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Effect of Alkali Metals in Catalytic and Stoichiometric Reactions of Main-Group Organometallic Complexes with Nitriles and β,γ-Unsaturated Amines

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Abstract

The chemistry of organoalkali complexes was probed, with an emphasis on the effects of different alkali metal cations in the interaction of the complexes with unsaturated substrates, primarily nitriles and β,γ-unsaturated amines.

The sodium aza-enolate complex derived from *N*-(1-phenylethyl)methallylamine, previously only characterised by NMR spectroscopy, was characterised by single-crystal X-ray diffraction. Potassium complexes derived from *N*-(1-phenylethyl)methallylamine were synthesised, and NMR spectroscopic studies in a predominantly non-coordinating solvent, or in rigorously dried tetrahydrofuran showed the immediate formation of a 1-aza-allyl complex similar to that observed in the sodium congener. This complex rearranged to form the aza-enolate complex via an intermediate 2-aza-allyl complex previously unobserved in related systems.

Dilithiation of *N*-(1-phenylethyl)prop-2-yn-1-amine resulted in the formation of a solid which proved difficult to characterise due to failure to crystallise the species, and the extremely poor quality of NMR spectra which were obtained. Infrared spectroscopy produced some usable information, identifying the complex as the doubly lithiated complex, deprotonated at the terminal alkyne and amine positions.

Metallation of the silylated derivative *N*-(1-phenylethyl)-3-(trimethylsilyl)prop-2-yn-1-amine with *n*-butyllithium or lithium diisopropylamide in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine resulted in a rearrangement of the complex, which upon quenching yielded 1-phenyl-*N*-((*Z*)-3-(trimethylsilyl)prop-1-en-1-yl)ethan-1-imine, exclusively as the *cis*-isomer. The same rearrangement induced by potassium bases without the addition of a Lewis donor resulted in a mixture of *cis*- and *trans*-isomers.

Reaction of *N*-(1-phenylethyl)prop-2-yn-1-amine with three equivalents of organolithium reagents was found to induce a substitution reaction, displacing dilithium acetylide and forming a methanediylamine, substituted at the methylene position with the anionic part of the organolithium used, and a range of compounds were synthesised this way. This reaction was proposed to proceed via a tandem elimination-addition mechanism, with evidence for a metastable methanimine intermediate being found by proton NMR spectroscopy. The decomposition was hypothesised to be initiated by complexation of the third equivalent of the organolithium reagent.

The synthesis of potassium hydridoaluminates was attempted in a collaborative project at Strathclyde University in Glasgow with Professor Robert Mulvey. Nearly all of the efforts to synthesise isolable potassium complexes failed, with redistribution being implicated in the instability of the compounds synthesised. A related lithium hydridoaluminate was able to be synthesised from (trimethylsilyl)methyllithium and diisobutylaluminium, and isolated as a crystalline solid, though attempts to characterise this complex by X-ray diffraction failed due to the propensity of single crystals to liquefy when warmed above cryogenic temperatures.

The lithium hydridoaluminate was employed as a catalyst in hydroboration reactions, and performed reasonably well in the hydroboration of carbonyl substrates, while providing very limited or no activity with alkyne and pyridine substrates. The catalyst was found to be effective in the double hydroboration of nitrile substrates, achieving rates and conversions comparable to those reported for other main-group metal catalysts.

Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

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Publications During Enrolment

Loss of Chirality through Facile Lewis Base Mediated Aza-enolate Formation in Na and K (*S*)-*N*-(*α*-Methylbenzyl)methallylamides

Matthew T. Flynn, Rachel Stott, Victoria L. Blair, and Philip C. Andrews

Organometallics **2016**, *35*, 2707−2714

DOI: 10.1021/acs.organomet.6b00445

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

Matthew T. Flynn, Victoria L. Blair, and Philip C. Andrews

Organometallics **2018**, *37*, 1225−1228

10.1021/acs.organomet.8b00047

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To Dr. Victoria Blair, thank you for all the guidance in and out of the lab, it was great to have a supervisor with me in the lab, and you were always available to answer any little questions I might have.

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Thanks also to Prof. Robert Mulvey, for hosting me during my exchange in Glasgow, and taking the time to provide plenty of advice while I was there.

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Abbreviations

9-BBN - 9-borabicyclo(3.3.1)nonane

C_6D_6 - deuterated benzene

COSY - homonuclear correlation spectroscopy

d_8-THF - deuterated tetrahydrofuran

DIBALH - diisobutylaluminium hydride

DMI - 1,3-dimethyl-2-imidazolinone

DOSY - diffusion ordered spectroscopy

HBpin - pinacolborane

HMDS(H) - hexamethyldisilazane

HMPA - hexamethylphosphoramide

HSQC - heteronuclear single quantum correlation

KTMP - potassium 2,2,6,6-tetramethylpiperidide

LDA - lithium diisopropylamide

LiHMDS - lithium hexamethyldisilazide

LiTMP - lithium 2,2,6,6-tetramethylpiperidide

n-BuK - *n*-butylpotassium

n-BuLi - *n*-butyllithium

n-BuMgBr - *n*-butylmagnesium bromide

n-BuNa - *n*-butylsodium

NMR - nuclear magnetic resonance

PMDETA - *N*,*N*,*N*',*N*",*N*"-pentamethyldiethylenetriamine

t-BuOK - potassium *tert*-butoxide

t-BuONa - sodium *tert*-butoxide

THF - tetrahydrofuran

TMEDA - *N*,*N*,*N*',*N*'-tetramethylethylenediamine

TMP(H) - 2,2,6,6-tetramethylpiperidine

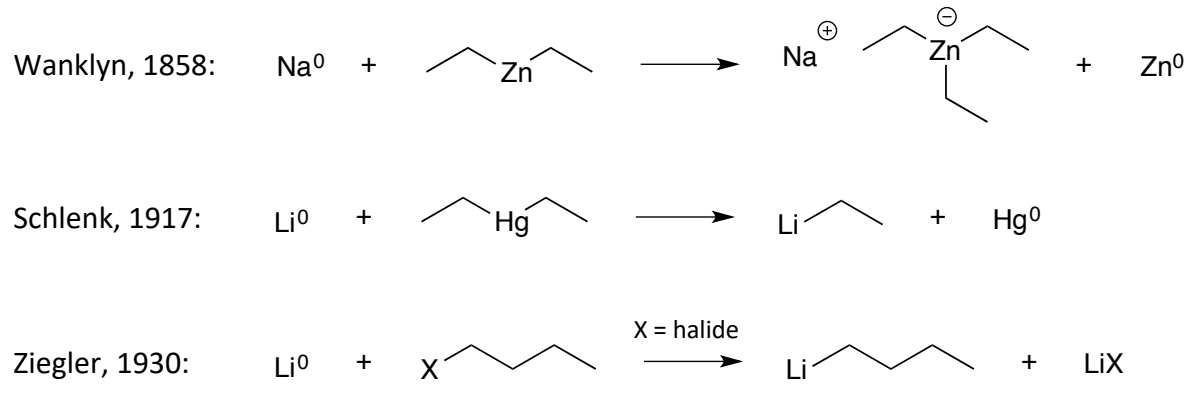
TMSCl - chlorotrimethylsilane

TON - turnover number

General Introduction

Discovery and early development of organolithium reagents

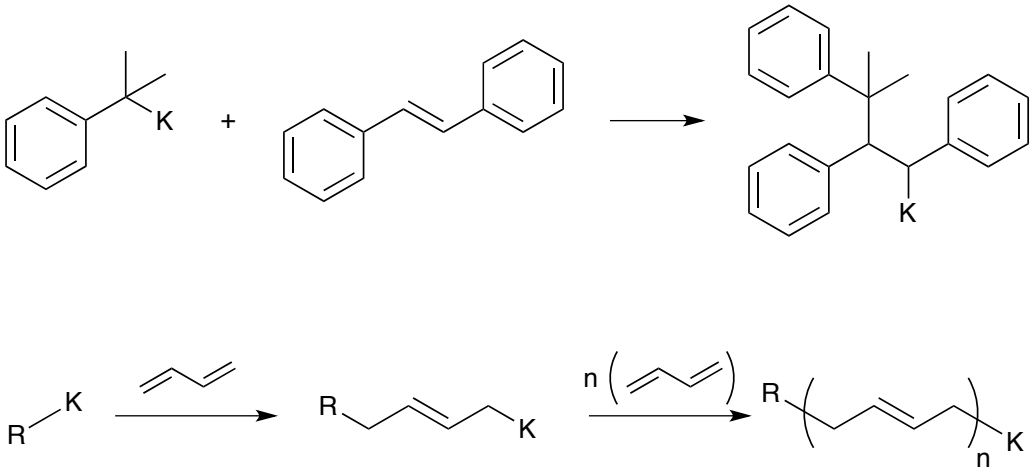
In 1858, Wanklyn synthesised the first organoalkali compound from the reaction of diethylzinc with metallic sodium.[1,2] This produced what is now recognised as an 'ate' complex, sodium triethylzincate.[3] The analogous lithium and potassium complexes were also reported. It wasn't until almost 60 years later, in 1917, that Schlenk reported the first synthesis of monometallic organolithium reagents, made by redox transmetallation of the corresponding organomercury compounds.[4] It was some years later, with the implementation of a more convenient (and less toxic) synthesis of organolithiums, that they began to become more widespread in the literature. The development of the reduction of organohalides with lithium metal by Ziegler in 1930,[5] facilitating the preparation of organolithium reagents in a manner comparable to that of Grignard reagents, allowed the field of organolithium chemistry to bloom. Shortly afterwards, the metal-halogen exchange reaction was reported almost concurrently by Wittig[6] and by Gilman.[7] This brought the synthesis of organolithium reagents on par with the predecessing Grignard reagents, as they could now be synthesised from a wide variety of organohalide precursors, as well as some which do not form Grignard reagents. In addition, organolithium reagents are generally more reactive than their Grignard counterparts, so their newfound accessibility paved the way for organolithium chemistry to flourish.



Scheme 1: Early synthesis of organoalkali compounds.

Prior to discovering the reductive lithiation of organohalides, Ziegler pioneered the field of carbometallation chemistry, reporting the first carbometallation reactions of organoalkali reagents in 1928 and 1929,[8–10] which were later extended to use butadiene and ethylene as

substrates. Thus, polymerisation reactions could be achieved by addition of more and more monomer substrate.[11,12] These reactions represent early examples of living polymers, and ultimately led to the development of the Ziegler-Natta catalysts for the low-pressure polymerisation of ethylene.[13] Anionic living polymerisation now represents an important reaction, especially for the synthesis of polystyrene and its derivatives.[14,15]



Scheme 2: Ziegler's initial experiments with carbometallation.

In the decades following the development of Ziegler's process for the facile synthesis of organolithium compounds, Gilman proceeded to improve this procedure,[16,17] and systematise the reactivities and preparations of organolithium compounds. Demonstration of their versatility in deprotonative lithiation reactions,[18] lithium-halogen exchange,[19] and transmetallation reactions with organolithium reagents, an important contribution also to the synthesis of many other organometallic species,[20] contributed to the adoption of organolithium reagents throughout the wider organic synthetic community.[21]

Following their development in the early-mid 20th century, organolithium reagents have come to form a cornerstone in organic and organometallic synthetic methodology.

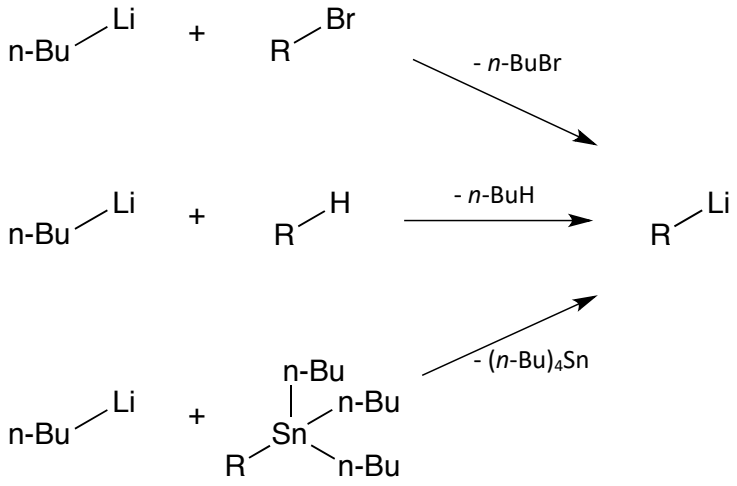
Modern synthesis of organolithium reagents

Nearly 90 years on, the industrial synthesis of organolithium reagents still follows the method pioneered by Ziegler,[5] and subsequently improved upon by Gilman.[16,17] Nowadays, *n*-butyllithium (*n*-BuLi) is the most common organolithium used, owing to its stability and solubility in hydrocarbon solvents, as well as its versatile reactivity. Its high basicity, and propensity to undergo both lithium-halogen exchange and transmetallation reactions make it a universal starting point for the synthesis of a large variety of other organolithium reagents.

The transmetallation route with mercury initially used by Schlenk has largely been phased out in favour of the reductive lithiation of alkyl halides, though transmetallation using tin compounds is still a commonly used route to the synthesis of organolithium reagents with sensitive functionalities, as the tin-lithium exchange proceeds readily, and the tetraalkyltin by-products do not interfere with the reaction.[30] The synthetic routes to organotin compounds also provide another avenue to functionalisations that would be difficult or impossible to achieve using only organolithium reagents. The transmetallation can also be performed with retention of stereochemistry, providing an easy route to stereoselective formation of organolithium compounds.[31]

Lithium-halogen exchange represents one of the most powerful methods of generating organolithium reagents, as the reaction takes place extremely rapidly, allowing the selective formation of a carbon-lithium bond even in the presence of other sensitive functional groups.[32–34] The reaction has even been shown to occur faster than proton-exchange with methanol.[35] Because of the rapidity of the reaction, intramolecular cyclisations can be achieved using substrates bearing an electrophilic moiety, providing a powerful method to synthesise cyclic and bicyclic compounds.[36] This also allows for reactions to be carried out in the presence of external electrophiles, with lithium-halogen exchange taking place before the electrophile can quench the organolithium species.

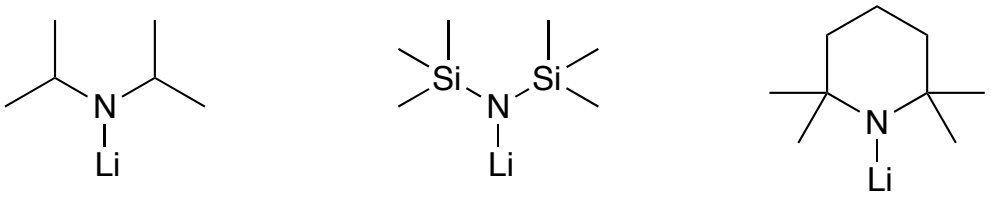
The final major route to formation of organolithium reagents is deprotonation. Alkyllithium reagents constitute some of the most powerful bases available, allowing for the lithiation of even weakly acidic compounds. The ubiquitousness of the carbon-hydrogen bond in organic compounds makes this an attractive method for the functionalisation of a great many compounds.



Scheme 3: Modern methods for organolithium synthesis, which commonly rely on the use of n-*butyllithium.*

Adding to the utility of deprotonative metallation is the directed *ortho*-metallation (DoM), which allows for selective *ortho*-deprotonation of aryl and heteroaryl substrates with directing substituents, granting a synthetic route to functionalise substrates which would normally substitute in the *meta*-position in an electrophilic aromatic substitution.[34,37–39]

One of the most prevalent uses of organolithium reagents is in the generation of lithium amides, most often hindered amides such as lithium diisopropylamide (LDA), lithium hexamethyldisilazide (LiHMDS), and lithium tetramethylpiperidide (LiTMP), the so-called 'utility amides' (Figure 1).[40] LDA in particular has become one of the most popular reagents used in total synthesis procedures,[41] as the combination of steric bulk and lower nucleophilicity of the nitrogen-lithium bond compared with a carbon-lithium bond makes it very selective in deprotonative lithiations. Although lithium amides are not organolithium reagents by the classical definition (they do not contain a metal-carbon bond), they share many of the same characteristics of organolithium reagents, in particular the high Brønsted basicity. The modern definition of organometallic compounds has generally come to include metal-nitrogen bonded compounds, and metal amides shall be considered as organometallic compounds here.



Lithium diisopropylamide (LDA)

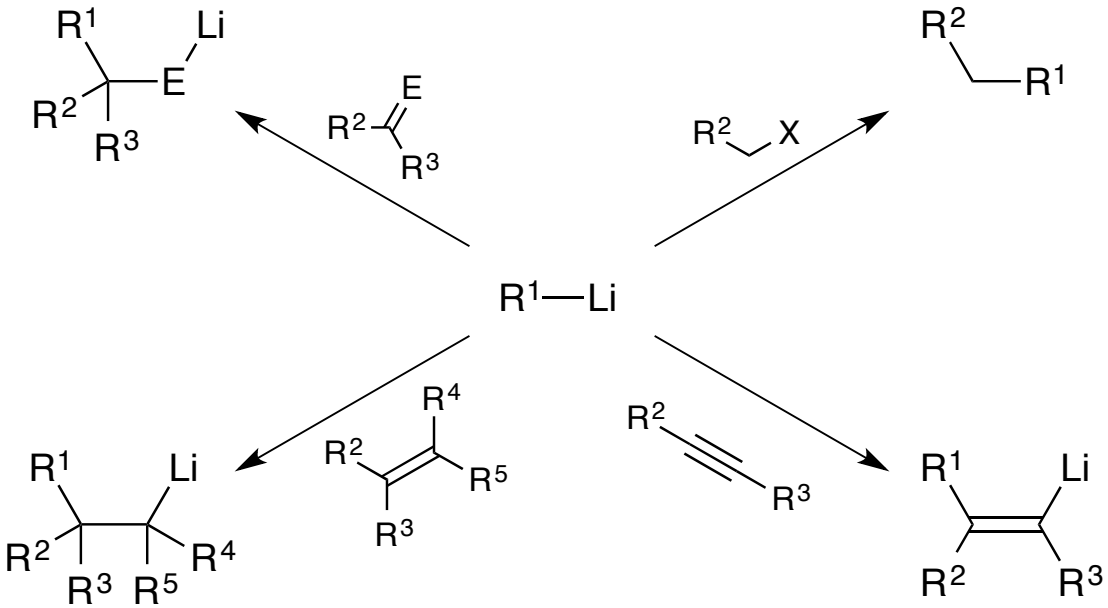
Lithium hexamethyldisilazide (LiHMDS)

Lithium 2,2,6,6-tetramethylpiperidide (LiTMP)

Figure 1: The lithium 'utility amides', commonly used as powerful non-nucleophilic bases.

Functionalisation using organolithium reagents

The high polarity of the lithium-carbon bond allows organolithium reagents to act as powerful nucleophiles, readily adding across carbon-heteroatom multiple bonds such as in carbonyl, imine, and nitrile groups. They also undergo facile S_N2 reactions, and will react via carbometallation with alkenes and alkynes, forming both a new carbon-carbon bond, and a carbon-lithium bond which can be further functionalised. The propensity for organolithium reagents to undergo carbometallation reactions also forms the basis of their use as initiators in anionic polymerisation.



Scheme 4: Synthetic routes utilising organolithium reagents.

The high affinity of lithium for halogens, and relatively low affinity for carbanions, makes organolithium reagents excellent transmetallation reagents with other metal halides. Due to this, as well as the variety of established methods to synthesise them, organolithium reagents

have become one of the most popular routes used to synthesise other organometallic reagents.

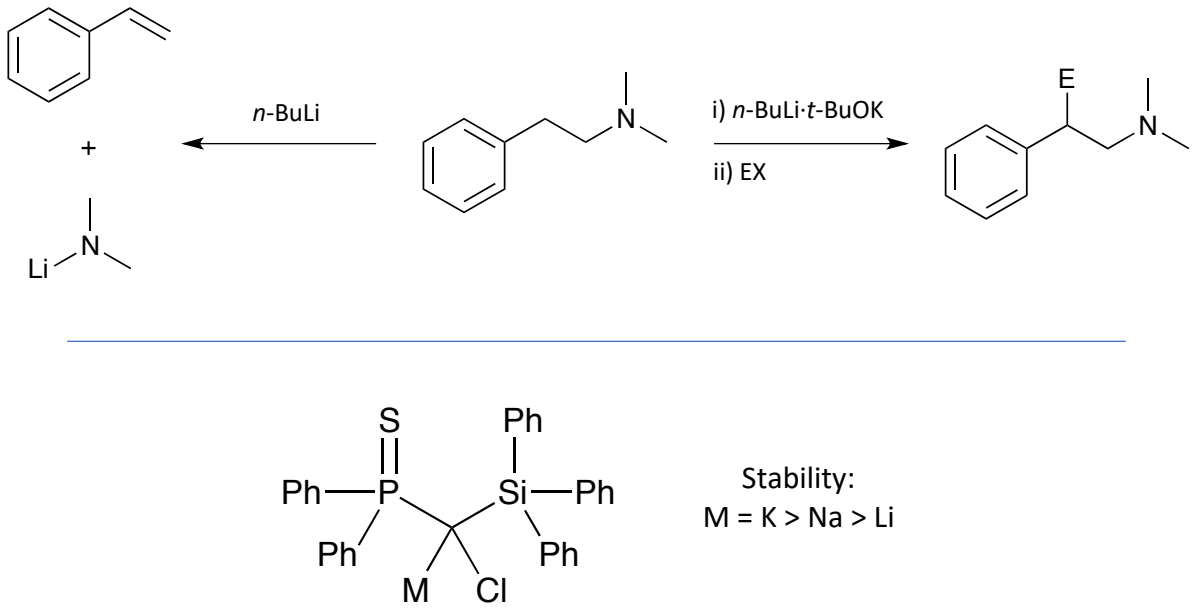
Organolithium reagents were the second class of organometallic reagents to be used as substrates in transition-metal-catalysed cross-coupling, however due to the high reactivity of organolithium complexes, stringent control of reaction conditions are required, and results are often unsatisfactory.[42] Recent developments in palladium-catalysed cross-coupling have overcome these problems, allowing for the rapid coupling of organohalides with organolithium reagents, including carbon-carbon bond formation between two aryl groups.[43–45] The rate of transformation can even be accelerated to the point where the reaction can take place in an emulsion in water.[46] Due to the plethora of procedures available to prepare organolithium reagents, the addition of organolithium reagents to the catalogue of reliable cross-coupling reactions opens up new avenues in cross-coupling chemistry (or simplifies those that relied on transmetallation of organolithium reagents prior to cross-coupling). This synthetic route also serves to expand the already large catalogue of functionalisations that can be achieved with organolithium reagents, and further demonstrates their value to the synthetic community.

Comparison with sodium and potassium reagents

Most of the early studies of organoalkali complexes were done with sodium, and to a lesser extent, potassium, primarily due to the easy availability of these metals compared with lithium. The advent of organolithium reagents largely supplanted the heavier organoalkali complexes, favoured because of their ease of preparation, and especially because of their solubility and higher compatibility with coordinating solvents. Nonetheless, there are still applications for organosodium and potassium complexes, particularly when a more reactive reagent is required. Sodium and potassium amides especially are used where lithium amides fall short, as the amido complexes tend to be more soluble and stable than are the carbon-based sodium and potassium compounds.

The heavier alkali metals still hold an important place in synthetic chemistry however, and recently have found application in 'ate' chemistry, altering and improving the reactivity of other metal complexes.[47,48] Some studies have even found that the use of heavier alkali metal can actually stabilise the resulting complexes relative to their lithium congeners (Scheme 5).[49,50] With the recent proliferation of green chemistry, complexes of the heavier alkali

metals are also becoming attractive alternatives to organolithium compounds, as sodium and potassium are considerably more abundant, and possess lower toxicity than lithium. For these complexes to be able to replace organolithium compounds to any extent requires a greater understanding of their reactivity.



Scheme 5: Examples of organometallic systems in which the use of potassium instead of lithium improves the stability of the complex.

Structural studies of organoalkali reagents

Right from their inception, organoalkali reagents have delivered surprising reactivity. Many of the transformations developed during their establishment were discovered, rather than planned. Since then, structural studies have revealed a great deal about the nature of organoalkali reagents. An understanding of their structures, and the inherent structure-activity relationship has allowed for some degree of predictions to be made about their reactivities, and reactions planned accordingly.[51] Nonetheless, the reactivity observed from organoalkali reagents continues to surprise, and the structures of many complexes continue to elude.

One of the basic structural features of organoalkali complexes is their oligomeric nature, and understanding this attribute has helped to develop methods to reduce (or optimise)[52,53] the aggregation, improving the reactivity and selectivity of the reagents.[54,55] Alkyllithium reagents mostly exist as larger oligomers such as tetramers or hexamers in the absence of Lewis donors, while the addition of donors can reduce the aggregation to dimers or monomers.[56,57]

Meanwhile, bulky lithium amides tend to form smaller aggregate states, generally dimers or monomers.[58–60]

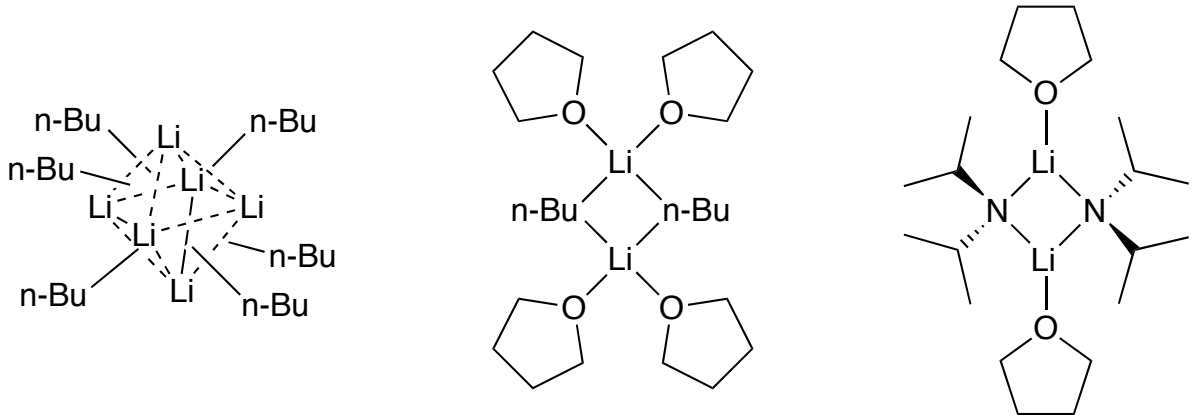


Figure 2: Examples of observed structures of commonly used organolithium reagents: n-BuLi hexamer (left), THF-solvated n-BuLi dimer (middle), and THF-solvated LDA dimer (right).

Understanding the relationship between aggregation and reactivity is not straightforward however: many factors influence the aggregation, including concentration, temperature, solvent, presence of salts such as LiCl (either as contaminant or additive), and of course, the identity of the organolithium.[61]

Enantioselective syntheses with lithium reagents

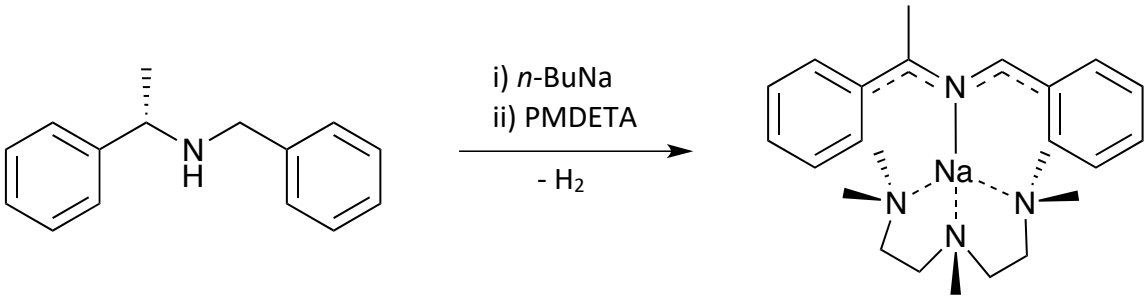
As with any synthetic protocol, the ability to achieve a transformation with enantioselective (or diastereoselective) generation of new stereocentres is a highly desirable prospect. To this end, a great deal of research has been focused on chiral chemistry with organolithium reagents.[62] These procedures generally involve complexation of the organolithium reagent with a chiral Lewis donor to induce enantioselectivity, rather than producing an enantiopure organolithium reagent. This takes advantage of the varied methods to generate organolithium reagents, and avoids problems associated with the low barrier to inversion about the carbanionic centre. The complexing agents used may be neutral compounds such as (-)-sparteine, or more ionic species such as lithium amides or alkoxides.

Chiral lithium amides are also frequently used for enantioselective synthesis.[63] As in the case of carbon-bonded organolithium reagents, lithium amides can be used either as powerful Brønsted bases, or as nucleophiles. Davies has reported a huge catalogue of diastereoselective conjugate additions using chiral lithium amides as nucleophiles, primarily using derivatives of 1-phenylethylamine.[64–66] The 1-phenylethyl group is used for chiral

induction, and can later be removed by palladium catalysed hydrogenation. The second substituent of the amine is important to the degree of diastereoselectivity, but can be tuned to allow further reactivity, as well as to be more or less easily removed than the 1-phenylethyl group. In this way, these chiral lithium amides can be used as "chiral ammonia equivalents", enabling the asymmetric synthesis of a wide variety of more complex chemicals with great control over the chirality. Nitrogen containing compounds make up over 80 % of all unique small molecule drugs,[67] making the synthesis of amine-based compounds extremely valuable to the pharmaceutical industry. The ability to selectively incorporate stereocentres into these molecules adds significant value to these syntheses.

Alkali metal dibenzyl- and (1-phenylethyl)amides

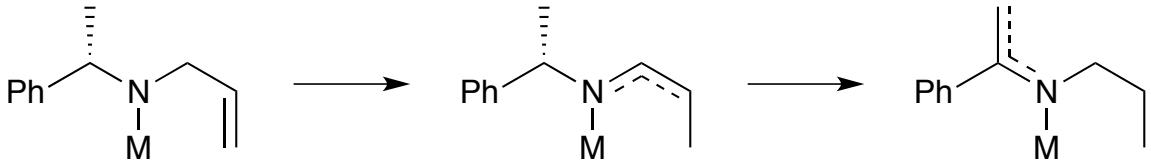
Research into the formation of 2-aza-allylic systems formed from the metallation of dibenzylamine has been extended into related systems based on chiral 1-phenylethylamine, with the goal of better understanding the structure and reactivity of these compounds.[68–76] The dehydrogenative transformation of (*S*)-*N*-(1-phenylethyl)benzylamine into a 2-aza-allyl species results in the destruction of the chiral centre,[72–74] which has dramatic consequences for the use of these species in enantioselective synthesis. The disaggregation of dibenzylamides was implicated in the formation of the 2-aza-allyl species,[70] and therefore the common approach to organolithium chemistry of adding Lewis donors in an attempt to monomerise the reagent will increase the likelihood of decomposition to the 2-aza-allyl species and consequent loss of chirality.



Scheme 6: Synthesis of a sodium 2-aza-allyl complex from (S)-N-(1-phenylethyl)benzylamine, resulting in a loss of chirality.

Similarly, deprotonation reactions of *N*-(1-phenylethyl)allylamine and its derivatives have resulted in a variety of sigmatropic rearrangements, resulting in either 1-aza-allyl or aza-enolate species depending on the extent of the rearrangement (note: while the descriptors 1-aza-allyl and aza-enolate essentially describe the same structural features, in publications

the term 1-aza-allyl is used to describe the product of the [1,3]-sigmatropic rearrangement, while the term aza-enolate is used to describe the further rearrangement to relocate the π-bond adjacent to the phenyl ring. In order to avoid confusion, this same distinction shall be used within this text). The rearrangement of allylamides to form aza-enolate complexes results in a loss of chirality at the benzylic carbon, removing the capacity for the complex to act as a chiral auxiliary or base. As with the transformation of dibenzylamine complexes, the sigmatropic rearrangements of allylamides has been found to be promoted by the use of chelating Lewis donors, though in the case of the sigmatropic rearrangements, separation of the anion and cation was implicated, rather than disaggregation to form a monomer.[77]



Allyl amide 1-Aza-allyl Aza-enolate

Scheme 7: Anion forms observed from metallation of (S)-N-(1-phenylethyl)allylamine.

Anionic sigmatropic rearrangements

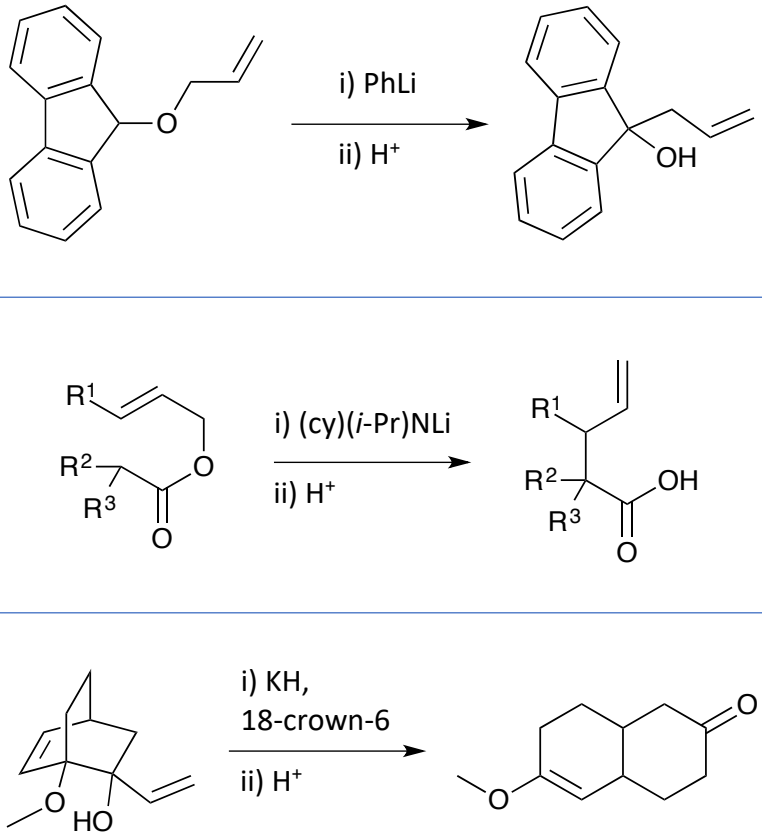
Sigmatropic rearrangements are important methods used in organic synthesis, and commonly utilise allyl moieties, with prominent examples in the Claisen[78] and Cope rearrangements.[79]

Wittig found in 1942 that metallation of ethers results in a [1,2]-rearrangement, and later described the [2,3]-sigmatropic rearrangement of 9-(allyloxy)-9*H*-fluorene to yield 9-allyl-9*H*-fluoren-9-ol (Scheme 8, top),[80] the first example of the now well-known [2,3]-Wittig rearrangement, as well as an early example of anionic sigmatropic rearrangement.

Similarly, certain allylic esters were found to rearrange upon deprotonation using a Grignard reagent (Scheme 8, middle).[81] This method was later made more generally applicable in the development of the Ireland-Claisen rearrangement.[82]

Likewise, the oxy-Cope rearrangement has been developed to take advantage of the enhanced reactivity of anionic intermediates. Evans reported that deprotonation of the parent alcohol with potassium hydride lead to a dramatic increase in the rate of rearrangement, and addition of 18-crown-6 or hexamethylphosphoramide (HMPA)

accelerated this further, allowing for rate increases of up to 10^{17}-fold (Scheme 8, bottom).[83] The calculated reduction in activation energy was greater than 70 kJ/mol, highlighting the potential for anionic processes in sigmatropic rearrangements.



Scheme 8: Base-mediated sigmatropic rearrangements: [2,3]-Wittig rearrangement of an allyl ether (top), Ireland-Claisen rearrangement of an allyl ester (middle), and anionic oxy-Cope rearrangement of a 1,5-dien-3-ol (bottom).

The initial report of the related anionic amino-Cope rearrangement found that some of the amino dienes used required the use of *n*-BuLi/*t*-BuOK to facilitate rearrangement, as *n*-BuLi alone gave no, or alternate, reactivity.[84] The same group found interesting solvent effects on the rearrangements, and though the use of higher polarity solvents correlated with higher yields, regioselectivity was also dramatically affected.[85] Most recently, it was found that the use of potassium as the counter-ion in the anionic rearrangements of sulfinamide based amino-Cope substrates was detrimental when compared with lithium or sodium.[86] The authors propose that this is due to potassium promoting dissociation of the molecule.

These results reflect those obtained within the Andrews group, and given the wide range of sigmatropic rearrangements which are facilitated by deprotonation,[87] acquiring a better

understanding of these rearrangements is merited. Additionally, the *N*-(1-phenylethyl)allylamine substrates are also substructures of some of the dienes used for amino-Cope rearrangements,[88] so the rearrangement to an aza-allyl or aza-enolate structure will clearly impact the outcome of the reaction.

Objectives

This thesis focuses on the characterisation of alkali metal complexes, and explores some of their applications in synthesis. The research is aimed to provide a better understanding of the structures of these complexes, and relate this to the reactivity observed within the complex, as well as reactivity with other compounds.

Chapter one is concentrated on the further characterisation of intermediates in the anionic rearrangements of unsaturated amides in order to better understand these processes. Alkali metal complexes derived from *N*-(1-phenylethyl)methallylamine are more thoroughly investigated, and the isomerisation reactions followed closely to identify more intermediates in the process.

Chapter two centres on the reactions of alkali metal complexes of *N*-(1-phenylethyl)prop-2-yn-1-amine, and characterisation of the metallated intermediates. Some unusual reactions are probed in an attempt to elucidate a mechanism, and the synthetic scope of the reactions is examined.

Chapter three explores the synthesis of alkali metal aluminates with the goal of catalysis for hydroboration reactions. A series of alkali-metal-aluminium-hydride complexes are synthesised, and solution studies used to rationalise the relative stabilities of these complexes. Finally, hydroboration catalysis is investigated using an aluminate complex, and a preliminary substrate scope is established.

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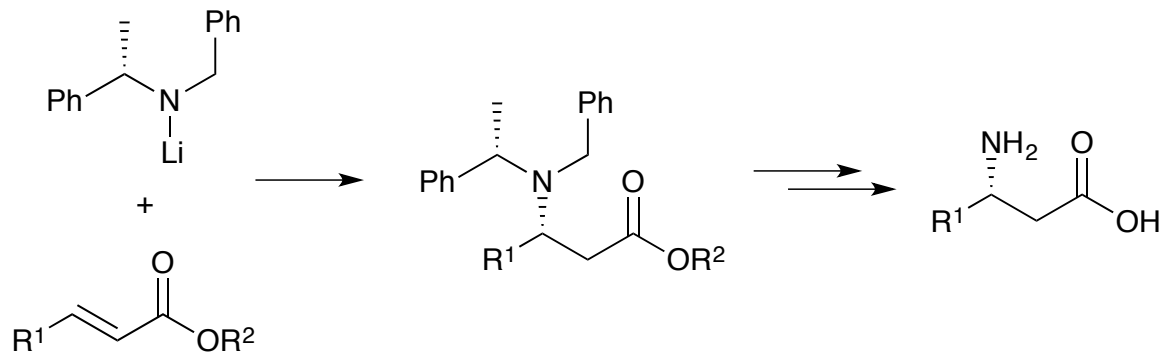
Chapter 1: Anion Rearrangements within Alkali Metal Complexes of (*S*)-(*N*)-(1-Phenylethyl)methallylamine

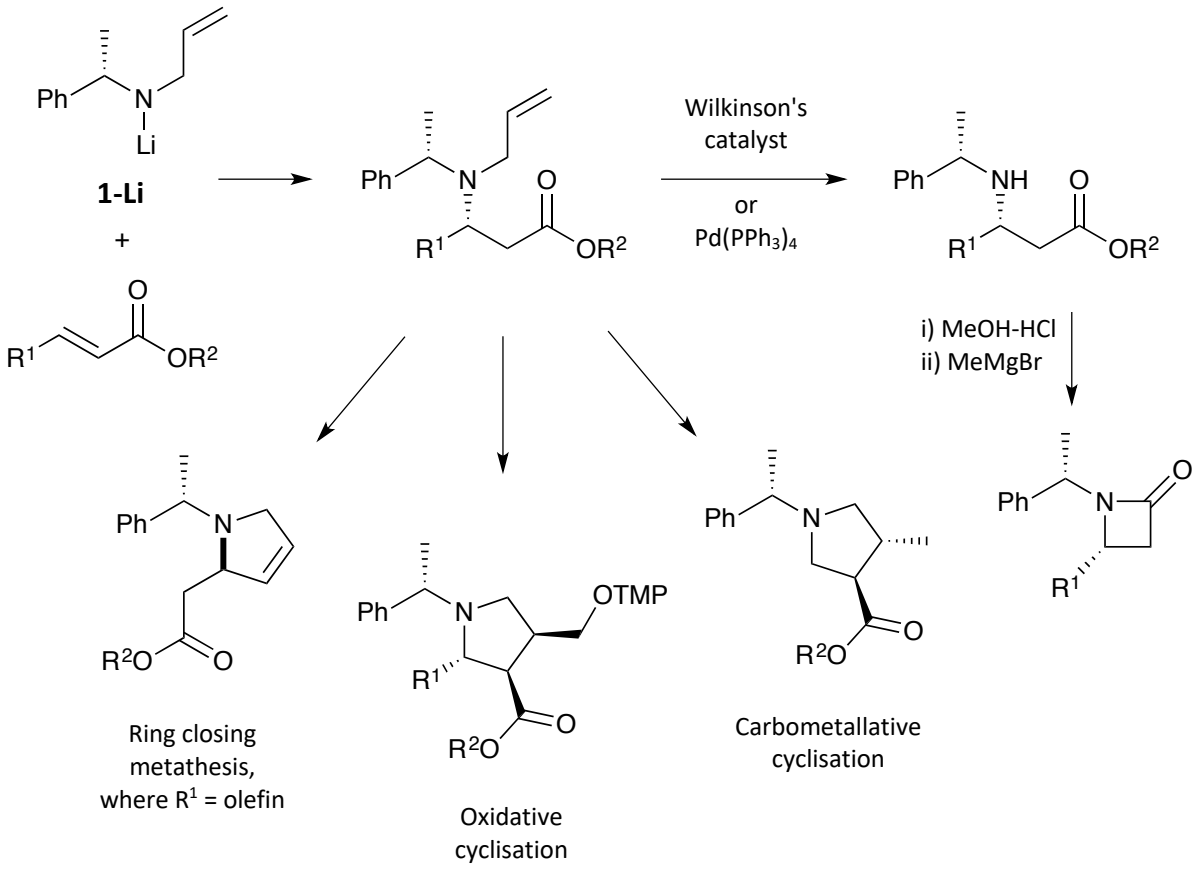
Introduction

Lithium amides based on 1-phenylethylamine have been used extensively in conjugate additions with α,β-unsaturated esters, producing β-amino esters with good diastereoselectivity (depending on the substituents of both substrates). Davies has utilised this technique to great effect, and published extensive reviews on the topic.[1–3] *N*-(1-phenylethyl)benzylamine has proved effective in this regard, and the 1-phenylethyl and benzyl groups can be selectively removed afterwards by palladium catalysed hydrogenation, and the ester hydrolysed to furnish enantiopure β-amino acids.



Scheme 9: Synthesis of β-amino acids via the conjugate addition of a chiral lithium amide and α,β-unsaturated esters.

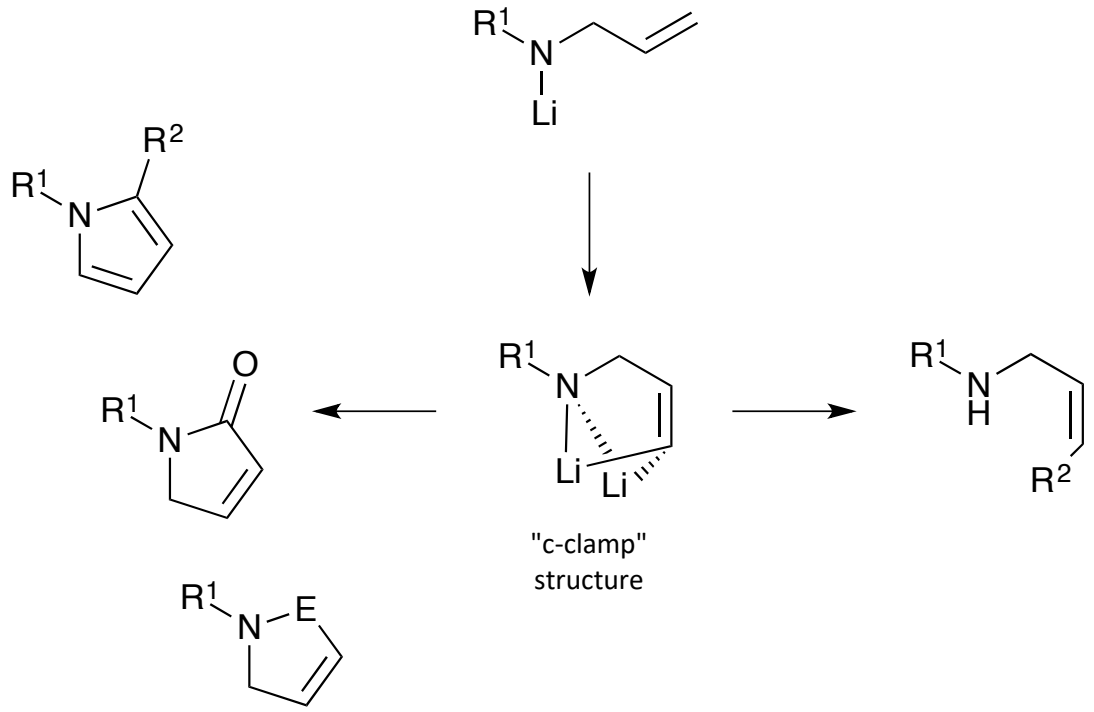
Similarly, *N*-(1-phenylethyl)allylamine (**1**) performs well in these applications, and the allyl group can be selectively removed using Wilkinson's catalyst or tetrakis(triphenylphosphine)palladium, providing a route to β-amino esters which can be further reacted to give β-lactams.[4] Alternatively, the allyl group can be used in further functionalisation, such as ring closing metathesis using Grubbs catalyst,[5–11] oxidative cyclisations,[12–14] and carbometallation cyclisations,[15,16] among others.[17–21] Some of these transformations were also achieved using functionalised allyl groups, such as a methallyl group.[13–15,21]



*Scheme 10: Transformations of β-amino esters derived from chiral allylamine **1**.*

Allylamines have also proved useful as precursors to dilithiated intermediates, with the initially formed amide being easily deprotonated at the terminal vinylic carbon.[22–25] While deprotonation of allyl groups at the sp^3 hybridised carbon generally leads to the formation of delocalised allylic anions,[26] secondary allylamines can be deprotonated selectively at the *cis*-vinyl position. In an attempt to explain the regioselectivity of this second lithiation, Williard has performed a series of studies on the dilithiation of *N*-(*t*-butyldimethylsilyl)allylamine (**2**), showing that the allyl group adopts a "c-clamp" structure, with the complex crystallising as a hexamer.[24] Though this c-clamp structure may be expected to stabilise the terminal anion, computational studies showed that allylic lithiation would be stabilised to a greater extent by the same structure.[27] In-depth NMR spectroscopic studies showed that the c-clamp structure is maintained in solution, and that the monolithiated amide forms a mixed aggregate with *n*-BuLi, which was proposed to promote terminal metallation by a proximity effect.[28] This rationalisation is consistent with the suggestions from the computational study that the vinylic anion is kinetically favoured over the allylic anion, rather than thermodynamically.

