1 H), 7.19–7.04 (m, 3 H), 4.13 (s, 2 H), 2.49 (q,  $J$  = 6.4 Hz, 4 H), 1.11 (t,  $J$  = 6.4 Hz, 6 H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 165.0, 141.4, 131.6, 128.5, 126.5, 42.8, 24.8, 14.4.

Anal. Calcd for  $\text{C}_{12}\text{H}_{16}\text{ClNO}$ : C, 63.85; H, 7.14; N, 6.21. Found: C, 64.00; H, 7.22; N, 6.35.

### 2-Chloro-*N*-(2,6-diisopropylphenyl)acetamide (**4t**)<sup>30</sup>

By following GP1, starting from 2,4-diisopropylphenyl isocyanate (0.77 g, 3.8 mmol),  $\text{ICH}_2\text{Cl}$  (1.0 g, 0.41 mL, 5.7 mmol), and  $\text{MeLi-LiBr}$  (3.04 mL, 4.56 mmol) in  $\text{Et}_2\text{O}$  gave **4t** (935 mg, 97%) as a white solid; mp 149  $^\circ\text{C}$ .

IR (NaCl): 3248, 1678, 1660, 1533, 998  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.87 (s, 1 H), 7.46–7.20 (m, 3 H), 4.30 (s, 2 H), 3.07 (sept,  $J$  = 6.9 Hz, 2 H), 1.26 (d,  $J$  = 6.9 Hz, 12 H).

$^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 165.5, 146.1, 130.1, 129.0, 123.8, 42.9, 28.9, 23.7.

Anal. Calcd for  $\text{C}_{14}\text{H}_{20}\text{ClNO}$ : C, 66.26; H, 7.94; N, 5.52. Found: C, 66.09; H, 8.10; N, 5.69.

### Dichloromethylation of Phenyl Isocyanate with Lithium Diisopropylamide and Lithium Dicyclohexylamide; General Procedure 2

A 1.5 M  $\text{MeLi-LiBr}$  solution (3.0 mL, 4.5 mmol, 4.5 equiv) was added dropwise to a precooled solution of the corresponding amine (4.5 equiv) in THF (4 mL) at 0  $^\circ\text{C}$ .<sup>32f</sup> The generated lithium amide was transferred to a cooled (-78  $^\circ\text{C}$ ) solution of phenyl isocyanate (0.11 mL, 119 mg, 1.0 mmol, 1.0 equiv) and  $\text{CH}_2\text{Cl}_2$  (425 mg, 0.32 mL, 5.0 mmol, 5.0 equiv) in dry THF (1 M concentration) over 5 min. The resulting solution was stirred for 1 h at this temperature, and then sat. aq  $\text{NH}_4\text{Cl}$  was added (2 mL/mmol substrate). After removal of the cooling bath, the mixture was stirred till it reached r.t. and then extracted with additional  $\text{Et}_2\text{O}$  (2  $\times$  5 mL) and washed with 3 M HCl and brine. The organic phase was dried (anhyd  $\text{Na}_2\text{SO}_4$ ), filtered, and, after removal of the solvent under reduced pressure, afforded a mixture of compounds **5** and **6a** or **6b** (Table 2).

### 2,2-Dichloro-*N*-phenylacetamide (**5**; Table 2, Entry 9)

Yield: 177 mg (87%); white solid; mp 106–107  $^\circ\text{C}$  (Lit.<sup>41</sup> 109  $^\circ\text{C}$ ).

IR (NaCl): 1673, 1601, 1498  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.12 (br s, 1 H, NH), 7.56 (m, 2 H,  $\text{H}_{2\text{ph}}$ ,  $\text{H}_{6\text{ph}}$ ), 7.39 (m, 2 H,  $\text{H}_{3\text{ph}}$ ,  $\text{H}_{5\text{ph}}$ ), 7.21 (m, 1 H,  $\text{H}_{4\text{ph}}$ ), 6.05 (s, 1 H,  $\text{Cl}_2\text{CH}$ ).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 161.7 (C=O), 136.2 ( $\text{C}_{1\text{ph}}$ ), 129.2 ( $\text{C}_{3\text{ph}}$ ,  $\text{C}_{5\text{ph}}$ ), 125.7 ( $\text{C}_{4\text{ph}}$ ), 120.2 ( $\text{C}_{2\text{ph}}$ ,  $\text{C}_{6\text{ph}}$ ), 66.9 ( $\text{Cl}_2\text{CH}$ ).

$^{15}\text{N}$  NMR (40 MHz,  $\text{CDCl}_3$ ):  $\delta = -259.3$  (NH).

### 1,1-Diisopropyl-3-phenylurea (**6a**; Table 2, Entry 4)

Yield: 189 mg (86%); white solid; mp 112–114 °C (Lit.<sup>42</sup> 114–116 °C).

IR (NaCl): 1632, 1521, 1445, 1332, 1247  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.38$  (m, 2 H,  $\text{H}_{2\text{Ph}}$ ,  $\text{H}_{6\text{Ph}}$ ), 7.28 (m, 2 H,  $\text{H}_{3\text{Ph}}$ ,  $\text{H}_{5\text{Ph}}$ ), 7.01 (m, 1 H,  $\text{H}_{4\text{Ph}}$ ), 6.18 (br s, 1 H, NH), 3.99 (sept,  $J = 6.9$  Hz, 2 H,  $\text{CHMe}_2$ ), 1.34 [br s, 12 H,  $\text{CH}(\text{CH}_3)_2$ ].

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta = 154.6$  (C=O), 139.3 ( $\text{C}_{1\text{Ph}}$ ), 128.9 ( $\text{C}_{3\text{Ph}}$ ,  $\text{C}_{5\text{Ph}}$ ), 122.6 ( $\text{C}_{4\text{Ph}}$ ), 119.7 ( $\text{C}_{2\text{Ph}}$ ,  $\text{C}_{6\text{Ph}}$ ), 45.4 ( $\text{CHMe}_2$ ), 21.5 [ $\text{CH}(\text{CH}_3)_2$ ].

$^{15}\text{N}$  NMR (40 MHz,  $\text{CDCl}_3$ ):  $\delta = -276.4$  (PhNH),  $-268.2$  (*i*-PrN).

Anal. Calcd for  $\text{C}_{13}\text{H}_{20}\text{N}_2\text{O}$ : C, 70.87; H, 9.15; N, 12.72. Found: C, 70.93; H, 9.31; N, 12.86.

### 1,1-Dicyclohexyl-3-phenylurea (**6b**; Table 2, Entry 6)

Yield: 234 mg (78%); white solid; mp 170–171 °C.

IR (NaCl): 1635, 1520  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.36$  (m, 2 H,  $\text{H}_{2\text{Ph}}$ ,  $\text{H}_{6\text{Ph}}$ ), 7.27 (m, 2 H,  $\text{H}_{3\text{Ph}}$ ,  $\text{H}_{5\text{Ph}}$ ), 7.00 (m, 1 H,  $\text{H}_{4\text{Ph}}$ ), 6.25 (br s, 1 H, NH), 3.48 (m, 2 H,  $\text{H}_{1\text{Cy}}$ ), 1.84 (m, 4 H,  $\text{H}_{3\text{Cy}}$ ,  $\text{H}_{5\text{Cy}}$ ), 1.76 (m, 8 H,  $\text{H}_{2\text{Cy}}$ ,  $\text{H}_{6\text{Cy}}$ ), 1.68 (m, 2 H,  $\text{H}_{4\text{Cy}}$ ), 1.35 (m, 4 H,  $\text{H}_{3'\text{Cy}}$ ,  $\text{H}_{5'\text{Cy}}$ ), 1.14 (m, 2 H,  $\text{H}_{4'\text{Cy}}$ ).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta = 154.9$  (C=O), 139.4 ( $\text{C}_{1\text{Ph}}$ ), 128.8 ( $\text{C}_{3\text{Ph}}$ ,  $\text{C}_{5\text{Ph}}$ ), 122.5 ( $\text{C}_{4\text{Ph}}$ ), 119.6 ( $\text{C}_{2\text{Ph}}$ ,  $\text{C}_{6\text{Ph}}$ ), 55.4 ( $\text{C}_{1\text{Cy}}$ ), 31.9 ( $\text{C}_{2\text{Cy}}$ ,  $\text{C}_{6\text{Cy}}$ ), 26.4 ( $\text{C}_{3\text{Cy}}$ ,  $\text{C}_{5\text{Cy}}$ ), 25.5 ( $\text{C}_{4\text{Cy}}$ ).

$^{15}\text{N}$  NMR (40 MHz,  $\text{CDCl}_3$ ):  $\delta = -276.1$  (NH), CyN not found.

Anal. Calcd for  $\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}$ : C, 75.96; H, 9.39; N, 9.32. Found: C, 76.09; H, 9.48; N, 9.40.

### Chemoselective Addition of Lithium Polyhalocarbenoids to Iso-cyanates; General Procedure 3

A 1.5 M MeLi–LiBr solution (3.0 mL, 4.5 mmol, 4.5 equiv) was added dropwise to a precooled solution of 2,2,6,6-tetramethylpiperidine (0.77 mL, 636 mg, 4.5 mmol, 4.5 equiv) in THF (4 mL) at 0 °C. The generated LTMP was transferred to a cooled (–78 °C) solution of the isocyanate (1.0 equiv) and dihalomethane (5.0 equiv) in dry THF (1 M concentration) over 5 min. The resulting solution was stirred for 1 h at this temperature, and then sat. aq  $\text{NH}_4\text{Cl}$  was added (2 mL/mmol substrate). After removal of the cooling bath, the mixture was stirred until it reached r.t. and then extracted with additional  $\text{Et}_2\text{O}$  (2  $\times$  5 mL) and washed with 3 M HCl and brine. The organic phase was dried (anhyd  $\text{Na}_2\text{SO}_4$ ), filtered and, after removal of the solvent under reduced pressure, the so-obtained crude mixture was subjected to chromatography (silica gel) to afford pure dihaloamides.

### 2,2-Dichloro-*N*-(1-naphthyl)acetamide (**8a**)

By following GP3, starting from 1-naphthyl isocyanate (0.14 mL, 169 mg, 1.0 mmol) and  $\text{CH}_2\text{Cl}_2$  (425 mg, 0.32 mL, 5.0 mmol) in THF (1 mL) with chromatography (silica gel, petroleum ether–EtOAc, 8:2,  $R_f = 0.4$ ) gave **8a** (216 mg, 85%) as a colorless solid; mp 135–137 °C.

IR (NaCl): 1675, 1605  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 8.59$  (br s, 1 H, NH), 7.90 (m, 1 H,  $\text{H}_{5\text{Naphth}}$ ), 7.88 (m, 1 H,  $\text{H}_{2\text{Naphth}}$ ), 7.86 (m, 1 H,  $\text{H}_{8\text{Naphth}}$ ), 7.78 (m, 1 H,  $\text{H}_{4\text{Naphth}}$ ), 7.58 (m, 1 H,  $\text{H}_{7\text{Naphth}}$ ), 7.54 (m, 1 H,  $\text{H}_{6\text{Naphth}}$ ), 7.49 (m, 1 H,  $\text{H}_{3\text{Naphth}}$ ), 6.17 (s, 1 H,  $\text{CHCl}_2$ ).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta = 162.6$  (C=O), 134.0 ( $\text{C}_{4\text{aNaphth}}$ ), 130.4 ( $\text{C}_{1\text{Naphth}}$ ), 128.9 ( $\text{C}_{5\text{Naphth}}$ ), 127.2 ( $\text{C}_{8\text{aNaphth}}$ ), 127.1 ( $\text{C}_{4\text{Naphth}}$ ), 126.9 ( $\text{C}_{7\text{Naphth}}$ ), 126.4 ( $\text{C}_{6\text{Naphth}}$ ), 125.6 ( $\text{C}_{3\text{Naphth}}$ ), 121.2 ( $\text{C}_{2\text{Naphth}}$ ), 120.2 ( $\text{C}_{8\text{Naphth}}$ ), 67.1 ( $\text{CHCl}_2$ ).

$^{15}\text{N}$  NMR (40 MHz,  $\text{CDCl}_3$ ):  $\delta = -266.4$  (NH).

Anal. Calcd for  $\text{C}_{12}\text{H}_9\text{Cl}_2\text{NO}$ : C, 56.72; H, 3.57; N, 5.51. Found: C, 56.81; H, 3.60; N, 5.58.

### 2,2-Dichloro-*N*-(2-phenylethyl)acetamide (**8b**)

By following GP3, starting from phenethyl isocyanate (0.14 mL, 147 mg, 1.0 mmol) and  $\text{CH}_2\text{Cl}_2$  (425 mg, 0.32 mL, 5.0 mmol) in THF (1 mL) with chromatography (silica gel, petroleum ether–EtOAc, 8:2,  $R_f = 0.45$ ) gave **8b** (190 mg, 82%) as a colorless solid; mp 67–68 °C.

IR (NaCl): 1667, 1598, 1454  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.33$  (m, 2 H,  $\text{H}_{3\text{Ph}}$ ,  $\text{H}_{5\text{Ph}}$ ), 7.26 (m, 1 H,  $\text{H}_{4\text{Ph}}$ ), 7.22 (m, 2 H,  $\text{H}_{2\text{Ph}}$ ,  $\text{H}_{6\text{Ph}}$ ), 6.57 (br s, 1 H, NH), 5.89 (s, 1 H,  $\text{Cl}_2\text{CH}$ ), 3.59 (m, 2 H,  $\text{NHCH}_2$ ), 2.88 (t,  $J = 7.0$  Hz, 2 H,  $\text{PhCH}_2$ ).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta = 164.0$  (C=O), 138.0 ( $\text{C}_{1\text{Ph}}$ ), 128.8 ( $\text{C}_{2\text{Ph}}$ ,  $\text{C}_{6\text{Ph}}$ ), 128.7 ( $\text{C}_{3\text{Ph}}$ ,  $\text{C}_{5\text{Ph}}$ ), 126.8 ( $\text{C}_{4\text{Ph}}$ ), 66.4 ( $\text{Cl}_2\text{CH}$ ), 41.5 ( $\text{NHCH}_2$ ), 35.2 ( $\text{PhCH}_2$ ).

$^{15}\text{N}$  NMR (40 MHz,  $\text{CDCl}_3$ ):  $\delta = -273.5$  (NH).

Anal. Calcd for  $\text{C}_{10}\text{H}_{11}\text{Cl}_2\text{NO}$ : C, 51.75; H, 4.78; N, 6.03. Found: C, 51.87; H, 4.90; N, 6.13.

### 2,2-Dibromo-*N*-phenylacetamide (**8c**)<sup>13</sup>

By following GP3, starting from phenyl isocyanate (0.11 mL, 119 mg, 1.0 mmol) and  $\text{CH}_2\text{Br}_2$  (869 mg, 0.35 mL, 5.0 mmol) in THF (1 mL), with chromatography (silica gel, petroleum ether–EtOAc, 8:2,  $R_f = 0.45$ ) gave **8c** (246 mg, 84%) as a colorless solid; mp 115–117 °C.

IR (NaCl): 1670, 1601, 1497  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 8.16$  (br s, 1 H, NH), 7.55 (m, 2 H,  $\text{H}_{2\text{Ph}}$ ,  $\text{H}_{6\text{Ph}}$ ), 7.38 (m, 2 H,  $\text{H}_{3\text{Ph}}$ ,  $\text{H}_{5\text{Ph}}$ ), 7.20 (m, 1 H,  $\text{H}_{4\text{Ph}}$ ), 5.94 (s, 1 H,  $\text{Br}_2\text{CH}$ ).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta = 162.1$  (C=O), 136.5 ( $\text{C}_{1\text{Ph}}$ ), 129.2 ( $\text{C}_{3\text{Ph}}$ ,  $\text{C}_{5\text{Ph}}$ ), 125.6 ( $\text{C}_{4\text{Ph}}$ ), 120.1 ( $\text{C}_{2\text{Ph}}$ ,  $\text{C}_{6\text{Ph}}$ ), 36.7 ( $\text{Br}_2\text{CH}$ ).

$^{15}\text{N}$  NMR (40 MHz,  $\text{CDCl}_3$ ):  $\delta = -258.3$  (NH).

Anal. Calcd for  $\text{C}_8\text{H}_7\text{Br}_2\text{NO}$ : C, 32.80; H, 2.41; N, 4.78. Found: C, 32.91; H, 2.48; N, 4.85.

### 2-Bromo-2-chloro-*N*-phenylacetamide (**8d**)<sup>43</sup>

By following GP3, starting from phenyl isocyanate (0.11 mL, 119 mg, 1.0 mmol) and  $\text{ClCH}_2\text{Br}$  (647 mg, 0.33 mL, 5.0 mmol) in THF (1 mL), with chromatography (silica gel, petroleum ether–EtOAc, 8:2,  $R_f = 0.40$ ) gave **8d** (176 mg, 71%) as a clear yellowish solid; mp 100–102 °C.

IR (NaCl): 1672, 1600, 1527, 1490  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 8.13$  (br s, 1 H, NH), 7.55 (m, 2 H,  $\text{H}_{2\text{Ph}}$ ,  $\text{H}_{6\text{Ph}}$ ), 7.38 (m, 2 H,  $\text{H}_{3\text{Ph}}$ ,  $\text{H}_{5\text{Ph}}$ ), 7.20 (m, 1 H,  $\text{H}_{4\text{Ph}}$ ), 6.04 (s, 1 H,  $\text{BrClCH}$ ).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta = 162.0$  (C=O), 136.3 ( $\text{C}_{1\text{Ph}}$ ), 129.2 ( $\text{C}_{3\text{Ph}}$ ,  $\text{C}_{5\text{Ph}}$ ), 125.6 ( $\text{C}_{4\text{Ph}}$ ), 120.1 ( $\text{C}_{2\text{Ph}}$ ,  $\text{C}_{6\text{Ph}}$ ), 52.2 ( $\text{BrClCH}$ ).

$^{15}\text{N}$  NMR (40 MHz,  $\text{CDCl}_3$ ):  $\delta = -259.2$  (NH).

Anal. Calcd for  $\text{C}_8\text{H}_7\text{BrClNO}$ : C, 38.67; H, 2.84; N, 5.64. Found: C, 38.75; H, 2.90; N, 5.71.

### 2,2-Diiodo-*N*-phenylacetamide (**8e**)<sup>11</sup>

A 1 M LHDMS solution in THF (2 mL, 2.0 mmol, 4.0 equiv) in THF– $\text{Et}_2\text{O}$  (3:2, 6 mL) was stirred at –78 °C for 10 min, then  $\text{CH}_2\text{I}_2$  (0.18 mL, 589 mg, 2.2 mmol, 4.4 equiv) in THF (1.5 mL) was added dropwise to the mixture in the dark.<sup>18c,d</sup> After 20 min at –78 °C, phenyl isocyanate (0.06 mL, 60 mg, 0.50 mmol, 1.0 equiv) added dropwise to the mixture over 5 min. The reaction was then stirred overnight from –78 °C to r.t. The reaction was then quenched by the addition of sat. aq  $\text{NH}_4\text{Cl}$ . The aqueous solution was extracted with  $\text{CH}_2\text{Cl}_2$  (3  $\times$  10 mL), the combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ), and the solvent was removed under reduced pressure. Pu-

rifification by flash chromatography (silica gel, petroleum ether–EtOAc, 8:2,  $R_f$  = 0.25) gave **8e** (298 mg, 77%) as a colorless solid; mp 163–165 °C.

IR (NaCl): 3081, 1671, 1602  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  = 10.32 (br s, 1 H, NH), 7.52 (m, 2 H,  $\text{H}_{2\text{ph}}$ ,  $\text{H}_{6\text{ph}}$ ), 7.33 (m, 2 H,  $\text{H}_{3\text{ph}}$ ,  $\text{H}_{5\text{ph}}$ ), 7.09 (m, 1 H,  $\text{H}_{4\text{ph}}$ ), 5.64 (s, 1 H,  $\text{I}_2\text{CH}$ ).

$^{13}\text{C}$  NMR (126 MHz, DMSO- $d_6$ ):  $\delta$  = 165.2 (C=O), 138.0 ( $\text{C}_{1\text{ph}}$ ), 128.9 ( $\text{C}_{3\text{ph}}$ ,  $\text{C}_{5\text{ph}}$ ), 124.0 ( $\text{C}_{4\text{ph}}$ ), 119.3 ( $\text{C}_{2\text{ph}}$ ,  $\text{C}_{6\text{ph}}$ ), –33.6 ( $\text{I}_2\text{CH}$ ).

$^{15}\text{N}$  NMR (40 MHz, DMSO- $d_6$ ):  $\delta$  = –260.3 (NH).

Anal. Calcd for  $\text{C}_8\text{H}_7\text{I}_2\text{NO}$ : C, 24.83; H, 1.82; N, 3.62. Found: C, 24.92; H, 1.86; N, 3.68.

### Synthesis of Optically Active Halomethylamides

#### (S)-2-Chloro-N-(1-phenylethyl)acetamide [(S)-4d]

By following GP1, starting from (S)- $\alpha$ -methylbenzyl isocyanate (96% ee) gave (S)-**4d** (721 mg, 96% ee). Spectroscopic data completely match those reported for the racemate **4d**.

HPLC (column: Chiralpak IA; *n*-hexane–*i*-PrOH, 95:5; 1 mL/min, 28 °C):  $t_R$  = 8.714 min [(R)-enantiomer, minor], 11.194 min [(S)-enantiomer, major]. Racemic sample:  $t_R$  = 9.173 min [(R)-enantiomer], 11.219 min [(S)-enantiomer].  $[\alpha]_D^{20}$  –56 (c 2,  $\text{CHCl}_3$ ).

#### (R)-2-Chloro-N-[1-(1-naphthyl)ethyl]acetamide [(R)-4e]

By following GP1, starting from (–)-(R)-1-(1-naphthyl)ethyl isocyanate (>99% ee purity) gave (R)-**4e** (910 mg, 97%); >99% ee. Spectroscopic data completely match those reported for the racemate **4e**.

HPLC (column: Chiralcel OD-H; *n*-hexane–*i*-PrOH, 80:20; 1 mL/min, 28 °C)  $t_R$  = 6.393 min [(R)-enantiomer, major], 11.586 min [(S)-enantiomer, minor]. Racemic sample:  $t_R$  = 6.481 min [(R)-enantiomer], 11.586 min [(S)-enantiomer];  $[\alpha]_D^{20}$  +68 (c 1.8,  $\text{CHCl}_3$ ).

#### 2-Chloro-N-[(1S)-2,3-dihydro-1H-inden-1-yl]acetamide [(S)-9a]

By following GP1, starting from (1S)-2,3-dihydro-1H-inden-1-yl isocyanate (320 mg, 2.0 mmol),  $\text{ICH}_2\text{Cl}$  (529 mg, 0.22 mL, 3.0 mmol), and MeLi–LiBr (1.60 mL, 2.4 mmol) in  $\text{Et}_2\text{O}$  gave (S)-**9a** (398 mg, 95%) as a white solid; >99% ee; mp 148–150 °C.

HPLC (column: Chiralpak IC; isohexane–*i*-PrOH, 95:5; 0.5 mL/min, 23 °C):  $t_R$  = 26.039 min [(R)-enantiomer, minor], 27.725 min [(S)-enantiomer, major]. Racemic sample:  $t_R$  = 26.031 min [(R)-enantiomer], 27.573 min [(S)-enantiomer];  $[\alpha]_D^{20}$  –21.4 (c 0.07,  $\text{CH}_2\text{Cl}_2$ ).

IR (NaCl): 1655, 1590, 1472  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.29 (m, 1 H,  $\text{H}_{7\text{indenyl}}$ ), 7.27 (m, 2 H,  $\text{H}_{4\text{indenyl}}$ ,  $\text{H}_{5\text{indenyl}}$ ), 7.25 (m, 1 H,  $\text{H}_{6\text{indenyl}}$ ), 6.79 (br s, 1 H, NH), 5.49 (q,  $J$  = 7.9 Hz, 1 H,  $\text{H}_{1\text{indenyl}}$ ), 4.12 and 4.09 (AB-system,  $^2J$  = 15.2 Hz, 2 H,  $\text{CH}_2\text{Cl}$ ), 3.02 (m, 1 H,  $\text{H}_{3\text{indenyl}}$ ), 2.90 (m, 1 H,  $\text{H}_{3'\text{indenyl}}$ ), 2.63 (m, 1 H,  $\text{H}_{2\text{indenyl}}$ ), 1.86 (m, 1 H,  $\text{H}_{2'\text{indenyl}}$ ).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 165.7 (C=O), 143.4 ( $\text{C}_{3a\text{indenyl}}$ ), 142.2 ( $\text{C}_{7a\text{indenyl}}$ ), 128.2 ( $\text{C}_{5\text{indenyl}}$ ), 126.9 ( $\text{C}_{6\text{indenyl}}$ ), 124.9 ( $\text{C}_{4\text{indenyl}}$ ), 123.9 ( $\text{C}_{7\text{indenyl}}$ ), 55.0 ( $\text{C}_{1\text{indenyl}}$ ), 42.6 ( $\text{ClCH}_2$ ), 33.8 ( $\text{C}_{2\text{indenyl}}$ ), 30.2 ( $\text{C}_{3\text{indenyl}}$ ).

$^{15}\text{N}$  NMR (40 MHz,  $\text{CDCl}_3$ ):  $\delta$  = –253.9 (NH).

Anal. Calcd for  $\text{C}_{11}\text{H}_{12}\text{ClNO}$ : C, 63.01; H, 5.77; N, 6.68. Found: C, 63.08; H, 5.83; N, 6.78.

#### 2-Chloro-N-[(2R)-3-methylbutan-2-yl]acetamide [(R)-9b]

By following GP1, starting from (2R)-3-methylbutan-2-yl isocyanate (0.26 mL, 226 mg, 2.0 mmol),  $\text{ICH}_2\text{Cl}$  (529 mg, 0.22 mL, 3.0 mmol), and MeLi–LiBr (1.60 mL, 2.4 mmol) in  $\text{Et}_2\text{O}$  gave (R)-**9b** (298 mg, 91%) as a white solid; 99% ee; mp 42–44 °C.

Chiral GC [Varian 3800 Gas Chromatographer, CP Chiralsil-DEX CB (25 m  $\times$  0.32 mm  $\times$  0.25 mm) capillary column; 90–170 °C]:  $t_R$  = 6.359 min [(S)-enantiomer, minor], 6.539 min [(R)-enantiomer,

major]. Racemic sample:  $t_R$  = 6.326 min [(S)-enantiomer], 6.544 min [(R)-enantiomer];  $[\alpha]_D^{20}$  –20.5 (c 1,  $\text{CH}_2\text{Cl}_2$ ).

IR (NaCl): 1652, 1595, 1468, 998  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 6.41 (br s, 1 H, NH), 4.03 (s, 2 H,  $\text{ClCH}_2$ ), 3.86 (m, 1 H,  $\text{NHCHCH}_3$ ), 1.72 (m, 1 H,  $\text{CH}_3\text{CHCH}_3$ ), 1.10 (d,  $J$  = 6.8 Hz, 3 H,  $\text{NHCHCH}_3$ ), 0.902 (d,  $J$  = 6.8 Hz, 3 H,  $\text{CH}_3\text{CHCH}_3$ ), 0.898 (d,  $J$  = 6.8 Hz, 3 H,  $\text{CH}_3\text{CHCH}_3$ ).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 165.0 (C=O), 50.5 ( $\text{CH}_3\text{CHNH}$ ), 42.8 ( $\text{ClCH}_2$ ), 32.8 ( $\text{CH}_3\text{CHCH}_3$ ), 18.35 ( $\text{CH}_3\text{CHCH}_3$ ), 18.31 ( $\text{CH}_3\text{CHCH}_3$ ), 17.3 ( $\text{NHCHCH}_3$ ).

$^{15}\text{N}$  NMR (40 MHz,  $\text{CDCl}_3$ ):  $\delta$  = –256.0 (NH).

Anal. Calcd for  $\text{C}_7\text{H}_{14}\text{ClNO}$ : C, 51.38; H, 8.62; N, 8.56. Found: C, 51.45; H, 8.73; N, 8.62.

#### trans-2-Chloro-N-(4-methylcyclohexyl)acetamide (trans-9c)

By following GP1, starting from *trans*-4-methylcyclohexyl isocyanate (0.27 mL, 278 mg, 2.0 mmol),  $\text{ICH}_2\text{Cl}$  (529 mg, 0.22 mL, 3.0 mmol), and MeLi–LiBr (1.60 mL, 2.4 mmol) in  $\text{Et}_2\text{O}$  gave *trans*-**9c** (345 mg, 91%) as a white solid; 99% ee; mp 98–100 °C.

Chiral GC [Varian 3800 Gas Chromatographer, CP Chiralsil-DEX CB (25 m  $\times$  0.32 mm  $\times$  0.25 mm) capillary column; 90–170 °C]:  $t_R$  = 12.447 min (*cis*-isomer, minor), 13.027 min (*trans*-isomer, major). Racemic sample:  $t_R$  = 12.447 min (*cis*-isomer), 12.932 min (*trans*-isomer).  $[\alpha]_D^{20}$  +5.9 (c 0.01,  $\text{CH}_2\text{Cl}_2$ ).

IR (NaCl): 1661, 1475, 1421  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 6.36 (br s, 1 H, NH), 4.00 (s, 2 H,  $\text{ClCH}_2$ ), 3.70 (m, 1 H,  $\text{H}_{1\text{cy}}$ ), 1.95 (m, 2 H,  $\text{H}_{2\text{cy}}$ ,  $\text{H}_{6\text{cy}}$ ), 1.72 (m, 2 H,  $\text{H}_{3\text{cy}}$ ,  $\text{H}_{5\text{cy}}$ ), 1.33 (m, 1 H,  $\text{H}_{4\text{cy}}$ ), 1.18 (m, 2 H,  $\text{H}_{2'\text{cy}}$ ,  $6'\text{cy}$ ), 1.04 (m, 2 H,  $\text{H}_{3'\text{cy}}$ ,  $\text{H}_{5'\text{cy}}$ ), 0.88 (d,  $J$  = 6.5 Hz, 3 H,  $\text{CH}_3$ ).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 164.9 (C=O), 48.9 ( $\text{C}_{1\text{cy}}$ ), 42.7 ( $\text{CH}_2\text{Cl}$ ), 33.6 ( $\text{C}_{3\text{cy}}$ ,  $\text{C}_{5\text{cy}}$ ), 32.8 ( $\text{C}_{2\text{cy}}$ ,  $\text{C}_{6\text{cy}}$ ), 31.8 ( $\text{C}_{4\text{cy}}$ ), 22.1 ( $\text{CH}_3$ ).

$^{15}\text{N}$  NMR (40 MHz,  $\text{CDCl}_3$ ):  $\delta$  = –252.7 (NH).

Anal. Calcd for  $\text{C}_9\text{H}_{16}\text{ClNO}$ : C, 56.99; H, 8.50; N, 7.38. Found: C, 57.10; H, 8.61; N, 7.46.

#### 2,2-Dichloro-N-[(1S)-1-phenylethyl]acetamide [(S)-9d]

By following GP3, starting from (1S)- $\alpha$ -methylbenzyl isocyanate (0.14 mL, 147 mg, 1.0 mmol, 96% ee) and  $\text{Cl}_2\text{CH}_2$  (647 mg, 0.33 mL, 5.0 mmol) gave (S)-**9d** (199 mg, 86%) as a colorless solid; 96% ee; mp 134–136 °C.

HPLC (Chiralpak IA; isohexane–*i*-PrOH, 95:5; 0.5 mL/min, 23 °C):  $t_R$  = 13.920 min [(S)-enantiomer, major], 15.337 min [(S)-enantiomer, minor]. Racemic sample:  $t_R$  = 13.824 min [(S)-enantiomer], 15.338 min [(R)-enantiomer].  $[\alpha]_D^{20}$  +44.5 (c 0.1,  $\text{CH}_2\text{Cl}_2$ ).

IR (NaCl): 1659, 1593, 1470  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.38 (m, 2 H,  $\text{H}_{3\text{ph}}$ ,  $\text{H}_{5\text{ph}}$ ), 7.33 (m, 2 H,  $\text{H}_{2\text{ph}}$ ,  $\text{H}_{6\text{ph}}$ ), 7.30 (m, 1 H,  $\text{H}_{4\text{ph}}$ ), 6.73 (br s, 1 H, NH), 5.91 (s, 1 H,  $\text{Cl}_2\text{CH}$ ), 5.09 (m, 1 H,  $\text{NHCHCH}_3$ ), 1.57 (d,  $J$  = 6.9 Hz, 3 H,  $\text{NHCHCH}_3$ ).

$^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 163.2 (C=O), 141.7 ( $\text{C}_{1\text{ph}}$ ), 128.9 ( $\text{C}_{3\text{ph}}$ ,  $\text{C}_{5\text{ph}}$ ), 127.8 ( $\text{C}_{4\text{ph}}$ ), 126.0 ( $\text{C}_{2\text{ph}}$ ,  $\text{C}_{6\text{ph}}$ ), 66.4 ( $\text{Cl}_2\text{CH}$ ), 49.8 ( $\text{NHCHCH}_3$ ), 21.3 ( $\text{NHCHCH}_3$ ).

$^{15}\text{N}$  NMR (40 MHz,  $\text{CDCl}_3$ ):  $\delta$  = –257.3 (NH).

Anal. Calcd for  $\text{C}_{10}\text{H}_{11}\text{Cl}_2\text{NO}$ : C, 51.75; H, 4.78; N, 6.03. Found: C, 51.83; H, 4.86; N 6.10.

### Synthesis of Ketone 11 According to Charette's Procedure<sup>39</sup>

To a solution of chloroacetamide **4a** (200 mg, 1.04 mmol, 1.0 equiv) in dry  $\text{CH}_2\text{Cl}_2$  (26 mL, concentration 0.044 M), was added 2-fluoropyridine (62 mg, 0.11 mL, 1.26 mmol, 1.1 equiv) and the resulting solution was cooled at –78 °C and stirred for 2 min.  $\text{TiF}_4$  (354 mg, 0.21 mL, 1.26 mmol, 1.1 equiv) was added dropwise at this tem-

perature and the mixture was then stirred for 10 min. The solution was warmed at 0 °C and the reaction was stirred for 20 min. The reaction was then cooled at –78 °C and a solution of 2.0 M BnMgCl in THF (1.04 mL, 2.08 mmol, 2.0 equiv) was added dropwise over 10 min and stirred for a further 50 min. The reaction was quenched with 0.5 M HCl (8 mL) and THF (8 mL). The biphasic system was warmed at 65 °C leaving the flask open for 2 h. After extraction of the organic phase with additional CH<sub>2</sub>Cl<sub>2</sub> (10 mL), the combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and the solvent removed under reduced pressure to give crude **11**. Chromatography (silica gel, petroleum ether–EtOAc, 95:5) gave pure chloro ketone **11**<sup>16a</sup> (152 mg, 87%) as a yellow oil.

IR (NaCl): 3082, 1737, 992, 897 cm<sup>–1</sup>.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 7.38–7.23 (m, 5 H), 4.13 (s, 2 H), 3.91 (s, 2 H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ = 199.1, 132.8, 129.4, 128.9, 127.5, 47.7, 46.8.

Anal. Calcd for C<sub>9</sub>H<sub>9</sub>ClO: C, 64.11; H, 5.38. Found: C, 64.29; H, 5.53.

**Supporting Information** for this article is available online at <http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000084>.

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*Publication n. 9*

**A robust, eco-friendly access to secondary thioamides through the addition of organolithium reagents to isothiocyanates in cyclopentyl methyl ether (CPME).**

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The Supporting Information is available on the website at  
[http://binarystore.wiley.com/store/10.1002/chem.201504247/asset/supinfo/chem\\_201504247\\_sm\\_miscellaneous\\_information.pdf?v=1&s=e964277bae863147d6c3d5f67a5b748fdaffe1d](http://binarystore.wiley.com/store/10.1002/chem.201504247/asset/supinfo/chem_201504247_sm_miscellaneous_information.pdf?v=1&s=e964277bae863147d6c3d5f67a5b748fdaffe1d)  
Details on experimental procedures, characterization data and copies of NMR spectra of all compounds are reported.



## Synthetic Methods

## A Robust, Eco-Friendly Access to Secondary Thioamides through the Addition of Organolithium Reagents to Isothiocyanates in Cyclopentyl Methyl Ether (CPME)

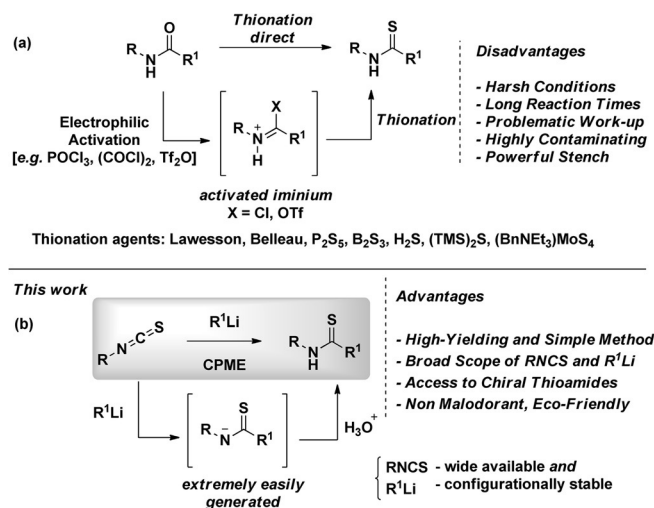
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Dedicated to Professor Norbert De Kimpe on the occasion of his retirement

**Abstract:** The nucleophilic addition of widely available and variously functionalized organolithium reagents to isothiocyanates represents a straightforward, high-yielding, one-pot method to access secondary thioamides. The simple reaction conditions required and the broad scope (> 50 cases examples) makes it a robust and reliable method to access both simple and complex thioamides, including enantiopure ones. Noxious and unpleasant-smelling sulfurating agents, usually employed in the literature established methods, are avoided during the whole synthetic procedure thus, rendering the protocol highly attractive, also for sustainability aspects.

