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Preparation of 2-azaallyl anions and imines from *N*-chloroamines and their cycloaddition and allylation

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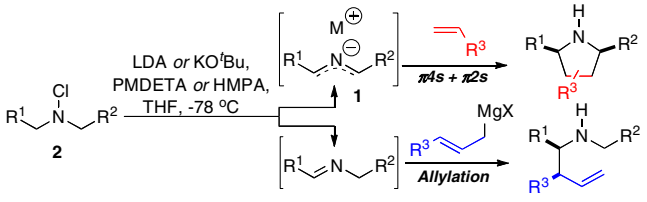
ABSTRACT

Exposure of *N*-chloroamines to KO^{t}Bu or LDA, in the presence of PMDETA or HMPA, provides 2-azaallyl anions capable of π4s + π2s cycloaddition reactions with a range of olefins. Good yields were achieved with stabilised systems, however, they were more modest when accessing semi-stabilised 2-azaallyl anions. By modifying the reaction conditions, one-pot dehydrochlorination/allylation can also be achieved with a range of *N*-chloroamines.

In the seminal work of Kauffmann and Köppelmann, the π4s + π2s cycloaddition of 2-azaallyl anions and olefins was discovered.[1] In these studies 2-azaallyl anions **1**, bearing two or more aryl substituents, were formed by deprotonation of the corresponding imine, however, with one or no aryl groups this reaction failed.[1b] Addressing this limitation Kanemasa and Tsuge developed silicon-based transmetalation approaches,[2] while Pearson exploited imino stannanes to access semi-stabilised (one aryl) and non-stabilised (no aryl) 2-azaallyl anions.[3] While the latter approach has proved highly useful, shortcomings remain. As stated by Pearson, methods for the generation of '*nonstabilized 2-azaallyl anions with a longer lifetime and preferably featuring tin-free techniques are required.*'[3a] Inspired by these challenges we commenced studies aimed at developing new methods for the preparation of 2-azaallyl anions. Herein we report a novel tin-free approach to stabilised and semi-stabilised 2-azaallyl anions exploiting *N*-chloroamines, that is, **2**, as starting materials. In addition, the use of *N*-chloroamines in a one-pot dehydrohalogenation/allylation is reported (Scheme 1).

Our strategy builds upon the observation that 2-azaallyl anions (i.e., **1**) can be formed from metalated dibenzylamides, which undergo β-hydride elimination and deprotonation, when exposed to appropriate ligands.[4,5] While this sequence provides 2-azaallyl anions, it requires multiple operations and as such has not been exploited in reaction development.[5a] We postulated that improved procedures for metalation should allow better access to 2-azaallyl anions. To this end we envisaged halogen–metal exchange of *N*-haloamines as a potentially useful method.

N-Chloroamines (i.e., **2**) are useful aminating agents that undergo substitution reactions with organometallics,[6,7] heteroaromatics[8] and enolates.[9] While the halogen–metal exchange of these reagents has not been developed, this process has been observed as a side reaction.[6,10,11a] To explore the use of *N*-chloroamines in 2-azaallyl anion formation, *N*-methyl benzylamine *N*-chloride (**2a**) was prepared and its π4s + π2s cycloaddition with styrene investigated. Using LDA in the absence of a donor failed to deliver pyrrolidine **4a**, however, reductive dechlorination of **2a** demonstrated the viability of halogen–metal exchange (Table 1, entry 1). To favour β-hydride elimination HMPA/TMEDA was trialed as a pseudo tridentate donor in the presence of LDA. Under these conditions, isomeric cycloadducts **4a** and **4a′** formed in a combined yield of 32% and with 1.3:1 regioselectivity (Table 1, entry 2).[3c] Changing the donor to *N*,*N*,*N*′,*N*′-pentamethyldiethylenetriamine (PMDETA) failed to increase the yield, however, the reaction now occurred with complete regioselectivity (Table 1, entry 3).



Scheme 1.