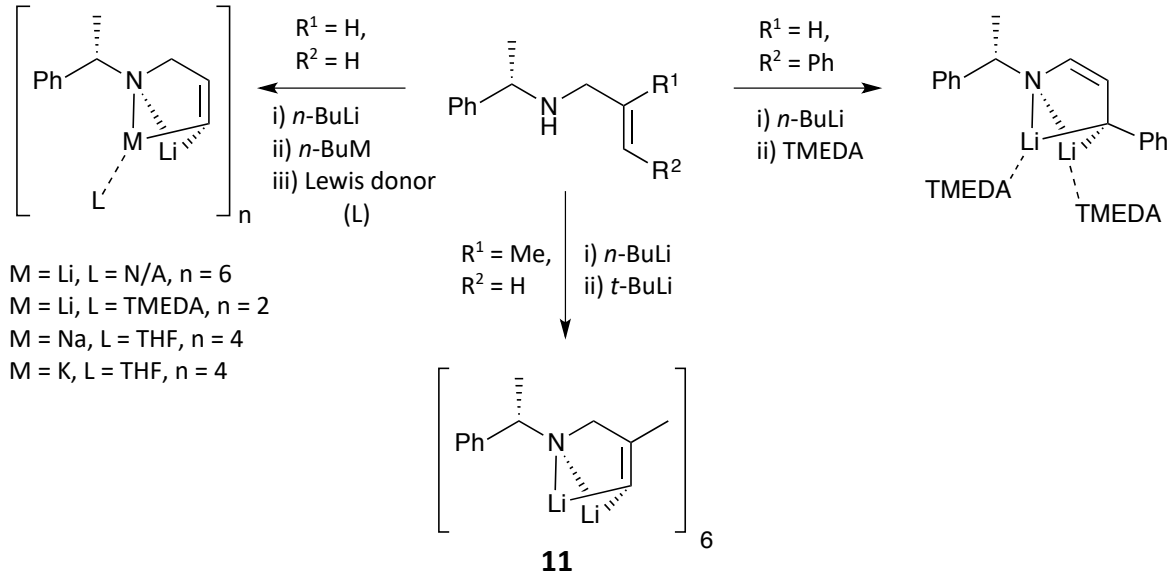
The regioselective generation of these dianions has proved useful in synthesis, with the dianion proving an effective precursor to a variety of *N*-heterocycles,[29–32] and the regioselectivity of the second deprotonation proving useful for the selective functionalisation of the allyl chain with various substituents, many of which can be used to produce more complex structures.[23,33–35]



Scheme 11: Synthesis and reactions of dilithiated allylamides.

As part of a study into the structures of unsaturated derivatives of 1-phenylethylamine, the solid-state structure of the dianion of *N*-(1-phenylethyl)allylamine **1**,[25] and more recently, that of related *N*-(1-phenylethyl)methallylamine (**3**)[36] were determined. The unsolvated dilithium complexes show the allyl groups adopting the same c-clamp structure as seen in the dianion of *N*-(*t*-butyldimethylsilyl)allylamine **2**, as well as forming very similar hexameric aggregates in the crystalline structure. The TMEDA-solvated dilithium complex of **1**, as well as the THF-solvated heterobimetallic lithium-sodium and lithium-potassium[37] complexes were also characterised crystallographically, and display the same c-clamp structure, though the aggregation states in the three complexes are reduced to dimeric, tetrameric, and tetrameric, respectively. The bond lengths within the dianions are essentially the same, showing no significant change to the localisation of charge within each dianion.

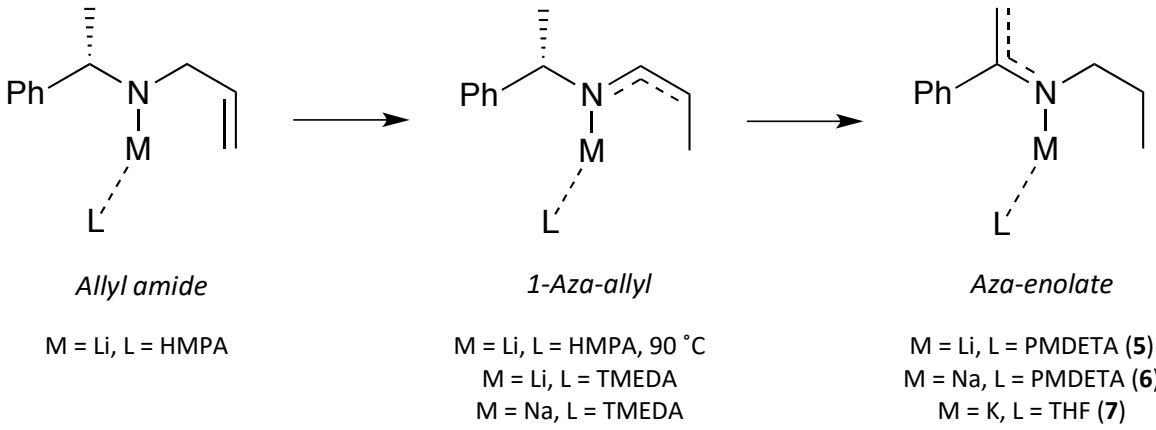
The dilithiated derivative of (*E*)-3-phenyl-*N*-(1-phenylethyl)prop-2-enamine (**4**) was also characterised by X-ray crystallography.[38] This structure was also lithiated at the nitrogen and the γ-carbon positions to give a c-clamp structure, however appeared to have the double bond relocated to between the α and β carbon atoms, to form an enamide. This could be either due to a sigmatropic rearrangement following vinylic deprotonation, or deprotonation of the α-carbon to produce an allylic anion.



Scheme 12: Synthesis of dilithiated complex from various allylic amines.

Characterisation of the monometallic species derived from *N*-(1-phenylethyl)allylamine **1** revealed some dramatically different structures (Scheme 13). Deprotonation of **1** with *n*-butylsodium (*n*-BuNa), followed by addition of TMEDA resulted in a [1,3]-sigmatropic rearrangement to yield the 1-aza-allyl complex sodium *N*-(1-phenylethyl)(prop-1-enyl)amide, as determined by X-ray diffraction studies.[39] The structure of this complex in the solution state was found to be consistent with the solid-state structure by NMR spectroscopy, with the π-bond being delocalised across the α,β-carbon bond and the nitrogen-carbon bond. The lithium complex of **1** was characterised as an HMPA coordinated complex, and found to exist in the amide form, before rearranging to the analogous 1-aza-allyl isomer when heated to 90 ˚C.[40] The lithium complex of **1** coordinated by TMEDA was found to undergo the same [1,3]-sigmatropic rearrangement at room temperature.[41] In the same study, lithium and sodium complexes of **1** coordinated with PMDETA were found to undergo a further rearrangement to the aza-enolate form, yielding lithium propyl(1-phenylvinyl)amide (**5**) sodium propyl(1-phenylvinyl)amide (**6**), with the π-bond delocalised across the carbon-carbon and carbon-

nitrogen bonds. As with the 1-aza-allyl anions, this structure was found to persist in the solution-state.

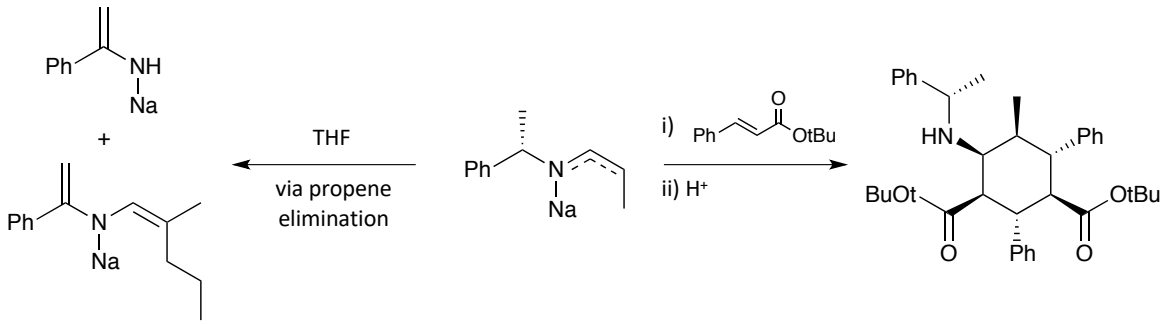


*Scheme 13: Anion-induced rearrangements in metal complexes of (1-phenylethyl)allylamine **1**.*

Calculations of the energies of each isomer showed a dramatic stabilisation is achieved upon rearrangement from the amide form to the 1-aza-allyl form, but showed very little difference between the 1-aza-allyl and aza-enolate isomers, especially for the lithium complex. The preferential formation of the aza-enolate complex with PMDETA was explained by the calculated stabilisation of this form over the 1-aza-allyl form when the complex was modelled with ion-pair separation induced by ammonia molecules (as a simplified model for chelating donors).[41] This postulation is supported by the propensity for heavier alkali metals, with their larger coordination spheres, to favour the sigmatropic rearrangements without the addition of polydentate Lewis donors. Thus, the potassium complex of **1** has been shown to rearrange at room temperature in THF solvent to give the aza-enolate structure, potassium propyl(1-phenylvinyl)amide (**7**), without the requirement of a chelating donor.[38]

The sodium complex obtained from deprotonation of **1** was also found to undergo a series of transformations initiated by the decomposition of the 1-aza-allylic structure, yielding a mixture of the deallylated enamide and a product of propyl addition to the 1-aza-allyl complex.[42] Additionally, the sodium 1-aza-allyl complex undergoes a conjugate addition with an α,β-unsubstituted ester in a similar fashion to the lithium amide reactions reported by Davies.[43] The final outcome of the reaction is dramatically different however, as the initial addition occurs at the β-position of the allyl group, instead of the nitrogen atom. This is followed by a second conjugate addition of the resultant sodium enolate with another equivalent of ester, and then a cyclisation of this species to form a highly substituted

cyclohexane derivative with six new stereocentres. This reaction highlights the importance of anion-induced rearrangements in the outcome of reactions using unsaturated metal amides.

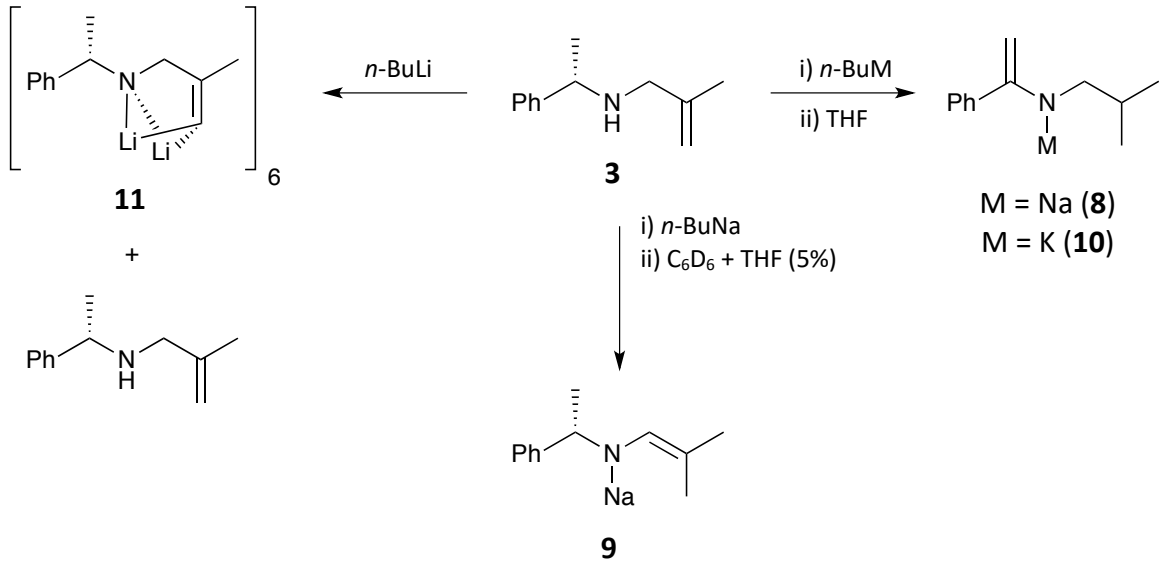


*Scheme 14: Transformations of the sodium 1-aza-allyl complex derived from **1**.*

The monometallated complexes of (*E*)-3-phenyl-*N*-(1-phenylethyl)prop-2-enamine **4** demonstrate similar behaviour, with the TMEDA coordinated sodium complex rearranging to the 1-aza-allyl form, and the potassium complex rearranging to the aza-enolate when dissolved in THF. Interestingly, the crystal structure of the potassium complex shows no incorporation of THF, suggesting that intra- and intermolecular interactions are sufficient to satisfy the coordination environment of the potassium ion.

Studies involving *N*-(1-phenylethyl)methallylamine **3** showed facile anion rearrangements of the sodium complex, with the PMDETA-coordinated complex undergoing the same rearrangement to the aza-enolate form to yield sodium isobutyl(1-phenylvinyl)amide (**8**), as seen in the sodium derivative of allylamine **1**.[36] Surprisingly, the use of the bidentate donor TMEDA, and even monodentate THF yielded the same rearrangement, indicating that the presence of the extra methyl group in **3** accelerates the isomerisation. The use of benzene as a non-coordinating solvent was investigated to determine if the 1-aza-allyl isomer could be observed. Due to the insolubility of the sodium complex in benzene, the solution was doped with a small amount of THF, allowing for the solution-state characterisation of the 1-aza-allyl complex sodium (2-methylprop-1-enyl)(1-phenylethyl)amide (**9**). This complex rearranged spontaneously at room temperature to give the aza-enolate form **8**, with complete conversion of the 1-aza-allyl isomer. A potassium complex synthesised from **3** was also characterised, and similar to the sodium complex rearranged completely in THF to give potassium isobutyl(1-phenylvinyl)amide (**10**), the aza-enolate isomer. As with the phenyl-substituted allylamine **4**, the potassium complex **10** was found to contain no THF within the solid, as determined by ^{1}H NMR spectroscopy. Attempts to synthesise monolithiated

complexes from **3** failed, with all reactions yielding a complex mixture of products, or a mixture of starting material and the dilithiated complex (*Z*)-(2-methyl-3-(lithium(1-phenylethyl)amido)prop-1-en-1-yl)lithium (**11**).



*Scheme 15: Previously characterised anionic rearrangements of alkali metal complexes of methallylamine **3**.*

The work presented in this chapter is focused on the further characterisation of monometallic complexes of *N*-(1-phenylethyl)methallylamine **3**, to form a comparison with complexes of *N*-(1-phenylethyl)allylamine **1**. In this way, a better understanding of the effects of substitution of the allyl group on the anionic rearrangements can be obtained, as well as more insight into the driving forces of, and mechanism behind the rearrangement.

Results and discussion

Crystal structure of sodium aza-enolate complex 8

With the product of sodiation of methallylamine **3** in THF having been identified as the aza-enolate structure **8**, efforts were made to obtain a crystal structure, so that the structure of **8** could be comprehensively compared to that of the analogous structures obtained from metallation of *N*-(1-phenylethyl)allylamine **1**. Addition of methallylamine **3** to a suspension of *n*-butylsodium in hexane resulted in formation of a yellow suspension, which turned orange upon addition of an excess of THF. Filtration of this suspension yielded a red solution from which yellow crystals deposited. Single crystal X-ray diffraction analysis of these crystals revealed the structure to be the expected aza-enolate **8** (Figure 3).

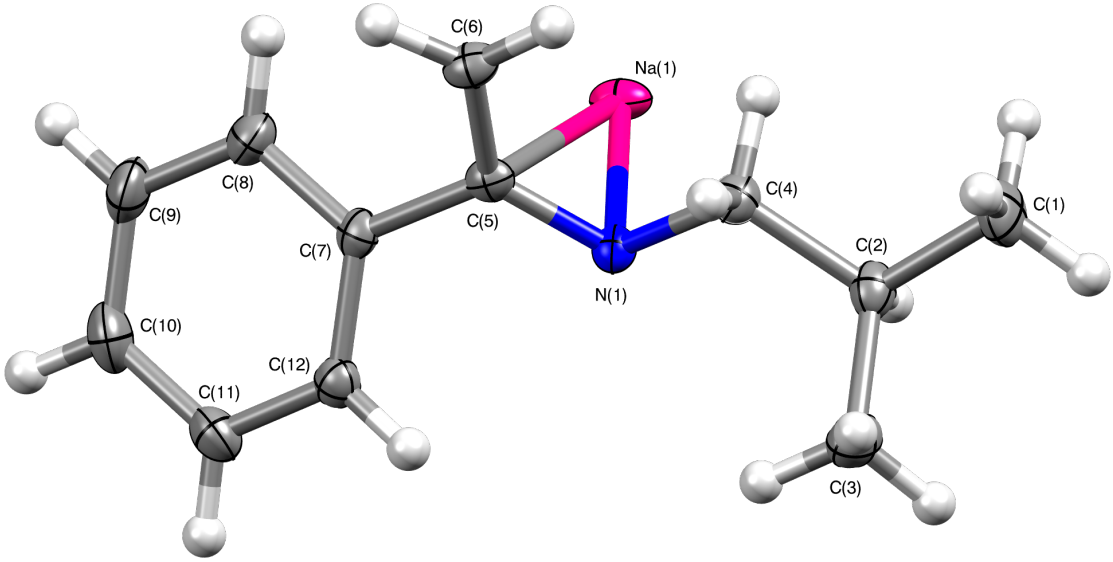


*Figure 3: Asymmetric unit of the molecular structure of **8** showing thermal ellipsoids at 50% probability. Selected bond lengths: N(1)-Na(1), 249.1(1) pm; C(5)-Na(1), 276.8(1) pm; C(5)-C(6), 138.3(1) pm; C(5)-N(1), 134.4(1) pm; C(4)-N(1), 145.0(1) pm; C(2)-C(4), 152.2(2) pm; C(1)-C(2), 151.9(2) pm; C(2)-C(3), 152.0(2) pm; C(5)-C(7), 150.2(1) pm.*

Despite being crystallised with an excess of THF, no THF molecules were incorporated into the crystal structure, with the coordination environment of sodium instead being satisfied by intermolecular electrostatic interactions. This results in the crystallisation of **8** as a polymer of dimers, each dimer being centred around an Na_2N_2 ring, with long and short sodium-nitrogen bonds of 239.9 pm (Na(1)a-N(1)b) and 249.1 pm (Na(1)a-N(1)a). The sodium atom makes further contacts within the dimer with a nearby phenyl ring (Na(1)a-C(12)b, 300.0 pm), and with a benzylic carbon (Na(1)a-C(5)a, 276.8 pm). Finally, an interaction with the terminal alkenyl carbon of a nearby dimer (257.9 pm, Na(1)a-C(6)c) serves to bridge the dimers into a 2D polymeric network.

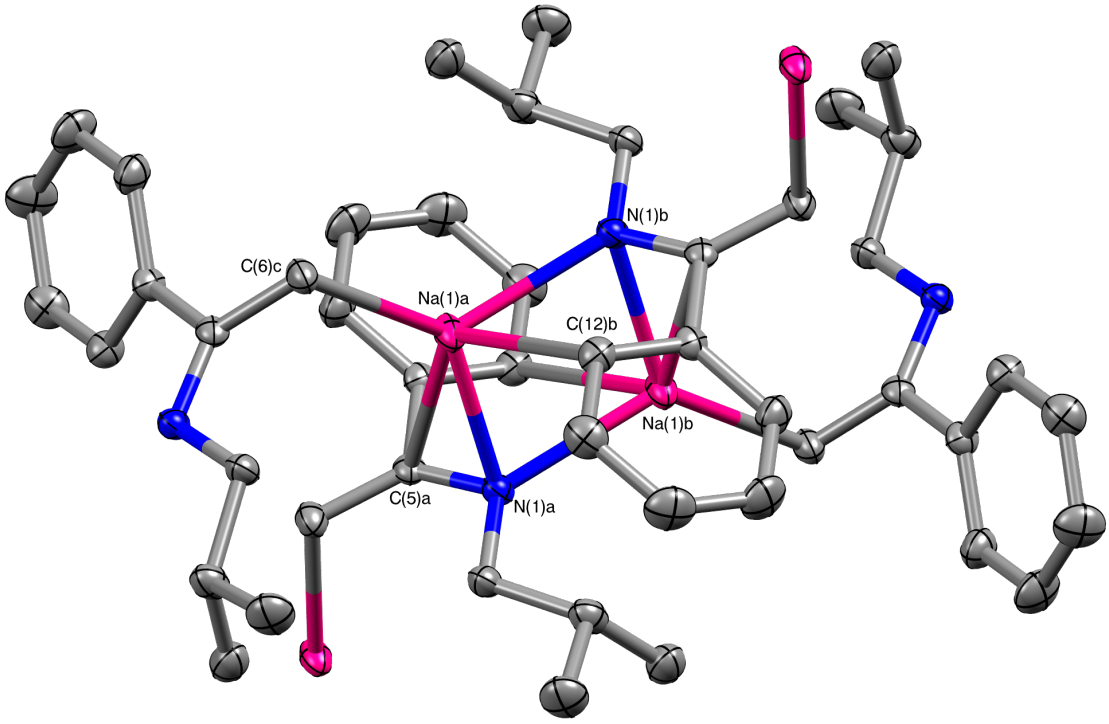


*Figure 4: Extended structure of **8** showing the central Na_2N_2 ring and intermolecular contacts forming the polymeric structure, showing thermal ellipsoids at 50% probability. Hydrogen atoms are omitted for clarity. Selected bond lengths and angles: Na(1)a-C(5)a, 276.8(1) pm; Na(1)a-N(1)a, 249.1(1) pm; Na(1)a-C(12)b, 300.0(1) pm; Na(1)a-N(1)b, 239.9(1) pm; Na(1)a-C(6)c, 257.9(1)pm, Na(1)a-N(1)a-Na(1)b, 79.69(3)˚; N(1)a-Na(1)a-N(1)b, 100.31(3)˚.*

Within each monomer, the bond lengths of the carbon-nitrogen (C(5)-N(1)) and alkenyl carbon-carbon (C(5)-C(6)) bonds of the benzylic carbon are 134.4 pm and 138.3 pm respectively, and lie between the expected bond lengths of a single and double bond in each case. Accompanying the loss of chirality about the benzylic carbon, the aliphatic chain has become saturated, as shown by the bond lengths (N(1)−C(4), 145.0 pm; C(4)−C(2), 152.2 pm; C(2)−C(3), 152.0 pm; C(2)−C(1), 151.9 pm), and tetrahedral geometry about the carbon atoms.

The bond lengths within the organic backbone are essentially identical to those previously reported for the analogous sodium complex **6** (Scheme 18, page 34), formed from (*S*)-*N*-(1-phenylethyl)allylamine **1**,[41] with bond lengths falling within the standard deviation. The bonding environment around the sodium cation is dramatically different due to the presence of a chelating PMDETA donor in **6** making any comparison of the coordination and aggregation of the two complexes largely irrelevant. Interestingly, the allylamine derivative **6** has been found to be unstable in THF,[42] and eliminates propene in its decomposition. Thus, it appears the addition of a methyl group to the allyl moiety stabilises the sodium complex against this decomposition.

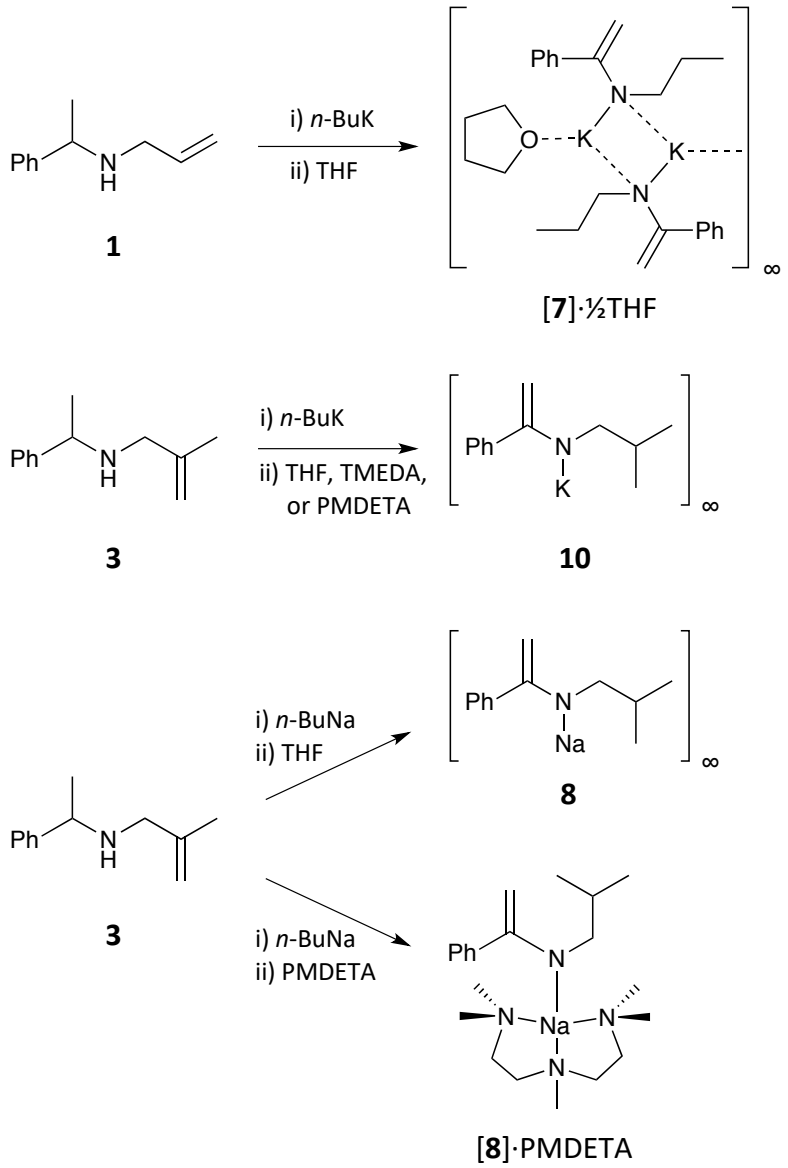
This structural data is in agreement with the solution state data for **8**, where the signals of the isobutyl group all exhibited the expected chemical shifts for an amine-substituted alkyl chain (2.75, 1.74, and 0.99 ppm). Meanwhile, the signals for the alkenyl moiety appear at 2.86 ppm and 2.48 ppm, which is between the expected chemical shifts for the methylbenzyl group (1.36 ppm), and a phenyl-substituted enamine (4.16, 4.07 ppm),[44] showing that the delocalised aza-enolate structure of **8** is maintained in the solution state.

Comparison of potassium aza-enolate structures

Having characterised the sodium aza-enolate complex crystallographically, it was of interest to crystallise the analogous potassium aza-enolate complex **10** to compare the bonding (Scheme 16). Unfortunately, due to repeated issues with twinning, coupled with the extreme air sensitivity of the crystals, the crystal data that was obtained was insufficient to establish anything beyond connectivity.

It has been previously noted that **10** crystallises without THF in the crystal lattice, based on the connectivity data, and supported by NMR studies.[36] This is not surprising based on the results with the sodium analogue **8**: given the softer Lewis acidity of potassium, it could be expected that interactions with the oxygen atom in THF would be excluded in favour of electrostatic interactions with the anion. It is interesting to compare this to the structure of potassium propyl(1-phenylvinyl)amide **7**, which crystallises as a 1D polymer with one THF molecule coordinated for every two molecules of **7** (Scheme 16).[38] This may be related to the slight increase in steric bulk from the extra methyl group in the aliphatic chain: this chain in **7** lies in a plane with the aza-enolate moiety, while the chain in **10** cannot exist in planarity with the aza-enolate group, and therefore methyl group may interfere with coordination of donors.

It is noteworthy that NMR studies showed no inclusion of the larger chelating donors TMEDA or PMDETA into the structure of **10**, in contrast with the related sodium system **8**. This likely precludes the use of these donors to aid in the crystallisation of **10**.



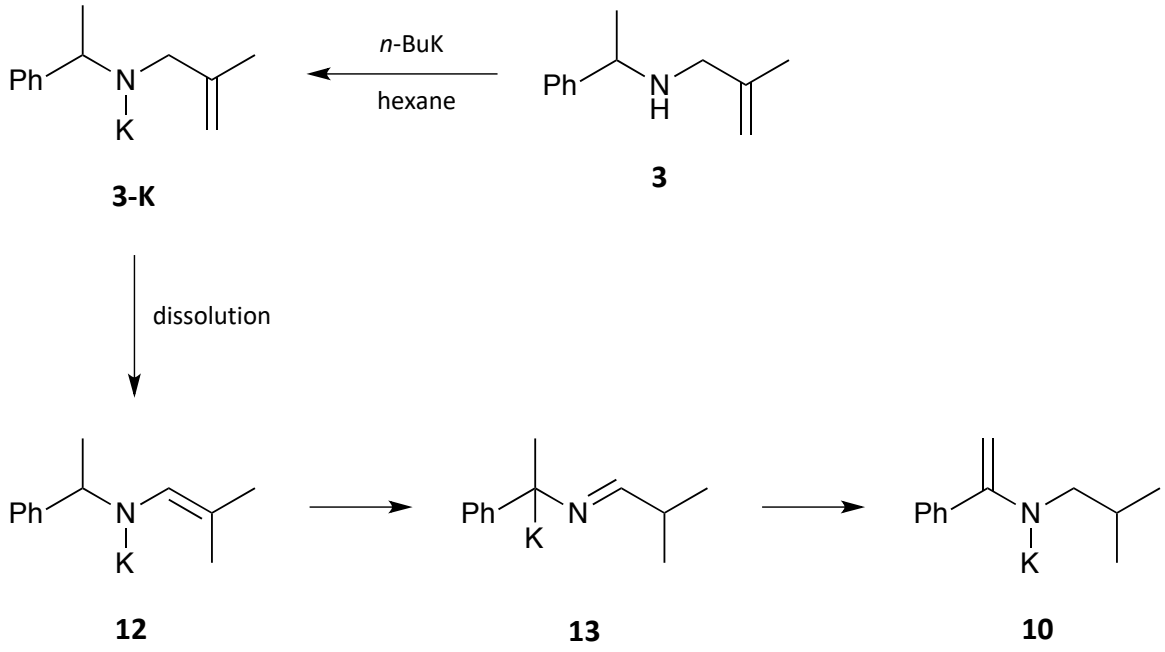
Scheme 16: Inclusion or non-inclusion of Lewis donors into the solid-state structures of sodium and potassium aza-enolate complexes.

Solution state studies of potassium complexes of *N*-(1-phenylethyl)methallylamine **3**.

Given that metallating **3** with sodium gave the partly rearranged 1-aza-allyl species **9** when dissolved in a predominantly non-coordinating solvent, it was of interest to determine whether the potassium amide would behave in the same manner. Deprotonation of **3** with *n*-butylpotassium (*n*-BuK) yielded a brown powder, which, as was the case with the sodium species, proved to be insoluble in benzene. Doping with a small amount of anhydrous THF gave a brown solution, which analysis by ^{1}H NMR and ^{13}C NMR showed to be the same initial rearrangement product as is obtained with sodium, that is: potassium (2-methylprop-1-enyl)(1-phenylethyl)amide (**12**).

This same product can be observed in neat THF, however full conversion to the aza-enolate structure **10** occurs within a day. Interestingly, the use of rigorously dried THF slows this rearrangement dramatically, so that the conversion is not complete even after a period of one month. This suggests that the rearrangement is catalysed either by the presence of free amine, or by potassium hydroxide. Given that washing the precipitate with hexane does not always remove all of the starting material, potassium hydroxide is the more likely catalyst in this situation. Quenching the brown powder obtained initially from deprotonation with *n*-butylpotassium returned only starting material **3**, showing that the potassium amide formed does not undergo a sigmatropic rearrangement until dissolved. This amide is not observed in the ^{1}H NMR spectrum recorded immediately after dissolution, showing that the first rearrangement occurs rapidly.

While observing the rearrangement of **12** to **10**, an unknown species was observed in the solution by ^{1}H NMR. By comparing the chemical shifts and coupling constants, as well as the ^{13}C, COSY, and HSQC NMR spectra, this species could be assigned as another anion in the rearrangement process, (1-((2-methylpropylidene)amino)-1-phenylethyl)potassium (**13**). Based on the coupling constants and 2D NMR spectra, this complex appears to be deprotonated at the benzylic carbon, rather than at the nitrogen atom as in the 1-aza-allyl and aza-enolate complexes.



3-K **3** **12** **13** **10**

*Scheme 17: Deprotonation of methallylamine **3**, and its subsequent rearrangement to 1-aza-allylic **12**, iminic **13**, and aza-enolic **10**.*

The ^{1}H NMR spectrum of the reaction mixture containing **13** is shown in Figure 5. The most striking feature of both the ^{1}H and ^{13}C NMR spectra of **13** is the set of signals corresponding to the phenyl group: not only are the signals shifted dramatically upfield, but the *ortho*- and *ortho*'-positions of the ring now produce two individual signals, unlike the single signal observed in the parent amine and all of the other metallated isomers.

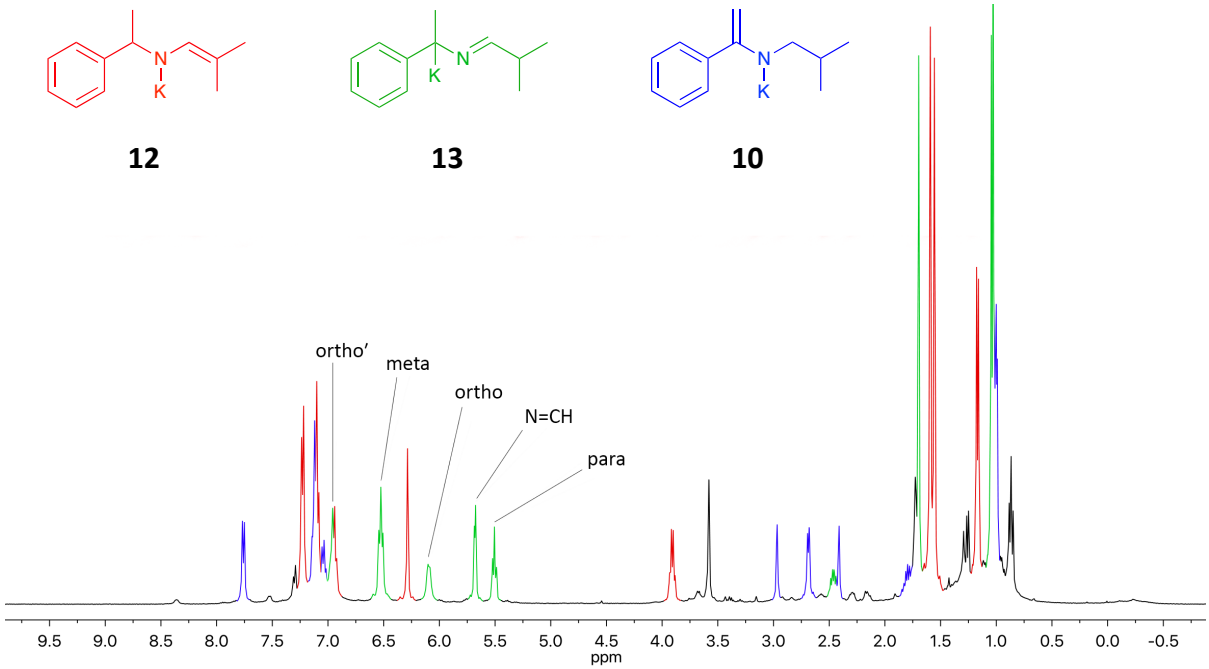


*Figure 5: ^{1}H NMR spectrum of the reaction of methallylamine **3** with n-BuK after five days in d_8-THF. There are three isomers present: 1-aza-allyl (**12**, red), 2-aza-allyl (**13**, green), and aza-enolate (**10**, blue).*

The most likely explanation for this is resonance between the ring and a lone pair on the benzylic carbon, which restricts rotation around the *ipso*- and benzylic carbon-carbon bond, allowing for resolution of the different positions of the ring on the NMR timescale. This resonance would also lead to an increase in electron density on the *ortho*- and *para*-positions in the ring, making it likely that there will be some interaction of the potassium cation with one of the *ortho*-carbons.

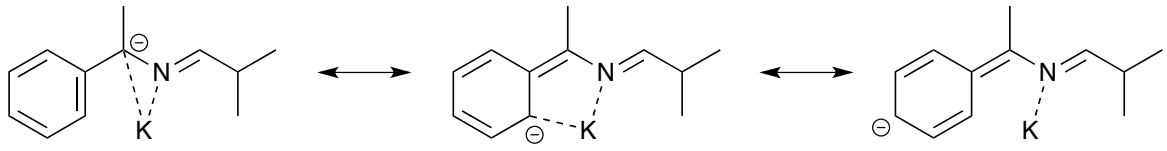
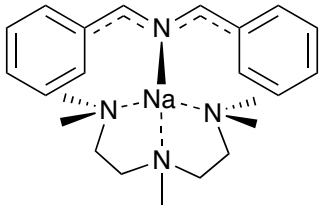


*Figure 6: Resonance structures of the anion of **13**, showing the pseudo-double-bond character about the ipso-benzylic carbon bond, and interaction of the potassium cation with one of the ortho-positions.*

A similar desymmetrisation of the ring signals has been seen before in the PMDETA coordinated sodium 1,3-diphenyl-2-aza-allyl complex (**14**), however this was only observed when the ^{1}H NMR spectrum was recorded at low temperatures (-7 ˚C for the *ortho*-signals, and -30 ˚C for the *meta*-signals).[45] Likewise, the complexes containing benzylic anions (*α*-(dimethylamino)benzyl)potassium (**15**), and (1-(dimethylamino)-1-phenylethyl)potassium (**16**), are reported as having both *ortho*/*ortho*'- and *meta*/*meta*'-carbon atoms which can be distinguished by NMR spectroscopy at room temperature.[46]



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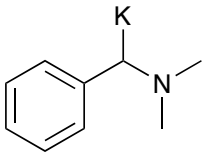

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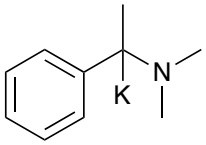


16

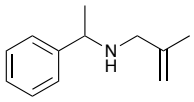
Figure 7: Structures of alkali metal complexes which display unsymmetrical chemical environments in the phenyl rings by NMR spectroscopy.

Complex **13** appears to lie somewhere between the structures of **14** and **15**/**16**; the upfield shifting of both the proton and carbon signals in **13** is greater than in **14**, but less than in **15** and **16**. The *ortho*- and *ortho*'- signals, but not the *meta*- and *meta*'- signals in **13** can be distinguished at room temperature, while **14** requires cooling to separate the two signals. In complexes **15** and **16** on the other hand, the *ortho*-/*ortho*'- *and meta*-/*meta*'- signals can be differentiated at room temperature. The ^{1}H NMR spectra largely share the features of the ^{13}C spectra, with one important difference: the *ortho*- and *ortho*'-signals in **14** at -50 ˚C are further separated (Δδ = 1.05 ppm) than those of **15** (Δδ = 0.28 ppm). In the case of **14**, this dramatic difference was attributed to interaction of one *ortho*-proton with the sodium cation, consistent with the solid-state structure of the complex. Given the similar magnitude of Δδ of the *ortho*-protons in **13** (0.88 ppm), it seems likely that a similar interaction is occurring with the potassium cation.

An analysis of the chemical shifts of the iminic carbon and proton allows some understanding of the structure of the rest of the complex. The chemical shifts of the α-proton(s) and α-carbon atom for the three isomeric potassium complexes, the parent amine **3**, and the related imine 2-methyl-*N*-(1-phenylethyl)propan-1-imine (**17**) are shown in Table 1. The chemical shifts for complex **13** fall in between the values found for those of compounds with sp^2 hybridisation at the α-position (**12** and **17**), and those of compounds with sp^3 hybridisation (**3**

and **10**). This is the same phenomenon that was observed for the aza-enolic protons in the sodium complex **8** described above. This suggests that the π-system of the imine bond is delocalised to some extent, and can be described as a 2-aza-allyl system.

Table 1: Chemical shifts of potassium complexes and related unmetallated compounds.



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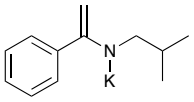

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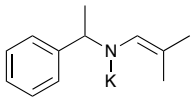

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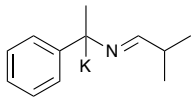
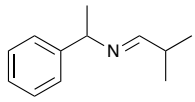


13



17

Position	Nucleus	Compound 3	10	12	13	17	
para	^{1}H	7.23	7.04	6.94	5.50	7.13	Chemical shift δ (ppm)
	^{13}C	127.1	125.8	124.7	105.6	126.9	
meta	^{1}H	7.32	7.10	7.11	6.52	7.24	
	^{13}C	128.7	128.0	128.0	129.2	128.7	
ortho	^{1}H	7.32	7.76	7.23	6.97, 6.09	7.33	
	^{13}C	127.0	127.5	127.2	112.8, 112.6	127.0	
ipso	^{13}C	146.5	151.2	154.9	144.7	146.8	
benzylic	^{1}H	3.76	--	3.91	--	4.21	
	^{13}C	57.9	164.0	67.6	94.6	70.4	
aliphatic-α	^{1}H	3.02	2.69	6.29	5.68	7.66	
	^{13}C	53.9	63.2	150.6	120.0	167.4	

Attempts to crystallise the 2-aza-allyl complex **13** were complicated by the extreme sensitivity of the potassium complexes, the presence of other isomers, as well as the relatively short lifespan of the complex. To make matters worse, the rate of isomerisation from **12** to **13**, and from **13** to **10** was sensitive to the concentration of the complex, the amount of THF used to solubilise the complex, as well as any contaminants in the solutions (such as potassium hydroxide: see above). This means that while attempting to crystallise complex **13**, it is uncertain what proportion of the solution is compound **13**, and what proportion is complex **12** or **10**. The related imine **17** was reacted with *n*-butylpotassium with the purpose of synthesising **13** in a high enough concentration to facilitate crystallisation, however this reaction yielded largely the same results as deprotonation of **3**, producing a mixture of isomers.

The 2-aza-allylic anion structure has not been previously observed from the sigmatropic rearrangements of unsaturated aliphatic amides, and structures of this type are generally

stabilised by the presence of two or more aryl groups.[47] Complex **13** is likely an intermediate in the rearrangement of **12** to form **10**, as it has one proton shifted from the structure of **12**, and requires one more proton to shift to become **10**, rather than the transfer of two protons required for the transformation of **12** directly into **10**. While an analogous structure has not been observed in the sodium system, it likely exists as a transition state in the anion rearrangement, but rearranges again too quickly to be observed by NMR studies.

Computational studies

In order to better understand the formation of the 2-aza-allyl system in **13**, and to explain the reason for the stabilisation of this system exclusively in the potassium compound, computational studies were undertaken in collaboration with the research group of Katya Pas. The stability of every isomer for each of lithium, sodium, and potassium were calculated, and gleaned some insight into the rearrangement. The results obtained were as expected for the sodium complexes, with the stability of the isomers increasing in the order: amide < 2-aza-allyl (**13**) < 1-aza-allyl (**9**) < aza-enolate (**8**). Interestingly, the energy of the 1-aza-allyl system for each metal is roughly the same, as are the energies of the 2-aza-allyl systems with lithium and sodium.

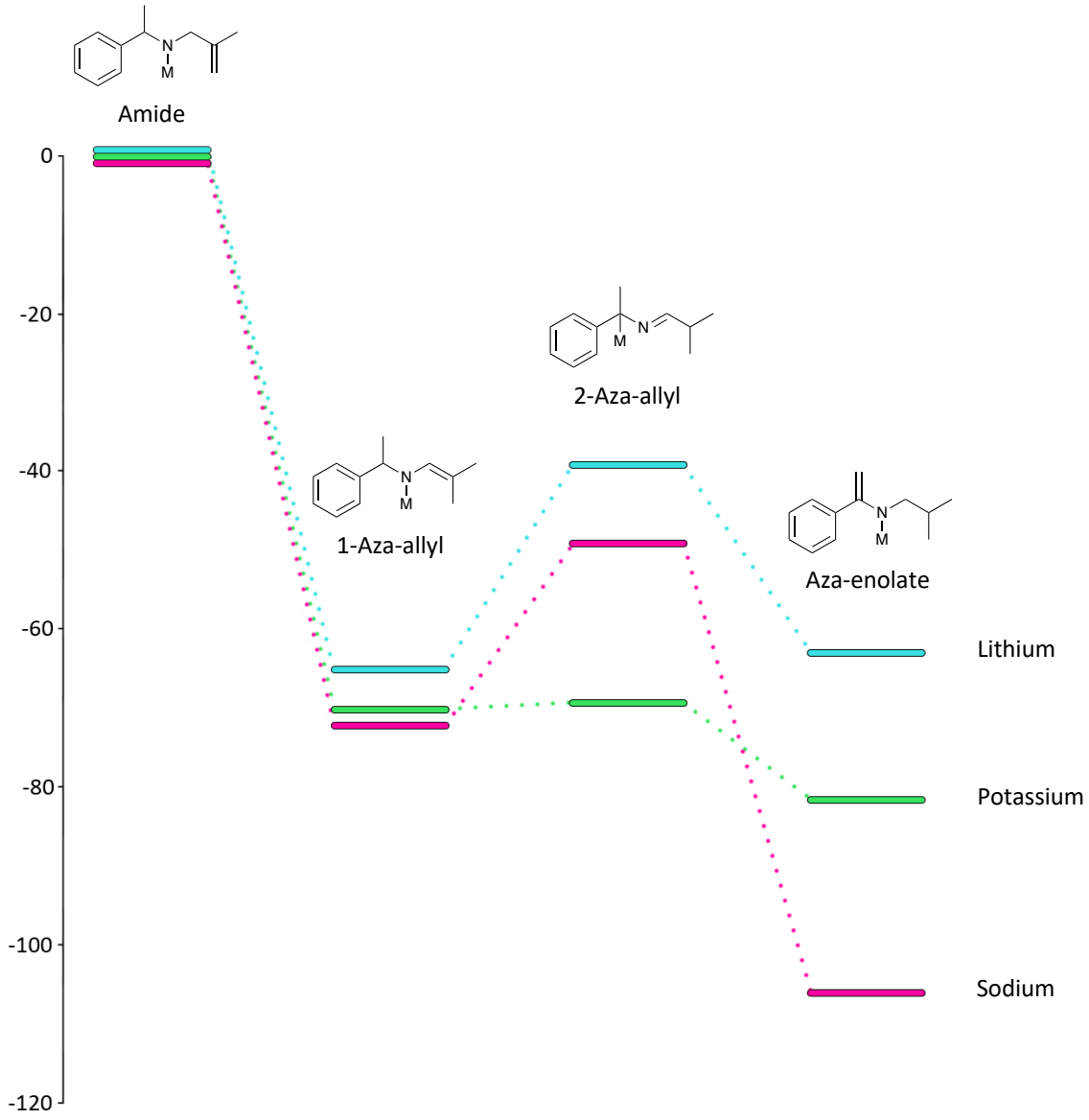


Figure 8: Calculated relative energies of isomers of alkali metal complexes of N-(1-phenylethyl)methallylamide.

In the lithium complexes, the difference between the energies of the 1-aza-allyl and aza-enolate isomers was negligible. This would suggest that both isomers are likely to exist in equilibrium, however as has been seen in previous computational studies,[41] the addition of various equivalents of ammonia into the model (to simulate the presence of Lewis donors such as TMEDA and PMDETA) changes the relative energies of these two isomers. The studies described here used a conductor-like polarisable continuum model to emulate THF, but no explicit molecules were modelled to simulate the effect of the Lewis donors. Nonetheless, the calculated energy of the 2-aza-allyl isomer is 24 kJ/mol higher that the other rearrangement products, suggesting that it is unlikely that this structure would be observed.

In the potassium complexes, an interesting change in the relative energies can be seen. Overall, the energies of each isomer are much closer to each other, with the 1-aza-allyl and 2-aza-allyl forms being calculated at almost identical energies. The aza-enolate form is only slightly more stable than these, with a difference of 12.5 kJ/mol. This minor change in energies shows that there is significantly less thermodynamic drive to form any one isomer over another.

By comparing the bond lengths and charge densities within the theoretical model, it can also be seen that the potassium cation is calculated to have a greater interaction with the benzylic carbon atom, while maintaining a strong contact with the nitrogen atom. This is not seen in the lithium or sodium models, and is likely a result of the larger ionic radius of potassium, allowing for more effective orbital interaction with the delocalised anionic system. This helps to explain why the 2-aza-allylic system is able to form with potassium, and why it hasn't been observed in the case of lithium or sodium.