Thioamides constitute a pivotal class of organic molecules, the chemo-, physico- and biological properties of which differ substantially from their corresponding oxoamide analogues.<sup>[1]</sup> The pronounced resonance stabilization in the thioamide moiety arising from the donation from the nonbonding nitrogen lone pair is increased by the high polarizability of the sulfur atom.<sup>[2]</sup> Unlike other thiocarbonyl derivatives, they present attractive features, such as stability, crystallizability, and the absence of unpleasant smells; thus, the combination of the chemical reactivity and the physical properties renders them highly valuable scaffolds across the chemical sciences.<sup>[3]</sup> Among the most striking advantages of using thioamides (in place of oxoamides), the feasibility of nucleophilic additions of reducing agents or organometallics to the electrophilic carbon (by the straightforward transformation into thioiminium salts) plays a prominent role, as showcased in elegant works by Murai and co-workers.<sup>[4]</sup>

Compared to the extensive studies available on amide-link syntheses, conceptual approaches towards thioamides are rather limited.<sup>[5]</sup> In fact, despite the huge, non-discussed importance, the most common methods for the synthesis of thioamides still relies on thionation (direct or by previous electrophilic activation)<sup>[6]</sup> of carboxamides with sulfurating agents, such as the Lawesson's reagent (Scheme 1 a).<sup>[7]</sup> The effectiveness of these



Scheme 1. Conceptually distinct approaches towards thioamides.

procedures is highly dependent on the harsh reaction conditions employed; in particular, the use of high-boiling-point solvents or even carcinogenic ones, such as hexamethylphosphoramide (HMPA), are frequently required to solubilize the sulfur source or to promote these long-time requiring reactions. Tedious work-up techniques and purifications, the persistent and powerful malodour together with the high toxicity of the reagents and chemoselectivity issues, severely limit the synthetic appeal of such non-uniformly high-yielding and expensive approaches. Sulfur incorporation through different techniques, such as the Willgerdt–Kindler reaction,<sup>[8]</sup> decarboxylative thioamidation,<sup>[9]</sup> and multicomponent reactions,<sup>[10]</sup> are often plagued by analogous drawbacks or by a limited functional-group tolerance.

In this scenario, an alternative approach involving the addition of a carbon nucleophile to an extremely electrophilic iso-

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thiocyanate can be envisaged. Although firstly illustrated by Worrall<sup>[11]</sup> and Gilman<sup>[12]</sup> in 1920s, the addition of organometallics to these electrophiles has not emerged as the method of choice for the synthesis of thioamides; unfortunately applications in organic synthesis are rare, thus obscuring the synthetic potential of the methodology.<sup>[13]</sup>

Considering the wide availability of both isothiocyanates and methods to prepare organolithium reagents (configurationally stable),<sup>[14]</sup> herein we report a robust protocol to prepare a broad series of thioamides, including enantiopure ones, through a simple nucleophilic addition (Scheme 1b). Key features of the method are: 1) uniform efficiency under mild conditions, and high yields regardless of the nature of the two reacting partners used; 2) obtention of the desired thioamides as the exclusive reaction products, thus simplifying the work-up and purification procedures; 3) absence of unpleasant odors during the whole reaction process; 4) use of cyclopentyl methyl ether<sup>[15]</sup> as the ideal reaction medium; and 5) retention of optical purity when chiral isothiocyanates and/or organolithium reagents are used.

Our investigations commenced by selecting the highly sterically hindered 1-adamantyl isothiocyanate **1** (Table 1) as the model substrate. Upon the addition of MeLi (2 equiv) in THF at 0 °C, the desired thioamide **2** was formed in a satisfactory isolated yield of 71% after a simple recrystallization (entry 1). Lowering the loading of the nucleophile to 1.5 or 1.0 equivalents decreased the yields, thus suggesting 2 equivalents as the ideal amount of the reactant (entries 1–3). Switching to a more apolar media, such as 2-MeTHF<sup>[16]</sup> and toluene (entries 4 and 5), benefited the reaction compared to polar solvents (entries 9 and 10). A further improvement and the best result was achieved by running the reaction in cyclopentyl methyl ether (CPME; entry 6),<sup>[15]</sup> which is an attractive alternative to classical ethereal solvents, such as THF and 1,4-dioxane.

**Table 1.** Model reaction optimization.<sup>[a]</sup>

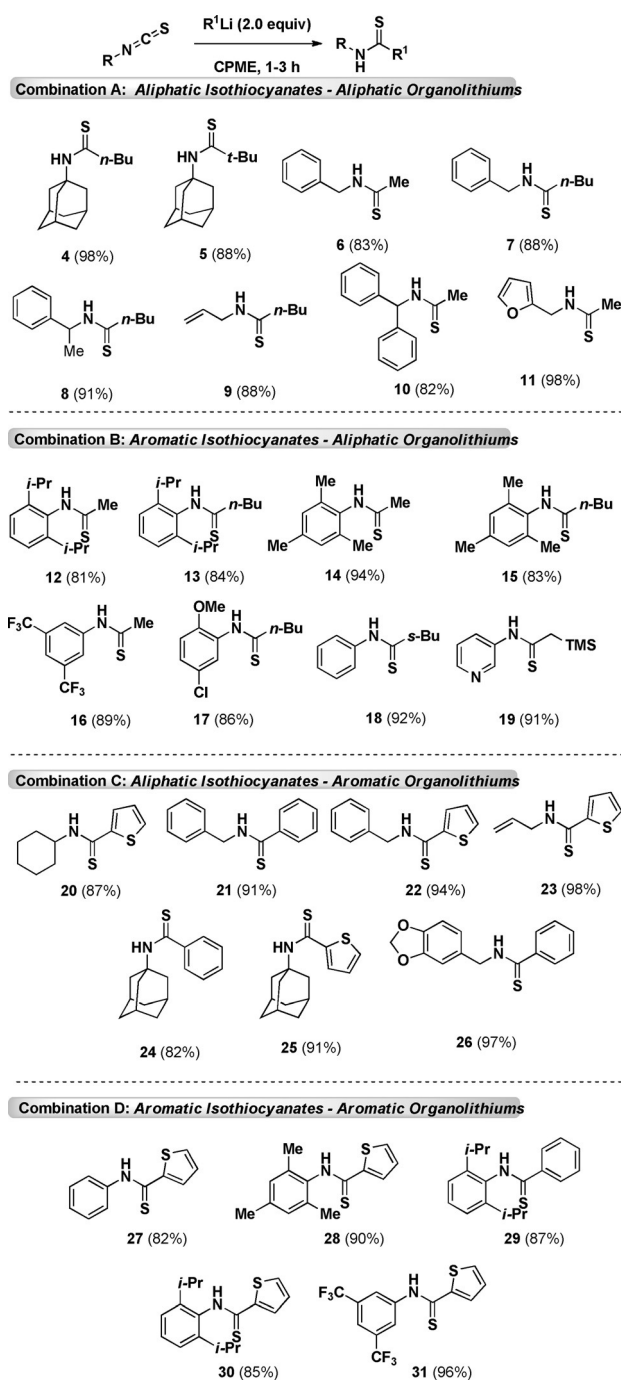
| Entry | MeLi [equiv] | Solvent <sup>[b]</sup> | T [°C]/t [h] | Isolated yield [%] |
|-------|--------------|------------------------|--------------|--------------------|
| 1     | 2.0          | THF                    | 0/1          | 71                 |
| 2     | 1.5          | THF                    | 0/1          | 65                 |
| 3     | 1.0          | THF                    | 0/1          | 59                 |
| 4     | 2.0          | 2-MeTHF                | 0/1          | 88                 |
| 5     | 2.0          | toluene                | 0/1          | 91                 |
| 6     | 2.0          | CPME                   | 0/1          | 98                 |
| 7     | 1.5          | CPME                   | 0/1          | 92                 |
| 8     | 1.0          | CPME                   | 0/1          | 84                 |
| 9     | 2.0          | 1,4-dioxane            | 0/1          | 75                 |
| 10    | 2.0          | Et <sub>2</sub> O      | 0/1          | 81                 |
| 11    | 2.0          | CPME                   | rt/1         | 85                 |

[a] See Experimental Section in the Supporting Information for details.

[b] THF = tetrahydrofuran, 2-MeTHF = 2-methyltetrahydrofuran, and CPME = cyclopentyl methyl ether.

Increasing the temperature up to 23 °C (rt, entry 11), resulted in a lower efficiency, thus revealing 0 °C as the optimal temperature.

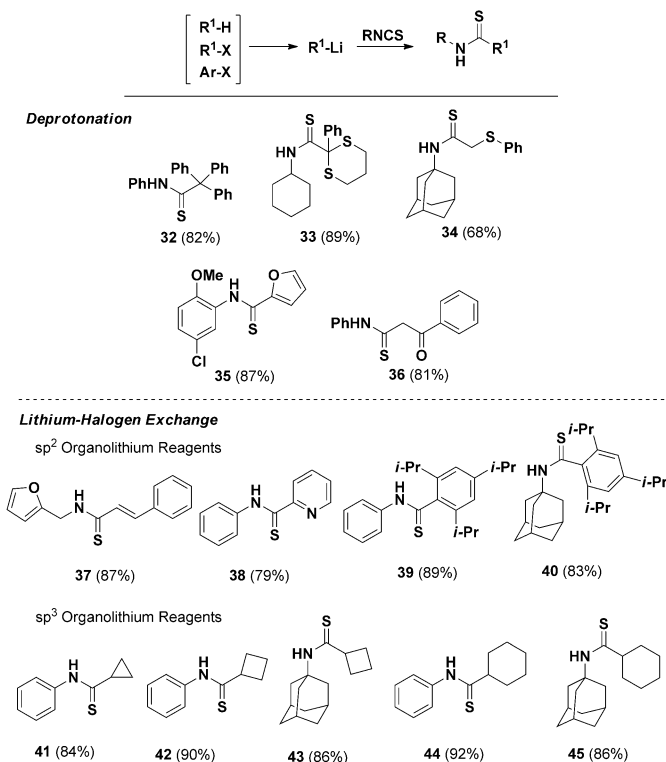
Once the optimal conditions for accessing thioamides from isothiocyanates and organolithium reagents were established, we next focused on the scope of the method. As presented in Scheme 2, the reaction of variously functionalized commercially available isothiocyanates with organolithium reagents afforded a wide range of thioamides (**4–31**) in very high yields after simple purification by recrystallization from CPME, thus



**Scheme 2.** Use of commercially available organolithium reagents in the syntheses of thioamides.

simplifying significantly the overall procedure. The observed reactivity is quite general, allowing the combination of reactions of both aliphatic and aromatic isothiocyanates with both types of organolithium reagents (combinations A–D). The steric hindrance on both sides of the reaction partners was perfectly tolerated and allowed to prepare sterically demanding thioamides (**4**, **5**, **12–15**, **24**, **25**, and **28–30**) in excellent yields. Analogously, (hetero)aromatic isothiocyanates containing different electron-donating or -withdrawing substituents were also viable and gave the corresponding products (**16**, **17**, and **31**). Allylic moieties (**9** and **19**) or heteroaromatic nuclei (**11**, **19**, **23**, and **26**) as substituents on the carbon-bearing isothiocyanates did not affect the feasibility of the process. The employment of a substituted alkyl lithium (**19**) or heteroaryl lithium (**20**, **22**, **23**, **25**, **27**, **28**, **30**, and **31**) species proceeded equally well. No enolization processes were detected during the addition of lithium reagents to isothiocyanates bearing acidic  $\alpha$ -protons (**10**).

The wide availability of established methods to generate organolithium reagents permits further expansion of the versatility of the protocol.<sup>[17]</sup> As such, we employed two common accesses to such reagents, namely deprotonation and lithium–halogen exchange (Scheme 3). Triphenylmethane (**32**), a thioacetal (**33**), thioanisole (**34**), furan (**35**), or an enolate (**36**) served as excellent pronucleophiles regardless of the electronic and/or steric features on the isothiocyanate. A lithium–halogen exchange method was employed to generate  $sp^2$  organolithium reagents; thus, the obtained styryllithium was smoothly added to a furyl-containing isothiocyanate to give the  $\alpha,\beta$ -unsaturat-

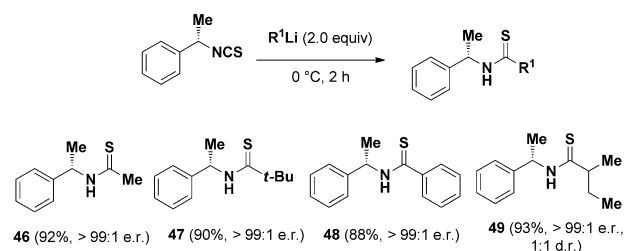


**Scheme 3.** Use of organolithium reagents, generated by deprotonation or lithium–halogen exchange methods.

ed thioamide **37** in high yield. Analogously, 2-lithiopyridine, which was obtained from the metalation of 2-bromopyridine, afforded compound **38** in 79% isolated yield. Of particular interest is the possibility to generate the highly sterically demanding 2,4,6-triisopropylphenyllithium, which was able to attack not only the simple phenylisothiocyanate yielding **39**, but also the 1-adamantyl congener, affording the thioamide **40**, which had not been previously reported. To the best of our knowledge, the latter represents one of the most bulky examples of thiocarbonyls known. The ease of addition was also evidenced by using  $sp^3$  lithium species as the corresponding cyclopropyl, cyclobutyl or cyclohexyl derivatives (**41–45**). It is worth remarking the independence of the effectiveness from the nature of both organolithium reagents and isothiocyanates employed. This is evidently a big advantage compared to procedures based on thionation methods, the effectiveness of which is also influenced by the not always smooth availability of the starting amides.

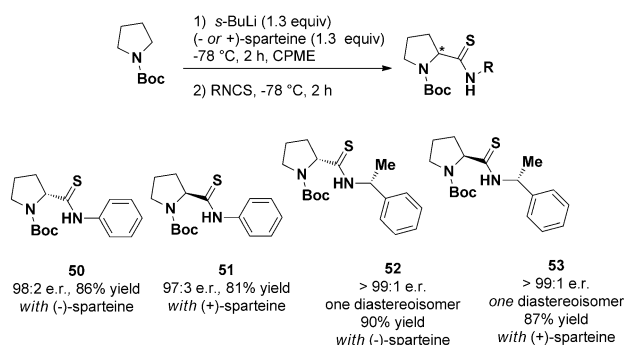
Optically active isothiocyanates underwent the addition of highly basic alkyl- or aryllithium reagents in excellent yields without loss of the chirality (Scheme 4, **46–49**).<sup>[18]</sup> Importantly, chiral lithiated species performed equally well in the nucleophilic addition, as showcased by the use of *N*-Boc-substituted pyrrolidine<sup>[19]</sup> in the formation of **50–53**, as well as Hoppe's carbamate (**54**),<sup>[20]</sup> which resulted in the isolation of compound

#### From Enantiopure Isothiocyanates

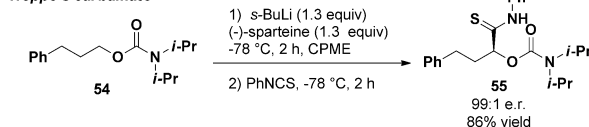


#### Use of Chiral Organolithium Reagents

##### *N*-Boc-pyrrolidine

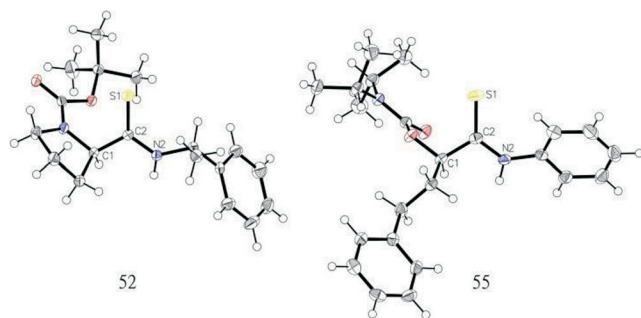


##### Hoppe's carbamate



**Scheme 4.** Addition to enantiopure isothiocyanates and employment of enantioenriched organolithium reagents.

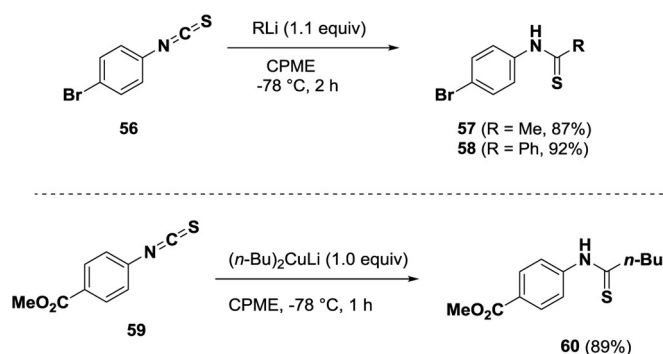
**55.** In both cases, the enantiopure  $\alpha$ -oxo and  $\alpha$ -amino functionalized carbanions were generated by (–)-sparteine-assisted deprotonation in CPME (98:2 to 99:1 e.r.).<sup>[21]</sup> The opposite enantiomers (**51** and **53**) could be prepared in analogous excellent enantiopurity by switching to (+)-sparteine. Finally, the addition of the generated chiral organolithium to an optically active isothiocyanate proceeded with an excellent diastereoselectivity (**52** and **53**). X-ray crystallography analyses of **50**, **52**, **53**, and **55** (Figure 1 and the Supporting Information) determined the absolute configuration of the newly formed carbon–carbon bond.



**Figure 1.** Molecular structures of **52** and **55** drawn with 50% displacement ellipsoids. According to the resulting chiral space group  $P2_12_12_1$  for both,  $C_1$  can be determined in *R* conformation (Flack<sub>52</sub> = –0.012(11), Flack<sub>55</sub> = 0.003(2)). Details about X-ray structure analysis<sup>[24]</sup> and further results for **50** and **53** can be found in the Supporting Information.

It should be highlighted how this protocol shows superior performances in terms of both synthetic economy and efficiency compared to previously reported preparations of 2-substituted pyrrolidinyll thioamides, which are organocatalyst precursors. In fact, Lawesson's reagent mediated thionation of the corresponding oxoamides occurred with uniformly lower yields and in the case of compound **51** with dramatic erosion of the enantiopurity down to 26% ee.<sup>[22]</sup>

To gain a definitive proof of the robustness of the method, the chemoselectivity of the process was investigated. Pleasingly, the addition of MeLi or PhLi to 4-bromoisothiocyanate (**56**) proceeded with an exclusive attack at the heterocumulene moiety at –78 °C, leaving the exchangeable aromatic bromide completely unaffected (Scheme 5). The excellent electrophilicity



**Scheme 5.** Study of the chemoselectivity.

of the isothiocyanate is also manifested in the chemoselective reaction with a mixed lithium–copper reagent [(*n*Bu)<sub>2</sub>CuLi].<sup>[23]</sup> This so-called Gilman reagent, presenting evidently a tamed nucleophilicity compared to a classical organolithium, is able to attack the isothiocyanate exclusively, regardless of the concomitant presence of an ester (**59**), providing the methoxycarbonyl-substituted thioamide (**60**).

In conclusion, we have reported a robust, highly efficient access to variously functionalized secondary thioamides through the addition of widely available or prepared organolithium reagents to isothiocyanates. The method is characterized by an excellent versatility, which renders it applicable to the synthesis of thioamides ranging from the simplest to sterically hindered and complex ones. Preservation of the enantiopurity when using chiral isothiocyanates or organolithium reagents further showcases its potential. A complete avoidance of noxious and unpleasant-smelling conventional thionating agents together with conducting the reaction in CPME maximizes the eco-compatibility of this otherwise limited synthetic process.

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**Keywords:** isothiocyanates • lithiation • nucleophilic addition • one-pot synthesis • thioamides

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- [24] CCDC 1418885 (**50**), 1418884 (**52**), 1418887 (**53**), and 1418886 (**55**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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**Chemoselective addition of halomethylolithiums to functionalized isatins: a straightforward access to spiro-epoxyoxindoles.**

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Details on experimental procedures, characterization data and copies of NMR spectra of all compounds are reported.



# Chemoselective Addition of Halomethylolithiums to Functionalized Isatins: A Straightforward Access to Spiro-Epoxyoxindoles

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**Abstract:** An efficient, chemoselective approach to spiro-epoxyoxindoles *via* the addition of chloromethylolithium followed by ring-closure of the intermediate alkoxide is reported. Chemoselectivity is fully preserved in the presence of different electrophilic sites. The synthetic potential of selected spiro-epoxyindoles has been exploited in the copper(I)-catalyzed intramolecular oxyarylation of an alkyne and in the formation of *N,N*-dimethylisoidingo *via* the addition of dihalocarbenoids.

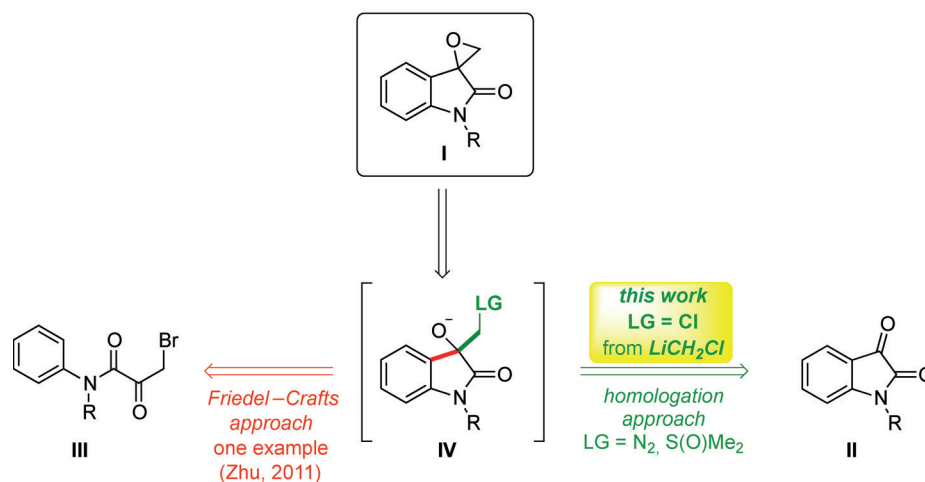
**Keywords:** carbenoids; chemoselectivity; epoxidation; Grignard reaction; homologation

Because of the structural relationship with the tryptamine nucleus, the 3,3-disubstituted 2-oxindole motif constitutes an important synthetic scaffold.<sup>[1]</sup> In particular, the presence of a spiro-type moiety at the 3-position of the oxindole provides a unique polycyclic system frequently found in natural products or in pharmacologically active structures.<sup>[2]</sup> Among the plethora of spiro-oxindoles known, a prominent position is occupied by the corresponding spiro-epoxy analogues, whose oxirane ring bestows not only a privileged molecular architecture but, also a highly reactive fragment.<sup>[2a,3]</sup> In recent years, the synthesis of spiro-epoxyoxindoles represented a significant challenge for the synthetic community and, in this sense the elegant work from the laboratories of Metzner and Brière opened the field to access them in a stereoselective fashion through Darzens-type processes carried out on an isatin derivative.<sup>[4]</sup> Further developments came from the work of Lu, Xiao and co-workers who achieved impressive levels of enantio- and diastereoselection by employing chiral sulfur ylides as methylene donors.<sup>[5]</sup> Moreover, truly asymmetric Dar-

zens reactions between *N*-protected isatins and phenacyl bromides have been disclosed by Feng in the presence of chiral *N,N'*-dioxide-Co(acac)<sub>2</sub> complexes.<sup>[6]</sup> On the other hand, non-substituted analogues (**I**, Scheme 1) constitute a less explored class of structures whose retrosynthetic analysis indicates the homologation of an isatin (**II**) as a conceptually simple approach to access them. Arndt and Eistert<sup>[7]</sup> pioneered the field of diazomethane-based homologations, however, as shown later by Capuano and Velter<sup>[8]</sup> and, more recently by Alcaide and Almen-dros (with TMSCHN<sub>2</sub>),<sup>[9]</sup> formation of rearranged products limits the appeal of this tactic. Alternatively, Howe,<sup>[10]</sup> Westwood,<sup>[11]</sup> Nair<sup>[12]</sup> and Hajra<sup>[13]</sup> applied the Corey–Chaykovsky epoxidation<sup>[14]</sup> to *simple, non-functionalized isatins*, although non-uniformly high yields were observed, probably depending on the specific nature of the substrate employed. As a consequence, to the best of our knowledge, chemoselectivity issues arising from the presence of concomitant reactive sites have not been addressed. A distinct retrosynthetic tactic developed in 2011 by Zhu and co-workers for providing a single example of spiro-epoxyoxindole relies on an intramolecular Friedel–Crafts process of an  $\alpha$ -oxo-*N*-anilide (**III**) assisted by trifluoroacetic acid followed by alkali treatment.<sup>[15]</sup> Effectively, the latter technique requires the formation of the anion of halohydrin (**IV**, LG = Br) which cyclizes to afford the desired spiro compound.

We postulated that accessing anion **IV** *via* an alternative disconnection would provide an effective and reliable route to the desired scaffolds starting from simple and easily obtainable materials such as isatins (**II**).<sup>[16]</sup> For such a purpose, the chemoselective addition of a lithium halocarbenoid<sup>[17]</sup> to the electrophilic ketone moiety of isatin appeared as a valuable alternative to Zhu's Friedel–Crafts tactic.<sup>[15]</sup> Should this strategy prove to be effective, a wide range of spiro-epoxyoxindoles could be accessed through a simple

Retrosynthetic analysis of unsubstituted spiro-epoxyoxindoles



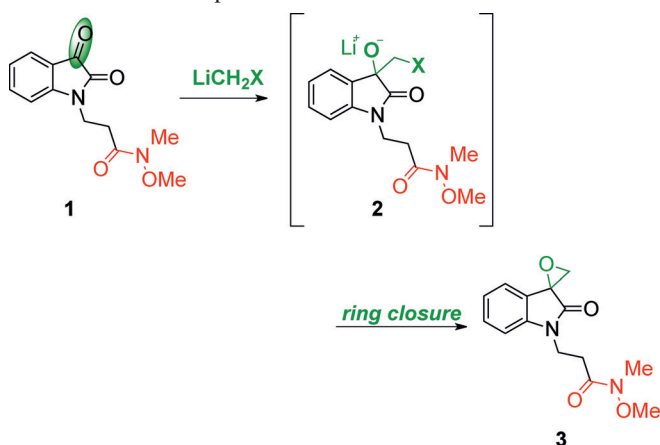
**Scheme 1.** Context of the presented work.

nucleophilic addition–cyclization sequence. The choice of halocarbenoids was motivated by their excellent versatility in homologation processes of various electrophiles as shown by ongoing research by ourselves<sup>[18]</sup> and others.<sup>[19]</sup> To ensure the effectiveness of halocarbenoids-based homologations, the following points should be considered: (i) by keeping the temperature at  $-78^{\circ}\text{C}$ <sup>[20]</sup> the inherent electrophilicity of the reagents is practically overcome and, consequently, the degradative  $\alpha$ -elimination processes<sup>[21]</sup> are avoided, thus allowing valuable applications in organic synthesis; (ii) their own basicity (and reactivity) may sometimes hamper the achievement of highly chemoselective transformations.<sup>[17c]</sup> With the aim to study the feasibility of the epoxidation and gaining further insights into the chemoselectivity<sup>[22]</sup> of the process, we selected the Weinreb amide-containing isatin **1** as the model substrate. We wondered if the concomitant presence of this functionality<sup>[23]</sup> – known to be an excellent substrate for carbenoids homologations<sup>[18a,c,f]</sup> – would interfere with the challenging transformation we were looking for. By using the standard Barbier-type conditions for the generation of chloromethylolithium (1.3 equiv.) in THF, followed by increasing the temperature up to room temperature,<sup>[19r]</sup> the desired epoxide **3** was obtained in 73% isolated yield (Table 1, entry 1). Further optimization followed and we found that the use of 2.5 equiv. of carbenoid generated from 3.0 equiv. of chloriodomethane and 2.5 equiv. of MeLi–LiBr improved the yield up to 83% (entries 2–4). Remarkably, when the reaction was quenched with saturated aqueous ammonium chloride and, thereafter smoothly redissolved in acetonitrile and treated with potassium carbonate overnight, the desired epoxide **3** could be isolated in an excellent 94% yield (entry 5). Interestingly, the use of a less nucleophilic magnesium carbenoid did not pro-

vide any product (entry 7).<sup>[24]</sup> The versatility of this method was apparent also in the case of homologating the isatin with analogous bromo- and iodomethylolithiums<sup>[25]</sup> (entries 8–11): analogously, it was preferable to realize the ring-closure on the crude halohydrins instead of the one-pot process, thus suggesting the possibility of a deleterious effect of the degradation products of the carbenoids and/or of the organometallics. Some points merit mention: (i) the nucleophilic  $\text{LiCH}_2\text{Cl}$  reacts exclusively at the isatin carbonyl without any concomitant attack on the Weinreb amide site (even when using an excess of  $\text{LiCH}_2\text{Cl}$ , entry 6); (ii) this unexpected behaviour can be attributed to the high electrophilicity of the isatin carbon compared to the Weinreb amide one. Importantly, by scaling up to a 10 mmol scale, the procedure maintains its features (chemoselectivity and efficiency, entry 12). The desired epoxide **3** proved to be highly unstable during silica gel (eventually deactivated with 1–4%  $\text{NEt}_3$  or 1%  $\text{TMSCl}$ ) chromatographic purifications; finally, we found it highly beneficial to perform chromatography on neutral alumina (Brockmann degree IV) and employing benzene- $d_6$  as the best solvent medium for the NMR recordings in order to avoid any decomposition.

With the optimized conditions in hand, the scope of the reaction was subsequently investigated. As indicated in Scheme 2, the protocol allows us to prepare spiro-epoxyoxindoles presenting a wide range of functionalities both on the nitrogen and the aromatic ring of the isatin core. Accordingly, aliphatic (**5a–d**), aromatic (**5e**) allylic (**5f**), and alkynyl (**5g**, **5h**) moieties can be present therein, thus affording the desired targets in uniformly high yields. The full chemoselectivity for the attack of the carbenoid at the isatin carbonyl was further evidenced in the case of esters (**5i**, **5j**), Weinreb amide **5k** (i.e., the shortened homologue of

**Table 1.** Reaction optimization.<sup>[a]</sup>



**Conditions A:**  $-78^\circ\text{C}$  to r.t., 1–12 h.

**Conditions B:** 1)  $\text{NH}_4\text{Cl}$  (aq.) [ $\text{O}^-\text{Li}^+ \rightarrow \text{OH}$ ];

2)  $\text{K}_2\text{CO}_3$  (1.5 equiv.), MeCN, overnight.

| Entry             | $\text{LiCH}_2\text{X}$<br>[equiv.] | Work-up Condi-<br>tions | Yield of <b>3</b><br>[%] <sup>[b]</sup> |
|-------------------|-------------------------------------|-------------------------|-----------------------------------------|
| 1                 | 1.3 (X=Cl)                          | <b>A</b>                | 73                                      |
| 2                 | 1.0 (X=Cl)                          | <b>A</b>                | 64                                      |
| 3                 | 2.0 (X=Cl)                          | <b>A</b>                | 80                                      |
| 4                 | 2.5 (X=Cl)                          | <b>A</b>                | 83                                      |
| 5                 | 2.5 (X=Cl)                          | <b>B</b>                | 94                                      |
| 6                 | 4.0 (X=Cl)                          | <b>B</b>                | 92                                      |
| 7 <sup>[c]</sup>  | 2.5 (X=Cl)                          | <b>B</b>                | — <sup>[d]</sup>                        |
| 8 <sup>[e]</sup>  | 2.5 (X=Br)                          | <b>A</b>                | 75                                      |
| 9 <sup>[e]</sup>  | 2.5 (X=Br)                          | <b>B</b>                | 85                                      |
| 10 <sup>[f]</sup> | 2.5 (X=I)                           | <b>A</b>                | 71                                      |
| 11 <sup>[f]</sup> | 2.5 (X=I)                           | <b>B</b>                | 80                                      |
| 12 <sup>[g]</sup> | 2.5 (X=Cl)                          | <b>B</b>                | 89                                      |

<sup>[a]</sup> Unless otherwise indicated  $\text{LiCH}_2\text{Cl}$  was generated from  $\text{ICH}_2\text{Cl}$  and  $\text{MeLi-LiBr}$ .

<sup>[b]</sup> Isolated yield.

<sup>[c]</sup>  $\text{ClCH}_2\text{MgCl-LiCl}$  was used.

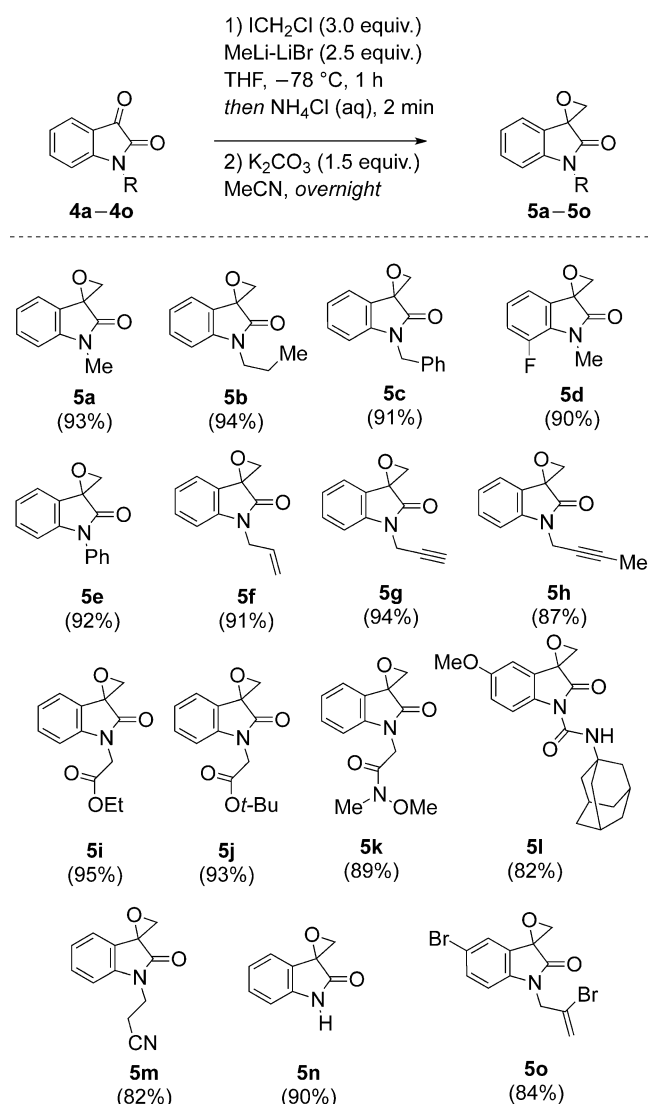
<sup>[d]</sup> Compound **1** was completely recovered.

<sup>[e]</sup> Generated from  $\text{ICH}_2\text{Br}$ .

<sup>[f]</sup> Generated from  $\text{CH}_2\text{I}_2$ .

<sup>[g]</sup> On a 10 mmol scale.

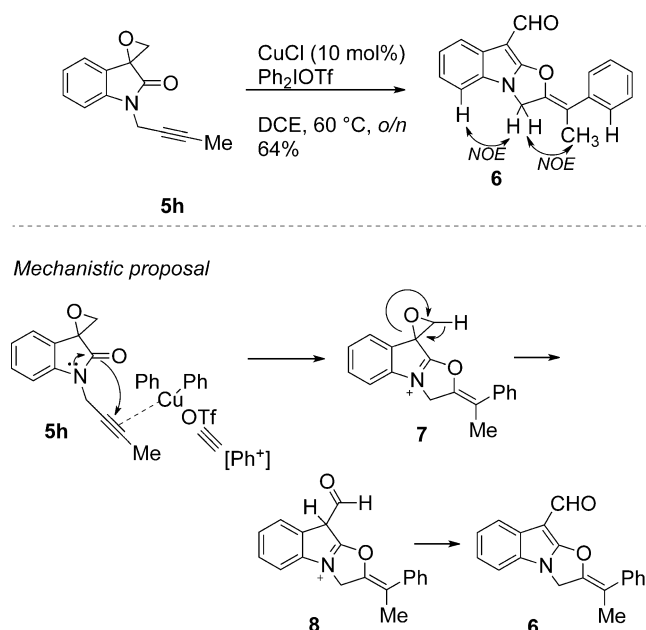
**1**), amide **5l** and nitrile **5m**. It is worth highlighting the success in the reaction involving the simple (unprotected) isatin **5n**; in fact, as previously reported, substrates bearing acidic protons are reluctant to undergo carbenoid additions in the absence of a suitable protection group.<sup>[18c,26]</sup> It is conceivable that the carbenoid (acting as a base) firstly abstracts the proton giving a lithiated lactam which in turn is attacked by the chloromethylenic reagent. Furthermore, the presence of two easily exchangeable bromines placed simultaneously on the aromatic ring and the allylic moiety (**5o**) does not influence even minimally the iodine–lithium exchange (on  $\text{ICH}_2\text{Cl}$ ) required to form the reactive carbenoid.



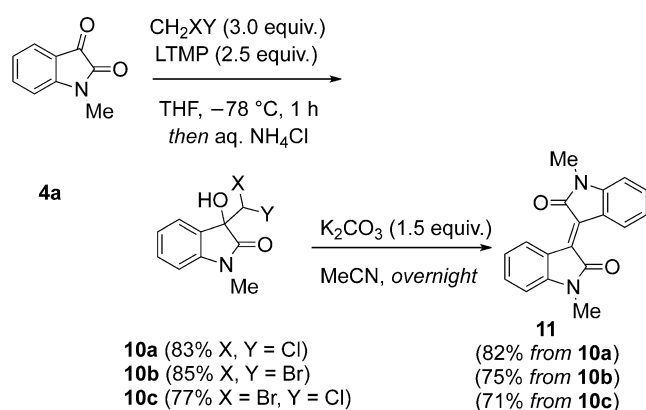
**Scheme 2.** Scope of the method.

To exploit the synthetic potential offered by functionalized spiro-epoxyoxindoles, we evaluated the copper-catalyzed functionalization of alkynes with diphenyliodonium triflate elegantly introduced by Gaunt in 2013 (Scheme 3).<sup>[27]</sup> Accordingly, by using the established conditions on compound **5h**, the complex tricyclic compound **6** was obtained as the unique reaction product in 64% yield. Mechanistically, we propose the intramolecular oxyarylation<sup>[27c,28]</sup> of the propargyl-containing spiro-epoxyoxindole giving the epoxy-iminium structure **7**, susceptible to Lewis acid-promoted isomerization to the corresponding aldehyde **8** which, upon rearomatization, affords **6**. The *Z*-configuration at the exocyclic  $\text{C}=\text{C}$  bond of the latter was unambiguously established by NOE experiments.

