

Further reactions of phenyldimethylsilyllithium with *N,N*-dimethylamides

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Phenyldimethylsilyllithium reacts with several *N,N*-dimethylamides, and the intermediates, formulated here as successively a carbene and an α -silyllithium species, may be trapped with nucleophiles and electrophiles, respectively, although not always with the nucleophile or electrophile of your choice.

We reported earlier in three preliminary communications that the phenyldimethylsilyllithium reagent reacts with the *N,N*-dimethylamide **1** to give one of three different products **2**, **5** or **8**, depending upon the conditions used, but each in high yield (Scheme 1).^{1–3} If one equivalent of the silyllithium reagent is used at -78°C , and the mixture is quenched at -78°C , the product is the acylsilane **2**. If the same reaction mixture is first warmed to -20°C before quenching, the product is the enediamine **5**. If two equivalents of the silyllithium reagent are used and the mixture allowed to come to -20°C before quenching, the product is the α -silylamine **8**. We provided evidence that the initial reaction at -78°C gives the tetrahedral intermediate **3**, and that when this is warmed Brook rearrangement and elimination of silanoxide gives a species which we draw for simplicity as a carbene **6**, but about which we have no detailed information.⁴ The same Brook rearrangement creates a nucleophile which can react with the carbene to give the intermediate **4**, leading to the enediamine **5**. If, instead, there is a second equivalent of the silyllithium reagent, it reacts with the carbene to give the α -aminolithium species **7**, which is quenched by a proton source to give the amine **8**.

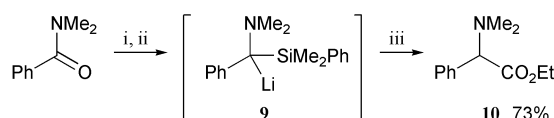
Similar reactions take place with other *N,N*-dialkylamides, the carbene or carbenoid intermediates can be trapped by other nucleophiles such as alkyl- and aryllithium reagents, and the α -aminolithium species can be trapped with other electrophiles than a proton when a phenyl group is present to stabilise them, as in the acylation of the intermediate lithium reagent **9** giving the phenylglycine **10** (Scheme 2), which we now add to the alkylation reactions reported earlier. The silyl group in this new reaction is removed during the aqueous workup, because it is adjacent to the carbonyl group.

We report in this and the following communications other higher-yielding or informative results from more recent investigations. Given that our earlier work was full of unexpected reactions, we have not been too surprised to find that almost every change we have made has given us more.

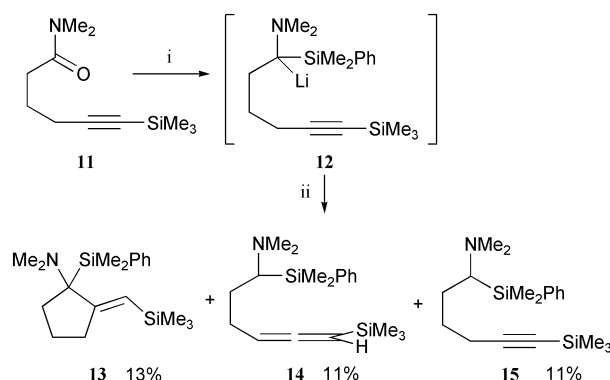
One limitation that we particularly wanted to address was how to trap the lithium reagent with an electrophile when the lithium reagent was not stabilised by an adjacent phenyl group. The problem is that the electrophile must not react with the silyllithium reagent that is used to initiate the sequence of reactions, which severely limits the possibilities. The only success that we had earlier was with an isolated terminal double bond built into the starting amide, but the yield of cyclic product was low. To try to improve on this result, we replaced the double bond with a triple bond **11**, in the hope that the intermediate lithium reagent **12** would lead to the cyclopentane **13**. In the event, cyclisation took place in even lower yield, and the minor products **14** and **15** showed that propargylic proton transfer had taken place in competition with nucleophilic attack on the triple bond (Scheme 3). In the absence of the silyl group at the acetylenic terminus, the acetylenic C–H quenched the lithium reagent.

