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Metal Acetylide Elimination: The Key Step in the Cascade Decomposition and Transformation of Metalated Propargylamines

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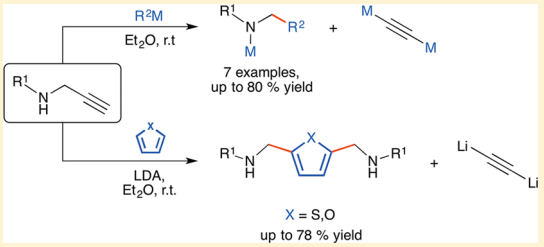
Supporting Information

ABSTRACT: Metal acetylide elimination facilitates a novel one-pot cascade metalation and elimination/addition route to a series of unsymmetrical secondary amines from the reaction of secondary propargylamines with organometallic reagents. Spectroscopic evidence suggests a dimetalated amido intermediate rather than an allene.



Chiral alkali-metal amides are important and well-established reagents in asymmetric synthesis, used widely in desymmetrization reactions involving selective proton removal and lithiation[1] and in conjugate addition reactions where they provide a convenient and expansive route to ammonia equivalents and valuable compounds such as β-amino acids and β-lactams.[2,3] This widespread use, coupled with the often unpredictable reactivity and selectivity of organo-alkali-metal reagents, has underpinned many efforts to understand the structural chemistry and hence structure−reactivity relationships in an attempt to interpret and control reaction outcomes.

In our studies on commonly used chiral benzylic and allylic amides we have discovered and reported on decomposition and rearrangement processes which are dependent on the metal (Li, Na, or K), reaction temperature, and the nature of any Lewis base(s) and/or solvents present.[4−7] Since our initial discovery of facile anion rearrangements in metalated *N*-(α-methylbenzyl)allylamide systems,[8] we have been exploring the chemistry of related amines in an attempt to understand better the factors which drive these rearrangements and which ultimately result in the relocation of the π bond within the molecule. These processes can have a significant effect, changing completely the nature of the amido moiety and often negating the chiral nature of the α-methylbenzyl moiety, resulting in aza-allylic and aza-enolate systems.[9,10]

In diverging from allylic amines, we recently began to probe the chemistry of related *N*-propargylic systems. Propargylamines are key building blocks in the synthesis of many heterocyclic compounds,[11−15] and as such there is a deep and ongoing interest in their synthesis and reactivity.[16−20] With the exception of simple deprotonation/metalation reactions at the terminal acidic alkynyl proton, there has been a surprising dearth of studies into their behavior and reactivity toward organometallic bases. Sato,[21] Shimizu,[22] Normant,[23] and Brandsma[24] have all reported studies involving metalation of an *N*-propargylamine moiety ($R_2NCH_2C{\equiv}CR$), though the last two researchers used tertiary amines, thereby precluding the formation of metal amides. Shimizu's work indicates the possibility of anion rearrangements in observing the rearrangement of the *N*-propargyl group in *N*-(α,α-diphenylethyl)-propargylamine or *N*-(trityl)propargylamine to an *N*-allylideneamine ($RN{=}CHCH{=}CH_2$). Sato describes using the lithium derivative of *N*-(α-methylbenzyl)-3-(trimethylsilyl)-2-propynylamine in a conjugate addition to α,β-unsaturated esters to yield β-amino esters.

Importantly, in none of the aforementioned studies was the metalated intermediate ever isolated and described; thus, the nature and chemistry of these intermediates remain largely unknown.

To establish greater knowledge and a better understanding of the structural and solution chemistry of such complexes, we have studied the reaction of the series of *N*-propargylamines *N*-(α-methylbenzyl)propargylamine (**1a**), *N*-(α-methylbenzyl)-3-(trimethylsilyl)-2-propynylamine (**1b**), *N*-(cyclohexyl)-propargylamine (**1c**), and *N*-propargylaniline (**1d**), with varying equivalents of s-block organometallic reagents (*n*-BuLi, *n*-BuNa, and *n*-BuMgCl and *tert*-butyl-, phenyl-, furyl-, thienyl-, 5-methylthienyl, and 2-picolyllithium) (Scheme 1). Herein we now describe these reactions and the subsequent decomposition of dimetalated propargylamines to yield metal acetylides and aminomethylated derivatives of the organometallic bases.