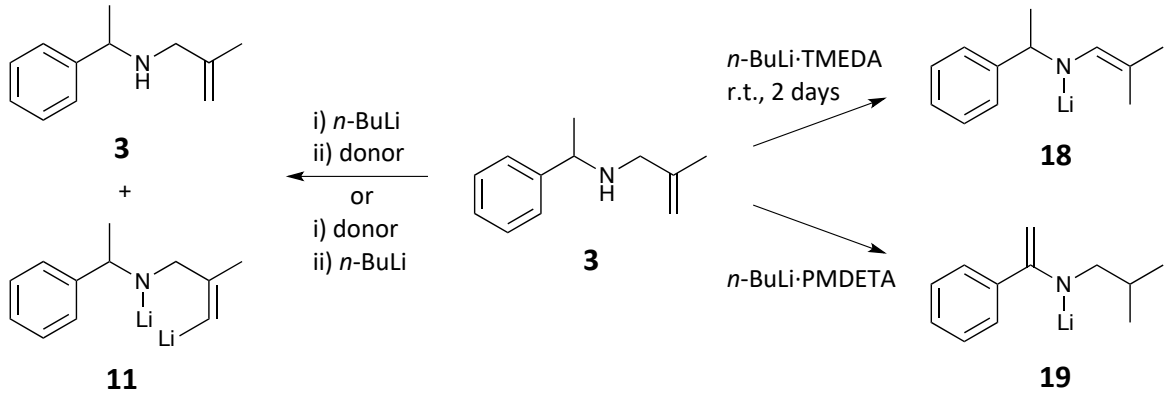
In addition, the bond lengths calculated for the 2-aza-allyl system show a considerably shortened benzylic carbon-nitrogen bond of about 137 pm, close to the bond length seen in sodium aza-enolate **8**, and in previously characterised aza-enolate systems.[38,41] Thus the calculations support the hypothesis that the structure of potassium complex **13** includes a delocalised π-system, rather than a distinct imine double bond.

Synthesis of monolithiated complexes from methallylamine 3

Based on the results from the computational study, efforts were redoubled to synthesise a monolithio complex from methallylamine **3**. Related monolithio complexes have been synthesised from allylamine **1** (structure shown in Scheme 16, page 26), and crystallographically characterised. Reaction of **1** with *n*-BuLi, followed by addition of HMPA yielded the allylamide form of the complex, which was able to be isomerised to the 1-aza-allyl form by heating.[40] Reaction of *n*-BuLi with a mixture of **1** and TMEDA or PMDETA gave the 1-aza-allyl and aza-enolate forms of the complex, respectively.[41] In contrast, reaction of methallylamine **3** with *n*-BuLi gives only a mixture of the dilithiated complex **11** and starting material, which cannot be made to equilibrate to give a monolithiated complex (Scheme 18). Taking the approach used with **1**, and using a mixture of methallylamine **3** and TMEDA or PMDETA yielded complex mixtures, or the same results as performing the reaction without donor.

Success was achieved by precomplexing the Lewis donor to *n*-BuLi, and addition of this complex to **3**. Thus, the use of TMEDA-coordinated *n*-BuLi yielded a yellow solid, which was dissolved in C_6D_6. Analysis of this solution showed the presence of several complexes, however recording the spectrum of the same sample two days later showed a resolved spectrum with only two major species present: unreacted amine **3**, and the 1-aza-allyl species lithium (2-methylprop-1-enyl)(1-phenylethyl)amide (**18**).

Reaction of **3** with one equivalent of *n*-BuLi precomplexed to PMDETA also gave a yellow solid, which NMR analysis showed to be the expected aza-enolate form of the anion, lithium isobutyl(1-phenylvinyl)amide (**19**). Unlike the reaction with TMEDA as a donor, this complex did not require any incubation period to rearrange completely, and analysis by NMR spectroscopy immediately after synthesis showed a clean isomerisation had occurred, with only **19** and a small amount of starting material present. The difference between the facility of the rearrangements with TMEDA and PMDETA may be due to an enhancement of the rate of rearrangement, due to steric factors reducing the extent to which side reactions occur, or perhaps a combination of both.

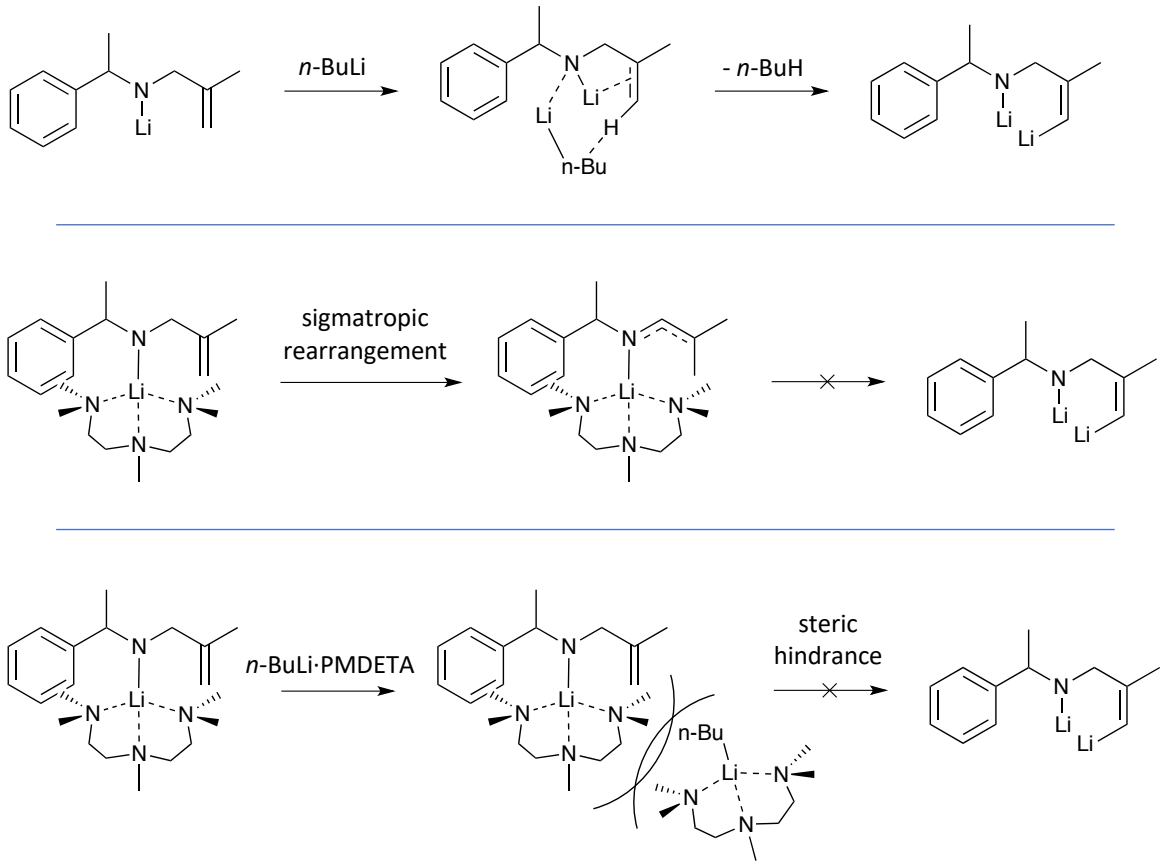


*Scheme 18: Outcomes of lithiation reactions of methallylamine **3** using n-BuLi. In order to obtain selective monolithiation, the n-BuLi must be pre-complexed with a chelating Lewis donor.*

A comparison of the spectral data of the 1-aza-allyl complexes **9**, **12**, and **18**, and aza-enolate complexes **8**, **10**, and **19** shows a broad similarity between the complexes when changing the metal, however the chemical shifts of the signals are heavily dependent on solvent and concentration, presumably as a result of changing aggregation.

The requirement for pre-complexation of *n*-BuLi can be explained by the occurrence of a rapid anionic rearrangement removing the acidic site from the aliphatic chain (Scheme 19, middle), or by steric hindrance of the monolithiated complex preventing a second lithiation with the

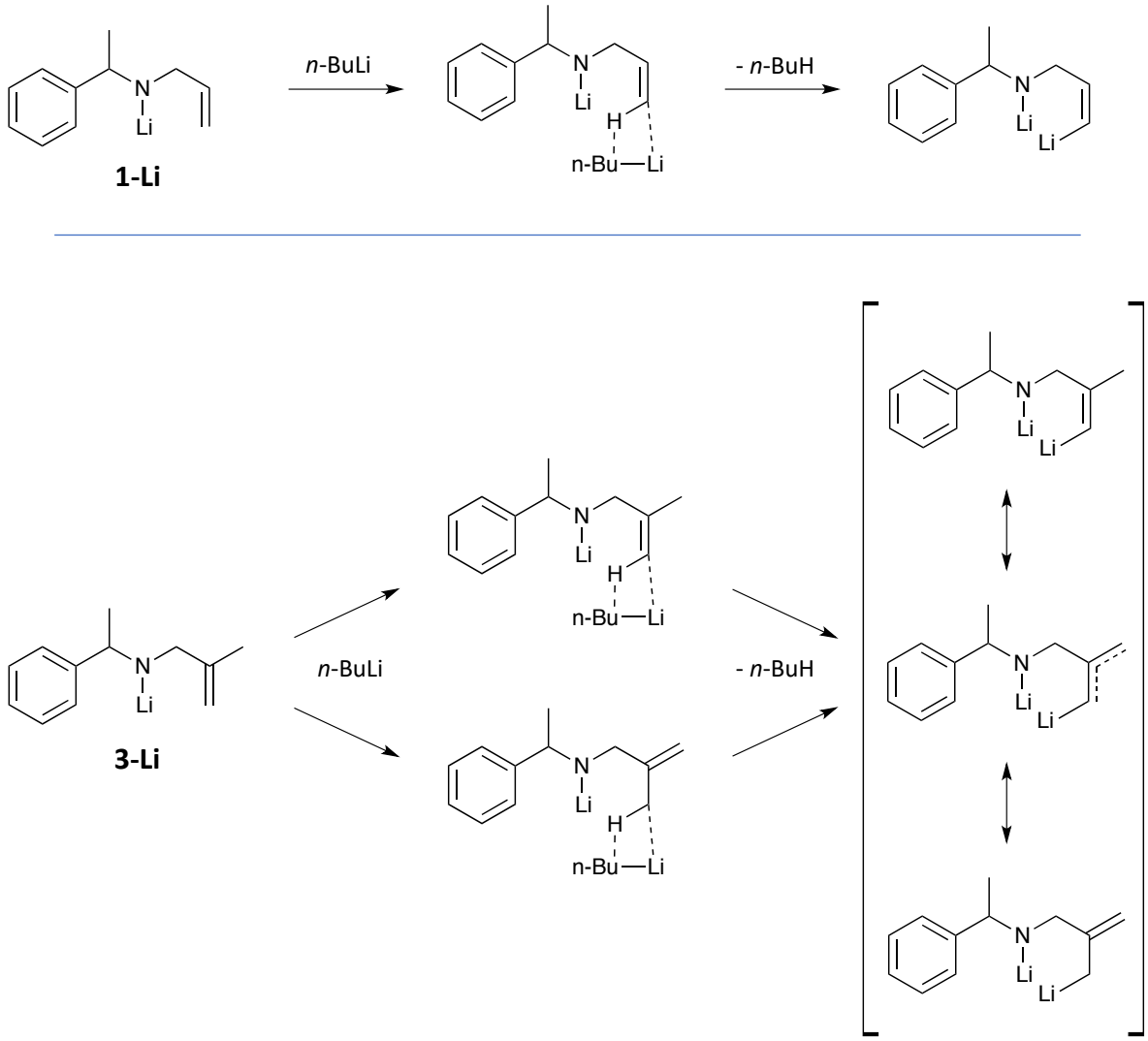
bulky *n*-BuLi-donor complex (Scheme 19, bottom). Barluenga has proposed that deprotonation of the allylic position in such compounds is facilitated by coordination of the amido-lithium to the incoming base, activating the organolithium and bringing it into the proximity of the allyl group (Scheme 19, top).[22]



*Scheme 19: Proposed mechanism of dilithiation of methallylamine **3** (top), and possible reasons for selective monolithiation with pre-complexed base: rapid anion rearrangement (middle), or steric hindrance (bottom).*

This does not explain why a monolithiated derivative of allylamine **1** can be synthesised with *n*-BuLi, followed by later addition of HMPA, whereas methallylamine **3** dilithiates under these conditions. One reason for this could be the formation of an allylic anion instead of a vinylic anion (Scheme 20); Barluenga has also shown that deprotonation of the nitrogen and the methyl position of the methallyl group, instead of the terminal vinyl position, occurs in *N*-methallylaniline,[33] as well as in alkyl derivatives of methallylamine when deprotonated in the presence of PMDETA.[23] Additionally, during the formation of trianions from *N*-(methallyl)allylamine, the methallyl group is selectively deprotonated over the allyl group, marking the greater propensity of methallyl groups to be deprotonated.[22] The faster lithiation

of the methallyl group in **3**, compared with the allyl analogue **1** may make selective monolithiation more difficult.



Scheme 20: Dilithiation of N-(1-phenylethyl)allylamide can only occur through deprotonation of one site (top), while dilithiation of N-(1-phenylethyl)methallylamide can occur through deprotonation of two sites, and the resulting anion may be stabilised through the resonance structures shown (bottom).

The deprotonation of different positions on the methallyl group may explain the initial complexity of the spectrum obtained from the reaction of TMEDA complexed *n*-BuLi with **3**, as it is possible different dilithiated species were formed, as well as the monolithiated and protonated species, which then equilibrated to form the monolithiated species **18**.

Conclusions and future work

The results within this chapter describe the characterisation of a variety of alkali metal derivatives of *N*-(1-phenylethyl)methallylamine **3**. Previously, the sodium complexes sodium (2-methylprop-1-enyl)(1-phenylethyl)amide **9** and sodium isobutyl(1-phenylvinyl)amide **8**

had been characterised by NMR spectroscopy.[36] Compound **8** has now also been characterised crystallographically, and displays the same core structure as has been seen in the related sodium propyl(1-phenylvinyl)amide **6**, derived from (*S*)-*N*-(1-phenylethyl)allylamine **1**. Differences were observed in the coordination environment of the sodium cation in each complex, and this was attributed primarily to the change of Lewis donor from chelating PMDETA in **6**, to monodentate THF in **8**, which is excluded from the structure in favour of intermolecular interactions. Crystallisation of **8** with PMDETA as a Lewis donor may give a structure which can be more readily compared, but given that the organic fragment of each of the complexes show almost identical bonding, it is expected that the structures will be essentially the same.

Attempts were made to characterise crystallographically the related aza-enolate complex potassium isobutyl(1-phenylvinyl)amide **10**, but due to twinning problems, and the extreme reactivity of the crystals, no suitable structure could be obtained. Changing the Lewis donor used did not alleviate these problems, and it was found through NMR studies that bidentate TMEDA, and even tridentate PMDETA were not incorporated into the structure of **10**.

The 1-aza-allylic complex potassium (2-methylprop-1-enyl)(1-phenylethyl)amide **12** was generated by dissolution of the potassium amide derived from **3** in benzene doped with THF. This complex exhibits similar NMR spectra to the sodium 1-aza-allyl complex **9**, and was found to be formed from rearrangement of the parent potassium amide immediately upon dissolution. Compound **12** was also able to be observed in neat THF, however complete rearrangement to the aza-enolate form occurred within one day. The use of rigorously dried THF drastically slowed this rearrangement, extending the lifetime of **12** to beyond one month. The NMR spectra obtained this way, as well as in benzene doped with THF, showed the formation of a previously unobserved isomer, the 2-aza-allyl complex (1-((2-methylpropylidene)amino)-1-phenylethyl)potassium **13**. This structure appears to be an intermediate in the rearrangement of the 1-aza-allyl complex **12** into the aza-enolate form **10**.

Compound **13**, unlike the 1-aza-allylic and aza-enolic systems, is deprotonated at the benzylic carbon, and displays interesting features in the NMR spectra. The complex shows extensive interaction of the potassium cation and of the benzylic anion with the phenyl ring, as evidenced by the significant upfield shifting of the aromatic signals, and desymmetrisation of

the *ortho*- and *ortho*'-signals. Comparison of the ^{1}H and ^{13}C NMR spectra of **13** with those of related compounds showed that there was some extent of delocalisation of the iminic π-bond, leading to its description as a 2-aza-allylic system.

Attempts to crystallise **13** were hampered by the extreme sensitivity of the complex, and by the presence of other isomeric potassium complexes, as well as the uncertainty of the composition of solutions. The use of non-enolisable amine substituents, such as benzyl or neopentyl groups would simplify the characterisation of the 2-aza-allylic system, by preventing the formation of the 1-aza-allyl and aza-enolate isomers. However, this necessarily changes the nature of the complex, and may make any comparison of the structures irrelevant.

Computational studies showed that the potassium complexes derived from **3** are closer in energy to each other than the analogous lithium or sodium complexes, likely due to the larger ionic radius of potassium, allowing it to maintain interactions with both the anionic benzylic carbon, and the nitrogen atom in **13**.

Finally, the lithium 1-aza-allyl and aza-enolate complexes **18** and **19** were synthesised through the use of *n*-BuLi precomplexed to TMEDA or PMDETA, respectively. These complexes could not be formed by later addition of the chelating donor, or by adding *n*-BuLi to a mixture of amine **3** and a donor. The lithium complexes obtained this way showed broadly similar features to the analogous sodium and potassium complexes, with solvation effects apparently dominating the differences in chemical shifts between the complexes.

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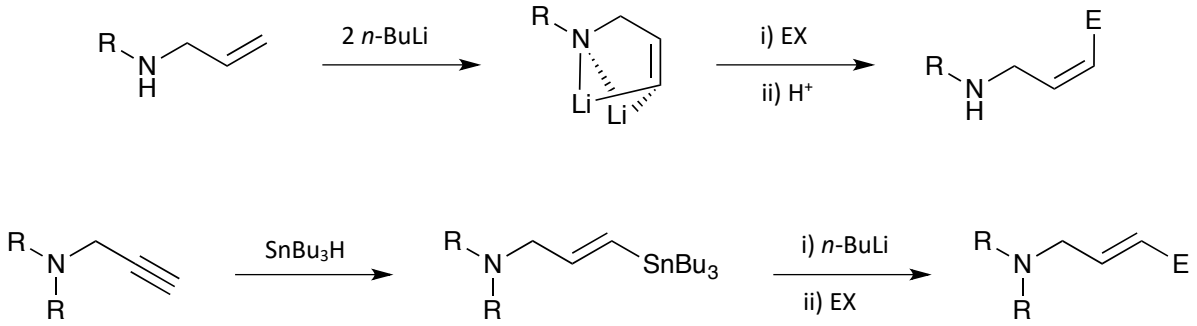
Chapter 2: Reactivity of s-Block Metal Complexes of Propargylamines

Introduction

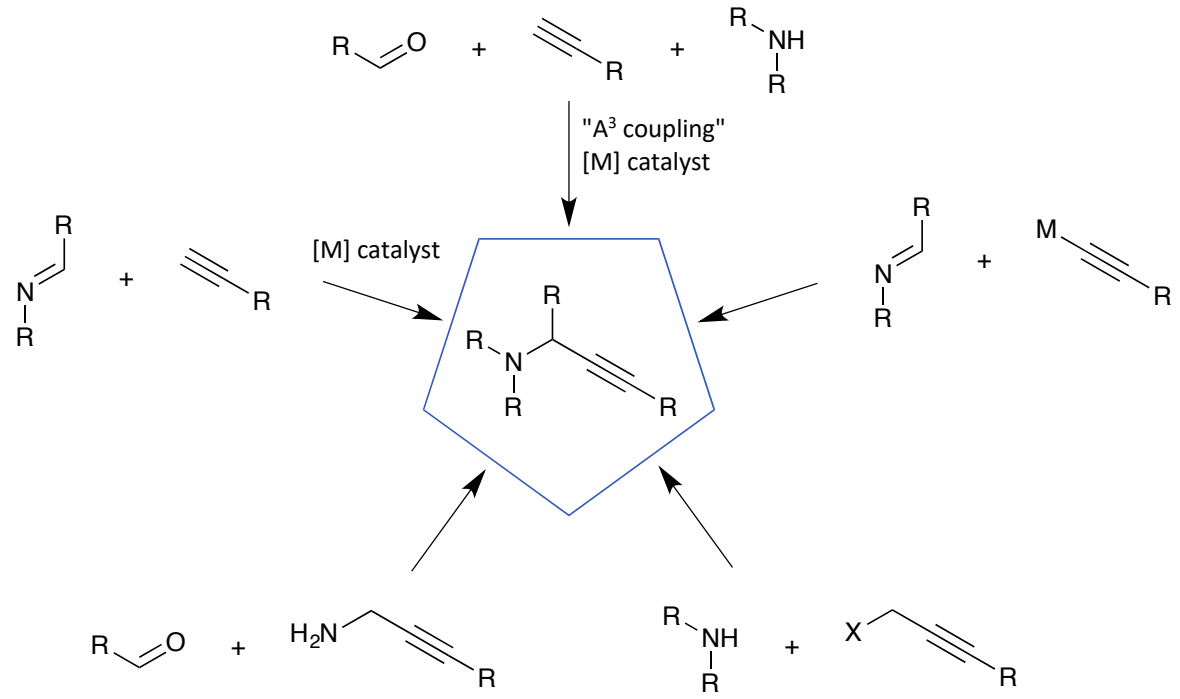
Propargylamines represent important building blocks in organic synthetic procedures. The combined functionalities of the amine and alkyne groups impart an incredible versatility to the applications of these compounds in synthesis, which have been recently reviewed.[1,2] In particular, propargylamines make excellent precursors for the synthesis of an impressive variety of nitrogen heterocycles. Nitrogen heterocycles make up 59 % of unique small molecule drugs approved by the FDA,[3] highlighting the importance of such building blocks. In addition, several secondary and tertiary propargylamines have been shown to have biological activity as monoamine oxidase inhibitors, used to treat Alzheimer's and Parkinson's diseases.[4–7] Propargylamines can be also be used as precursors to terminally metallated allylic amines in the *E*-configuration,[8] a reversal of the regioselectivity observed with the deprotonative metallation of allylamines described in the previous chapter.



Scheme 21: Regioselective synthesis of cis- and trans- terminally substituted allylamines from unsubstituted allylamines and propargylamines.

The synthesis of propargylamines can be achieved through several routes: the typical methods for synthesis of substituted amines, such as alkylation and reductive amination are applicable, but there are also several routes available due to the specific reactivity of the precursors. These routes primarily involve nucleophilic addition of an alkyne to an unsaturated carbon-nitrogen bond.[1] While this method is commonly employed utilising s-block metal acetylides, the high reactivity of these complexes precludes their use with sensitive functionalities, and often requires strict control of reaction temperatures and inert conditions. Thus, the use of less electropositive metals allows access to a wider variety of compounds, using reaction conditions which are more easily achieved.[9] Additionally, many of

these metals can be used in catalytic quantities, which has obvious advantages in terms of cost and environmental impact, but also allows finer control of selectivity by tuning the catalyst.[10] The A^3-coupling reaction (aldehyde-alkyne-amine) utilises this feature to synthesise propargylamines in a one-pot metal-catalysed reaction from three precursors.[11,12]

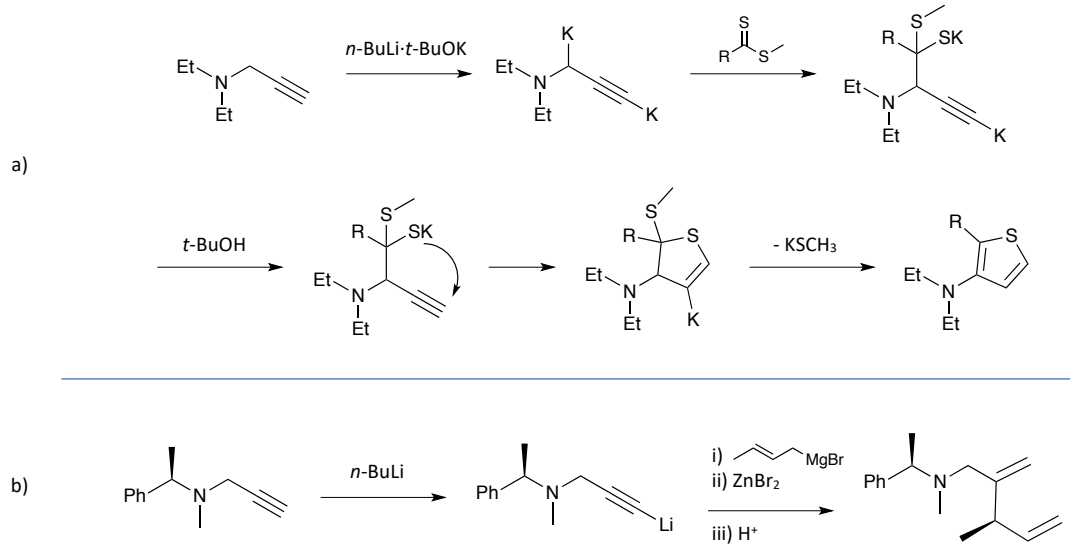


Scheme 22: Common synthetic routes to propargylamines. [M] denotes various copper or palladium catalysts.

While the use of s-block metal complexes in the synthesis of propargylamines is well established, the use of these same reactive complexes in their further functionalisation is rather undeveloped. Excluding reactions involving mild bases such as potassium carbonate, and base-mediated transition-metal-catalysed syntheses, there is a surprising dearth of syntheses involving propargylamines which utilise strong bases, especially organometallic bases of the s-block metals. Many of those reactions which do employ these bases are not deprotonated at the propargylamine moiety, but instead involve an intramolecular nucleophilic attack of another site onto the alkyne,[13,14] or a nucleophilic substitution at the α-position.[15]

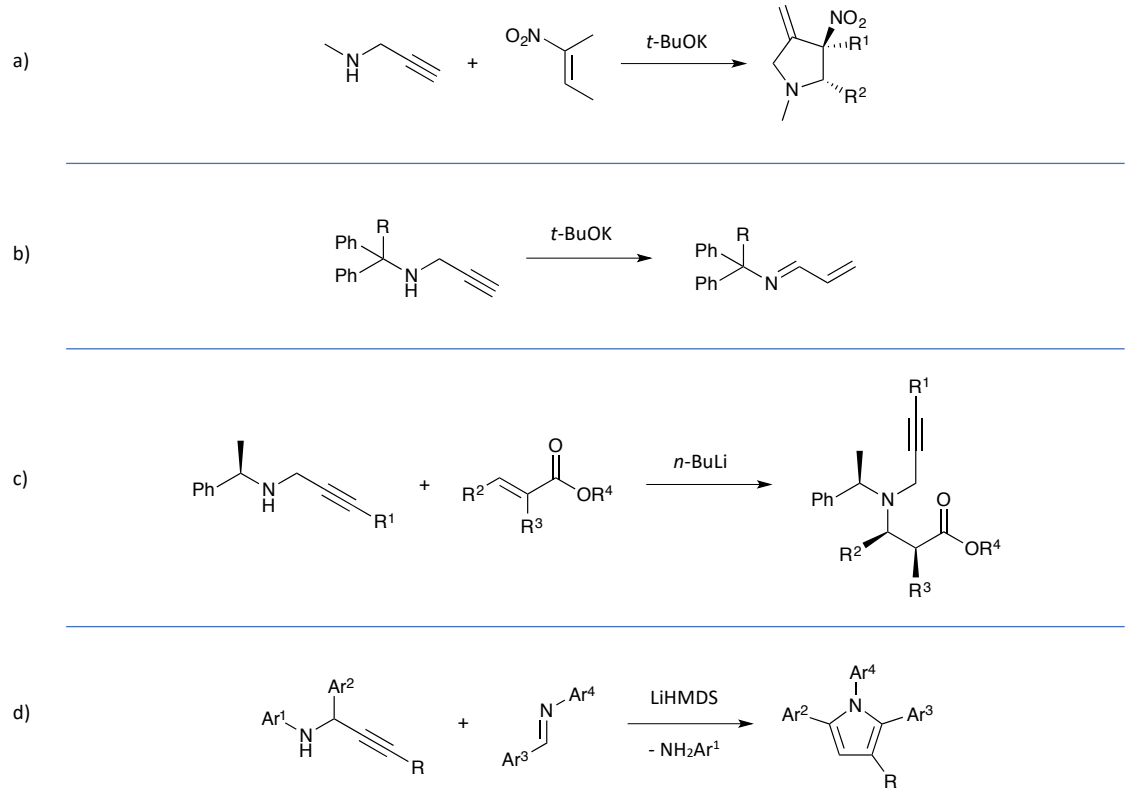
A thorough survey of the literature reveals only a handful of examples involving reaction of an s-block organometallic reagent directly with a propargylamine moiety.

Tertiary propargylamines have been dimetallated using *n*-BuLi-*t*BuOK, and reacted with non-enolisable dithioesters, resulting in formation of substituted thiophenes by nucleophilic attack followed by ring closure (Scheme 23a).[16] The diastereoselective carbometallation of monolithiated tertiary propargylamines has been reported, utilising zinc-mediated addition of allylic organometallic reagents across the alkyne triple bond (Scheme 23b).[17]



Scheme 23: Reactions of tertiary propargylamines involving s-block metal complexes.

A series of reactions involving Michael additions facilitated by potassium *tert*-butoxide allowed for the synthesis of cyclic amines from *N*-methyl-propargylamine and nitroolefins (Scheme 24a).[18,19] The initial conjugate addition is followed by a diastereoselective nucleophilic carbocyclisation to provide the product 3-methylene-4-nitropyrrolidines. The synthesis of *N*-allylideneamines has been achieved through the isomerisation of bulky secondary *N*-trityl- and *N*-diphenylmethyl-propargylamines using potassium *tert*-butoxide (Scheme 24b).[20] Propargylamines with less substitution at the α-carbon, including *N*-*tert*butyl- and *N*-diphenylmethyl-propargylamines failed to undergo the same reaction. The reaction of *N*-lithiated propargylamides with α,β-unsaturated esters has also been reported, yielding β-amino esters (Scheme 24c).[21,22] The products of these reactions still contain the propargyl group, and so can be functionalised through reactions at this site. Finally, reaction of imines with propargylamines in the presence of *n*-BuLi yields 1,2,3,5-tetrasubstituted pyrroles (Scheme 24d).[23] These reactions proceed by formation of a lithium amide, which isomerises to give the allylic anion. The imine inserts into the lithium-carbon bond, followed by a ring closure to form the five-membered ring, and elimination of aniline to generate the pyrrole product. The reactions were restricted to aryl substituents on the imine.



Scheme 24: Reactions of secondary propargylamines involving s-block metal complexes.

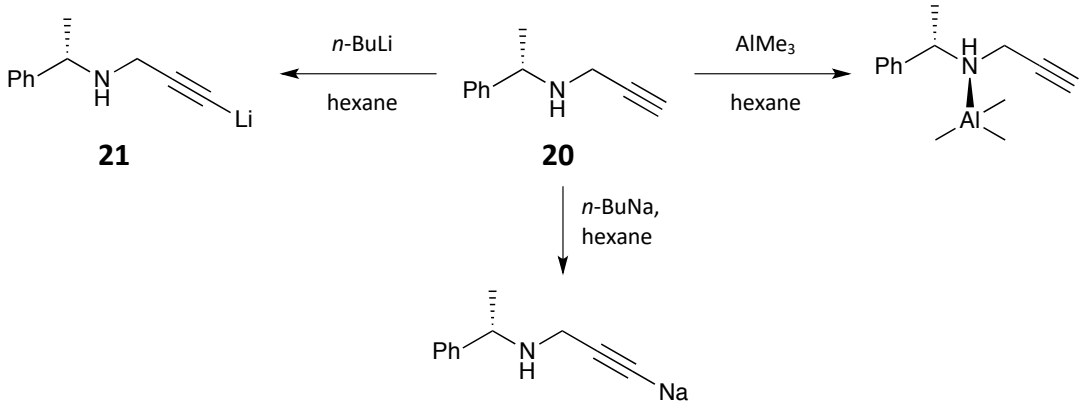
Though this is likely not a complete list of the reactions of propargylamines with s-block organometallic reagents, the rarity of this type of reaction amongst the wealth of synthetic routes involving propargylamines is surprising. Additionally, in none of the aforementioned reactions was a metallated intermediate characterised, instead relying on reaction outcomes to postulate the structures of intermediates.

Structural studies on metallated intermediates have been undertaken on polylithiated alkynes, through a combination of quench studies, NMR, and infrared spectroscopy.[24–27] Reich has also used NMR spectroscopy to investigate the solution-state structures of propargylic (and allenic) anions derived from alkyl- and silyl-substituted compounds, as well as those containing chalcogens.[28–32] A common outcome of these studies was the isomerisation of propargylic anions to form allenic anions, and vice versa.

As of yet, characterisation of s-block complexes of propargylamines appear not to have been undertaken. Despite the relatively few reactions so far reported involving this type of complex, the huge variety of syntheses able to be performed using propargylamines, coupled with the diverse reactivity offered by organoalkali complexes should allow access to some unique synthetic pathways. Additionally, those reactions which utilise transiently formed s-block complexes in transition-metal-catalysed cross-coupling may benefit from an improved understanding of the nature of these intermediates, allowing for easier and more effective optimisation of reaction conditions.

Previous research has investigated the potential for *N*-(1-phenylethyl)prop-2-yn-1-amine (**20**) to undergo anion-induced rearrangements analogous to those seen in the related allyl derivatives.[33,34] Deprotonation of **20** with *n*-BuLi yielded the lithium acetylide (3-((1-phenylethyl)amino)prop-1-yn-1-yl)lithium (**21**, Scheme 25, left). This compound was characterised by NMR spectroscopy in d_8-THF, with all attempts to grow single crystals suitable for X-ray diffraction analysis failing. Both ^{1}H and ^{13}C NMR analysis showed only small differences between the parent amine and lithium acetylide **21**. Addition of chelating Lewis donors, used previously to induce anionic rearrangements in allylamides, improved the solubility of the complex in hydrocarbon solvents, but brought about no observable change in the structure of the complex. Efforts to synthesise other metal complexes analogous to **21** using heavier organoalkali congeners were largely unfruitful: the product of reaction with *n*-butylsodium (*n*-BuNa) was proposed to be the sodium acetylide equivalent of **21** (Scheme 25,

bottom), however once again crystallisation of the complex proved inaccessible, and in this case NMR studies in d_8-THF yielded a series of broad signals, rendering the data largely uninterpretable. Attempts to synthesise an aluminium complex from **20** bore some success, with an adduct of trimethylaluminium and propargylamine **20** being characterised crystallographically (Scheme 25, right). Despite being highly crystalline and soluble, the NMR spectra obtained from the aluminium adduct in C_6D_6 consisted of broad signals, which sharpened over several days in solution, but produced a complex spectrum, apparently due to the formation of different products. This behaviour exhibited by the aluminium adduct is demonstrative of the difficulties involved in characterising these propargylamine-metal complexes. Heating this complex to induce a deprotonation resulted in a complex mixture, which was unable to be separated or characterised.



*Scheme 25: Characterised metal complexes derived from N-(1-phenylethyl)prop-2-yn-1-amine **20**.*

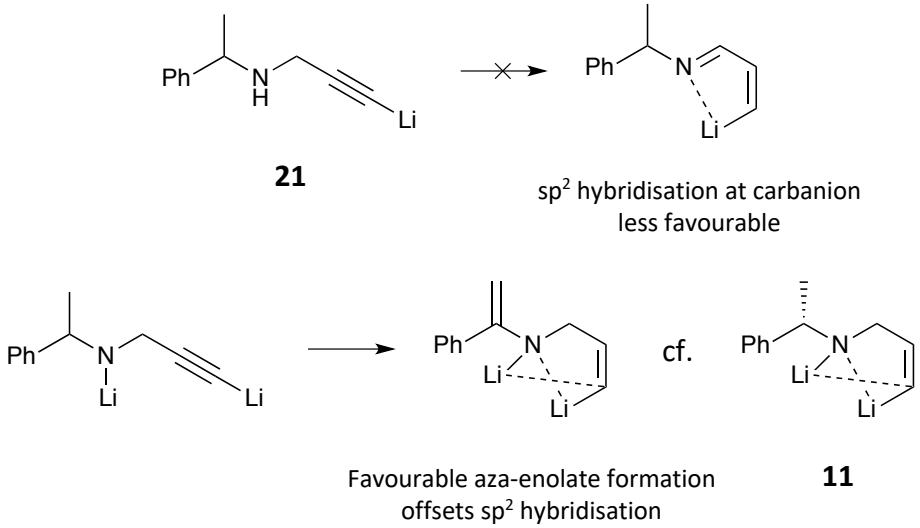
The experiments described within this chapter focus on expanding on the characterisation of alkali metal complexes of propargylamines, and further attempts to induce anionic rearrangements in **20**. Understanding the structural features of these complexes and their reactivities should facilitate their use in synthesis, adding the valuable class of organoalkali reagents to the already broad catalogue of substrates available for the transformation of propargylamines. In addition, comparison of anionic rearrangements within the propargylic system with analogous rearrangements in allylic complexes allows for a more total understanding of the anionic rearrangements which have already been characterised.

Results and discussion

Attempts at synthesising and characterising dilithiated species

Given the preference for terminal alkyne deprotonation over amine deprotonation, and based on the relative stability an alkynide anion versus an aza-enolate anion, it seems unlikely

that an anion rearrangement could be induced in lithium acetylide **21** in the same manner that they have been in analogous allylic systems. It was envisaged that a second deprotonation of the amino proton would allow an anion rearrangement to occur, with stabilisation of the secondary amide acting as a driving force and compensating for the loss of stability caused by the change in the terminal carbon from sp hybridisation to sp^2 hybridisation. The product of this rearrangement could be further stabilised by the formation of a metallocyclic structure like that seen in the dilithiated methallylamine derivative **11**.

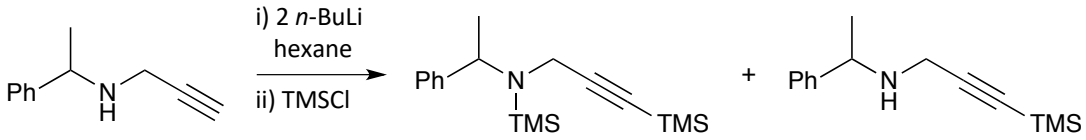


*Scheme 26: Sigmatropic rearrangements in **21** are unfavourable due to a change from sp to sp^2 hybridisation at the carbanion. These same rearrangements in the dilithiated derivative of **20** may be favourable due to an increase in stability at the amide through aza-enolate formation.*

Deprotonation of **20** with two equivalents of *n*-BuLi at low temperature immediately yielded a white solid, which was allowed to warm to room temperature, slowly turning to an orange colour. Washing this solid with hexane and drying it under vacuum yielded a yellow powder. ^{1}H NMR analysis of this powder in deuterated benzene was somewhat inconclusive, as only a range of broad signals appeared in the spectrum. This is similar to what was seen with the monolithiated derivative **21**, which gave a well resolved spectrum in deuterated THF, but only broad signals in benzene, presumably due to the formation of an array of oligomers in solution. Based on this, the yellow powder was analysed as a solution in d_8-THF. Surprisingly, despite complete solubility of the complex in THF, the ^{1}H NMR spectrum still showed only broad signals, suggesting either that THF is not a strong enough donor to prevent self-association of the complex, or perhaps that the π-system of the dianion is fluxional in solution. ^{13}C NMR is similarly uninformative, displaying a multitude of signals, many of which are broad and unresolved. Meanwhile ^{7}Li NMR in toluene shows a single broad singlet at 25 ˚C, which

broadens further upon cooling the solution to -60 ˚C, suggesting the presence of multiple lithium environments undergoing rapid exchange, though it is unclear how many exist, or what the individual environments may be. Thus, NMR spectroscopy proved to be an inadequate technique for characterisation of this complex.

Single crystal X-ray diffraction was the next choice for characterisation of the dilithiated complex, however repeated attempts to crystallise the complex from various solvents yielded only powder deposition, which NMR analysis showed to be the same composition as the crude product. Elemental analysis repeatedly failed to give consistent results due to the sensitivity of the complex. Quenching the complex with water or methanol yielded starting material **20**, as well as trace amounts of by-products (see below). Quenching the complex with trimethylsilylchloride (TMSCl) produced the terminally silylated alkyne *N*-(1-phenylethyl)-3-(trimethylsilyl)prop-2-yn-1-amine (**22**), and with sufficient heating, the bis-silylated compound *N*-(trimethylsilyl)-*N*-(1-phenylethyl)-3-(trimethylsilyl)prop-2-yn-1-amine (**23**) was also produced, evidence for a second deprotonation of the amine. This also suggested that no anion rearrangements were occurring in the dilithiated complex, or at least that the *N*,*C*-dilithiated complex was the predominant (or most reactive) species in an equilibrium.



20 **23** **22**

*Scheme 27: Dilithiation and trimethylsilylation of **20***

Speculating that the reason for the complexity of the NMR spectra was due to an equilibrium involving multiple species with different π-systems (for example, an allenic system), infrared spectroscopy was expected to be informative, as allenes have distinctive bands in their infrared spectra. The infrared spectrum of both the unmetallated amine **20**, and the monolithiated amine **21** showed no absorption bands corresponding to the alkyne triple bond (expected between 2250 and 2100 cm^{-1}), though the bands corresponding to the alkynyl proton at 3291 cm^{-1} (≡C-H stretch) and 624 cm^{-1} (≡C-H bend) which were present in **20** were absent in **21**. Therefore, the presence of an absorption band in the dilithiated complex at 1968 cm^{-1} suggested a change in the π-bond of the propargyl group.

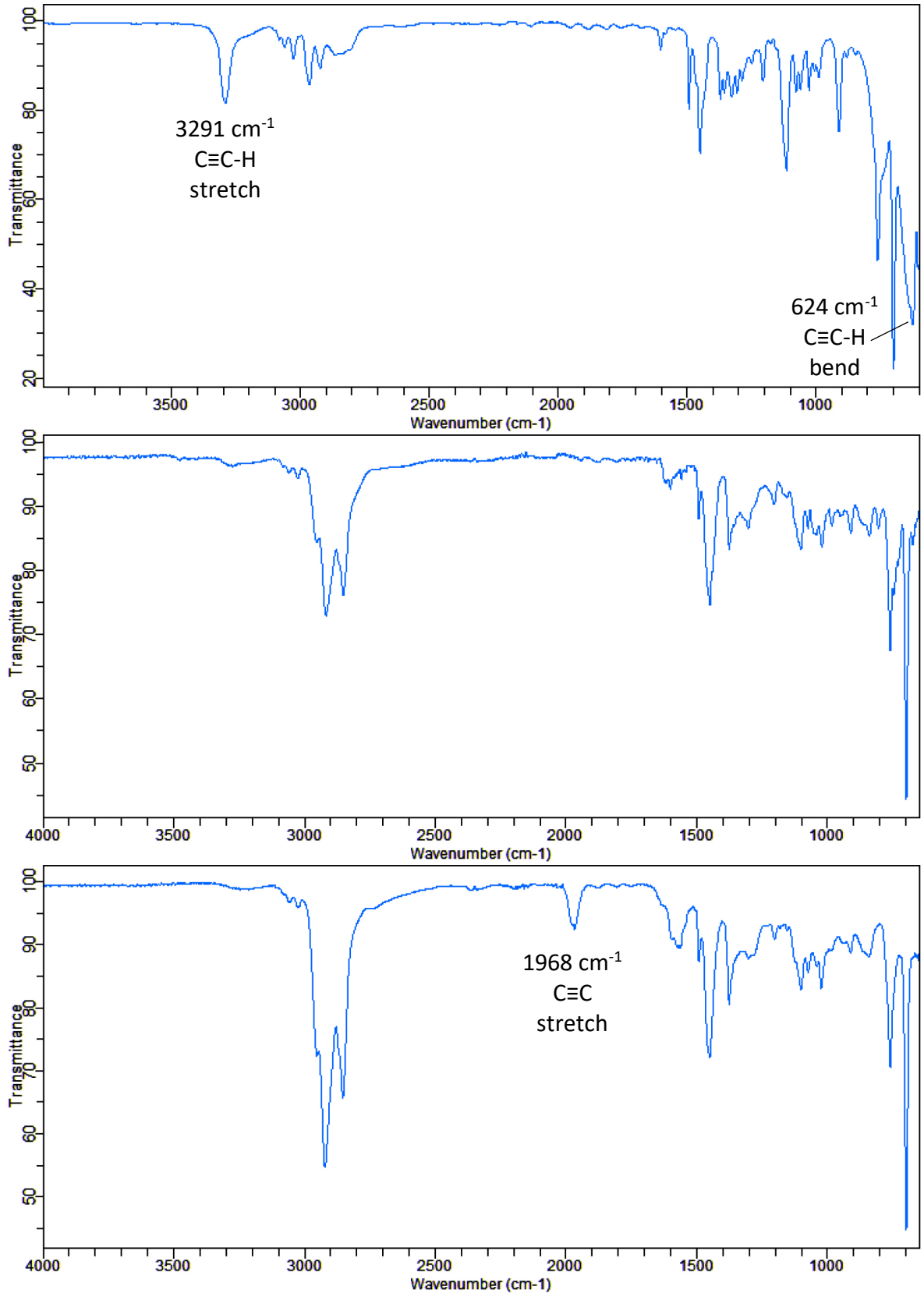


*Figure 9: Infrared spectra of propargyl amine **20** (top), monolithiated derivative **21** (middle), and the dilithiated derivative (bottom). The spectrum of **20** was recorded as a neat liquid, while the spectra of the lithiated compounds were recorded as a Nujol mull.*

Initially this band was believed to correspond to an allenic structure, as the infrared spectrum of allene (propadiene) has an absorption band at 1970 cm^{-1}. However, further research revealed that the infrared spectra of polylithiated alkynes and allenes are significantly affected by the substitution of protons for lithium.[27] This substitution of atoms causes a bathochromic shift in the stretching vibration of the C≡C or C=C=C bond by about 80-90 cm^{-1}, dubbed the "lithium effect". Therefore, the initial deprotonation of the alkyne to form **21** can be expected to cause a decrease in the stretching frequency of the triple bond by 80-90 cm^{-1}. While the absorption band for this vibration is not visible in the infrared spectrum, similar compounds reported in the literature exhibit stretches exclusively in the range 2120 to 2100 cm^{-1},[35–42] and it is assumed that **20** will also fall within this range. Applying the lithium effect to this value yields an expected frequency of approximately 2030 cm^{-1} for monolithiated **21**, while a second lithiation of the propargyl group could be expected to shift this further to the range of 1960 to 1930 cm^{-1}. Formation of a metallated allene would be expected to produce a significantly redshifted stretching band, with the lithium effect reducing the frequency from 1970 cm^{-1} to about 1890 cm^{-1}, and reducing it further in the case of a dilithiated species. Similarly, the propargylide structure (Figure 10) suggested by West would be further redshifted to below 1900 cm^{-1}. The observed vibration at 1968 cm^{-1}, representing a bathochromic shift of about 140 cm^{-1} from the expected vibration in the parent amine, is therefore believed to be caused by the lithium effect from terminal lithiation of the alkyne (a shift of 80-90 cm^{-1}), in conjunction with a second, lesser lithium effect from nitrogen lithiation (50-60 cm^{-1}), mitigated by the distance between the nitrogen and the alkyne bond. Based on this, the structure of the dilithiated propargylamine is expected to be that of **24**, with the π-system unchanged from that of either free amine **20**, or of monolithiated **21**.