Proton transfer became the only pathway in the reaction with a terminal alkene and one extra methylene unit (Scheme 4). The amide **16** gave the α -silylamines **19** and **20**, with the latter a mixture of *cis* and *trans* isomers. All three of the products could have come by proton transfer from the intermediate **17**, followed by protonation of the allyllithium species **18** on work up.

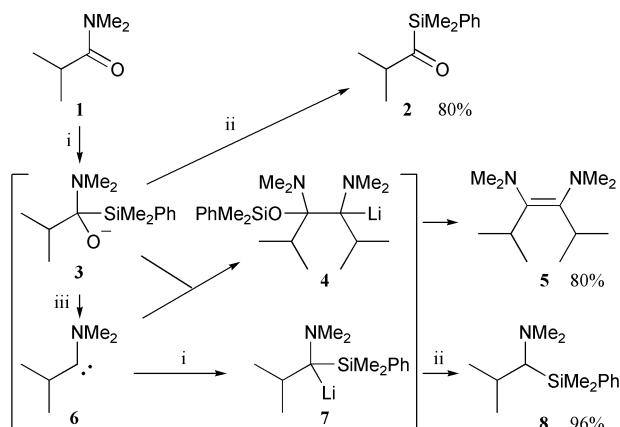
Although alkyl halides react with silyllithium reagents,⁵ there was some hope that both the amide group in the amide **21**, and the carbene derived from it, would react more rapidly than the chloride. Cyclisation of the intermediate lithium reagent **22**



Scheme 2 Reagents and conditions: i, PhMe_2SiLi , -78°C ; ii, warm to -20°C ; iii, ClCO_2Et .



Scheme 3 Reagents and conditions: i, 2.4 equiv. PhMe_2SiLi , THF, -78°C \rightarrow -20°C ; ii, NaHCO_3 , H_2O .

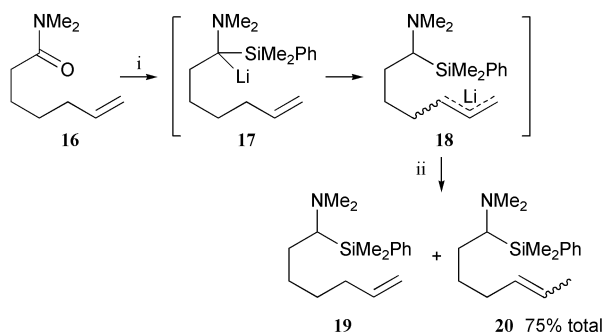


Scheme 1 Reagents and conditions: i, PhMe_2SiLi , -78°C ; ii, NH_4Cl , H_2O ; iii, warm to -20°C .

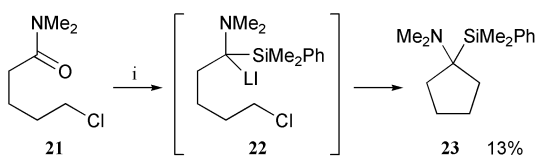
would then lead to the cyclopentane **23** (Scheme 5), which it did, but in low yield.

An alternative to having an electrophilic group within the starting amide was to have it embedded in the nucleophile used to trap the carbene, at which stage the silyllithium reagent would have been consumed. This worked well in the reaction between the amide **1**, and successively the silyllithium reagent and Beak's reagent **25**,⁶ in which the electrophilic centre is protected as a chelate. The only product that we isolated **24** had presumably been formed by ring formation in the intermediate **26** (Scheme 6).

