Formation of α-dialkylamino alkyllithium intermediates in the reaction of *N*,*N*-dialkylamides with $PhMe_2SiLi$ followed by a second lithium reagent, and their alkylation, fragmentation, cyclisation and rearrangement by proton transfer

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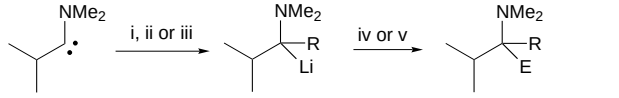
Tertiary amides ($RCONMe_2$) react with $PhMe_2SiLi$, followed by a second lithium reagent NuLi, to give α-dialkylamino alkyllithium intermediates $R(Me_2N)CLiNu$ that undergo protonation 2 → 3, alkylation 2a → 3ab, β-elimination 5 → 6, intramolecular attack on an isolated double bond 9 → 10, intramolecular proton transfer 12, 17 and 22 (arrows), and fragmentation 28 and 34 (arrows), depending upon the structures of the various components R and Nu.

In the preceding paper[1] we described how an intermediate carbene **1** derived from the remarkable reaction between 1 equiv. of $PhMe_2SiLi$ and *N*,*N*-dimethylisobutyramide could be trapped by a second equivalent of the silyllithium reagent. We now report that when we prepared the tetrahedral intermediate from the amide with 1 equiv. of $PhMe_2SiLi$ at −78 °C as usual, and then added PhLi, Bu^nLi or Bu_3SnLi, before warming the mixture to −20 °C, we obtained the amines **3aa**, **3ba** and **3ca**, presumably by way of the intermediate lithium reagents **2a**–**c**. We also quenched the phenyl-stabilised lithium reagent **2a** with allyl bromide to give the amine **3ab** (Scheme 1). These reactions establish a new way of assembling secondary alkyl and, more remarkably, tertiary alkyl tertiary amines, and an α-stannyl tertiary amine.



1

2a R = Ph
b R = Bu^n
c R = $SnBu_3$

3aa R = Ph, E = H 68%
ab R = Ph, E = allyl 60%
ba R = Bu^n, E = H 42%
ca R = $SnBu_3$, E = H 21%

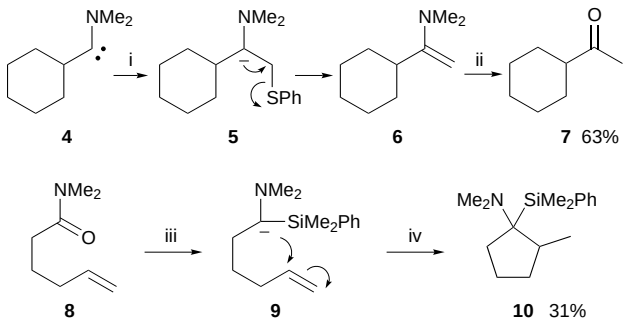
Scheme 1 *Reagents and conditions*: i, PhLi; ii, Bu^nLi; iii, Bu_3SnLi; iv, $NaHCO_3$, H_2O; v, allylBr

We achieved umpolung in another way, by building a leaving group into the nucleophile (Scheme 2). We treated *N*,*N*-dimethylcyclohexanecarboxamide with 1 equiv. of the silyllithium reagent, followed by 1 equiv. of $PhSCH_2Li$, and then warmed to −20 °C to give the lithium reagent **5**, drawn here and from now on as an anion, in order to allow us to use uncomplicated curly arrows. β-Elimination gave the enamine **6**, and hence the ketone **7** on hydrolysis. We also intercepted the intermediate anion **9**, setting it up with 2 equiv. of the silyllithium reagent, and found that nucleophilic attack by the anion (arrows) is possible on the isolated double bond built in to be at the appropriate distance for a known[2] type of 5-*exo*-*trig* reaction of α-amino alkyllithium reagents (Scheme 2). The isolated cyclopentane product **10** was a single diastereoisomer, but we do not know which one. These simple extensions of the pathways recorded in the preceding paper confirm the intermediacy of α-amino alkyllithium intermediates **2**, **5** and **9**.

