The reductive coupling of tertiary amides to give enediamines using PhMe$_2$SiLi

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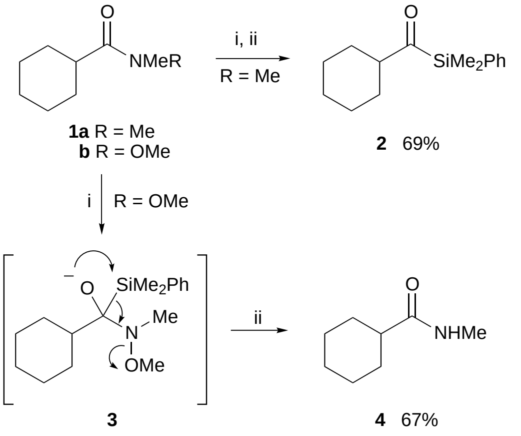
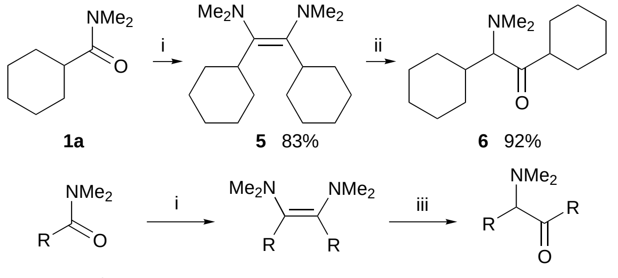
PhMe$_2$SiLi reacts with tertiary amides to give enediamines, which can be isolated in good yield when the α-carbon is branched; the enediamines can be hydrolysed more or less easily to α-amino ketones, isomerised from *Z* to *E*, oxidised to dienediamines and isomerised to amino enamines.

We have been studying the reactions of PhMe$_2$SiLi[1] with a variety of substrates, including carbon electrophiles at the oxidation state of a carboxylic acid. One goal in this work had been to find a synthesis of acylsilanes that might be even easier than the reaction between an acid chloride and a silyl cuprate.[2] We reported almost no success, and several surprises, in the reaction between the silyllithium reagent and nitriles,[3] some success in the reaction with esters,[4] and some success with tertiary amides **1a**$\rightarrow$**2**, *provided that the reaction is carried out and quenched at dri ice–acetone temperatures*.[4] To avoid this delicate operation, the standard device when synthesising aldehydes or ketones from amides is to use a Weinreb amide,[5] but we find that this does not work for the synthesis of acylsilanes, because the Weinreb amide **1b** gives N–O cleavage instead (Scheme 1), presumably by elimination of methoxide from the tetrahedral intermediate **3** giving the secondary amide **4**.[6] Among the variety of unexpected reactions of the silyllithium reagent that we have already reported, none has been as surprising as the reactions with tertiary amides carried out at higher temperatures, which we report here and in the following two papers.

When we treated the same *N*,*N*-dimethylamide **1a** with a little over 1 equiv. of the silyllithium reagent at −20 °C, and quenched the mixture with aq. NaHCO$_3$ at that temperature, we obtained a good yield of the crystalline enediamine **5** (Scheme 2). Although there is one precedent for this type of reaction, where a 14% yield of an enediamine was obtained from *N*,*N*-diethylbenzamide with Et$_3$SiLi,[7] we were at first uneasy about the structure of this compound, since it had survived dissolution in dilute hydrochloric acid overnight at room temperature—conditions that are far more vigorous than those usually needed for the hydrolysis of an enamine. An X-ray crystal structure (Fig. 1) confirmed that it was the enediamine and showed also that it was the *Z* isomer.[8]‡



Scheme 1 *Reagents and conditions*: i, PhMe$_2$SiLi (1.2 equiv.) THF, −78 °C, 1.5 h; ii, NH$_4$Cl, H$_2$O, −78 °C → room temp.



7	8	9
7a R = Pr^i	**8a** 80%	**9a** 79%
b R = Bu^t		**b** 6%
c R = Pr^n		**c** 81%
d R = Me(CH$_2$)$_8$		**d** 72%
e R = CH$_2$=CH(CH$_2$)$_2$		**e** 75%
f R = CH$_2$=CH(CH$_2$)$_3$		**f** 59%
g R = Bn		**g** 52%
h R = Ph(CH$_2$)$_2$		**h** 69%
i R = PH(CH$_2$)$_3$		**i** 60%
j R = Ph(CH$_2$)$_4$		**j** 46%
k R = Ph		**k** 51%

Scheme 2 *Reagents and conditions*: i, PhMe$_2$SiLi (1.1 equiv.) THF, −78 → −20 °C, 1 h; ii, 3 M HCl, 70 °C, 18 h; iii, 3 M HCl, various times and temperatures

The stability in acid was now convincingly explained—the lone pairs on both nitrogen atoms are in the plane of the double bond, and not conjugated to it as they are in a typical enamine. Hydrolysis of the enediamine **5** required heating to 70 °C in dilute hydrochloric acid for 18 h in order to obtain the α-amino ketone **6**. Clearly, in contrast to the one precedent, the reductive coupling of amides can be a high-yielding reaction. We find that the amides **7a–k** undergo reductive coupling followed by hydrolysis to give the α-amino ketones **9a–k**, but the enediamines **8a–k**, although detectably intermediates, were only easily isolated when they carry branched substituents, as with **8a**, to confer on them this remarkable hydrolytic stability.