Treatment of propargylamine **1** with *n*BuLi yields lithium acetylide **2**, characterized by the disappearance of the terminal proton in the ^{1}H NMR spectrum and the absence of the alkynyl C−H stretching and bending frequencies at 3291 and 624 cm^{-1}, respectively, in the IR spectrum. Addition of a second equivalent of *n*BuLi yields the dilithio species **3**, while addition of a third equivalent of *n*BuLi in weakly polar or nonpolar solvents causes the elimination of dilithioacetylide, accompanied by formation of methanediylamine **4a**. The dilithioace-

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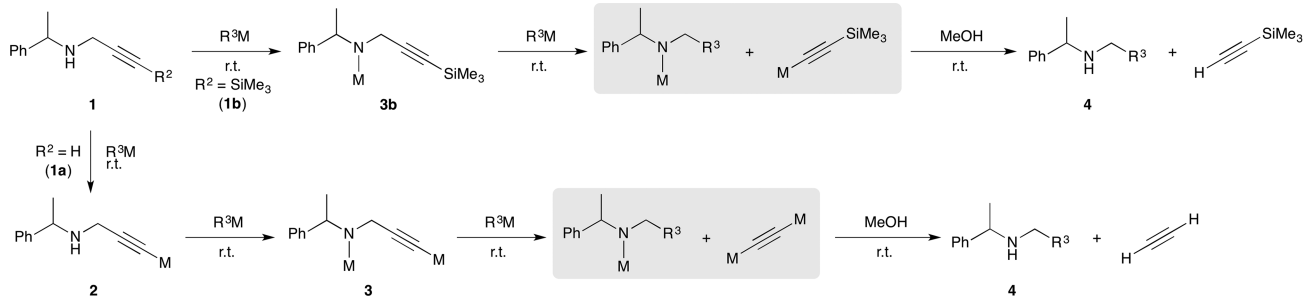
Organometallics XXXX, XXX, XXX−XXX

Scheme 1. Metal Acetylide Elimination during the Transformation of Propargyl Amines 1 to Methanediylamines 4[a]



[a]R^3M = *n*-BuLi, *n*-BuNa, *n*-BuMgCl, *t*-BuLi, PhLi, furyllithium, thienyllithium, 5-methylthienyllithium.

tylide formed can be trapped with trimethylsilyl chloride (TMSCl) to yield bis(trimethylsilyl)acetylene. To the best of our knowledge, there are only two previous reports of metal acetylide elimination from an organic compound: the reverse Diels–Alder reaction of norbornadiene following metalation with sodium to yield sodium acetylide[25] and the decomposition of copper(II) acetylenedicarboxylate to yield copper acetylide.[26] Thus, this is the first general reaction to produce metal acetylides from organic substrates.

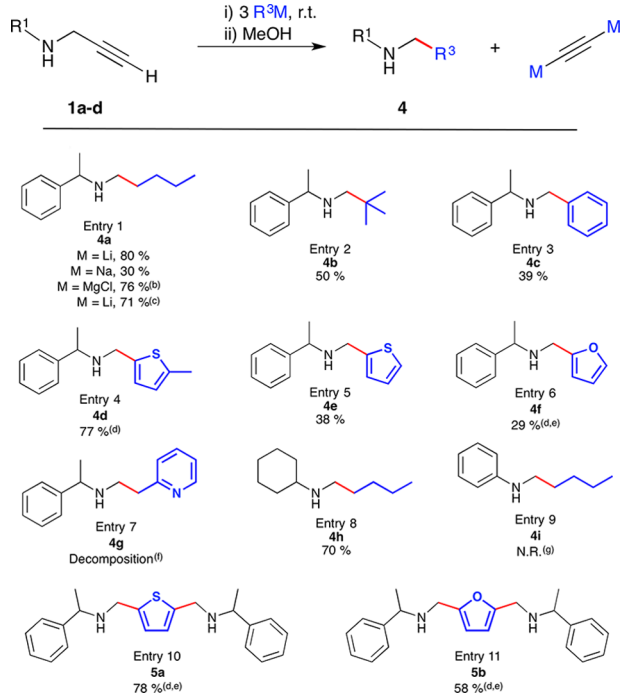
The reaction proceeds with a variety of organometallic reagents; products of the unoptimized reactions are shown in Table 1. Propargylamine **1** reacts with a variety of organolithium reagents in diethyl ether or hexane to yield the aminomethylated derivatives **4a–f**. It is also possible to synthesize the organolithium in situ using 3 equiv of lithium diisopropylamide (LDA) and only 1 equiv of R^3H (Table 1, entries 4 and 6).

