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Easy transformations of vinyl *N,N*-diisopropyl carbamates into silyl enol ethers or aldehydes by addition of methyllithium

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Abstract

Homoaldols and 4-hydroxy silyl enol ethers have been prepared upon addition of methyllithium to 4-hydroxyvinyl *N,N*-diisopropyl carbamates obtained from Hoppe's homoaldolisation reaction followed by addition, in presence of an excess of HMPA, of water or *tert*-butyldimethylsilyl chloride, respectively. In the case of silyl enol ethers, a total retention of the Z configuration of the double bond was observed. This simple procedure allows an easy preparation of γ-lactones from the homoaldol adducts. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Keywords: carbamates; lithium; lithium compounds; enol ethers; aldehydes.

The interest of synthetic chemists in allyl and vinyl carbamates is continuously increasing due to their high chemical versatility and their ease to handle. Moreover, one very interesting chemical property of the *O*-alkyl or *O*-allylic carbamates is their ability to give configurationally stable α-anionic species through deprotonation with lithium bases.[1] In the case of allylic species **1**, thermodynamic controlled equilibrium in the presence of (−)-sparteine led to a homochiral lithium intermediate, which can be subsequently transmetallated with tetra(isopropoxy)titanium with inversion of configuration.[2] Further condensation of these species with various electrophiles such as aldehydes or trialkyl tin chlorides[3] led to vinyl carbamoyl adducts with excellent chirality transfer. In all cases the configuration of the resulting vinyl carbamate moiety is *Z*.[4]

Towards further synthetic applications, the vinyl *N,N*-diisopropyl carbamates **2** resulting from the preceding condensation reactions with aldehydes have already been transformed in many different directions (Scheme 1). Partial or total oxidation of the double bond has been carried out.[5] New C–C bonds have also been built from this vinyl function through nickel-catalysed cross-coupling reactions.[4a] Alternatively, vinyl carbamates are readily functionalised in the α-position through kinetic deprotonation with *n*-butyllithium or *sec*-butyllithium at low temperatures followed by quenching by various electrophiles. One particularly interesting type of reaction involves metallate rearrangements.[6] Under forcing conditions, the

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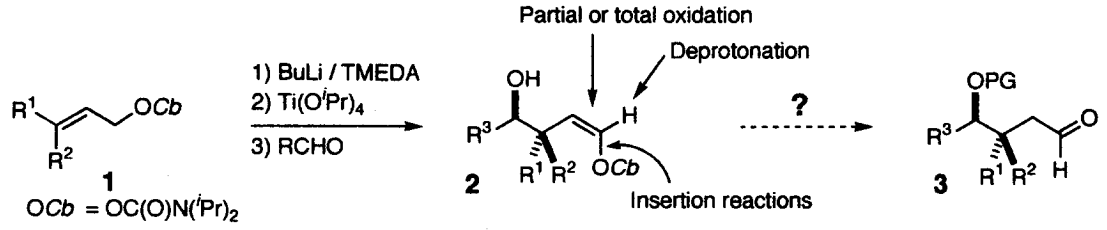
intermediate carbenoid lithium can also lead to acetylenic adducts through Fritsch–Buttenberg–Wiechell type rearrangements.[7] All these non-exhaustive examples clearly illustrates the synthetic potential of the vinyl *N,N*-diisopropyl carbamoyl adducts obtained after condensation/isomerisation of convenient allylic precursors.

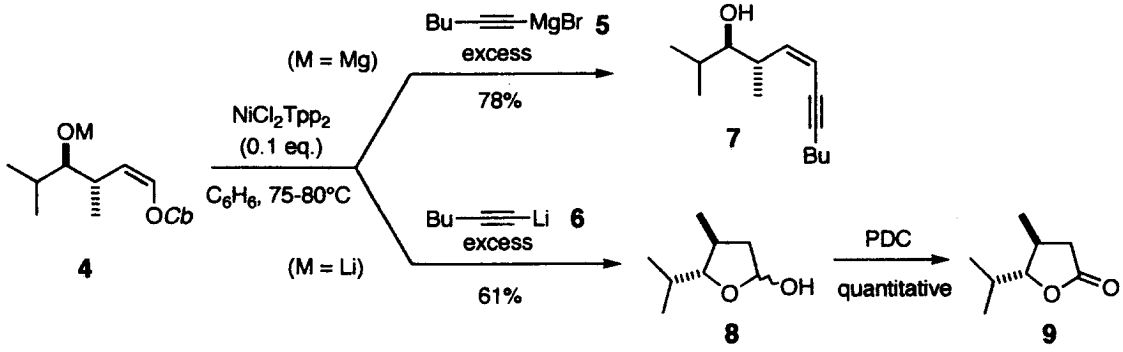


Scheme 1.