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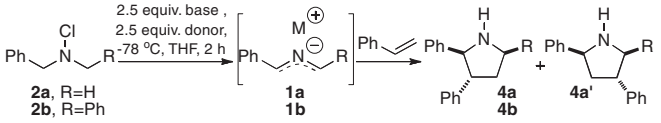
Table 1
Selected optimisation of 2-azaallyl anion/cycloaddition[a]



Entry	R	Base	Donor	Solvent	Yield[b] (%)
1	H	LDA	—	THF	—
2	H	LDA	HMPA/TMEDA	THF	32 (1.3:1)[c]
3	H	LDA	PMDETA	THF	26 (>95:5)[c]
4	H	BuLi	PMDETA	THF	—
5	H	NaH	PMDETA	THF	—
6	Ph	LDA	PMDETA	THF	50
7	Ph	KO^{t}Bu	HMPA	THF	82
8	Ph	KO^{t}Bu[d]	HMPA	THF	—[e]

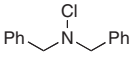
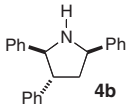
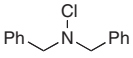
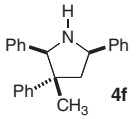
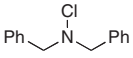
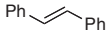
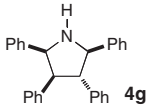
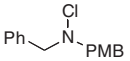
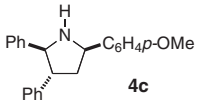
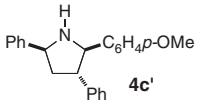
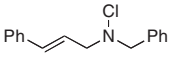
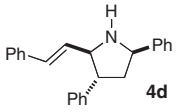
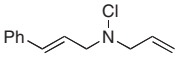
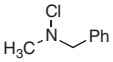
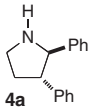
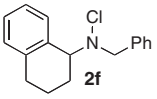
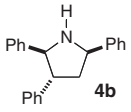
[a] For details of conditions, see the Supplementary data.
[b] Isolated yield following flash column chromatography.
[c] Ratio of **4a**:**4a**′ determined from ^{1}H NMR analysis.
[d] 1 equiv KO^{t}Bu.
[e] Imine formation.

Unfortunately, systematic modification of temperature, solvent, donor, order-of-addition and stoichiometry failed to improve upon this result. In each case the starting material was consumed and broad signals in the ^{1}H NMR corresponding to decomposition products were observed.

Attempts to access stabilised 2-azaallyl anions proved more successful. With *N*-chloroamine **2b**, pyrrolidine **4b** was formed in 50% isolated yield using the previously developed conditions (Table 1, entry 6). After screening a number of bases and ligands we found KO^{t}Bu and HMPA improved the yield of cycloadduct **4b** to 82% (Table 1, entry 7). Although metalation of the *N*-chloroamine **2b** under these conditions is plausible,[11a] it is more likely that dehydrochlorination,[11b] followed by deprotonation provides the 2-azaallyl anion **1b** (M=K). Further support for this explanation can be derived from the use of one equivalent of KO^{t}Bu, in this case providing the imine as the sole product (Table 1, entry 8). If halogen–metal exchange and β-hydride elimination were occurring then one equivalent of KH would be generated in this reaction allowing 2-azaallyl anion **1b** (M=K) to form.

In effect, two distinct methods have been developed for the assembly of 2-azaallyl anions from *N*-chloroamines. The first

Table 2
Scope of the cycloaddition of 2-azaallyl anions **1a**–**f**[a]

Entry	*N*-Chloride	Olefin	Product	Yield[b] (%)
1	 **2b**		 **4b**	82
2	 **2b**		 **4f**	62 (dr 5:1)[d]
3	 **2b**		 **4g**	85
4	 **2c**		 **4c**  **4c′**	83
5[c]	 **2d**		 **4d**	20
6[a,c]	 **2e**		—	—
7[c]	 **2a**		 **4a**	26
8[c]	 **2f**		 **4b**	33

[a] See Ref. 13 and Supplementary data for conditions.
[b] Isolated yield following flash column chromatography.
[c] Conducted as in Table 1, entry 3.
[d] Diastereomeric ratio determined by ^{1}H NMR analysis.

exploits halogen–metal exchange and constitutes a rare example of a tin-free preparation of semi-stabilised 2-azaallyl anions;[12] while the second likely involves dehydrochlorination/deprotonation and is suited to stabilised 2-azaallyl anion formation.