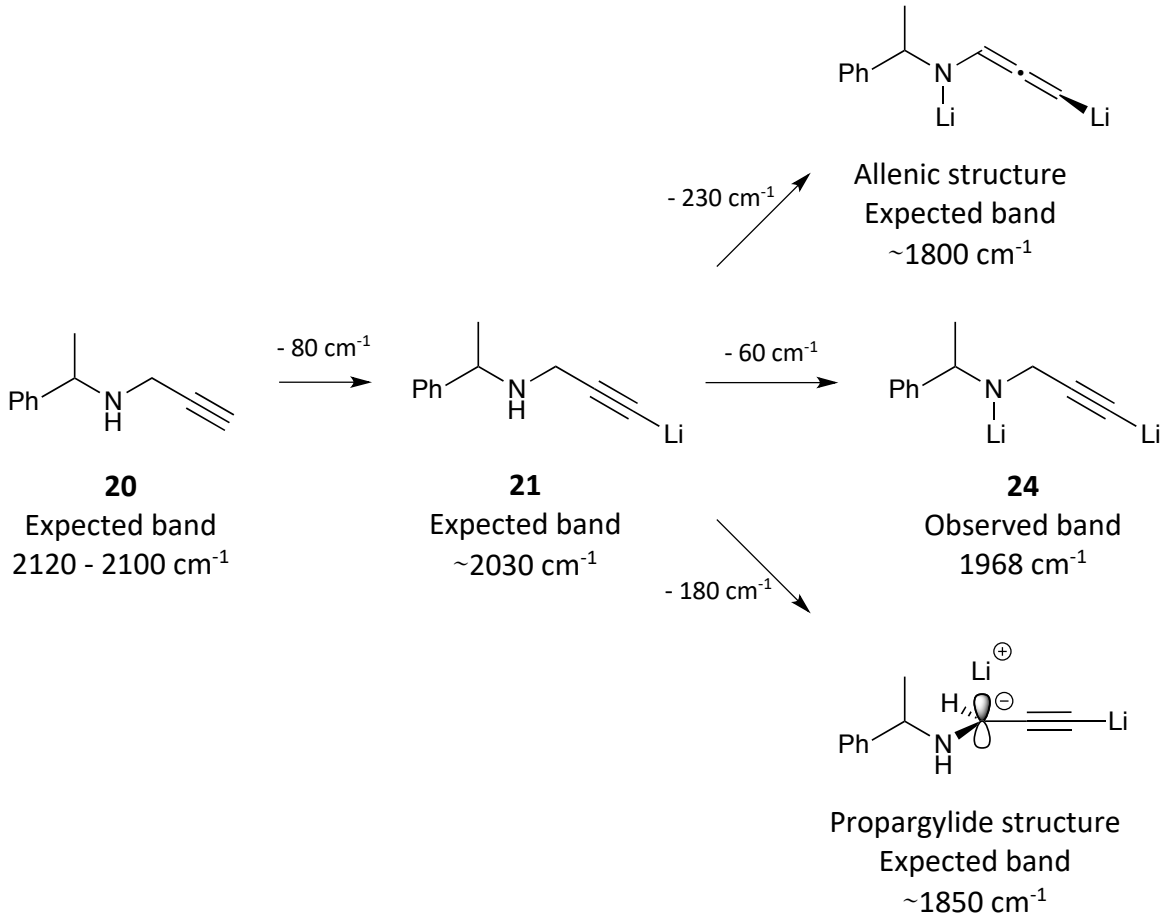


*Figure 10: Expected and observed infrared absorption bands for **20** and its lithiated derivatives. The allenic structure (top right) and propargylide structure (bottom right) do not match the observed infrared absorption band, so the structure of the dilithiated compound is assigned as **24**.*

The evidence that **24** exists as a propargylic amido dianion, and not as an allenic or propargylide structure leaves an unanswered question as to why the NMR spectra are so poorly resolved. An argument could be made that acetylides are prone to form strongly interacting aggregates, exemplified by the extremely low solubility of potassium, rubidium, and caesium carbide, even in liquid ammonia.[43] Additionally, the stability of copper acetylides is attributed to their tendency to form polymeric structures, which also leads to low solubility.[44] However, the ability to obtain a well resolved NMR spectrum of the lithium acetylide **21** in THF solvent shows that acetylide anions formed from this class of compound are not intrinsically insoluble. Therefore, it seems likely that interaction of the two different anionic sites with the two different lithium atoms increases the propensity of the dilithiated complex **24** to aggregate in solution. It is also possible there is in fact some degree of structural change occurring in solution, which is either not occurring in the solid state, so cannot be observed by solid-state infrared spectroscopy, or is occurring in small enough

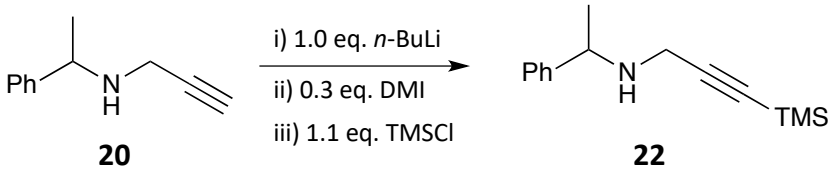
quantities that it is not apparent. In an attempt to probe this, the magnesium bromide analogue of the dilithium complex **24** was synthesised.

As described earlier, research within the Andrews group has correlated the separation of anion-cation pairs in alkali metal amides with their tendency to rearrange. Based on this, it seems likely that magnesium, which is less electropositive than the alkali metals, and forms bonds with less ionic (more covalent) character, would be less likely to promote rearrangements within a complex. This should reduce the complexity of the NMR spectra, if indeed the complexity is caused by flux within the π-system of the organic backbone. Deprotonation of **20** with two equivalents of phenylmagnesium bromide in THF yielded a pale-yellow solution, which was heated to produce a dark red solution. Filtration of this solution and storage at -18 ˚C produced a large crop of colourless cubic crystals. Single crystal X-ray diffraction revealed these crystals to be $MgBr_2{\cdot}THF_2$, evidence that a diorganomagnesium complex had been formed through the Schlenk equilibrium (Scheme 28). Attempts to crystallise this complex failed, and given the added complexity of multiple organomagnesium species existing, this approach was not pursued further.

Scheme 28: Proposed formation of a diorganomagnesium complex through the Schlenk equilibrium.

Terminal silylation and promotion of anion rearrangements

In light of the difficulties in characterising the dilithiated complex **24**, and with evidence suggesting that anion rearrangements would not be induced by the dilithiation of propargylamine **20**, the terminally silylated propargylamine **22** was investigated. It was anticipated that the presence of the trimethylsilyl group would increase solubility of the lithiated complex, while the absence of an anionic centre in the terminal position of the propargyl group should allow for anion rearrangements with greater facility. **22** can be synthesised in high yield from **20** by lithiation with one equivalent of *n*-BuLi in THF, followed by addition of 0.3 equivalents of 1,3-dimethyl-2-imidazolinone (DMI), and then 1.1 equivalents of TMSCl. This solution is refluxed, quenched with water, extracted with diethyl ether, and then distilled to yield a yellow oil with nearly quantitative conversion to **22**.

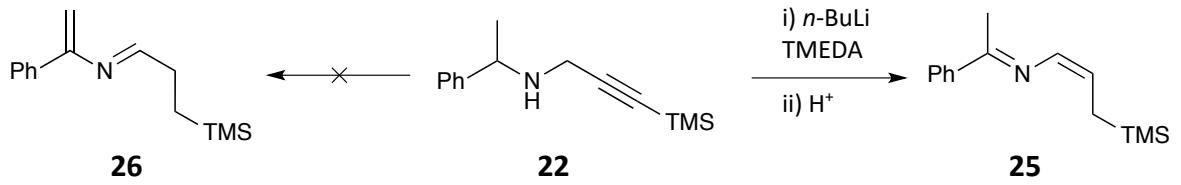


20 **22**

*Scheme 29: Synthesis of internal alkyne **22**.*

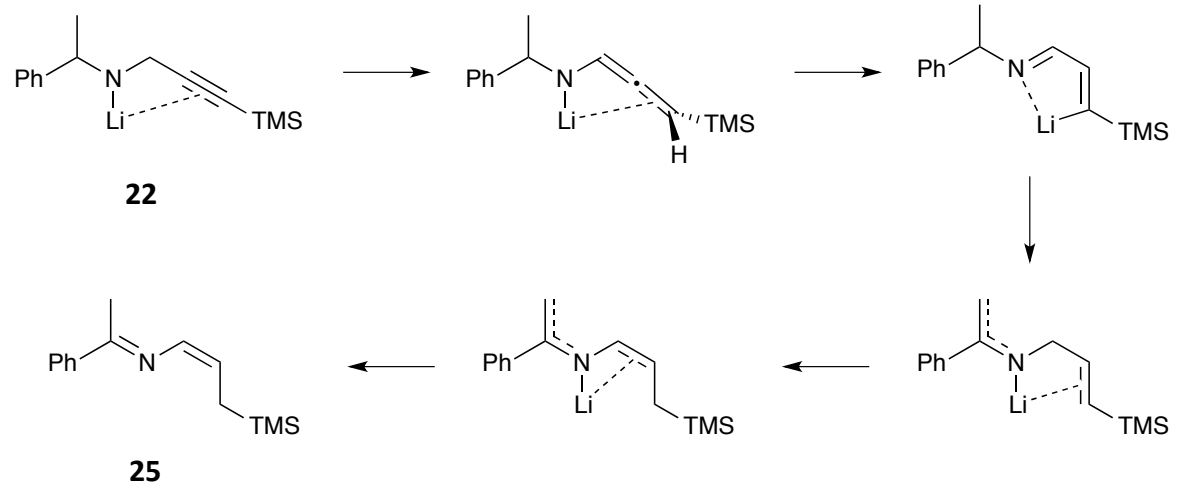
Metallation of **22** with *n*-BuLi in hexane at either 0 ˚C or -78 ˚C formed a yellow solution, which turned red upon standing at room temperature. Quenching this solution with saturated sodium bicarbonate solution, followed by an aqueous workup with diethyl ether yielded a yellow oil, which ^{1}H NMR analysis showed to be a complex mixture of products. Repeating the reaction in THF solvent yielded similar results, though the distribution of products was different. Importantly, some signals appeared between 5 and 7 ppm in the proton NMR, indicative of the formation of alkenes. This suggested that either a nucleophilic addition of *n*-BuLi across the triple bond was occurring, or that an anion rearrangement was being induced. Given the previously established relationship between coordination of the metal cation and the rate and extent of anion rearrangements, it could be expected that replacing THF as a Lewis donor with the bidentate donor TMEDA would accelerate any anion rearrangements.

Thus, metallation of **22** with *n*-BuLi in the presence of TMEDA rapidly forms a bright red solution, which gradually turns to a deep red colour when left stirring at room temperature. Quenching this solution with saturated sodium bicarbonate solution, and an aqueous workup with diethyl ether once again yielded a yellow oil. ^{1}H NMR analysis revealed this oil to consist mostly of one product, which could be identified as the rearrangement product 1-phenyl-*N*-((*Z*)-3-(trimethylsilyl)prop-1-en-1-yl)ethan-1-imine (**25,** Scheme 30). This product is analogous to the product of rearrangements induced in allylic systems, with migration of a π-bond from the unsaturated carbon chain through to the benzylamine moiety, resulting in an imine when quenched. **25** differs from the products of the allylic rearrangements however in that there is a second π-bond, which only migrates by one bond, to form an aza-diene system. The migration of the second π-bond is not unexpected: the resulting compound has a conjugated π-system involving the phenyl ring. The only other outcome which would achieve conjugation with both π-bonds is the formation of the isomer *N*-(1-phenylvinyl)-3-(trimethylsilyl)propan-1-imine (**26**). This isomer however contains a cross-conjugated system, in which the benzylic carbon is part of two π-systems which cannot fully interact with each other.[45] Therefore the formation **25** is expected to be more favourable than formation of **26**.



*Scheme 30: Sigmatropic rearrangement of **22** to form the conjugated imine **25**. The isomeric conjugated imine **26** is not formed, presumably due to the less favoured cross-conjugated system.*

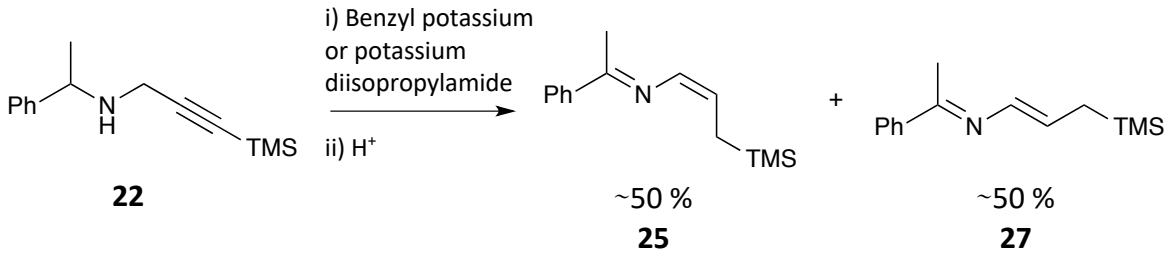
Interestingly, aza-diene **25** is formed nearly exclusively as the *cis*-isomer, as determined by proton NMR coupling constants compared with those in the *trans*-isomer (see below). This provides some insight into the mechanism of rearrangement, as alkenes are generally more stable in the *trans*-conformation due to steric repulsions. Therefore, preferential formation of the *cis*-isomer suggests that there is some conformational restriction in the transition states. Following deprotonation of the amine, interaction of the lithium cation to the π-electrons in the alkyne bond could form a pseudo-cyclic system through coordination. This cyclic conformation would encourage formation of the *cis*-isomer, as only a rearrangement to the *cis*-conformation can maintain these interactions (Scheme 31).



*Scheme 31: Proposed mechanism for the stereoselective sigmatropic rearrangement of **22** to give **25**.*

Based on the previously observed acceleration of anion rearrangements with heavier alkali metals,[46,47] it was expected that replacing lithium for potassium would hasten the rearrangement of propargylamine **22** into aza-diene **25**. Benzylpotassium, as well as potassium diisopropylamide (generated in situ from benzylpotassium) were reacted with **22** in hexane to attempt to induce this rearrangement. Using potassium bases, aza-diene **25** is produced, though the speed of the reaction was not dramatically changed from the reaction

with *n*-BuLi, and there are several by-products apparent in the reaction (see below). Most interestingly, the reaction with potassium no longer proceeds with *cis*-selectivity; instead a mixture of the *cis*-isomer **25** and the *trans*-isomer 1-phenyl-*N*-((*E*)-3-(trimethylsilyl)prop-1-en-1-yl)ethan-1-imine (**27**) was obtained upon quenching.



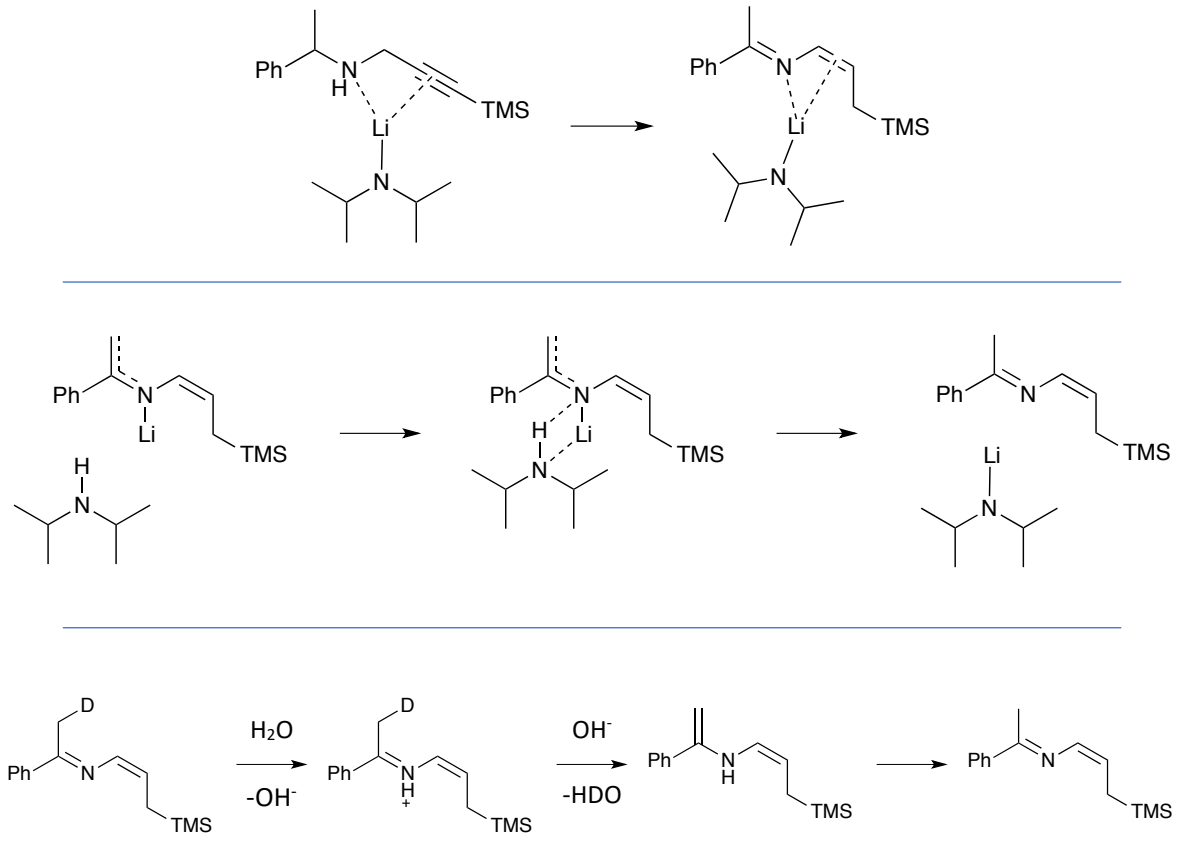
22 ~50 % **25** ~50 % **27**

*Scheme 32: Non-stereoselective sigmatropic rearrangement induced by potassium bases to yield a 50:50 mixture of cis- and trans- imines **25** and **27**.*

The ratio of the two isomers varies slightly depending on reaction conditions, but is consistently close to a 50:50 mixture. This suggests a change in the mechanism of rearrangement (or at least a change in the coordination of the transition states). This is perhaps due to the larger ionic radius of potassium when compared with lithium, leading to a less constrained intermediate in the rearrangement. Also of importance are the types of interactions which lithium and potassium tend to form: lithium is prone to interact strongly with hard Lewis donors such as oxygen and nitrogen atoms. Potassium, with its larger coordination sphere, has a tendency to interact with softer Lewis donors, such as π-electrons in aromatic rings and conjugated systems, as well as forming longer bonds due to the increased size of the ion. These combined factors mean that potassium may be able to stabilise the anionic charge of the intermediate without enforcing the same geometric constraints that lithium does. In this case, it is possible that moving to an even larger metal cation, such as rubidium or caesium, would further reduce the conformational restrictions in the transition states, and allow formation of the thermodynamically more favourable isomer. Changing the solvent system to prevent these interactions may also improve the yield of the *trans*-isomer **27**.

^{1}H NMR analysis of the product of reaction of propargylamine **22** with *n*-BuLi/TMEDA gave evidence for the formation of n-butyl group inclusion in the product (see below). Changing the base used to LDA/TMEDA at -78 ˚C, followed by warming to room temperature for four hours resulted in approximately 80 % conversion to the rearranged *cis*-aza-diene **25**, with only

trace amounts of by-products present. Quenching this reaction with D_2O, followed by the same workup procedure as before surprisingly yielded the same product, with only trace amounts of deuterium incorporation. It is possible that the isomerisation proceeds without deprotonation occurring, and coordination to the lithium cation in LDA is all that is required. It is also possible that the deprotonated complex is in equilibrium with diisopropylamide, and that the D_2O quench results in deuteration of diisopropylamine preferentially over deuteration of **25**. Given the high basicity of LDA, it seems most likely that deuterium incorporation is occurring, and then proton exchange occurs during the workup procedure, replacing the deuterium with protium.

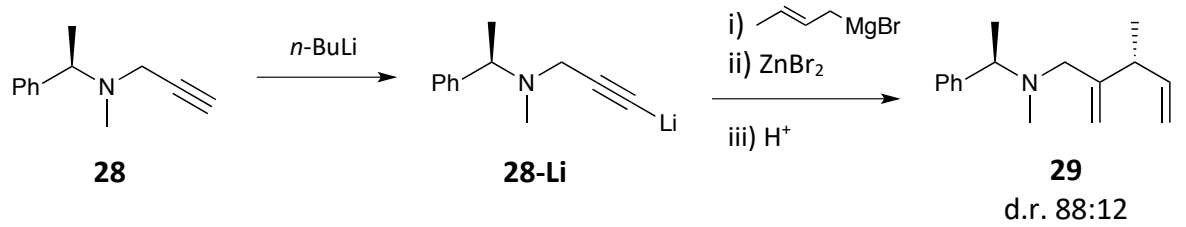


*Scheme 33: Proposed mechanisms for the lack of deuterium incorporation in **25**: coordination induced rearrangement (top), proton-lithium exchange with diisopropylamine (middle), and deuterium-protium exchange with water (bottom).*

Excess organometallic reagent and substitution of acetylene moiety

While attempting to induce anion rearrangements in propargylamines **20** and **22**, several by-products were repeatedly observed in the product mixtures. In reactions using *n*-BuLi, incorporation of an alkyl chain into the product was apparent. The most obvious reaction pathway for this to occur is addition of *n*-BuLi across the alkyne triple bond, analogous to the

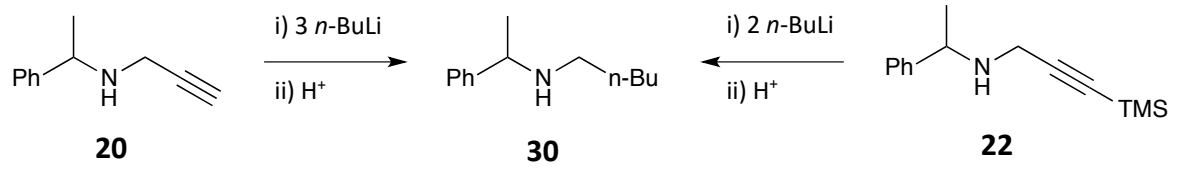
reported reaction of *N*-methyl-*N*-(1-phenylethyl)prop-2-yn-1-amine (**28**) (a tertiary amine analogue of propargylamine **20**) with *n*-BuLi followed by crotylmagnesium bromide and zinc bromide, to yield the substituted alkene *N*-methyl-*N*-(3-methyl-2-methylene-pent-4-enyl)-1-phenylethylamine (**29**).[17]



28 **28-Li** **29**
d.r. 88:12

*Scheme 34: Nucleophilic addition of crotylmagnesium bromide across the alkyne bond of **28** to yield **29**.*

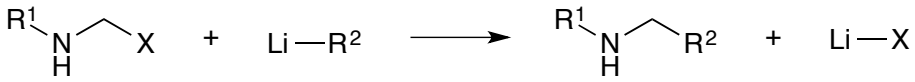
Analysis of the proton NMR spectra from reactions with **20** or **22** gave no indication of the presence of an alkene moiety within any of the products, suggesting that an addition across the alkyne bond was not occurring. By optimising the reaction conditions, the proportion of by-products could be increased, and it was found that addition of more than two equivalents of *n*-BuLi (or more than one equivalent in the case of **22**) and longer reaction times gave a higher yield of the alkyl chain bearing product. Thus, reaction at -78 ˚C of propargyl amine **20** or **22** with three or two equivalents of *n*-BuLi respectively, followed by warming to room temperature and stirring overnight gave, after an aqueous workup, a yellow oil which was identified as *N*-(1-phenylethyl)pentan-1-amine (**30**) by NMR spectroscopy and mass spectrometry.



20 **30** **22**

*Scheme 35: Conversion of propargylamines **20** and **22** into alkyl-substituted amine **30** by treatment with n-BuLi.*

The conversion of a three-carbon chain to a five-carbon chain from addition of *n*-BuLi is clearly not the result of an addition across the triple bond. Analysis of the literature shows some precedents for substitution reactions occurring with organolithium reagents of the type R^2Li to yield secondary amines of the form $R^1NHCH_2R^2$ (**31**).[48–52] These reactions show elimination of a leaving group as LiX, with "X" being replaced by the anionic part of the organolithium used to furnish the secondary amine.



31

*Scheme 36: Synthesis of methanediylamines **31** from secondary amines with leaving group X.*

Interestingly, the pK_a (and stability of the lithium salt) of each of the leaving groups does not correlate with the rate of elimination of the group. For example, the pK_a of the methoxide anion which is eliminated in the work by Barluenga[48–50] is 15.5, while the pK_a of the cyanide anion from the work of Overman[51] is 9.3. However, despite the much higher stability of the cyanide anion, the elimination of the methoxy group is far more rapid. Additionally, in the reactions reported by Overman, the replacement of the cyano group with the more basic benzotriazole or benzimidazole groups improves the yield, suggesting a more facile elimination. This shows that the stability of the leaving group does not entirely dictate its nucleofugality.

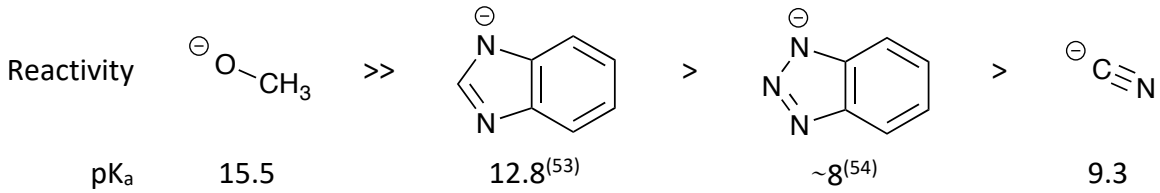
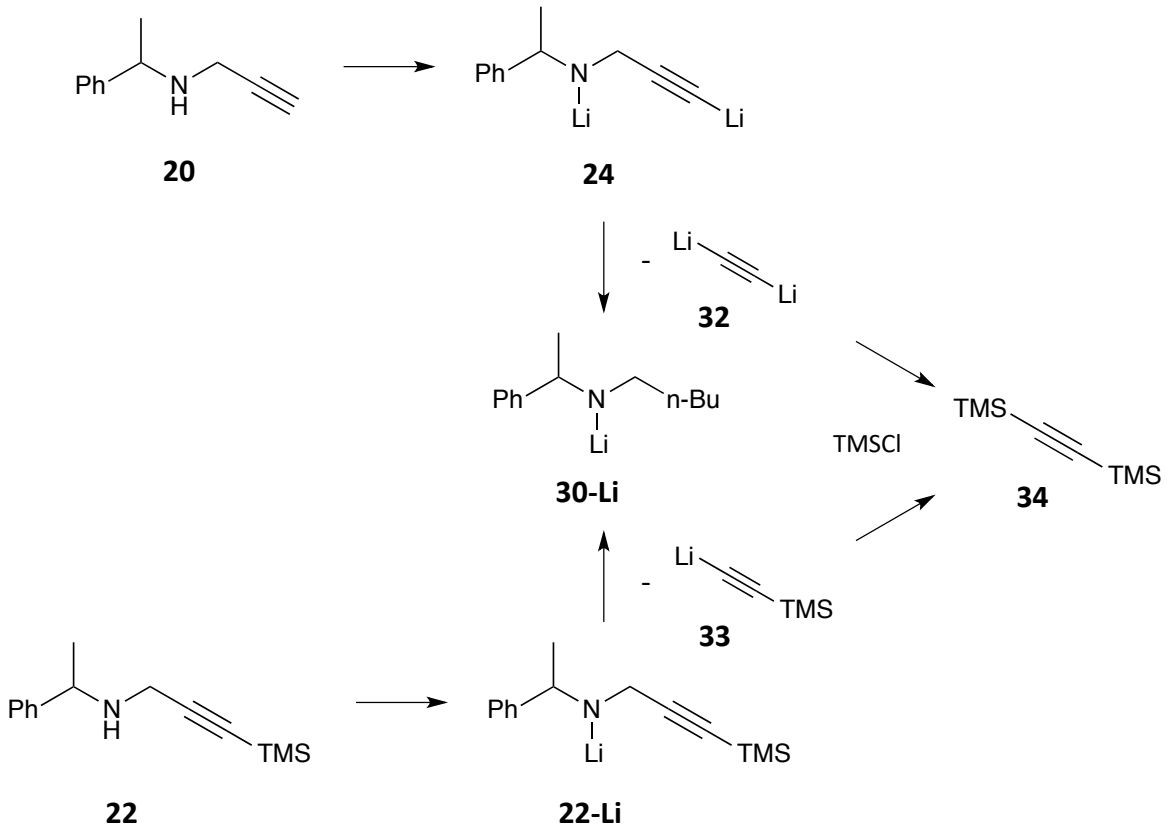


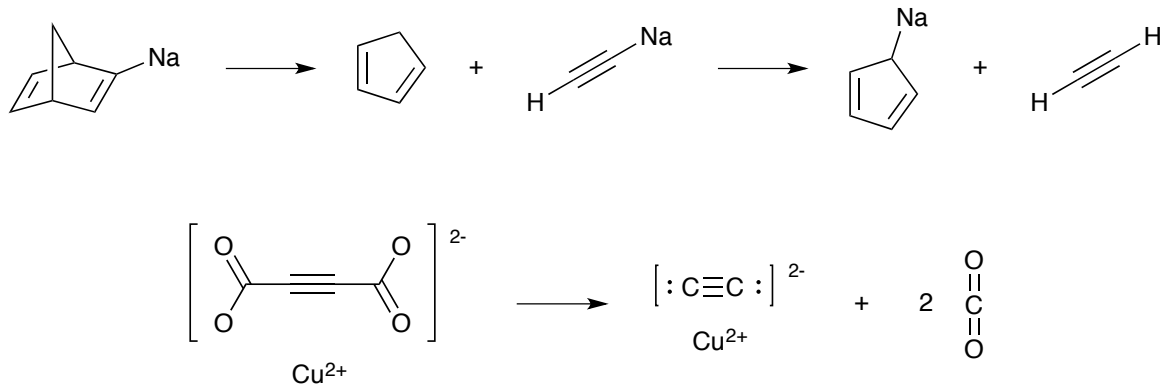
Figure 11: pK_a values and relative reactivities of leaving groups (X from Scheme 36).

This suggests that in the reaction of **20** with three equivalents of *n*-BuLi, lithium carbide (**32**) is eliminated as a by-product of formation of the lithiated amide **30-Li** (**22** reacts analogously with two equivalents of *n*-BuLi to yield ((trimethylsilyl)ethynyl)lithium (**33**)). Indeed, quenching either reaction mixture with TMSCl, and then an aqueous workup under mildly acidic conditions to remove the amine yields bis(trimethylsilyl)acetylene (**34**) as the exclusive product.



*Scheme 37: Formation of **30-Li** via elimination of lithium acetylides. These acetylides can be trapped with TMSCl to yield bis(trimethylsilyl)acetylene **34**.*

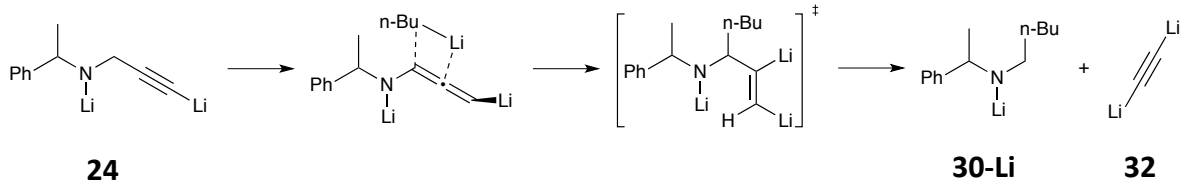
The elimination of lithium acetylides **32** and **33** provide one of the only examples of a metal acetylide acting as a leaving group from an organic molecule. The only other cases of metal acetylide formation reported in the literature are the production of sodium acetylide in a reverse-Diels-Alder reaction from norbornadiene,[55] and elimination of copper acetylide from the decarboxylative decomposition of copper acetylenedicarboxylate (Scheme 38).[56]



Scheme 38: Formation of metal acetylides through decomposition of metal complexes.

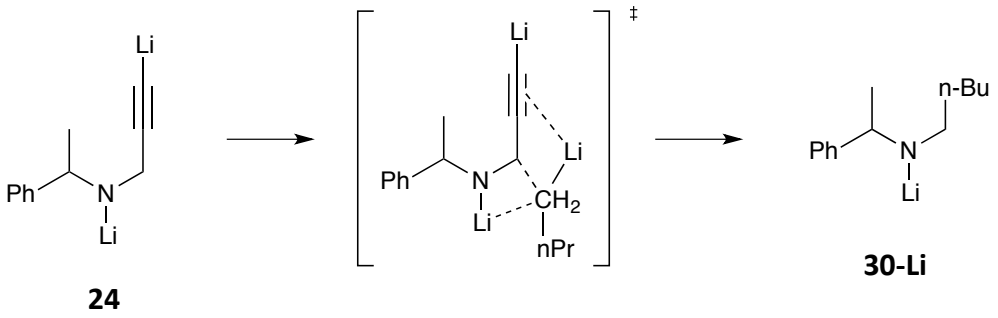
The acetylide anion would generally be considered too basic to constitute a good leaving group, thus it is of interest to determine the mechanistic driving force for this elimination. There are three general mechanisms which could explain this reaction: a nucleophilic addition followed by a β-elimination, a concerted substitution (S_N2 mechanism), or an elimination followed by nucleophilic addition of the organolithium reagent.

Nucleophilic addition preceding a β-elimination could occur if a sigmatropic rearrangement of the dilithiated complex **24** took place first to form for example an allene, which then inserts into the carbon-lithium bond (Scheme 39). As has been seen previously, the actual distribution of π-electrons within such a system may not be well defined, so the intermediate may exist as some hybrid of isomers. Despite no anion rearrangement being observed in **24**, this pathway cannot be ruled out, as the reactive isomer may exist in only small quantities, exist only in the solution state, or the rearrangement may be induced by the presence of a third equivalent of *n*-BuLi.



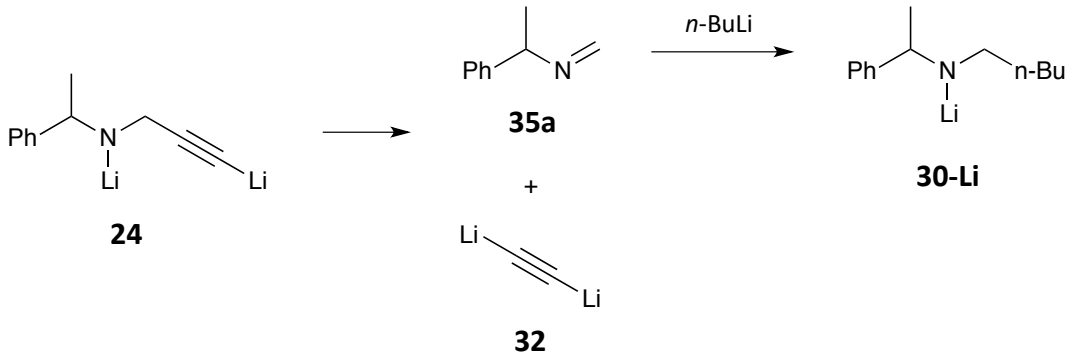
*Scheme 39: Proposed tandem addition/elimination pathway for decomposition of **24**.*

An S_N2 mechanism is plausible, as the substitution is occurring at a primary carbon, so steric hindrance is minimal. This mechanism explains why no decomposition of the dilithiated intermediate **24** is seen unless a nucleophile is present. This mechanism should see inversion of stereochemistry at the α-carbon, and in theory the reaction will not be restricted to secondary propargyl amines, but could work for other classes of compounds, such as ethers, thioethers, esters, and tertiary amines. However, it may be that the nitrogen-lithium bond is necessary for activation of the acetylide as a leaving group (see Scheme 51 below).



*Scheme 40: Proposed S_N2 mechanism for substitution of **24**.*

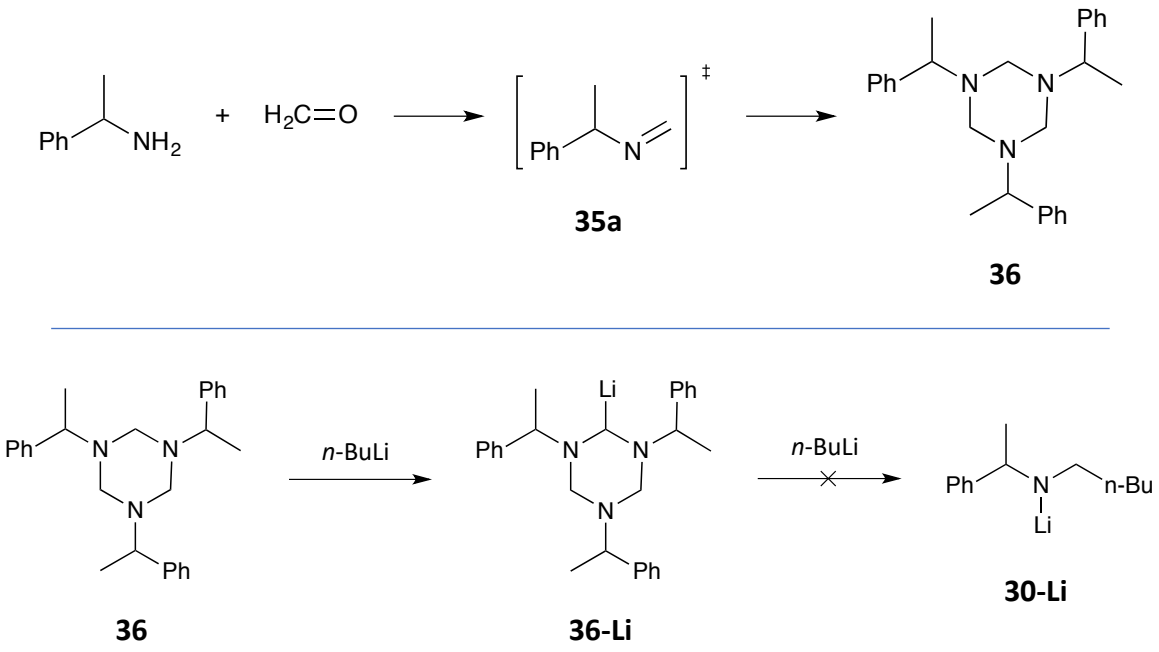
A β-elimination, followed by nucleophilic addition of the organolithium across the methanimine generated would also form the substitution product **30** (Scheme 41). This mechanism will be driven by increasing entropy upon cleavage of the propargyl group, so elevated temperatures would favour this reaction.



*Scheme 41: Proposed mechanism for elimination/addition pathway for decomposition of **24**.*

All of the aforementioned analogous studies suggest that the reaction proceeds via elimination of LiX to yield an *N*-substituted methanimine (**35**), which then inserts into the carbon-lithium bond of an organolithium to yield the lithiated secondary amide **31-Li** (Scheme 36, R^1 = $PhC(CH_3)H$). This reaction mechanism requires the spontaneous elimination of lithium carbide from the dilithiated intermediate **24** to generate *N*-(1-phenylethyl)methanimine (**35a**). While the formation of insoluble lithium carbide could be expected to drive the equilibrium towards production of methanimine **35a**, the elimination of ((trimethylsilyl)ethynyl)lithium **33** from protected propargylamine **22** proceeds at a similar rate in diethyl ether, a solvent in which the lithium acetylide is soluble in. Furthermore, the attempted synthesis of **35a** from 1-phenylethylamine and formaldehyde results exclusively in formation 1,3,5-tris(1-phenylethyl)-1,3,5-triazinane (**36**), as the methanimine intermediate cyclises as soon as it is formed. The cyclic trimer **36** does not react analogously to

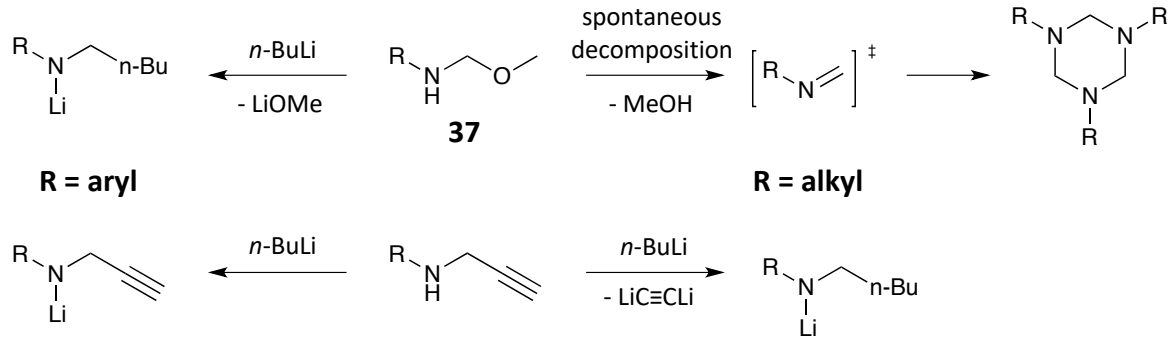
methanimine **35a**, and reactions with related triazinanes have shown that only a single deprotonation at one of the CH_2 positions occurs when reacted with *n*-BuLi.[57] Even heating **36** with three equivalents of *n*-BuLi in THF gave only starting material when the reaction was quenched. None of the reactions of propargylamines **20** or **22** showed even traces of formation of the triazinane **36**, while the dilithiated propargylamine **24** was stable at room temperature for long periods of time, and showed no evidence of decomposition to methanimine **35a** or the trimerised derivative **36**.



*Scheme 42: Trimerisation of unstable methanimine **35a** synthesised from 1-phenylethylamine and formaldehyde (top). This cyclic triamine is deprotonated by n-BuLi, but no addition to form **30-Li** occurs (bottom).*

Of the literature reports proposing this mechanism, none of the authors characterised the metallated intermediates, and only the studies by Barluenga provided any evidence of the formation of methanimines as intermediates.[49] The formation of these imines was inferred by the isolation of triazinanes upon heating the *N*-(methylmethoxy)amine precursors (**37**). Interestingly, *N*-(methylmethoxy)amines with alkyl substituents were found by Barluenga to decompose by β-elimination to form triazinanes too quickly to be able to be isolated or used in synthesis. This pattern of reactivity is reflected in the reactions of propargylamines, where the reactivity of *N*-propargylaniline (**38**) is much lower than the alkyl equivalents: reaction of *N*-propargylaniline with three equivalents of *n*-BuLi only returns starting material when quenched, even after refluxing in THF. This was reasoned by Barluenga to be due to the

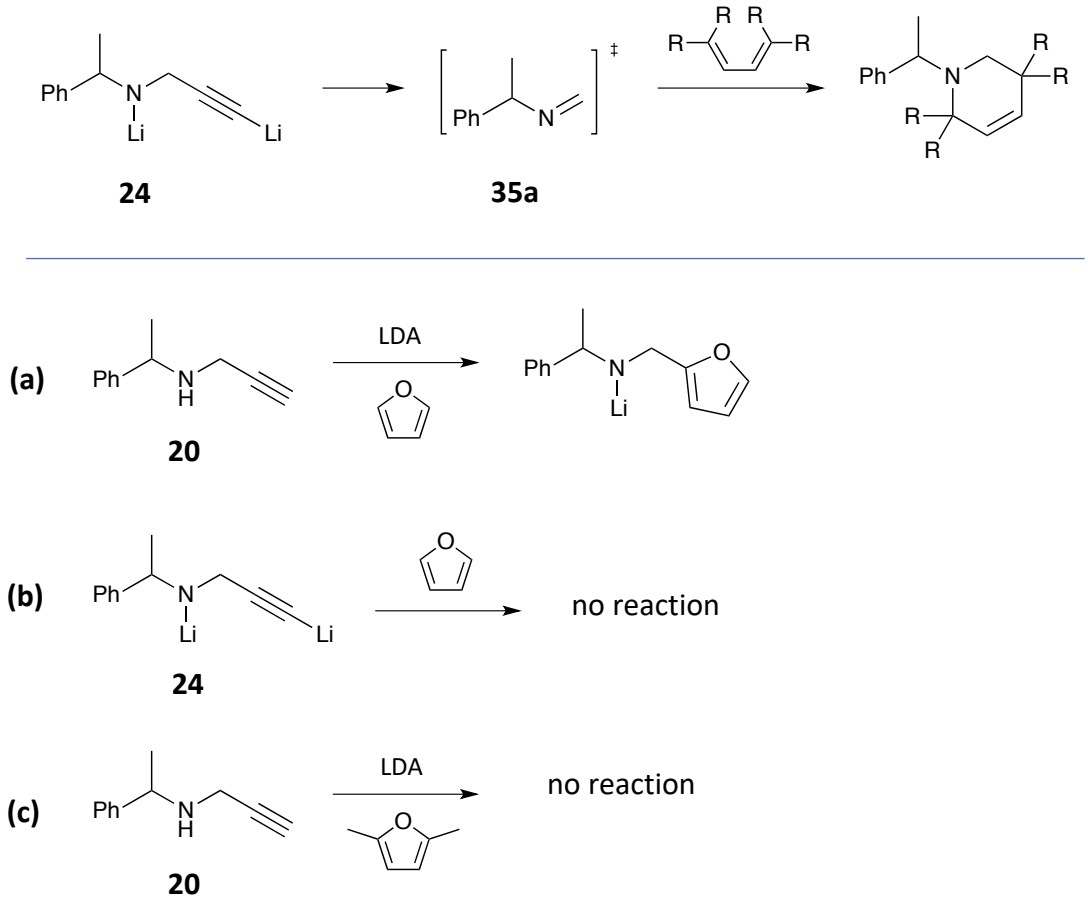
increased nitrogen basicity of the alkyl substituted amines compared with the aryl substituted *N*-(methylmethoxy)amines.[49]



Scheme 43: Comparison of the reactivity of N-methylmethoxy- and propargylamines.

Attempts to trap imine intermediate

In an attempt to prove the existence of methanimine **35a** as an intermediate in the conversion of propargylamines into secondary methanediylamines **31** (Scheme 36, page 58), several reactions were carried out to try to capture the methanimine fragment. Unfortunately, the range of reactions which can be used for this task are limited, as many classes of compounds which will react with the imine bond are nucleophilic, and hence may substitute the acetylide group regardless of the substitution mechanism. Alternatively, other reagents are sensitive to the organolithium compounds used to generate the reactive intermediate in the first place. Thus, a Diels-Alder reaction was attempted, as dienes are sufficiently robust to tolerate the highly basic and nucleophilic compounds in the reaction, yet not nucleophilic enough themselves to react in a substitution reaction with the propargylamine. Initially furan was used as a diene, and the dilithiated propargylamide **24** generated in situ using LDA, however furan proved to be acidic enough to be deprotonated by LDA, and the furyllithium generated interfered with the reaction by substituting the alkyne. Synthesising and isolating **24**, followed by addition of furan prevented these problems, but no reaction was observed, even upon heating the reaction mixture to reflux in THF. Furan was substituted for 2,5-dimethylfuran in order to prevent the possibility of deprotonation of the diene, yet still reaction of propargylamine **20** with three equivalents of LDA in the presence of 2,5-dimethylfuran gave no reaction.