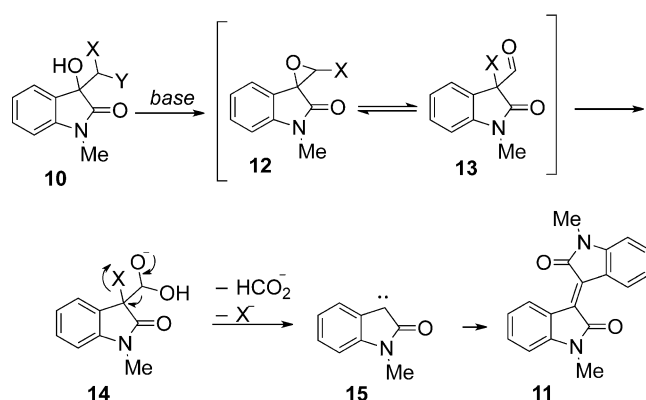
To expand the overview of the addition of carbenoids reagents to isatin derivatives, we also evaluated the reactivity of dihalomethylcarbenoids [ $\text{LiCHCl}_2$ ,



**Scheme 3.** Intramolecular electrophilic oxyarylation of a propargyl-substituted spiro-epoxyoxindole.



*Plausible mechanism*



**Scheme 4.** Obtainment of an indigo-type compound from the rearrangement of unstable  $\alpha$ -haloepoxide formed upon the addition of dihalocarbonyls to *N*-methylisatin.

LiCHBr<sub>2</sub> and LiCHBrCl – generated *via* the LTMP (lithium 2,2,6,6-tetramethylpiperide)-mediated de-

protonation of the corresponding dihalomethanes, Scheme 4].<sup>[18e]</sup> By employing the usual procedure (carbenoid addition–ring closure) we observed the exclusive formation of the interesting *N,N*-dimethylisindigo structure **11**.<sup>[29]</sup> An analogous outcome was evidenced by running the ring closure on analytically pure isolated dihalohydrins **10a–c** or, by modifying reaction parameters such as the nature of the base (NEt<sub>3</sub>, KF-Celite,<sup>[30]</sup> LHDMS), the solvent (CH<sub>2</sub>Cl<sub>2</sub>, MeOH, DMF) or the temperature (–78 °C). Considering the relative instability of the initially formed  $\alpha$ -haloepoxide **12** which might easily isomerize to the  $\alpha$ -haloaldehyde **13**,<sup>[31]</sup> it can be assumed that the base attacks the carbonyl giving the intermediate **14**, which, upon elimination of formate and halide provides a free carbene **15** able to dimerize. The *E*-configuration at the central double bond of *N,N'*-dimethylisindigo (**11**) unambiguously follows from the exceptionally large chemical shift of indole H-4 (and *vice versa* H-4')<sup>[32]</sup> ( $\delta$  = 9.80 ppm in C<sub>6</sub>D<sub>6</sub>, for comparison: the <sup>1</sup>H NMR chemical shift for H-4 in *N*-methylisatin is 7.57 ppm)<sup>[15b]</sup> which can be easily explained by the spatial closeness of this proton and the C=O group of the neighbouring ring which leads to a marked deshielding due to the anisotropy of the magnetic susceptibility of the C=O bond.

In conclusion, an efficient chemoselective access to rare spiro-epoxyoxindoles has been developed through the addition of the carbenoid chloromethyl-lithium to various *N*-functionalized isatins followed by the ring closure. The protocol showcases an excellent scope and the chemoselectivity is fully maintained in the presence of additional electrophilic functionalities such as Weinreb amide, ester, nitrile, exchangeable bromine, or acidic secondary lactam. Analogous additions of dihalocarbonyls afford indigo-type structures through the rearrangement of unstable  $\alpha$ -haloepoxides, while Gaunt's Cu-catalyzed intramolecular electrophilic oxyarylation of an *N*-propargyl-type spiro-epoxyoxindole affords a complex tricyclic system.

## Experimental Section

### General Procedure

To a cooled (–78 °C) solution of the appropriate isatin (1.0 equiv.) in dry THF (0.5 M concentration) was added chloriodomethane (3 equiv.). After 2 min, an ethereal 2.2 M solution of MeLi–LiBr (2.5 equiv.) was added dropwise over 5 min. The resulting solution was stirred for 1 h at that temperature. After quenching with saturated aqueous NH<sub>4</sub>Cl at –78 °C, the cooling bath was removed and, the mixture was stirred until it reached room temperature. After adding diethyl ether, the resulting organic phase was extracted (with brine), dried over Na<sub>2</sub>SO<sub>4</sub> and, finally the solvent was removed under vacuum. The resulting crude



mixture was re-dissolved in acetonitrile and potassium carbonate (1.5 equiv.) was added. The so obtained suspension was stirred at room temperature overnight; then, water and diethyl ether were added and, after extraction of the organic phase, drying over  $\text{Na}_2\text{SO}_4$ , and filtering, the solvent was removed under vacuum. The resulting crude compounds were purified through neutral alumina chromatography (Brockmann degree IV).

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- [32] See the Supporting Information.

*Publication n. 11*

**Eco-friendly chemoselective *N*-functionalization of isatins mediated by supported KF in 2-MeTHF.**

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Details on experimental procedures, characterization data and copies of NMR spectra of all compounds are reported.



## COMMUNICATION



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## Eco-friendly chemoselective *N*-functionalization of isatins mediated by supported KF in 2-MeTHF†

Ashenafi Damtew Mamuye,‡ Serena Monticelli,‡ Laura Castoldi, Wolfgang Holzer and Vittorio Pace\*

**A sustainable, efficient method for the chemoselective *N*-functionalization of isatins based on the use of KF-Celite in 2-methyltetrahydrofuran is reported. Notably, the protocol allows reactions with a wide range of electrophiles such as alkyl halides, isocyanates and Michael acceptors.**

The *N*-functionalization of amides or their cyclic analogues – lactams – through the introduction of a carbon chain constitutes one of the most common operations in organic synthesis.<sup>1</sup> The operation resembles analogous functionalization protocols observed in peptide chemistry.<sup>2</sup> In this sense, it can be regarded as a conceptually simple transformation which would allow the replacement of a hydrogen with a carbon-containing moiety. It is rather common to perform such reactions under basic conditions which would render the nitrogen nucleophilic enough to carry out the desired N–C bond formation.<sup>3</sup> In this scenario a prominent role is played by isatins (1*H*-indole-2,3-diones), a naturally occurring nucleus first isolated in plants of genus *Isatis*, *Calanthe discolor* and *Couropita guianensis*, often expressed in biologically active substances.<sup>4</sup> The synthesis of complex isatins through a simple and direct *N*-functionalization-type tactic appears preferable over conceptually distinct approaches due to the wide commercial availability of the starting secondary isatins (*i.e.* bearing a N–H group) at competitive prices. In fact, preparative methods based on the use of anilines as starting materials (*e.g.* Sandmeyer-type and related approaches)<sup>4b</sup> present the following disadvantages: (i) the sustainable impact is severely hampered – this being a clear violation of both the 3<sup>rd</sup> (less hazardous chemical synthesis) and 4<sup>th</sup> (designing safer chemicals) principles of Green Chemistry<sup>5</sup> – as a consequence of the employment of toxic, and environmentally problematic acylating reagents (*e.g.* chloral); and (ii) accessing *N*-alkyl substrates might represent a

significant challenge in the synthetic route. As observed by Page and co-workers, a critical and challenging issue associated with a base-mediated *N*-functionalization of isatins is the possibility of hydrolyzing the lactam moiety and thus, particular care should be taken in the choice of the base.<sup>6</sup> Motivated by our commitment to design and develop chemical processes with low environmental impact, recently our group reported the use of coated potassium fluoride<sup>7</sup> for the functionalization of amines,<sup>8</sup> imides,<sup>9</sup> thiols<sup>10</sup> or acidic carbons.<sup>11</sup> Interestingly, in the case of imides<sup>9</sup> efficiency benefited from running the reactions in 2-methyltetrahydrofuran (2-MeTHF) which represents a valuable alternative<sup>12</sup> to the normally used ethereal solvents in organic synthesis.<sup>13</sup> In particular, there has been a growing interest towards this medium as a consequence of its adherence with several Anastas' Green Chemistry principles.<sup>5</sup> Among them, the 5<sup>th</sup> (safer solvents and auxiliaries) and the 7<sup>th</sup> (use of renewable feedstocks – *cfr.* it is derived from corn-cobs and bagasse)<sup>14</sup> principles are usually invoked in support of its eco-compatibility. Key properties<sup>13c,15</sup> which contribute to straighten its appeal as a green solvent can be summarized as follows: (a) the immiscibility with water offers to obtain reaction crudes without the employment of common organic solvents (hydrocarbons, halogenated ones, ethers or esters) during the work-up procedures; (b) the higher boiling point (compared to THF) allows for running processes at temperatures which would minimize reaction times; and (c) transformations involving organometallics are not plagued by the well-known (thermal) instability of ethereal solvents to these reagents. In recent years, Antonucci *et al.*<sup>16</sup> reported minimal toxicological risks associated with the use of 2-MeTHF thus, underlining its ability in fine-chemical synthesis. These undoubtable potentialities of the solvent jointly with often improved efficiency in terms of chemical yield or enantioselectivities (compared to classical ethereal solvents) favoured in recent years its widespread use in different areas ranging from biocatalysis,<sup>17</sup> to carbanion<sup>18</sup> and organometallic<sup>19</sup> chemistries or heteroatom functionalizations.<sup>20</sup>

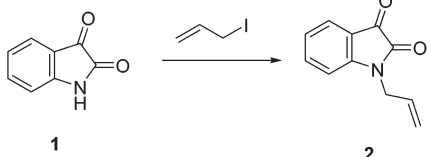
Given these premises, we wondered if the combination of KF-Celite and 2-MeTHF could be used for accomplishing the

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Table 1 Optimization of the *N*-allylation reaction<sup>a</sup>

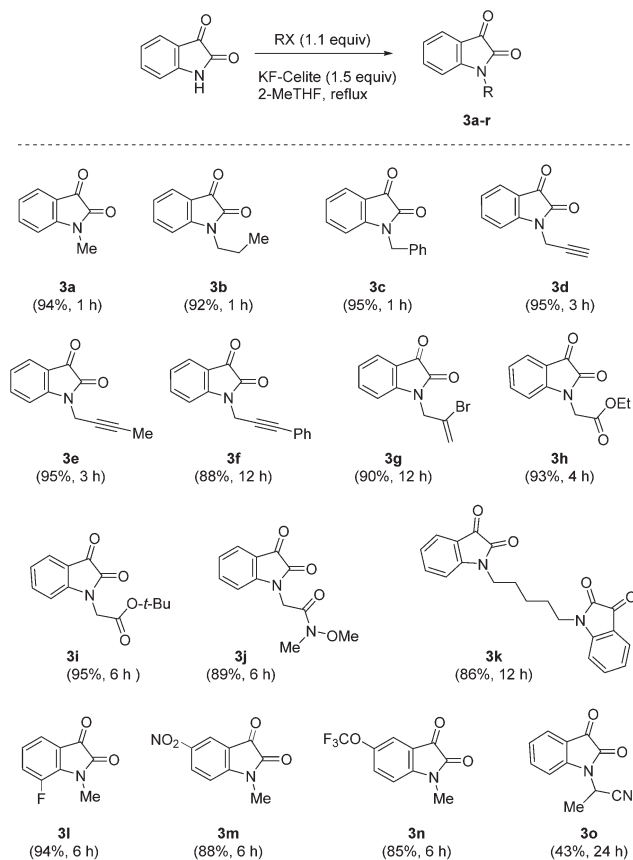
|  |                                 |                                   |                                        |                                    |
|-----------------------------------------------------------------------------------|---------------------------------|-----------------------------------|----------------------------------------|------------------------------------|
| Entry                                                                             | Solvent                         | Base (equiv.)                     | Temperature (°C)/<br>reaction time (h) | Yield of <b>2</b> <sup>b</sup> (%) |
| 1                                                                                 | 2-MeTHF                         | KF-Celite                         | 83/2                                   | 97                                 |
| 2 <sup>c</sup>                                                                    | 2-MeTHF                         | KF-Celite                         | 83/4                                   | 88                                 |
| 3 <sup>d</sup>                                                                    | 2-MeTHF                         | KF-Celite                         | 83/1                                   | 96                                 |
| 4                                                                                 | 2-MeTHF                         | KF-Celite                         | rt/6                                   | 85                                 |
| 5                                                                                 | CPME                            | KF-Celite                         | 90/4                                   | 81                                 |
| 6                                                                                 | DMF                             | KF-Celite                         | 90/3                                   | 91                                 |
| 7                                                                                 | MeCN                            | KF-Celite                         | 83/3                                   | 93                                 |
| 8                                                                                 | 1,4-Dioxane                     | KF-Celite                         | 90/6                                   | 74                                 |
| 9                                                                                 | Acetone                         | KF-Celite                         | 55/5                                   | 88                                 |
| 10                                                                                | CH <sub>2</sub> Cl <sub>2</sub> | KF-Celite                         | 45/8                                   | 47                                 |
| 11                                                                                | AcOEt                           | KF-Celite                         | 77/8                                   | 55                                 |
| 12                                                                                | Toluene                         | KF-Celite                         | 90/12                                  | 41                                 |
| 13                                                                                | 2-MeTHF                         | KF-Al <sub>2</sub> O <sub>3</sub> | 83/6                                   | 84                                 |
| 14                                                                                | 2-MeTHF                         | K <sub>2</sub> CO <sub>3</sub>    | 83/6                                   | 89                                 |
| 15                                                                                | 2-MeTHF                         | K <sub>3</sub> PO <sub>4</sub>    | 83/6                                   | 84                                 |

<sup>a</sup> Otherwise stated 1.5 equiv. of base were used. <sup>b</sup> Isolated yield.

<sup>c</sup> KF-Celite (1.0 equiv.). <sup>d</sup> KF-Celite (2.0 equiv.).

chemoselective *N*-functionalization of isatins and, herein we report the results of our investigations.

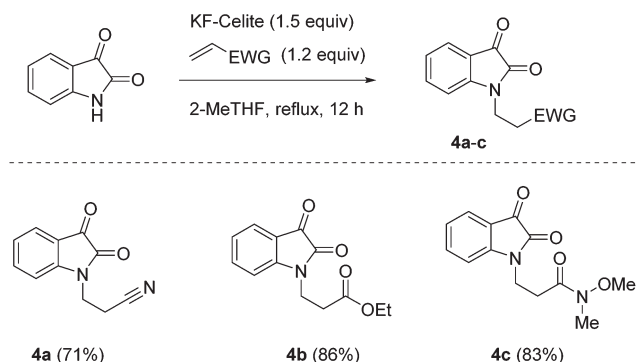
The *N*-allylation of isatin (**1**) was selected as the model reaction (Table 1): it shows a high degree of dependence on the solvent employed. The superiority of the eco-friendly aprotic 2-MeTHF compared to other solvents such as CPME, DMF, MeCN, 1,4-dioxane, acetone, DCM, ethyl acetate or toluene (entries 5–12) appears evident regardless of the temperature used. Reactions run in this solvent reached completion within 4 h (entries 1–3), although the use of a small excess (1.5 equiv.) of the coated base allowed to shorten the reaction time to 2 h (entry 1). In this sense, by increasing the loading of the base to 2.0 equiv. (entry 3) does not alter the positive outcome: thus, the employment of 1.5 equiv. can be considered an excellent compromise between the efficiency of the process and related costs. Running the reactions at higher temperatures improves the yields considerably (entry 1 vs. 4) and contemporaneously, contributes to minimize the time. The relatively high boiling point (83 °C) which in combination with its apolarity maximizes the efficiency – by minimizing *inter alia* the time to reach completion – of the process. Remarkably, the use of Celite as a support for the base does not alter the basicity of the resulting reagent,<sup>7b,21</sup> in contrast to analogous operations involving *per se* basic supports such as Al<sub>2</sub>O<sub>3</sub>.<sup>22</sup> It is worth noting that under the reaction conditions no isomerisation of the double bond takes place, thus illustrating the excellent chemoselective profile of the protocol. An additional crucial point makes the procedure ideal for sustainability purposes: the work-up of the reaction simply consists in filtering-off the coated base and removing the solvent under reduced pressure.



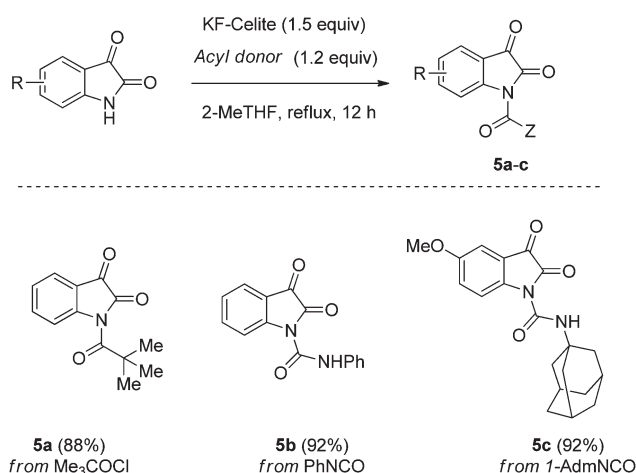
Scheme 1 Alkylation of isatins: scope of the reaction.

After careful washing with the same 2-MeTHF, the filtered KF-Celite still maintains its activity as a base albeit with lower efficiency (82%). The analytically pure compound is obtained by re-crystallization from another so-called green solvent such as cyclopentyl methyl ether (CPME)<sup>23</sup> thus, avoiding contaminating and time-consuming chromatographic purifications.

With the optimized conditions in hand, the scope of the reaction was subsequently determined. As indicated in Scheme 1, the protocol allows to alkylate the isatins' nitrogen with a wide range of functionalized electrophiles ranging from simple ones (*e.g.* benzyl, alkynylmethyl, bromoallyl, **3a–g**) to more complex species incorporating electron-withdrawing functionalities able to increase the acidity of vicinal protons (esters, Weinreb amides, **3h–j**). In this latter context, the mildness of the base used preserves the chemoselectivity of the reaction. A bis-electrophilic reagent such as 1,5-dibromopentane reacts with isatin at both methylenic positions, thus providing in high yield the linked bis-isatin **3k**. The presence of substituents on the aromatic ring of isatins obviously does not influence the efficiency of the reaction regardless of the electronic behaviour of the functional groups involved (**3l–n**). The alkylation with a multi-functionalized secondary halide such as 2-bromopropionitrile proceeds with lower yield compared to the primary analogue (**3o**) because of the inherent lower reactivity of this particular secondary alkyl halide.



**Scheme 2** Isatin functionalizations with Michael-type acceptors.



**Scheme 3** Acylation of isatins with different acyl donors.

The robustness of the developed method appears evident in conjugate additions which, as previously reported, have been problematic when performed under different conditions. Michael-type acceptors such as  $\alpha,\beta$ -unsaturated nitriles (**4a**), esters (**4b**), and Weinreb amides (**4c**) can be employed, thus delivering the resulting  $\beta$ -functionalized adducts **4a-c** in high yield. Importantly, no concomitant 1,2-additions take place as evidenced by the  $^1\text{H}$ -NMR analysis of the reaction crudes (Scheme 2).

The effectiveness of the protocol was further showcased by the synthesis of urea-type adducts through the addition of isatin-type anions to isocyanates (Scheme 3): pleasingly, even the highly sterically hindered adamantyl isocyanate is suitable for the transformation, giving compound **5c** in high yield. Moreover, the procedure can be adapted for the synthesis of  $\alpha$ -oxoimide **5a** from pivaloyl chloride, thus expanding the versatility of the method to the formation of acylated products.

## Conclusions

In conclusion, an efficient *N*-functionalization of isatin derivatives promoted by the combination of the coated base

KF-Celite and the biomass derived solvent 2-MeTHF has been disclosed. The high yielding method shows excellent versatility and applicability to different electrophilic agents ranging from simple primary alkyl halides to isocyanates, acyl halides or Michael acceptors. Notably, crystallization from the green solvent cyclopentyl methyl ether affords analytically pure substances thus, avoiding the need to perform chromatographic purifications.

## Acknowledgements

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*Publication n. 12*

**Chemoselective additions of chloromethyl lithium carbenoid to cyclic enones: a direct access to chloromethyl allylic alcohols.**

Pace, V.;\* Castoldi, L.; Holzer, W.

*Adv. Synth. Catal.* **2014**, 356, 1761-1766 (DOI: 10.1002/adsc.201301042)

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Details on experimental procedures, characterization data and copies of NMR spectra of all compounds are reported.





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

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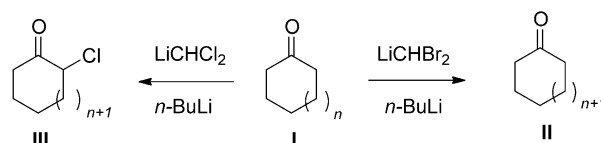
**Abstract:** Chloromethylithium carbenoid has been chemoselectively added to cyclic enones (5-, 6- and 7-membered systems, including two natural products) to provide chloromethyl allylic alcohols. Under the optimized reaction conditions neither concomitant ( $n+1$ ) homologation nor conjugate addition 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  $\beta$ -heteroatom-containing substituents promotes the attack of the reagent at the most activated position.

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

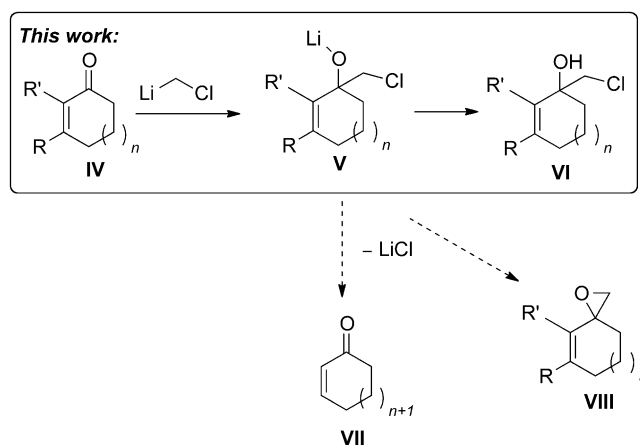
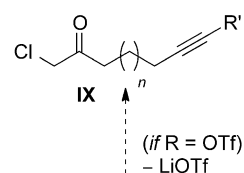
Cyclic ketones are ubiquitous motifs in nature and from a synthetic perspective they constitute versatile building blocks susceptible of multiple transformations.<sup>[1]</sup> In particular, the reaction with functionalized carbon nucleophiles (e.g., sulphur ylides,<sup>[2]</sup> diazo compounds<sup>[3]</sup>) has been frequently employed as a useful strategy to access homologated structures such as epoxides<sup>[4]</sup> or ( $n+1$ ) cyclic units.<sup>[5]</sup> In this sense, such reactions constitute effective alternatives to the classic Tiffeneau–Demjanov reaction<sup>[6]</sup> which, despite its synthetic potential, is not straightforward provided that it is a multi-step route.<sup>[6d,7]</sup> Indeed, in this scenario a prominent position is occupied by lithium carbenoid reagents<sup>[8]</sup> pioneered by Nozaki and co-workers who developed in the 1970s a series of useful protocols to access the aforementioned homologated *saturated* structures.<sup>[9]</sup> In these seminal works, they showed that upon reaction of a cyclic ketone (**I**) with dihalomethylithium reagents (i.e., LiCHCl<sub>2</sub> or LiCHBr<sub>2</sub>) followed by the so-called  $\beta$ -oxido carbenoid rearrange-

ment in the presence of a lithium base, it is possible to obtain a homologated  $\alpha$ -chloro ketone (**III**) or a simple homologated ketone (**II**), respectively (Scheme 1, *top*).<sup>[8c,10]</sup> On the other hand, the employment of monohalomethylithium carbenoids (e.g.,

Nozaki (1970s)  
Reaction of dihalomethylithium carbenoids with saturated cyclic ketones

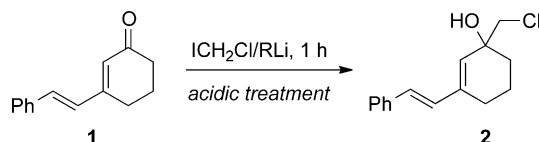


Addition of LiCH<sub>2</sub>Cl to  $\alpha,\beta$ -unsaturated cyclic ketones:  
the fates of the Tiffeneau–Demjanov-type intermediates



**Scheme 1.** Context of the presented work.

**Table 1.** Reaction optimization.<sup>[a]</sup>



| Entry | ICH <sub>2</sub> Cl (equiv.) | RLi (equiv.)    | Solvent               | Temp. [°C] | Yield of <b>2</b> [%] <sup>[b]</sup> |
|-------|------------------------------|-----------------|-----------------------|------------|--------------------------------------|
| 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 <sub>2</sub> O     | −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 <sub>2</sub> O | −78        | 93                                   |
| 12    | 4.5                          | MeLi (4.0)      | THF                   | −78        | 35                                   |

<sup>[a]</sup> Reactions time: 1 h.

<sup>[b]</sup> Isolated yields.

LiCH<sub>2</sub>X)<sup>[11]</sup> in analogous processes has been practically limited to the formation of epoxides starting from *saturated* cyclic ketones,<sup>[12]</sup> leaving almost unexplored in-depth investigations on their reactivity with multifunctionalized structures such as  $\alpha,\beta$ -unsaturated (cyclic) ketones.<sup>[13]</sup> 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)<sup>[14]</sup> and isocyanates,<sup>[15]</sup> we have been attracted by the possibility to access cyclic allylic alcohols incorporating at the quaternary carbon a reactive chloromethylene 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;<sup>[16]</sup> 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.<sup>[2a,5b,17]</sup> 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<sup>[18]</sup> as an alternative to Eschenmoser–Tanabe processes.<sup>[19]</sup> Finally, we considered as another possible shortcoming the inherent known tendency of lithium carbenoids to promote cyclopropanation-type reactions with olefins.<sup>[20]</sup>

In this work, we disclose a chemoselective 1,2-addition of LiCH<sub>2</sub>Cl 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  $\beta$ -oxo-,  $\beta$ -thio- and  $\beta$ -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.<sup>[21]</sup> Upon generation of the LiCH<sub>2</sub>Cl carbenoid in the presence of **1** through the reaction of MeLi-LiBr (1.5 equiv.) with ICH<sub>2</sub>Cl (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<sup>[22]</sup> (THF:Et<sub>2</sub>O:*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<sup>[23]</sup> (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<sub>2</sub>Cl.<sup>[12a,24]</sup> 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,<sup>[14]</sup> is known to react with this carbenoid (Scheme 2). Thus, by treating an equimolar mixture of **1** and **3** with LiCH<sub>2</sub>Cl 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<sub>2</sub>Cl performs better than the addition of simple MeLi solution to a mixture of ICH<sub>2</sub>Cl 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

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

| Entry | Additive                           | Equiv. | Yield of <b>2</b> [%] <sup>[b]</sup> |
|-------|------------------------------------|--------|--------------------------------------|
| 1     | LiBr <sup>[c]</sup>                | 4.0    | 93                                   |
| 2     | LiBr <sup>[d]</sup>                | 4.0    | 82                                   |
| 3     | LiBr <sup>[c]</sup>                | 0.2    | 74                                   |
| 4     | MgBr <sub>2</sub>                  | 4.0    | 68                                   |
| 5     | MgBr <sub>2</sub> -etherate        | 4.0    | 75                                   |
| 6     | MgI <sub>2</sub>                   | 4.0    | 72                                   |
| 7     | Mg(ClO <sub>4</sub> ) <sub>2</sub> | 4.0    | 77                                   |
| 8     | Mg(OTf) <sub>2</sub>               | 4.0    | 74                                   |
| 9     | ZnBr <sub>2</sub>                  | 4.0    | 66                                   |
| 10    | ZnI <sub>2</sub>                   | 4.0    | 69                                   |
| 11    | Zn(OTf) <sub>2</sub>               | 4.0    | 64                                   |

<sup>[a]</sup> Reaction time: 1 h.

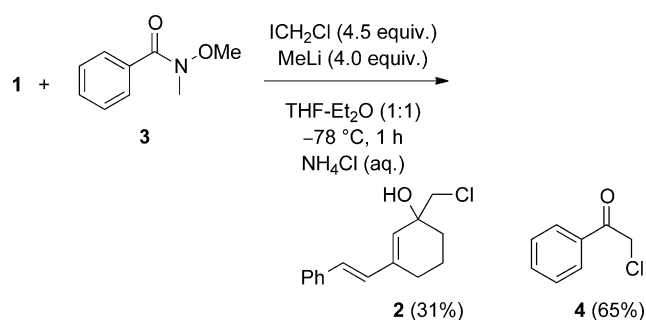
<sup>[b]</sup> Isolated yields.

<sup>[c]</sup> From MeLi-LiBr ethereal solution.

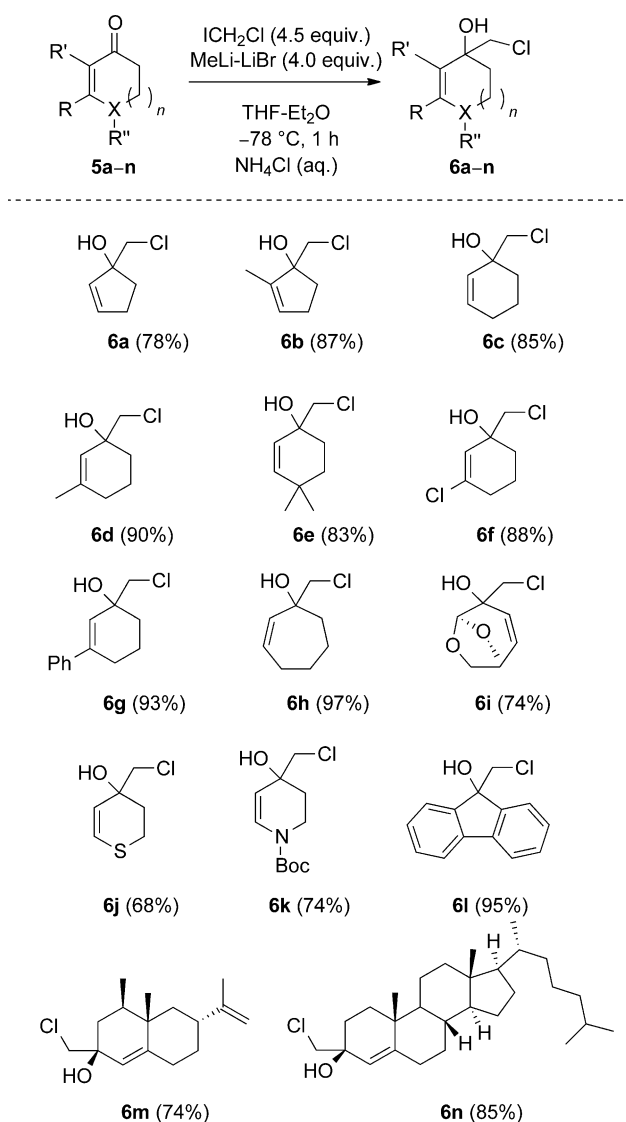
<sup>[d]</sup> Added as a powder.

(20 mol%, entry 3) resulted in a lower yield. Subsequently, we screened other known Lewis acids such as MgBr<sub>2</sub>, MgBr<sub>2</sub>-etherate, MgI<sub>2</sub>, Mg(ClO<sub>4</sub>)<sub>2</sub>, Mg(OTf)<sub>2</sub>, ZnBr<sub>2</sub>, ZnI<sub>2</sub>, Zn(OTf)<sub>2</sub> (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<sup>[25]</sup> through *in situ* transmetalations 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.<sup>[26]</sup> 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 2.** Control experiment in the presence of a Weinreb amide: study of the effect of LiBr.



**Scheme 3.** Scope of the reaction<sup>[28]</sup>.

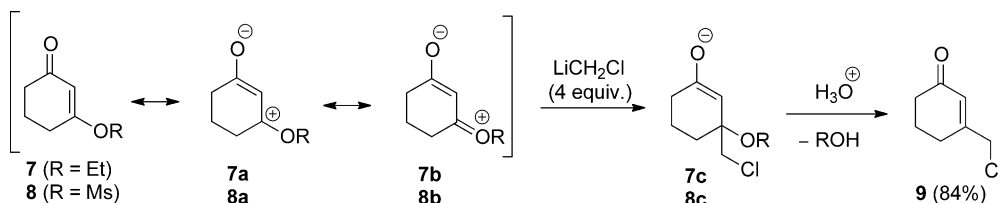
this latter substrate. Remarkably, the methodology could be efficiently applied to complex enone systems incorporated into natural products such as nootkatone (**5m**), a sesquiterpene derived from grapefruit with insecticide-repellent properties towards deer ticks.<sup>[27]</sup> With much of our delight 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**).

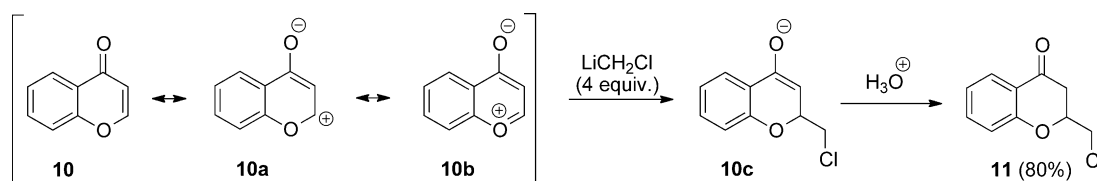
Of particular significance is the presence of an electron-releasing oxygen atom at the  $\beta$ -position of the olefinic bond which, formally transforms the enone systems **7** and **8** into masked 1,3-dicarbonyl derivatives (Scheme 4).<sup>[29]</sup> The resulting mesomeric effect, as showed by the 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)  $\beta$ -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  $\beta$ -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  $\beta$ -oxo species (compounds **7**, **8**, **10**, Scheme 4 and Scheme 5) and the corresponding  $\beta$ -thio analogue **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.

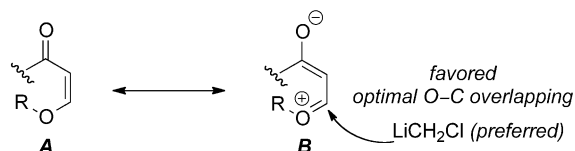


**Scheme 4.**  $\beta$ -Activating effect of an RO group: the case of 3-alkoxy systems.

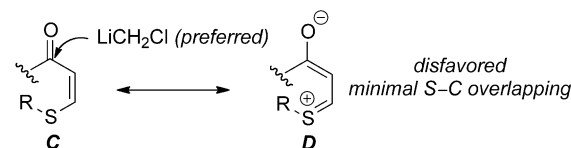


**Scheme 5.**  $\beta$ -Activating effect of an RO group: the case of chromone.

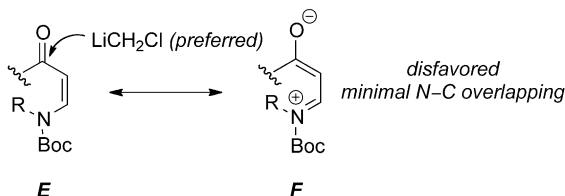
a)  $\beta$ -oxy substituent



b)  $\beta$ -thio substituent



c)  $\beta$ -aza substituent



**Scheme 6.** Mechanistic explanation of the different behavior of  $\beta$ -oxo,  $\beta$ -thio and  $\beta$ -aza (protected) substituents.

In conclusion, we have reported the reactivity of a lithium carbenoid ( $\text{LiCH}_2\text{Cl}$ ) with a series of cyclic  $\alpha,\beta$ -unsaturated enones. Key features disclosed within this study are: (i)  $\text{LiBr}$  not only acts as a carbenoid stabilizer but also as a mild Lewis acid activator of the  $\text{C}=\text{O}$  bond; (ii) in the case of  $\beta$ -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- $\text{Et}_2\text{O}$  (2 mL, 1:1, v/v) cooled at  $-78^\circ\text{C}$  was added freshly distilled chloriodomethane (794 mg, 0.33 mL, 4.5 mmol, 4.5 equiv.), followed by the dropwise addition of

a solution of  $\text{MeLi-LiBr}$  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  $\text{NH}_4\text{Cl}$  (2 mL) and extracted with  $\text{Et}_2\text{O}$  ( $3 \times 5$  mL). The organic layer was washed with brine (5 mL), dried over  $\text{Na}_2\text{SO}_4$ , 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  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra are available in the Supporting Information.

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*Publication n. 13*

**efficient access to all-carbon quaternary and tertiary  $\alpha$ -functionalized homoallyl-type aldehydes from ketones.**

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Details on experimental procedures, characterization data and copies of NMR spectra of all compounds are reported.





## Synthetic Methods

International Edition: DOI: 10.1002/anie.201706236  
German Edition: DOI: 10.1002/ange.201706236Efficient Access to All-Carbon Quaternary and Tertiary  $\alpha$ -Functionalized Homoallyl-type Aldehydes from Ketones

Vittorio Pace,\* Laura Castoldi, Eugenia Mazzeo, Marta Rui, Thierry Langer, and Wolfgang Holzer

**Abstract:**  $\beta,\gamma$ -Unsaturated aldehydes with all-carbon quaternary or tertiary  $\alpha$ -centers were rapidly assembled from ketones through a unique synthetic operation consisting of 1)  $C_1$  homologation, 2) Lewis acid mediated epoxide–aldehyde isomerization, and 3) electrophilic trapping. The synthetic equivalence of a vinyl oxirane and a  $\beta,\gamma$ -unsaturated aldehyde is the key concept of this previously undisclosed tactic. Mechanistic studies and labeling experiments suggest that an aldehyde enolate is a crucial intermediate. The homologating carbenoid formation plays a critical role in determining the chemoselectivity.