The enediamines **5** and **8a** showed a number of unexpected reactions (Scheme 3). When we treated the enediamine **5** with methyl acrylate, attempting to induce a cycloaddition characteristic of enamines,[9] it isomerised to the *E* isomer **11a**, which was remarkable for the substantial difference in its properties from the *Z* isomer: the R_f value on silica gel eluting with hexane changed from 0.1 to 0.7 and the mp changed from 89–90 °C to 175–176 °C. The isomerisation from the *Z* isomers **5** and **8a** to

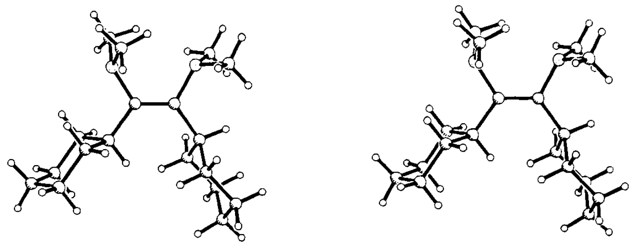
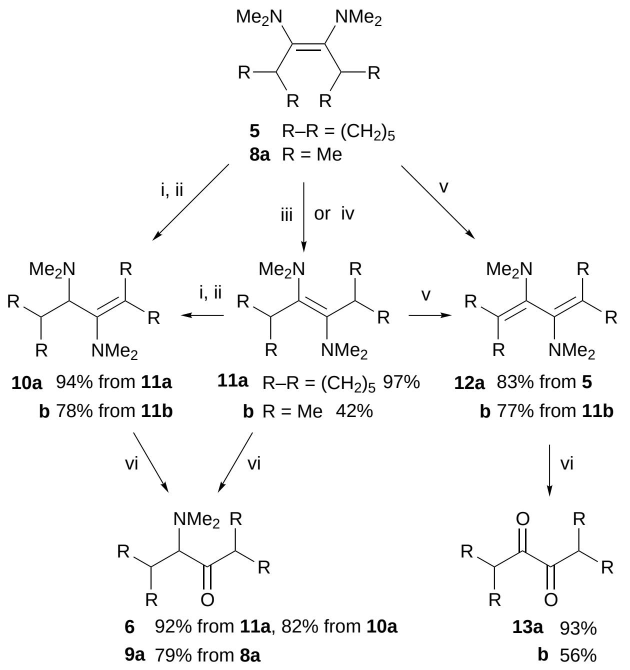


Fig. 1 Stereoview of the enediamine **5**



Scheme 3 *Reagents and conditions*: i, $(CO_2H)_2$, recrystallise from EtOAc; ii, NaOH, H_2O; iii, CH_2=$CHCO_2Me$, 60 °C, 24 h; iv, PtO_2, MeOH, 50 °C, 15 min; v, Pd/C, MeOH, room temp., 4 h; vi, 3 M HCl, 70 °C, 18 h

the *E* isomers **11a**, **b**, respectively, is actually better carried out using a short treatment with Adams' catalyst. The enediamines, both the *Z* and *E* isomers, gave oxalate salts, but simple recrystallisation of these salts, followed by basification, gave the isomers **10a** and **10b** of the enediamines in which the double bond had moved. All of the enediamines could be hydrolysed to the α-amino ketones **6** and **9a**, but all attempts to reduce any of them to the saturated vicinal diamine failed. Most remarkable amongst our attempts was the oxidation of the enediamines **5** or **11a** *using hydrogen and palladium on charcoal*, which gave the dienediamine **12a**. Needless to say, this oxidation was better performed without the hydrogen, and the first step, when carried out on the *Z* isomers, appears to be isomerisation to the *E* isomers. Hydrolysis of the dienediamines **12** gave the α-diketones **13**.

The reductive coupling of the amide carbonyls resembles the McMurry coupling of aldehydes and ketones, and even more closely the reductive coupling of amides using samarium and its iodide,[10] and other lanthanides and their salts.[11] While an electron transfer mechanism might be operating in our reaction, the very different reagent that we have used led us to suspect otherwise. We describe our investigations into the mechanism of the coupling in the following paper.

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Notes and References

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‡ *Crystal data* for **5**: $C_{18}H_{34}N_2$, FM = 278.47, monoclinic, $P2(1)/n$, a = 6.3930(6), b = 13.3934(11), c = 20.962(2) Å, β = 91.6833(11)°, T = 293(2) K, Z = 4, μ = 0.443 mm^{-1}, 5035 reflections collected, of which 3621 were independent, $R1$ = 0.0884, $wR2$ = 0.1811. CCDC 182/765.

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