*Scheme 44: Planned Diels-Alder reaction to trap methanimine intermediate (top). Reactions with furan and LDA (a), furan and the dilithiated complex **24** (b), and dimethylfuran and LDA (c) all failed to yield a Diels-Alder-type product.*

Due to the lack of reactivity of **24** with dienes, a stable methanimine was synthesised to test if the N=CH_2 moiety would be reactive in Diels-Alder reactions. It has been reported previously that sterically hindered amines can undergo condensation with formaldehyde to yield methanimines which do not trimerise: *N*-*tert*-butylmethanimine forms an equilibrium between methanimine **35b** and the corresponding triazinane, while *tert*-octyl- (**35c**), adamantyl- (**35d**), 2-methyl-1-phenylpropan-2- (**35e**), and 1-(4-chlorophenyl)-2-methylpropan-2-amine (**35f**) gave monomeric methanimines.[58]

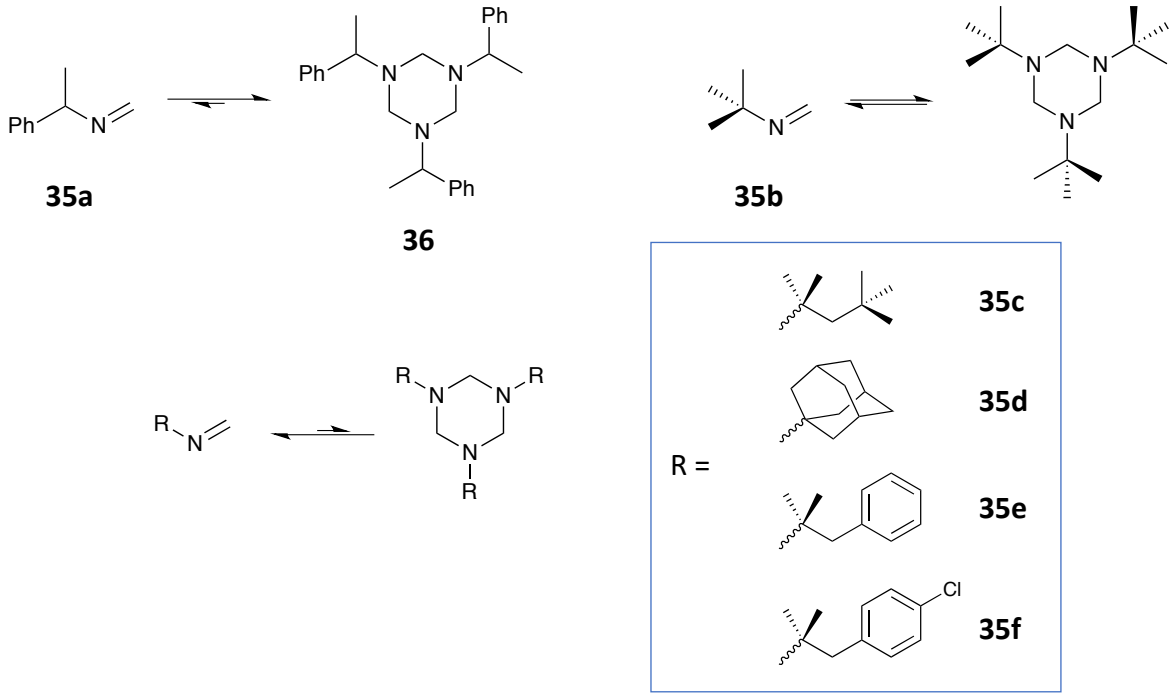
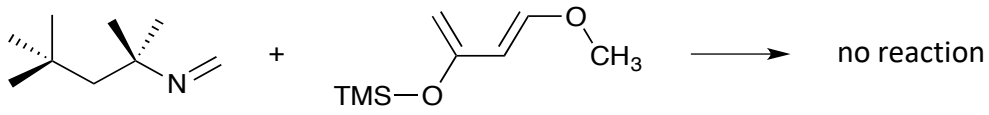


Figure 12: Increasing the steric demands of the N-substituent on methanimines makes trimerisation less favourable.[58]

Therefore *tert*-octylmethanimine was synthesised by reaction of *tert*-octylamine and paraformaldehyde in methanol in a microwave vessel, using 3 Å molecular sieves as a desiccant. **35c** was reacted with furan under various conditions, but even with vigorous heating, no reaction was observed. The more reactive diene (*E*)-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene, **39**) was then used, and although Danishefsky's diene is known to be reactive in aza-Diels-Alder reactions, no formation of the Diels-Alder product was observed in the reaction with **35c**. It is unclear whether this is due to the steric bulk of the *tert*-octyl group, or whether all methanimines are unreactive in Diels-Alder reactions.

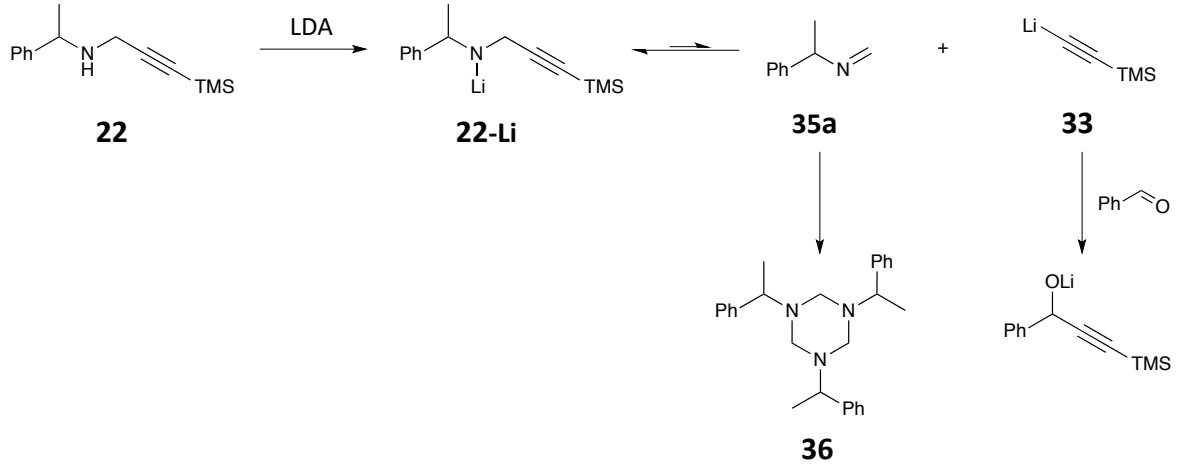


35c **39**

*Scheme 45: The isolated methanimine **35c** failed to react with even activated dienes such as **39**.*

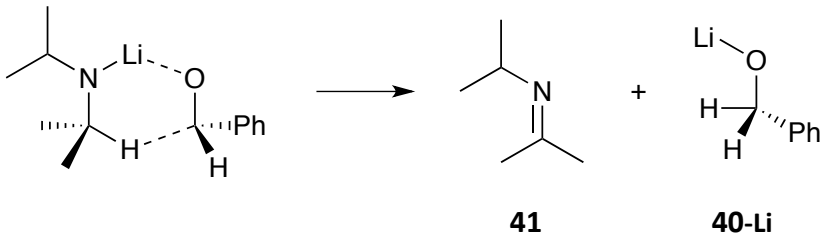
As the imine fragment of the decomposition was unable to be trapped, a reaction was attempted to instead trap the lithium acetylide without a nucleophile attacking the imine. It was expected that reaction of the TMS-substituted propargylamine **22** with LDA in the presence of benzaldehyde would form the lithium amide **22-Li**, which would then eliminate

(trimethylsilyl)ethynyllithium **33**. The nucleophilic acetylide produced should react with benzaldehyde irreversibly, driving the equilibrium between lithium amide **22-Li** and methanimine **35a** towards formation of the methanimine, which would then presumably trimerise to form triazinane **36**.



*Scheme 46: Proposed reaction to trap decomposition intermediate **35a**.*

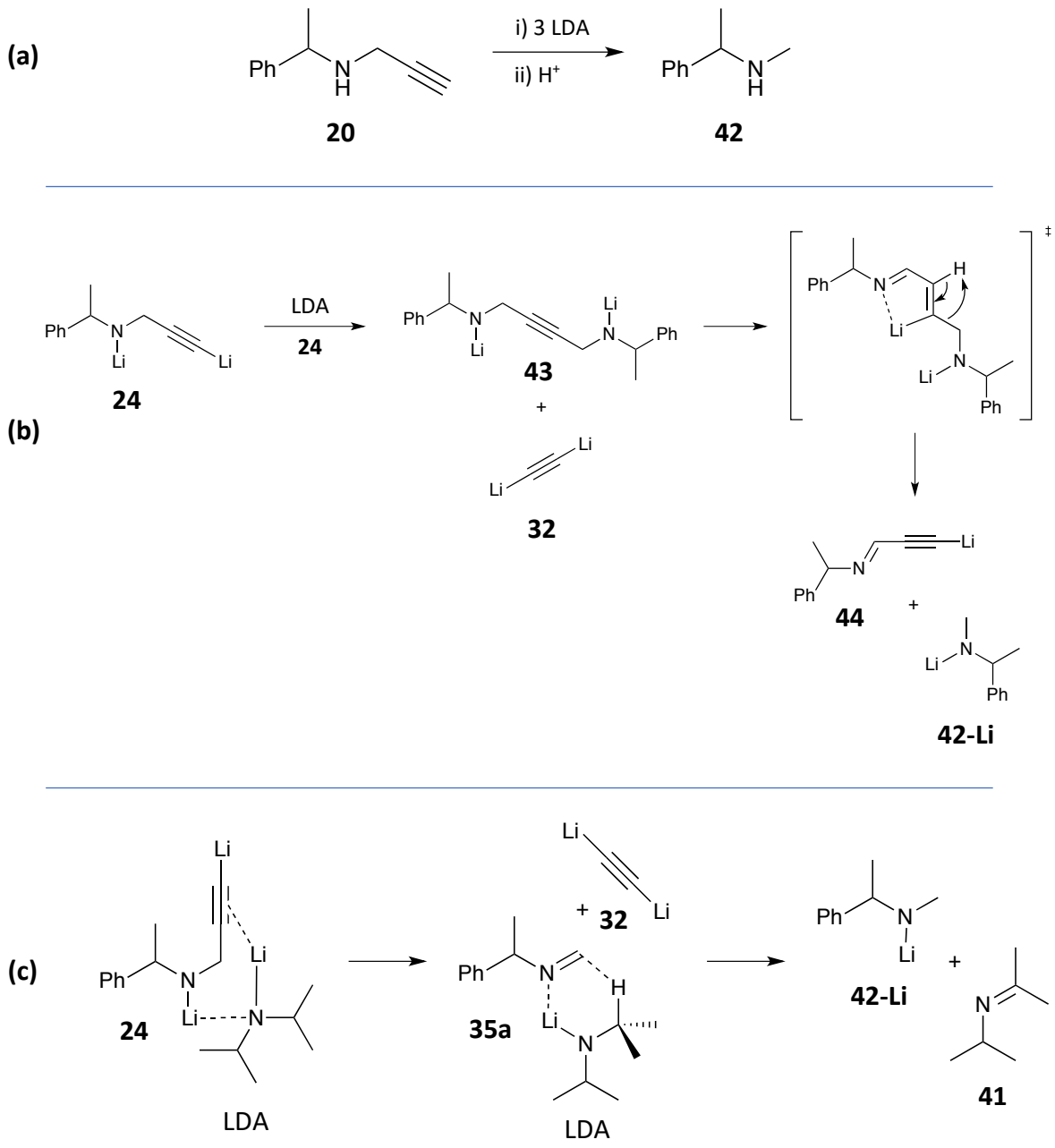
Unexpectedly, after quenching the reaction and performing an aqueous workup, **22** was recovered unchanged. Analysis of the reaction product showed exclusively the presence of propargylamine **22** and benzyl alcohol (**40**). The reaction of benzaldehyde with LDA has been documented to produce lithium benzyloxide by reduction of benzaldehyde, and concomitant oxidation of LDA to *N*-isopropylpropan-2-imine (**41**).[59] This reaction proceeds rapidly at low temperature, and so will easily outcompete the decomposition of the lithiated amide **22-Li**.



Scheme 47: Reduction of benzaldehyde by LDA.[59]

The reaction of propargylamine **20** with three equivalents of LDA was assessed, with the expectation that an intermediate involved in the elimination of lithium carbide, or a decomposition product of an intermediate would be obtained. After quenching the reaction, and performing an aqueous workup, a mixture of products was obtained, the majority of which consisted of *N*-methyl-1-phenylethylamine (**42**) (Scheme 48a). This product had been previously observed as a minor by-product in the reaction of **20** with *n*-BuLi, and was

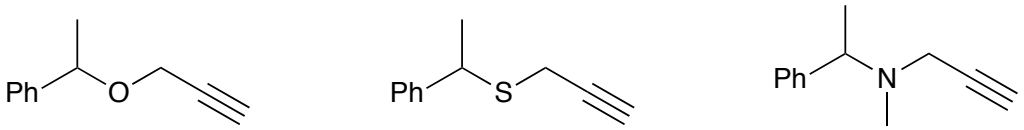
presumed to be the product of reaction with some lithium hydride contaminant, however the production of **42** when using phenyllithium, as well being the major product in 41 % yield when using LDA shows that lithium hydride is not the source of this product. Instead, it is hypothesised that two molecules of **24** react with each other, where one lithium acetylide attacks the other at the α-position of the propargyl group to yield the intermediate lithium but-2-yne-1,4-diylbis((1-phenylethyl)amide) (**43**). **43** then presumably undergoes a sigmatropic rearrangement, followed by a decomposition to yield **42-Li** and an unsaturated fragment such as (3-((1-phenylethyl)imino)prop-1-yn-1-yl)lithium (**44**) (Scheme 48b). Though this other fragment has not been detected, the overall reduction of **20** to form **42** implies oxidation of another reaction component. In agreement with this hypothesis, the protected alkyne **22**, which cannot form a nucleophilic acetylide, does not form any quantity of the decomposition product **42** when reacted with LDA. Alternatively, a reaction mechanism proceeding via methanimine intermediate **35a**, with subsequent reduction by LDA as is seen with benzaldehyde could occur, producing *N*-isopropylpropan-2-imine **41** (Scheme 48c). The use of the internal alkyne **22** may not react in this case due to a competing anion rearrangement. This reaction pathway does not however explain the formation of **42** when using phenyllithium.



*Scheme 48: Decomposition of propargylamine **20** in the presence of LDA to yield N-methyl-1-phenylethylamine **42** after hydrolysis (a). Two mechanisms are proposed for this process: a self-reaction of dilithiated amide **24**, followed by a sigmatropic rearrangement and decomposition to **42-Li** (b); and a reduction of methanimine intermediate **35a** by LDA to yield **42-Li** and **41** (c).*

Attempts to prove the existence of a methanimine intermediate had produced inconclusive results. To investigate the potential of an S_N2 reaction taking place, the related complexes (1-phenylethyl)prop-2-yn-1-ylether (**45**), (1-phenylethyl)prop-2-yn-1-ylthioether (**46**), and *N*-methyl-*N*-(1-phenylethyl)prop-2-yn-1-amine (**28**) were synthesised and their reactivity with *n*-BuLi assessed. Both oxygen and sulfur are isoelectronic to a nitrogen anion, so the reactivity of **45** and **46** should be somewhat similar to that of the analogous propargylamine **20**. None

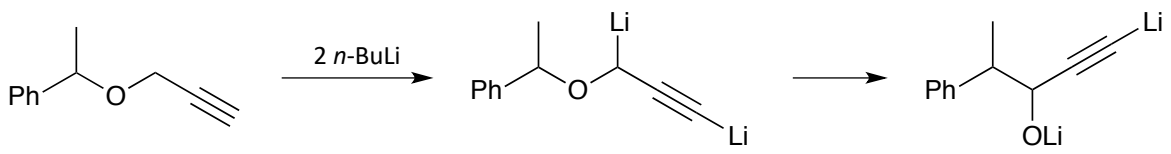
of these three analogues however can support the formation of a double bond which accompanies the elimination mechanism, without forming a cationic intermediate. Therefore, the substitution reaction is unlikely to proceed with these compounds if the reaction mechanism involves a β-elimination as the first step.



45 **46** **28**

*Figure 13: Analogues of propargylamine **20** to be tested in reactions with n-BuLi.*

Reaction of **45** with three equivalents of *n*-BuLi in diethyl ether at room temperature formed a dark brown solution, which was left stirring at room temperature before being quenched with 1 M hydrochloric acid. The product was extracted with diethyl ether, yielding a brown oil consisting primarily of 4-phenylpent-1-yn-3-ol (**47**). **47** is the product of a [1,2]-Wittig rearrangement of **45**, following lithiation of the α-carbon of the propargyl group. A mixture of (*S*,*R*) and (*S*,*S*) diastereomers was produced, with negligible diastereomeric excess observed. This outcome shows that the enhanced stabilisation of a carbanion by oxygen compared with nitrogen, and/or the lack of an acidic amine proton leads to deprotonation of the α-carbon in preference to any substitution or elimination that may be induced. This leads to a facile [1,2]-Wittig rearrangement, cleaving the benzylic carbon-oxygen bond, and forming a new carbon-carbon bond between the benzylic and anionic α-carbon atoms. While this shows that the [1,2]-Wittig rearrangement pathway dominates over any other reactions under these conditions, it does not exclude the possibility of an S_N2 reaction occurring in **45** under the right conditions.



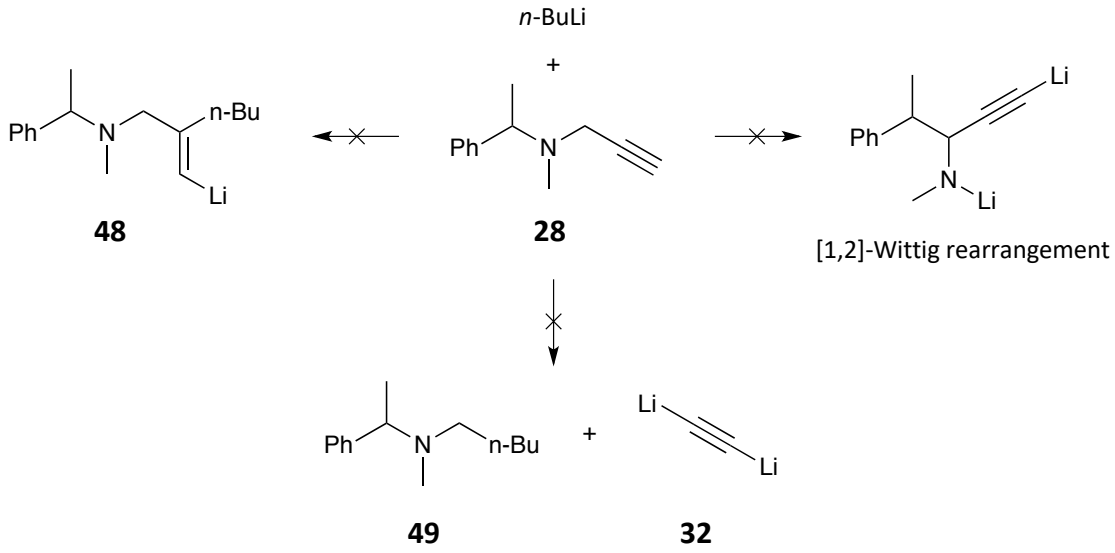
45 **45-Li_2** **47-Li_2**

*Scheme 49: [1,2]-Wittig rearrangement of dilithiated propargyl ether **45** to yield **47-Li_2** as a mixture of diastereomers.*

The reactivity of **46** with *n*-BuLi was evaluated next. The diagonal relationship of sulfur with nitrogen was expected to make the reactivity of thioester **46** more similar to that of

propargylamine **20**. However, reaction of **46** with three equivalents of *n*-BuLi resulted in a complex mixture of species upon quenching which could not be resolved. The acidities of α-carbons in sulfur compounds are known to be generally higher than those in the analogous oxygen compounds,[60] so it is expected that the same initial deprotonation that was seen in ether **45** would occur in thioether **46**. Whether or not the same [1,2]-Wittig rearrangement would occur is unclear, though given the lower bond dissociation energy for carbon-sulfur bonds compared with carbon-oxygen bonds, it is likely that it could. Given that **46** is likely more acidic than **45**, it may be that the reaction needed to be conducted at a lower temperature to prevent very rapid competing reactions.

The reaction of tertiary amine **28** with *n*-BuLi was then investigated, to see if the lithium-nitrogen bond was essential in the conversion of the propargyl group to a pentyl chain. As mentioned above, the reaction of **28** with one equivalent of *n*-BuLi to form the carbanionic species **28-Li**, followed by reaction with crotylmagnesium bromide and zinc bromide was reported to yield the carbometallation product **29** (Scheme 34, page 57). Thus, it was expected that reaction of **28** with three equivalents of *n*-BuLi would yield the analogous butyl addition product to yield (2-((methyl(1-phenylethyl)amino)methyl)hex-1-en-1-yl)lithium (**48**) (Scheme 50). Instead, the reaction produced a mixture of compounds which could not be identified. There was however no evidence of the formation of **48**, or of the product of a [1,2]-Wittig rearrangement analogous to **47**. A substitution of the alkyne to form *N*-methyl-*N*-(1-phenylethyl)pentan-1-amine (**49**) was also not observed, indicating that either the formation of a lithium-nitrogen bond activates the alkyne as a leaving group, or that the methyl substitution of the amine blocks the formation of the methanimine intermediate **35a**.



*Scheme 50: N-methylated propargylamine **28** reacts with n-BuLi, but the reaction product could not be identified. The expected outcomes, carbometallation (left), [1,2]-Wittig rearrangement (right), and substitution (bottom) could be ruled out as reaction products.*

N-(1-phenylethyl)prop-2-yn-1-amine **20** was then reacted with an excess of LDA in a sealed NMR tube under inert atmosphere, in an attempt to observe any intermediate(s) in the reaction. Immediately after addition of **20** to LDA in benzene, broad signals similar to those seen when attempting to characterise the dilithiated amide **24** were seen. Over the course of several hours however, signals corresponding to the formation of methanimine **35a** were observed, characterised by two doublets centred at 6.88 ppm. These doublets have a coupling constant of 17.1 Hz, typical of the ^{2}J coupling present in the methylene group in methanimines.

After several days in solution, the signals corresponding to **35a** disappear, and are replaced by a set of signals which have been attributed to the propargyl-substitution product **43** (Figure 15). These signals are very similar to those observed for **20** in benzene, however in the ^{13}C NMR spectrum, there is only one signal at 81.8 ppm from the alkyne group, compared with two signals at 82.8 and 71.3 ppm observed in **20**, suggesting a symmetrical alkyne has formed. Additionally, the signal in the ^{1}H NMR spectrum at 3.95 ppm is actually two signals at the same chemical shift, as can be seen by the change in apparent multiplicity when the spectrum is recorded at a different frequency. These two nearly identical signals are due to the formation of diastereomers resulting from the use of racemic **20**.

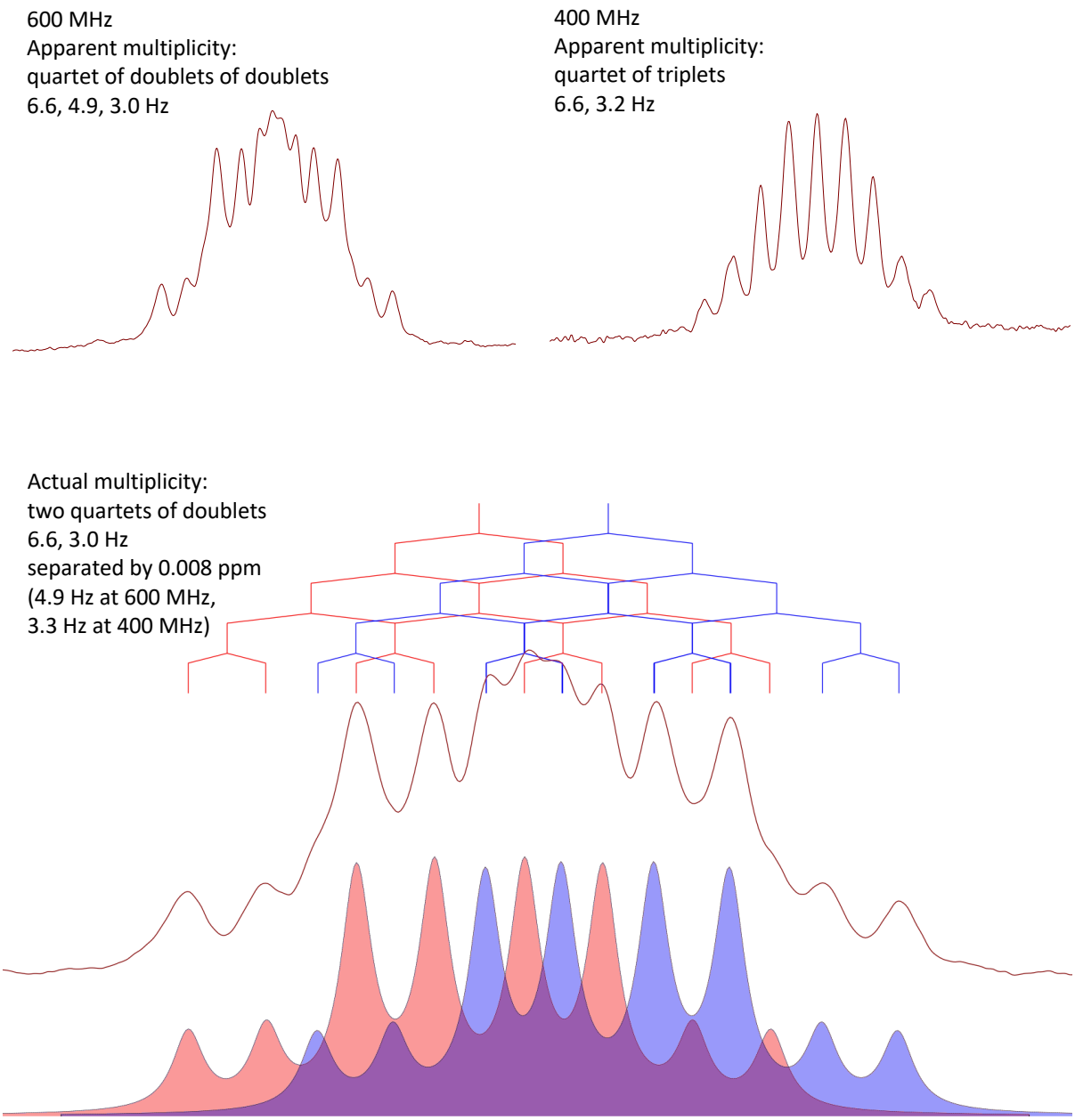


*Figure 14: ^{1}H NMR spectra of the reaction of propargylamine **20** with LDA. The spectra were recorded on spectrometers running at different frequencies from the same sample, and show that what appears to be a small coupling constant is actually two signals overlapping very closely. This type of signal is characteristic of diastereomeric compounds due to the very similar chemical properties of the diastereomers.*

Finally, the signals present at 3.28 and 3.16 ppm in the proton NMR spectrum, corresponding to the protons of the α-carbon, display a much higher degree of multiplicity than those of **20**, consistent with additional ^{5}J coupling across the triple bond which could be expected from the symmetrical alkyne **43**, as well as extra complexity arising from a mixture of diastereomers.

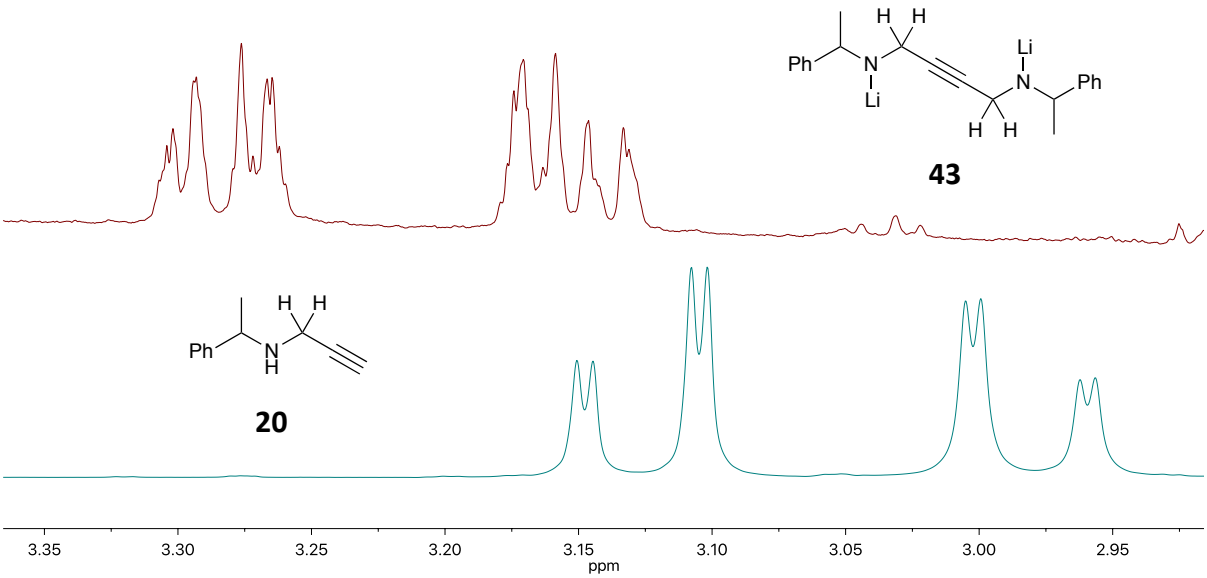


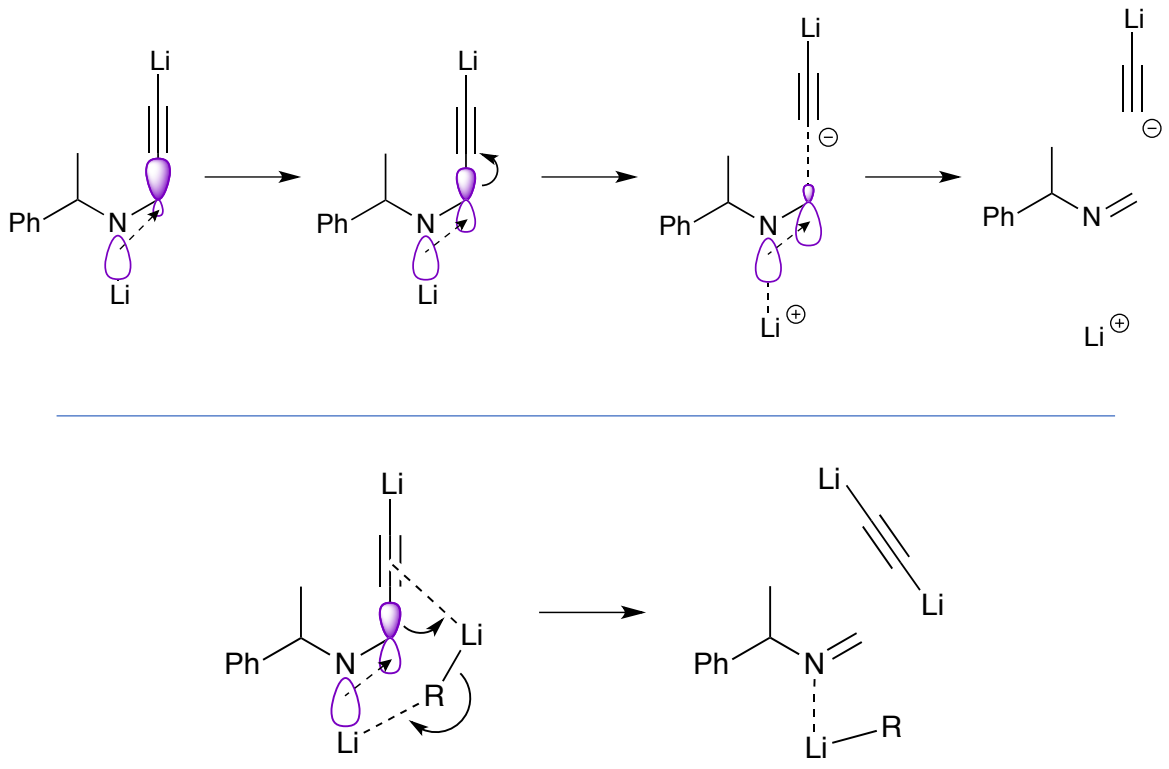
*Figure 15: ^{1}H NMR spectra of the reaction of **20** with LDA (top), and of **20** in C_6D_6 (bottom), showing the increased multiplicities of the α-propargylic proton signals in the product assigned as **43** due to ^{5}J coupling.*

Interestingly, despite the formation of *N*-(1-phenylethyl)methanimine **35a** and apparent formation of **43** in the reaction mixture, quenching the reaction mixture yielded primarily the starting amine **20**, as well as a small amount of what may be protonated **43**, but neither decomposition product *N*-methyl-1-phenylethylamine **42** or triazinane **36** was visible in the ^{1}H NMR spectrum. It is worth noting that the reaction time for the in-situ observation of **43** was on the order of days, while the reaction of **20** with LDA to yield **42** happens in hours. This is similar to what was observed when trying to study the in-situ decomposition of **20** with *n*-BuLi; when the reaction is conducted in a Schlenk flask equipped with a stir bar, the conversion is completed within hours, however when the reaction is conducted in an NMR tube without stirring, the conversion fails to proceed even after several weeks. It is unclear why the change in reaction vessel slows or stops decomposition of the dilithiated propargylamine **24**, but it perhaps has to do with the coordination and (in)solubility of lithium carbide generated during the decomposition.

These results demonstrate that formation of methanimine intermediate **35a** occurs in the presence of LDA, and strongly suggest that the decomposition of propargylamine **20** occurs through a β-elimination pathway, followed by nucleophilic attack at the resultant imine. Interestingly, the observation of **35a** was only possible in the presence of an excess of LDA, and only when the reaction was not stirred. The absence of decomposition of dilithiated propargylamine **24** alone suggests that an extra equivalent of base is needed to trigger the

decomposition pathway, perhaps through coordination of the Lewis acidic cation, the Lewis basic anion, or some combination of the two.

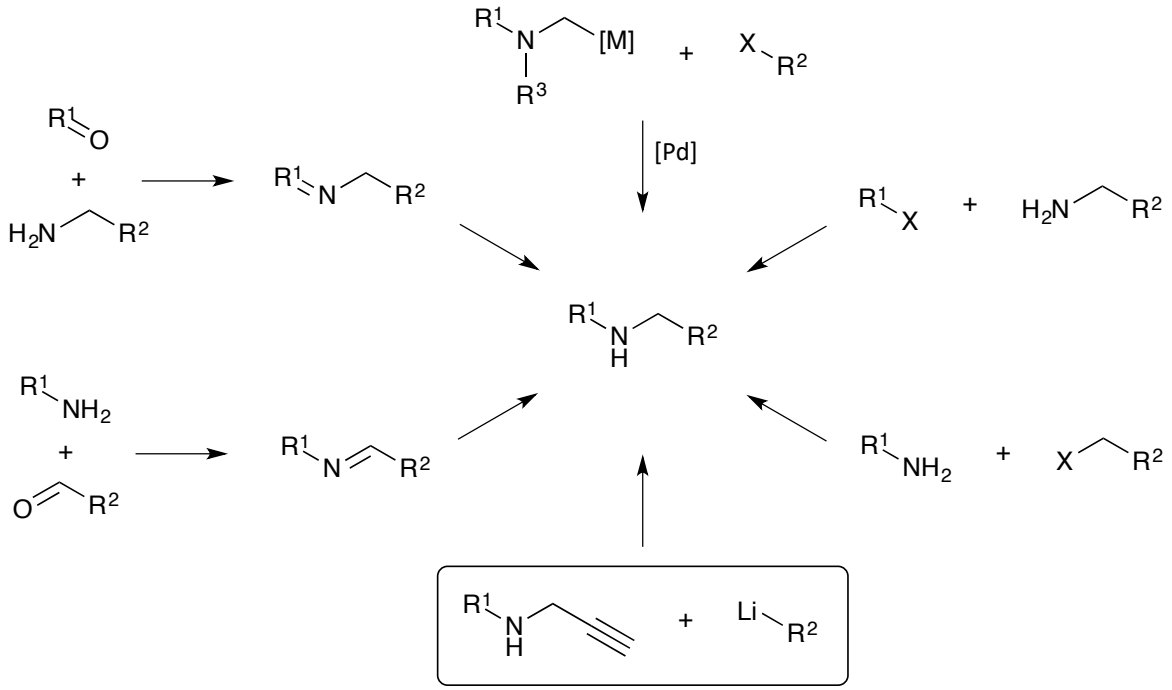
An explanation for the requirement of an organolithium reagent for decomposition of the dilithiated intermediate **24**, as well as the elimination of the normally unfavourable leaving group lithium carbide can be made by considering negative hyperconjugation. Interaction of the electrons in the nitrogen-lithium bond could interact with the σ* antibonding orbital of the adjacent carbon-carbon bond, weakening the carbon-carbon σ-bond, and priming the acetylide group for elimination. Meanwhile, the donation of electrons from the nitrogen into the σ* orbital gives some double bond character to the nitrogen-carbon bond, giving it reactivity akin to the methanimine intermediate **35a** seen in the reaction with non-nucleophilic LDA. Electrostatic interaction of this structure with an organolithium reagent should stabilise the lithium cation, and create a more favoured geometry for the elimination of lithium carbide.



*Scheme 51: Negative hyperconjugation in **24**, where electron density from the lithium-nitrogen bond is donated into the σ* antibonding orbital of the α,β-carbon-carbon bond, could explain the leaving ability of lithium acetylide (top). The formation of lithium acetylide is hampered by the separation of anion and cation, which must occur in this mechanism. The inclusion of an organolithium (RLi) compound into the coordination environment of the transition state facilitates the decomposition by stabilising the incipient anion and cation, as well as priming the complex for nucleophilic attack where R is nucleophilic (bottom).*

Testing substrate scope

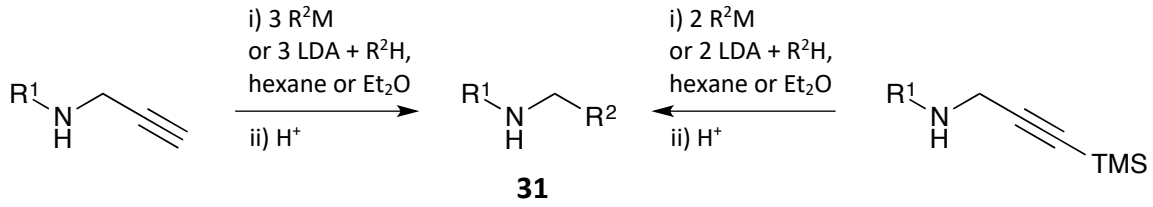
Having established that *n*-BuLi can eliminate lithium carbide from propargyl amine **20** (or lithium (trimethylsilyl)acetylide from **22**) to yield *N*-(1-phenylethyl)pentan-1-amine **30** (Scheme 35, page 57), other nucleophilic organometallic reagents were tested to see if analogous reactions would be successful. This reaction represents an alternative method of synthesising secondary methanediylamines, instead of the commonly used methods of reductive amination, nucleophilic substitution, or palladium catalysed cross-coupling.[61–64]



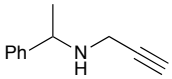
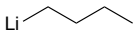
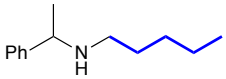
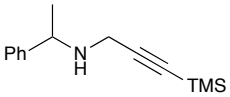
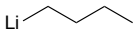
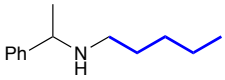
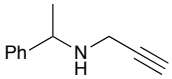
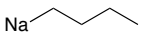
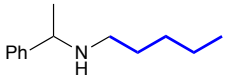
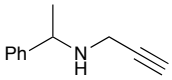
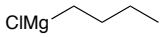
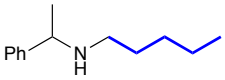
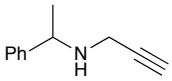
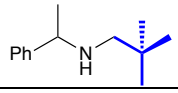
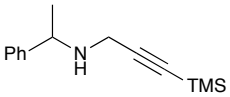
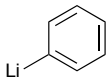
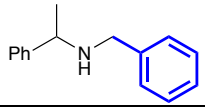
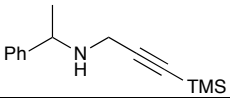
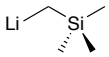
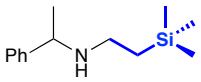
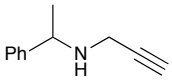
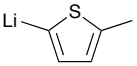
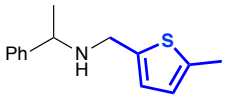
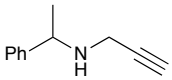
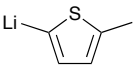
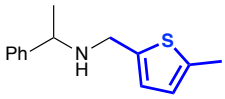
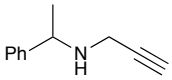
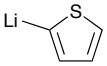
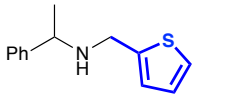
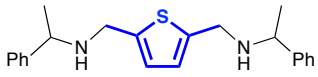
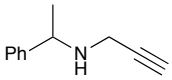
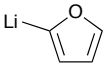
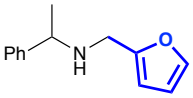
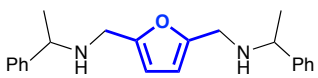
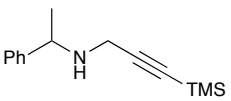
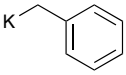
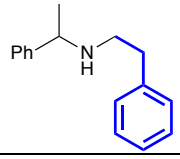
Scheme 52: Synthetic methods employed in the synthesis of methanediylamines. [Pd] denotes various palladium catalysts.

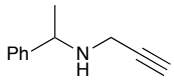
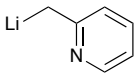
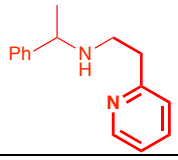
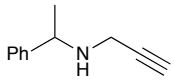
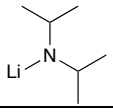
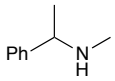
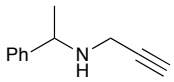
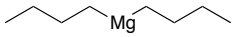
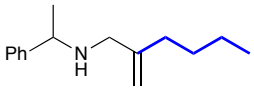
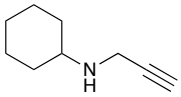
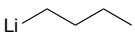
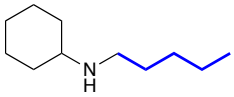
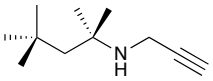
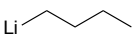
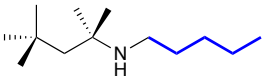
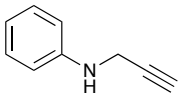
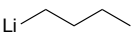
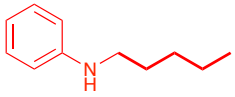
The reaction of **20** with three equivalents, or **22** with two equivalents of organolithium reagent RLi in most cases gave the expected substitution product **31** (Table 2). Replacing the phenylethyl group of the secondary amine for another alkyl substituent also furnished the expected products with *n*-BuLi in good yield. As mentioned earlier, the transformation of propargylaniline into other secondary amines was unable to be achieved.

*Table 2: Reactions of organolithium reagents with propargylamine **20** or **22** to yield methanediylamines.*



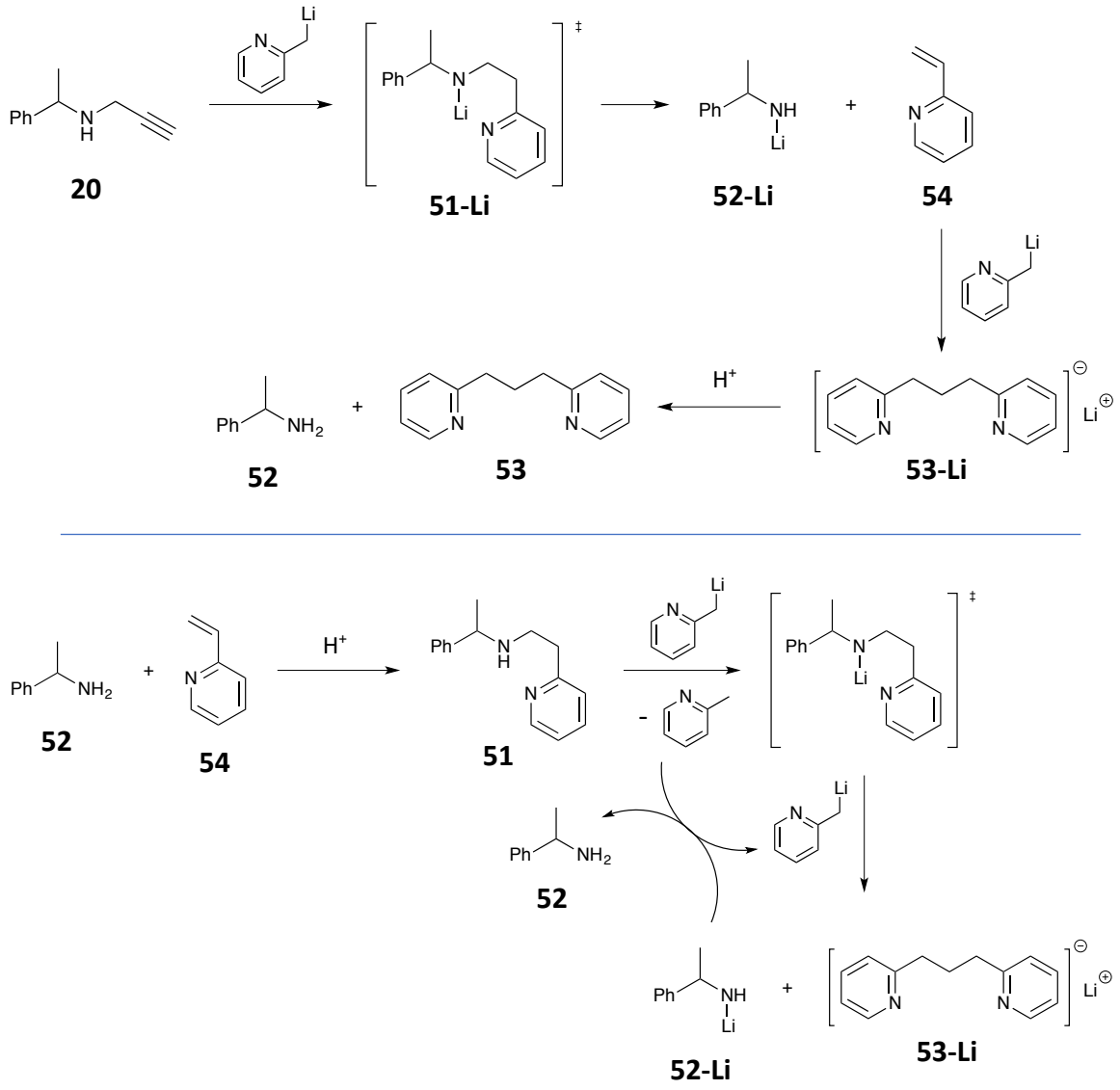
31

Entry	Substrate	R^2M	Product	Yield (%)
1				80[(a)]
2				95[(a)]
3				30[(b)]
4				65[(b,c)]
5				50[(b)]
6				73[(a)]
7				68[(a)]
8				72[(a,d)]
9				61[(b,e)]
10			 	38[(b)] 78[(b,d,f)]
11			 	29[(b,d)] 58[(b,d,f)]
12				60[(b)]

13				0[(g)]
14				41[(b)]
15				47[(b,h)]
16				70[(a)]
17				80[(a)]
18				0[(i)]

notes: (a) isolated yield; (b) yield calculated by NMR; (c) the reaction was conducted in THF at reflux temperature; (d) the organolithium reagent was generated in situ using LDA; (e) the reaction was conducted with only 2.4 equivalents of *n*-BuLi; (f) a 2:1 ratio of amine to heterocycle was used; (g) the product decomposed spontaneously; (h) some *n*-butyl substitution was also observed; (i) starting material was recovered unchanged.

Reaction of **20** with three equivalents of α-lithio-2-picoline (**50**) was expected to yield *N*-(1-phenylethyl)-2-(pyridin-2-yl)ethyl)amine (**51**) after quenching (Table 2, Entry 13). Surprisingly, the two major products obtained from this reaction were instead 1-phenylethylamine (**52**) and 1,3-di(pyridin-2-yl)propane (**53**) (Scheme 53). This presumably results from the decomposition of the intermediately formed product **51-Li** to form **52-Li** and vinylpyridine (**54**), which then inserts into the lithium-carbon bond of another equivalent of α-2-lithiopicoline to yield **53-Li**. To probe this reaction, **51** was synthesised through the hydroamination of vinylpyridine with 1-phenylethylamine, and then reacted with α-lithio-2-picoline. Even when only one equivalent of α-lithio-2-picoline was used, **52** and **53** were obtained in good yield. This suggests that the deprotonation of 2-picoline can occur to some degree with **52-Li** as a base, allowing for the lithiation of **51**, followed by its decomposition to **52-Li** and **54**, deprotonation of 2-picoline, and addition of this α-lithio-2-picoline across the vinylpyridine double bond to yield **53-Li**.