Aldehydes with all-carbon  $\alpha$ -quaternary centers constitute an important motif across the chemical sciences.<sup>[1]</sup> From a reactivity perspective, the high electrophilicity of the aldehyde moiety represents an excellent tool for constructing sterically hindered quaternary centers. In this context, the  $\alpha$ -allylation of aldehydes to generate the corresponding homoallyl derivatives has been extensively investigated (Scheme 1 A1). The palladium-catalyzed (Tsuji–Trost) approach reported by Tamaru and co-workers in 2001 can be considered as a breakthrough in this field.<sup>[2]</sup> Fine-tuning of the reaction conditions enabled the development of highly enantioselective variants by the groups of List<sup>[3]</sup> and Yoshida,<sup>[4]</sup> which complement asymmetric organocatalytic (Jacobsen)<sup>[5]</sup> and stereodivergent dual-catalytic (Carreira)<sup>[6]</sup> approaches. The process also benefits from switching to nickel catalysis, as recently disclosed by Sauthier and co-workers.<sup>[7]</sup> Interestingly, for simple linear aldehydes, this reaction could be incorporated into a tandem aldol condensation/allylation process. The development of these strategies also allowed overcoming the reluctance of the conceptually simplest strategy based on the use of aldehyde enolates as nucleophiles in alkylation chemistry.<sup>[8]</sup> A major advancement in the field was reported in 2016 by Evans and Wright, who developed an enantioselective rhodium-catalyzed allylation of prochiral  $\alpha,\alpha$ -disubstituted aldehyde enolates with allyl benzoate (Scheme 1 A2).<sup>[9]</sup> Furthermore, the selective ring fragmentation of diastereomerically pure and enantioen-

riched cyclopropanols represents a versatile process for synthesizing acyclic *n*-butenals with all-carbon quaternary centers, as shown in elegant work by Marek and co-workers (Scheme 1 A3).<sup>[10]</sup> However, the high efficiency of these methods in terms of their enantioselectivity or general applicability is counterbalanced by the limited availability of  $\alpha,\beta$ -unsaturated and  $\alpha$ -quaternary  $\beta,\gamma$ -unsaturated aldehydes, and there are hardly any methods for the synthesis of differently substituted aldehydes with all-carbon  $\alpha$ -quaternary centers. Prior to Evans' work,<sup>[9]</sup> the  $\alpha$ -derivatization of aldehydes by enolate-type chemistry—albeit limited to the synthesis of  $\alpha$ -tertiary species—has been achieved by Hodgson and co-workers<sup>[11]</sup> by epoxide–aldehyde isomerization (Scheme 1 B1).<sup>[12]</sup> Accordingly, the treatment of a monosubstituted epoxide with a hindered lithium amide base provided a nucleophilic enamine susceptible to alkylation to finally afford  $\alpha$ -substituted aliphatic aldehydes. Remarkably, the use of chiral lithium bases led to high asymmetric induction.<sup>[13]</sup> The simple, but not fully explored,<sup>[14]</sup> homologation, that is, the direct transformation of a ketone into an aldehyde, is analogously almost limited to the synthesis of  $\alpha$ -tertiary aldehydes (Scheme 1 B2).<sup>[15]</sup>

Thus the isomerization of an epoxide into an aldehyde under different conditions (e.g., Meinwald-type rearrangement triggered by a Lewis acid)<sup>[16]</sup> inspired us to employ an epoxide as a carbonyl equivalent that is susceptible to  $\alpha$ -functionalization with a particular electrophile. In turn, the key oxirane could be easily installed by  $C_1$  homologation of a ketone, as we recently reported.<sup>[17]</sup>

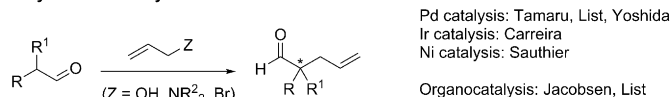
Herein, we present the versatility of the planned strategy for the synthesis of  $\alpha$ -quaternary aldehydes through a single synthetic operation consisting of 1) ketone homologation, 2) epoxide–aldehyde isomerization, and 3)  $\alpha$ -derivatization.

At the outset of our investigations to expand the 1,2-chemoselective addition of lithium carbenoids to  $\alpha,\beta$ -unsaturated ketones,<sup>[17a]</sup> we surmised that a simple increase in temperature (from  $-78^\circ\text{C}$  to room temperature)<sup>[18]</sup> might be enough for generating the highly versatile vinyl epoxide<sup>[19]</sup> **2** directly from enone **1**. To our surprise, we observed the formation of  $\alpha$ -methyl aldehyde **3** as the unique reaction product, which was isolated in 89% yield (Table 1, entry 1). No trace of the expected epoxide **2** was observed in an  $^1\text{H}$  NMR spectrum of the crude reaction mixture.<sup>[20]</sup>

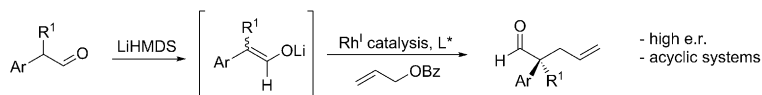
To fully understand this unusual transformation, the two separately occurring events<sup>[21]</sup> were investigated, albeit under Barbier-type conditions (Table 1). Switching to a different 1,1-dihalomethane carbenoid precursor did not effect a change in the ratio of the products (entry 2). Two fundamental observations were made when the carbenoid

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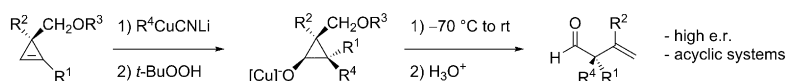
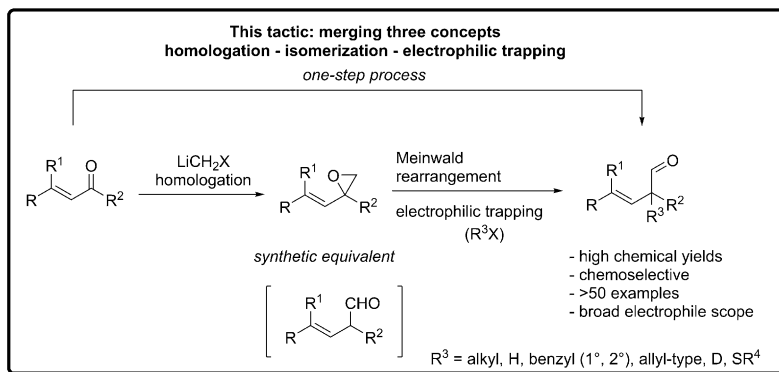
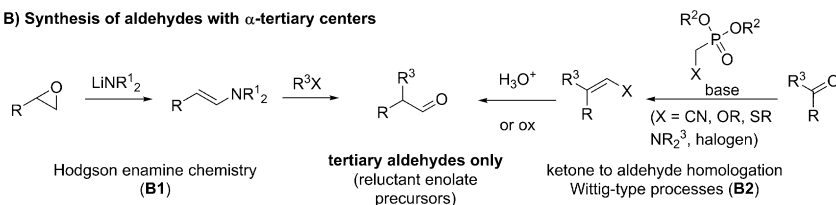
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:  
<https://doi.org/10.1002/anie.201706236>.

A) Synthesis of  $\beta,\gamma$ -unsaturated aldehydes with  $\alpha$ -quaternary centersA1)  $\alpha$ -Allylation of aldehydes

## A2) Aldehyde enolate approach: Evans



## A3) Fragmentation of cyclopropanols: Marek

B) Synthesis of aldehydes with  $\alpha$ -tertiary centers

Scheme 1. General context of the presented work.

was generated by employing different organolithium reagents (RLi) or carbenoid precursors ( $\text{XCH}_2\text{Z}$ ). Accordingly, upon forming the carbenoid with *n*-BuLi, PhLi, or  $\text{TMSCH}_2\text{Li}$ , the reaction afforded exclusively the  $\beta,\gamma$ -unsaturated nonsubstituted aldehyde **4'** (which isomerized spontaneously to the more stable  $\alpha,\beta$ -unsaturated aldehyde **4**).<sup>[22]</sup> The formation of these compounds suggests that the electrophilic byproducts obtained during the carbenoid formation (*n*-BuI, PhI, and  $\text{TMSCH}_2\text{I}$ , respectively), which are less reactive than MeI, might be involved in the process (entries 3–5). Furthermore, generating the carbenoid by Li/Sn transmetalation<sup>[23]</sup> (entry 6) provided, once more, compound **4** as the sole product, and interestingly, the corresponding stannane byproduct [ $(n\text{-Bu})_3\text{SnMe}$ ] was isolated by chromatographic purification. Combining these results, it seemed likely that the methyl iodide (MeI) formed during the generation of the carbenoid ( $\text{LiCH}_2\text{X}$ ;  $\text{X} = \text{Cl, Br}$ ) in the presence of MeLi-LiBr could be the source of the methyl unit. It should also be noted that the presence of a Lewis acid (e.g., LiBr)<sup>[24]</sup> and an increase in temperature from  $-78^\circ\text{C}$  to room temperature

were essential for the formation of the  $\alpha$ -quaternary center. Performing the reaction with LiBr-free MeLi gave a 1:0.7 mixture of **3** and **4** (entry 7). On the other hand, when the reaction was conducted at  $-78^\circ\text{C}$ , even for prolonged periods of time (24 h), the simple halohydrin **5** was formed in 91% yield.

As outlined in Scheme 2, aldehydes with methyl-substituted  $\alpha$ -quaternary centers were readily formed under the optimized reaction conditions (Scheme 2). The reactions proceeded cleanly and gave the corresponding products in high chemical yields regardless of the nature [cyclic (**6–15**) or acyclic (**3, 16**)] of the substrates and the substitution pattern across the starting ketones. We anticipated that our method would provide access to important  $\alpha$ -methyl aldehydes (e.g., **8–10**), which are used as substrates for a plethora of chemical transformations,<sup>[25]</sup> in just one chemical operation, without the need for the multistep (four) and complex procedures routinely employed.<sup>[26]</sup> Gratifyingly, more complex natural products (isophorone and nootkatone) also underwent this novel high-yielding transformation to give products **17** and **18**.

The feasibility of this method for the efficient synthesis of aldehydes with methyl-substituted  $\alpha$ -quaternary centers encouraged us to attempt the formation of more challenging fully substituted derivatives that feature a moiety resulting from the addition of a second electrophile. Based on our optimization study (Table 1, entry 4), we considered  $\text{TMSCH}_2\text{Li-LiBr}$  to be the ideal reagent for the generation

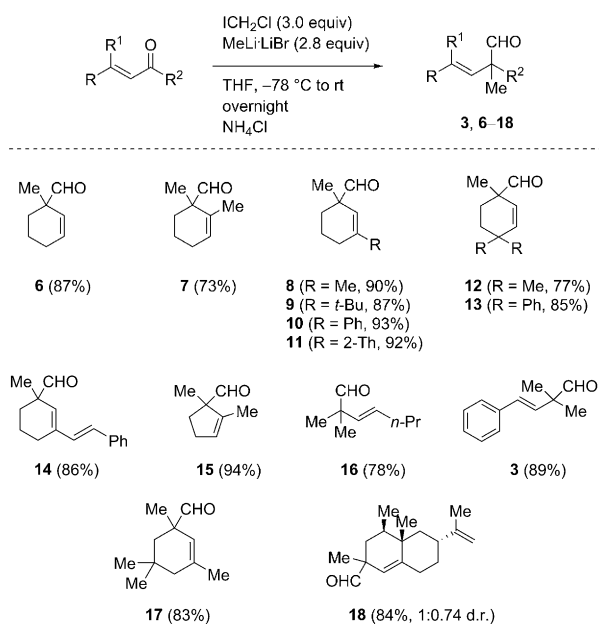
of the  $\text{LiCH}_2\text{Cl}$  carbenoid. As shown before,  $\text{TMSCH}_2\text{Li}$  resulting from the carbenoid formation event is completely unreactive towards the intermediate epoxide. Pleasingly, by simply adding 3 equiv of an electrophile, our strategy could be successfully extended to the synthesis of aldehydes with functionalized all-carbon quaternary  $\alpha$ -centers in high yields and with high chemoselectivity (Scheme 3). Benzyl halides proved to be excellent coupling partners for the reaction, without significant differences in reactivity displayed by the employed carbonyl substrates (to give products **19–34**). The following points should be noted:

- 1) The presence of a potentially exchangeable iodine did not alter the chemoselectivity (**20**).
- 2) Substitution across the aromatic ring of the benzyl halide is well tolerated (**21, 23–25**, and **28–30**), even the presence of a nitro group.
- 3) No decrease in reactivity was observed when sterically hindered benzyl halides were used (**23**) or when the starting carbonyl substrate featured a substituent at the  $\alpha$ -position (**25**).

**Table 1:** Optimization of the reaction conditions.

| 1. Carbenoid generation event                  |                                                   |                       |                                                  |       |                          |
|------------------------------------------------|---------------------------------------------------|-----------------------|--------------------------------------------------|-------|--------------------------|
|                                                |                                                   |                       |                                                  |       |                          |
| 2. Homologation<br>3. $\alpha$ -Derivatization |                                                   |                       |                                                  |       |                          |
|                                                |                                                   |                       |                                                  |       |                          |
| Entry                                          | Carbenoid precursor                               | RLi                   | Byproduct                                        | 3/4   | Yield [%] <sup>[a]</sup> |
| 1                                              | ICH <sub>2</sub> Cl                               | MeLi-LiBr             | MeI                                              | 1:0   | 89                       |
| 2                                              | ICH <sub>2</sub> Br                               | MeLi-LiBr             | MeI                                              | 1:0   | 83                       |
| 3 <sup>[b]</sup>                               | ICH <sub>2</sub> Cl                               | <i>n</i> -BuLi        | <i>n</i> -BuI                                    | 0:1   | 66                       |
| 4 <sup>[b]</sup>                               | ICH <sub>2</sub> Cl                               | TMSCH <sub>2</sub> Li | TMSCH <sub>2</sub> I                             | 0:1   | 90                       |
| 5 <sup>[b]</sup>                               | ICH <sub>2</sub> Cl                               | PhLi                  | PhI                                              | 0:1   | 80                       |
| 6                                              | ( <i>n</i> -Bu) <sub>3</sub> SnCH <sub>2</sub> Cl | MeLi-LiBr             | ( <i>n</i> -Bu) <sub>3</sub> SnMe <sup>[c]</sup> | 0:1   | 88                       |
| 7 <sup>[b]</sup>                               | ICH <sub>2</sub> Cl                               | MeLi                  | MeI                                              | 1:0.7 | — <sup>[d]</sup>         |

[a] Yield of isolated product for either compound **3** or **4**. [b] LiBr (1.5 M in THF) was added. [c] Isolated in 82% yield. [d] Compound **3** isolated in 52% yield, compound **4** isolated in 36% yield. For additional optimization studies, see the Supporting Information.

**Scheme 2.** Direct synthesis of aldehydes with methyl-substituted  $\alpha$ -quaternary centers.

- A secondary benzyl bromide could be used for the trapping, but the corresponding product was obtained in lower yield (**26**).
- The bicyclic natural product nootkatone was also amenable to  $\alpha$ -benzylation (**34**).

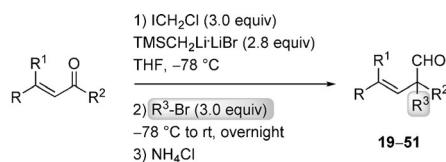
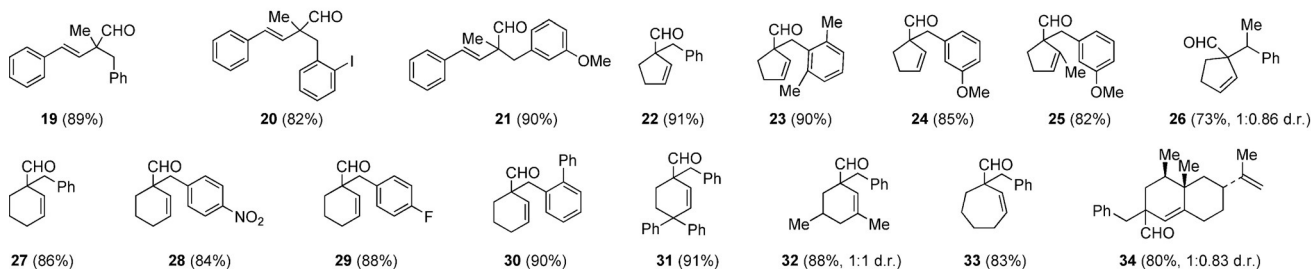
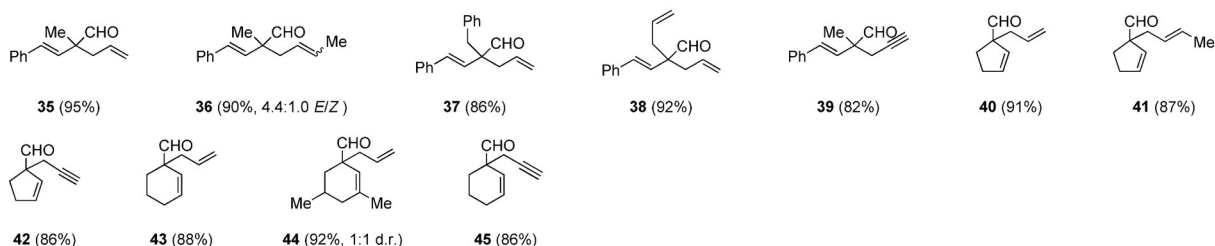
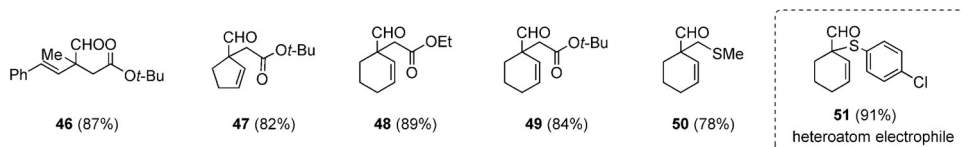
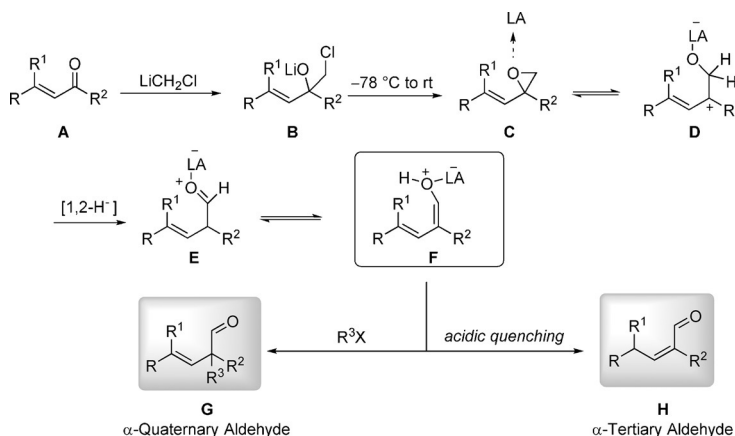
Unsaturated functional groups (allyl, crotyl, propargyl) with halide leaving groups also served as excellent trapping agents for the transformation of both acyclic (**35–39**) and cyclic systems (again without effect of the ring size; **40–45**). Analogously, coupling partners with multiple electrophilic moieties such as  $\alpha$ -bromo esters did react according to the general scheme, providing interesting  $\gamma$ -oxo esters (**46–49**). The trapping with an  $\alpha$ -halomethyl sulfide provided the  $\beta$ -sulfur-substituted aldehyde **50** in comparable chemical yield. This method could also be applied to an aldehyde with a quaternary heteroatom-substituted  $\alpha$ -position, as showcased by an example with a sulfur electrophile [(4-ClC<sub>6</sub>H<sub>4</sub>S)<sub>2</sub>, **51**].

The mechanism of the transformation can be rationalized as follows (Scheme 4). The attack of carbonyl compound **A** by the nucleophilic LiCH<sub>2</sub>Cl produces the O-lithiated halohydrin **B**, which cyclizes to vinyl epoxide **C** upon an increase in temperature. In agreement with Lautens' work on the amphoteric character of vinyl oxiranes,<sup>[27]</sup> the Lewis acid (LiBr) triggers the ring opening of epoxide **C**, favored by the formation of the allylic carbocation **D**, to furnish enolate **F** through a 1,2-hydride shift and tautomerization. The latter can then react with an adequate electrophile to yield  $\alpha$ -quaternary aldehyde **G** or, for  $\alpha$ -tertiary aldehydes, product **H** upon simple acidic quenching and tautomerization.

To confirm the enolate-type mechanism, additional experiments with deuterium-labeled carbenoids and/or methyllithium were conducted (Scheme 5).

- The use of the deuterated carbenoid LiCD<sub>2</sub>Br, which was generated from CD<sub>2</sub>Br<sub>2</sub> and MeLi-LiBr, afforded aldehyde **52** with an  $\alpha$ -CH<sub>3</sub> group and a deuterated carbonyl moiety.
- The employment of CD<sub>3</sub>Li-LiI and CH<sub>2</sub>Br<sub>2</sub>, which evidently form LiCH<sub>2</sub>Br, gave the CHO aldehyde **53** featuring a CD<sub>3</sub> group at the  $\alpha$ -position.
- The homologation with LiCD<sub>2</sub>Br, formed from CD<sub>2</sub>Br<sub>2</sub> and CD<sub>3</sub>Li-LiI, yielded aldehyde **54** with deuteration at both the aldehyde and the  $\alpha$ -position.
- Homologation with LiCD<sub>2</sub>Br, generated from TMSCH<sub>2</sub>Li and quenching with an acid, delivered the deuterated  $\alpha,\beta$ -unsaturated aldehyde **55**.

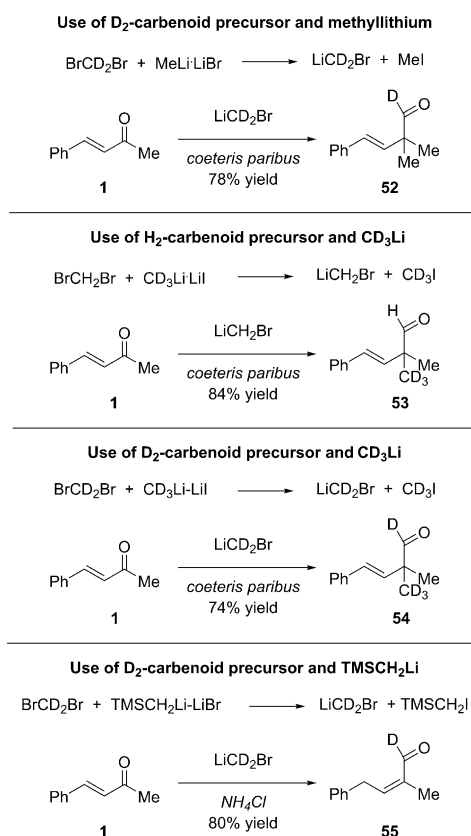
In agreement with the postulated mechanism (Schemes 4 and 5) and with the aim of taking full advantage of the potential of our approach, we attempted the generation of  $\alpha$ -tertiary  $\beta,\gamma$ -unsaturated aldehydes through the one-step homologation-isomerization procedure (Scheme 6). Significantly, during work-up and purification, the  $\beta,\gamma$ -unsaturated aldehydes spontaneously isomerized to the more stable  $\alpha,\beta$ -unsaturated ones (**4**, **56–62**). The substrate scope was broad, and interestingly, an important intermediate (**57**) for the synthesis of vitamin D<sup>[28]</sup> was obtained in a single high-yielding synthetic operation.

**Benzyl halide electrophiles****Allyl, crotyl, and propargyl electrophiles****Electrophiles with multiple electrophilic moieties****Scheme 3.** Synthesis of aldehydes with fully substituted  $\alpha$ -quaternary centers with different electrophiles.**Scheme 4.** Plausible mechanism.

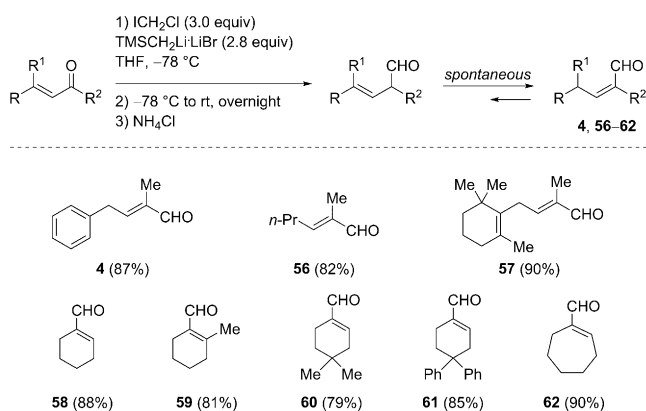
(carbon or heteroatom) of the putative aldehyde enolate, whose intermediacy was confirmed by labeling experiments. For the first time, the effect of the lithium organometallic species employed for generating a carbenoid and the nature of the carbenoid precursor were found to be critical for the chemoselectivity. This method features an excellent substrate scope, also enabling the synthesis of  $\alpha,\beta$ -unsaturated aldehydes when no external electrophile is added. We are currently investigating the development of an asymmetric variant of this process.

In conclusion, we have developed a rapid and high-yielding synthesis of aldehydes with all-carbon  $\alpha$ -quaternary centers from  $\alpha,\beta$ -unsaturated acyclic and cyclic ketones. The single-step transformation results from the merging of three concepts, namely homologation, epoxide–aldehyde isomerization, and functionalization with an added electrophile





**Scheme 5.** Mechanistic evidence for the formation of the enolate intermediate with deuterated species. coeteris paribus = under the same reaction conditions.



**Scheme 6.** Synthesis of  $\alpha,\beta$ -unsaturated aldehydes by homologation and isomerization followed by acidic quenching.

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## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** aldehydes · carbenoids · enolates · homologation · isomerization

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**Merging lithium carbenoid homologation and enzymatic reductions: a combinative approach to the HIV-protease inhibitor Nelfinavir.**

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## Merging Lithium Carbenoid Homologation and Enzymatic Reduction: A Combinative Approach to the HIV-Protease Inhibitor Nelfinavir

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**Abstract** An effective stereocontrolled synthesis of the HIV protease inhibitor Nelfinavir is reported. Two transformations were identified crucial for achieving success: the formation of a densely functionalized  $\alpha$ -chloroketone *via* the homologation of a Weinreb amide with chloromethylithium (LiCH<sub>2</sub>Cl), followed by its *erythro* selective reduction into the corresponding chiral chlorohydrin. A commercially available enzyme P2-C02 was particularly well suited for this purpose, affording the key alcohol (in an excellent 99% *de*), which was then smoothly converted into the active biologically active agent.

### Introduction

The pharmaceutical treatment of HIV diseases ranks at the frontier of modern medicine as a consequence of the important and dramatic repercussions it causes within the society (*e.g.* 40 M infected individuals worldwide).<sup>1</sup> As such, the development of active and resistant-free drugs continues to represent an actively pursued research area for medicinal chemistry.<sup>2</sup> The highly structural differentiation among currently employed drugs constitutes a significant task in synthetic methodology for ensuring rapid and straightforward routes to agents active *via* progressively new identified biological targets, as exemplified by 3'-azido-3'-deoxythymidine (AZT, the first approved nucleoside analogue) and HIV protease inhibitors (Figure 1).<sup>3</sup> Undoubtedly, the introduction of these agents in the mid 1990s<sup>4</sup> benefited considerably the treatment of the pathology *via* the inhibition of the virus replication guaranteed by the not cleavable peptide bioisosteric hydroxyethylene unit.<sup>5</sup> A prominent example of the class is Nelfinavir, whose mesylate salt (Viracept®) conjugates an effective anti-HIV activity with a convenient pharmacokinetic behaviour (oral administration), thus improving patient compliance.<sup>6</sup>

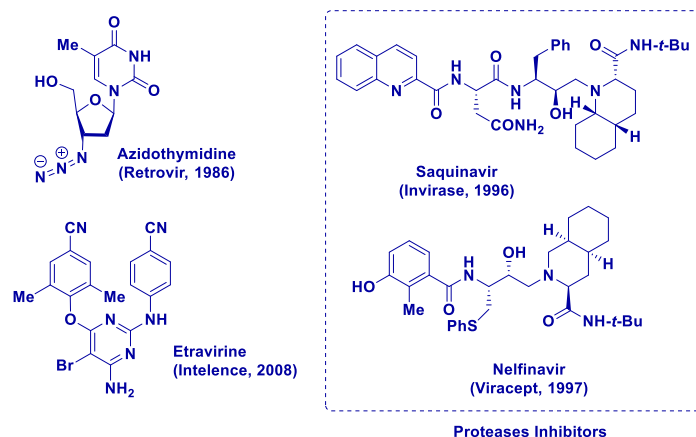
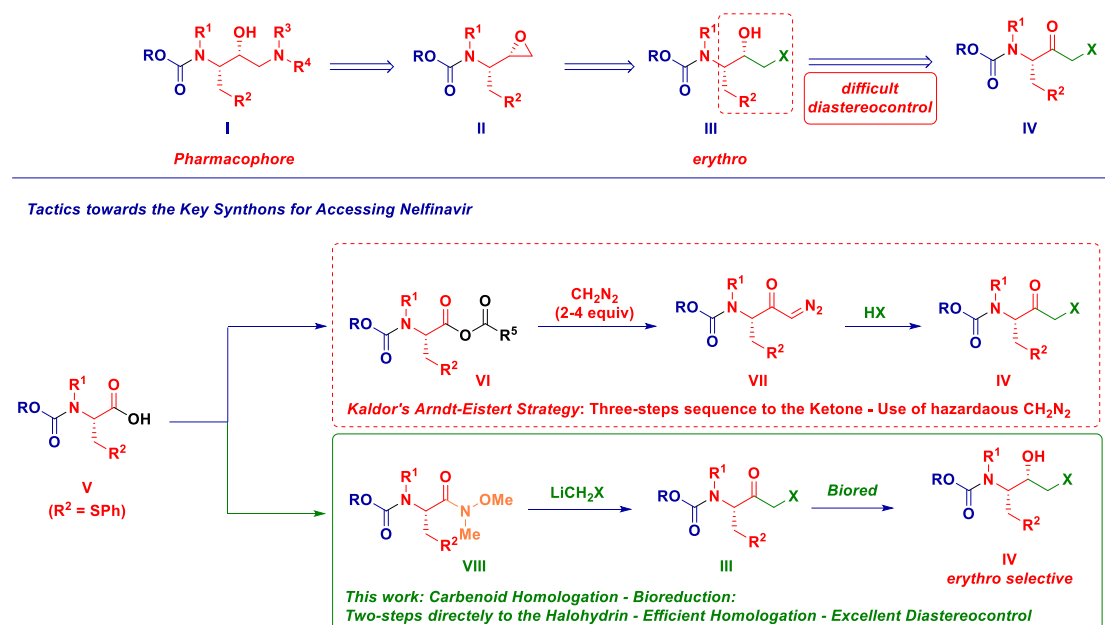


Figure 1. Commonly used anti-HIV agents.

The rational drug design individuates - *inter alia* - the presence of a chiral substituted 1,3-diamino-butan-2-ol (**I**, Scheme 1) featuring an *anti* (*erythro*) configuration for observing optimal therapeutic activity.<sup>5,7</sup> Accordingly, the retrosynthetic analysis depicted in Scheme 1 highlights the fundamental role displayed by the epoxide-synthon **II** (derived from the halohydrin **III**) whose efficient obtainment in terms of both chemical yield and optical purity represents the most intriguing and relevant event within the whole production process.<sup>5,8</sup> The classical approach towards it is paved on a three-steps sequence – involving a suitable  $\alpha$ -aminoalkyl- $\alpha'$ -halomethylketone **IV** as the key synthon<sup>7,9</sup> - constituted by: *i*) carboxylic acid derivative homologation, followed by *ii*) stereocontrolled reduction to a chiral halohydrin **III**, direct precursor – under retentive conditions - of the targeted epoxide **II**.<sup>5</sup> Some points merit mention: a) Focusing on the homologation event it is quite interesting how the usual method employed for synthesizing the ketone **IV** still relies on the Arndt-Eistert procedure<sup>10</sup>, involving the use of highly toxic and hazardous diazomethane.<sup>11</sup> Since the first preparation by Kaldor in 1997, this formally *direct* homologation requires three different synthetic operations: 1) activation of the carboxylic acid **V** to a more reactive anhydride **VI**; 2) formal  $\text{CH}_2\text{N}_2$  homologation reaction and, 3) acyldolysis<sup>12</sup> to convert the intermediate diazoketone **VII** to the requested  $\alpha$ -haloketone **IV**. Notably, a significant excess of  $\text{CH}_2\text{N}_2$  is required to obtain good yields of diazoketone. [(73% with 4 equiv),<sup>6b</sup> (62% with 2 equiv)<sup>13</sup>], while the adoption of microfluidic techniques enables to get directly ketone **IV** in 73% yield as elegantly introduced by Kappe.<sup>14</sup> b) Controlling the diastereoselectivity in the reduction to the halohydrin **III** is troublesome and, in the case of Nelfinavir, no available completely stereoselective methods are known.<sup>5,13</sup>



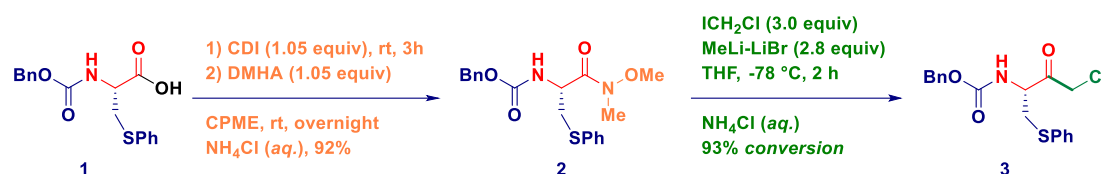
Scheme 1. General context of the presented work.

With the aim to design a diazomethane-free homologation strategy and direct carbenoid mediated tactic towards Nelfinavir, herein we detail an effective route in which the key haloketone is in turn reduced to the chiral halohydrin with excellent stereocontrol *via* a straightforward enzymatic reduction finally conducting to this important drug.

In recent years our group reported highly effective and reliable tactics for enabling the formal insertion of a CH<sub>2</sub>X fragment into an acyl type electrophile by using lithium carbenoid reagents<sup>15</sup> (*i.e.* LiCH<sub>2</sub>X, X = Cl, Br, I, F, OR, CN).<sup>16</sup> Such a direct operation presents the intrinsic advantage of installing the nucleophilic unit with the exact degree of functionalization, therefore affording the targeted structure through a single experimental operation. Among the portfolio of electrophiles studied, we introduced Weinreb amides<sup>17</sup> as privileged acylating agents for such reagents:<sup>18</sup> the formation of a stable (isolable)<sup>19</sup> tetrahedral intermediate guarantees excellent levels of chemoselectivity and, as a consequence, no undesired overaddition processes could be observed.

## Results and Discussion.

The commercially available *N*-Carbobenzoxy-*S*-phenyl-L-cysteine **1** activated with carbonyldiimidazole (CDI) provided the corresponding Weinreb amide **2** upon reaction with *N,O*-dimethylhydroxylamine hydrochloride (DMHA).<sup>18a,20</sup> Interestingly, the reaction highly benefited from using cyclopentyl methyl ether (CPME)<sup>16f,21</sup>: it proved by far to be the optimal choice compared to other organic solvents (classical dichloromethane or green solvent 2-MeTHF,<sup>22</sup> 78% and 53% respectively) affording the requested synthon – just after recrystallization - in an excellent 92% yield. With the Weinreb amide **2** in hands, we next focused our attention on the halomethylation procedure. With the goal of rapidly assembling the haloketone **3**, pleasingly we found LiCH<sub>2</sub>Cl - generated from ICH<sub>2</sub>Cl (3.0 equiv) and MeLi-LiBr (2.8 equiv) – suitable for attacking the Weinreb amide **2** (Scheme 2).



Scheme 2. Preparation and homologation of the Weinreb amide to the key  $\alpha$ -chloroketone.

Although <sup>1</sup>H-NMR analysis of the reaction crude showed an excellent conversion into **3** (93%), purification through silica gel chromatography provided it pure in a modest 41% isolated yield (Table 1). Analogously troublesome purification was obtained switching to aluminium oxide (neutral, basic or acidic) - Brockmann degree 1, 3 and 4 (entries 2-8).<sup>19</sup> Deactivation of silica gel with triethylamine (2-5%) allowed to increase the isolated yield up to 48% and 55% isolated yields (entries 9-10), respectively. Finally, deactivating silica with TMSCl maximized the isolated yield up to 84% (entry 12), while, using Florisil, decomposition phenomena again were predominant, allowing to recover the desired target in substantially decreased yield (entry 14). Importantly, despite the use of notoriously basic reagents as lithium carbenoids are, full preservation of the optical purity was observed [ $\alpha_D$  (20 °C) = + 10.9 (c 0.3 CHCl<sub>3</sub>), lit.<sup>14b</sup> + 12.7 (c 1.01 CHCl<sub>3</sub>)].

Table 1. Chromatographic purification of ketone **3**: Study of the stationary phase.

| Entry          | Stationary phase | Deactivating agent (w/w %) | Isolated Yield of <b>3</b> (%) <sup>a</sup> |
|----------------|------------------|----------------------------|---------------------------------------------|
| 1              | SiO <sub>2</sub> | -                          | 41                                          |
| 2 <sup>a</sup> | AloxN-BG1        | H <sub>2</sub>             | 16                                          |
| 3 <sup>a</sup> | AloxN-BG3        | H <sub>2</sub> O           | 24                                          |
| 4 <sup>a</sup> | AloxB-BG1        | -                          | 20                                          |
| 5 <sup>a</sup> | AloxB-BG3        | H <sub>2</sub> O           | 29                                          |
| 6 <sup>a</sup> | AloxB-BG4        | H <sub>2</sub> O           | 34                                          |
| 7 <sup>a</sup> | AloxA-BG1        | -                          | 11                                          |
| 8 <sup>a</sup> | AloxA-BG4        | -                          | 20                                          |
| 9              | SiO <sub>2</sub> | NEt <sub>3</sub> (2%)      | 48                                          |
| 10             | SiO <sub>2</sub> | NEt <sub>3</sub> (5%)      | 55                                          |
| 11             | SiO <sub>2</sub> | TMSCl (1%)                 | 73                                          |
| 12             | SiO <sub>2</sub> | TMSCl (2%)                 | 84                                          |
| 13             | SiO <sub>2</sub> | TMSCl (5%)                 | 82                                          |
| 14             | Florisil         | -                          | 43                                          |

BG = Brockmann grade. <sup>a</sup> Deactivation of Alox N, B, A was realized according to ref. 19.