We also report that the generality of these routes is compromised by the ease with which the intermediate anion, suitably constituted, undergoes proton transfer to give better stabilised anions, and how other similarly constituted anions suffer extraordinary elimination reactions with a benzyl anion leaving group. The intermediate lithium reagents are evidently unstable, and find a disconcerting variety of ways to decompose.

Thus, the phenylacetamide **11** gave, as well as the normal product **13**, small amounts of a cyclic product **15** (Scheme 3). This appears to be a result of a proton transfer **12** → **14**, to give a phenyl anion, followed by displacement of the phenyl group from silicon (**14** → **15**). Displacement of a phenyl group from silicon with an oxy anion nucleophile is well established,[3] and there are a few examples of the displacement of a phenyl or vinyl group by a carbon–lithium reagent.[4]

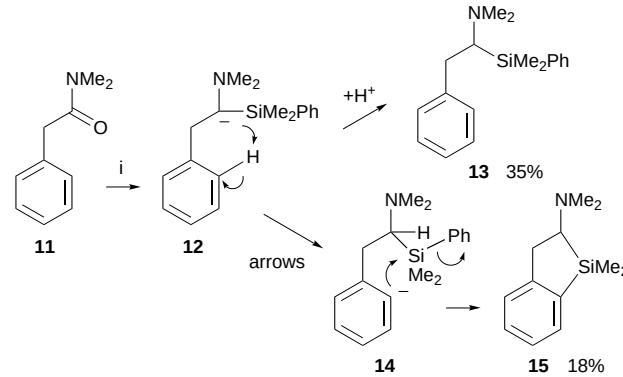
Similarly, the bis-homologue **16** gave the normal product **18** together with a product of proton transfer (**20**) in this case with a benzyl anion displacing the phenyl group (**19** → **20**) (Scheme 4).



4 **5** **6** **7** 63%

8 **9** **10** 31%

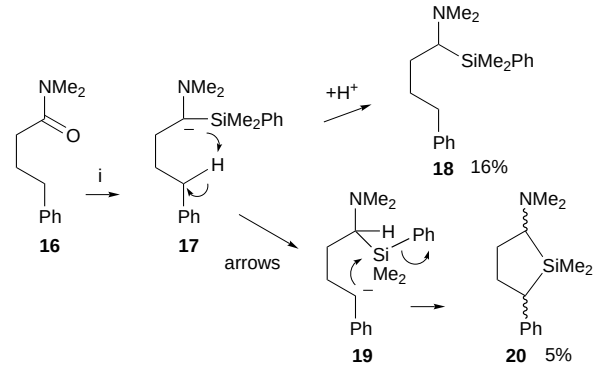
Scheme 2 *Reagents and conditions*: i, $PhSCH_2Li$, −20 °C; ii, HCl, H_2O; iii, $PhMe_2SiLi$ (2.4 equiv.) THF, −78 → −20 °C, 1.5 h; iv, $NaHCO_3$, H_2O



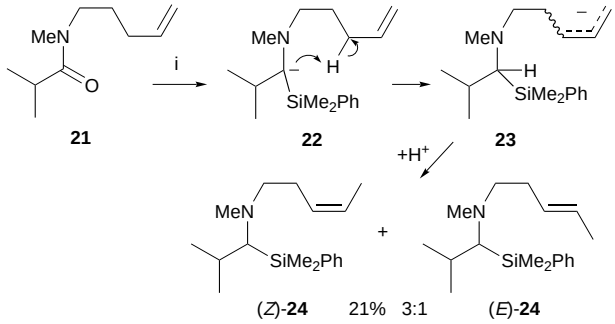
11 **12** **13** 35%

14 **15** 18%

Scheme 3 *Reagents and conditions*: i, $PhMe_2SiLi$ (2.4 equiv.), THF, −78 → −20 °C, 1.5 h



Scheme 4 *Reagents and conditions*: i, $PhMe_2SiLi$ (2.4 equiv.), THF, −78 → −20 °C, 1.5 h