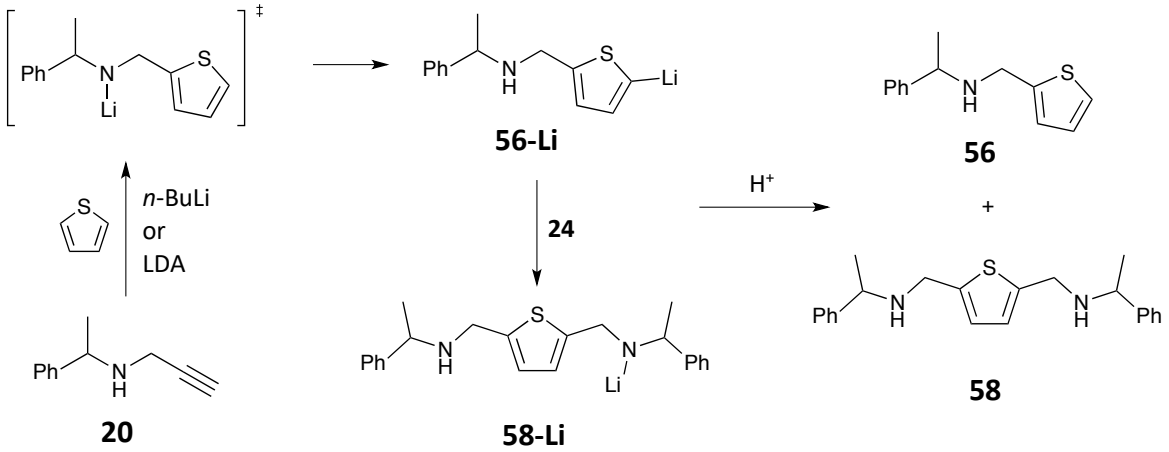
*Scheme 53: The substitution product of **20** with picolyllithium spontaneously decomposes via vinylpyridine elimination, and then reacts to yield **52** and **53** upon quenching (top). The expected product **51** can be synthesised by hydroamination of vinylpyridine, and reacts with just one equivalent of picolyllithium to yield the same products (bottom).*

It was hypothesised that using a less electropositive metal, such as magnesium or zinc, would prevent the decomposition from happening, so 2-picoline was deprotonated with a Grignard reagent to form (pyridin-2-ylmethyl)magnesium bromide. Reaction of this reagent with propargylamine **20** yielded the same decomposition products as the lithium reagent, so the same reaction was attempted with a zinc reagent. Transmetallation of α-lithio-2-picoline with zinc bromide, followed by reaction with **20** failed to induce any reaction, even after refluxing the reaction for an extended period of time. While it may be possible to stabilise the metallated reaction intermediate **51-M** under the right reaction conditions, it seems likely that its formation from the substitution of **20** requires conditions which will lead to the

immediate decomposition of **51-M**. While this shows that the reaction of **20** with α-lithio-2-picoline cannot be used to synthesise **51**, it does give a method for the in-situ generation of vinylpyridine, which can be used in an insertion reaction with α-lithio-2-picoline. The reaction of vinylpyridine with α-lithio-2-picoline in ether does not proceed cleanly, and so this could prove to be a useful source of masked vinylpyridine in reactions with strong nucleophiles.

The heterocyclic organolithium compounds 2-furyllithium and 2-thienyllithium react with **20** or **22** to give the expected products, *N*-(1-phenylethyl)-furan-2-ylmethyl-1-amine (**55**) and *N*-(1-phenylethyl)-thiophen-2-ylmethyl-1-amine (**56**) (Table 2, Entries 10 and 11). The close acidities of the nitrogen and heterocyclic *ortho*-carbon in these products however also leads to the formation of the bis-amino products *N*,*N*'-(furan-2,5-diylbis(methylene))bis(1-phenylethan-1-amine) (**57**) and *N*,*N*'-(thiophene-2,5-diylbis(methylene))bis(1-phenylethan-1-amine) (**58**). The ratio of mono- and di-substituted products depends on the solvent, ratio of starting materials, and the base used: using diethyl ether instead of hexane, an excess of propargylamine to furan or thiophene, and generating the organolithium in situ using LDA (limiting the amount of furyl- or thienyllithium in solution) all favour the formation of the bis-amino product (Table 3).

*Table 3: Reaction conditions for the synthesis of mono- and bis-amino products from the reaction of **20** with thiophene and an organolithium base.*

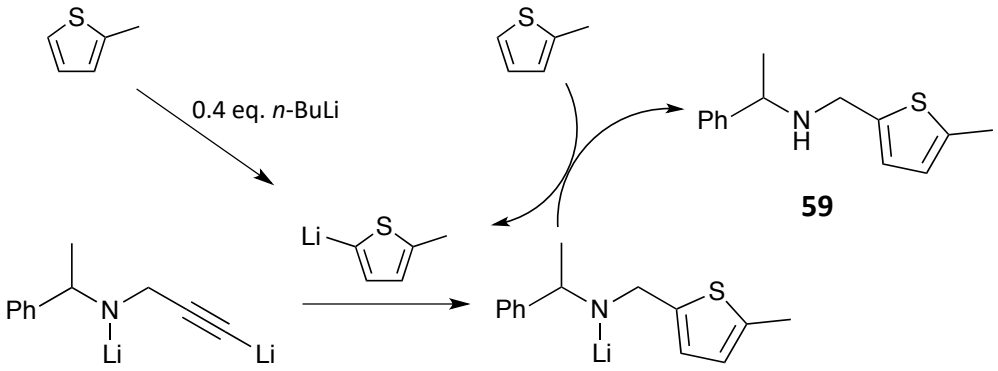


Solvent	Reagent used (equivalents)				Ratio	Yield (%)
	20	Thiophene	*n*-BuLi	LDA	**56**:**58**	**56**/**58**
Hexane	1	3	3	-	86:14	38/13
Et_2O	1	3	3	-	66:34	34/34
Et_2O	1	1	-	3	36:64	16/61
Et_2O	2	1	-	6	13:87	12/78

Using racemic propargylamine **20** gives a mixture of diastereomers in **58**, while the use of enantiopure amine yields a single diastereomer. This shows that the substitution of **20** with nucleophiles to give secondary amines **31** does not lead to any racemisation of the nearby chiral centre, as occurs as a result of the rearrangements of related unsaturated 1-phenylethylamine derivatives.[46,47]

The efficient one-pot synthesis of bis-amino heterocycles **57** and **58** from easily synthesised **20** represents an attractive route to access these compounds, which may be useful as non-nucleophilic chiral bases, or as chiral Lewis donors. This route is advantageous compared to the alternative methods, as the 2,5-bis(carboxaldehyde) heterocycles used in the reductive amination route are expensive, and the use of propargylamines does not require expensive transition metal catalysts.

Blocking deprotonation of the 5-position prevents double substitution at the heterocycle. Thus, reaction of (5-methylthiophen-2-yl)lithium with **20** or **22** yields exclusively *N*-(1-phenylethyl)-(5-methylthiophen-2-yl)methyl-1-amine (**59**) (Table 2, Entry 8). Additionally, reaction of **20** with 2.4 equivalents instead of three equivalents of *n*-BuLi in the presence of one equivalent of 2-methylthiophene still gives **59** in 61 % yield (compared to 72 %) after quenching (Table 2, Entry 9). This shows that the intermediate product **59-Li** is capable of deprotonating 2-methylthiophene, allowing *n*-BuLi to act in substoichiometric quantities following the initial deprotonation of **22**.



*Scheme 54: Substitution of dilithiated propargylamide **24** with 2-methylthiophene and substoichiometric amounts of n-BuLi shows that the lithium amide produced (**59-Li**) is basic enough to deprotonate the 2-methylthiophene substrate.*

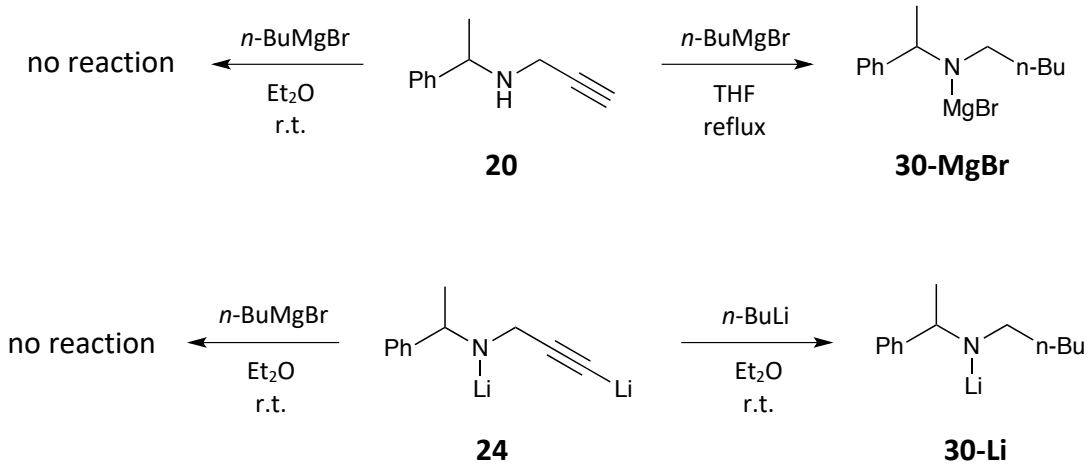
Lithiopyridine was trialled as a nucleophile, by metallating pyridine at low temperature, followed by addition of propargylamine **20**. The reaction led to a complex mixture of products, likely because lithiopyridine is too unstable, and decomposes before the substitution can take place. To allow this reaction to take place, either the lithiopyridine complex needs to be stabilised to decomposition, or the propargylamine needs to be made more reactive.

Heavier alkali metal bases were tested to see if the same reactivity could be achieved with sodium and potassium. Thus, propargylamine **20** was added to three equivalents of *n*-BuNa in hexane at -78 ˚C. After warming to room temperature, the reaction was quenched, and an aqueous workup performed. While the major product obtained was the butyl substitution **30**, several side products were also observed, in contrast to the results obtained with *n*-BuLi, which gave exclusively one product.

Benzylpotassium was also trialled in substitution reactions with both **20** and **22**, and was found to be sensitive to reaction conditions: most reactions yielded a mixture of products, including the sigmatropic rearrangement of TMS-protected propargylamine **22** mentioned above to give a mixture of aza-butadienes **25** and **27** (Scheme 32, page 55). Addition of **22** to a suspension of benzylpotassium at room temperature was found to give the best results, yielding primarily the substitution product *N*-(2-phenylethyl)-1-phenylethylamine (**60**) after quenching (Table 2, Entry 12). Interestingly, despite the structural similarity to the picolyllithium substitution product **51** (Table 2, Entry 13), the metallated amide **60-K** appears to be stable to decomposition. This could be due to the substitution of lithium for potassium, however given the tendency for lithium organometallics to be more stable than their heavier congeners, it is more likely that either the electron withdrawing effect of the electron deficient pyridine ring, the Lewis donor capacity of the pyridyl nitrogen atom, or some combination of the two destabilises the ethylpyridine derivative.

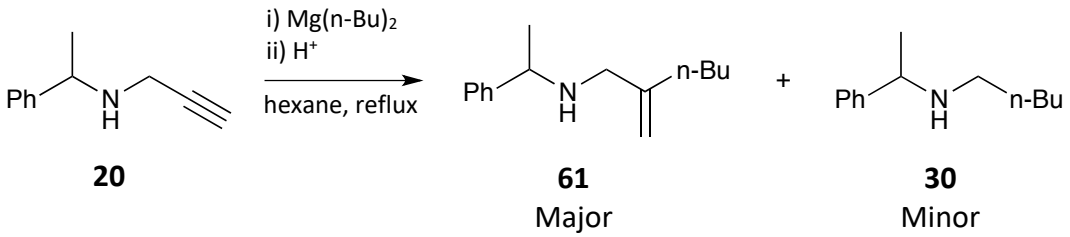
n-Butylmagnesium bromide was also assessed in its reactivity with propargylamine **20**. Under the same conditions as used for the organolithium reagents, no reaction was observed with *n*-BuMgBr. However, unlike the lithium reagents, the reaction was able to be conducted in THF without producing a mixture of products. Thus, carrying out the reaction at reflux temperature in THF yielded the substitution product **30** (Table 2, Entry 4). The requirement of harsher conditions may be due to the lower nucleophilicity of Grignard reagents compared to organolithium reagents, or that the dimagnesiated intermediate is less destabilised, so that

elimination of the acetylide requires more energy to occur. Interestingly, reaction of *n*-BuMgBr with the dilithiated complex **24** in diethyl ether at room temperature (conditions which induce substitution with *n*-BuLi) leads to no substitution, with only starting material **20** isolated upon quenching (Scheme 55). This suggests that it is due to the (relatively) low nucleophilicity of *n*-BuMgBr, or perhaps some solvation effect in THF, that the substitution reaction must be conducted in THF. The effects of metal halide salts also cannot be discounted, as these would be better solvated in THF, and are known to have dramatic effects on reactions involving organomagnesium complexes.[65,66] As mentioned earlier, the reaction of 2-picolylzinc bromide with **20** failed to yield any product, and this result was also observed when using *n*-butylzinc bromide formed from *n*-BuLi and zinc bromide, even when refluxed in THF. This implies that nucleophilicity is at least part of the reason for the lower reactivity of less electropositive metals.



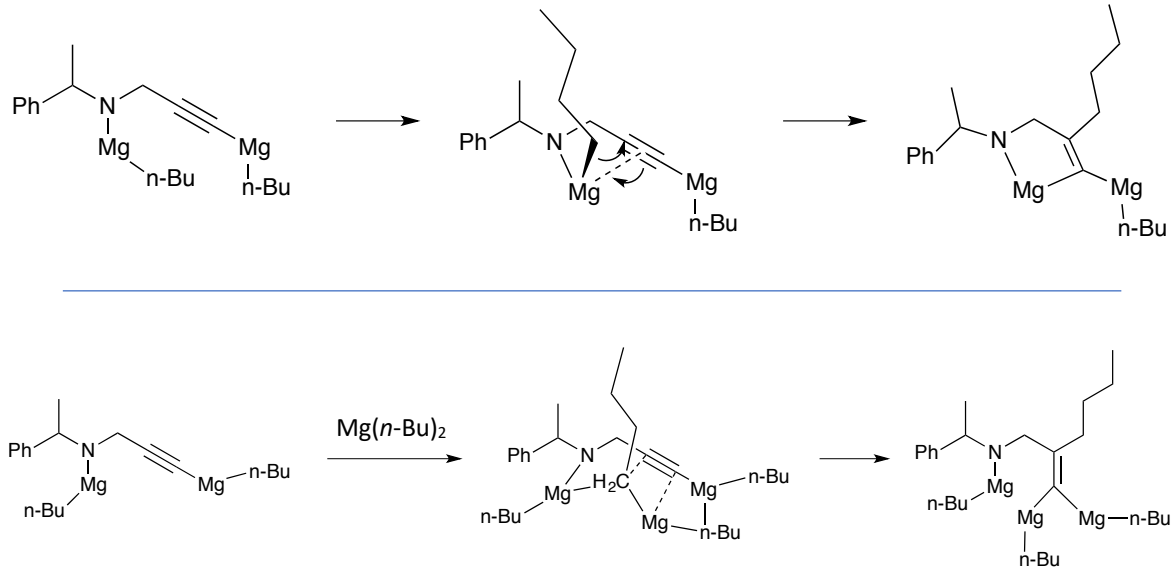
*Scheme 55: Propargylamine **20** substitutes with Grignard reagents only under forcing conditions. Even the dilithiated amide **24** doesn't react at ambient temperature, showing that the identity of the metal is important.*

Di-*n*-butylmagnesium was then reacted with propargylamine **20**, with the expectation that the higher reactivity would allow for the substitution to occur under milder conditions than needed for *n*-BuMgBr. Unexpectedly, only a small amount of substitution to yield **30** occurred, with the major product being 2-methylene-*N*-(1-phenylethyl)hexan-1-amine (**61**) (Table 2, Entry 15). The addition reaction of di-*n*-butylmagnesium is analogous to the reaction with crotylmagnesium bromide reported by Marek and Normant,[17] described above, however the propargylamine used in that report was a tertiary amine, unable to be metallated at the nitrogen atom as in **20**.



*Scheme 56: Reaction of propargylamine **20** with di-n-butylmagnesium yields primarily the carbometallation product **61** after quenching, with only a small amount of the substitution product.*

It is unclear why di-*n*-butylmagnesium is the only reagent observed to undergo a nucleophilic addition across the triple bond of **20**. It is possible that after deprotonation of the alkyne and amine positions, an intramolecular insertion of the alkyne into the amido magnesium-carbon bond occurs to produce a metallocyclic complex, induced by the forced proximity of the butyl group. It is also possible that after deprotonation, another equivalent of di-*n*-butylmagnesium coordinates to the complex, and this intermolecular interaction induces the addition reaction through a proximity effect. If intermolecular coordination is the controlling factor, then similar reactivity could be expected of Grignard reagents, which is not seen. This can be explained as a difference in the nature of the solvent: di-*n*-butylmagnesium is soluble in, and was reacted in hexane, while Grignard reagents must be reacted in THF, which would disrupt these intermolecular interactions. In agreement with this, no evidence of the addition product is seen from the reaction using *n*-butylmagnesium bromide, despite the likely presence of di-*n*-butylmagnesium in the reaction, formed through the Schlenk equilibrium.



*Scheme 57: Proposed mechanisms for carbomagnesiation of **20**: intramolecular reaction to yield a metallocyclic complex (top), and intermolecular reaction induced by coordination of magnesium centres*

(bottom). This second mechanism could occur with Grignard reagents, however the use of THF solvents would likely disrupt this highly aggregated structure.

Conclusions and future work

The results here have shown that lithiated complexes of *N*-(1-phenylethyl)prop-2-yn-1-amine **20** do not undergo sigmatropic rearrangements. Though the structure of the dilithiated derivative of **20** could not be fully elucidated, infrared spectroscopy and derivatisation studies showed the complex to be deprotonated at the nitrogen and terminal alkynyl positions, with no significant change in the distribution of the π-electrons, leading to the assignment of the structure as the propargylic amido dianion **24**. A Grignard analogue of **24** was synthesised, however determination of the structure of this compound was complicated by the same factors as the lithium complex, as well as the formation of a dialkynylmagnesium complex through the Schlenk equilibrium. If crystallisation of any of these complexes could be achieved, single crystal X-ray diffraction studies would be vastly informative about the structure of the compounds, and what inter- and intramolecular interactions exist.

It was found that sigmatropic rearrangements could be induced if the terminal alkynyl position was protected, preventing deprotonation of the alkyne. Thus, deprotonation of the internal alkyne *N*-(1-phenylethyl)-3-(trimethylsilyl)prop-2-yn-1-amine **22** in the presence of TMEDA allowed for the stereoselective rearrangement to form the aza-diene 1-phenyl-*N*-((*Z*)-3-(trimethylsilyl)prop-1-en-1-yl)ethan-1-imine **25** exclusively in the *cis*- conformation. The selectivity was hypothesised to be the due to coordination of the lithium cation to the π-electrons of the aliphatic group, constraining the transition states into a *cis*- geometry. The use of potassium bases to effect the rearrangement resulted in a mixture of *cis*- and *trans*-isomers, presumably due to the larger radius of the potassium ion resulting in a looser interaction with the π-system, and less restriction of the transition states. The metallated complex could not be characterised, and quenching with D_2O failed to incorporate deuterium into the compound, either because of the absence of metallated compound in solution, or because of proton exchange during the workup procedure. Modifying the workup procedure may allow for the detection of deuterium in the resultant aza-diene, and give some idea of the structure of the compound before quenching. Once again, crystallographic structural data would prove invaluable in determining the nature of the compound and the rearrangement process.

It was discovered that reaction of **20** with three equivalents, or **22** with two equivalents of *n*-BuLi resulted in the elimination of lithium carbide and (trimethylsilyl)ethynyllithium respectively, accompanied by addition of an equivalent of *n*-BuLi to yield the secondary amide lithium *N*-(1-phenylethyl)pentan-1-amide **30-Li**. In the course of investigating the potential mechanisms for this reaction, evidence was found for the elimination of lithium carbide from dilithiated amide **24** to form the intermediate *N*-(1-phenylethyl)methanimine **35a**. All of the attempts made to trap this intermediate failed, suggesting that the formation only occurs when the complex interacts with an organolithium reagent, which in most cases results in immediate insertion of the methanimine fragment into the carbon-lithium bond. The use of an excess of LDA allowed for the direct observation of **35a** as a transient species, which then reacted with another equivalent of **24** to produce the bis(amido) complex lithium but-2-yne-1,4-diylbis((1-phenylethyl)amide) **43**. This complex readily decomposes, yielding *N*-methyl-1-phenylethylamine **42** upon quenching. Negative hyperconjugation was proposed to be involved in the mechanism, as an explanation for both the unusual elimination, and the requirement for an extra equivalent of organolithium for the elimination to proceed. Testing the reaction using geometrically constrained propargylamines, such as 2-ethynylpiperidine, could be informative as to whether negative hyperconjugation is important in the mechanism. Computational studies, kinetics studies, as well as further characterisation of the intermediates of these reactions would also prove useful in revealing which factors contribute to the instability of the lithiated propargylamides.

Reactions of *n*-BuLi with ether, thioether, and tertiary amino analogues of **20** yielded dramatically different results. For (1-phenylethyl)prop-2-yn-1-ylether **45**, a [1,2]-Wittig rearrangement occurred to produce the dilithiated derivative of 4-phenylpent-1-yn-3-ol **47-Li_2**. The thioether analogue (1-phenylethyl)prop-2-yn-1-ylthioether **46** produced a complicated mixture of products which could not be elucidated. Similarly, the outcome of the reaction using tertiary amine analogue *N*-methyl-*N*-(1-phenylethyl)prop-2-yn-1-amine **28** could not be determined, however the expected products of *n*-butyl substitution, carbometallation, or a [1,2]-Wittig rearrangement were not detected.

A preliminary substrate scope was established, and shows some promise in the synthesis of secondary methanediylamines, especially in the formation of bis(amino)heterocycles synthesised from thiophene and furan. Using picolyllithium as a substrate, the product was

found to spontaneously decompose to produce vinyllithium, which reacted with picolyllithium to yield, upon quenching, 1,3-di(pyridin-2-yl)propane **53**. Grignard reagents were able to be used in the substitution reaction when refluxed in THF, but no reaction occurred under milder conditions. Meanwhile, reaction with di-*n*-butylmagnesium in hexane predominantly carbometallates the alkyne bond, producing a substituted alkene, with only a small amount of the substitution product being observed. Optimising the reaction conditions for these substitutions, and finding conditions under which other heterocycles, such as pyridine, can be transformed into bis(amino)heterocycles would greatly increase the utility of this reaction. The bis(amino)heterocycles, especially those produced as the enantiopure 1-phenylethylamino derivatives, should be tested as chelating amide bases or Lewis donors, as they may have potential in enantioselective synthesis.

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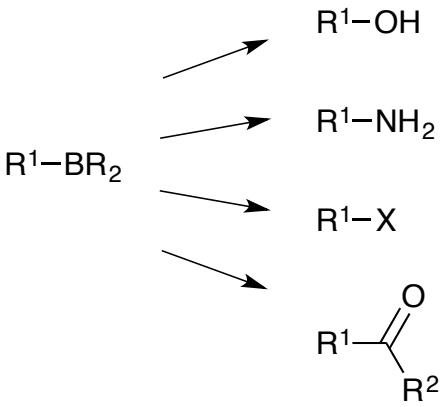
Chapter 3: Alkali Metal Aluminate Complexes for Hydroboration Catalysis

Introduction

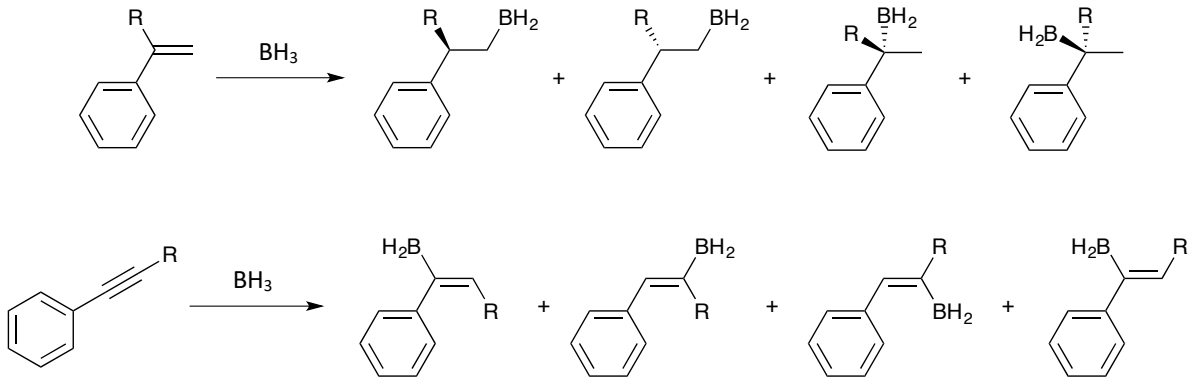
Hydroboration

Boron reagents represent a versatile precursor to a wide variety of potential functionalisations. Organoborane compounds strike a balance between reactivity, allowing for facile derivatisation at the boron-carbon bond, and stability, making the complexes easy to work-up and purify. Thus, organoboranes are often stable to hydrolysis, though they are easily oxidised. This property means that the facile oxidation of organoboranes is possible, where many organometallic complexes would require strictly controlled conditions and suffer from side-reactions. Organoboranes therefore are useful precursors to the formation of alcohols, amines, organohalides, and carbonyl compounds.[1–6]



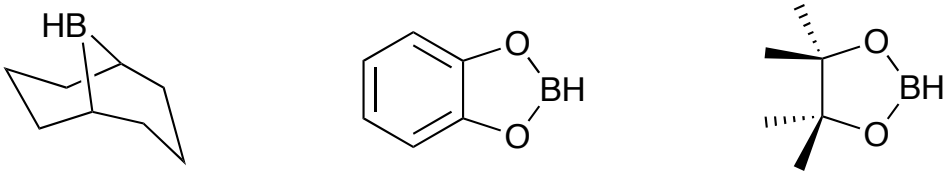
Scheme 58: Derivatisations of organoborane compounds.

Hydroboration offers an attractive method to the synthesis of these useful intermediates, generating organoborane compounds from unsaturated carbon bonds, including alkenes and alkynes, under mild conditions. The use of the most simple boron hydride, borane (which exists as diborane B_2H_6 in non-coordinating solvents), in the hydroboration of unsaturated aliphatics is generally non-selective, giving a mix of regio- and stereoisomers.[2] Borane also presents problems with solubility: the THF complex exhibits limited solubility in THF, while the dimethylsulfide complex has greater solubility, but presents other problems, particularly in regards to the strong odour produced by volatile dimethylsulfide.



Scheme 59: Hydroboration of alkenes and alkynes with borane can result in a lack of selectivity.

This has led to the development of boron hydride reagents with greater selectivity and ease of handling. 9-Borabicyclo(3.3.1)nonane (9-BBN) is one of the most popular of these modified borane reagents, which demonstrates higher regioselectivity in reactions with alkenes.[7] Catecholborane has also proved popular as a less air sensitive reagent, as the presence of the phenoxide substituents on the boron centre stabilise the borane, preventing the redistribution reactions often seen when using boranes derived from other diols.[8,9] The reaction of alkenes and alkynes also results in the formation of boronic esters, which have proved tremendously useful in the Suzuki cross-coupling reaction.[3] For the same reasons, pinacolborane has recently become popular in these applications, as it enjoys similar stability to that of catecholborane, but reacts at lower temperatures to hydroborate alkenes and alkynes.[10] The boronic esters produced from pinacolborane are also more stable than those from catecholborane, and many of the products of alkyne hydroboration can be purified by chromatography on silica gel.[11]



9-BBN Catecholborane Pinacolborane

Figure 16: Hydroboration reagents with better selectivity than BH_3.

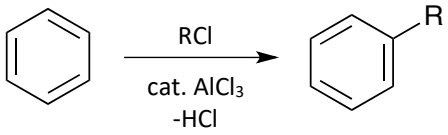
While hydroboration using catecholborane and pinacolborane is significantly slower than when using 9-BBN, and generally requires higher temperatures, the availability of catalysts for this reaction allows hydroboration to proceed at room temperature within reasonable time frames. The first example of this with deactivated boranes (in this case catecholborane), using rhodium complexes such as Wilkinson's catalyst enabled rapid hydroboration of alkenes

and alkynes, even in the presence of ketones.[12] The use of catalysts has also allowed for reversal of regioselectivity,[13–16] while chiral catalysts can afford product mixtures with good enantiomeric excess.[17–19]

Recently, a surge in research has produced a large number of catalysts for the selective and facile hydroboration of functional groups such as alkenes,[20–23] alkynes,[24–27] aldehydes and ketones,[28–37] imines,[38–43] nitriles,[44–48] and pyridines,[49–56] using pinacol- or catecholborane. Many of these examples use non-transition-metal based catalysts, and catalysis has also been achieved using common laboratory reagents such as diisobutylaluminium hydride,[57] lithium aluminium hydride,[58] sodium hydride,[59] *n*-butyllithium,[60] and sodium hydroxide.[61] The hydroboration of aldehydes using pinacolborane has also been shown to proceed rapidly in the absence of a catalyst under solvent free conditions.[62]

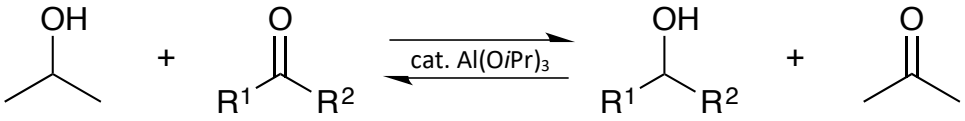
Aluminium catalysts

Aluminium has a long history of use in catalysis, with applications in the Friedel-Crafts reaction, and the Meerwein-Ponndorf-Verley and Oppenauer reactions. Aluminium compounds are also used as co-catalysts in the Ziegler-Natta polymerisation.

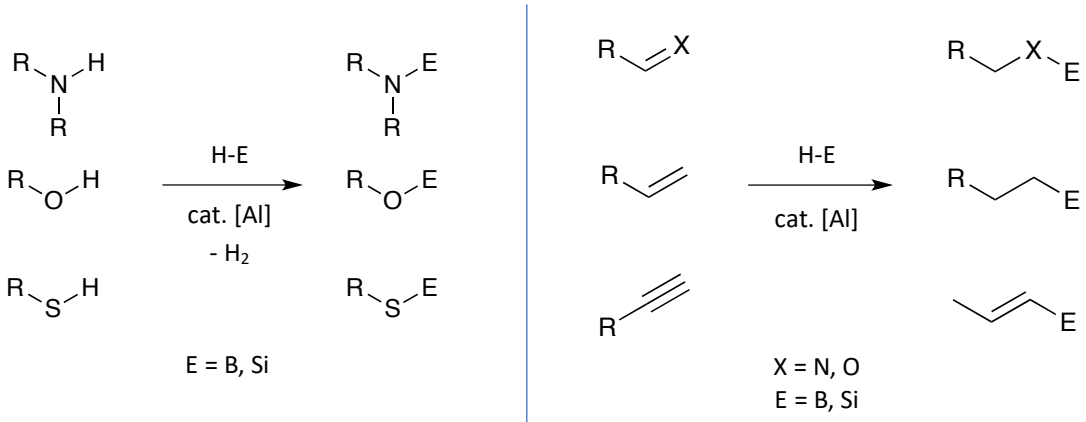


Friedel Crafts reaction

Meerwein-Ponndorf-Verley reduction
(excess alcohol)



Oppenauer oxidation
(excess ketone)



Dehydrocoupling

Hydroelementation

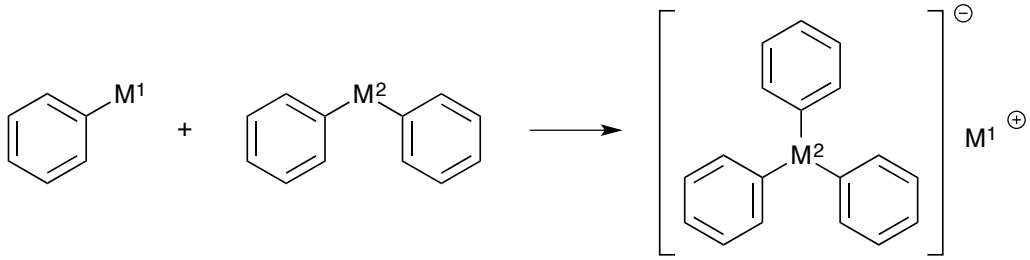
Scheme 60: Reactions utilising aluminium catalysts.

The development of efficient transition metal catalysis largely constrained the advancement of aluminium catalysts for many years, however recent interest in green chemistry has shifted the focus of research to more earth-abundant and less toxic metals. Aluminium, being the most abundant metal in the crust, and possessing a relatively low toxicity, is an attractive choice for the development of sustainable 'green' catalysts. Thus, the past few years have seen a resurgence in the development of catalytic processes utilising aluminium catalysts. In particular, aluminium compounds have proved to be effective catalysts in reduction chemistry, with examples in dehydrocoupling, hydroboration, and hydrosilylation.[63] The high reactivity of the aluminium-hydrogen bond has made soluble aluminium hydrides particularly

valuable in these applications.[64] While oxidation states of aluminium beyond the +3 state are difficult to access, the existence of aluminium complexes as cationic, neutral, or anionic species, coupled with the use of non-innocent ligands allows these complexes to replicate the chemistry of the transition metals. Despite the prevalence of anionic aluminium complexes in synthesis, such as lithium aluminium hydride, few examples of catalysis with these compounds exist in the literature.

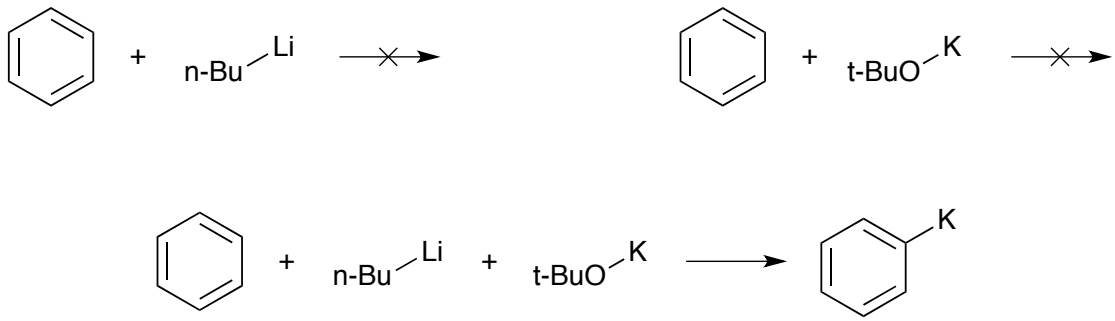
'Ate' complexes

The combination of an organometallic complex with a highly electropositive metal with another which is more electronegative tends to lead to the formation of mixed metal complexes. In researching the complexation of various phenyl-substituted organometallics, Wittig recognised this fact, and termed these mixtures 'ate' complexes.[65]



Scheme 61: Synthesis of homoleptic (phenyl) 'ate' complexes.

Since then, mixed metal complexes have found various applications in synthesis. For example, the popular Lochmann-Schlosser base, a mixture of *n*-BuLi and *t*-BuOK is capable of effecting deprotonations which cannot be achieved with either of the individual components, such as the rapid metallation of benzene and toluene.[66,67]



Scheme 62: The use of the Lochmann-Schlosser base allows for reactivity that is unachievable with the individual components.

Despite numerous efforts, the structure of this heterobimetallic mixture remains elusive. The homometallic lithium analogue produced from the reaction of *n*-BuLi and *t*-BuOLi has been characterised both by NMR[68] and crystallographically,[69] which gives some insight into the structure of such mixed-anion complexes, however the monometallic species does not possess the same metallating power as the *n*-BuLi/*t*-BuOK complex. Similarly, mixed metal complexes containing alternate anions have been characterised, notably a mixed lithium/sodium phenoxy/alkyl system,[70] a lithium/potassium *tert*-butoxide cluster,[71] and a lithium/potassium *tert*-butylamide/*tert*-butoxide compound,[72] which demonstrates enhanced basicity over its individual substituents. More recently, complexes closely related to the *n*-BuLi/*t*-BuOK system have been characterised by X-ray crystallography: intermediary complexes from the metallation of benzene and toluene utilising the Lochmann-Schlosser base were crystallographically characterised,[73] and complexes arising from the reaction of neopentyllithium with *t*-BuOK were characterised by a combination of X-ray diffraction and NMR spectroscopic studies.[74] While these complexes could be considered as separate from the 'ate' complex class, they demonstrate the importance of the heterobimetallic nature of the systems in modulating their reactivity.

In the past few years, interest in the chemistry of 'ate' complexes has intensified, with new understandings of their structures guiding their applications in synthesis. Nowadays, 'ate' complexes are generalised into several categories based on their components and the structures they adopt.[75] Structurally, they can exist as either contact-ion-pairs (CIPs) or solvent-separated-ion-pairs (SSIPs), based on whether the metal centres interact directly or, as the name suggests, are solvated to a degree where they exist as separate ions. Another structural distinction can be made between lower and higher-order complexes, depending on the number of anions bound to the central metal. In terms of their components, complexes can be characterised based on the identity of the ligands (homo- or heteroleptic), and similarly on the identity of the metal centres, which can be homo- or heterometallic.

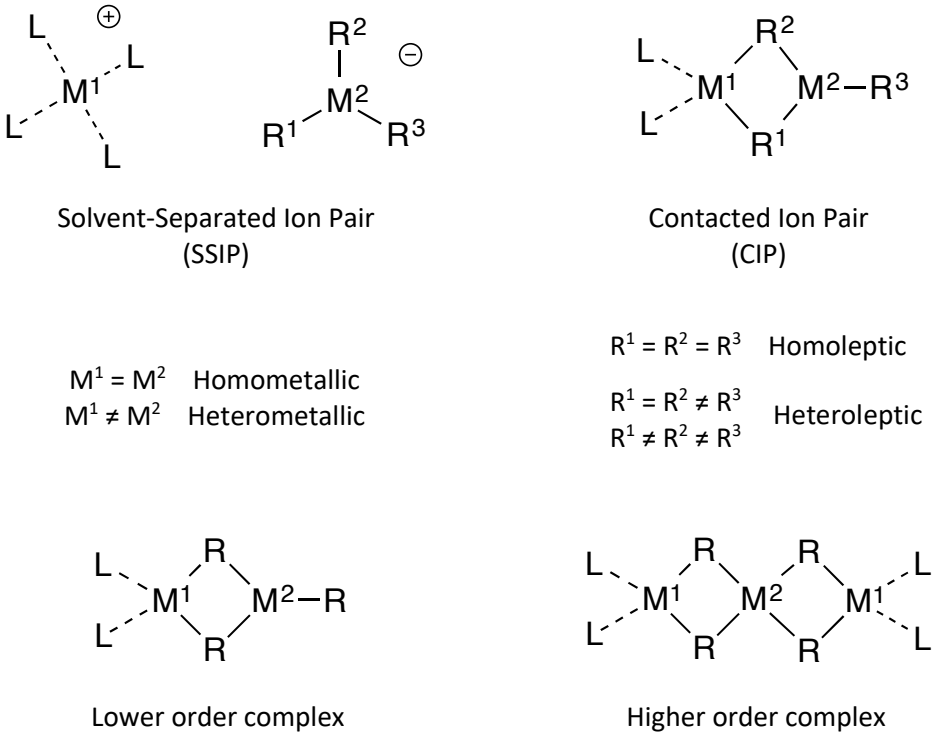
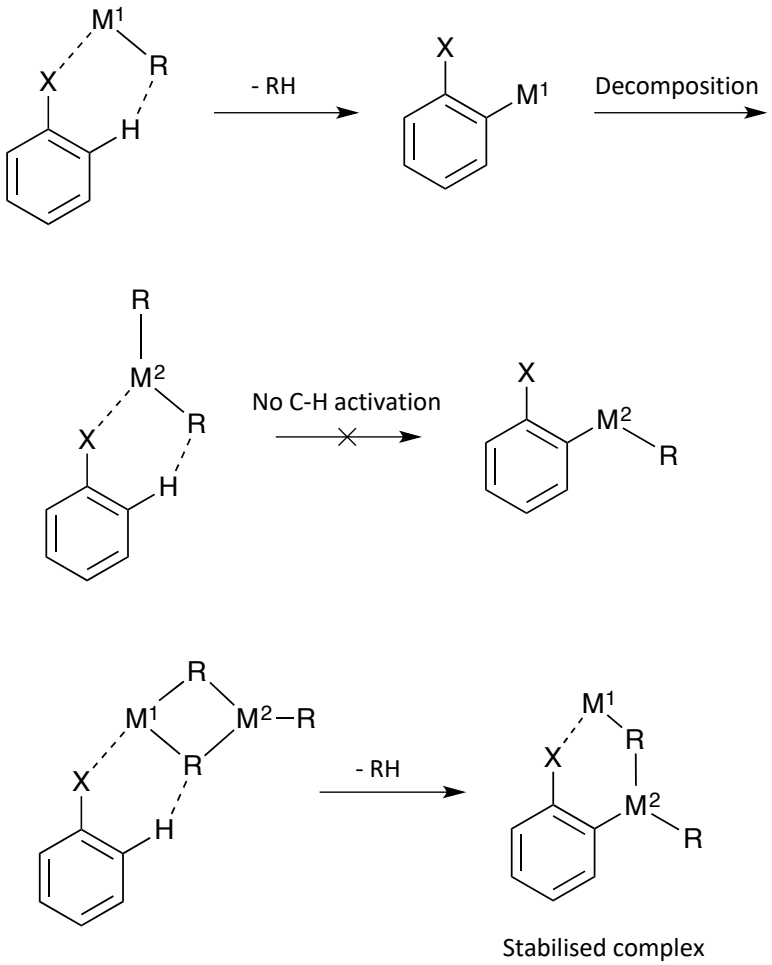


Figure 17: Different classifications of 'ate' complexes (L = Lewis donor).

While the majority of 'ate' complexes described in the literature are heterometallic complexes (largely due to the higher propensity for mixed-metal systems to form 'ate' complexes), homometallic systems have found applications, nicely demonstrated in the work of Caubère.[76] Improvements in the reactivity of these complexes compared with the parent organometallics are due to changes in the aggregation states adopted, whether it be in the reactants, in the transition states, in the products formed, or some combination of the three.

Variations in the aggregation states also occur within heterometallic 'ate' complexes, however in this case the nature of each metal centre is also important.[77–79] In general, the reactivity can be altered by a difference in the binding of each metal, either in binding to the substrate to lower the energy barrier to a transition state, or in binding to the product to stabilise the resulting complex. In this way, the typically more reactive s-block metals (less electronegative), which nearly always form the cationic part of the 'ate' complex, can activate substrates upon coordination, while the less reactive (more electronegative) metal, often d- or p-block metals, form the anionic part of the complex, and stabilise the intermediates and products. This allows formation of reaction products which would often decompose or undergo side reactions were the more reactive metal used in isolation, and would not react at all with only the less reactive metal.

Utilising these principles, the chemistry of 'ate' complexes has been exploited to undertake reactions such as reductions (possible when one metal is able to be oxidised), nucleophilic substitutions, and deprotonation reactions which are only possible using the synergy between the two metal centres.[80]



Scheme 63: The formation of 'ate' complexes gives a synergistic effect, combining useful aspects of both of the individual organometallic reagents.

In addition to these reactions, there exist examples such as that of *i*-PrMgCl·LiCl, commonly known as the turbo-Grignard reagent, which undergoes facile metal halogen exchange reactions, allowing for the synthesis of Grignard reagents from organobromides which are ordinarily very slow to react.[81,82] Boron 'ate' complexes (although they are not strictly metalates, the same principles apply) have been also been utilised in hydroboration reactions,[83–86] or implicated as intermediates in the catalytic cycle.[25,53–55,60,61]

Aluminate catalysts

Recently, aluminium 'ate' complexes (aluminates) have been shown to be effective catalysts for hydroboration of aldehydes, ketones, alkynes, and imines.[87,88] Comparisons between the catalytic activity of aluminates and analogous neutral aluminium compounds demonstrated the benefits of using an 'ate' complex for these applications.[89] The anionic aluminium species showed superior catalytic properties in the hydroboration reactions, except in the case of diphenylacetylene, where sterics were proposed to reduce the efficacy of the bulkier aluminate catalyst.

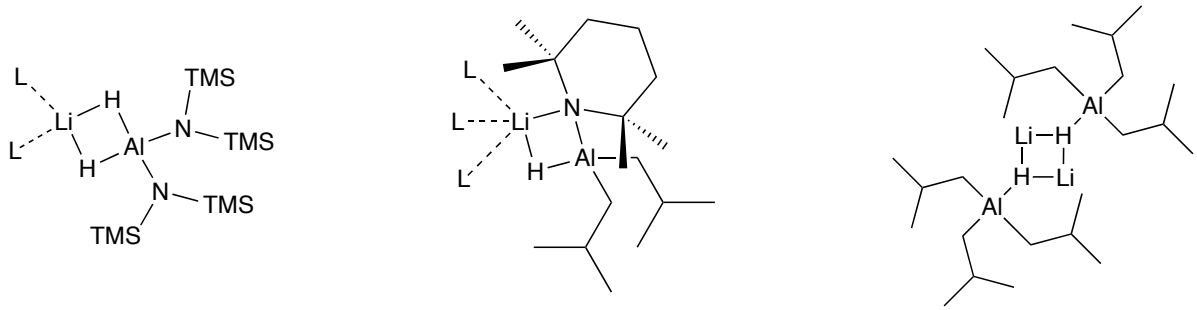


Figure 18: Lithium hydridoaluminates previously used in hydroboration catalysis (L = Lewis donor).

The research presented herein was performed at the University of Strathclyde in collaboration with Professor Robert Mulvey, and aims to expand on these results, primarily targeting the synthesis of potassium aluminates. Compared with lithium, the larger potassium cation preferences binding to softer Lewis bases and should enhance the interactions of the aluminate complexes with π-systems such as alkynes and alkenes. Thus, potassium aluminates are expected to better activate these substrates toward hydroboration, and display greater efficiency as catalysts.

Results and discussion

Initial experiments with various potassium sources and donors

(Trimethylsilyl)methylpotassium (**62**) was chosen as the starting point for synthesising a potassium hydrido aluminate, as it was expected that the stability (due to the inability to β-hydride eliminate) and the high basicity of (trimethylsilyl)methylpotassium would impart these properties on the resultant aluminium complex. Previously synthesised bimetallic complexes involving the (trimethylsilyl)methyl moiety demonstrate the worth of this anionic fragment in the formation and stabilisation of alkali metal –ate complexes.[90–93]

Several reactions were attempted with diisobutylaluminium hydride (DIBALH, **63**) and (trimethylsilyl)methylpotassium **62**, varying the Lewis donors used to support the complex. Unfortunately, all of these produced oils, which upon analysis by ^{1}H NMR proved to be a mixture of products, likely from the redistribution of ligands to form complexes of the form $(Al(CH_2SiMe_3)_x iBu_y H_z)^-$. This was evident from the appearance of multiple sets of signals in the NMR spectrum, showing multiple chemical environments for each of the alkyl substituents.

Zakharkin has described the redistribution of various alkali metal aluminium hydrides, including aryloxy,[94] alkyl,[95] alkynyl,[96] and amido[97] complexes. Most of these complexes were stable as the monohydrido complex $M[AlR_3H]$, while the dihydrido and trihydrido complexes were sometimes prone to disproportionation, dependent on solvent, temperature, and the nature of the anionic group R and the alkali metal M. In addition, the stability of the alkynyl complexes were studied in depth, and a trend observed relating the interaction of the cationic and anionic metal centres, and the propensity to redistribute.[96] It was concluded that greater electron density at the aluminium centre improved the stability of the complex, thus complexes of the more basic alkynes are more stable, and complexes with two or three hydride ligands are less stable. Solvation of the complexes with stronger or chelating Lewis donors, or the use of smaller alkali metal cations was also found to destabilise the complexes. This was attributed to separation of the ion pair, leading to formation of anion-cation-anion triple ions ($[AlR_4]^-M^+[AlR_4]^-$), which brings two aluminate centres into close contact and promotes redistribution.

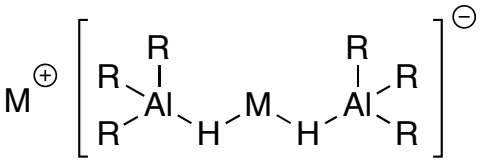
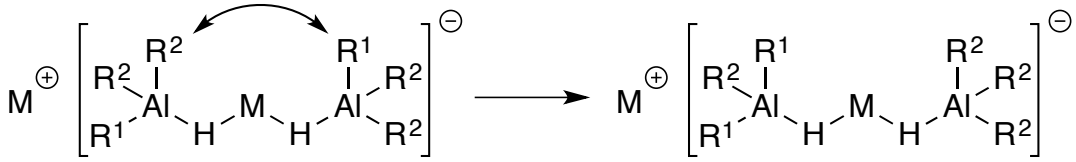


Figure 19: Structure of the triple ion suggested as the intermediate in redistribution.