Previous studies on homologation chemistry by Izawa with LiCH<sub>2</sub>X reagents pointed out important difficulties in reactions involving common amino acid derivatives such as esters:<sup>2a,5</sup> in fact, the halogen-lithium exchange responsible for the carbenoid formation event starting from XCH<sub>2</sub>Cl (X = Br, I) could be interfered by the presence of an acidic NH functionality. Because of the needing of using Barbier type conditions in analogous processes,<sup>23</sup> full substitution on the nitrogen was considered the unique available strategy. Accordingly, Barluenga proposed the use of *N,N*-dibenzyl esters,<sup>24</sup> while Izawa introduced *N*-protected 3-oxazolidin-5-ones<sup>25</sup> or, alternatively, *N*-imino protected amino acid esters.<sup>26</sup> Additionally, scientists at Roche described the use of *in situ* protected carbamates formed upon reaction of TMSCl with the corresponding lithium amide base, prior to the generation of the carbenoid.<sup>27</sup> It should be highlighted none of these techniques has been adapted

to the synthesis of Nelfinavir<sup>28</sup> thus, restricting homologation-based tactics towards it to the previously discussed CH<sub>2</sub>N<sub>2</sub> paved ones.<sup>5,6b,7,13</sup>

With the key  $\alpha$ -amino- $\alpha'$ -chloroketone **3** in hand, we then considered the stereoselective reduction to the crucial (*R*, *S*)-chlorohydrin **4** required for accomplishing the synthesis of Nelfinavir. Indeed, the reduction *via* standard chemical methods (*e.g.* NaBH<sub>4</sub>) has been reported to proceed with incomplete stereocontrol – giving variable mixtures of the *erythro* (**4**) and *threo* (**5**) products - thus, making challenging a protocol for the selective *erythro* reduction.<sup>13,28c,29</sup> In this sense, nowadays biocatalytic reductions represent a reliable and effective tool for organic synthesis able to overcome serious issues associated with the employment of classical chemistry, including not only a favourable comparison in term of eco-compatibility, but mainly the possibility to achieve excellent levels of stereocontrol.<sup>30</sup> Cognizant of the recent work by De Souza and Kappe who developed a whole-cells based protocol for accessing enantiopure halohydrins,<sup>31</sup> we investigated the *erythro*-selective reduction by means of a commercially available set of engineered ketoreductases (Codex® KRED Screening Kit, provided by Codexis),<sup>32</sup> in the presence of the corresponding cofactor NAD(P)H, which was continuously regenerated *via* the *i*-propanol-acetone oxidative cycle. As indicated in Table 2, the screened enzymes<sup>33</sup> are able to induce a different stereocontrol at variable conversion rates under standardized conditions (24 h, 30 °C, pH 7). Few KRED enzymes (P2-B02, P2-D11, P2-D12, P2-G3, – entries 4, 6-8) showed few selectivity (*de* 51-64%) and, therefore were not further screened. Albeit, only low to moderate conversions were evidenced, two enzymes P1-A04 (entry 1) and P2-C02 (entry 5) resulted very promising since excellent opposite selectivities (*de* 99%) were achieved, affording the *threo* (*R,R*) and the desired *erythro* (*R,S*) products, respectively. Presumably, the not optimal conversions were consequence of the limited solubility of ketone **3** in the reaction medium (*i*-propanol-acetone) and, as such, we analysed the effect of a cosolvent. The addition of DMSO (5% *v/v*) provoked the reversal of selectivity (*erythro* to *threo* - entries 9-11) for the KREDs P1-B02, P1-C01 and P2-C02, while in the case of P2-D11 it did not modify the stereochemical outcome (entry 12 *vs* 6). However, this cosolvent conducted consistently to the *threo* chlorohydrin **5** not suitable as precursor of Nelfinavir.

THF (5% *v/v*) had a positive effect on conversions (98-99% - entries 13-16) in the case of P1-B02, P1-C01, P2-C02 and P2-D11. This solvent showed a significant preference for the targeted *erythro* product **4** and, remarkably P2-C02 resulted again the best KRED giving 96% *de*. Further screening of this same KRED in the presence of sustainable cosolvents such as 2-methyltetrahydrofuran (2-MeTHF – entry 17) or, tetrahydrofurfuryl alcohol (THFA – entry 18) confirmed the pattern in terms of both *erythro* selectivity (97 – 96%, respectively) and conversion (>96%). Finally, by running the reaction in the presence of the more sustainable solvent cyclopentyl methyl ether (CPME, 5% *v/v*, entry 19) maximized both crucial parameters, thus affording the transformation with full stereocontrol – desired *erythro* product **4** - (*de* 99%) and conversion (99%). With our delight the transformation was amenable for scale-up (1 mmol scale): analytically and optically pure (*de* 99%) compound **4** was obtained in an excellent 91% isolated yield after chromatography on silica gel (entry 20).

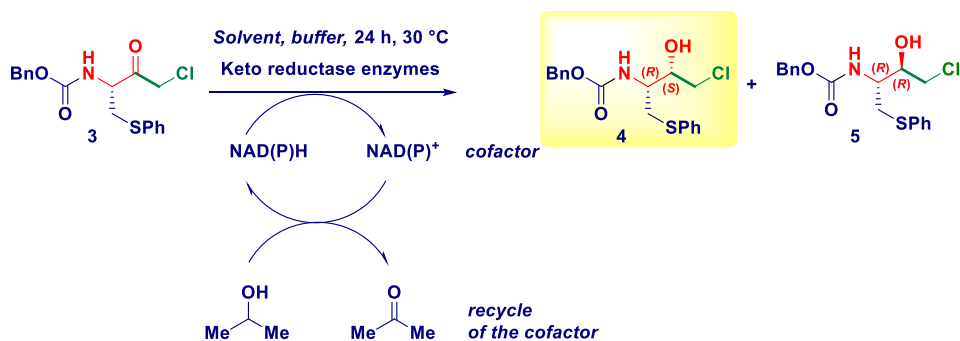
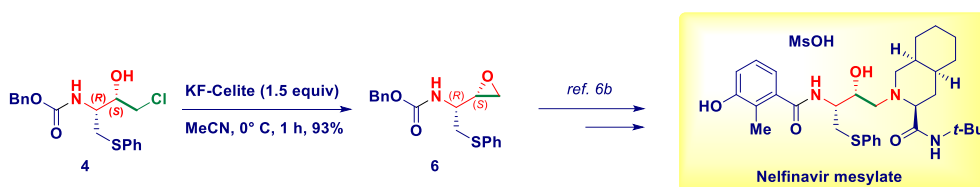


Table 2. Screening of KREDs and optimization of the reduction process.

| Entry           | Biocatalyst (KRED) | Conversion [%] <sup>[a]</sup> | Cosolvent (v/v) % | de [%] <sup>[a]</sup>  |
|-----------------|--------------------|-------------------------------|-------------------|------------------------|
| 1               | P1-A04             | 31                            | -                 | 99 ( <i>R,R</i> )      |
| 2               | P1-B02             | 99                            | -                 | 84 ( <i>R,S</i> )      |
| 3               | P1-C01             | 67                            | -                 | 78 ( <i>R,S</i> )      |
| 4               | P2-B02             | 99                            | -                 | 63 ( <i>S,S</i> )      |
| 5               | P2-C02             | 95                            | -                 | 99 ( <i>R,S</i> )      |
| 6               | P2-D11             | 99                            | -                 | 64 ( <i>R,R</i> )      |
| 7               | P2-D12             | 99                            | -                 | 52 ( <i>R,R</i> )      |
| 8               | P2-G03             | 51                            | -                 | 51 ( <i>R,S</i> )      |
| 9               | P1-B02             | 73                            | DMSO (5%)         | 94 ( <i>R,R</i> )      |
| 10              | P1-C01             | 95                            | DMSO (5%)         | 82 ( <i>R,R</i> )      |
| 11              | P2-C02             | 84                            | DMSO (5%)         | 84 ( <i>R,R</i> )      |
| 12              | P2-D11             | 74                            | DMSO (5%)         | 98 ( <i>R,R</i> )      |
| 13              | P1-B02             | 99                            | THF (5%)          | 50 ( <i>R,S</i> )      |
| 14              | P1-C01             | 98                            | THF (5%)          | 85 ( <i>R,S</i> )      |
| 15              | P2-C02             | 98                            | THF (5%)          | 96 ( <i>R,S</i> )      |
| 16              | P2-D11             | 98                            | THF (5%)          | 56 ( <i>R,S</i> )      |
| 17              | P2-C02             | 97                            | 2-MeTHF (5%)      | 97 ( <i>R,S</i> )      |
| 18              | P2-C02             | 96                            | THFA (5%)         | 96 ( <i>R,S</i> )      |
| <b>19</b>       | <b>P2-C02</b>      | <b>99</b>                     | <b>CPME (5%)</b>  | <b>99 (<i>R,S</i>)</b> |
| 20 <sup>c</sup> | <b>P2-C02</b>      | 99 <sup>d</sup>               | CPME (5%)         | 99 ( <i>R,S</i> )      |

(*R,R*) refers to the *threo* product **5**. (*R,S*) refers to the – desired – *erythro* product **4**. <sup>a</sup> Otherwise stated NADPH was the cofactor. <sup>b</sup> NADH was the cofactor. <sup>c</sup> Reaction run at 1 mmol scale. <sup>d</sup> 91% Isolated yield.

Having established the conditions for preparing with full stereocontrol the key halohydrin **4**, a formal synthesis conducting to Nelfinavir mesylate was realized (Scheme 3). Interestingly, the reactive epoxide **6** was directly prepared from the chlorohydrin through a heterogeneous base (KF-Celite)<sup>34</sup>-mediated ring-closure we reported in 2011.<sup>35</sup> Finally, by applying the reported procedure Nelfinavir mesylate was obtained in 75% yield (starting from epoxide **6**).



Scheme 3. Formal synthesis of Nelfinavir mesylate.

## Conclusions.

In conclusion, we developed an efficient strategy for accessing the HIV protease inhibitor Nelfinavir in high chemical yield under excellent stereocontrol. The tactic is paved on a straightforward preparation of an  $\alpha$ -chloroketone through the reaction of an easily accessible Weinreb amide and the carbenoid chloromethyl lithium. Such a homologation event proceeds with efficiency and full retention of the stereochemical information. Subsequently, a biocatalytic reduction performed with the commercially available P2-CO2 enzyme in the presence of CPME, considered a green cosolvent, provides the *erythro* chlorohydrin product – requested for the synthesis of the drug – in an excellent 99% *de*. The transformation of such an alcohol into an intermediate epoxide, followed by known procedures, finally affords Nelfinavir mesylate in 75% yield.

## Experimental part.

### General Methods.

Melting Points were determined on a Reichert-Kofler hot-stage microscope and are uncorrected. Mass spectra were obtained on a Shimadzu QP 1000 instrument (EI, 70 eV) and on a Bruker MaXis 4G instrument (ESI-TOF, APCI, HRMS).  $^1\text{H}$ ,  $^{13}\text{C}$ , and  $^{15}\text{N}$  NMR spectra were recorded on a Bruker Avance III 400 spectrometer (400 MHz for  $^1\text{H}$ , 100 MHz for  $^{13}\text{C}$ , and 40 MHz for  $^{15}\text{N}$ ) or on a Bruker Avance 200 spectrometer (200 MHz for  $^1\text{H}$ , 50 MHz for  $^{13}\text{C}$ ) at 297 K using a directly detecting broadband observe (BBFO) probe. The centre of the (residual) solvent signal was used as an internal standard which was related to TMS with  $\delta$  7.26 ppm ( $^1\text{H}$  in  $\text{CDCl}_3$ ),  $\delta$  77.00 ppm ( $^{13}\text{C}$  in  $\text{CDCl}_3$ ).  $^{15}\text{N}$  NMR spectra were referenced against external nitromethane (0.0 ppm). Spin-spin coupling constants ( $J$ ) are given in Hz. In nearly all cases, full and unambiguous assignment of all resonances could be performed by combined application of standard NMR techniques, such as APT, HSQC, HMBC, COSY and NOESY experiments. Solutions were evaporated under reduced pressure with a rotary evaporator.

All the reactions involving organolithium reagents were carried out under inert atmosphere of argon. THF was distilled over Na / benzophenone. Chemicals were purchased from Sigma-Aldrich, Fluorochem Acros, Alfa Aesar and TCI Europe.

The mixture of alcohols **4** and **5** for HPLC traces was obtained *via* chemical reduction ( $\text{NaBH}_4$ ).

### Benzyl [(2*R*)-1-[methoxy(methyl)amino]-1-oxo-3-(phenylsulfanyl)-2-propanyl]carbamate (**2**)

To a solution of *N*-Carbobenzoxy-*S*-phenyl-L-cysteine **1** (3.0 g, 9 mmol, 1.0 equiv) in CPME (30 mL) was added 1,1'-carbonyldiimidazole (CDI, 1.61 g, 9.9 mmol, 1.05 equiv) in one portion and it was allowed to stir for 3 h at rt. Then, *N,O*-dimethylhydroxylamine hydrochloride (DMHA, 1.05 g, 10.8 mmol, 1.05 equiv) was added all at once, turning the solution a cloudy white. The reaction mixture was stirred overnight at rt and then quenched with 10 mL of a saturated aq. solution of  $\text{NH}_4\text{Cl}$  and, the aqueous layer was extracted with diethyl ether (2 x 15 mL). The combined organic layers were washed with water (30 mL) and brine (40 mL) then, dried over  $\text{Na}_2\text{SO}_4$  and the solvent was removed *in vacuo*. The crude product was then purified by recrystallization from *i*-



propanol washed with *n*-hexane (20 mL) to afford the amide as a pale yellow solid (3.13 g, 92%; mp: 79-80 °C). [ $\alpha$ ]<sub>D</sub><sup>20</sup>: +12.2° (c 0.3 CHCl<sub>3</sub>).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.44 (m, 2H, Sph H-2,6), 7.35 (m, 4H, Ph H-2,3,5,6), 7.33 (m, 1H, Ph H-4), 7.28 (m, 2H, Sph H-3,5), 7.20 (m, 1H, Sph H-4), 5.66 (br d, *J* = 8.4 Hz, 1H, NH), 5.10 and 5.09 (AB-System, <sup>2</sup>*J*<sub>AB</sub> = 12.3 Hz, 2H, CH<sub>2</sub>O), 4.89 (m, 1H, NHCH), 3.58 (s, 3H, OCH<sub>3</sub>), 3.32 (dd, *J* = 13.9, 4.7 Hz, 1H, SCH<sub>2</sub>), 3.10 (dd, *J* = 13.9, 7.1 Hz, 1H, SCH<sub>2</sub>), 3.07 (s, 3H, NCH<sub>3</sub>). **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 170.3 (C=O), 155.8 (OC=O), 136.2 (Ph C-1), 134.9 (Sph C-1), 130.9 (Sph C-2,6), 128.9 (Sph C-3,5), 128.5 (Ph C-2,6), 128.1 (Ph C-4), 128.0 (Ph C-3,5), 126.8 (Sph C-4), 66.9 (CH<sub>2</sub>O), 61.5 (OCH<sub>3</sub>), 50.6 (NHCH), 36.9 (SCH<sub>2</sub>), 32.0 (NCH<sub>3</sub>). **<sup>15</sup>N NMR** (40 MHz, CDCl<sub>3</sub>)  $\delta$ : -296.7 (NHCH), -196.1 (NCH<sub>3</sub>). **HRMS (ESI)**, *m/z*: calcd. for C<sub>19</sub>H<sub>22</sub>N<sub>2</sub>NaO<sub>4</sub>S: 397.1192 [M+Na]<sup>+</sup>; found. 397.1201.

#### Benzyl [(2*R*)-4-chloro-3-oxo-1-(phenylsulfanyl)-2-butanyl]carbamate<sup>14b</sup> (**3**)

To a solution of benzyl [(2*R*)-1-[methoxy(methyl)amino]-1-oxo-3-(phenylsulfanyl)-2-propanyl]carbamate **2** (0.374 g, 1.0 mmol, 1.0 equiv) in THF, ICH<sub>2</sub>Cl (0.22 mL, 3.0 mmol, 3.0 equiv) was added and the solution was cooled at -78 °C for 10 minutes. Then MeLi-LiBr (1.5 M, 1.87 mL, 2.8 equiv) was added dropwise over 30 minutes. After 2 hours the reaction was quenched with saturated aq. NH<sub>4</sub>Cl (3.0 mL), the cooling bath was removed and the reaction was left under stirring until reached rt. The mixture was extracted with diethyl ether (2 x 20 mL) and the organic phase was further washed with brine (10 mL). The combined organic layers were washed with water (20 mL) and then dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography on silica gel – previously deactivated with 2% (v/v) TMSCl – using *n*-hexane / ethyl acetate (6:4, v/v) as the eluent. Analytically pure compound **3** was obtained as a white solid (0.305 g, 84%; mp: 89-91 °C - lit.<sup>14b</sup> 91-92 °C). [ $\alpha$ ]<sub>D</sub><sup>20</sup>: +10.8° (c 0.4 CHCl<sub>3</sub>), lit.:<sup>14b</sup> [ $\alpha$ ]<sub>D</sub><sup>20</sup>: +12.7° (c 1.01 CHCl<sub>3</sub>).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.38 (m, 2H, Sph H-2,6), 7.37 – 7.30 (m, 5H, Ph H-2,3,4,5,6), 7.28 (m, 2H, Sph H-3,5), 7.25 (m, 1H, Sph H-4), 5.57 (br d, *J* = 6.3 Hz, 1H, NH), 5.08 (s, 2H, CH<sub>2</sub>O), 4.73 (m, 1H, NHCH), 4.20 (part A of an AB-System, <sup>2</sup>*J*<sub>AB</sub> = 15.9 Hz, 2H, CH<sub>2</sub>Cl), 4.14 (part B of an AB-System, <sup>2</sup>*J*<sub>AB</sub> = 15.9 Hz, 2H, CH<sub>2</sub>Cl), 3.42 (dd, *J* = 14.0, 5.4 Hz, 1H, SCH<sub>2</sub>), 3.33 (dd, *J* = 14.0, 6.1 Hz, 1H, SCH<sub>2</sub>). **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 199.6 (C=O), 155.7 (OC=O), 135.8 (Ph C-1), 133.8 (Sph C-1), 130.9 (Sph C-2,6), 129.4 (Sph C-3,5), 128.6 (Ph C-2,6), 128.4 (Ph C-4), 128.1 (Ph C-3,5), 127.5 (Sph C-4), 67.4 (CH<sub>2</sub>O), 57.0 (NHCH), 46.9 (CH<sub>2</sub>Cl), 35.7 (SCH<sub>2</sub>). **<sup>15</sup>N NMR** (40 MHz, CDCl<sub>3</sub>)  $\delta$ : -296.7 (NHCH). **HRMS (ESI)**, *m/z*: calcd. for C<sub>18</sub>H<sub>18</sub>ClNNaO<sub>3</sub>S: 386.0588 [M+Na]<sup>+</sup>; found 386.0593.

#### Benzyl [(2*R*,3*S*)-4-chloro-3-hydroxy-1-(phenylsulfanyl)-2-butanyl]carbamate<sup>28c</sup> (**4**)

Benzyl [(2*R*)-4-chloro-3-oxo-1-(phenylsulfanyl)-2-butanyl]carbamate **3** (0.018 g, 0.05 mmol) was dissolved in *i*-propanol (2 mL). Contemporaneously, ketoreductase enzyme P1-C02 (0.01 g) was suspended in an eppendorf containing KRED recycle mix P (0.030 g) solubilized in H<sub>2</sub>O (0.8 mL). The solution of substrate **3** in *i*-propanol was added to the latter suspension and, the eppendorf was positioned in a shaker at 200 rpm/ 30 °C and monitored by TLC. After 24 h AcOEt (1.0 mL) was added, the eppendorf was shaken with vortex for 30 s and the phases separated by centrifugation (10 min 16000 rpm). The procedure is repeated and the organic phase was transferred into another eppendorf and dried on Na<sub>2</sub>SO<sub>4</sub>. Then, the organic phase is filtered, transferred in a vial and concentrated under reduced pressure. The (*R,S*)-isomer has been isolated as white solid (17 mg, 95%, mp: 111-113 °C, lit.:<sup>28c</sup> 113-114 °C) after chromatography on silica gel (*n*-hexane – ethyl acetate 8/2). [ $\alpha$ ]<sub>D</sub><sup>20</sup>: -69.3° (c 0.7 MeOH), lit.:<sup>28c</sup> [ $\alpha$ ]<sub>D</sub><sup>20</sup>: -73.4° (c 0.96 MeOH).

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.38 (m, 2H, Sph H-2,6), 7.36 – 7.30 (m, 5H, Ph H-2,3,4,5,6), 7.27 (m, 2H, Sph H-3,5), 7.20 (m, 1H, Sph H-4), 5.15 (br s, 1H, NH), 5.07 (s, 2H, CH<sub>2</sub>O), 3.93 (m, 1H, OHCH), 3.92 (m, 1H, NHCH), 3.68 (dd, *J* = 11.4, 3.5 Hz, 1H, CH<sub>2</sub>Cl), 3.60 (dd, *J* = 11.4, 3.5 Hz, 1H, CH<sub>2</sub>Cl), 3.30 (m, 2H, SCH<sub>2</sub>), 2.81 (br s, 1H, OH). **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 156.1 (OC=O), 136.0 (Ph C-1), 135.2 (Sph C-1), 130.1 (Sph C-2,6), 129.2 (Sph C-3,5), 128.6 (Ph C-3,5), 128.3 (Ph C-4), 128.1 (Ph C-2,6), 126.8 (Sph C-4), 72.9 (CHOH), 67.2 (CH<sub>2</sub>O), 53.3

(NHCH), 47.2 (CH<sub>2</sub>Cl), 35.3 (SCH<sub>2</sub>). <sup>15</sup>N NMR (40 MHz, CDCl<sub>3</sub>) δ: -295.5 (NHCH). HRMS (ESI), *m/z*: calcd. for C<sub>18</sub>H<sub>20</sub>ClNNaO<sub>3</sub>S: 388.0745 [M+Na]<sup>+</sup>; found 388.0748. The sample was analyzed by HPLC (Chiralpak IA Column, λ 220 nm, 90 *n*-hexane/ 10 *i*-propanol, 1ml/min, 20 °C; *t<sub>R</sub>* (*R,R*): 14,85 min; *t<sub>R</sub>* (*R,S*): 18,47 min, *de* 99:1.

#### Synthesis of compound 4 in 1 mmol scale (entry 36 – Table 2)

By following an analogous procedure, starting from compound **3** (0.364 g, 1.0 mmol) in *i*-propanol (40 mL) containing CMPE 5% (v/v), KRED-P1-C02 (0.2 g) and KRED recycle mix P (0.60 g in 16 mL of H<sub>2</sub>O), compound **4** was obtained as a white solid (332 mg) in 91% yield. Spectroscopic data, optical rotation power and HPLC charts perfectly match with those ones reported above.

#### Benzyl [(2*R*,3*R*)-4-chloro-3-hydroxy-1-(phenylsulfanyl)-2-butanyl]carbamate<sup>13</sup> (**5**)

Benzyl [(2*R*)-4-chloro-3-oxo-1-(phenylsulfanyl)-2-butanyl]carbamate **3** (0.018 g, 0.05 mmol) was dissolved in *i*-propanol (2 mL) containing CMPE 5% (v/v). Contemporaneously, ketoreductase enzyme P1-A04 (0.01 g) was suspended in an eppendorf containing KRED recycle mix P (0.030 g) solubilized in H<sub>2</sub>O (0.8 mL). The solution of substrate **3** in *i*-propanol was added to the latter suspension and, the eppendorf was positioned in a shaker at 200 rpm/ 30 °C and monitored by TLC. After 24 h AcOEt (1.0 mL) was added, the eppendorf was shaken with vortex for 30 sec and the phases separated by centrifugation (10 min, 16000 rpm). The procedure is repeated and the organic phase was transferred into another eppendorf and dried over NaSO<sub>4</sub>. Then, the organic phase is filtered, transferred in a vial and concentrated under reduced pressure. Compound **5** was isolated as pale yellow oil (6 mg, 31%). [α]<sub>D</sub><sup>20</sup>: +26.2° (c 0.2 MeOH) <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.41 (m, 2H, SPh H-2,6), 7.39 – 7.32 (m, 5H, Ph H-2,3,4,5,6), 7.30 (m, 2H, SPh H-3,5), 7.21 (m, 1H, SPh H-4), 5.26 (d, *J* = 8.9 Hz, 1H, NH), 5.10 (part A of an AB System, <sup>2</sup>*J*<sub>AB</sub> = 12.2 Hz, 1H, CH<sub>2</sub>O), 5.09 (part B of an AB System, <sup>2</sup>*J*<sub>AB</sub> = 12.2 Hz, 1H, CH<sub>2</sub>O), 4.19 (m, 1H, OHCH), 3.87 (m, 1H, NHCH), 3.52 (m, 2H, CH<sub>2</sub>Cl), 3.27 (dd, *J* = 13.8, 6.1 Hz, 1H, SCH<sub>2</sub>), 3.12 (dd, *J* = 13.8, 8.1 Hz, 1H, SCH<sub>2</sub>), 2.83 (d, *J* = 2.8 Hz, 1H, OH). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 156.3 (OC=O), 136.1 (Ph C-1), 135.0 (SPh C-1), 129.5 (SPh C-2,6), 129.2 (SPh C-3,5), 128.6 (Ph C-3,5), 128.3 (Ph C-4), 128.1 (Ph C-2,6), 126.6 (SPh C-4), 70.8 (CHOH), 67.2 (CH<sub>2</sub>O), 52.3 (NHCH), 47.5 (CH<sub>2</sub>Cl), 35.6 (SCH<sub>2</sub>). <sup>15</sup>N NMR (40 MHz, CDCl<sub>3</sub>) δ: -299.2 (NHCH). HRMS (ESI), *m/z*: calcd. for C<sub>18</sub>H<sub>20</sub>ClNNaO<sub>3</sub>S: 388.0745 [M+Na]<sup>+</sup>; found 388.0749. The sample was analysed by HPLC (Chiralpak IA Column, λ 220 nm, 90 *n*-hexane / 10 *i*-propanol, 1mL/min, 20 °C; Rt (*R,R*): 14,85 min; Rt (*R,S*): 18,47 min. *de* 1:99.

#### Benzyl [(1*R*)-1-[(2*S*)-2-oxiranyl]-2-(phenylsulfanyl)ethyl]carbamate (**6**).<sup>6b,13</sup>

To a solution of benzyl [(2*R*,3*S*)-4-chloro-3-hydroxy-1-(phenylsulfanyl)-2-butanyl]carbamate **4** (365 mg, 1.0 mmol, 1.0 equiv) in MeCN (5 mL) at 0 °C, potassium fluoride supported on Celite (50% w/w, 232 mg, 2.0 mmol, 2.0 equiv) was added and the mixture was stirred for 1 h. After cooling to rt, the mixture was filtered under reduced pressure and washed with dichloromethane (10 mL). The resulting organic solution was concentrated *in vacuo* to afford pure epoxide **6** as colourless crystals (306 mg, 93%, mp: 61 °C, lit.<sup>28e</sup> mp 61-62°C). [α]<sub>D</sub><sup>20</sup>: -24.4° (c 1.0 CHCl<sub>3</sub>), lit.:<sup>28e</sup> -26.2 (c 1.01 CHCl<sub>3</sub>).

<sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>) δ: 7.50 – 7.09 (m, 10H), 5.09 (s, 3H), 3.71 (dtd, *J* = 12.1, 6.4, 2.8 Hz, 2H), 3.22 (d, *J* = 5.7 Hz, 2H), 3.00 (dt, *J* = 6.5, 3.3 Hz, 1H), 2.77 (d, *J* = 3.2 Hz, 2H). <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>) δ: 155.8, 136.1, 135.1, 130.0, 129.1, 128.5, 128.4, 128.1, 126.8, 67.0, 52.6, 52.3, 46.9, 36.1. HRMS (ESI), *m/z*: calcd. for C<sub>18</sub>H<sub>19</sub>NNaO<sub>3</sub>S: 352.0978 [M+Na]<sup>+</sup>; found 352.0981.

#### Nelfinavir mesylate - (3*S*,4*aS*,8*aS*)-*N*-(*tert*-butyl)-2-[(2*R*,3*R*)-2-hydroxy-3-(3-hydroxy-2-methylbenzamido)-4-(phenylthio)butyl]decahydroisoquinoline-3-carboxamide (as mesylate salt)

By applying a reported procedure<sup>6b</sup> Nelfinavir mesylate was prepared from compound **6** in 75% isolated yield.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ: 8.31 (br s, 1H), 7.99 (br s, 1H), 7.40 – 7.35 (m, 3H), 7.23 (m, 3H), 7.15 (m, 1H), 6.85 (m, 1H), 6.78 (m, 1H), 6.68 (m, 1H), 5.74 (br s, 1H), 4.25 (m, 3H), 3.47 – 3.21 (m, 5H), 2.68 (s, 3H), 2.14 (br s, 3H), 2.05 (br s, 4H), 1.78 – 1.26 (complex, 13H). **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ: 172.2, 167.3, 155.1, 136.8, 135.3, 129.8, 129.1, 126.5, 126.4, 122.1, 118.4, 117.1, 68.5, 66.8, 60.1, 59.8, 52.9, 52.2, 39.5, 34.1, 31.1, 31.0, 29.8, 28.7, 28.3, 25.6, 24.3, 20.0, 12.8. **HRMS (ESI)**, *m/z*: calcd. for C<sub>32</sub>H<sub>45</sub>N<sub>3</sub>NaO<sub>4</sub>S: 590.3023 [M+Na]<sup>+</sup>; found 590.3023.

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**$\alpha$ -arylamino diazoketones: diazomethane-loading controlled synthesis, spectroscopic investigations and structural X-ray analysis.**

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# **$\alpha$ -Arylamino Diazoketones: Diazomethane-Loading Controlled Synthesis, Spectroscopic Investigations and Structural X-ray Analysis**

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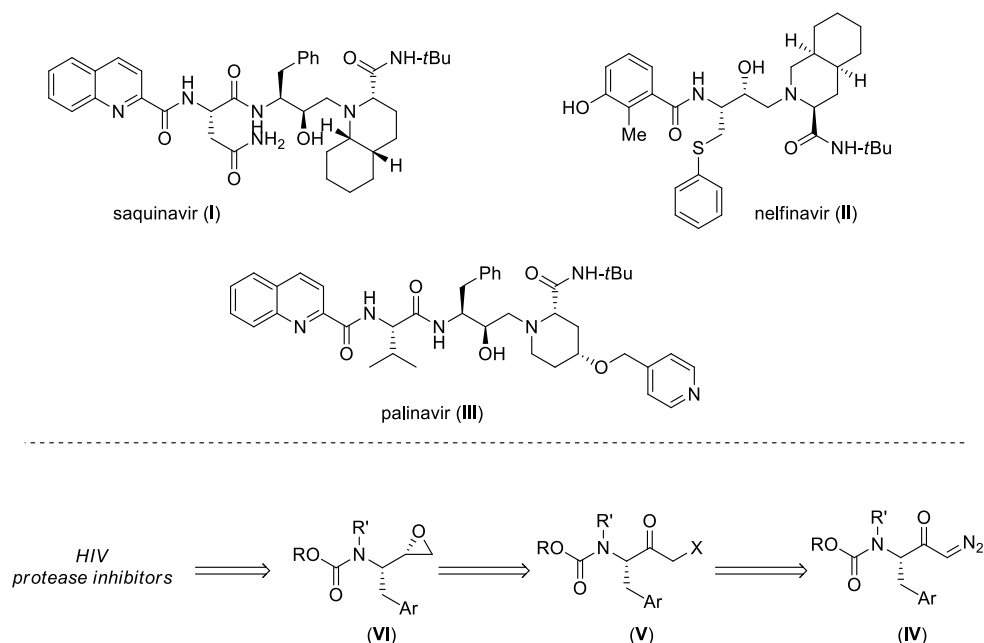
## **Abstract**

Primary and secondary  $\alpha$ -halomethyl diazoketones generated *via* Arndt-Eistert chemistry with minimum loading of diazomethane efficiently alkylate aromatic amines in the presence of calcium oxide to furnish the corresponding  $\alpha$ -arylamino diazoketones under full chemocontrol. Such a simple inorganic acid scavenger fully neutralizes the hydrohalic acid formed during the nucleophilic displacement which otherwise would immediately react to produce the corresponding  $\alpha$ -haloketone. The methodology can be further exploited in analogous acylation-type processes on secondary arylamino diazoketones. In depth spectroscopic (<sup>1</sup>H, <sup>13</sup>C and <sup>15</sup>N-NMR) and crystallographic analyses document interesting structural features of these previously unknown diazo derivatives.



## Introduction

$\alpha$ -Diazoketones represent a versatile class of organic compounds given the plethora of transformations that the reactive diazo moiety can undergo.<sup>1</sup> In particular, it could act as precursor of  $\beta$ -lactams,<sup>2</sup>  $\beta$ -amino acid derivatives<sup>3</sup> and in general  $\beta$ -peptides *via* the Wolff rearrangement<sup>4</sup> or as placeholder for transition-metal-catalyzed reactions (*e.g.* carbenoid chemistry, cyclopropanation, ylide-mediated processes).<sup>5</sup> Effectively, the contemporaneous presence of an amino group renders the corresponding  $\alpha$ -amino diazoketones very interesting from a synthetic medicinal chemistry perspective (Figure 1).<sup>6</sup> In this regard, because of the synthetic equivalence of diazo compounds to carbocations, this motif has been often employed for the preparation of  $\alpha$ -haloketones through the reaction with hydrohalic acids<sup>5a,7</sup> in alternative to lithium carbenoids<sup>8</sup> or sulfur-ylides<sup>9</sup> based strategies on different acyl donors. In fact, they represent valuable scaffolds for the preparation of HIV inhibitors<sup>10</sup> such as saquinavir<sup>11</sup> (**I**), nelfinavir<sup>12</sup> (**II**) or palinavir<sup>13</sup> (**III**), in which the diazo moiety (**IV**) acts as precursor of the  $\alpha$ -haloketone (**V**) which, upon stereoselective reduction-closure sequence to the epoxide<sup>6,10</sup> (**VI**), provides the core of such important drugs.



**Figure 1.** Importance of the  $\alpha$ -amino diazoketone motif in medicinal chemistry. Examples of drugs prepared *via* an intermediate diazo ketone (*top*). General synthetic sequence to convert an  $\alpha$ -amino diazoketone into an HIV protease inhibitor (*down*).

So far, the most common access to  $\alpha$ -amino diazoketones is constituted by the Arndt-Eistert type diazotization<sup>1c,14</sup> of an activated carboxylic functionality (**VII**, Scheme 1) such as a chloride<sup>15</sup> or a (mixed) anhydride with diazomethane ( $\text{CH}_2\text{N}_2$ ).<sup>6,16</sup> However, a series of widely known drawbacks limits the applicability of these procedures: a) the approach is evidently non attractive from a synthetic perspective because the activation and the diazotization steps need to be repeated in parallel for the full series of amino acids; b) as a consequence of the hazardous and safety issues of using an explosive (bp  $-23\text{ }^\circ\text{C}$ ) and a carcinogenic and skin irritant as diazomethane is,<sup>17</sup> it does not represent an ideal process for suitable industrial applications;<sup>18</sup> c) the success of the method strongly depends on the nature of the substituents on the aminic nitrogen which could lead to substantial decomposition of the products;<sup>19</sup> d) from a chemoselective perspective the resulting  $\alpha$ -amino diazoketones are contaminated by variable amounts of the corresponding methyl esters<sup>20</sup> or  $\alpha$ -halomethyl ketones (Nierenstein process)<sup>21</sup> generated through side reactions dependent on the conditions employed for the activation; e) the direct diazotization of an optically active acid chloride leads to considerable racemization and thus, the employment of synthetically non-economical activation as mixed anhydride still remains the preferred method to overcome this issue.<sup>3,16b</sup> For example, Siciliano and Liguori reported an effective *one-pot* preparation of *N*-Fmoc protected diazoketones highlighting the dual role of Fmoc-Cl as both protecting group source and carboxylic moiety activator agent for the diazotization.<sup>19</sup> Notwithstanding, the innate potential of  $C_1$  homologations<sup>22</sup> realized with diazomethane still continues to attract interest within the synthetic community<sup>1b,1c</sup> and, the advent of microfluidic techniques allowed to design safe reliable processes for methyl esters production,<sup>23</sup> synthesis of pyrazoles or  $\beta$ -amino acids,<sup>23b,24</sup> as well as, Pd-catalyzed cyclopropanations,<sup>23b</sup> *inter alia*.<sup>25</sup> Remarkably, Kappe documented the direct synthesis of  $\alpha$ -halo ketones<sup>23b,26</sup> from *N*-protected amino acids *via* Arndt-Eistert chemistry *without* isolating the intermediate  $\alpha$ -diazoketones.

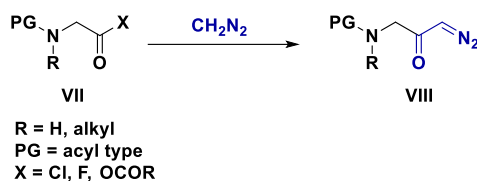
A conceptually distinct approach to  $\alpha$ -amino diazoketones (**X**) would involve the use of a preformed  $\alpha$ -halo diazoketone (**IX**) to alkylate the nitrogen atom of amines (Scheme 1). Although this strategy has been employed for the functionalization of different nucleophiles such as alcohols<sup>27</sup> and thiols,<sup>28</sup> analogous reactions in the case of amines are limited to *aliphatic* ones, thus leaving unexplored the full synthetic

potential.<sup>29</sup> An excess was required for ensuring good chemical yields and significantly, as far as we know, more challenging aromatic amines have not been employed in these processes.<sup>29a</sup>

As part of our research program aimed at the identification and development of homologation strategies,<sup>8c,30</sup> we have been seeking approaches for the preparation of  $\alpha$ -diazoketones by using only minimal loadings (1 equiv, *i.e.* stoichiometric) of diazomethane<sup>21b</sup> introducing the beneficial effect displayed by a cheap and simple earth-alkaline metal oxide (*i.e.* CaO) as an effective hydrohalic acid scavenger for the acylation of diazomethane. The formation of innocuous by-products as calcium halide (CaX<sub>2</sub>) and water, together with excellent chemoselectivities, makes the method versatile and considerably more convenient than previously employed techniques. In fact, the addition of amines could trigger ketene formation events on acid halides featuring acidic  $\alpha$ -protons,<sup>31</sup> while realizing chemistry with big excesses of CH<sub>2</sub>N<sub>2</sub> (2-6 equiv, *i.e.* 200-600 mol %) poses serious questions on the real practicability of using such a hazardous reagent.<sup>18a</sup> The reliability of the method was further documented in the synthesis of enantiopure diazoketones, as reported in recent works by Deska<sup>32</sup> and Gaich.<sup>33</sup> Additionally, we also extended its use to the chemoselective acylation of different nucleophiles such as amines and alcohols<sup>34</sup> in the biomass-derived solvent 2-methyltetrahydrofuran (2-MeTHF).<sup>35</sup>

Cognizant of the substantial improvement introduced in *acylation* processes by running reaction in the presence of CaO, we deemed similar *alkylation* procedures could benefit as well. In fact, considering that also in the latter case the deleterious (for the diazo group) by-product was the liberated hydrohalic acid (HX), its simple removal *via* CaO-mediated chemisorption appeared worth of investigations and herein, we present our results on a straightforward route to  $\alpha$ -arylamino diazoketones. We anticipate the role of CaO consists in the formation - upon reaction with HX - of the innocuous CaX<sub>2</sub> salt which can be easily eliminated *via* filtration. Notably, only one diazotization procedure was accomplished and the full series of compounds was simply obtained by a simple nucleophilic displacement.