It is interesting to note that product **4g** is not isolated from the reaction of **1a** with picolyllithium; instead, the reaction yields a mixture of α-methylbenzylamine and 1,3-bis(2-pyridyl)propane. This is apparently due to decomposition of the intermediate product in the presence of organolithium reagents, to form lithiated derivatives of α-methylbenzylamine and 2-vinylpyridine. 2-Vinylpyridine can then react with picolyllithium to yield 1,3-bis(2-pyridyl)propane. Indeed, reaction of **4g**, synthesized by other means, with 1 equiv of picolyllithium yields the same mixture of α-methylbenzylamine and 1,3-bis(2-pyridyl)propane.

Organolithium reagents with a second acidic site (R^3 = thiophene, furan) react with a second equivalent of **1** to yield bis-amino derivatives **5a,b** (Table 1, entries 10 and 11). This is presumably due to rearrangement of the product to yield the ortho-metalated heterocycle, which then reacts with **1** in the same fashion as before (Scheme 2). The **4e**:**5a** ratio depends on the reaction conditions, with Et_2O solvent favoring formation of the bis-amino derivative **5a** and generating thienyllithium in situ with LDA further favoring the bis-amino product (see the Supporting Information).

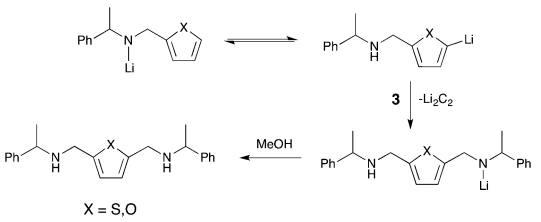
The reaction also proceeds with *n*BuMgCl; however, it requires THF at reflux for the reaction to go to completion (Table 1, entry 1). Reaction in Et_2O yields only the mono-metalated product **2** (M = MgCl). This greatly increases the scope of the reaction, as exotic Grignard reagents are generally easier to prepare than their organolithium counterparts. nBu_2Mg does not give analogous reactivity, the major product instead being carbometalation of the alkyne, analogous to the previously reported reaction of a Grignard reagent in the presence of zinc chloride with a lithium acetylide, the tertiary amine equivalent of **2**.[23] The internal alkyne **1b** reacts in the same manner as terminal alkyne **1a**, indicating that the terminal metalation is not involved in the reaction mechanism. This also means that the equivalents of organometallic reagent used can be reduced, as **1b** reacts to yield **4a** with only 2 equiv of *n*BuLi.

Table 1. Aminomethylated Products Formed by Metal Acetylide Elimination from Metalated Propargylamines[a]



[a]Isolated yields after aqueous workup, calculated by NMR where impurities remained. [b]The reaction was conducted in THF solvent at reflux. [c]The internal alkyne **1b** was used instead of **1a**. [d]The organolithium R^3Li was generated in situ with LDA. [e]A 2:1 ratio of amine to heterocycle was used. [f]The product decomposes in the presence of picolyllithium (see above). [g]No reaction occurred.

Scheme 2. Proposed Mechanism for Formation of 5a,b



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Organometallics XXXX, XXX, XXX–XXX

The use of propargylaniline (**1d**) yields only starting material when it is reacted with *n*BuLi, even when it is refluxed in THF. This is the inverse of the results obtained by Barluenga's studies on in situ generated methyleneamines and their reactivity with organometallic reagents, in which arylamines yielded addition products, while alkylamines only cyclized to form the corresponding hexahydrotriazines.[27,28] In addition, while the *N*-(methoxymethyl)amines used by Barluenga decomposed within hours at room temperature and were unstable to column chromatography, propargylamines **1** appear to be stable indefinitely at room temperature and can be purified by column chromatography with silica gel.

The structure of the dilithiated intermediate **3** is elusive. NMR spectra in C_6D_6, d_8-toluene, and d_8-THF are poorly resolved or show many species present in solution. Variable-temperature NMR studies at −60 and 25 °C also failed to shed any light on what was happening in solution. A single signal in the ^{7}Li NMR in d_8-toluene with a line width of 210 Hz at 25 °C, which broadens to 269 Hz at −60 °C, suggests that there are at least two lithium environments in rapid exchange.