The reaction of (trimethylsilyl)methylpotassium and DIBALH in hexane meets all of the criteria identified by Zakharkin for stability described above, and yet the product appears to redistribute readily. This may be due to the large steric bulk of two isobutyl groups and a (trimethylsilyl)methyl group, but given that sodium tetra(isobutyl)aluminium is reported not to redistribute in the presence of sodium aluminium hydride in THF,[95] it is likely that the instability observed here is instead related to the heterolepticity of the complex. As all of the

complexes studied by Zakharkin were homoleptic (excluding the hydrido ligands), it is possible that ligand exchange occurs more rapidly within ligands with similar properties, so that complexes with multiple different alkyl groups are more prone to redistribution.



Scheme 64: Redistribution of a heteroleptic aluminate complex. When R1 = R2, the product of redistribution is identical to the initial complex.

A reaction with benzylpotassium was then attempted, with the expectation that coordination of the π-system of the benzyl anion to the potassium cation would inhibit the dissociation of the complex and prevent redistribution. Unfortunately, this reaction still only produced oils, showing a similar mixture of products as was obtained from the reactions of (trimethylsilyl)methylpotassium.

A shift was then made to target amido bases, as the higher affinity of alkali metals for nitrogen should allow them to bridge the two metal centres better than an alkyl substituent, and theoretically should impede redistribution. As well as this, some lithium amidoaluminates have been characterised previously, and proved to be stable to redistribution.[87–89]

Potassium diisopropylamide was used first, generated in situ from *n*-butylpotassium and diisopropylamine. Once again, the product obtained from this reaction was an oil, which analysis by ^{1}H NMR spectroscopy proved to be a mixture of complexes.

2,2,6,6-tetramethylpiperidine (TMP(H)) was used next, as the lack of β-hydrogen atoms makes the derived potassium amide more stable. Potassium 2,2,6,6-tetramethylpiperidide (KTMP, **64**) is also easily isolated, so that the potassium amide being used does not have to be generated in situ, which avoids the complications associated with this method. The TMP anion is also slightly bulkier than the diisopropylamide anion, which may reduce the tendency to form complexes with multiple amido basic groups. Unfortunately, all initial reactions with KTMP also yielded complex mixtures of products.

In order to provide some proof of concept for the ability of the potassium cation in these complexes to interact with π-systems and enhance reactivity, the synthesis of a potassium dialkylacetylidoaluminium hydride was attempted. Potassium phenylacetylide was

synthesised from phenylacetylene and *n*-butylpotassium, to which DIBALH was added. The suspension of potassium phenylacetylide gave way to a solution, which when concentrated yielded an oil. Once again, analysis of the oil revealed a complex mixture of products, likely due to redistribution of the anionic groups.

Switch to lithium and production of a lithium aluminate

Due to the lack of success of forming pure complexes with a large variety of organopotassium reagents, attempts were made using the alkyllithium reagent (trimethylsilyl)methyllithium (**65**). Related lithium amidoaluminates have been synthesised from $LiAlH_4$ and hexamethyldisilazane (HMDS(H)),[87] or from DIBALH and lithium 2,2,6,6-tetramethylpiperidide (LiTMP),[88] as well as a lithium trialkylaluminium hydride synthesised from DIBALH and isobutyllithium.[89] These complexes proved to be well defined, and stable to redistribution, despite the trend observed by Zakharkin that smaller alkali metal cations tend to destabilise the complex towards redistribution.[96]

These complexes were also effective catalysts for the hydroboration of a variety of substrates with pinacolborane (HBpin, **66**). The complex $Li(Al(iBu)_2(TMP)H)$ (**67**), formed from the reaction of DIBALH and LiTMP was particularly efficient in catalytic reactions, and was also able to be characterised crystallographically with an array of Lewis donors.[88] Thus the reaction of DIBALH with (trimethylsilyl)methyllithium was expected to produce an analogous lithium trialkylaluminium hydride, which may possess superior reactivity due to the higher basicity of the (trimethylsilyl)methyl anion over the TMP anion.

Reaction of (trimethylsilyl)methyllithium **65** with DIBALH **63** yielded a colourless oil, which ^1H NMR analysis showed to be yet again a mixture of products from redistribution of the alkyl groups. Addition of a variety of Lewis donors immediately following formation of the oil yielded similar results. It was found however that addition of one equivalent of *N*,*N*,*N*',*N*'',*N*''-pentamethyldiethylenetriamine (PMDETA) to the oil, followed by freezing the entire mixture in liquid nitrogen and thawing at -70 ˚C in a freezer yielded a crystalline solid. Leaving the solid in the mother liquor at this temperature formed large single crystals over the course of several days, presumably accelerated by temperature fluctuations as the freezer was repeatedly opened and closed throughout the crystallisation period. While these crystals appeared suitable for single crystal X-ray diffraction, they diffracted too weakly to be able to obtain any usable data. Additionally, the crystals dissolved or melted when allowed to warm

to approximately -40 ˚C, making isolation difficult. Removal of the mother liquor at -78 ˚C failed to solve this, as the residual solvent coating the crystals was enough to drive them into a liquid state. Isolating the solid by filtration, followed by removal of residual solvent under high vacuum from -78 ˚C to room temperature did however allow for isolation of a white crystalline solid, which was stable and remained solid under argon at room temperature. The presence of single crystals, and subsequent isolation of a crystalline solid suggested a pure compound, and ^{1}H NMR analysis of the crystals indeed showed a marked reduction in the complexity of the solution. Only two signals for each of the expected proton environments on the alkyl groups were observed, presumably the result of oligomer formation or different PMDETA binding modes in solution. ^{7}Li NMR showed a single sharp signal, while ^{13}C NMR showed the expected set of only nine sharp signals, suggesting that the two complexes observed by proton NMR were not distinguishable by ^{13}C NMR. Additionally, a very broad singlet at 2.75 ppm in the ^{1}H NMR spectrum showed the presence of a hydrido ligand in the complex. In accordance with this, ^{27}Al decoupled proton NMR showed a significant sharpening of the singlet, due to the cessation of coupling with the quadrupolar aluminium nucleus. Based on this information, it seemed most likely that the product was the desired heteroleptic lithium trialkylaluminium hydride Li[Al(CH_2($SiMe_3$))(*i*Bu)$_2$H]·PMDETA (**68**), coordinated to PMDETA in a mixture of bridging and chelating modes, or existing as a mixture of monomeric and dimeric forms. It is also possible that a separated ion pair is formed by complexation of one of the lithium cations, as is seen in the diglyme complex of **67**, however the additional bulk of PMDETA compared with diglyme makes it difficult to coordinate two equivalents of PMDETA to one lithium cation.[88]

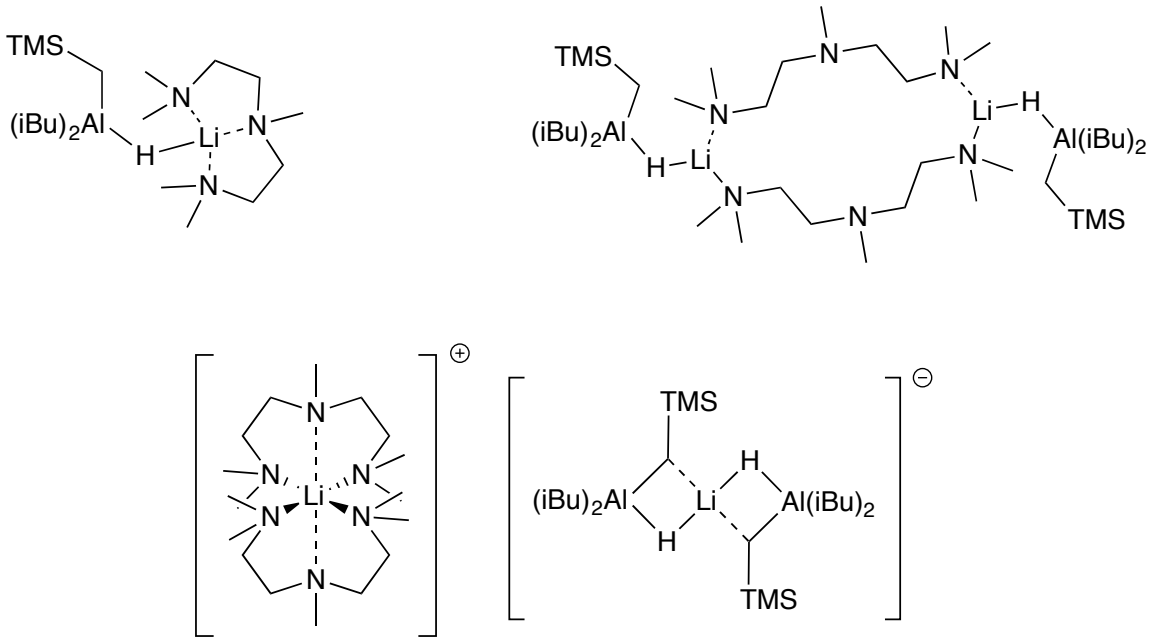


*Figure 20: Some plausible solution state structures of **68**. Top left: Monomer, top right: PMDETA bridged dimer, bottom: separated ion pair.*

Reproduction of these results proved difficult, with reactions repeatedly forming oils similar to those obtained as products in the reactions using potassium sources. Cooling the oil in liquid nitrogen, and thawing at -78 ˚C, or just cooling the mixture to -78 ˚C still yielded a microcrystalline solid, however ^{1}H NMR analysis yet again showed this solid to be a mixture of redistribution products. With the knowledge that the reaction of (trimethylsilyl)methyllithium and DIBALH was capable of producing a pure product, the reaction conditions were systematically varied in order to reproduce the results obtained previously. Changing the reaction temperature from room temperature to 0 ˚C, -20 ˚C, or to -78 ˚C had little effect on the purity of the product, as did changing the solvent medium between various hydrocarbon solvents or doping with ethereal or halogenated solvents. All of the products of these reactions returned to an oil when warmed to room temperature, despite the workup procedure employed being able to previously isolate a crystalline solid. Attempts to replace PMDETA with other Lewis donors such as TMEDA or 12-crown-4, or removing the donor altogether yielded similar mixtures of redistribution products.

Changing the order of addition of reagents so that PMDETA was complexed to one of the organometallic reagents before addition of (trimethylsilyl)methyllithium improved the results, with solid material being isolated and remaining solid at room temperature, however the product still had some impurities, and the reaction outcome was unreliable. Changing the

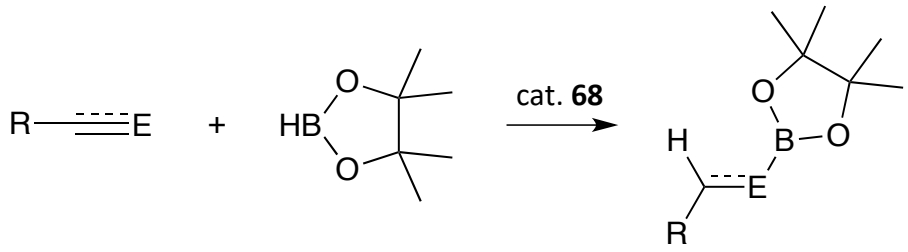
solvent in which (trimethylsilyl)methyllithium was dissolved proved to have the most beneficial effect, with a 0.5 M solution in hexane providing much more reliably pure solid product than a 1.0 M solution in pentane. This is most likely due to the low solubility of (trimethylsilyl)methyllithium in pentane: the reagent readily crystallises from pentane at room temperature at a concentration of 1.0 M, and requires heating to return to the solution state. Unfortunately, the boiling point of pentane is 36 ˚C, so a warmed solution of (trimethylsilyl)methyllithium in pentane has a very high vapour pressure, and as a result it is difficult to transfer accurate quantities by syringe.

With an optimised synthesis in hand, a large batch of the complex was synthesised to test its capabilities in catalysis. Unexpectedly, using the optimised conditions for synthesis yielded a microcrystalline solid which ^{1}H NMR analysis showed to be a single complex, i.e. there were only one set of signals for each expected environment in the complex, compared with two sets observed previously. This suggests that the previously characterised crystalline product was most likely a mixture of different binding modes of PMDETA which co-crystallise, rather than a solution equilibrium. Despite numerous attempts, this result was unable to be repeated, and all future preparations of the compound bore at least two sets of signals, similar to the initial successful synthesis. These results suggest that the synthesis is very sensitive to minor changes in the experimental procedure, perhaps the rate of addition or efficiency of stirring during addition, and these changes appear to affect the binding mode of PMDETA in the product. Without an X-ray diffraction structure, it is very difficult to assess the structural differences between the two apparently different complexes. Attempts to recrystallise the compound and obtain the crystal structure using a synchrotron X-ray source have been unsuccessful due to the extreme solubility of the complex at ambient temperatures, and the tendency to liquefy when in the presence of even minute quantities of residual solvent. Even large masses of crystalline material liquefy before they reach the crystallography oil (i.e. in two or three seconds), meaning that relatively large single crystals are likely to be needed to be able to obtain a structure. The difficulty with growing and isolating sizeable crystals largely stems from the dramatic change in solubility when the temperature is varied: the complex is virtually insoluble in hexane at -78 ˚C, but is extremely soluble at temperatures as low as -30 ˚C. This means that to achieve the slow crystal growth

necessary for large crystals, careful temperature control at low temperatures is required, which is difficult to achieve without specialised equipment.

Catalysis studies with pinacolborane

Despite difficulties fully characterising the complex, a repeatable synthesis had been developed which yields a pure product. The catalytic capabilities of the complex were then assessed for the hydroboration of a variety of functional groups using pinacolborane. As expected, based on the similarity to previously reported complexes, complete conversions of benzaldehyde and cinnamaldehyde were achieved in very short times.

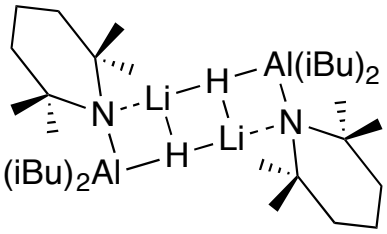


Scheme 65: Hydroboration of unsaturated substrates. E = O, N, C.

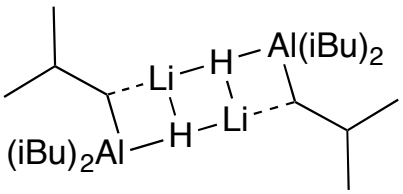
The hydroboration of acetophenone only proceeded to 87% conversion in 20 hours at room temperature. This is inferior to the performance reported with the related lithium diamidodihydrido,[87] dialkylamidohydrido,[88] and trialkylhydrido[89] aluminates, perhaps due to the increased basicity of the (trimethylsilyl)methyl anion compared to that of TMP, HMDS, or a hydride anion. One of the postulated reasons for the slower rate of hydroboration of acetophenone compared to benzaldehyde or benzophenone is a competing deprotonation at the methyl group, resulting in an enolate which cannot easily be hydroborated.[88] While the hydroboration of acetophenone using Li(Al(*i*Bu)$_2$(TMP)H) **67** proceeds to full conversion, and therefore any deprotonative process occurring must be part of an equilibrium, an increased basicity of the catalyst would presumably shift the position of this equilibrium to more heavily favour the enolate, reducing the rate of hydroboration. More importantly, the higher basicity of the (trimethylsilyl)methyl group means that after a deprotonation has occurred, the likelihood of the conjugate acid (here tetramethylsilane compared to TMP(H) or HMDS(H)) being deprotonated to regenerate the catalyst is dramatically lower. That is, while the amido basic groups can exist in an equilibrium with the protonated amine in the presence of mildly acidic substrates, the same is not true of the (trimethylsilyl)methyl anion. Therefore, any

deprotonation that occurs in competition with hydroboration is likely to deactivate the catalyst.

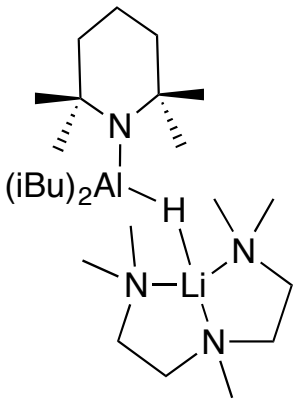
Following promising results with carbonyl substrates, other hydroboration substrates were investigated. Reaction with pyridine showed only trace amounts of reactivity. Reaction of pinacolborane with phenylacetylene, catalysed by **68** also gave only trace amounts of hydroborated product, while no reaction was observed with diphenylacetylene. This is in keeping with the results observed for the TMP analogue Li(Al(*i*Bu)$_2$(TMP)H) **67**, which was unreactive with diphenylacetylene, and gave only trace amounts of hydroboration of phenylacetylene when the PMDETA coordinated complex Li(Al(*i*Bu)$_2$(TMP)H)·PMDETA (**67**·PMDETA) was used.[88,89] Reaction of phenylacetylene with the uncoordinated amido aluminate Li(Al(*i*Bu)$_2$(TMP)H) **67** gave the hydroboration product in 76% yield, suggesting that steric hindrance plays an important role. This may also explain why the Lewis donor-free trialkylhydrido aluminate Li(Al(*i*Bu)$_3$H) (**69**) is an effective catalyst for the hydroboration of phenylacetylene,[89] while **68** is not. Therefore, replacement of PMDETA in **68** with a smaller or more labile Lewis donor may improve its catalytic activity in this reaction.



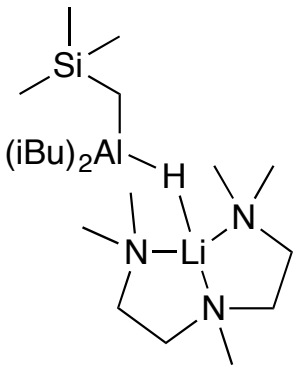
67: Active



69: Active



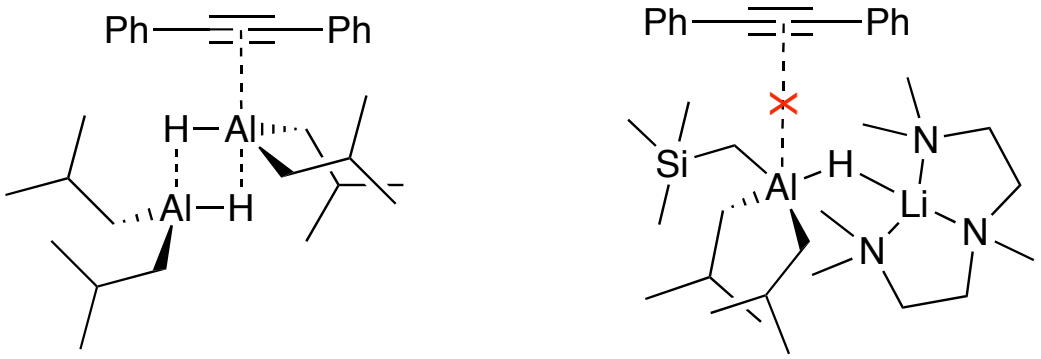
67·PMDETA: Inactive



68: Inactive

Figure 21: Structures of lithium aluminates and their activity in hydroboration catalysis of phenylacetylene.

The lack of reactivity with diphenylacetylene is postulated to arise from the lack of an acidic site, as it has been proposed that hydroboration proceeds via an acetylide intermediate, rather than insertion of the alkyne into the aluminium-hydride bond.[88] It is interesting to note that DIBALH **63** is able to catalyse the hydroboration of diphenylacetylene, which suggests that deprotonation is not vital to the mechanism with aluminium complexes, and perhaps steric hindrance is the reason for the lack of reactivity of **68**, as well as for the related Li(Al(*i*Bu)$_2$(TMP)H) **67**. Another possible cause is the increase in Lewis basic sites (both anionic and neutral) in **68** compared to DIBALH, which may inhibit the coordination of the Lewis acidic aluminium centre to the alkyne π-bond, preventing the interaction necessary for catalysis.

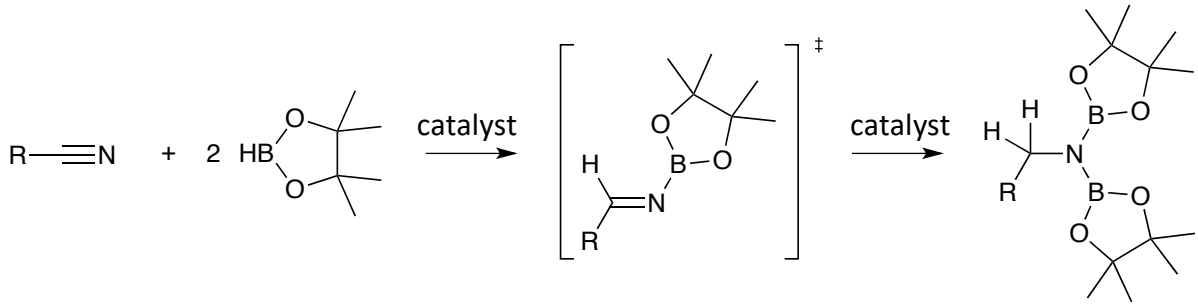


Unsaturated aluminium coordination sphere: interaction with π-bond

Saturated aluminium and lithium coordination spheres: no interaction with π-bond

*Figure 22: Diagrams of the interactions of DIBALH **63** (left) and **68** (right) with diphenylacetylene. Both steric and electrostatic interactions can be expected to prevent the coordination of **68**.*

Nitriles were then investigated as substrates. Benzonitrile was used as a model substrate to test the ability of **68** to catalyse the hydroboration of the carbon-nitrogen bond. All of the literature examples of catalytic hydroboration using deactivated boranes (HB(OR)$_2$) proceed by double hydroboration of the nitrile to furnish bis(borylated) amines, presumably as the intermediate borylated imine is much more reactive towards hydroboration.



Scheme 66: Catalytic hydroboration of nitriles to yield bis(borylated)amines.

Thus, benzonitrile was reacted with two equivalents of pinacolborane in deuterated benzene in the presence of Li[Al(CH_2($SiMe_3$))(*i*Bu)$_2$H]·PMDETA **68** as catalyst. Loading as low as 1 % was trialled, and yielded a maximum 30% conversion of benzonitrile to bis(borylated) benzylamine after 28 hours at 60 ˚C. Increasing the catalyst loading to 5% gave 80% conversion in 13 hours at 60 ˚C, which is comparable to other reported catalysts for nitrile hydroboration in the literature (Table 4).

Table 4: Comparison of catalysts used for the hydroboration of nitriles using deactivated boranes (pinacolborane or catecholborane).

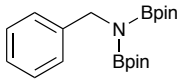
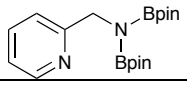
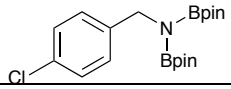
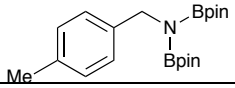
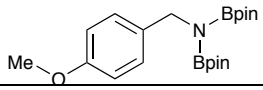
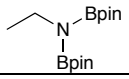
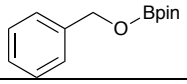
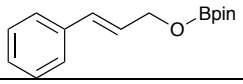
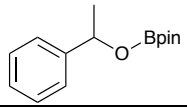
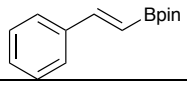
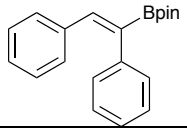
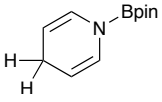
Catalyst based on	**R**	**Loading (mol %)**	**Temperature (˚C)**	**Time (h)**	**Conversion (%)**	**Reference**
Molybdenum	Ph	5	r.t.	12	100	[23]
Ruthenium	Ph	5	r.t.	18	99	[44]
Molybdenum	Ph	5	r.t.	24	99	[98]
Magnesium	Ph	10	60	12	92	[46]
Ruthenium	Ph	1	60	15	96	[99]
Cobalt	Ph	2.5	70	16	67	[22]
Cobalt	Ph	1	60	24	99	[100]
Nickel	Ph	0.5	r.t.	18	99	[47]
Iron/indium	Ph	5 10	80 80	24 24	65 81	[48]
Magnesium	Ph	1	60	8	98	[101]
Aluminium	Ph	1	60	10	99	[45]
Aluminium (Compound **68**)	Ph	1 5 10	60 60 60	28 13 13	30 80 94	This work
Aluminium (DIBALH **63**)	Ph	10	60	21	30	This work
Magnesium	*t*-Bu	1 10	60 60	1 5.5	100 100	[83]
Aluminium ($LiAlH_4$)	4-$(CF_3)C_6H_4$	1	r.t.	6	71	[58]

The turnover number (TON) of **68** for this reaction is 30 at 1% catalyst loading, but falls to 16 at 5% loading, suggesting that deactivation of the catalyst is occurring faster at higher loading. This may be due to product inhibition, as the reaction with 1% loading never reached a product : substrate ratio above 0.5 : 1, while the reaction at 5% loading halted at a product :

substrate ratio of 4 : 1, meaning that there is a much higher chance of interaction with product in the reaction mixture than with substrate, and therefore the catalyst will likely be deactivated faster. There are other possibilities for the change in TON between the two catalyst loading levels, but kinetic studies are required before any of these can be confirmed or excluded.

Several different nitriles were tested as substrates with **68**, and the results are summarised in Table 5. Acetonitrile only proceeds to 20 % conversion, with significant quantities of unidentified by-products. The lack of selectivity of the reaction is likely a result of the relative acidity of acetonitrile, allowing deprotonation to occur in competition with hydroboration, and likely deactivating the catalyst in the process.

Table 5: Substrate scope for hydroboration with pinacolborane catalysed by 68.

Substrate	Product	Loading (mol %)	Temperature (˚C)	Time (h)	Conversion (%)
Benzonitrile		1	60	28	30
		5	60	13	80
		10	60	13	94
2-Cyanopyridine		5	r.t.	13	> 99
4-Chlorobenzonitrile		5	60	13	> 99
4-Tolunitrile		5	60	38	65
4-Methoxybenzonitrile		5	60	13	77
Acetonitrile		5	60	18	20
Benzaldehyde		10	r.t.	< 1	> 99
Cinnamaldehyde		5	r.t.	< 1	> 99
Acetophenone		5	r.t.	20	87
Phenylacetylene		5	60	20	trace
Diphenylacetylene		5	60	20	0
Pyridine		5	60	20	trace

Of the arylnitrile substrates tested, a trend can be observed between the rate and extent of conversion of the substrate, and the electron donating or withdrawing properties of the substituents of the ring. The electron withdrawing para-chloro substituent allows the hydroboration to proceed to full conversion with 13 hours at 60 ˚C, while the electron

deficient pyridine ring allows the reaction to proceed to completion in the same period of time at room temperature. Notably, the reduction of 2-cyanopyridine occurs exclusively at the nitrile group, and no reduction of the pyridine ring is observed.

The accelerated hydroboration of electron deficient arylnitriles is expected, as the withdrawal of electron density from the nitrile carbon results in enhanced electrophilicity of the carbon atom. Similarly, electron donating substituents can be expected to have the opposite effect, and slow the rate of hydroboration. While this is what is seen, the magnitude of this effect is unexpected in relation to the 4-methoxy and 4-tolyl nitriles: para-methoxy groups are significantly more electron donating than para-methyl groups, so a more dramatic retardation of the reaction would be expected for 4-methoxybenzonitrile than for 4-tolunitrile. Instead, the reaction of 4-methoxybenzonitrile proceeds faster and to higher conversion. This may be due to the methoxy group coordinating to the catalyst or pinacolborane in a transition state, or simply that 4-tolunitrile or its hydroborated derivative deactivates the catalyst more effectively than the 4-methoxy analogues.

The ability of **68** to catalyse the hydroboration of the strong carbon-nitrogen bond in nitriles, but not the triple bond in alkynes may be related to the coordination sphere of the lithium cation: PMDETA is a strong chelating Lewis donor which, coupled with the hydride anion, is providing a four-coordinate environment which is favoured by lithium. To access the lithium ion, at least one of the arms of the PMDETA molecule must be displaced. The triple bond in an alkyne is a very soft and relatively weak Lewis donor, so this displacement is unlikely to be energetically favourable. Nitrile groups however are hard Lewis donors, and are likely to form strong enough interactions with the lithium cation to displace the amino arms of PMDETA. The same is true of the carbonyl groups of aldehydes and ketones, and explains the ability of **68** to catalyse the hydroboration of these functional groups. While pyridine may be expected to also displace PMDETA due to its status as a strong Lewis donor, steric bulk may play a role here, as nitrile and carbonyl groups are relatively uncrowded compared with the nitrogen atom of pyridine. Of course, it is possible that pyridine hydroboration is not catalysed by aluminate complexes, and so far there are no reports of pyridine hydroboration by an aluminium complex.

Mechanistic studies with benzonitrile

To investigate the mechanism of the hydroboration of nitriles with **68**, and the nature of the synergistic interaction of the two metals, the interactions of the individual components of the complex with benzonitrile were analysed.

(Trimethylsilyl)methyllithium **65** was added to a solution of benzonitrile in hexane, yielding a solution from which two different types of crystal deposited. A set of very tiny brown crystals were formed, which were of unsatisfactory quality to analyse by single crystal X-ray diffraction. Larger colourless crystals also formed, which showed the structure to be $(PhC(NH)N(Li)C(CHSiMe_3)Ph)_6((Me_3)SiOLi)_2O_2Li_2$ (**70**) shown in Figure 23. Although unfortunately the diffraction data obtained was of relatively poor quality, this is mainly caused by disorder of the peripheral trimethylsilyl groups, and therefore an analysis of the main features of the complex can be made.

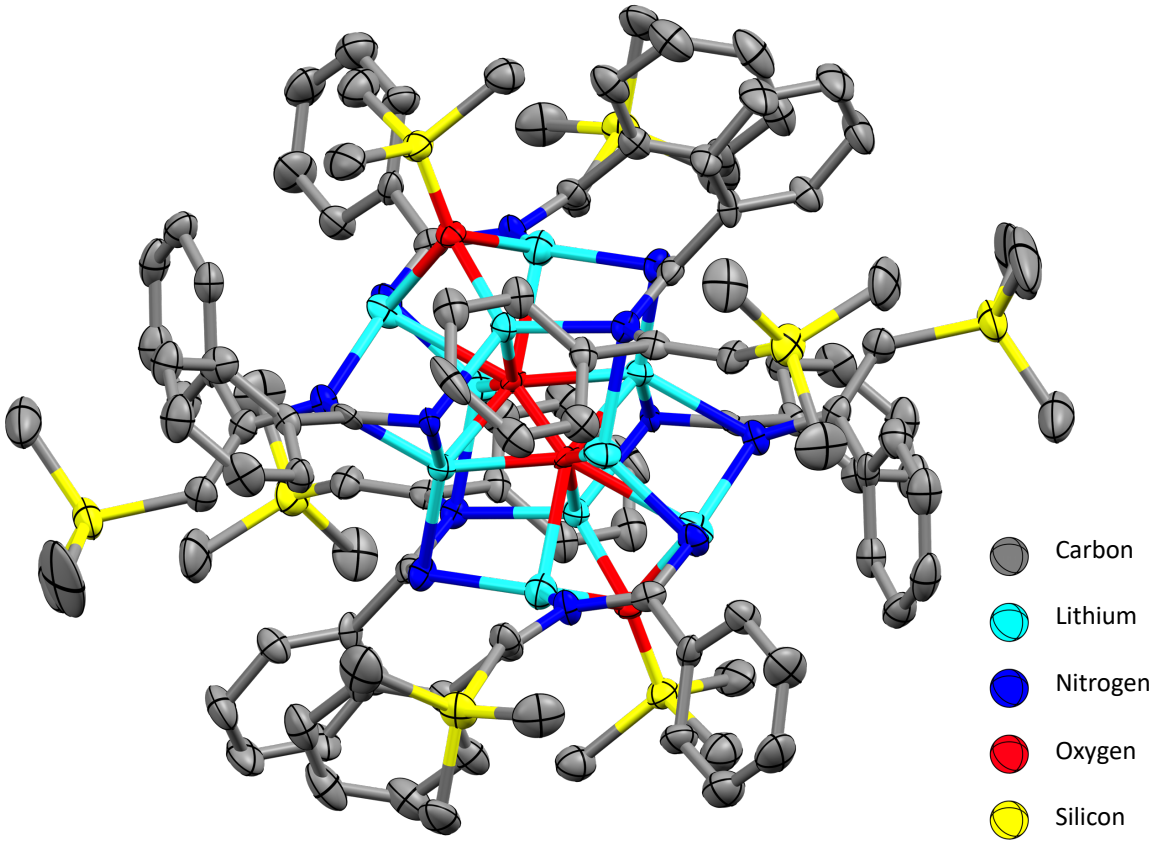


*Figure 23: Molecular structure of **70**. Hydrogen atoms are omitted for clarity. Ellipsoids are shown at 50% probability.*

Perhaps the most striking feature of the structure is the Li_{10} cluster, which possesses distorted elongated square bipyramidal geometry (Figure 24). It is immediately obvious that the

reaction was exposed to oxygen at some point as the centre of the lithium cluster contains a peroxide unit, based on the oxygen-oxygen bond length of 151 pm. Each of these oxygen atoms are coordinated to six lithium atoms, as well as the other oxygen atom, giving a distorted pentagonal bipyramidal geometry about the oxygen atom. The Li_{10} cluster is capped on either end by a trimethylsiloxide group, formed either from the oxidation of (trimethylsilyl)methyllithium, or from the decomposition of the polydimethylsiloxane grease used. The siloxide oxygen bonds to three lithium atoms, with bond lengths averaging 190 pm, while the peroxide Li-O bond lengths vary between 190 and 235 pm. The siloxy oxygen atom is in a distorted tetrahedral environment: the Si-O-Li angles range between 124˚ and 134˚, while the Li-O-Li bond angles range between 82˚ and 90˚.

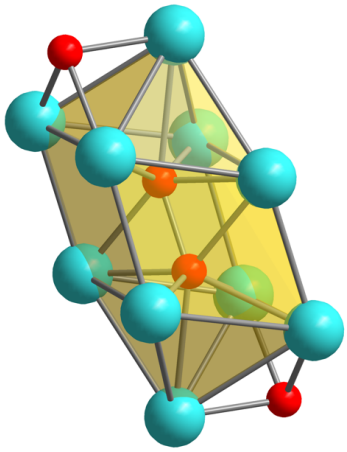


Figure 24: Representation of the geometry of the Li_{10} central cluster. All atoms other than lithium and oxygen are omitted for clarity.

The coordination of the lithium cluster is completed by six amidinate anions, forming two nearly planar twelve-membered $(Li\text{-}N\text{-}C\text{-}N)_3$ rings which lie between the siloxy and peroxido oxygen atoms on each end of the cluster, with Li-N bond distances averaging 206 pm. The angles between the amidinate ligands and the centroid of the ring deviate only slightly from 120˚. These ligands also form interactions with the other four lithium atoms which lie between the two 12-membered rings; there are five Li-N contacts in the range 202 to 219 pm, two Li-C contacts between the amidinato carbon atoms of 244 and 251 pm, and one interaction with a benzylic carbon of 268 pm.

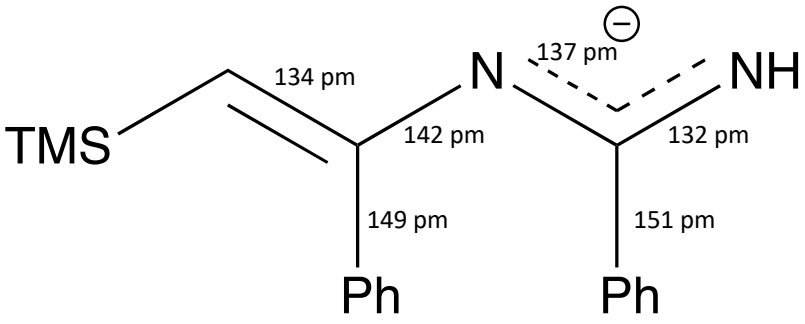
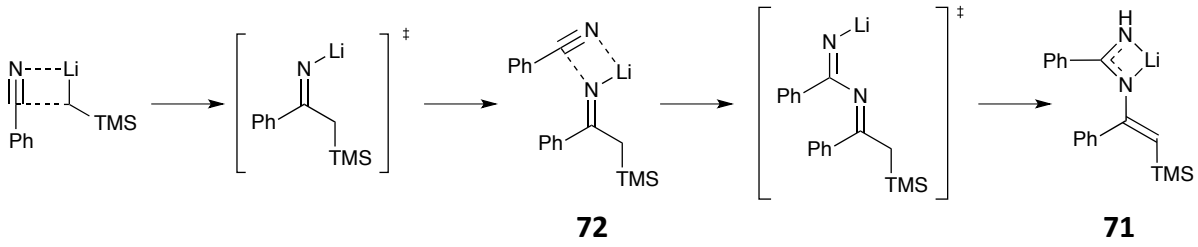


*Figure 25: Structure of amidinate anion **71**, showing important bond lengths.*

The amidinate anions exist as (*E*)-[PhC(NH)NC(CHSiMe$_3$)Ph]$^-$ (**71**), which consist of two benzonitrile residues bonded between one nitrogen and an α-carbon atom, as well as a (trimethylsilyl)methyl residue attached at the other α-carbon. The C-N bond lengths of the amidinate moiety are 132 pm for the terminal nitrogen, and 137 pm for the substituted nitrogen, showing that incomplete delocalisation of the electron density of the π-system across the two bonds has occurred. Meanwhile, the bond between the nitrogen of the amidinate group and the benzylic carbon is 142 pm, and the C-C bond between the (trimethylsilyl)methyl group and the benzylic carbon is 134 pm, showing that the π-bonds which existed in one nitrile moiety have completely relocated.

The presence of amidinate groups in the structure is informative about the reactivity of (trimethylsilyl)methyllithium with benzonitrile. This functionality presumably arises from the nucleophilic addition of (trimethylsilyl)methyllithium across the C-N bond in benzonitrile to form the lithiated benzylimide PhC(CH$_2$SiMe$_3$)NLi (**72**), followed by a nucleophilic addition of this complex across another equivalent of benzonitrile to yield a new nitrogen-carbon bond between the two molecules (Scheme 67).



*Scheme 67: Mechanism for the formation of lithium amidinate **71**.*

This shows that (trimethylsilyl)methyllithium is nucleophilic enough to add across the triple bond of a nitrile substrate, forming an imide which is still nucleophilic enough to attack a second equivalent of nitrile. The formation of a new carbon-carbon bond, followed by

formation of a nitrogen-carbon bond will clearly impede the ability of (trimethylsilyl)methyllithium to act on nitriles in hydroboration catalysis, highlighting the necessity of complexation with an aluminium centre to control the reactivity.

Investigating the impact of the other major component of **68**, hydroboration of benzonitrile with pinacolborane catalysed with DIBALH alone was attempted, and proceeded to 30% conversion in 21 hours at 60 ˚C. When compared with the conversion of 80% in 13 hours at the same temperature obtained with **68**, this shows that the formation of the bimetallic complex significantly accelerates catalysis.

There are several possible reasons for the enhanced catalytic performance of **68**: similar to that proposed for phenylacetylene, a deprotonation of the substrate could occur, yielding an aryl aluminate complex which coordinates to pinacolborane and directs the hydroboration of the nitrile bond. The electron withdrawing nature of the nitrile group means that the initial complex would most likely stabilise the carbanion better than the bis(borylated)amine product, allowing the product to deprotonate a free benzonitrile molecule, and establishing a catalytic cycle.

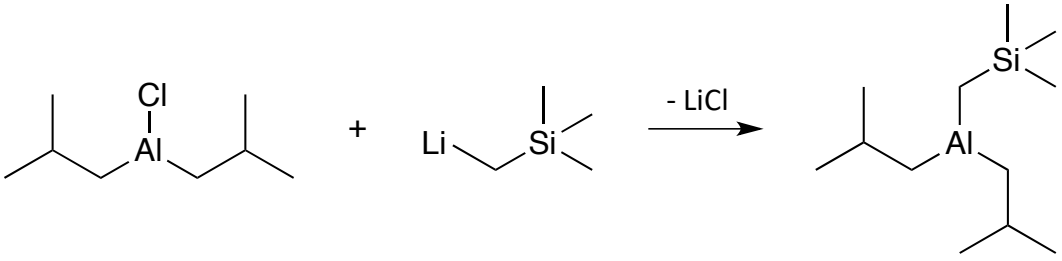
Another explanation for the augmented reactivity of **68** compared to the parent aluminium hydride DIBALH arises from a combination of the higher affinity of lithium (compared to aluminium) for heteroatoms, and from the change in electron distribution about the aluminium centre. That is, the complex changes from a neutral dimeric or trimeric complex bridged by 3-centre-2-electron bonds to an anionic complex with four covalent bonds to the alkyl and hydrido substituents. This effectively increases the polarisation of the complex, which may be beneficial to the hydroboration process.

In an attempt to understand the interaction of the aluminium complex **68** with HBpin **66**, the two compounds were mixed in deuterated benzene and analysed by NMR spectroscopy. Both ^{11}B and ^{1}H NMR showed a complex series of signals had developed, showing that **68** does not form a simple 1:1 stoichiometric complex with HBpin. In the proton NMR spectrum, many signals for each of the alkyl environments of **68** had appeared, while the signals belonging to free HBpin had disappeared. Similarly, in the ^{11}B NMR spectrum, the large singlet belonging to HBpin was gone, replaced by a very broad signal further upfield, as well as several very small sharp signals even further upfield. This suggests that complex **68** is either forming a

variety of adducts with HBpin with different stoichiometries, or is undergoing a redistribution of ligands.

Synthesis of related trialkylaluminium complex (diisobutyl)(trimethylsilyl)methylaluminium

In order to better understand the structure of **68**, the related neutral complex (diisobutyl)(trimethylsilyl)methylaluminium (**73**) was synthesised. Reaction of diisobutylaluminium chloride with (trimethylsilyl)methyllithium in hexane eliminated lithium chloride, yielding a colourless oil when the solvent was removed. This oil was able to be distilled under reduced pressure to produce the highly pure, extremely air sensitive trialkylaluminium complex. ^{1}H and ^{13}C NMR spectroscopy in benzene showed the expected signals for the complex, while diffusion ordered spectroscopy (DOSY) estimated the molecular weight to be 214 g/mol, a -7% difference from the calculated molecular weight of 228 g/mol, revealing that the complex exists in benzene predominantly (if not exclusively) as a monomer. This shows that the three alkyl groups incorporated in both **68** and **73** introduce sufficient steric demand to inhibit aggregation, even in a very weakly coordinating solvent such as benzene.



73

*Scheme 68: Synthesis of **73** from diisobutylaluminium chloride and (trimethylsilyl)methyllithium.*

The additional lithium and hydride atoms present in **68** present a means by which the complex could overcome the steric bulk and dimerise, by bridging through lithium-hydride interactions. Coordination of the lithium atom by PMDETA would likely impede this bridging however, by saturating the coordination environment of the lithium atom. A pertinent example for comparison is the related amido system $Li(Al(iBu)_2(TMP)H)$ **67**: the neutral aluminium complex (diisobutyl)(2,2,6,6-tetramethylpiperidyl)aluminium (**74**) is monomeric in solution, as determined by DOSY studies, while the same characterisation technique identifies the lithium aluminate **67** as a dimer in benzene, bridged by Li-H interactions.[88] Additionally,

the PMDETA complex of **67** is monomeric in the solid state. By analogy, it seems likely that compound **68** will likely exist as a monomer.

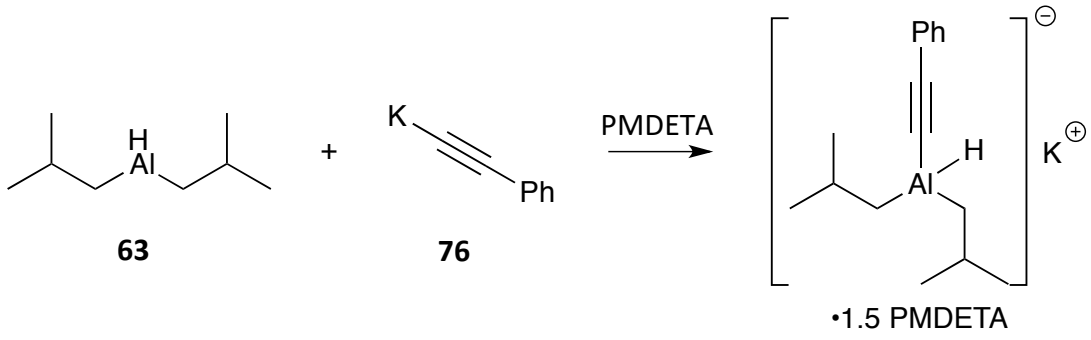
Return to synthesis of potassium aluminates

Once a successful synthetic route to complex **68** had been established, it was of interest to see if the same methods could be applied to obtain pure complexes of the previously unobtainable potassium aluminates. Thus, application of the technique of freezing solutions of potassium aluminates in liquid nitrogen, thawing at -78 ˚C, and filtering the mother liquor off the residue allowed for the isolation of pure solids from two previously unsuccessful reactions.

Reaction of KTMP **64**, DIBALH **63**, and PMDETA yielded a solid product when frozen and thawed at -78 ˚C. NMR analysis of this solid indicated a mostly pure product, however on comparison with the analogous lithium aluminate **67**, the ^{1}H and ^{13}C NMR signals were found to be completely identical, indicating that the KTMP used in the reaction was contaminated with significant quantities of LiTMP, and therefore **67** was isolated instead of the desired potassium complex.

The same synthetic route was used to generate potassium (diisobutyl)(phenylethynyl)hydridoaluminate (**75**), with KTMP substituted for phenylethynyl potassium (**76**). This complex is the potassium analogue of the previously reported PMDETA coordinated lithium (diisobutyl)(phenylethynyl)hydridoaluminate (**77**). Once again, isolation of this solid by freezing the solution and thawing at -78 ˚C produced a pure compound which could be isolated as a solid. ^{1}H and ^{13}C NMR data of complexes **75** and **77** are quite similar, with only a few small differences. Compared to the lithium complex, there is a downfield shift of the hydride signal by approximately 0.8 ppm in the potassium complex, while the rest of the chemical shifts are nearly identical, with the exception of the PMDETA signals. In the lithium aluminate **77**, broad signals between 2.1 and 1.6 ppm in the proton NMR spectrum are present, typical of a PMDETA molecule coordinating to a metal centre. In the ^{1}H NMR spectrum of potassium aluminate **75** however, the signals corresponding to PMDETA are confined to the range 2.0 to 1.9 ppm, and are comparatively very sharp signals. This suggests that the potassium complex **75** incorporates PMDETA into the structure, but it is not coordinating strongly in solution. Additionally, integration of the proton NMR spectrum

shows that there are 1.5 molecules of PMDETA for every molecule of **75**, compared with the 1:1 ratio observed for the lithium congener.



63 **76** **75**

*Scheme 69: Synthesis of potassium alkynylaluminate **75**.*

Given that the goal of synthesising potassium analogues of the lithium aluminates was to promote interaction of the alkali metal with π-systems in substrates, it seems pertinent to try to compare the bonding environments of **75** and **77**. While neither system has any crystallographic characterisation available, the ^{13}C NMR spectra can be informative about the environments of the carbon atoms of the alkynyl groups. Reports by Uhl and co-workers have shown that the chemical shifts of these carbon environments depend on various factors, including the alkynyl substitution, the other ligands on the aluminium centre, as well as any other substituents or Lewis donors.[102] In dimeric alkynyl aluminium complexes, the difference between the chemical shifts of the two alkynyl carbon atoms was shown to be indicative of the type of bonding between the monomeric units. The only difference between **75** and **77** is the identity of the alkali metal, so any change should be due to a change in the coordination environment of the alkynyl anion. While the signals for the alkynyl carbon atoms are unassigned in the literature report of lithium aluminate **77**, the spectrum is given in the supporting information, and a small signal at 108.5 ppm is apparent. This signal is shifted in the spectrum of potassium aluminate **75**, with a small signal present at 100.4 ppm. Without identifying the chemical shift of the other alkynyl carbon atom, it is difficult to infer anything from this information, however the similarity between these signals is indicative that the two alkynyl moieties have very similar bonding environments. The dramatic difference in the ^{1}H NMR signals of PMDETA in each complex suggests that potassium in **75** is much less strongly coordinated to the chelating Lewis donor than lithium in **77**, which may mean that there is a stronger interaction with the alkynyl π-system to satisfy the coordination sphere of the potassium cation.