Application of the conditions described above (Table 1, entries 3 and 7) to alternative *N*-chloroamines allowed the scope of the two procedures to be examined.[13] Reaction of other olefins with the stabilised 2-azaallyl anion **1b** (M=K) provided the expected pyrrolidines in good isolated yields (Table 2, entries 1–3) and with stereoselectivity as previously described (Table 2, entry 2).[3,14] The effect of electronics was subsequently investigated, with *N*-chloroamine **2c** providing a 2:1 mixture of **4c** and **4c′**, in a combined yield of 83% (Table 2, entry 4). Reaction with cinnamyl *N*-chloride **2d** was selective for isomer **4d**, however, the yield was a modest 20% (Table 2, entry 5). The related allyl system decomposed under the reaction conditions (Table 2, entry 6). The π4s + π2s cycloaddition of semi-stabilised 2-azaallyl anions derived from *N*-chloride **2f** surprisingly gave pyrrolidine **4b** as the only isolable product. Its formation either occurs via cycloaddition followed by excision of an allylic anion or by 2-azaallyl anion formation, followed by disproportionation and cycloaddition. Although the latter may be more conceivable, attempts to demonstrate disproportionation with labelled substrates have failed to date.

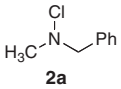
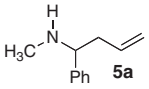
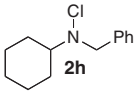
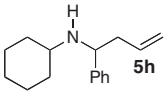
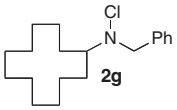
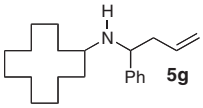
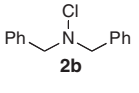
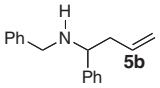
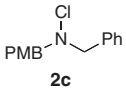
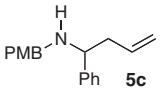
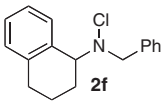
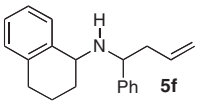
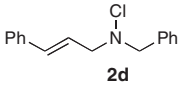
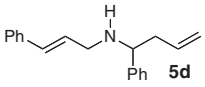
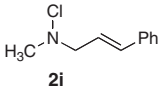
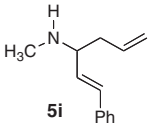
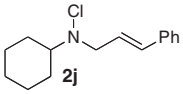
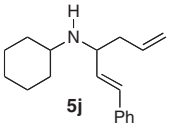
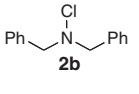
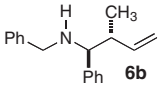
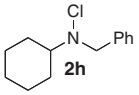
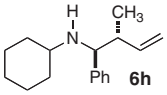
Imine formation from *N*-chloroamines has been extensively investigated from a mechanistic perspective,[11] although the application of this reaction has largely been neglected. An exception being the recent work of Davis[10,15] who found that cyclic pyrrolidine-derived *N*-chloroamines could be converted into the corresponding imine using DBU, isolated, then reacted with nucleophiles. Surprisingly, although imine formation was facile with our acyclic substrates using KO^{t}Bu, DBU failed to deliver these products. The conversion of amines into the corresponding imine is a useful transformation,[16] since it enables functionalisation of α-to the nitrogen, thus we decided to examine the utility of our reaction conditions with a range of *N*-chloroamines poorly suited to 2-azaallyl anion formation. For this study we surveyed one-pot dehydrochlorination/allylation of *N*-chloroamines **2a**–**h** using allylmagnesium reagents (Table 3).[17] Using *N*-chloroamines **2a**, **2h** and **2g**, derived from primary and secondary amines, the allylation with allylmagnesium bromide proceeded in good to excellent yields to provide the expected homoallylic amines (Table 3, entries 1–3). The allylation of dibenzyl amine **2b** gave the expected product in excellent yield (Table 3, entry 4). With all reactions 2.5 equiv of KO^{t}Bu gave optimal results. The *N*-chloroamine **2c**, derived from PMB benzylamine and **2f** from tetralone, allowed the stereoelectronic requirements to be investigated. In both cases single products were obtained, in good yield, with addition occurring at the carbon distal to the electron-releasing group, (Table 2, entry 5) and at the least hindered carbon (Table 2, entry 6). Addition to the benzylic over the cinnamic carbon was demonstrated with *N*-chloroamine **2d** (Table 2, entry 7), providing dienes useful for tetrahydropyridine preparation.[18]