West and co-workers have studied a variety of polylithiated alkynes and their substituted derivatives and have given a solid foundation on which to analyze and understand the IR spectroscopy of the lithiated intermediates.[29] They found that monolithiated alkynes with propargylic structures have absorption bands above 2000 cm^{-1}, while those with allenic structures have bands below 1900 cm^{-1}. Furthermore, they propose that dilithiation of those compounds with a propargylic structure results in the formation of a propargylide structure, with absorption bands just below 1900 cm^{-1}. This is based on the occurrence of what they dubbed the "lithium effect", where substitution of a proton for a lithium atom results in a bathochromic shift of 80−90 cm^{-1}. As the second substitution of a proton for lithium in these compounds results in a much larger shift of 180 cm^{-1}, it is inferred that a change in structure occurs.

With this in mind, it is possible to interpret the results of our experiments through IR spectroscopy. While the free amine shows no absorption bands in the 2200−1600 cm^{-1} region, propargylamine derivatives described in the literature with discernible absorption bands are exclusively in the range 2100−2120 cm^{-1}.[30−37] The IR spectrum of the dilithiated intermediate **3** in the solid state shows a single band at 1968 cm^{-1}, a bathochromic shift of about 140 cm^{-1} from the expected absorption band in the free amine. The substitution of two protons for lithium would be expected to produce a bathochromic shift of at least 160 cm^{-1} and much more if an isomerization to an allenic structure were occurring. On this basis, it is expected that the second lithiation site is the nitrogen, causing a reduced influence of the lithium effect due to the more remote site of metalation (Figure 1).

This is in agreement with the results obtained by Sato using the lithium amide **2b** in a conjugate addition, which reacts at the nitrogen rather than at the propargylic carbon.[21] Additionally, quenching **3** with TMSCl yields the bis(trimethylsilyl) derivative, silylated at the alkynyl and N positions.

The decomposition is presumably related to this metalation of the amine, as there have been several reports of polymetalated alkynes,[29,38−40] including tertiary propargylamines,[24,41] which are stable and are able to be derivatized using electrophiles.

In addition, we have seen no evidence for the imine intermediate proposed by both Barluenga and Plaquevent.[27,42]

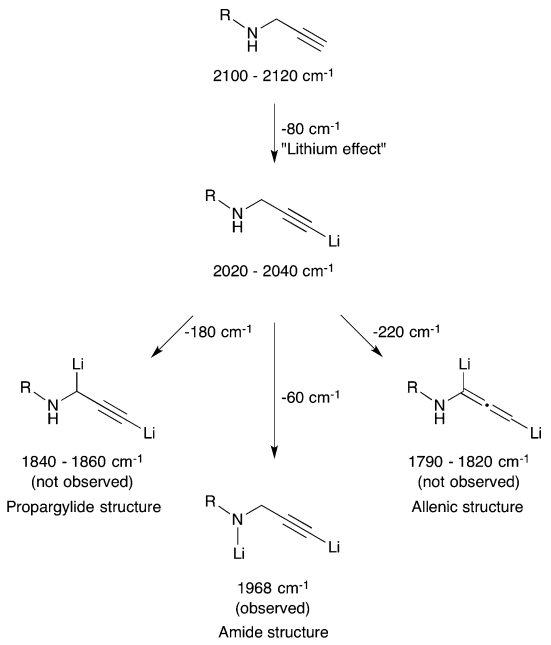

Figure 1. Comparison of expected and observed IR bands for plausible dilithiated intermediates.

No products relating to the oligomerization of the imine were observed, and the hexahydrotriazine obtained on reaction of α-methylbenzylamine with formaldehyde (through trimerization of the intermediate imine) does not react with excess *n*BuLi, even under forcing conditions. Moreover, quenching the dilithiated intermediate **3** with a proton source yields only starting material **1**, suggesting that cleavage of the alkyne group occurs only on reaction with the third equivalent of organometallic reagent.

In summary, we report an unprecedented metal acetylide elimination from metalated propargylamines. The reaction yields secondary methanediylamines and comprises a novel method to synthesize these compounds, which complements those already reported in the literature. Preliminary studies suggest that the reaction proceeds via a metal amide intermediate, and studies are underway to further elucidate the mechanism of this reaction as well as to more fully explore the scope of the reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.8b00047.

Experimental and analytical data (PDF)

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Notes

The authors declare no competing financial interest.

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Organometallics XXXX, XXX, XXX−XXX

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Organometallics XXXX, XXX, XXX−XXX