Classical approach:

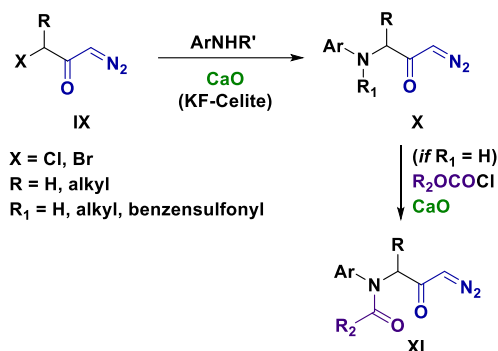


Drawbacks:

- Needing to prepare several activated carboxylic derivatives;
- The Arndt-Eistert procedure (i.e. repeated use of  $\text{CH}_2\text{N}_2$ ) must be realized on each one of the substrates;
- Chemoselective issues: effect of the PG on the transformation and formation of undesired contaminant compounds:



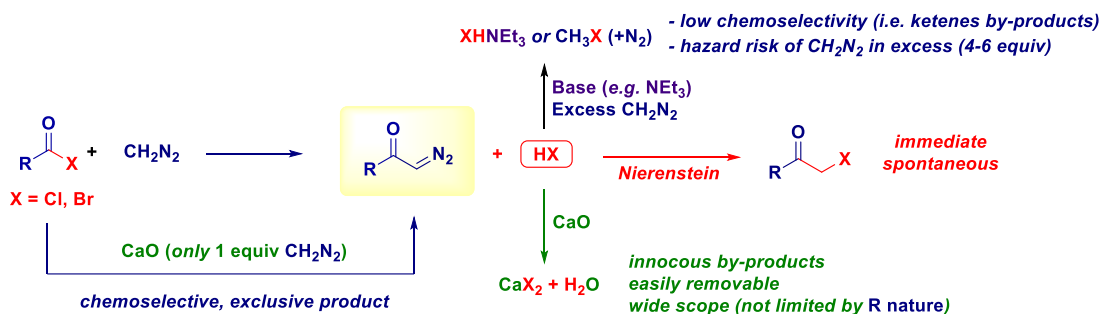
This work:



Advantages:

- The common diazo precursors are easily obtained in high yields;
- The use of diazomethane is limited to the preparation of the alkylating agents;
- High yields and full control of chemoselectivity

CaO beneficial effect in  $\text{CH}_2\text{N}_2$  acylation (2010)



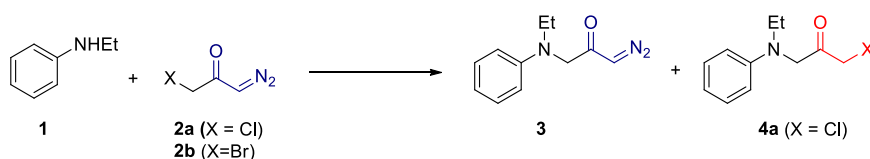
**Scheme 1.** Preparation of  $\alpha$ -amino diazoketones: classical approach vs. this study (top). Concept of CaO-mediated diazomethane acylation (down).

## Results and Discussion

Using *N*-ethylaniline **1** and  $\alpha$ -chlorodiazooacetone **2a**<sup>21b</sup> as the model substrates, we explored the nucleophilic displacement under different conditions (Table 1). Interestingly, when the reaction was run in the absence of any base under stoichiometric conditions, we could isolate the corresponding  $\alpha$ -chloroketone **4** in 54% yield together with only 16% of the desired diazo ketone **3** (entry 1). It appeared clear that eliminating the so-called Nierenstein reaction<sup>21a</sup> between the incipient  $\alpha$ -diazoketone and the HCl liberated during the nucleophilic substitution was critical to achieve full chemoselectivity. Accordingly, when the loading of **1** was

progressively increased to 4 equiv a substantial improvement of the yield of the target compound up to 49% (entries 2-3) was observed. These preliminary results suggest that the excess of amine neutralizes the HCl by-product formed during the reaction. The addition of an external base (2 equiv.) such as DIPEA and TEA or inorganic ones ( $\text{K}_2\text{CO}_3$ ,  $\text{KHCO}_3$ ,  $\text{Na}_2\text{CO}_3$ ) confirms this trend but, unfortunately the concomitant formation of the  $\alpha$ -chloroketone could not be suppressed at all (entries 4-8). Pleasingly, by using a simple acid scavenger (under stoichiometric conditions) such as CaO we could obtain exclusively the desired diazoketone in a satisfactory 61% yield (entry 9). A brief screening of other metal oxides such as MgO, ZnO and  $\text{Al}_2\text{O}_3$  revealed the better performance of CaO (entries 10-12). Interestingly, by employing earth-alkaline metal bases (*i.e.*  $\text{CaCO}_3$  and  $\text{MgCO}_3$ , entries 13-14) an analogous result to the above seen potassium and sodium (bi)-carbonates was observed, albeit the formation of  $\alpha$ -chloroketone was somewhat reduced. The solvent effect was remarkable in order to maximize the yield of **3**, though the chemoselectivity was not affected : DMSO proved to be the best solvent to accomplish the reaction (entries 15 and 24) compared to other media such as dichloromethane, 1,2-dichloroethane, DMF, THF, 2-MeTHF and acetonitrile (entries 16-21 and 25). Temperature was crucial to optimize the reaction: at rt reaction reached to completion within 12 h (entry 15), while attempts to increase up to 60 °C resulted in obtaining low yields of the desired diazoketone **3** jointly with complex decomposition products (entries 22-23). Finally, the use of the corresponding  $\alpha$ -bromodiazooacetone **2b** allowed to shortening reaction time to 8 h thus, obtaining the desired diazoketone **3** in a very good 86% yield (entry 24).

Table 1. Reaction optimization.<sup>a</sup>



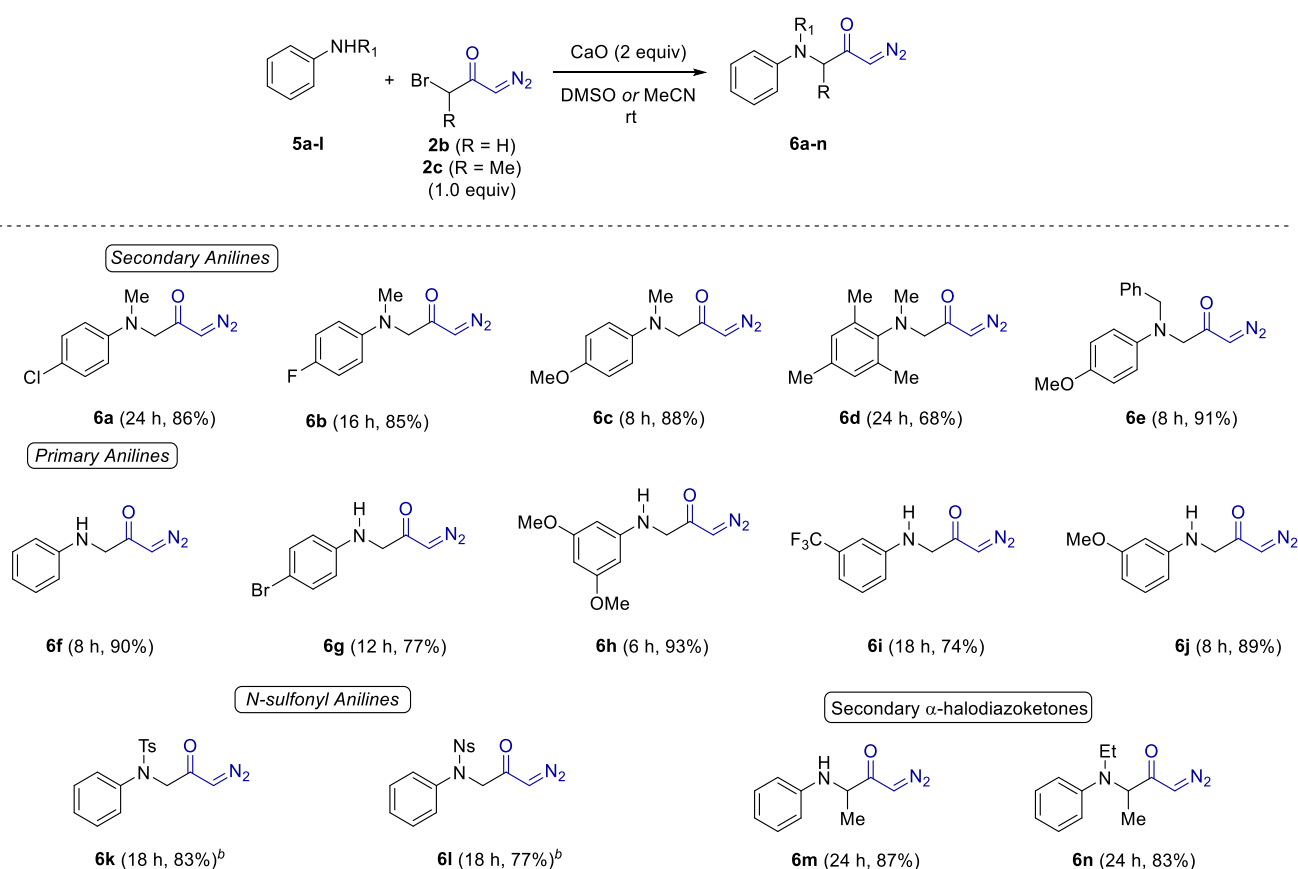
| Entry           | <b>1</b> (equiv.) | Base or acidic sponge (equiv)         | Solvent / Temperature (° C) | Reaction time (h) | Yield of <b>3</b> (%) <sup>a</sup> | Yield of <b>4a</b> (%) <sup>a</sup> |
|-----------------|-------------------|---------------------------------------|-----------------------------|-------------------|------------------------------------|-------------------------------------|
| 1               | 1.0               | -                                     | Et <sub>2</sub> O / rt      | 24                | 16                                 | 54                                  |
| 2               | 2.5               | -                                     | Et <sub>2</sub> O / rt      | 24                | 34                                 | 31                                  |
| 3               | 4.0               | -                                     | Et <sub>2</sub> O / rt      | 12                | 49                                 | 18                                  |
| 4               | 4.0               | DIPEA (2.0)                           | Et <sub>2</sub> O / rt      | 12                | 55                                 | 16                                  |
| 5               | 3.0               | TEA (2.0)                             | Et <sub>2</sub> O / rt      | 12                | 58                                 | 21                                  |
| 6               | 3.0               | K <sub>2</sub> CO <sub>3</sub> (2.0)  | Et <sub>2</sub> O / rt      | 12                | 57                                 | 13                                  |
| 7               | 3.0               | KHCO <sub>3</sub> (2.0)               | Et <sub>2</sub> O / rt      | 12                | 53                                 | 17                                  |
| 8               | 3.0               | Na <sub>2</sub> CO <sub>3</sub> (2.0) | Et <sub>2</sub> O / rt      | 12                | 55                                 | 15                                  |
| 9               | 1.0               | CaO (2.0)                             | Et <sub>2</sub> O / rt      | 12                | 61                                 | -                                   |
| 10              | 1.0               | MgO (2.0)                             | Et <sub>2</sub> O / rt      | 12                | 55                                 | 8                                   |
| 11              | 1.0               | ZnO (2.0)                             | Et <sub>2</sub> O / rt      | 12                | 51                                 | 14                                  |
| 12              | 1.0               | Al <sub>2</sub> O <sub>3</sub> (2.0)  | Et <sub>2</sub> O / rt      | 12                | 46                                 | 8                                   |
| 13              | 1.0               | CaCO <sub>3</sub> (2.0)               | Et <sub>2</sub> O / rt      | 12                | 54                                 | 13                                  |
| 14              | 1.0               | MgCO <sub>3</sub> (2.0)               | Et <sub>2</sub> O / rt      | 12                | 51                                 | 15                                  |
| 15              | 1.0               | CaO (2.0)                             | DMSO / rt                   | 12                | 81                                 | -                                   |
| 16              | 1.0               | CaO (2.0)                             | DCM / rt                    | 12                | 54                                 | -                                   |
| 17              | 1.0               | CaO (2.0)                             | DCE / rt                    | 12                | 64                                 | -                                   |
| 18              | 1.0               | CaO (2.0)                             | DMF / rt                    | 12                | 57                                 | -                                   |
| 19              | 1.0               | CaO (2.0)                             | THF / rt                    | 12                | 49                                 | -                                   |
| 20              | 1.0               | CaO (2.0)                             | 2-MeTHF / rt                | 24                | 38                                 | -                                   |
| 21              | 1.0               | CaO (2.0)                             | DMF / rt                    | 12                | 72                                 | -                                   |
| 22              | 1.0               | CaO (2.0)                             | MeCN / 40                   | 8                 | 46                                 | -                                   |
| 23              | 1.0               | CaO (2.0)                             | MeCN / 60                   | 6                 | 32                                 | -                                   |
| 24 <sup>b</sup> | 1.0               | CaO (2.0)                             | DMSO / rt                   | 8                 | 86                                 | -                                   |
| 25 <sup>b</sup> | 1.0               | CaO (2.0)                             | MeCN / rt                   | 12                | 80                                 | -                                   |

<sup>a</sup> Isolated yield. <sup>b</sup> **2b** was employed as the alkylating agent.

Once the optimal conditions have been established, we next turned our attention to the scope of the reaction. As shown in Scheme 2, various secondary aromatic amines react smoothly to afford the desired diazo compounds (**6a-e**): the presence of steric hindrance on the aromatic ring (**6d**) or, the use of less nucleophilic anilines (**6a-b**) do not influence the effectiveness - although a substantial increase of the reaction time was noticed compared to more nucleophilic ones (**6c**, **6e**). Analogously, the protocol is applicable to primary aromatic amines which showed a similar trend based on the nucleophilicity of the amines (**6f-j**). When *N*-sulfonamido-type protected anilines were employed, only traces of diazoketones were recovered after prolonged reaction times; however, by adding a proper base such as KF-Celite (2 equiv) in acetonitrile<sup>36</sup>

prior to the addition of **2b** permitted a successful outcome thus, giving diazo ketones **6k** and **6l** in very good yields. Remarkably the fluoride base chemoselectively deprotonates the sulfonamide anilines, thus simply increasing the nucleophilicity of the conjugate base. No concomitant proton abstraction at the alkali-sensitive C-H bond<sup>37</sup> of the diazo moiety was noticed. Interestingly, the procedure could be efficiently applied also for the alkylation of aniline derivatives with a secondary bromide (**2c**) thus, providing  $\alpha$ -arylamino- $\alpha'$ -diazoketones **6m** and **6n** in high yields after 24 h.

Scheme 2. Scope of the reaction.<sup>a</sup>

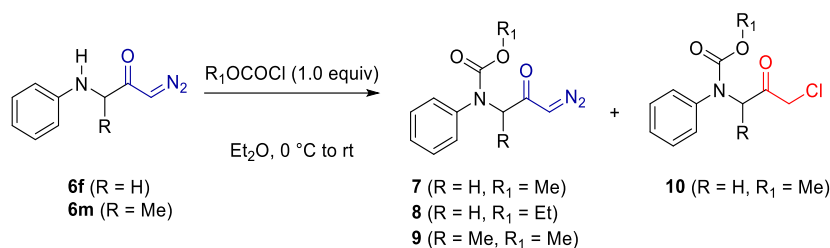


<sup>a</sup> Isolated yields. <sup>b</sup> Reaction run in MeCN; KF-Celite 2.0 equiv was added to the suspension of *N*-benzensulfonyl-type aniline. Ns = 4-nitrobenzensulfonyl.

Calcium oxide was also effective in preserving the highly sensitive diazo moiety to the acidic environment generated through the release of HCl during the acylation of diazoketones **6f** and **6m** with chloroformates. As showed in Table 2, in its absence exclusively chloroketone **10** was formed within only 10 min thus, further showcasing its capability to act as an innocuous acid scavenger to completely impede deleterious

Nierenstein-type phenomena. Thus, upon the addition of CaO (2 equiv), we could obtain the desired acyl-type protected diazoketones **7-9** in a fully chemoselective fashion, without observing any collateral chloroketone.

Table 2. Chemoselective CaO-mediated acylation of a secondary  $\alpha$ -aminodiazoketone with chloroformates.



| Entry | Diazoketone | Chloroformate | Acid scavenger (equiv) | Reaction time (min) | Acyl-diazoketone (%) <sup>a</sup> | Acyl-chloroketone (%) <sup>a</sup> |
|-------|-------------|---------------|------------------------|---------------------|-----------------------------------|------------------------------------|
| 1     | <b>6f</b>   | MeOCOC(=O)Cl  | -                      | 10                  | -                                 | <b>(10)</b> 84                     |
| 2     | <b>6f</b>   | MeOCOC(=O)Cl  | CaO (2.0)              | 60                  | <b>(7)</b> 95                     | -                                  |
| 3     | <b>6f</b>   | EtOCOC(=O)Cl  | CaO (2.0)              | 60                  | <b>(8)</b> 88                     | -                                  |
| 4     | <b>6m</b>   | MeOCOC(=O)Cl  | CaO (2.0)              | 60                  | <b>(9)</b> 91                     | -                                  |

<sup>a</sup> Isolated yield.

## X-ray Analysis

The diazo group (C=N=N) in **6k\_ortho** (Figure 2) is nearly coplanar with the carbonyl group (C=O) (a torsion angle O<sub>3</sub>-C<sub>15</sub>-C<sub>16</sub>-H<sub>16</sub> of -176.4° and the torsion angle O<sub>3</sub>-C<sub>15</sub>-C<sub>16</sub>-N<sub>2</sub> of 3.5°; Z orientation). The diazomethylene group deviates from planarity by approx. 20° (H<sub>16</sub>-C<sub>16</sub>-N<sub>2</sub>-N<sub>3</sub> of -163°, C<sub>15</sub>-C<sub>16</sub>-N<sub>2</sub>-N<sub>3</sub> of 17°). These values suggest that conjugation is possible between the carbonyl and the azomethylene groups in **6k\_ortho**. In addition, the C<sub>14</sub>-C<sub>15</sub>-C<sub>16</sub>-N<sub>2</sub> angle of -172.3° and C<sub>14</sub>-C<sub>15</sub>-C<sub>16</sub>-H<sub>16</sub> of -7.8° indicate that all six substituents around carbonyl lie in one plane. The C<sub>16</sub>-N<sub>2</sub> bond length of 1.322 Å is intermediate between an average sp<sup>3</sup> C-N (1.477-1.493 Å) and an average sp<sup>2</sup> C=N bond (~ 1.28 Å). The C<sub>16</sub>-N<sub>2</sub> bond length is comparable with the analogous bond in dibenzoyl diazomethane (1.338 Å). The N<sub>2</sub>-N<sub>3</sub> bond length in **6k** (1.123 Å) is slightly longer than an average sp<sup>2</sup> N=N bond (1.101 Å). In addition, the C<sub>15</sub>-C<sub>16</sub> bond length of 1.422 Å is slightly shorter than an average sp<sup>3</sup> C-C bond (1.542 Å). All results discussed for **6k\_ortho** strongly match to **6k\_mono**.



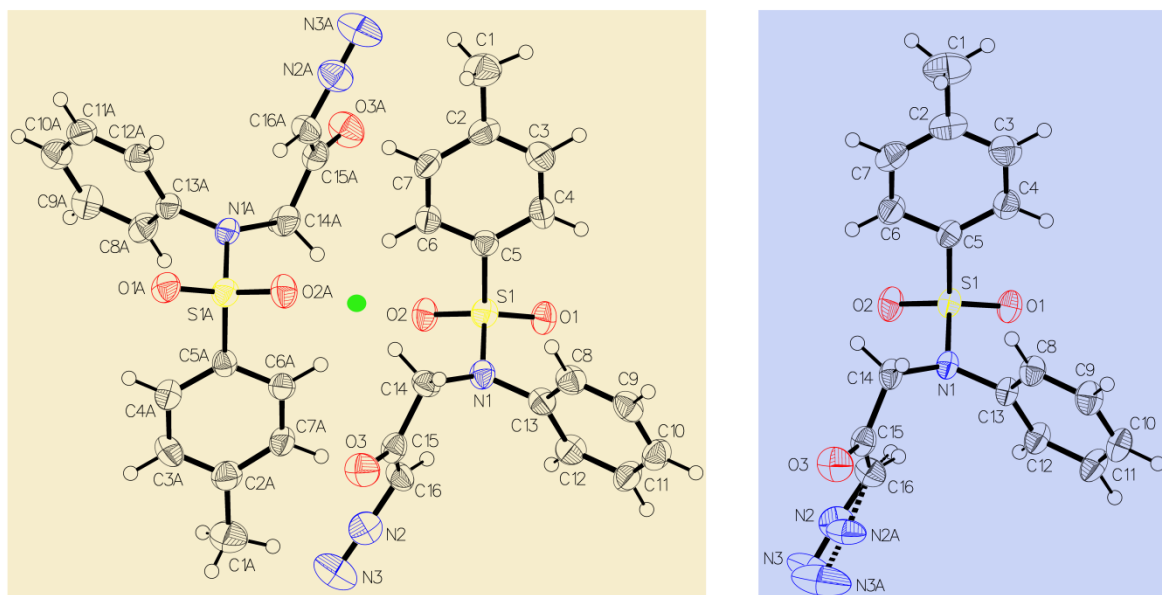


Figure 2. Compound 6k crystallizes in two different conformations. Asymmetric units of **6k\_ortho** (left, light orange) and **6k\_mono** (right, blue), drawn with 50% displacement ellipsoid.

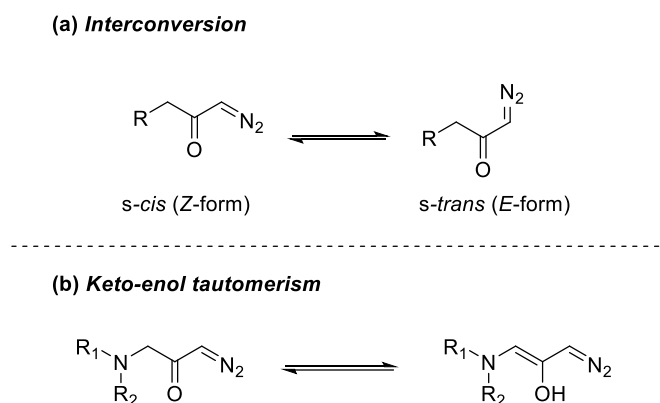
The three independent molecules have almost the same geometric data. In **6k\_mono** the solvent area was removed. It was not possible to proof the correct positions of the solvent. The volume of 194.8 Å<sup>3</sup> was removed. The according number of electrons cut is 45.1. This implies a too big volume in ratio to the available number of electrons and, therefore a very high degree of flexibility in this area for small possible solvent molecules such as water, methanol and ethanol. In **6k\_ortho** the probability of an inversion twin could be detected with TWIN LAW (-1.0, 0.0, 0.0, 0.0, -1.0, 0.0, 0.0, 0.0, -1.0) and BASF [0.57(11)]. Also a pseudo centre of symmetry (green) located at centre of mass for the asymmetric unit is visualized. Outside the asymmetric unit this pseudo centre is not valid.

### NMR Spectroscopic Investigations

The NMR data of selected diazoketones prepared are summarized in Tables 3 (<sup>1</sup>H-NMR data), 4 (<sup>13</sup>C-NMR data) and 5 (<sup>15</sup>N-NMR data). Characteristic features observed in all types of spectra recorded at ambient

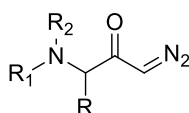
temperature are somewhat broadened lines for the nuclei belonging to the CH<sub>2</sub>-CO-CHN<sub>2</sub> system (see SI). This phenomenon can be attributed to hindered rotation around the central OC-CN<sub>2</sub> bond caused by the resonance contribution of the enolate form **e** (Scheme 4b) somewhat decelerating the interconversion between the *s-cis* (*Z*) and the *s-trans* form (*E*) with regard to the NMR timescale (Scheme 3a).<sup>38</sup> It has been shown that at lower temperatures with slower interconversion rates separate signals for both rotamers can be detected.<sup>38</sup> Moreover, it has been ruled out that this dynamic behavior arises from an intermolecular process such as a possible keto-enol tautomerism as indicated in Scheme 3b.<sup>38a</sup>

*Scheme 3.* Plausible physical phenomena existing in substituted  $\alpha$ -aminodiazo ketones.



In the <sup>1</sup>H NMR spectra of compound **3**, **6a-n**, **7-9** the methinic protons appear in the range of 5.44-6.24 ppm, whereas the CH<sub>2</sub> resonances are located between 3.75-4.78 ppm, the latter being expectedly somewhat influenced by the electronic properties of the substituents attached to the aminic nitrogen atom. Thus, compounds carrying an electron withdrawing *N*-substituent (Tos, Moc, COOEt) exhibit larger chemical shifts for the concerning methylene protons.

Table 3. <sup>1</sup>H NMR Data of 3-Aminodiazoketones presented in this study.<sup>a</sup>



| No.                   | H of R <sub>1</sub>                                                                                           | H of R <sub>2</sub>                                                                           | CH(R)                                                                          | CH=N <sub>2</sub> |
|-----------------------|---------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-------------------|
| <b>3</b>              | 7.26 (Ph H-3,5), 6.78 (Ph H-4), 6.68 (Ph H-2,6)                                                               | 3.47 (q, <i>J</i> = 7.1 Hz, CH <sub>2</sub> ), 1.21 (t, <i>J</i> = 7.1 Hz, CH <sub>3</sub> )  | 3.93 (s, CH <sub>2</sub> )                                                     | 5.58              |
| <b>6a</b>             | 7.18 (Ph H-3,5), 6.58 (Ph H-2,6)                                                                              | 3.03 (s, CH <sub>3</sub> )                                                                    | 3.94 (s, CH <sub>2</sub> )                                                     | 5.44              |
| <b>6b</b>             | 6.96 (Ph H-3,5), 6.61 (Ph H-2,6)                                                                              | 3.02 (s, CH <sub>3</sub> )                                                                    | 3.91 (s, CH <sub>2</sub> )                                                     | 5.53              |
| <b>6c</b>             | 6.85 (Ph H-3,5), 6.65 (Ph H-2,6), 3.76 (Ph-4-OCH <sub>3</sub> )                                               | 2.99 (s, CH <sub>3</sub> )                                                                    | 3.88 (s, CH <sub>2</sub> )                                                     | 5.59              |
| <b>6d</b>             | 6.84 (Ph H-3,5), 2.33 (Ph-2,6-CH <sub>3</sub> ), 2.33 (Ph-2,6-CH <sub>3</sub> ), 2.25 (Ph-4-CH <sub>3</sub> ) | 2.76 (s, CH <sub>3</sub> )                                                                    | 3.75 (s, CH <sub>2</sub> )                                                     | 6.10              |
| <b>6e</b>             | 6.82 (Ph H-3,5), 6.70 (Ph H-2,6), 3.75 (Ph-4-OCH <sub>3</sub> )                                               | 4.56 (s, CH <sub>2</sub> ), 7.33 (Ph H-3,5), 7.27 (Ph H-4), 7.22 (Ph H-2,6)                   | 3.97 (s, CH <sub>2</sub> )                                                     | 5.59              |
| <b>6f</b>             | 7.21 (Ph H-3,5), 6.78 (Ph H-4), 6.60 (Ph H-2,6)                                                               | 4.47 (s, NH)                                                                                  | 3.89 (s, CH <sub>2</sub> )                                                     | 5.63              |
| <b>6f<sup>b</sup></b> | 7.09 (Ph H-3,5), 6.59 (Ph H-4), 6.55 (Ph H-2,6)                                                               | 6.18 (t, <i>J</i> = 5.6 Hz, NH)                                                               | 3.81 (d, <i>J</i> = 5.6 Hz, CH <sub>2</sub> )                                  | 6.06              |
| <b>6g</b>             | 7.30 (Ph H-3,5), 6.50 (Ph H-2,6)                                                                              | 4.52 (NH)                                                                                     | 3.90 (s, CH <sub>2</sub> )                                                     | 5.58              |
| <b>6h</b>             | 5.92 (Ph H-4), 5.76 (Ph H-2,6), 3.74 (Ph-3,5-OCH <sub>3</sub> )                                               | 4.48 (NH)                                                                                     | 3.85 (s, CH <sub>2</sub> )                                                     | 5.59              |
| <b>6i</b>             | 7.29 (Ph H-5), 6.99 (Ph H-4), 6.78 (Ph H-2), 6.74 (Ph H-6)                                                    | 4.73 (NH)                                                                                     | 3.93 (s, CH <sub>2</sub> )                                                     | 5.55              |
| <b>6j</b>             | 7.10 (Ph H-5), 6.33 (Ph H-4), 6.21 (Ph H-6), 6.14 (Ph H-2), 3.74 (Ph 3-OCH <sub>3</sub> )                     | 4.46 (NH)                                                                                     | 3.87 (s, CH <sub>2</sub> )                                                     | 5.59              |
| <b>6k</b>             | 7.28 (Ph H-3,4,5), 7.09 (Ph H-2,6)                                                                            | 7.42 (Ph H-2,6), 7.23 (Ph H-3,5), 2.40 (Ph-4-CH <sub>3</sub> )                                | 4.25 (s, CH <sub>2</sub> )                                                     | 5.92              |
| <b>6l<sup>b</sup></b> | 7.35 (Ph H-3,5), 7.34 (Ph H-4), 7.20 (Ph H-2,6)                                                               | 8.37 (Ph H-3,5), 7.86 (Ph H-2,6)                                                              | 4.52 (s, CH <sub>2</sub> )                                                     | 6.24              |
| <b>6m</b>             | 7.19 (Ph H-3,5), 6.77 (Ph H-4), 6.58 (Ph H-2,6)                                                               | 4.05(s, NH)                                                                                   | 3.91 (q, <i>J</i> = 7.0 Hz, CH), 1.46 (d, <i>J</i> = 7.0 Hz, CH <sub>3</sub> ) | 5.71              |
| <b>6n</b>             | 7.25 (Ph H-3,5), 6.79 (Ph H-4), 6.76 (Ph H-2,6)                                                               | 3.27-3.40 (m, CH <sub>2</sub> ), 1.21 (t, <i>J</i> = 7.0 Hz, CH <sub>3</sub> )                | 4.25 (q, <i>J</i> = 6.9 Hz, CH), 1.44 (d, <i>J</i> = 6.9 Hz, CH <sub>3</sub> ) | 5.56              |
| <b>7</b>              | 7.23-7.44 (Ph H)                                                                                              | 3.74 (s, OCH <sub>3</sub> )                                                                   | 4.37 (s, CH <sub>2</sub> )                                                     | 5.46              |
| <b>8</b>              | 7.30 (Ph H-3,5), 7.26 (Ph H-2,6), 7.19 (Ph H-4)                                                               | 4.15 (q, <i>J</i> = 7.1 Hz, OCH <sub>2</sub> ), 1.19 (t, <i>J</i> = 7.1 Hz, CH <sub>3</sub> ) | 4.31 (s, CH <sub>2</sub> )                                                     | 5.44              |
| <b>9</b>              | 7.23 (Ph H-2,6), 7.30 (Ph H-4), 7.36 (Ph H-3,5)                                                               | 3.68 (OCH <sub>3</sub> )                                                                      | 4.78 (q, <i>J</i> = 7.2 Hz, CH), 1.21 (d, <i>J</i> = 7.2 Hz, CH <sub>3</sub> ) | 5.62              |

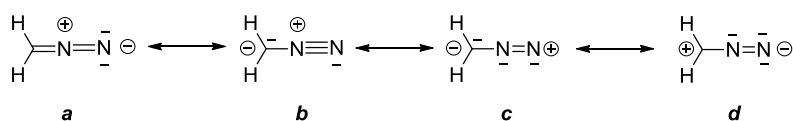
<sup>a</sup> Except otherwise stated spectra were recorded in CDCl<sub>3</sub>. <sup>b</sup> Recorded in DMSO-*d*<sub>6</sub>.

It is well known that diazo carbon atoms (CN<sub>2</sub>) are extremely shielded compared to 'normal' sp<sup>2</sup>-hybridized C-atoms: for instance, the carbon atom in diazomethane appears at δ 23.1 ppm.<sup>39</sup> This extraordinarily small

chemical shift can be attributed to the contribution of resonance forms with a negative charge located at the diazo C-atom (forms **b** and **c** in Scheme 4a). In the series of  $\alpha$ -diazoketones studied herein we found  $^{13}\text{C}$  chemical shifts for the  $\alpha$ -carbon of approximately 53 ppm, which resembles those of  $\omega$ -diazacetophenone ( $\delta$  54.2 ppm)<sup>32</sup> and ethyl diazoacetate ( $\delta$  46.3 ppm)<sup>32</sup>. The larger chemical shift compared to the corresponding C-atom in diazomethane may be (partly) attributed to the delocalization of the negative charge into the carbonyl moiety (form **e**, Scheme 4b). The one-bond  $^{13}\text{C},^1\text{H}$  spin coupling constant  $^1J(\text{CHN}_2)$  for the diazoketones presented was found to be within a narrow range (199-204 Hz, Table 4) and corresponds well to those found with related compounds ( $\omega$ -diazacetophenone:  $^1J$  = 199.2 Hz; ethyl diazoacetate:  $^1J$  = 202.6 Hz).<sup>40</sup>

*Scheme 4.* Resonance forms of diazomethane (**a**) and 3-aminodiazoketones (**b**)

**a) diazomethane**



**b) 3-aminodiazoketones (*this study*)**

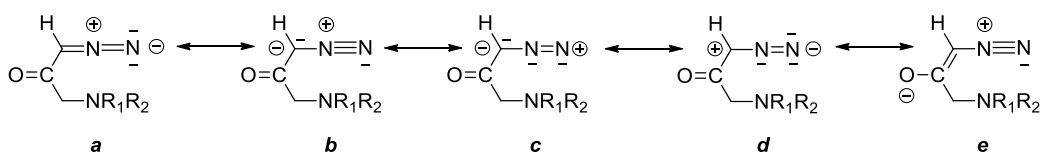
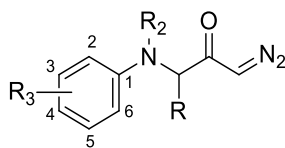


Table 4. <sup>13</sup>C-NMR Data of 3-Aminodiazoketones presented in this study.<sup>a</sup>



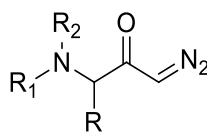
| No.                   | C of aryl |                       |                        |                       |       |       | C of R <sub>3</sub>                                    | C of R <sub>2</sub>                                                                 | CHR                                | C=O   | CHN <sub>2</sub><br>( <sup>1</sup> J <sub>CH</sub> ) |
|-----------------------|-----------|-----------------------|------------------------|-----------------------|-------|-------|--------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------|-------|------------------------------------------------------|
|                       | C-1       | C-2                   | C-3                    | C-4                   | C-5   | C-6   |                                                        |                                                                                     |                                    |       |                                                      |
| <b>3</b>              | 147.3     | 112.3                 | 129.4                  | 117.5                 | 129.4 | 112.3 | --                                                     | 46.1 (CH <sub>2</sub> ), 11.9 (CH <sub>3</sub> )                                    | 59.1 (CH <sub>2</sub> )            | 195.6 | 50.0 (203.4)                                         |
| <b>6a</b>             | 147.1     | 113.4                 | 129.1                  | 122.5                 | 129.1 | 113.4 | --                                                     | 39.8 (CH <sub>3</sub> )                                                             | 61.5 (CH <sub>2</sub> )            | 194.3 | 53.2 (201.9)                                         |
| <b>6b</b>             | 145.4     | 113.4                 | 115.8                  | 156.0                 | 115.8 | 133.4 | --                                                     | 40.2 (CH <sub>3</sub> )                                                             | 62.2 (CH <sub>2</sub> )            | 195.0 | 53.2                                                 |
| <b>6c</b>             | 143.3     | 114.0                 | 114.8                  | 152.4                 | 114.8 | 114.0 | 55.7 (OCH <sub>3</sub> )                               | 40.3 (CH <sub>3</sub> )                                                             | 62.6 (CH <sub>2</sub> )            | 195.7 | 53.1 (201.1)                                         |
| <b>6d</b>             | 146.4     | 136.1                 | 129.9                  | 135.3                 | 129.9 | 136.1 | 20.6 (4-CH <sub>3</sub> ), 19.5 (2,6-CH <sub>3</sub> ) | 41.3 (CH <sub>3</sub> )                                                             | 65.1 (CH <sub>2</sub> )            | 196.4 | 53.1 (200.9)                                         |
| <b>6e</b>             | 142.5     | 114.7                 | 114.8                  | 152.6                 | 114.8 | 114.7 | 55.6 (OCH <sub>3</sub> )                               | 56.4 (CH <sub>2</sub> ), 137.8 (Ph-1), 128.7 (Ph-3,5), 127.3 (Ph-4), 127.1 (Ph-2,6) | 59.9 (CH <sub>2</sub> )            | 195.3 | 53.4 (201.7)                                         |
| <b>6f</b>             | 146.8     | 112.8                 | 129.4                  | 118.4                 | 129.4 | 112.8 | --                                                     | --                                                                                  | 52.0 (CH <sub>2</sub> )            | 193.7 | 53.3                                                 |
| <b>6f<sup>b</sup></b> | 147.9     | 112.1                 | 129.0                  | 116.6                 | 129.0 | 112.1 | --                                                     | --                                                                                  | 51.3 (CH <sub>2</sub> )            | 195.2 | 52.6 (204.1)                                         |
| <b>6g</b>             | 145.8     | 114.4                 | 132.1                  | 110.1                 | 132.1 | 114.4 | --                                                     | --                                                                                  | 51.7 (CH <sub>2</sub> )            | 192.2 | 53.5 (200.4)                                         |
| <b>6h</b>             | 148.8     | 91.7                  | 161.8                  | 90.5                  | 161.8 | 91.7  | 55.2 (3,5-OCH <sub>3</sub> )                           | --                                                                                  | 51.8 (CH <sub>2</sub> )            | 193.2 | 53.4 (202.6)                                         |
| <b>6i</b>             | 147.0     | 109.0 (q, J = 4.0 Hz) | 131.1 (q, J = 31.9 Hz) | 114.8 (q, J = 4.0 Hz) | 129.8 | 115.9 | 124.1 (CF <sub>3</sub> ) (q, J = 272.4 Hz)             | --                                                                                  | 51.2 (CH <sub>2</sub> )            | 191.5 | 53.6 (201.4)                                         |
| <b>6j</b>             | 148.2     | 99.0                  | 160.8                  | 103.4                 | 130.2 | 105.7 | 55.1 (OCH <sub>3</sub> )                               | --                                                                                  | 51.9 (CH <sub>2</sub> )            | 193.4 | 53.3 (200.8)                                         |
| <b>6k</b>             | 139.4     | 127.7                 | 129.2                  | 128.1                 | 129.2 | 127.7 | --                                                     | 144.1 (Ph-4), 133.9 (Ph-1), 129.5 (Ph-3,5), 127.7 (Ph-2,6), 21.5 (CH <sub>3</sub> ) | 58.1 (CH <sub>2</sub> )            | 190.5 | 54.7 (202.0)                                         |
| <b>6l<sup>b</sup></b> | 138.9     | 128.2                 | 129.3                  | 128.3                 | 129.3 | 128.2 | --                                                     | 150.0 (Ph-4), 143.2 (Ph-1), 129.0 (Ph-2,6), 124.5 (Ph-3,5)                          | 57.6 (CH <sub>2</sub> )            | 189.6 | 54.2                                                 |
| <b>6m</b>             | 146.3     | 113.0                 | 129.3                  | 118.5                 | 129.3 | 113.0 | --                                                     | --                                                                                  | 57.7 (CH), 19.3 (CH <sub>3</sub> ) | 198.5 | 52.2                                                 |
| <b>6n</b>             | 147.0     | 114.2                 | 129.3                  | 117.9                 | 129.3 | 114.2 | --                                                     | 42.3 (CH <sub>2</sub> ), 13.8 (CH <sub>3</sub> )                                    | 63.3 (CH), 13.8 (CH <sub>3</sub> ) | 197.2 | 53.1                                                 |
| <b>7</b>              | 142.0     | 126.4                 | 129.1                  | 126.9                 | 129.1 | 126.4 | --                                                     | 156.0 (CO), 53.3 (OCH <sub>3</sub> )                                                | 57.7 (CH <sub>2</sub> )            | 190.3 | 53.5                                                 |
| <b>8</b>              | 142.0     | 126.1                 | 128.8                  | 126.4                 | 128.8 | 126.1 | --                                                     | 155.3 (CO), 62.1 (OCH <sub>2</sub> ), 14.3 (CH <sub>3</sub> )                       | 57.4 (CH <sub>2</sub> )            | 190.4 | 53.2 (199.2)                                         |
| <b>9</b>              | 138.8     | 128.8                 | 128.9                  | 127.7                 | 128.9 | 128.8 | --                                                     | 156.2 (CO), 53.2 (OCH <sub>3</sub> )                                                | 60.2 (CH),                         | 193.5 | 53.8 (202.1)                                         |

|  |  |  |  |  |  |  |  |  |                            |  |  |
|--|--|--|--|--|--|--|--|--|----------------------------|--|--|
|  |  |  |  |  |  |  |  |  | 14.9<br>(CH <sub>3</sub> ) |  |  |
|--|--|--|--|--|--|--|--|--|----------------------------|--|--|

<sup>a</sup> Except otherwise stated spectra were recorded in CDCl<sub>3</sub>. <sup>b</sup> Recorded in DMSO-*d*<sub>6</sub>.