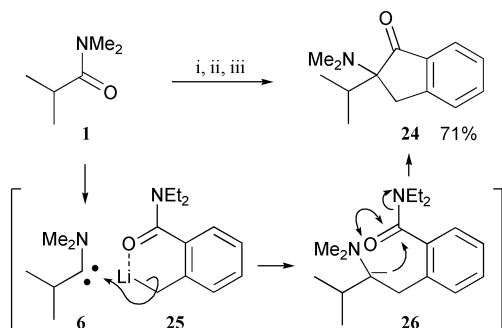
Since a phenyl ring adjacent to the carbon atom carrying the lithium stabilises intermediates like **9**, making them amenable to alkylation and acylation, we tried the reaction on the crotonamide **27**, where a double bond might have the same effect. The only recognisable products, obtained in low yield, were the conjugate addition product **28** and the analogue **29** of the α -silylamine **7**. In contrast, when we slowed down conjugate addition by having a second β -methyl group in the amide **30**, and added the silyllithium reagent to the amide, the product was the enamine-amide **31** in good yield (Scheme 7). This product can be explained as the result of a regioselective conjugate addition of the intermediate allyllithium reagent **32** with the starting material. We have illustrated this reaction with an ionic mechanism, because it can then be related to all our other reactions, but it is conceivable that all the reactions of the silyllithium reagent follow an SET pathway, particularly in this



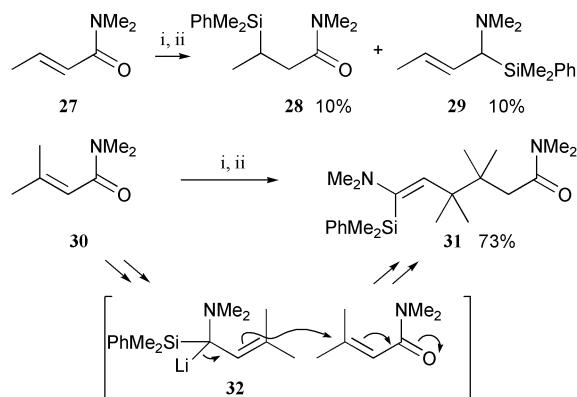
Scheme 4 Reagents and conditions: i, PhMe_2SiLi , THF, $-78^\circ\text{C} \rightarrow -20^\circ\text{C}$; ii, NaHCO_3 , H_2O .



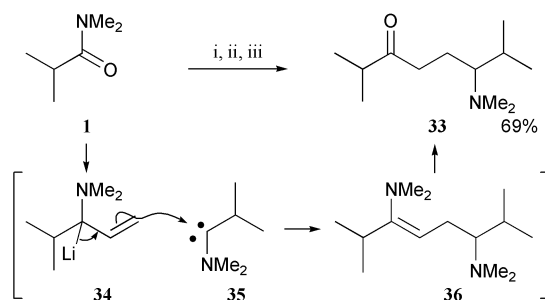
Scheme 5 Reagents and conditions: i, 2.4 equiv. PhMe_2SiLi , THF, $-78^\circ\text{C} \rightarrow -20^\circ\text{C}$.



Scheme 6 Reagents and conditions: i, PhMe_2SiLi , THF, -78°C ; ii, **16**, THF, -78°C , then $\rightarrow -20^\circ\text{C}$, 1 h; iii, NaHCO_3 , H_2O .



Scheme 7 Reagents and conditions: i, PhMe_2SiLi , THF, -78°C , 1 h, -20°C , 1 h; ii, PhMe_2SiLi (inverse addition), THF, -78°C , 1 h, -20°C , 1 h.



Scheme 8 Reagents and conditions: i, PhMe_2SiLi , THF, -78°C ; ii, vinylLi, THF, then $\rightarrow -20^\circ\text{C}$, 1 h; iii, NaHCO_3 , H_2O .

reaction, where it may help to explain the remarkable β - β coupling creating adjacent quaternary centres.

An alternative way of setting up an allyllithium intermediate is to use a vinylolithium as the second nucleophile, the one that reacts with the carbene or carbenoid. We carried out this sequence using the amide **1**, adding one equivalent of the silyllithium reagent at -78°C , then adding one equivalent of vinylolithium, and finally warming the mixture to -20°C before quenching. The only identifiable product, obtained in reasonable yield, was the γ -aminoketone **33** (Scheme 8). This product can be explained as the result of conjugate addition between the allyllithium intermediate **34** with the carbene **35** (= **6**), followed by hydrolysis of the enamine **36**. This sequence can be compared with the original reaction giving the enediamine **5**, hydrolysis of which gives an α -aminoketone. The γ -aminoketone **33** differs in having two methylene groups, derived from the vinylolithium, between the two functional groups.

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Notes and references

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