However, one main drawback of these vinyl carbamates is their unusual stability towards acid solvolysis. Harsh conditions involving methanolysis in the presence of methanesulfonic acid/mercuric acetate are generally required for this transformation.[8] A general method for deprotection of enol carbamate to generate aldehydes **3** is still lacking and we wish to present our preliminary data in this area.

It is important to recall that allyl *N,N*-diisopropyl carbamates have been chosen by Hoppe for the allylation reactions as being less prone to direct nucleophilic attack at the carbonyl group by butyllithium than other functionalised enol esters analogues, as for example the *N,N*-diethyl carbamates.[9] To our knowledge, the only direct efficient nucleophilic attack experienced by *N,N*-diisopropyl carbamates is hydride attack at the carbonyl centre to give the corresponding primary alcohol.[10]

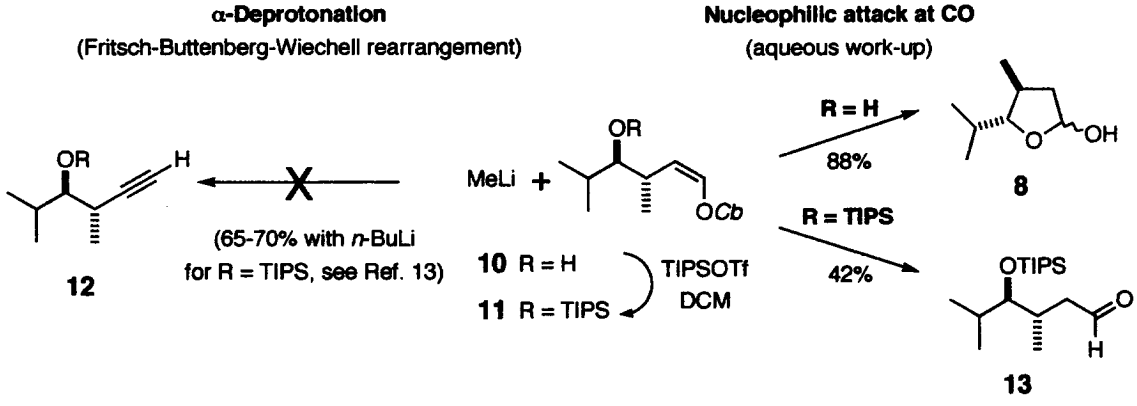
A previous study from our laboratories has shown that vinyl carbamates **4** undergo very divergent reactivities towards acetylenic nucleophiles when exposed to Wenkert type nickel(0) catalysed cross-coupling conditions (Scheme 2).[11] With hexynylmagnesium bromide **5** the expected cross-coupling reactions took place to give the enyne **7** in good yield. Moreover, a comparative assay has been carried out with the corresponding hexynyllithium **6** and, to our surprise, the only isolated product after aqueous NH_4Cl work-up was the γ-lactol **8** (mixture of epimers). This result which can be easily claimed to occur from direct attack of the lithium species onto the carbamoyl function, is in sharp contrast with the reactivity of butyllithium which is known to be unable to add to the carbonyl group of *N,N*-diisopropyl carbamates. The low steric hindrance of the lithiated acetylenic electrophile is obviously responsible for the observed reactivity.



Scheme 2.

The structure of **8** has been confirmed through its transformation into the known *trans*-disubstituted γ-lactone **9**.[12]

Based on these preliminary results obtained with lithium acetylide, it was then decided to test the less expensive commercially available methyllithium as a nucleophile. Therefore, *N,N*-diisopropyl carbamate **10** was treated with four equivalents of methyllithium at 0°C for 1 hour, then quenched at this temperature by addition of aqueous ammonium chloride solution.† No trace of starting material was observed and the only isolated product was the same lactol **8** as above (ca. 1:1 epimeric mixture) in 88% yield (Scheme 3). The corresponding rearranged acetylenic product 12 has not been detected,[13] which clearly demonstrates a preferential kinetic attack of methyllithium onto the carbamoyl function.[14] The preceding conditions were applied to the corresponding *O*-triisopropylsilyl protected vinyl carbamate **11**. After reaction work-up, the corresponding aldehyde **13** was subsequently isolated in 42% yield (not optimised).



Scheme 3.