To the best of our knowledge, <sup>15</sup>N-NMR studies on diazo compounds are rather limited.<sup>40-41</sup> The difficulties associated with the unambiguous and correct assignment of the two diazo nitrogen atoms resonances has been solved by Albright and Freeman employing selective enrichment with <sup>15</sup>N.<sup>40</sup> According to these experiments the terminal nitrogen atom, in general, is more deshielded and, thus presents a larger chemical shift than the central one. As summarized in Table 4, this principle was also applied for the distinction between the diazo nitrogen atoms in our series of aminodiazoketones. Whereas the central diazo *N*-atom resonates between -119.3 and -112.6 ppm (referencing against external nitromethane), the shifts of the terminal *N*-atom are located between -11.5 and -8.5 ppm. Obviously, these shifts are only little influenced by the residual part of the molecule. There is a fairly good agreement with shifts of related compounds such as, for instance, ethyl diazoacetate (-112.6 and 3.7 ppm)<sup>40,33</sup> or ω-diazoacetophenone (-112.6 and -6.4 ppm).<sup>40,33</sup> The <sup>15</sup>N NMR chemical shifts of the aminic nitrogen atom are mostly dependent from the nature of substituent R<sub>2</sub> (Table 5). The presence of an electron withdrawing group (Ts, Ns, COOMe) at this nitrogen atom causes a considerable increase of the chemical shift, as observed in the cases of compounds **6k**, **6l** and **9**. An interesting phenomenon can be observed in the case of *N*-methyl substituted compounds (R<sub>2</sub> = CH<sub>3</sub>) **6a-d**: while in **6a** (R<sub>1</sub> = 4-chlorophenyl) and **6c** (R<sub>1</sub> = 4-methoxyphenyl) the shifts of the amine-nitrogen atoms are closely together (δ -332.5 and δ -337.4 ppm), the corresponding signal in **6d** (R<sub>1</sub> = 2,4,6-trimethylphenyl) is distinctly shifted upfield (δ -355.0 ppm). This can be explained by the lack of conjugation between phenyl ring and the nitrogen's lone pair owing to sterical reasons (distorsion of the aromatic system).

Table 5.  $^{15}\text{N}$  NMR data of selected compounds.<sup>a</sup>



| No.                   | R <sub>1</sub>        | R <sub>2</sub>     | R               | NR <sub>1</sub> R <sub>2</sub> | CH= <u>N</u> =N | CH=N= <u>N</u>           |
|-----------------------|-----------------------|--------------------|-----------------|--------------------------------|-----------------|--------------------------|
| <b>3</b>              | Ph                    | Et                 | H               | -318.8                         | -117.9          | -11.2                    |
| <b>6a</b>             | 4-chlorophenyl        | CH <sub>3</sub>    | H               | -332.5                         | -118.7          | -11.6                    |
| <b>6b</b>             | 4-fluorophenyl        | CH <sub>3</sub>    | H               | -335.3                         | -118.5          | -11.4                    |
| <b>6c</b>             | 4-methoxyphenyl       | CH <sub>3</sub>    | H               | -337.4                         | -117.9          | -11.0                    |
| <b>6d</b>             | 2,4,6-trimethylphenyl | CH <sub>3</sub>    | H               | -355.0                         | -116.3          | -8.5                     |
| <b>6e</b>             | 4-methoxyphenyl       | CH <sub>2</sub> Ph | H               | -326.6                         | -118.1          | -10.6                    |
| <b>6f</b>             | Ph                    | H                  | H               | -325.6                         | -118.1          | <i>n.f.</i> <sup>c</sup> |
| <b>6f<sup>b</sup></b> | Ph                    | H                  | H               | -321.3                         | -112.6          | -10.3                    |
| <b>6g</b>             | Ph                    | Ts                 | H               | -269.7                         | -119.3          | -11.4                    |
| <b>6j<sup>b</sup></b> | Ph                    | NS <sup>d</sup>    | H               | -271.3                         | -115.2          | -11.5                    |
| <b>6n</b>             | Ph                    | Et                 | CH <sub>3</sub> | -309.8                         | -116.0          | <i>n.f.</i> <sup>c</sup> |
| <b>9</b>              | Ph                    | COOCH <sub>3</sub> | CH <sub>3</sub> | -273.3                         | -117.9          | <i>n.f.</i> <sup>c</sup> |

<sup>a</sup> Otherwise stated spectra were recorded in CDCl<sub>3</sub>. <sup>b</sup> Recorded in DMSO-*d*<sub>6</sub>. <sup>c</sup> n.f. = not found.

<sup>d</sup> -13.1 (NO<sub>2</sub>).

## Conclusions.

A straightforward synthesis of  $\alpha$ -arylamino diazoketones *via* nucleophilic displacement of widely substituted anilines on primary and secondary  $\alpha$ -halodiazoketones has been developed. Crucial for the chemoselectivity of the process is the action of innocuous and inexpensive calcium oxide (CaO) as acid scavenger. In fact, the deleterious Nierenstein-type side reaction of immediate conversion of the intermediate diazoketones to the corresponding  $\alpha$ -haloketones was completely suppressed. The protocol is quite convenient in terms of versatility and practical applicability: only a unique Arndt-Eistert diazotization – again, under minimal diazomethane loadings – is required for furnishing the key alkylating diazo compound to be employed in the whole process. In-depth NMR and X-ray analyses contribute to understand key characteristics of such densely functionalized synthons.

## Experimental Section.

### Materials and methods.

$\alpha$ -halodiazoketones **2a-b**<sup>21b</sup> and **2c**<sup>42</sup> were prepared according to our previously reported method.<sup>21b</sup> All <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on Bruker Avance spectrometers operating at 200, 400 or 500 MHz and at 50, 100 or 125 MHz, respectively, at 25 °C. The (residual) solvent peak was used as an internal standard which was related to TMS with  $\delta$  7.26 ppm (<sup>1</sup>H, CDCl<sub>3</sub>) and  $\delta$  2.49 ppm (<sup>1</sup>H, DMSO-*d*<sub>6</sub>),  $\delta$  77.0 ppm (<sup>13</sup>C, CDCl<sub>3</sub>) and 39.5 (<sup>13</sup>C, DMSO-*d*<sub>6</sub>). The <sup>19</sup>F NMR experiments were conducted on a Bruker Avance 400 spectrometer (377 MHz), here absolute referencing via the  $\Xi$  ratio was used. The <sup>15</sup>N NMR spectra (gs-HSQC, gs-HMBC, or 'direct' detection via inverse gated decoupling) were recorded on a Bruker Avance 500 or a Bruker Avance 400 machine (50 and 40 MHz, respectively) and were referenced against external nitromethane. Spin-spin coupling constants (*J*) are given in Hz. Full and unambiguous assignment of all <sup>1</sup>H, <sup>13</sup>C, <sup>15</sup>N and <sup>19</sup>F-NMR resonances was achieved by combining standard NMR techniques, such as fully <sup>1</sup>H-coupled <sup>13</sup>C-NMR spectra, APT, DEPT, HSQC, HMBC, and NOESY experiments. In some cases <sup>15</sup>N NMR chemical shifts were determined via the inverse gated decoupling technique in long term experiments (4000 scans, relaxation delay 15s). HRMS were measured on a Bruker maXis 4G instrument (ESI-TOF).

The X-ray intensity data were measured on Enraf Nonius KappaCCD diffractometer equipped with graphite monochromator and monocapillary optics, Mo K $\alpha$  Siemens KFF Mo sealed tube and Oxford Cryosystems Cryostream 600 cooling device. The structures were solved by *direct methods* and refined by *full-matrix least-squares techniques*. Non-hydrogen atoms were refined with *anisotropic displacement parameters*. Hydrogen atoms were inserted at calculated positions and refined with riding model and as rotating groups. All calculations were performed using Enraf Nonius software and the SHELX97<sup>43</sup> program package. Additionally OLEX2<sup>44</sup> was used for refinement, molecular diagrams and graphical user-interface. *Platon*<sup>45</sup> was employed for symmetry check. Experimental data and CCDC-Codes can be found in the Supporting Information.

### **General procedure for the synthesis of $\alpha$ -arylamino diazoketones (GP1).**



To a suspension of CaO (2.0 equiv) in dry DMSO (8 mL) at rt was added a solution of  $\alpha$ -halodiazoketones (1.0 equiv) (**2a-c**) in DMSO (1 mL) followed by the addition of the proper amine (1.0 equiv). The resulting mixture was stirred for the appropriate time (Tables 1 and 2) and then, filtered under vacuum, washed successively with Et<sub>2</sub>O, NaHCO<sub>3</sub> (sat. aq.) and NaCl (sat. aq., 5 times). After liquid chromatographic (LC) purification on silica gel, pure samples of diazoketones **3**, **6a-n** were obtained.

#### **1-diazo-3-(ethyl(phenyl)amino)propan-2-one. (3)**

By following GP1, starting from CaO (112 mg, 2.0 mmol, 1.0 equiv), **2b** (163 mg, 1.0 mmol, 1.0 equiv) and *N*-ethylaniline (121 mg, 1.0 mmol, 1.0 equiv), compound **3** was obtained in 86% yield (175 mg) as a yellow oil after LC (eluent: hexanes / AcOEt 10%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.26 (m, 2H, Ph H-3,5), 6.78 (m, 1H, Ph H-4), 6.68 (m, 2H, Ph H-2,6), 5.58 (s, 1H, CHN<sub>2</sub>), 3.93 (s, 2H, NCH<sub>2</sub>CO), 3.47 (q, *J* = 7.1 Hz, 2H, NCH<sub>2</sub>CH<sub>3</sub>), 1.21 (t, *J* = 7.1 Hz, 3H, NCH<sub>2</sub>CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 195.6 (C=O), 147.3 (Ph C-1), 129.4 (Ph C-3,5), 117.5 (Ph C-4), 112.3 (Ph C-2,6), 65.1 (CH<sub>2</sub>), 59.1 (CH<sub>2</sub>CO), 50.0 (CHN<sub>2</sub>), 46.1 (NCH<sub>2</sub>CH<sub>3</sub>), 11.9 (NCH<sub>2</sub>CH<sub>3</sub>). <sup>15</sup>N NMR (40 MHz, CDCl<sub>3</sub>)  $\delta$ : -318.8 (amine), -117.9 (CH=N=N), -11.2 (CH=N=N). **Elemental Analysis (%)** for C<sub>11</sub>H<sub>13</sub>N<sub>3</sub>O. Calcd: C, 65.01; H, 6.45; N, 20.68. Found: C, 65.07; H, 6.47; N, 20.73.

#### **1-chloro-3-[ethyl(phenyl)amino]acetone. (4)**

By following GP1, starting from **2b** (163 mg, 1.0 mmol, 1.0 equiv) and *N*-ethylaniline (121 mg, 1.0 mmol, 1.0 equiv) in diethyl ether (entry 1 – Table 1 in Results and Discussion), compound **4** was obtained in 54% yield (114 mg) as a yellow oil after LC (eluent: hexanes / AcOEt 10%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.31-7.23 (m, 2H), 6.83-6.76 (m, 1H), 6.67-6.62 (m, 2H), 4.22 (s, 2H), 4.20 (s, 2H), 3.51 (q, *J* = 7.1 Hz, 2H), 1.22 (t, *J* = 7.1 Hz, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  203.0, 147.7, 130.1, 118.2, 112.8, 59.2, 47.2, 47.1, 12.5. IR (KBr, cm<sup>-1</sup>) 3084, 1745. **Elemental Analysis (%)** for C<sub>11</sub>H<sub>14</sub>ClNO. Calcd.: C, 62.41; H, 6.67; N, 6.62. Found: C, 62.49; H, 6.72; N, 6.66.

#### **1-((4-chlorophenyl)(methyl)amino)-3-diazopropan-2-one. (6a)**

By following GP1, starting from CaO (112 mg, 2.0 mmol, 1.0 equiv), **2b** (163 mg, 1.0 mmol, 1.0 equiv) and 4-chloro-*N*-methylaniline (141 mg, 1.0 mmol, 1.0 equiv), compound **6a** was obtained in 86% yield (192 mg) as a yellow oil after LC (eluent: hexanes / AcOEt 5%). **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ: 7.18 (d, *J* = 9.0 Hz 2H, Ph H-3,5), 6.58 (d, *J* = 9.1 Hz, 2H, Ph H-2,6), 5.44 (s, 1H, CH=N<sub>2</sub>), 3.94 (s, 2H, CH<sub>2</sub>), 3.03 (s, 3H, CH<sub>3</sub>). **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ: 194.3 (C=O), 147.1 (Ph C-1), 129.1 (Ph C-3,5), 133.4 (Ph C-4), 113.4 (Ph C-2,6), 61.5 (CH<sub>2</sub>), 53.2 (CHN<sub>2</sub>), 39.8 (CH<sub>3</sub>). **<sup>15</sup>N NMR** (40 MHz, CDCl<sub>3</sub>) δ: -332.5 (amine), -118.7 (CH=N=N), -11.6 (CH=N=N). **Elemental Analysis (%)** for C<sub>10</sub>H<sub>10</sub>ClN<sub>3</sub>O. Calcd: C, 53.70; H, 4.51; N, 18.79. Found: C, 53.77; H, 4.56; N, 18.90.

#### 1-((4-fluorophenyl)(methyl)amino)-3-diazopropan-2-one. (6b)

By following GP1, starting from CaO (112 mg, 2.0 mmol, 1.0 equiv), **2b** (163 mg, 1.0 mmol, 1.0 equiv) and 4-fluoro-*N*-methylaniline (125 mg, 1.0 mmol, 1.0 equiv), compound **6b** was obtained in 85% yield (176 mg) as a yellow oil after LC (eluent: DCM). **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ: 6.96 (m, 2H, Ph H-3,5), 6.61 (d, m, 2H, Ph H-2,6), 5.53 (s, 1H, CH=N<sub>2</sub>), 3.91 (s, 2H, CH<sub>2</sub>), 3.03 (s, 3H, NCH<sub>3</sub>). **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ: 195.0 (C=O), 156.0 (d, *J* = 237.1 Hz, Ph C-4), 145.3 (Ph C-1), 115.8 (d, *J* = 22.2 Hz, Ph C-3,5), 113.4 (d, *J* = 7.4 Hz, Ph C-2,6), 62.6 (CH<sub>2</sub>), 53.2 (CHN<sub>2</sub>), 40.2 (CH<sub>3</sub>). **<sup>15</sup>N NMR** (40 MHz, CDCl<sub>3</sub>) δ: -335.3 (amine), -118.5 (CH=N=N), -11.4 (CH=N=N). **<sup>19</sup>F NMR** (376 MHz, CDCl<sub>3</sub>) δ: -127.6 (Ph F-4). **HRMS** (ESI), *m/z*: calcd. for C<sub>10</sub>H<sub>10</sub>FN<sub>3</sub>NaO 230.0701 [M+Na]<sup>+</sup>; found 230.0700.

#### 1-diazo-3-((4-methoxyphenyl)(methyl)amino)propan-2-one. (6c)

By following GP1, starting from CaO (112 mg, 2.0 mmol, 1.0 equiv), **2b** (163 mg, 1.0 mmol, 1.0 equiv) and 4-methoxy-*N*-methylaniline (137 mg, 1.0 mmol, 1.0 equiv), compound **6c** was obtained in 88% yield (193 mg) as a yellow oil after LC (eluent: hexanes / AcOEt 10%). **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ: 6.85 (m, 2H, Ph H-3,5), 6.65 (m, 2H, Ph H-2,6), 5.59 (s, 1H, CH=N<sub>2</sub>), 3.88 (s, 2H, CH<sub>2</sub>), 3.76 (s, 3H, Ph 3-OCH<sub>3</sub>), 2.99 (s, 3H, NCH<sub>3</sub>). **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ: 193.7 (C=O), 152.4 (Ph C-4), 143.3 (Ph C-1), 114.8 (Ph C-3,5), 114.0 (Ph C-2,6), 62.6 (CH<sub>2</sub>), 55.7 (OCH<sub>3</sub>), 53.1 (CHN<sub>2</sub>), 40.3 (CH<sub>3</sub>). **<sup>15</sup>N NMR** (40 MHz, CDCl<sub>3</sub>) δ: -337.4 (amine), -117.9 (CH=N=N), -11.0 (CH=N=N). **Elemental Analysis (%)** for C<sub>11</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>. Calcd: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.40; H, 5.93; N, 19.24.

### 1-diazo-3-(mesityl(methyl)amino)propan-2-one. (6d)

By following GP1, starting from CaO (112 mg, 2.0 mmol, 1.0 equiv), **2b** (163 mg, 1.0 mmol, 1.0 equiv) and *N*-2,4,6-tetramethyl-*N*-methylaniline (149 mg, 1.0 mmol, 1.0 equiv), compound **6d** was obtained in 68% yield (157 mg) as a yellow oil after LC (eluent: hexanes / AcOEt 20%). **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ: 6.84 (s, 2H, Ph H-3,5), 6.10 (s, 1H, CH=N<sub>2</sub>), 3.75 (s, 2H, CH<sub>2</sub>), 2.33 (s, 6H, Ph-2,6-CH<sub>3</sub>), 2.25 (s, 3H, Ph-4-CH<sub>3</sub>). **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ: 196.4 (C=O), 146.4 (Ph C-1), 136.1 (Ph C-2,6), 135.3 (Ph C-4), 129.9 (Ph C-3,5), 65.1 (CH<sub>2</sub>), 53.1 (CHN<sub>2</sub>), 41.3 (CH<sub>3</sub>), 20.6 (Ph 4-CH<sub>3</sub>), 19.5 (Ph 2,6-CH<sub>3</sub>). **<sup>15</sup>N NMR** (40 MHz, CDCl<sub>3</sub>) δ: -355.0 (amine), -116.3 (CH=N=N), -8.5 (CH=N=N). **Elemental Analysis (%)** for C<sub>13</sub>H<sub>17</sub>N<sub>3</sub>O. Calcd: C, 67.51; H, 7.41; N, 18.17. Found: C, 67.44; H, 7.33; N, 18.09. **HRMS (ESI)**, *m/z*: calcd. for C<sub>13</sub>H<sub>18</sub>N<sub>3</sub>O: 232.1444 [M+H]<sup>+</sup>; found 232.1448.

### 1-(benzyl(4-methoxyphenyl)amino)-3-diazopropan-2-one. (6e)

By following GP1, starting from CaO (112 mg, 2.0 mmol, 1.0 equiv), **2b** (163 mg, 1.0 mmol, 1.0 equiv) and *N*-(4-methoxyphenyl)-benzylaniline (213 mg, 1.0 mmol, 1.0 equiv), compound **6e** was obtained in 91% yield (269 mg) as a yellow oil after LC (eluent: hexanes / AcOEt 5%). **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ: 7.33 (m, 2H, CH<sub>2</sub>Ph H-3,5), 7.27 (m, 1H, CH<sub>2</sub>Ph H-4), 7.22 (m, 2H, CH<sub>2</sub>Ph H-2,6), 6.82 (m, 2H, NPh H-3,5), 6.70 (m, 2H, NPh H-2,6), 5.59 (s, 1H, CHN<sub>2</sub>), 4.56 (s, 2H, NCH<sub>2</sub>), 3.97 (s, 2H, NCH<sub>2</sub>CO), 3.75 (NPh-4-OCH<sub>3</sub>). **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ: 195.3 (C=O), 152.6 (NPh C-4), 142.5 (NPh C-4), 137.8 (CH<sub>2</sub>Ph-1), 128.7 (CH<sub>2</sub>Ph-3,5), 127.3 (CH<sub>2</sub>Ph-4), 127.1 (CH<sub>2</sub>Ph-2,6), 114.8 (NPh C-3,5), 114.7 (NPh C-2,6), 59.9 (CH<sub>2</sub>CO), 56.4 (NCH<sub>2</sub>Ph), 55.6 (OCH<sub>3</sub>), 53.4 (CHN<sub>2</sub>). **<sup>15</sup>N NMR** (40 MHz, CDCl<sub>3</sub>) δ: -326.6 (amine), -118.1 (CH=N=N), -10.6 (CH=N=N). **Elemental Analysis (%)** for C<sub>17</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub>. Calcd: C, 69.14; H, 5.80; N, 14.23. Found: C, 69.25; H, 5.86; N, 14.31.

### 1-diazo-3-(phenylamino)propan-2-one. (6f)

By following GP1, starting from CaO (112 mg, 2.0 mmol, 1.0 equiv), **2b** (163 mg, 1.0 mmol, 1.0 equiv) and aniline (93 mg, 1.0 mmol, 1.0 equiv), compound **6f** was obtained in 90% yield (158 mg) as a yellow oil after LC (eluent: hexanes / AcOEt 15%). **<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ: 7.09 (m, 2H, Ph H-3,5), 6.59 (m, 1H, Ph H-4), 6.55 (m, 2H, Ph H-2,6), 6.06 (br s, 1H, CH=N<sub>2</sub>), 6.18 (t, *J* = 5.6 Hz, 1H, NH), 3.81 (d, *J* = 5.6 Hz, 2H, CH<sub>2</sub>). **<sup>13</sup>C NMR**

**NMR** (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 195.2 (C=O), 147.9 (Ph C-1), 129.0 (Ph C-3,5), 116.6 (Ph C-4), 112.1 (Ph C-2,6), 52.6 (CHN<sub>2</sub>), 51.3 (CH<sub>2</sub>). **<sup>15</sup>N NMR** (40 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : -321.3 (amine), -112.6 (CH=N=N), -10.3 (CH=N=N). **Elemental Analysis (%)** for C<sub>9</sub>H<sub>9</sub>N<sub>3</sub>O. Calcd: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.79; H, 5.22; N, 24.08.

#### **1-(4-bromophenylamino)-3-diazopropan-2-one. (6g)**

By following GP1, starting from CaO (112 mg, 2.0 mmol, 1.0 equiv), **2b** (163 mg, 1.0 mmol, 1.0 equiv) and 4-bromo-aniline (172 mg, 1.0 mmol, 1.0 equiv), compound **6g** was obtained in 77% yield (196 mg) as a yellow oil after LC (eluent: hexanes / AcOEt 20%). **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.30 (m, 2H, Ph H-3,5), 6.50 (m, 1H, Ph H-2,6), 5.58 (br s, 1H, CH=N<sub>2</sub>), 4.52 (br s, 1H, NH), 3.90 (br s, 2H, CH<sub>2</sub>). **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 192.2 (C=O), 145.8 (Ph C-1), 132.1 (Ph C-3,5), 114.4 (Ph C-2,6), 110.1 (Ph C-4), 53.5 (CHN<sub>2</sub>), 51.7 (CH<sub>2</sub>). **<sup>15</sup>N NMR** (40 MHz, CDCl<sub>3</sub>)  $\delta$ : -325.6 (amine). **Elemental Analysis (%)** for C<sub>9</sub>H<sub>8</sub>BrN<sub>3</sub>O. Calcd: C, 42.54; H, 3.17; N, 16.54. Found: C, 42.62; H, 3.22; N, 16.62.

#### **1-diazo-3-((3,5-dimethoxyphenyl)amino)propan-2-one. (6h)**

By following GP1, starting from CaO (112 mg, 2.0 mmol, 1.0 equiv), **2b** (163 mg, 1.0 mmol, 1.0 equiv) and 3,5-dimethoxy-aniline (153 mg, 1.0 mmol, 1.0 equiv), compound **6h** was obtained in 93% yield (219 mg) as a yellow oil after LC (eluent: hexanes / AcOEt 5%). **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$ : 5.92 (t, *J* = 2.1 Hz, 1H, Ph H-4), 5.76 (d, *J* = 2.1 Hz, 2H, Ph H-2,6), 5.59 (s, 1H, CHN<sub>2</sub>), 4.48 (s, 1H, NH), 3.85 (s, 2H, CH<sub>2</sub>), 3.74 (s, 6H, Ph-3,5-OCH<sub>3</sub>). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>)  $\delta$ : 193.2 (C=O), 161.8 (Ph C-3,5), 148.8 (Ph C-1), 91.7 (Ph C2), 90.5 (Ph C-4), 55.2 (Ph-3,5-OCH<sub>3</sub>), 53.4 (CHN<sub>2</sub>), 51.8 (CH<sub>2</sub>). **Elemental Analysis (%)** for C<sub>11</sub>H<sub>13</sub>N<sub>3</sub>O<sub>3</sub>. Calcd: C, 56.16; H, 5.57; N, 17.86. Found: C, 56.27; H, 5.61; N, 17.95.

#### **1-diazo-3-(3-(trifluoromethyl)phenylamino)propan-2-one. (6i)**

By following GP1, starting from CaO (112 mg, 2.0 mmol, 1.0 equiv), **2b** (163 mg, 1.0 mmol, 1.0 equiv) and 3-(trifluoromethyl)-aniline (161 mg, 1.0 mmol, 1.0 equiv), compound **6i** was obtained in 74% yield (180 mg) as a yellow oil after LC (eluent: hexanes / AcOEt 10%). **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.29 (m, 1H, Ph H-5), 6.99 (m, 1H, Ph H-4), 6.78 (m, 1H, Ph H-2), 6.44 (m, 1H, Ph H-6), 5.55 (s, 1H, CH=N<sub>2</sub>), 4.73 (s, 1H, NH), 3.93 (s, 2H,

NHCH<sub>2</sub>CO). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 191.5 (C=O), 147.0 (Ph C-1), 131.1 (q, *J* = 31.9 Hz, Ph C-3), 129.8 (Ph C-5), 124.1 (<sup>1</sup>*J* = 272.4 Hz, CF<sub>3</sub>), 115.9 (Ph C-6), 114.8 (q, *J* = 4.0 Hz, Ph C-4), 109.0 (q, *J* = 4.0 Hz, Ph C-2), 53.6 (CHN<sub>2</sub>), 51.2 (CH<sub>2</sub>). <sup>15</sup>N NMR (40 MHz, CDCl<sub>3</sub>) δ: -324.4 (amine). <sup>19</sup>F (376 MHz, CDCl<sub>3</sub>) δ: -62.8 (CF<sub>3</sub>). **Elemental Analysis (%)** for C<sub>10</sub>H<sub>8</sub>F<sub>3</sub>N<sub>3</sub>O. Calcd: C, 49.39; H, 3.32; N, 17.28. Found: C, 49.50; H, 3.39; N, 17.41.

#### **1-diazo-3-(3-methoxyphenylamino)propan-2-one. (6j)**

By following GP1, starting from CaO (112 mg, 2.0 mmol, 1.0 equiv), **2b** (163 mg, 1.0 mmol, 1.0 equiv) and 3-methoxy-aniline (123 mg, 1.0 mmol, 1.0 equiv), compound **6j** was obtained in 89% yield (183 mg) as a yellow oil after LC (eluent: hexanes / AcOEt 10%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.10 ("t", *J* = 8.1 Hz, 1H, Ph H-3), 6.33 (ddd, *J* = 8.2, 2.3, 0.7 Hz, 1H, Ph H-4), 6.21 (ddd, *J* = 8.2, 2.3, 0.7 Hz, 1H, Ph H-6), 6.14 ("t", *J* = 8.1 Hz, 1H, Ph H-2), 5.61 (br s, 1H, CH=N<sub>2</sub>), 4.46 (br s, 1H, NH), 3.87 (br s, 2H, CH<sub>2</sub>), 3.76 (s, 3H, Ph 3-OCH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 193.4 (C=O), 160.8 (Ph C-3), 148.2 (Ph C-1), 130.2 (Ph C-5), 105.7 (Ph C-6), 103.4 (Ph C-4), 99.0 (Ph C-2), 55.1 (OCH<sub>3</sub>), 53.3 (CHN<sub>2</sub>), 51.9 (CH<sub>2</sub>). <sup>15</sup>N NMR (40 MHz, CDCl<sub>3</sub>) δ: -324.6 (amine). **Elemental Analysis (%)** for C<sub>10</sub>H<sub>11</sub>N<sub>3</sub>O<sub>2</sub>. Calcd: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.64; H, 5.48; N, 20.61.

#### **General procedure for the synthesis of *N*-aryl-*N*-benzenesulfonamido diazoketones (6k, 6l) (GP2).**

To a suspension of CaO (2.0 equiv) and KF-Celite (2.0 equiv) in dry MeCN (8 mL) at rt was added a solution of α-bromodiazoketone (**2b**, 1.0 equiv) in MeCN (1 mL) followed by the addition of the proper *N*-benzenesulfonamido-type aniline (1.0 equiv). The resulting mixture was stirred for the appropriate time (Table 2) and then, filtered under vacuum, washed successively with Et<sub>2</sub>O, NaHCO<sub>3</sub> (sat. aq.) and NaCl (sat. aq.). After liquid chromatographic (LC) purification on silica gel, pure samples of diazoketones **6k** and **6l** were obtained.

#### ***N*-(3-diazo-2-oxopropyl)-4-methyl-*N*-phenylbenzenesulfonamide. (6k)**

By following GP2, starting from CaO (112 mg, 2.0 mmol, 1.0 equiv), KF-Celite (50% w/w, 232 mg, 2.0 mmol, 1.0 equiv), **2b** (163 mg, 1.0 mmol, 1.0 equiv) and *N*-tosylaniline (247 mg, 1.0 mmol, 1.0 equiv) in dry MeCN (8 mL) compound **6k** was obtained in 83% yield (273 mg) as a white solid (mp 179 °C – recrystallized from 2-

butanone) after LC (eluent: hexanes / AcOEt 20%). **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ: 7.42 (m, 2H, SO<sub>2</sub>Ph H-2,6), 7.28 (m, 3H, NPh H-3,4,5), 7.23 (m, 2H, SO<sub>2</sub>Ph H-3,5), 7.09 (m, 2H, NPh H-2,6), 5.92 (s, 1H, CHN<sub>2</sub>), 4.25 (s, 2H, NCH<sub>2</sub>CO), 2.40 (SO<sub>2</sub>Ph-4-CH<sub>3</sub>). **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ: 190.5 (C=O), 144.1 (SO<sub>2</sub>Ph C-4), 139.4 (NPh C-1), 133.9 (SO<sub>2</sub>Ph-1), 129.5 (SO<sub>2</sub>Ph-3,5), 129.2 (NPh-3,5), 128.1 (NPh-4), 127.7 (NPh C-2,6), 127.7 (SO<sub>2</sub>Ph C-2,6), 58.1 (CH<sub>2</sub>), 54.2 (CHN<sub>2</sub>). **<sup>15</sup>N NMR** (40 MHz, CDCl<sub>3</sub>) δ: -269.7 (amine), -119.3 (CH=N=N), -11.4 (CH=N=N). **Elemental Analysis (%)** for C<sub>16</sub>H<sub>15</sub>N<sub>3</sub>O<sub>3</sub>S. Calcd: C, 58.34; H, 4.59; N, 12.76. Found: C, 58.45; H, 4.64; N, 12.88.

#### ***N*-(3-diazo-2-oxopropyl)-4-nitro-*N*-phenylbenzenesulfonamide. (6l)**

By following GP2, starting from CaO (112 mg, 2.0 mmol, 1.0 equiv), KF-Celite (50% w/w, 232 mg, 2.0 mmol, 1.0 equiv), **2b** (163 mg, 1.0 mmol, 1.0 equiv) and *N*-(4-nosyl)aniline (278 mg, 1.0 mmol, 1.0 equiv) in dry MeCN (8 mL) compound **6l** was obtained in 77% yield (277 mg) as a yellow solid (mp 199 °C - recrystallized from ethanol) after LC (eluent: hexanes / AcOEt 5%). **<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>) δ: 8.37 (m, 2H, SO<sub>2</sub>Ph H-3,5), 7.86 (m, 2H, SO<sub>2</sub>Ph H-2,6), 7.35 (m, 2H, NPh H-3,5), 7.34 (m, 1H, NPh H-4), 7.20 (m, 2H, NPh H-2,6), 6.24 (s, 1H, CHN<sub>2</sub>), 4.52 (s, 2H, NCH<sub>2</sub>CO). **<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>) δ: 189.6 (C=O), 150.0 (SO<sub>2</sub>Ph C-4), 143.2 (SO<sub>2</sub>Ph C-1), 138.9 (NPh-1), 129.3 (NPh-3,5), 129.0 (SO<sub>2</sub>Ph-2,6), 128.3 (NPh-4), 128.2 (NPh C-2,6), 124.5 (SO<sub>2</sub>Ph C-3,5), 57.6 (CH<sub>2</sub>), 54.2 (CHN<sub>2</sub>). **<sup>15</sup>N NMR** (40 MHz, DMSO-*d*<sub>6</sub>) δ: -271.3 (amine), -115.2 (CH=N=N), -13.1 (nitro), -11.5 (CH=N=N). **Elemental Analysis (%)** for C<sub>15</sub>H<sub>12</sub>N<sub>4</sub>O<sub>5</sub>S. Calcd: C, 50.00; H, 3.36; N, 15.55. Found: C, 49.89; H, 3.32; N, 15.44.

#### **1-diazo-3-(phenylamino)butan-2-one. (6m)**

By following GP1, starting from CaO (112 mg, 2.0 mmol, 1.0 equiv), **2c** (177 mg, 1.0 mmol, 1.0 equiv) and aniline (93 mg, 1.0 mmol, 1.0 equiv), compound **6m** was obtained in 87% yield (165 mg) as a yellow oil after LC (eluent: hexanes / AcOEt 10%). **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ: 7.19 (m, 2H, Ph H-3,5), 6.77 (m, 1H, Ph H-4), 6.58 (m, 2H, Ph H-2,6), 5.71 (s, 1H, CHN<sub>2</sub>), 4.05 (s, 1H, NH), 3.91 (q, 1H, *J* = 7.0 Hz, CH), 1.46 (d, 3H, *J* = 7.0 Hz, CH<sub>3</sub>). **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ: 198.5 (C=O), 146.3 (Ph C-1), 129.3 (Ph C-3,5), 118.5 (Ph C-4), 113.0 (Ph C-2,6), 57.7 (CH), 52.2 (CHN<sub>2</sub>), 19.3 (CH<sub>3</sub>). **Elemental Analysis (%)** for C<sub>10</sub>H<sub>11</sub>N<sub>3</sub>O. Calcd.: C, 63.48; H, 5.86; N, 22.21. Found: C, 63.59; H, 5.83; N, 22.30.

### **1-diazo-3-(ethyl(phenyl)amino)butan-2-one. (6n)**

By following GP1, starting from CaO (112 mg, 2.0 mmol, 1.0 equiv), **2c** (177 mg, 1.0 mmol, 1.0 equiv) and *N*-ethyl-aniline (121 mg, 1.0 mmol, 1.0 equiv), compound **6n** was obtained in 83% yield (180 mg) as a yellow oil after LC (eluent: hexanes / AcOEt 15%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ: 7.16 – 7.03 (m, 2H), 6.62 (dd, *J* = 20.8, 7.7 Hz, 3H), 5.40 (s, 1H), 4.09 (d, *J* = 7.2 Hz, 1H), 3.32 – 3.04 (m, 2H), 1.28 (d, *J* = 7.0 Hz, 3H), 1.04 (t, *J* = 7.0 Hz, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 197.2, 147.0, 129.3, 118.0, 114.3, 63.3, 53.1, 42.3, 13.8. **Elemental Analysis (%)** for C<sub>12</sub>H<sub>15</sub>N<sub>3</sub>O. Calcd: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.46; H, 7.02; N, 19.43.

### ***General procedure for the synthesis of α-aryl amino diazoketones (GP3).***

To a suspension of CaO (2.0 equiv) in dry Et<sub>2</sub>O (8 mL) at 0 °C was added a solution of α-arylaminodiazoketone (1.0 equiv) (**6f**, **6m**) in Et<sub>2</sub>O (1 mL) followed by the addition of the proper chloroformate (1.0 equiv). The resulting mixture was stirred for the 1h and then, filtered under vacuum, washed successively with Et<sub>2</sub>O, NaHCO<sub>3</sub> (sat. aq.) and NaCl (sat. aq.). Pure samples of diazoketones **7-9** were obtained after removal of the solvent under reduced pressure.

### **Methyl (3-chloro-2-oxopropyl)phenylcarbamate. (10)<sup>8a</sup>**

By following GP3, starting from diazoketone **6f** (175 mg, 1.0 mmol, 1.0 equiv) and methyl chloroformate (95 mg, 1.0 mmol, 1.0 equiv) – (Entry 1 – Table 2 in Results and Discussion), compound **10** was obtained as a colorless oil in 84% yield (203 mg). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 3.69 (s, 3H), 4.16 (s, 2H), 4.61 (s, 2H), 7.25-7.28 (m, 3H), 7.33-7.37 (m, 2H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 46.3, 53.3, 57.8, 126.8, 127.2, 129.1, 141.6 (detectable only *via* HMBC), 155.9 (detectable only *via* HMBC), 197.9. IR (KBr, cm<sup>-1</sup>) 3084, 1754, 1731, 1708, 905, 703. **Elemental Analysis (%)** for C<sub>11</sub>H<sub>12</sub>ClNO<sub>3</sub>. Calcd.: C, 54.67; H, 5.00; N, 5.80. Found: C, 54.78; H, 5.12; N, 5.91.