Next, the reactions of *N*-chloroamines **2i** and **2j** were investigated. In both cases, allylation proceeded with selectivity for the cinnamic carbon (Table 2, entries 8 and 9). The modest yields for these reactions arise as a result of conjugate addition providing aldehyde **7** (Scheme 2).

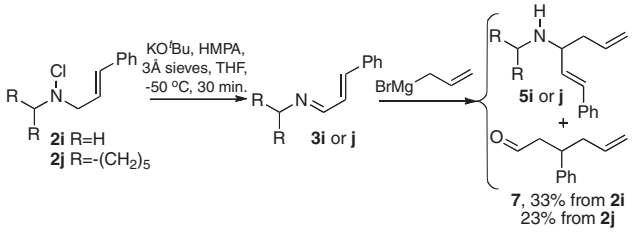
Finally, the reaction of the crotyl Grignard reagent with *N*-chloroamines **2b** and **2h** was investigated, providing the branched products in good yields (Table 3, entries 10 and 11). The reaction proceeded with reasonable diastereoselectivity in the former case (Table 3, entry 10) and 92:8 selectivity in the latter (Table 3, entry 11), favouring the *anti*-product.

Two sets of conditions for the formation of 2-azaallyl anions from the corresponding *N*-chloroamines have been developed. While this reaction proceeded with excellent yield to provide

Table 3
Allyation of imines derived from *N*-chloroamines **2a**-**h**[a]

Entry	*N*-Chloride	Product	Yield[b] (%)
1[c]	 **2a**	 **5a**	89
2[c]	 **2h**	 **5h**	85
3[c]	 **2g**	 **5g**	71
4[c]	 **2b**	 **5b**	86
5[c]	 **2c**	 **5c**	66
6[c]	 **2f**	 **5f**	64
7[c]	 **2d**	 **5d**	68
8[c]	 **2i**	 **5i**	27
9[c]	 **2j**	 **5j**	33
10[d]	 **2b**	 **6b**	65 (dr 7:3)[e]
11[d]	 **2h**	 **6h**	57 (dr 92:8)[e]

[a] See Ref. 17 and Supplementary data for detailed conditions.
[b] Isolated yield following flash column chromatography.
[c] *N*-Chloroamine was reacted with KO^{t}Bu (2.5 equiv) followed by HMPA (2.5 equiv) and allylmagnesium bromide (2 equiv).
[d] Following imine formation as described previously the solution was treated with crotylmagnesium bromide (2 equiv).
[e] Diastereomeric ratio determined by ^{1}H NMR analysis.



Scheme 2.

stabilised 2-azaallyl anions, competent in cycloaddition reactions, semi-stabilised systems were more difficult to access in high yields. Thus, while tin-free methods have been successfully

developed, further work is required to improve this process. In addition to 2-azaallyl anion formation and cycloaddition, one-pot allylation of *N*-chloroamines in good to excellent yields is reported. The halogen–metal exchange of *N*-chloroamines is underdeveloped in reaction discovery. The application of this process in other transformations is subject to ongoing studies.

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Supplementary data

Supplementary data associated with (procedures for the preparation of all new materials as well as copies of ^{1}H and ^{13}C NMR spectra of the compounds) this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.142.

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