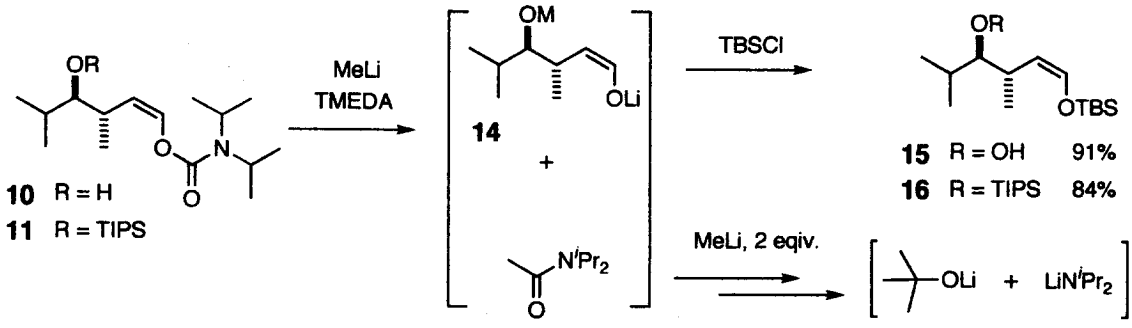
An interesting advantage of such a procedure involving the liberation of the aldehyde function through nucleophilic attack at the carbonyl function with methyllithium is that one can envision to trap in situ the intermediate lithium enolate **14** before work-up of the reaction mixture and such a strategy would open the route for all the well-known aldehyde enolate chemistry as well as further organometallic coupling reactions in the case of in situ transformation into the corresponding enol triflate.[15]. Such a strategy would be reminiscent of the already well known enol acetate chemistry developed by Stork.[16] A corollary benefit to be expected of such a strategy is that the *Z* configuration of the starting enol carbamate can be expected to be retained by trapping the kinetically formed *Z*-lithium enolate.

In order to test such possibilities, two experiments have been performed using *tert*-butyldimethylsilyl chloride in combination with HMPA to quench the reaction mixture after reaction of vinyl *N,N*-diisopropyl carbamates with methyllithium. Both the unprotected alcohol **10** and the *O*-triisopropylsilyl ether **11** have been treated under these conditions to give, after chromatographic separation, the silyl enol ethers **15** and **16** in 91% and 84% yield, respectively.‡ In both cases the configuration of the silyl

† General procedure for γ-lactol **8**: To a solution of vinyl carbamate **10** (1 mmol) in 15 mL of THF at 0°C was added dropwise a solution of methyllithium (4 mmol, 1.6 M in pentane, LiBr free). The reaction mixture was stirred for 1 hour at 0°C then 10 mL of saturated NH_4Cl aqueous solution and 20 mL of diethyl ether were added. After decantation and separation, the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution, brine then dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by silica gel flash-chromatography to give lactol **8**.

‡ Silyl enol ether **16**: To a solution of protected vinyl carbamate **11** (1 mmol), after the addition of 3 equivalents of MeLi in the same condition as above, the reaction mixture was stirred at 0°C for 1 hour, then TMEDA was added (10 mmol). The resulting

enol double bond has been shown to be exclusively Z as expected (Scheme 4). From a mechanistic point of view, it was reasonable to assume three successive nucleophilic additions of methyllithium for the total consumption of the various nucleophilic species (four equivalents were required in the case of **10** bearing a free hydroxyl group). Apart from the expected lithium enolate **14** (M=Li or TIPS), the two by-products of the process should be lithium diisopropylamide and lithium *tert*-butylate. Interestingly, despite an excess of *tert*-butyldimethylsilyl chloride in the quenching mixture, reaction of **10** led to the free alcohol **15**.



Scheme 4.

These two last efficient transformations will probably find interesting applications in syntheses of complex molecules where the homoaldolisation reaction developed by Hoppe is involved as pivotal step to build stereogenic centres and any acidic conditions are to be avoided for the further transformation of the resulting vinyl *N,N*-diisopropyl carbamates into aldehyde equivalents. As mentioned previously, this methodology allows an alternative access to chiral γ-lactones related to **9**, particularly when the isopropyl residue is replaced with acid sensitive substituents.

Acknowledgements

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solution was stirred at 0°C for 15 min then *tert*-butyldimethylsilyl chloride (4 mmol) in 15 mL of THF was added. The resulting mixture was stirred at 0°C for 30 min then allowed to rise to room temperature. The crude solution was treated as described in the preceding procedure and the silyl enol ether **16** purified by chromatography as before.

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