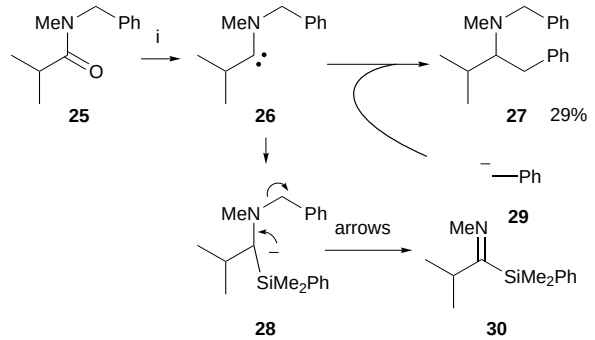


Scheme 5 *Reagents and conditions*: i, $PhMe_2SiLi$ (2.4 equiv.), THF, −78 → −20 °C, 1.5 h

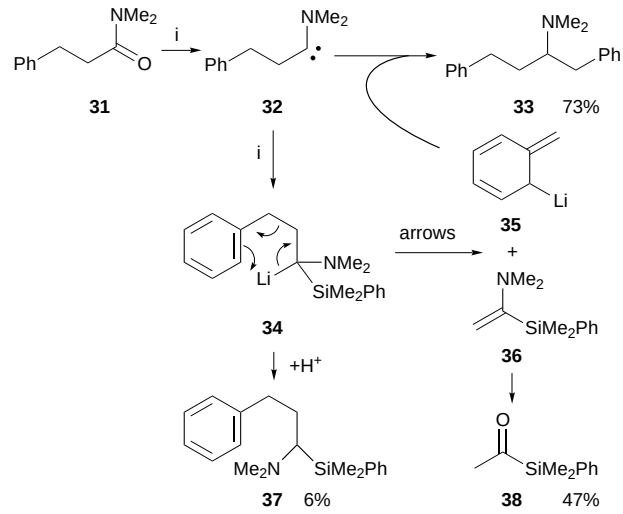
Proton transfer within a five-membered ring also took place from the pentenyl substituent in the amide **21**, where the minor, but the only recognisable, basic products were the pent-3-enylamines (*Z*)-**24** and (*E*)-**24**, similar to what we might call the normal product, except that the double bond had moved (Scheme 5). Proton transfer **22** → **23**, with the formation, as usual,[5] of more of the sickle-shaped allylic anion than of the W-shaped anion, accounts for this curious reaction.

We saw yet another pathway in the reaction with *N*-benzyl-*N*-methylamide **25** (Scheme 6), where the only basic product that we were able to identify from the reaction with 2 equiv. of $PhMe_2SiLi$ was the tertiary amine **27**. This can be accounted for by elimination **28** → **30** to release a benzyl anion **29**, followed by the attack of the benzyl anion on the carbene intermediate **26** and subsequent protonation.

Elimination to give a benzyllithium intermediate also explains what is perhaps the most remarkable reaction in the



Scheme 6 *Reagents and conditions*: i, $PhMe_2SiLi$ (2.4 equiv.), THF, −78 → −20 °C, 1.5 h



Scheme 7 *Reagents and conditions*: i, $PhMe_2SiLi$ (2.4 equiv.), THF, −78 → −20 °C, 1.5 h

cornucopia of remarkable reactions, both those described in this series of papers and those for which we have no room here. When we treated the amide **31**, intermediate between the amides **11** and **16**, with 2 equiv. of $PhMe_2SiLi$, the major basic product was the amine **33** (Scheme 7). Elimination from the usual intermediate **34** would give the enamine **36**. The elimination is drawn here (**34** arrows) as a retro metalla-ene reaction, and the elimination product is drawn as the 'allylic' isomer **35** of benzyllithium, to illustrate an alternative perception to that drawn for the related elimination **28** → **29** + **30** in Scheme 6. The benzyllithium or its allylic isomer **35** might then trap the carbene **32** to give, after protonation, the major product **33**. In support of this sequence, we also isolated the acylsilane **38** from the basic fraction, into which, presumably, it had been extracted as the enamine **36**. We are not aware of any precedent for carbon–carbon bond cleavage with a benzyllithium leaving group.

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Notes and References

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