### **Methyl (3-diazo-2-oxopropyl)(phenyl)carbamate. (7)**

By following GP3, starting from CaO (112 mg, 2.0 mmol, 2.0 equiv), diazoketone **6f** (175 mg, 1.0 mmol, 1.0 equiv) and methyl chloroformate (95 mg, 1.0 mmol, 1.0 equiv), compound **7** was obtained as a yellow oil in

95% yield (222 mg). **<sup>1</sup>H NMR** (200 MHz, CDCl<sub>3</sub>) δ: 7.54 – 7.13 (m, 5H), 5.47 (s, 1H), 4.38 (s, 2H), 3.76 (s, 3H). **<sup>13</sup>C NMR** (50 MHz, CDCl<sub>3</sub>) δ: 190.5, 156.2, 142.2, 129.2, 127.1, 126.6, 57.8, 53.6, 53.5, 53.5, 29.8. **Elemental Analysis (%)** for C<sub>11</sub>H<sub>11</sub>N<sub>3</sub>O<sub>3</sub>. Calcd: C, 56.65; H, 4.75; N, 18.02;. Found: C, 56.51; H, 4.68; N, 17.90.

#### **Ethyl 3-diazo-2-oxopropyl(phenyl)carbamate. (8)**

By following GP3, starting from CaO (112 mg, 2.0 mmol, 2.0 equiv), diazoketone **6f** (175 mg, 1.0 mmol, 1.0 equiv) and ethyl chloroformate (109 mg, 1.0 mmol, 1.0 equiv), compound **8** was obtained as a yellow oil in 88% yield (218 mg). **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ: 7.30 (m, 2H, Ph H-3,5), 7.26 (m, 2H, Ph H-2,6), 7.19 (m, 1H, Ph H-4), 5.44 (br s, 1H, CHN<sub>2</sub>), 4.31 (br s, 2H, NCH<sub>2</sub>CO), 4.15 (q, *J* = 7.1 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>), 1.19 (t, *J* = 7.1 Hz, 2H, CH<sub>2</sub>CH<sub>3</sub>). **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ: 190.4 (C=O), 155.3 (COO), 142.0 (Ph -1), 128.8 (Ph-3,5), 126.4 (Ph-4), 126.1 (Ph-2,6), 62.1 (COOCH<sub>2</sub>), 57.4 (CH<sub>2</sub>CO), 53.2 (CHN<sub>2</sub>), 14.3 (CH<sub>2</sub>CH<sub>3</sub>). **<sup>15</sup>N NMR** (40 MHz, CDCl<sub>3</sub>) δ: -284.8 (amine). **Elemental Analysis (%)** for C<sub>12</sub>H<sub>13</sub>N<sub>3</sub>O<sub>3</sub>. Calcd: C, 58.29; H, 5.30; N, 16.99. Found: C, 58.40; H, 5.38; N, 17.11.

#### **Methyl (4-diazo-3-oxobutan-2-yl)(phenyl)carbamate. (9)**

By following GP3, starting from CaO (112 mg, 2.0 mmol, 2.0 equiv), diazoketone **6m** (189 mg, 1.0 mmol, 1.0 equiv) and methyl chloroformate (95 mg, 1.0 mmol, 1.0 equiv), compound **9** was obtained as a yellow oil in 91% yield (225 mg). **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.40 – 7.28 (m, 3H), 7.25 – 7.21 (m, 2H), 5.62 (s, 1H), 4.78 (d, *J* = 7.4 Hz, 1H), 3.68 (s, 3H), 1.22 (d, *J* = 7.2 Hz, 3H). **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 193.5, 156.3, 128.9, 127.7, 53.8, 53.2, 15.0. **Elemental Analysis (%)** for C<sub>12</sub>H<sub>13</sub>N<sub>3</sub>O<sub>3</sub>. Calcd: C, 58.29; H, 5.30; N, 17.00. Found: C, 58.41; H, 5.36; N, 17.11.

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We dedicate this work to Professor Massimo Curini in the occasion of his 70<sup>th</sup> birthday.

#### **Associated Content**



Supporting Information: Copies of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for all the compounds. X-ray crystallographic information for **6k**. This material is available free of charge *via* the Internet at <http://pubs.acs.org>.

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## Appendix



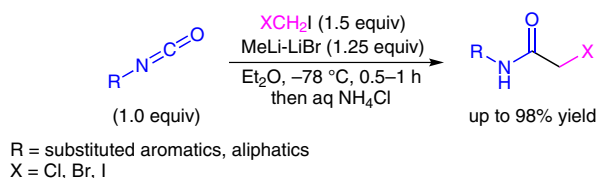


V. PACE,\* L. CASTOLDI, W. HOLZER (UNIVERSITY OF VIENNA, AUSTRIA)

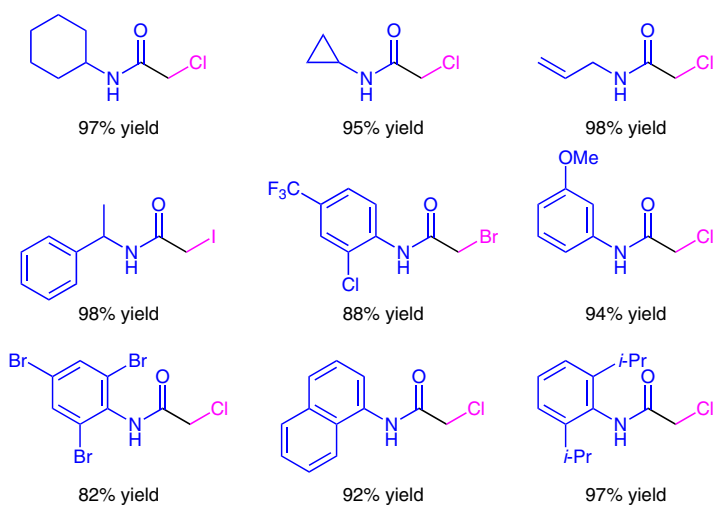
Addition of Lithium Carbenoids to Isocyanates: A Direct Access to Synthetically Useful N-Substituted 2-Haloacetamides

*Chem. Commun.* **2013**, 49, 8383–8385.

# Lithium-Mediated Synthesis of N-Substituted 2-Haloacetamides



## Selected examples:



**Significance:** A novel strategy for the synthesis of N-substituted 2-haloacetamides by addition of lithium carbenoids to isocyanates has been disclosed. The corresponding products are obtained in good to excellent yields in short reaction times.

**Comment:** The described protocol is very versatile since the homologation allows placing chloro-, bromo-, and iodo-methylenic fragments via a one-pot procedure in a chemoselective fashion. Moreover, the authors show that optically active isocyanates also react with full retention of stereochemistry at the stereogenic center.





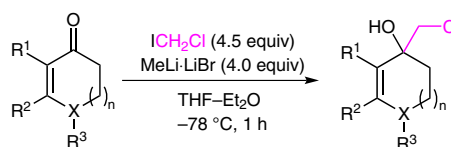
*Personal Copy*

V. PACE,\* L. CASTOLDI, W. HOLZER (UNIVERSITY OF VIENNA, AUSTRIA)

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

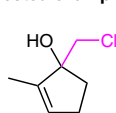
*Adv. Synth. Catal.* **2014**, 356, 1761–1766.

# Additions of Chloromethylithium Carbenoid to Cyclic Enones

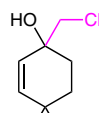


$R^1 = \text{H, Ar}$   
 $R^2 = \text{H, Alk, Cl, Ar}$   
 $R^3 = \text{H, Alk, Boc}$   
 $X = \text{CH, N, S}$

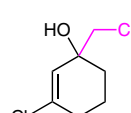
## Selected examples:



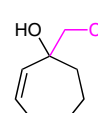
87% yield



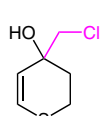
83% yield



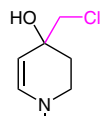
88% yield



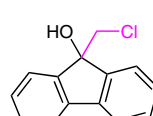
97% yield



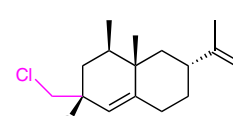
68% yield



74% yield



95% yield



74% yield

**Significance:** The authors report a method for the synthesis of chloromethyl allylic alcohols. Reaction of a lithium carbenoid ( $\text{LiCH}_2\text{Cl}$ ) with a variety of cyclic enones provides the described products. Interestingly, the attack of the reagent at the most activated position is promoted by the mesomeric effect due to  $\beta$ -heteroatom-containing substituents.

**Comment:** Noteworthy,  $\text{LiBr}$  does not only act as a stabilized carbenoid but also as a mild Lewis acid activator of the  $\text{C}=\text{O}$  bond. In addition, the protocol is tolerant to various enones of different ring size (5-, 6-, 7-membered and also complex natural product structures are reported).

## SYNFACTS Highlights in Current Synthetic Organic Chemistry

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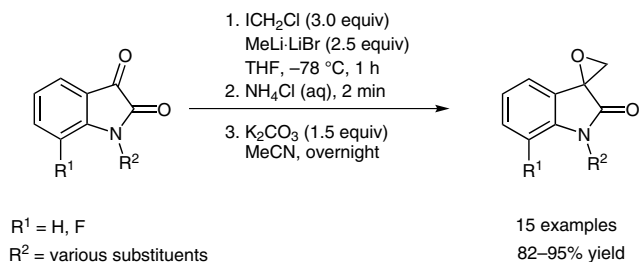
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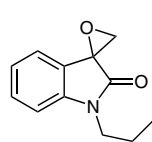
**Thieme**

V. PACE,\* L. CASTOLDI, A. D. MAMUYE, T. LANGER, W. HOLZER (UNIVERSITY OF VIENNA, AUSTRIA AND UNIVERSITY OF SASSARI, ITALY)  
Chemoselective Addition of Halomethylolithiums to Functionalized Isatins: A Straightforward Access to Spiro-Epoxyoxindoles  
*Adv. Synth. Catal.* **2016**, 358, 172–177.

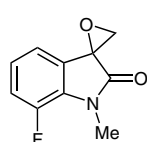
## Chemoselective Addition of Halomethylolithiums to Isatins



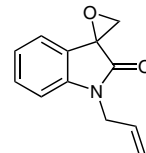
### Selected examples:



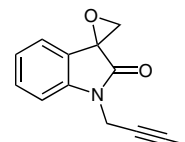
94% yield



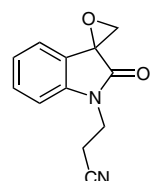
90% yield



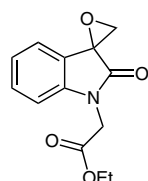
91% yield



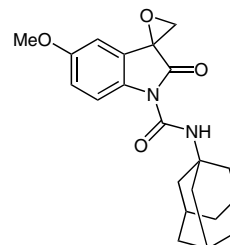
87% yield



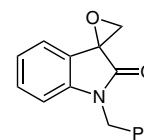
82% yield



95% yield



82% yield



91% yield

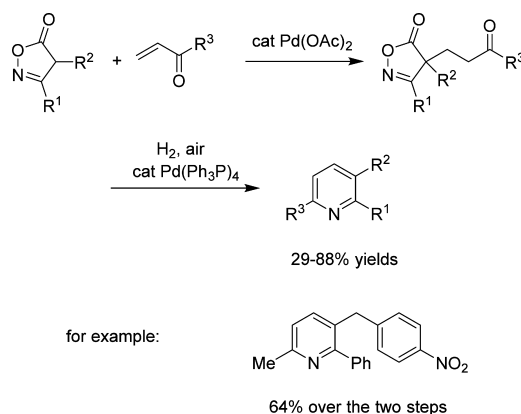
**Significance:** Pace and co-workers report an efficient chemoselective access to rare spiro-epoxy-oxindoles through addition of the carbenoid chloromethylolithium to various N-functionalized isatins followed by ring closure. The method is chemoselective in the presence of additional electrophilic functionalities.

**Comment:** By using dihalocarbenoids in analogous additions, indigo-type structures can be obtained through the rearrangement of unstable  $\alpha$ -haloepoxides.

**SYNFACTS Contributors:** Paul Knochel, Marthe Ketels  
 Synfacts 2016, 12(3), 0302 Published online: 16.02.2016  
 DOI: 10.1055/s-0035-1561252; Reg-No.: P00416SF

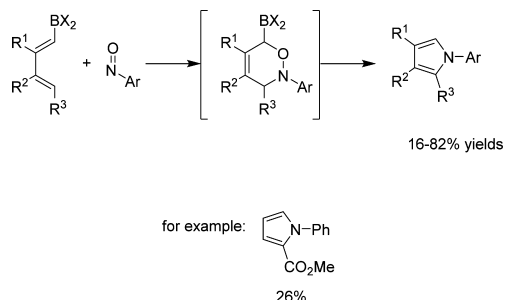
## Some Items of Interest to Process R&D Chemists and Engineers

### ■ SYNTHESIS OF 2,3,6-TRISUBSTITUTED PYRIDINES FROM ISOXAZOLINONES



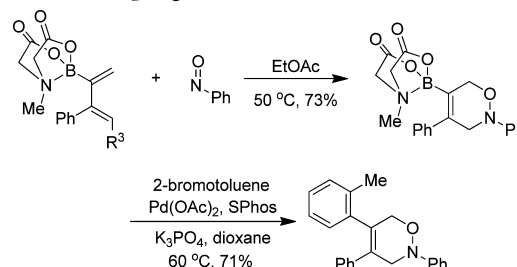
Substituted pyridines are an important class of organic compounds and ubiquitous in the chemistry world. Various methodologies have been developed to construct substituted pyridine derivatives. Recently, René Peters and co-workers developed a regioselective Pd-catalyzed synthesis of 2,3,6-trisubstituted pyridines from isoxazolinones (Peters, R., et al. *J. Org. Chem.* **2015**, *80*, 6822). The protocol involves a regioselective Pd(II)-catalyzed 1,4-addition of isoxazolinones to enones, followed by a Pd(0)-catalyzed dihydropyridine formation and oxidation. The formation of the dihydropyridine is hypothesized via a vinylnitrene-Pd complex species formed by oxidative addition of Pd(0) to the N–O bond of the 1,4-adduct followed by a decarboxylation. This two-step sequence allows a rapid and regioselective entry to substituted pyridines starting from readily accessible isoxazolinones. Despite these advantages, the safety issue needs to be addressed during application of this approach toward large-scale production as the second step required a mixture of hydrogen and air.

### ■ STEREOSELECTIVE HETERO-DIELS–ALDER REACTION AND RING CONTRACTION



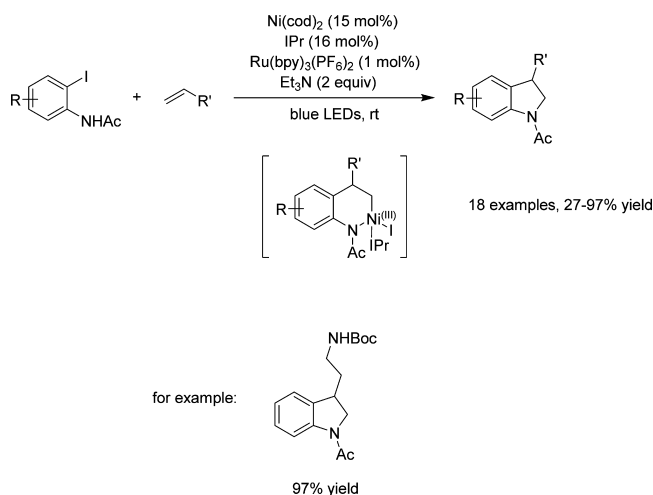
A hetero-Diels–Alder reaction between dienes and nitroso compounds has been widely utilized to synthesize 3,6-dihydro-1,2-oxazines, valuable intermediates in the organic synthesis. Carboni and co-workers studied on the [4 + 2] cycloaddition between boron substituted dienes and nitrosoarenes, and the results are revealed in a recent report (Carboni, B., et al. *J. Org. Chem.* **2015**, *80*, 6574). The researchers demonstrated that using an  $sp^2$  boron substituent, i.e., pinacol ester, a one-pot

hetero-Diels–Alder/ring contraction cascade afforded *N*-aryl-pyrroles. The corresponding oxazine cycloadducts were not observed during the course of the reaction. In contrast, reactions of dienes with  $sp^3$  boron substituents, i.e., *N*-methyliminodiacetic (MIDA) borodiene derivatives, led to formation of stable boroxazines in moderate to good yields and high regioselectivity. In addition, the isolated oxazine could participate in Suzuki–Miyaura cross-coupling reaction.



A proposed reaction mechanism for the ring contraction of the oxazines was provided.

### ■ HIGHLY REGIOSELECTIVE INDOLENE SYNTHESIS UNDER NICKEL/PHOTOREDOX DUAL CATALYSIS

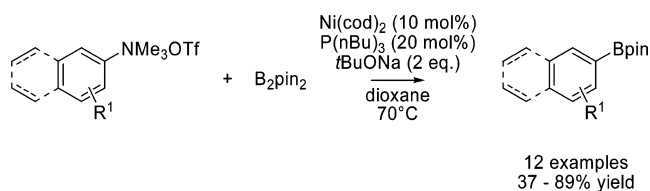


Nickel-catalyzed cross-coupling reactions involve either a Ni(0/II) pathway for aryl cross-coupling or a Ni(I/III) pathway for C- $sp^3$  cross-coupling. The nickel-catalyzed C- $sp^3$  cross-coupling reaction generally proceeds via an alkyl radical formed from SET process, which is trapped by Ni(II) species to give ArNi(III)RL<sub>2</sub>X complex. Jamison and co-worker of Massachusetts Institute of Technology, Cambridge, Massachusetts, reported a highly regioselective indoline synthesis under nickel/photoredox dual catalysis (Jamison, T. F., et al. *J. Am. Chem. Soc.* **2015**, *137*, 9531). It was found that the visible light photoredox catalyst Ru(bpy)<sub>3</sub>(PF<sub>6</sub>)<sub>2</sub> improved the indoline yield significantly. Using the optimized protocol, 3-substituted indolines were obtained in good yields. It is demonstrated that various 3-substituted indolines including

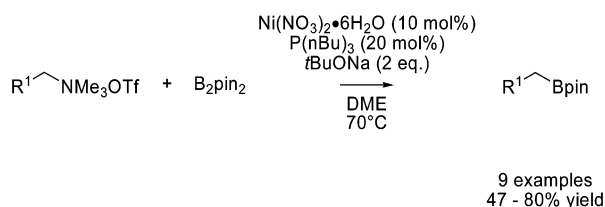
Published: February 11, 2016

rates. Following this procedure, the authors prepared enantiomerically pure  $\text{Cp}^{\text{R}}_2\text{TiCl}_2$  complexes with cytotoxic in vitro activities that were enantiomer-dependent.

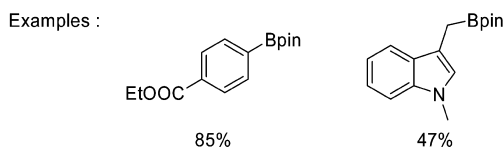
## NICKEL-CATALYZED C–N BORYLATION OF TRIMETHYLAMMONIUM SALTS



$\text{R}^1 = \text{Ph, alkyl, F, CF}_3, \text{OMe, COPh, COOEt}$



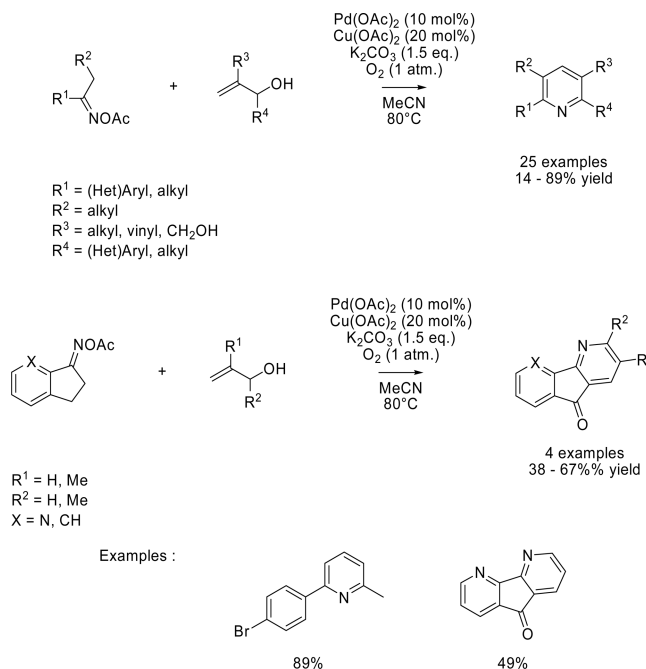
$\text{R}^1 = (\text{Het})\text{Aryl}$



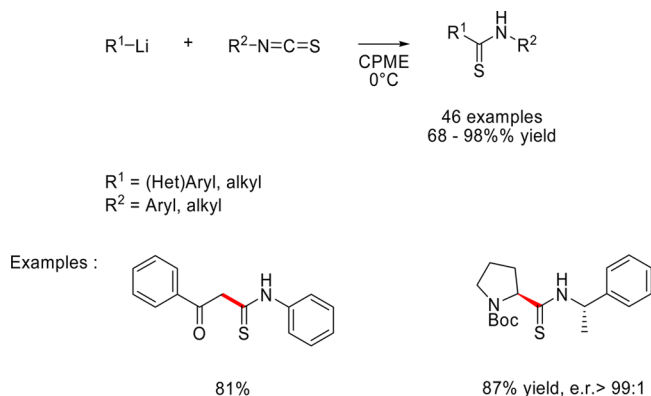
The dimethylamino group, directly attached to an aryl ring or in benzylic position, has found widespread use in site-selective directed aromatic functionalization, but a general method to transform this group into other functionalities hampers its wider application in organic synthesis. Itami and co-workers from Nagoya have recently addressed this issue by developing conditions that allow the C–N borylation of the dimethylamino moiety (*Chem. Eur. J.* **2015**, *21*, 16796). The dimethylamino group is first converted into the ammonium salt by quaternarization with methyl triflate. It then undergoes easy borylation with bis(pinacolatodiboron) in the presence of a catalytic amount of nickel salt ( $\text{Ni}(\text{cod})_2$  or  $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$  depending on the nature of the substrate) and tri-*n*-butylphosphine. Sodium *tert*-butoxide was found to be the base of choice in an ethereal solvent. The generality of the reaction has not been investigated in great detail, but ketones, esters, and an indole were demonstrated to be successful substrates under the developed conditions. A handful of examples are also provided involving the use of dimethylamino group as directing group followed by its borylation and further manipulation of the newly introduced reactive center.

## PALLADIUM-CATALYZED SYNTHESIS OF PYRIDINES BY A HECK-TYPE REACTION OF OXIME DERIVATIVES

Pyridines are one of the most significant building blocks which are present in pharmaceuticals, agrochemicals, and functional material. Although a myriad of methods for synthesizing this versatile scaffold exists, conceptually new methods that allow their regioselective assembly continue to be sought after. Jiang and co-workers from Gangzhou have recently described the palladium-catalyzed Heck reaction of oxime acetates with allylic alcohols as a new alternative to



synthesize pyridines and azafluorenones (*Chem. Commun.* **2016**, 52, 84). Screening revealed that two metal sources (palladium and copper acetate) were required for the reaction together with potassium carbonate as base and acetonitrile as solvent. A number of substituted oxime derivatives and allyl alcohols are suitable substrates for this reaction allowing the assembly of 2,3,5-trisubstituted pyridines in moderate-to-high yields. Surprisingly, a small set of indanone oxime acetates led to the formation of the corresponding azafluorenones under the same conditions.

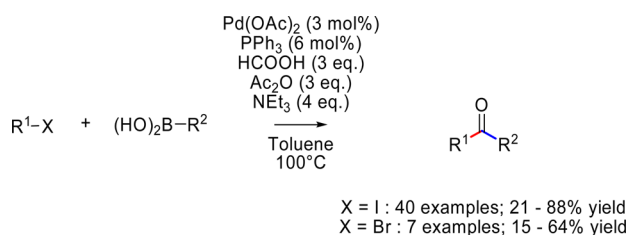


## THIOAMIDE SYNTHESIS BY ADDITION OF ORGANOLITHIUM REAGENTS TO ISOTHIOCYANATES

Thioamides constitute an important class of intermediates in organic synthesis for which the current method of preparation (direct or indirect thionation of carboxamide) are far from ideal in terms of reactants, conditions, and yields. Holzer' group from Vienna have described an interesting alternative for the synthesis of thioamide that relies on the nucleophilic addition of organolithium reagents to isothiocyanates (*Chem. Eur. J.* **2015**, *21*, 18966). The best conditions simply involved the addition of the lithium reagent on a solution of the isothiocyanate in cyclopentyl methyl ether at 0°C for a few hours. An extremely

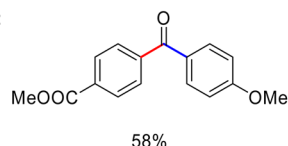
large variety of organolithium reagents (either commercially available or prepared by classical method such as lithium/halogen exchange or deprotonation) have been found to react with isothiocyanates in almost uniformly high yields. Worthy of note is that the procedure can be applied to the asymmetric synthesis of (almost) enantiopure thioamides by enantioselective deprotonation with sparteine.

### DIARYLKETONE SYNTHESIS BY PALLADIUM-CATALYZED CARBONYLATION WITH FORMIC ACID



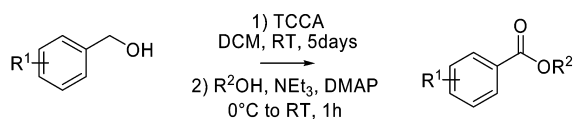
$\text{R}^1 = (\text{Het})\text{Ar}$   
 $\text{R}^2 = (\text{Het})\text{Ar}$

Example :



The synthesis of diarylketones by transition-metal-catalyzed three-component coupling of an aryl halide, an organometallic species, and a CO source (gaseous carbon monoxide or one of its surrogates) have witnessed major improvements during the last decade. Wu and co-workers from Hangzhou have recently described conditions that allow the use of a combination of formic acid and acetic anhydride as carbon monoxide source (*Chem. Eur. J.* **2015**, *21*, 17650). With a simple catalytic system composed of palladium acetate with triphenylphosphine and potassium carbonate as base in toluene, a number of aryl iodides and bromides are efficiently converted into diarylketones by reaction with different boronic acids. The substrate scope of the reaction is large with simple heteroaromatic substrates being tolerated as well as most common functional groups.

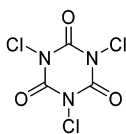
### METAL-FREE OXIDATIVE CROSS ESTERIFICATION



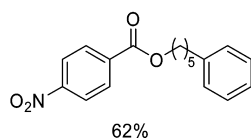
$\text{R}^1 = \text{Alkyl, aryl, COMe, F, Cl, NO}_2$   
 $\text{R}^2 = \text{Alkyl, aryl}$

29 examples  
62 - 97% yield

TCCA :



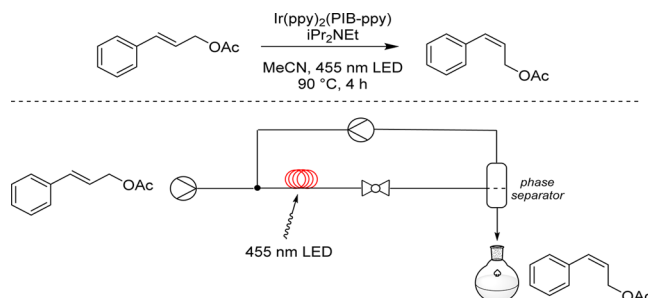
Example :



De Luca and co-workers from Italy have recently described a one-pot two-step metal-free protocol for the oxidation of benzyl alcohols into esters (*Adv. Synth. Catal.* **2016**, *358*, 154). They employed trichloroisocyanuric acid as a cheap and non-toxic oxidant in dichloromethane as solvent to convert the benzyl alcohols into the corresponding acid chlorides. The latter are

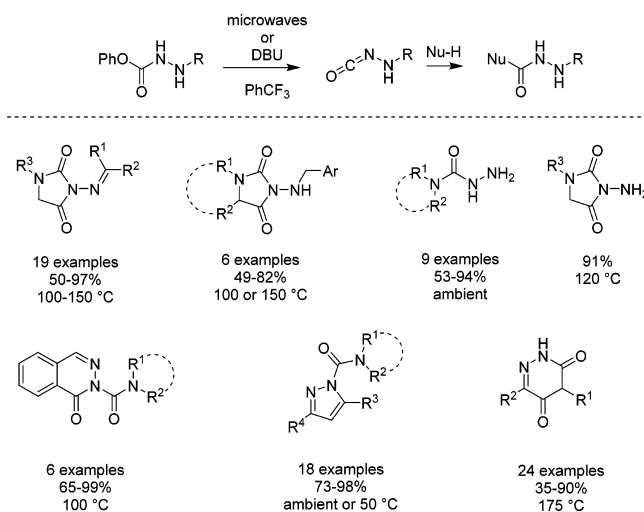
converted in situ to the ester by addition of an alcohol and a catalytic amount of DMAP. The reaction proved to be quite general but slow, 5 days being required at room temperature for the oxidation step. A tentative mechanism based on a radical pathway has been proposed by the author.

### RECYCLABLE PHOTOCATALYSIS IN MICROFLOW



Reiser and co-workers reported the synthesis of a recyclable polyisobutylene-tagged iridium photocatalyst and its use in batch and continuous processes (*Green Chem.* **2016**, *18*, 214–219). Recyclability was achieved using a thermomorphic acetonitrile/heptane binary solvent system which occurs as a single phase above 84.6 °C. A continuous flow microreactor was devised to carry out the photocatalyzed isomerization of cinnamyl acetate to (Z)-3-phenylallyl acetate at 90 °C. Cooling of the product mixture resulted in two phases which were separated in-line; the heptane phase containing the iridium photocatalyst was recycled. Catalyst mass balance measurements revealed an initial loss in catalyst presumably due to dissolution of catalyst species containing short polyisobutylene chains in acetonitrile. The isomerization reaction also proceeded at ambient temperature under biphasic conditions at lower flow rates.

### CASCADE REACTIONS BASED ON IN SITU GENERATION OF N-ISOCYANATES



Beauchemin and colleagues reported the development of a synthetic toolbox based on in situ generation of N-isocyanates (*Chem. Sci.* **2016**, *7*, 315–328). Upon irradiation with microwaves at high temperatures or addition of DBU at ambient temperatures, substituted phenyl carbazate precursors generated N-isocyanates in situ. The N-isocyanate intermediates were reacted with amines or  $\alpha$ -amino esters to generate a wide variety of heterocycles containing the N–N–C=O motif, which are prevalent in agrochemical and pharmaceutical products.





## SYNFACTS Highlights in Current Synthetic Organic Chemistry

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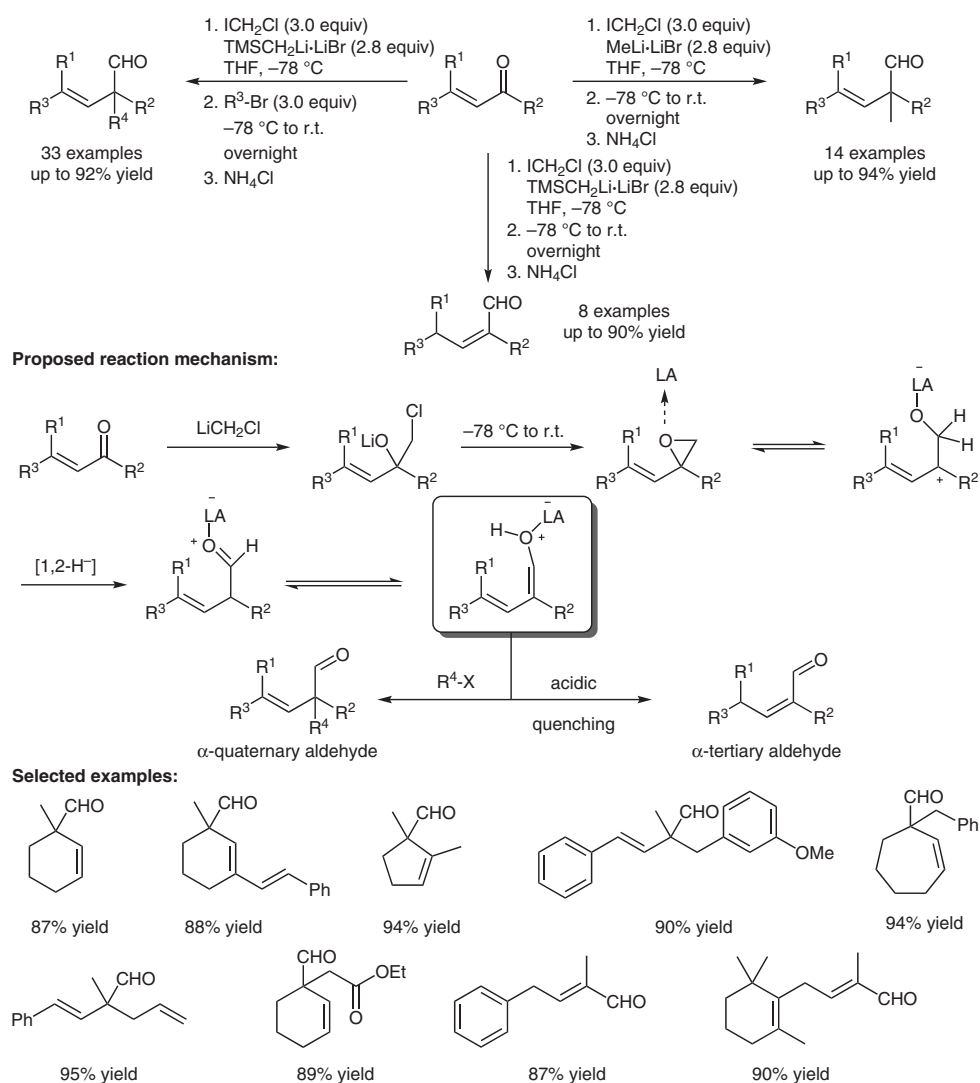


**Thieme**

V. PACE\*, L. CASTOLDI, E. MAZZEO, M. RUI, T. LANGER, W. HOLZER (UNIVERSITY OF VIENNA, AUSTRIA)

Efficient Access to All-Carbon Quaternary and Tertiary  $\alpha$ -Functionalized Homoallyl-Type Aldehydes and Ketones  
*Angew. Chem. Int. Ed.* **2017**, 56, 12677–12682.

## Synthesis of Aldehydes with All-Carbon $\alpha$ -Quaternary Centers



**Significance:** The authors report an efficient access to  $\beta,\gamma$ -unsaturated aldehydes with all-carbon quaternary and tertiary  $\alpha$ -centers from ketones. Thereby, the synthetic operation contains: 1) ketone homologation, 2) epoxide–aldehyde isomerization, and 3)  $\alpha$ -derivatization.

**SYNFACTS Contributors:** Paul Knochel, Dorothée Ziegler  
Synfacts 2017, 13(11), 1184 Published online: 19.10.2017  
**DOI:** 10.1055/s-0036-1591362; **Reg-No.:** P12617SF

**Comment:** Interestingly, the key concept of this synthetic method is the synthetic equivalence of a vinyl oxirane and a  $\beta,\gamma$ -unsaturated aldehyde. Furthermore, critical for the chemoselectivity are the effect of the lithium organometallic species to generate a carbenoid, and the nature of the carbenoid precursor.

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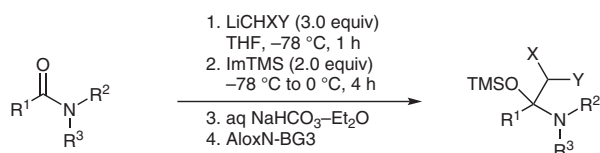
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## Addition of Halolithium Carbenoids to Weinreb Amides and *N*-Acylpyrroles

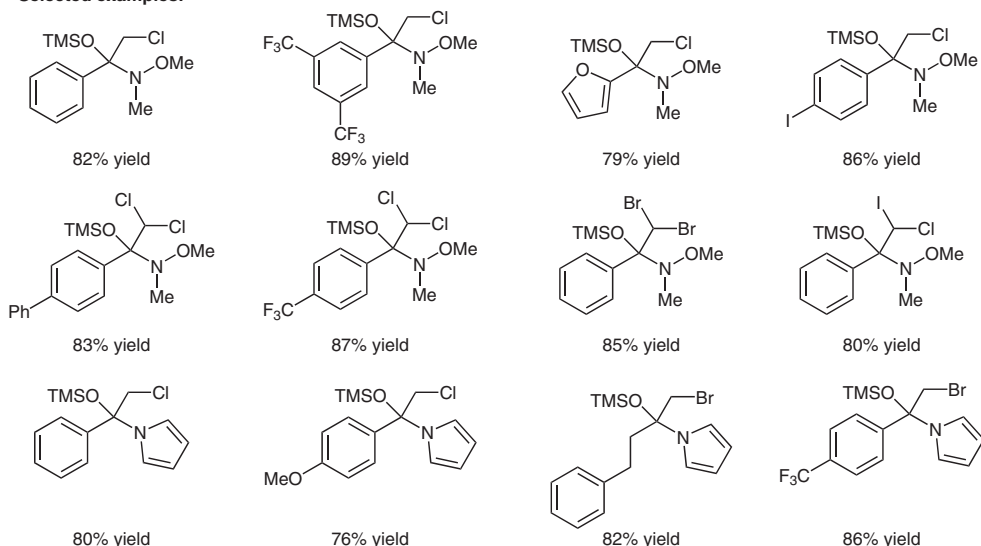


25 examples  
up to 95% yield

R<sup>1</sup> = Ar, HetAr, Bn  
 R<sup>2</sup> = OMe  
 R<sup>3</sup> = Me  
 NR<sup>2</sup>R<sup>3</sup> = pyrrol-1-yl  
 X = H, Cl, Br, I  
 Y = Cl, Br

ImTMS = 1-(trimethylsilyl)imidazole

### Selected examples:



**Significance:** The authors report an effective synthesis by the addition of halolithium carbenoids (LiCH<sub>2</sub>X or LiCHXY) to Weinreb amides or *N*-acylpyrroles to obtain protected hemiaminals in good to excellent yield.

**Comment:** Interestingly, the combination of ImTMS and Brockmann grade 3 neutral alumina (AloxN-BG3) was found to be the critical factor for the isolation of such labile tetrahedral intermediates.