In order to better compare the structures of the two complexes, infrared spectroscopic analysis of the C≡C bonds, as well as the aluminium-hydride bonds may be informative. Of course, crystallographic analysis would be invaluable in this regard. Complete characterisation through NMR spectroscopy may also help to elucidate how the individual components of each complex interact. Changing the Lewis donor used may also help to probe any structural differences between the two complexes.

Conclusions and future work

The results of this chapter have shown that PMDETA-chelated lithium (diisobutyl)(trimethylsilyl)methylaluminium hydride **68** can act as an effective catalyst for the hydroboration of various substrates, most notably in the hydroboration of nitriles, which has proven a challenging goal for catalysis. While **68** is not as efficient as some of the transition-metal based catalysts reported in the literature, its performance is comparable with many of the more earth-abundant materials. The economic and environmental benefits of replacing transition metals with widely abundant and relatively non-toxic aluminium, coupled with the simple one-pot synthesis of the complex from commercially available precursors makes the use of **68** an attractive alternative.

While the structure of **68** has not been completely elucidated, the data available suggest that the structure is sensitive to the conditions employed in its synthesis, with two different forms co-crystallising in most cases. The related aluminium complex (diisobutyl)(trimethylsilyl)methylaluminium **73** was synthesised, and diffusion-ordered spectroscopy (DOSY) showed this complex to be monomeric in solution in benzene. This information, coupled with comparison to related complexes reported in the literature, suggest that complex **68** is likely monomeric in solution, though the structure of the apparent second form of **68** is unclear.

Compound **68** was compared with the parent hydride DIBALH **63**, and was found to perform significantly better in nitrile hydroboration, while DIBALH had more activity in the hydroboration of alkynes. This was attributed to a combination of steric and electronic factors, with the large bulk of **68** inhibiting approach of the alkyne, and the coordinative saturation of the metal ions preventing inclusion of the π-bond into the coordination sphere of either of the metals. Meanwhile, the hydroboration of carbonyls and nitriles with **68** was

effective, presumably due to the ability of the heteroatom to displace one of the ligands from the coordination sphere of the complex.

Reaction of the other parent compound of **68**, (trimethylsilyl)methyllithium **65**, with benzonitrile resulted in the formation of crystals of the lithium peroxide cluster $(PhC(N)NC(CHSiMe_3)Ph)_6((Me_3)SiOLi)_2O_2Li_2$ **70**, containing amidinato ligands, evidence that (trimethylsilyl)methyllithium undergoes a nucleophilic attack upon reaction with benzonitrile.

An attempt was made to analyse the interaction of pinacolborane with **68** in order to better understand the mechanism of catalysis, however the product proved to be a complicated mixture of compounds, likely the result of formation of multiple adducts, and/or redistribution of the ligands of complex **68**.

To better understand the chemistry of **68**, the complex needs to be characterised more thoroughly. Changing the immersion oil used for crystallography to one that can be handled at -78 ˚C may also allow for the X-ray crystallographic characterisation of the microcrystals which liquefy almost instantly at room temperature. Alternatively, completely optimising the conditions for the synthesis should allow for better crystal growth, free from the interference of the oily redistribution products which plagued initial experiments. This may also allow for the synthesis of analogues of **68** using other Lewis donors, which may be easier to characterise. Replacement of PMDETA with a smaller or more labile donor may also lead to an increase in catalytic performance, especially with regards to alkynes, where the lack of reactivity appears to be due to steric hindrance.

Kinetic studies for the catalytic reactions using **68** could help to explain the mechanism of catalysis, as well as elucidating the reason for catalyst deactivation. This information could be used to rationalise the catalyst design and reaction conditions, improving the efficiency of the catalysis.

Attempts at the synthesis of potassium aluminates were largely unsuccessful: only the alkynyl complex potassium (diisobutyl)(phenylethynyl)hydridoaluminate **75** was able to be synthesised without redistribution occurring. NMR analysis of this complex showed pronounced similarity to the related lithium (diisobutyl)(phenylethynyl)hydridoaluminate **77** reported previously, with the most prominent difference in the spectra being the change in coordination of PMDETA. The lithium complex contained one equivalent of PMDETA

coordinating to the lithium ion, while 1.5 equivalents of PMDETA were observed in the potassium complex, with the PMDETA showing no evidence of strong binding to the potassium cation.

Application of the lessons learned in avoiding redistribution in the synthesis of **68** may allow for the successful synthesis of potassium aluminate complexes, which were found to be prone to redistribution reactions. In particular, the synthesis of the potassium analogue of **68**, as well as of other metal aluminates such as sodium or magnesium is of great interest, as these provide an avenue for the exploration of the role of the more electropositive metal in these aluminate complexes, as well as the potential to improve the catalytic performance.

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Experimental

Chapter 1

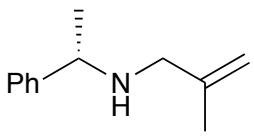
General procedures

Unless otherwise stated, all reactions were performed using Schlenk technique under an inert nitrogen atmosphere. Tetrahydrofuran and hexane were purified using the MBraun SPS-800 solvent purification system and stored over 4 Å molecular sieves. TMEDA and PMDETA were dried by reflux over CaH_2 and stored over 4 Å molecular sieves. *n*-Butyllithium (1.6 M in hexanes), *tert*-butyllithium (1.7 M in pentane), (*S*)-1-phenylethylamine, and 3-bromo-2-methylpropene were purchased from commercial suppliers and used without further purification. *n*-Butylsodium and *n*-butylpotassium were synthesised according to the literature procedure from the reaction of *n*-butyllithium with sodium or potassium *tert*-butoxide in hexane.[1] C_6D_6 and d_8-THF were degassed by three freeze-pump-thaw cycles, and stored over 4 Å molecular sieves (or potassium for ultra-dry d_8-THF). ^{1}H, ^{7}Li and ^{13}C NMR spectra were recorded on a Bruker DRX 400 MHz spectrometer, with chemical shifts referenced internally to C_6D_6 or d_8-THF.

Crystallographic data for compound **8** were obtained on a Bruker X8 APEXII CCD diffractometer equipped with an Oxford Cryosystems 700 Cryostream and cooled to 123(2) K. Data were collected with monochromatic (graphite) Mo Kα radiation (λ = 0.710 73 Å) and processed using the Bruker Apex2 v2012.2.0 software; Lorentz, polarization, and absorption corrections (multiscan, SADABS[2]) were applied. The crystals were mounted in Krytox GPL-107 perfluorinated oil. The structure was solved by standard methods and refined by full matrix least-squares using the SHELX-97 program.[3] Non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms attached to C were placed in calculated positions using a riding model with C−H distances of 0.99 Å and $U_{iso}(H) = 1.2 \times U_{eq}(C)$.

Synthesis and characterisation

(*S*)-*N*-(1-phenylethyl)methallylamine (**3**)



(*S*)-1-phenylethylamine (6.06 g, 50 mmol) was dissolved in 40 mL of THF, followed by addition of *n*-BuLi (31 mL [1.6 M solution in hexanes], 50 mmol) at −78 °C. The solution was stirred for

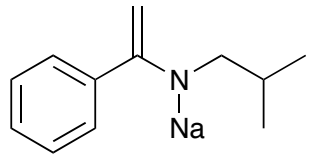
2 hours while warming to 0 °C. 3-Bromo-2-methylpropene (6.75 g, 50 mmol) was then added dropwise, and the resultant solution allowed to warm to room temperature and stirred overnight. The resultant orange solution was quenched with water (50 mL) and THF, evaporated in vacuo, and then extracted with diethyl ether (3 × 40 mL). The organic phase was washed with brine and dried over Na_2SO_4, and then the solvent removed in vacuo to yield a pale yellow liquid. This was distilled under vacuum to a colorless oil, which was stored under N_2 over 4 Å molecular sieves (7.84 g, 89%).

Bp: 40 °C/0.1 Torr.

^{1}H NMR (400 MHz, C_6D_6, 298 K): δ 7.29 (2H, m, *ortho*-**H**), 7.20 (2H, m, *meta*-**H**), 7.10 (1H, m, *para*-**H**), 4.97 (1H, s, $CH_2C(CH_3)=CH_2$*trans*), 4.83 (1H, s, $CH_2C(CH_3)=CH_2$*cis*), 3.59 (1H, q, ^3J = 6.6 Hz, $PhC(H)CH_3$), 2.94 (1H, d, ^2J = 14.4 Hz, $CH_2C(CH_3)=CH_2$), 2.92 (1H, dd, ^3J = 14.4 Hz, $CH_2C(CH_3)=CH_2$), 1.63 (3H, s, $CH_2C(CH_3)=CH_2$), 1.19 (3H, d, ^3J = 6.6 Hz, $PhC(H)CH_3$), 1.00 (1H, br s, N**H**).

^{13}C NMR (101 MHz, C_6D_6, 298 K): δ 146.5 (*ipso*-**C**), 144.9 ($CH_2C(CH_3)=CH_2$), 128.7 (*meta*-**C**), 127.1 (*para*-**C**), 127.0 (*ortho*-**C**), 110.5 ($CH_2C(CH_3)=CH_2$), 57.9 ($PhC(H)CH_3$), 53.9 ($CH_2C(CH_3)=CH_2$), 25.0 ($PhC(H)CH_3$), 20.9 ($CH_2C(CH_3)=CH_2$).

Sodium isobutyl(1-phenylvinyl)amide (**8**)



To a stirring suspension of *n*-BuNa (0.16 g, 2 mmol) in hexane (10 mL) at -60 °C was added (*S*)-*N*-(1-phenylethyl)methallylamine (0.35 g, 2 mmol). The suspension was allowed to warm slowly to room temperature and stirred overnight, forming a yellow suspension. An orange suspension was formed upon addition of THF (2.5 mL), which was filtered to isolate a red solution. From this solution, a large crop of yellow plate crystals deposited overnight (0.29 g, 74%).

Mp: 251-252 °C (dark brown melt).

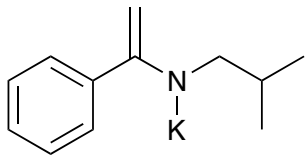
^{1}H NMR (400 MHz, d_8-THF, 298 K): δ 7.68 (2H, d, ^{3}J = 7.9 Hz, *ortho*-**H**), 7.10 (2H, t, ^{3}J = 7.4 Hz, *meta*-**H**), 7.01 (1H, t, ^{3}J = 7.2 Hz, *para*-**H**), 2.86 (1H, d, ^{2}J = 1.7 Hz, C=C**H**$_2$), 2.75 (2H, d, ^{3}J = 6.6 Hz, C**H**$_2$CH(CH$_3$)$_2$), 2.48 (1H, d, ^{2}J = 1.7 Hz, C=C**H**$_2$), 1.74 (1H, septet, ^{3}J = 6.6 Hz, CH$_2$C**H**(CH$_3$)$_2$), 0.99 (6H, d, ^{3}J = 6.5 Hz, CH$_2$CH(C**H**$_3$)$_2$).

^{13}C NMR (101 MHz, d_8-THF, 298 K): δ 164.2 (**C**=CH$_2$), 152.4 (*ipso*-**C**), 128.0 (*meta*-**C**), 127.5 (*ortho*-**C**), 125.6 (*para*-**C**), 63.2 (**C**H$_2$CH(CH$_3$)$_2$), 60.7 (C=**C**H$_2$), 31.6 (CH$_2$**C**H(CH$_3$)$_2$), 22.8 (CH$_2$CH(**C**H$_3$)$_2$).

Anal. Calcd. for $Na_2N_2C_{24}H_{32}$: C, 73.07; H, 8.18; N, 7.10 Found: C, 69.98; H, 8.30; N, 6.89

Crystal Data for **8**: $C_{24}H_{32}N_2Na_2$; M_r = 394.51; monoclinic; space group: P2 (1)/c; *a* = 11.4543(6), *b* = 11.3694(7), *c* = 8.8489(5); α = 90; β = 103.044(4); γ = 90; *V* = 1122.64(11)Å^3; *Z* = 2, reflections collected/unique: 10457/3178 (Rint = 0.0175); R_1 values ($I > 2\sigma(I)$) = 0.0413; $wR(F^2)$ values ($I > 2\sigma(I)$) = 0.1096; R_1 values (all data) = 0.0461; $wR(F^2)$ values (all data) = 0.1137; GOF = 1.048.

Potassium isobutyl(1-phenylvinyl)amide (**10**)



To a stirring suspension of *n*-BuK (0.19 g, 2 mmol) in hexane (10 mL) at -60 °C was added (*S*)-*N*-(1-phenylethyl)methallylamine (0.35 g, 2 mmol). The suspension was allowed to warm slowly to room temperature, and stirred overnight. Addition of THF (3 mL) resulted in a cloudy brown solution, which was filtered to isolate a dark brown solution. After standing at room temperature for several days, a large crop of brown crystals had formed (0.13 g, 30 %).

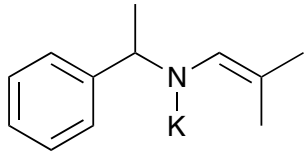
Mp: 271-272 °C (black melt).

^{1}H NMR (400 MHz, d_8-THF, 298 K): δ 7.66 (2H, d, ^{3}J = 6.9 Hz, *ortho*-**H**), 7.10 (2H, t, ^{3}J = 7.3 Hz, *meta*-**H**), 7.02 (1H, t, ^{3}J = 7.2 Hz, *para*-**H**), 2.91 (1H, d, ^{2}J = 1.0 Hz, C=C**H**$_2$), 2.58 (2H, d, ^{3}J = 6.6 Hz, C**H**$_2$CH(CH$_3$)$_2$), 2.38 (1H, d, ^{2}J = 1.0 Hz, C=C**H**$_2$), 1.65 (1H, septet, ^{3}J = 6.6 Hz, CH$_2$C**H**(CH$_3$)$_2$), 0.95 (6H, d, ^{3}J = 6.6 Hz, CH$_2$CH(C**H**$_3$)$_2$).

^{13}C NMR (101 MHz, d_8-THF, 298 K): δ 164.0 (**C**$=$$CH_2$), 151.2 (*ipso*-**C**), 128.0 (*meta*-**C**), 127.5 (*ortho*-**C**), 125.8 (*para*-**C**), 63.2 (**C**H_2CH$(CH_3)_2$), 58.7 (C$=$**C**H_2), 31.7 (CH_2**C**H$(CH_3)_2$), 22.8 (CH_2CH(**C**$H_3)_2$).

Anal. Calcd. for $KNC_{12}H_{16}$: C, 67.55; H, 7.56; N, 6.56 Found: C, 67.44; H, 7.50; N, 6.66

Potassium (2-methylprop-1-enyl)(1-phenylethyl)amide (**12**)



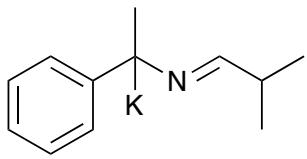
To a stirring suspension of *n*-BuK (0.19 g, 2 mmol) in hexane (10 mL) at -60 °C was added (*S*)-*N*-(1-phenylethyl)methallylamine (0.35 g, 2 mmol). The suspension was allowed to warm slowly to room temperature, and stirred overnight. The resulting light brown powder was washed with two 10 mL volumes of hexane and dried under vacuum (0.18 g, 42 %).

Mp: 100-103 °C (black melt).

^{1}H NMR (400 MHz, d_6-benzene with 5 % d_8-THF, 298 K): δ 7.29 (2H, d, ^{3}J = 7.5 Hz, *ortho*-**H**), 7.21 (2H, t, ^{3}J = 7.6 Hz, *meta*-**H**), 6.99 (1H, t, ^{3}J = 7.2 Hz, *para*-**H**), 6.58 (1H, s, C**H**$=$C), 4.03 (1H, q, ^{3}J = 6.5 Hz, PhC**H**(CH_3)), 2.03 (3H, s, C(C**H**$_3)_2$), 1.86 (3H, s, $=$C(C**H**$_3)_2$), 1.44 (3H, d, ^{3}J = 6.6 Hz, PhCH(C**H**$_3$)).

^{13}C NMR (101 MHz, d_6-benzene with 5 % d_8-THF, 298 K): δ 152.4 (*ipso*-**C**), 149.1 (**C**H$=$C), 129.0 (*meta*-**C**), 125.8 (*ortho*-**C**), 125.4 (*para*-**C**), 75.8 (CH$=$**C**), 67.5 (Ph**C**HCH_3), 25.4 (PhCH**C**H_3), 24.3 ($=$C**C**H_3), 18.1 ($=$C**C**H_3).

(1-((2-Methylpropylidene)amino)-1-phenylethyl)potassium (**13**)



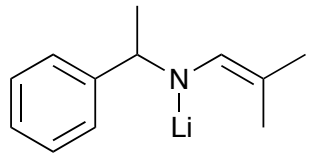
Complex **13** has only been observed as part of a solution equilibrium.

^{1}H NMR (400 MHz, d_8-THF, 298 K): δ 6.97 (1H, br s, *ortho*-**H**), 6.52 (2H, t, ^{3}J = 7.4 Hz, *meta*-**H**), 6.09 (1H, d, ^{3}J = 5.8 Hz, *ortho'*-**H**), 5.68 (1H, d, ^{3}J = 4.1 Hz, N$=$C**H**), 5.50 (1H, t, ^{3}J = 6.7 Hz, *para*-

H), 2.46 (1H, q, ^3J = 6.6 Hz, 4.9 Hz, C**H**$(CH_3)_2$), 1.70 (3H, s, PhC(C**H**$_3$)), 1.04 (6H, d, ^3J = 6.8 Hz, CH(C**H**$_3)_2$).

^{13}C NMR (101 MHz, d$_8$-THF, 298 K): *δ* 144.7 (*ipso*-**C**), 129.2 (*meta*-**C**), 120.0 (N＝**C**H), 112.8 (*ortho*-**C**), 112.6 (*ortho'*-**C**), 105.6 (*para*-**C**), 94.6 (Ph**C**CH_3), 34.7 (**C**H$(CH_3)_2$), 23.7 (CH(**C**H$_3)_2$), 12.1 (PhC**C**H$_3$).

Lithium (2-methylprop-1-enyl)(1-phenylethyl)amide (**18**)



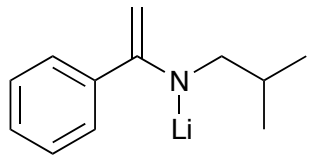
n-BuLi (1.25 mL, 1.6 M in hexanes, 2 mmol) was added to 10 mL of hexane, followed by TMEDA (0.30 mL, 2 mmol). The solution was cooled to -89 ˚C, and (*S*)-*N*-(1-phenylethyl)methallylamine (0.35 g, 2 mmol) was added, forming a yellow oil. Upon warming to room temperature, a gummy yellow solid was obtained, which was washed with hexane (2 x 20 mL), and dried under vacuum to yield a yellow solid.

^{1}H NMR (400 MHz, C_6D_6, 298 K): δ 7.47 (2H, d, ^3J = 7.4 Hz, *ortho*-**H**), 7.22 (2H, t, ^3J = 7.5 Hz, *meta*-**H**), 7.08 (1H, t, ^3J = 7.3 Hz, *para*-**H**), 6.59 (1H, bs, NC**H**＝), 4.24 (1H, bs, PhC**H**), 1.96 (3H, bs, ＝C(C**H**$_3)_2$), 1.85 (3H, bs, ＝C(C**H**$_3)_2$), 1.64 (12H, bs, C**H**$_3$-TMEDA), 1.56 (4H, C**H**$_2$-TMEDA), 1.51 (3H, d, ^3J = 6.6 Hz, PhCHC**H**$_3$).

^{13}C NMR (101 MHz, C_6D_6, 298 K): δ 152.6 (*ipso*-**C**), 147.4 (N**C**H＝), 128.6 (*meta*-**C**), 127.2 (*ortho*-**C**), 125.9 (*para*-**C**), 64.5 (Ph**C**H), 56.3 (**C**H$_2$-TMEDA), 45.2 (**C**H$_3$-TMEDA), 28.0 (PhCH**C**H$_3$), 24.1 (＝C(**C**H$_3)_2$), 17.7 (＝C(**C**H$_3)_2$).

^{7}Li NMR (156 MHz, C_6D_6, 298 K): δ 2.80 (bs), 2.11 (bs), 1.58 (bs), 0.78 (s).

Lithium isobutyl(1-phenylvinyl)amide (**19**)



n-BuLi (1.25 mL, 1.6 M in hexanes, 2 mmol) was added to 10 mL of hexane, followed by PMDETA (0.42 mL, 2 mmol). The solution was cooled to -89 ˚C, and (*S*)-*N*-(1-phenylethyl)methallylamine (0.35 g, 2 mmol) was added, forming a yellow oil. Upon warming to room temperature, a gummy yellow solid was obtained, which was washed with hexane (2 x 20 mL), and dried under vacuum to yield a yellow solid.

^{1}H NMR (400 MHz, C_6D_6, 298 K): δ 8.02 (2H, m, *ortho*-**H**), 7.20 (2H, m, *meta*-**H**), 7.11 (1H, m, *para*-**H**), 3.81 (1H, d, ^{2}J = 1.6 Hz, PhC═C**H**$_2$), 3.44 (1H, d, ^{2}J = 1.6 Hz, PhC═C**H**$_2$), 3.22 (2H, d, ^{3}J = 6.5 Hz, NC**H**$_2$), 2.50 (1H, nonet, ^{3}J = 6.6 Hz, CH_2C**H**$(CH_3)_2$), 1.85 (15H, bs, C**H**$_3$-PMDETA), 1.65 (8H, bs, C**H**$_2$-PMDETA), 1.27 (6H, d, ^{3}J = 6.6 Hz, $CH(CH_3)_2$).

^{13}C NMR (101 MHz, C_6D_6, 298 K): δ 164.1 (Ph**C**═CH_2), 151.9 (*ipso*-**C**), 127.9 (*meta*-**C**), 127.6 (*ortho*-**C**), 125.6 (*para*-**C**), 65.1 (═**C**H_2), 61.9 (N**C**H_2), 57.2 (**C**H_2-PMDETA), 45.5 (**C**H_3-PMDETA), 27.6 ($CH(CH_3)_2$), 22.9 ($CH(CH_3)_2$).

^{7}Li NMR (156 MHz, C_6D_6, 298 K): δ 2.98 (bs), 2.15 (bs), 1.74 (bs), 0.34 (s).

Chapter 2

General procedures

Unless otherwise stated, all reactions were performed using Schlenk technique under an inert nitrogen atmosphere. Tetrahydrofuran, diethyl ether, toluene, and hexane were purified using the MBraun SPS-800 solvent purification system and stored over 4 Å molecular sieves. 1,3-Dimethyl-2-imidazolinone and TMEDA were dried by reflux over calcium hydride, distilled under vacuum, and stored over 4 Å molecular sieves. Diisopropylamine and chlorotrimethylsilane were distilled from calcium hydride and stored over 4 Å molecular sieves. *n*-Butyllithium (1.6 M in hexanes) was purchased from Sigma-Aldrich and standardised before use. *n*-Butylsodium and benzylpotassium were synthesised according to the literature procedure from the reaction of *n*-butyllithium with sodium *tert*-butoxide in hexane, or potassium *tert*-butoxide in toluene.[1] C_6D_6, d_8-toluene, and d_8-THF were degassed by three freeze-pump-thaw cycles, and stored over 4 Å molecular sieves. Nujol for infrared spectroscopy was dried and degassed by heating at 110 ˚C under vacuum over sodium metal. Lithium diisopropylamide was synthesised from diisopropylamine and *n*-butyllithium in diethylether and used as a solution, or isolated as a white solid from the same reaction in hexane. All other reagents were purchased from commercial suppliers and used without further purification. ^{1}H, ^{7}Li, ^{13}C, and ^{29}Si NMR spectra were recorded on a Bruker DRX 400 or 600 MHz spectrometer, with chemical shifts referenced internally to C_6D_6, d_8-toluene, or d_8-THF. Infrared spectra were recorded using an Agilent ATR- FTIR machine.

General procedures for substitution reactions of propargylamines

Substitution procedure A (synthesis from organolithium):

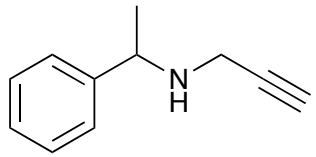
Propargyl amine (1 equivalent) was dissolved in hexane or diethyl ether, and the organolithium reagent (3 equivalents, or 2 equivalents with TMS-substituted propargylamine) was added dropwise, generally forming a white suspension. The reaction was allowed to stir overnight at room temperature, turning to a yellow solution with a small amount of white precipitate (lithium acetylide). The reaction was quenched with methanol, and then extracted three times with hexane or diethyl ether, washed with water and then brine, dried over magnesium sulfate, and the solution concentrated to yield the product as an oil.

Substitution procedure B (synthesis from lithium diisopropylamide):

Lithium diisopropylamide (3 equivalents) was prepared from diisopropylamine and *n*-butyllithium in diethyl ether. Heterocycle (0.5 or 1 equivalent) was added at 0 ˚C, followed by propargyl amine (1 equivalent). The reaction was allowed to stir overnight at room temperature, quenched with methanol, followed by water. The product was extracted three times with diethyl ether, washed with water and then brine, dried over magnesium sulfate, and concentrated to yield the product as an oil.

Synthesis and characterisation

N-(1-phenylethyl)prop-2-yn-1-amine (**20**)



In a flask open to air, potassium carbonate (60 mmol) was suspended in acetonitrile (200 mL) and cooled to 0 ˚C. 1-Phenylethylamine (150 mmol) was added, followed by addition of propargyl bromide (80 % in toluene, 50 mmol) dissolved in an extra 10 mL of toluene. The addition of propargyl bromide was done dropwise over 10 minutes in order to supress formation of tertiary dipropargylamine. The reaction was allowed to warm slowly to room temperature overnight, and then filtered to remove potassium carbonate, and concentrated to yield an oil. Excess 1-phenylethylamine was removed by distillation, and the residue purified by column chromatography through silica gel (neat ethyl acetate, Rf = 0.5). The resulting oil was distilled under high vacuum to yield the product, which was stored over 4 Å molecular sieves under a nitrogen atmosphere (7.02 g, 88 %).

B.p. 42-44 ˚C, 6×10^{-2} kPa.

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.39 – 7.27 (m, 4H, *ortho*/*meta*-**H**), 7.32 – 7.20 (m, 1H, *para*-**H**), 4.01 (q, *J* = 6.6 Hz, 1H, PhC**H**N), 3.35 (dd, *J* = 17.1, 2.4 Hz, 1H, NC**H**$_2$), 3.16 (dd, *J* = 17.1, 2.4 Hz, 1H, NC**H**$_2$), 2.20 (t, *J* = 2.4 Hz, 1H, C≡C**H**), 1.50 (broad s, 1H, N**H**), 1.36 (d, *J* = 6.6 Hz, 3H, C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ 144.5 (*ipso*-**C**), 128.4 (*meta*-**C**), 127.3 (*para*-**C**), 126.9 (*ortho*-**C**), 82.4 (**C**≡CH), 71.4 (C≡**C**H), 56.5 (Ph**C**HN), 36.0 (N**C**H$_2$), 24.0 (**C**H$_3$).

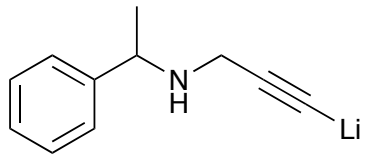
^{1}H NMR (400 MHz, C_6D_6, 298 K) δ 7.32 – 7.23 (m, 2H, *ortho*-**H**), 7.21 – 7.10 (m, 2H, *meta*-**H**), 7.13 – 7.02 (m, 1H, *para*-**H**), 3.87 (q, *J* = 6.5 Hz, 1H, PhC**H**N), 3.12 (dd, *J* = 17.2, 2.5 Hz, 1H,

NC**H**$_2$), 2.97 (dd, *J* = 17.1, 2.4 Hz, 1H, NC**H**$_2$), 1.90 (t, *J* = 2.4, 1H, C≡C**H**), 1.11 (d, *J* = 6.5 Hz, 3H, CH_3), 0.99 (broad s, 1H, N**H**).

^{13}C NMR (101 MHz, C_6D_6, 298 K) δ 145.3 (*ipso*-**C**), 128.7 (*meta*-**C**), 127.3 (*para*-**C**), 127.2 (*ortho*-**C**), 82.8 (**C**≡CH), 71.3 (C≡**C**H), 56.5 (Ph**C**HN), 36.1 (N**C**H$_2$), 24.5 (**C**H$_3$).

FTIR (neat) ν_{max}/cm^{-1} 3291w (≡C-H stretch), 2965w, 2924w, 1493w, 1450m, 1370m, 1325w, 1115m, 1077w, 1060w, 1027w, 911m, 760s, 699s, 624s (≡C-H bend).

(3-((1-phenylethyl)amino)prop-1-yn-1-yl)lithium (**21**)



N-(1-phenylethyl)prop-2-yn-1-amine (2 mmol) was dissolved in hexane (10 mL) and cooled to 0 °C. *n*-BuLi (1.6 M in hexane, 2 mmol) was added dropwise, forming a white precipitate, which was allowed to warm to room temperature and stirred for 20 minutes before being filtered and washed with hexane (2 × 10 mL). The white solid was dried under vacuum to yield a white powder (269 mg, 81 %).

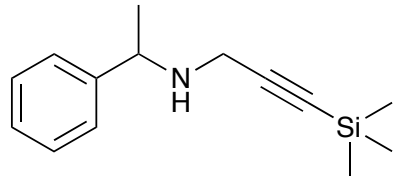
^{1}H NMR (400 MHz, d_8-THF, 298 K) δ 7.33 (d, *J* = 7.1 Hz, 2H, *ortho*-**H**), 7.19 (t, *J* = 7.5 Hz, 2H, *meta*-**H**), 7.11 (tt, *J* = 6.8, 1.5 Hz, 1H, *para*-**H**), 4.02 (q, *J* = 6.6 Hz, 1H, PhC**H**N), 3.11 (d, *J* = 15.8 Hz, 1H, NC**H**$_2$), 2.94 (d, *J* = 15.8 Hz, 1H, NC**H**$_2$), 1.63 (s, 1H, N**H**), 1.24 (d, *J* = 6.6 Hz, 3H, C**H**$_3$).

^{13}C NMR (101 MHz, d_8-THF, 298 K) δ 147.2 (*ipso*-**C**), 128.6 (*meta*-**C**), 127.5 (*ortho*-**C**), 126.9 (*para*-**C**), 123.9 (C≡**C**Li), 112.9 (**C**≡CLi), 57.2 (Ph**C**HN), 39.0 (N**C**H$_2$), 24.8 (**C**H$_3$).

^{7}Li NMR (156 MHz, d_8-THF, 298 K) δ 0.61.

FTIR (Nujol mull) ν_{max}/cm^{-1} 2954w, 2919m (Nujol), 2851m (Nujol), 1493w, 1450m (Nujol), 1375w (Nujol), 1303w, 1101w, 1021w, 760m, 699s.

N-(1-phenylethyl)-3-(trimethylsilyl)prop-2-yn-1-amine (**22**)



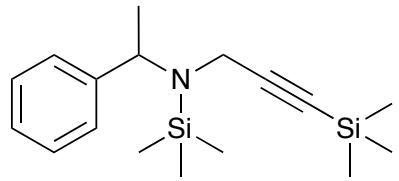
The synthesis follows the same procedure for *N*-(1-phenylethyl)prop-2-yn-1-amine (**20**) (50 mmol scale). After purifying the product by silica gel chromatography, instead of being distilled, the residue was dissolved in tetrahydrofuran (50 mL) under a nitrogen atmosphere. 1,3-Dimethyl-2-imidazolinone (1.55 mL, 15 mmol) was added, followed by *n*-BuLi (1.5 M in hexanes, 35 mL, 52 mmol) was added, forming a dark red solution. Chlorotrimethylsilane (7 mL, 55 mmol), forming a cloudy pale orange mixture, which was refluxed for 6 hours. The reaction was quenched with saturated sodium carbonate solution, and then diluted with water. The solution was extracted three times with diethyl ether, washed with water and then brine, dried over magnesium sulfate, and the solution concentrated to yield a brown oil. Distillation produced a yellow oil, which was stored under a nitrogen atmosphere (8.8 g, 78 %).

B.p. 70-74 ˚C, 1×10^{-2} kPa.

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.35 – 7.30 (m, 4H, *ortho*/*meta*-**H**), 7.28 – 7.22 (m, 1H, *para*-**H**), 3.98 (q, *J* = 6.6 Hz, 1H, PhC**H**N), 3.35 (d, *J* = 17.2 Hz, 1H, NC$\mathbf{H}_2$), 3.19 (d, *J* = 17.2 Hz, 1H, NC$\mathbf{H}_2$), 1.37 (d, *J* = 6.6 Hz, 3H, PhCC$\mathbf{H}_3$), 0.17 (s, 9H, Si(C$\mathbf{H}_3$)$_3$).

^{13}C NMR (151 MHz, $CDCl_3$, 298 K) δ 144.4 (*ipso*-**C**), 128.6 (*meta*-**C**), 127.4 (*para*-**C**), 127.1 (*ortho*-**C**), 104.4 (C≡**C**Si), 88.2 (**C**≡CSi), 56.7 (Ph**C**HN), 37.2 (N**C**H_2), 23.9 (**C**H_3), 0.2 (Si(**C**H_3)$_3$).

N-(trimethylsilyl)-*N*-(1-phenylethyl)-3-(trimethylsilyl)prop-2-yn-1-amine (**23**)

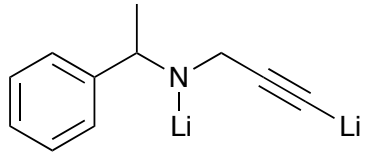


Dilithium *N*-(1-phenylethyl)(propyn-1-ide-3-yl)amide (**24**) was suspended in hexane and cooled to -89 °C (isopropanol/liquid nitrogen). Excess chlorotrimethylsilane was added, and the reaction mixture allowed to warm to room temperature before being heated to boiling

under reflux for 3 hours. The reaction was then cooled to room temperature, and quenched with saturated sodium hydrogen carbonate solution. The mixture was extracted three times with diethyl ether, washed with water and brine, and the organic phase dried over magnesium sulfate, and then concentrated to isolate a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.38 – 7.27 (m, 4H, *ortho*/*meta*-**H**), 7.25 – 7.18 (m, 1H, *para*-**H**), 4.34 (q, *J* = 6.9 Hz, 1H, PhC**H**N), 3.35 (d, *J* = 18.7 Hz, 1H, NC**H**$_2$), 3.20 (d, *J* = 18.7 Hz, 1H, NC**H**$_2$), 1.58 (d, *J* = 7.0 Hz, 3H, PhCC**H**$_3$), 0.20 (s, 9H, Si(C**H**$_3$)$_3$), 0.13 (s, 9H, Si(C**H**$_3$)$_3$).

Dilithium *N*-(1-phenylethyl)(propyn-1-ide-3-yl)amide (**24**)

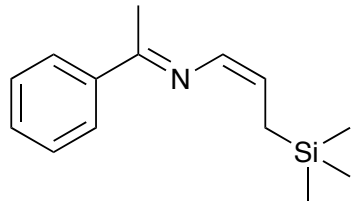


N-(1-phenylethyl)prop-2-yn-1-amine (**20**) (2 mmol) was dissolved in hexane (10 mL) and cooled to -89 °C (isopropanol/liquid nitrogen). *n*-BuLi (1.6 M in hexane, 4 mmol) was added dropwise, forming a white precipitate, which was allowed to warm to room temperature and stirred for 16 hours, turning an orange colour, before being filtered and washed with hexane (2 × 10 mL). The pale orange solid was dried under vacuum to yield a yellow powder.

^{7}Li NMR (156 MHz, d_8-Toluene, 298 K) δ 1.82.

FTIR (Nujol mull) ν_{max}/cm^{-1} 2952m (Nujol), 2922s (Nujol), 2853m (Nujol), 1968w (C≡C stretch), 1560w, 1492w, 1450m (Nujol), 1376w (Nujol), 1303w, 1101w, 1025w, 842w, 760m, 699s.

1-phenyl-*N*-((*Z*)-3-(trimethylsilyl)prop-1-en-1-yl)ethan-1-imine (**25**)

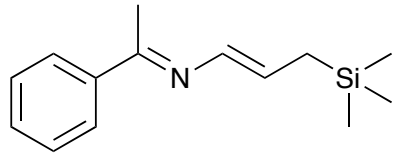


N-(1-phenylethyl)prop-2-yn-1-amine (**20**) (120 mg, 0.5 mmol) and TMEDA (0.08 mL, 0.5 mmol) were dissolved in diethyl ether (6 mL), and cooled to -78 ˚C. Lithium diisopropylamide (0.4 M in diethyl ether, 1.3 mL, 0.5 mmol) was added, forming a deep red solution, which was allowed to warm to room temperature and stirred overnight. The solution was quenched with

methanol, diluted with water, and extracted three times with diethyl ether. The combined extracts were washed with water and then brine, dried over magnesium sulfate, and concentrated to yield an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.94 – 7.91 (m, 2H, *ortho*-**H**), 7.39 – 7.37 (m, 2H, *meta*-**H**), 7.34 – 7.32 (m, 1H, *para*-**H**), 6.95 (dt, *J* = 7.7, 1.4 Hz, 1H, NC**H**═), 5.52 (td, *J* = 8.7, 7.7 Hz, 1H, NC═C**H**), 2.28 (s, 3H, CC$\mathbf{H}_3$), 2.01 (dd, *J* = 8.7, 1.4 Hz, 2H, CC$\mathbf{H}_2$Si), 0.02 (s, 9H, Si(C$\mathbf{H}_3$)$_3$).

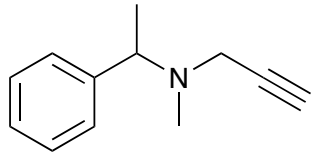
1-phenyl-*N*-((*E*)-3-(trimethylsilyl)prop-1-en-1-yl)ethan-1-imine (**27**)



Benzylpotassium (142 mg, 1 mmol) was suspended in hexane (10 mL) and cooled to -78 ˚C. *N*-(1-phenylethyl)prop-2-yn-1-amine (**20**) (230 mg, 1 mmol) was added, and stirred for three hours at -78 ˚C, before being warmed to room temperature and stirred for a further three hours. The reaction was quenched with methanol, diluted with water, and extracted three times with diethyl ether. The combined extracts were washed with water and then brine, dried over magnesium sulfate, and concentrated to yield an orange oil (mixture of *cis*- and *trans*-isomers).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.88 – 7.85 (m, 2H, *ortho*-**H**), 7.41 – 7.38 (m, 2H, *meta*-**H**), 7.36 – 7.33 (m, 1H, *para*-**H**), 7.02 (dt, *J* = 12.7, 1.3 Hz, 1H, NC**H**═), 6.16 (td, *J* = 12.7, 8.7 Hz, 1H, NC═C**H**), 2.30 (s, 3H, CC$\mathbf{H}_3$), 1.68 (dd, *J* = 8.7, 1.3 Hz, 2H, CC$\mathbf{H}_2$Si), 0.07 (s, 9H, Si(C$\mathbf{H}_3$)$_3$).

N-methyl-*N*-(1-phenylethyl)prop-2-yn-1-amine (**28**)

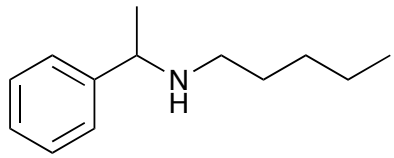


In a flask open to air, *N*-methyl-1-phenylethylamine (0.73 mL, 5 mmol) was dissolved in acetonitrile, and potassium carbonate (1.4 g, 10 mmol) was added at room temperature, followed by propargyl bromide (80 % in toluene, 0.67 mL, 6 mmol). The reaction was left stirring overnight before being diluted with 1 M hydrochloric acid, and then washed with

diethyl ether. The aqueous solution was then neutralised with sodium hydroxide solution, extracted with diethyl ether, and concentrated to yield a pale yellow oil (400 mg, 46 %).

^{1}H NMR (600 MHz, $CDCl_3$, 298 K) δ 7.35 – 7.29 (m, 4H, *ortho*/*meta*-**H**), 7.26 – 7.23 (m, 1H, *para*-**H**), 3.56 (q, *J* = 6.6 Hz, 1H, PhC**H**N), 3.45 (dd, *J* = 17.2, 2.4 Hz, 1H, NC**H**$_2$), 3.22 (dd, *J* = 17.2, 2.4 Hz, 1H, NC**H**$_2$), 2.31 (s, 3H, NC**H**$_3$), 2.24 (t, *J* = 2.4 Hz, 1H, C≡C**H**), 1.37 (d, *J* = 6.6 Hz, 3H, PhC(H)C**H**$_3$).

N-(1-phenylethyl)pentan-1-amine (**30**)



Produced from substitution procedure A using *n*-butyllithium and *N*-(1-phenylethyl)prop-2-yn-1-amine (**20**) or *N*-(1-phenylethyl)-3-(trimethylsilyl)prop-2-yn-1-amine (**22**).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.35 – 7.28 (m, 4H, *ortho*/*meta*-**H**), 7.27 – 7.21 (m, 1H, *para*-**H**), 3.75 (q, *J* = 6.6 Hz, 1H, PhC**H**N), 2.49 (ddd, *J* = 11.3, 8.1, 6.2 Hz, 1H, NC**H**$_2$), 2.41 (ddd, *J* = 11.3, 8.1, 6.6 Hz, 1H, NC**H**$_2$), 1.53 – 1.39 (m, 2H, $NCH_2C\mathbf{H}_2$), 1.35 (d, *J* = 6.7 Hz, 3H, PhC(C**H**$_3$)), 1.33 – 1.21 (m, 4H, (C**H**$_2$)$_2$), 0.87 (t, *J* = 6.9 Hz, 3H, $(CH_2)_4C\mathbf{H}_3$).

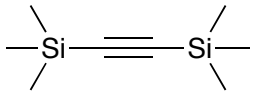
^{13}C NMR (101 MHz,$CDCl_3$, 298 K) δ 150.0 (*ipso*-**C**), 128.5 (*meta*-**C**,) 127.0 (*para*-**C**), 126.7 (*ortho*-**C**), 58.6 (Ph**C**HN), 48.0 (N**C**H$_2$), 30.0 ($NCH_2\mathbf{C}H_2$), 29.7 ($N(CH_2)_2\mathbf{C}H_2$), 24.4 (PhC(H)**C**H$_3$), 22.7 (**C**H$_2$CH$_3$), 14.2 (CH$_2$**C**H$_3$).

^{1}H NMR (400 MHz, C_6D_6, 298 K) δ 7.36 – 7.32 (m, 2H, *ortho*-**H**), 7.25 – 7.19 (m, 2H, *meta*-**H**), 7.14 – 7.08 (m, 1H, *para*-**H**), 3.61 (q, *J* = 6.5 Hz, 1H, PhC**H**N), 2.39 (t, *J* = 7.0 Hz, 2H, NC**H**$_2$), 1.39 – 1.31 (m, 2H, $NCH_2C\mathbf{H}_2$), 1.24 (d, *J* = 6.5 Hz, 3H, PhC(C**H**$_3$)), 1.24 – 1.14 (m, 4H, (C**H**$_2$)$_2$), 0.85 (t, *J* = 6.8 Hz, 3H, $(CH_2)_4C\mathbf{H}_3$).

^{13}C NMR (101 MHz, C_6D_6, 298 K) δ 147.0 (*ipso*-**C**), 128.7 (*meta*-**C**), 127.1 (*para*-**C**), 127.0 (*ortho*-**C**), 59.0 (Ph**C**HN), 48.2 (N**C**H$_2$), 30.6 ($NCH_2\mathbf{C}H_2$), 29.9 ($N(CH_2)_2\mathbf{C}H_2$), 25.1 (PhC(H)**C**H$_3$), 23.1 (**C**H$_2$CH$_3$), 14.3 (CH$_2$**C**H$_3$).

GCMS (EI) *m/z*: 191.3 (M^-, 5 %), 176.3 (100), 134.2 (43), 105.2 (98).

Bis(trimethylsilyl)acetylene (**34**)



The reaction product from substitution procedure A was quenched with chlorotrimethylsilane, refluxed for six hours, and then quenched with methanol. The solution was acidified with 1 M acetic acid, and then extracted three times with diethyl ether, washed with water and then brine, dried over magnesium sulfate, and the solution concentrated to yield a colourless oil.

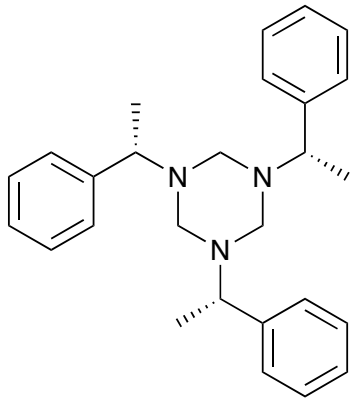
^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 0.17 (s, 18H).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ 114.87 (**C**≡**C**), 2.08 (Si(**C**H_3)$_3$).

^{29}Si NMR (80 MHz, $CDCl_3$, 298 K) δ -19.20.

GCMS (EI) *m/z*: 170.2 (M^-, 9 %), 155.1 (100).

(*S*,*S*,*S*)-1,3,5-tris(1-phenylethyl)-1,3,5-triazinane (**36**)



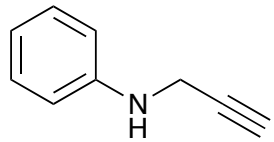
In a flask open to air, (*S*)-1-phenylethylamine (6.5 mL, 50 mmol) was dissolved in methanol (30 mL). Formaldehyde (40 % w/v in water, 3.5 mL, 50 mmol) was added in an exothermic reaction, forming a colourless solution, which turned cloudy upon cooling to room temperature. The solvent was removed under high vacuum and dried under vacuum at 130 ˚C for several hours to yield a very sticky, gummy, colourless solid (4.22 g, 63 %).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.43 – 7.38 (m, 6H, *ortho*-**H**), 7.35 – 7.29 (m, 6H, *meta*-**H**), 7.28 – 7.22 (m, 3H, *para*-**H**), 3.85 (q, *J* = 6.7 Hz, 3H, PhC**H**N), 3.56 (s, 6H, NC**H**$_2$), 1.42 (d, *J* = 6.7 Hz, 9H, C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ 144.5 (*ipso*-**C**), 128.2 (*meta*-**C**), 127.5 (*para*-**C**), 126.8 (*ortho*-**C**), 70.1 (N**C**H_2), 59.5 (Ph**C**HN), 20.2 (**C**H_3).

^{1}H NMR (400 MHz, C_6D_6, 298 K) δ 7.27 – 7.23 (m, 6H, *ortho*-**H**), 7.13 – 7.07 (m, 6H, *meta*-**H**), 7.06 – 7.00 (m, 3H, *para*-**H**), 3.67 (q, *J* = 6.7 Hz, 3H, PhC**H**N), 3.44 (broad s, 6H, NC**H**$_2$), 1.20 (d, *J* = 6.7 Hz, 9H, C**H**$_3$).

N-propargylaniline (**38**)

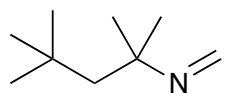


In a flask open to air, potassium carbonate (60 mmol) was suspended in acetonitrile (200 mL), and cooled to 0 ˚C. Aniline (150 mmol) was added, followed by addition of propargyl bromide (80 % in toluene, 50 mmol) dissolved in an extra 10 mL of toluene. The addition of propargyl bromide was done dropwise over 10 minutes in order to supress formation of tertiary dipropargylamine. The reaction was allowed to warm slowly to room temperature overnight, and then filtered to remove potassium carbonate, and concentrated to yield an oil. Excess aniline was removed by distillation, and the residue purified by column chromatography through silica gel (3:1 petroleum benzine : ethyl acetate) (5.05 g, 77 %).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.29 – 7.15 (m, 2H, *meta*-**H**), 6.85 – 6.74 (m, 1H, *para*-**H**), 6.73 – 6.66 (m, 2H, *ortho*-**H**), 3.94 (d, *J* = 2.5 Hz, 2H, NC**H**$_2$), 3.88 (broad s, 1H, N**H**), 2.22 (t, *J* = 2.4 Hz, 1H, C≡C**H**).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ 147.0 (*ipso*-**C**), 129.4 (*meta*-**C**), 118.8 (*para*-**C**), 113.6 (*ortho*-**C**), 81.1 (**C**≡CH), 71.4 (C≡**C**H), 33.8 (N**C**H_2).

N-(2,4,4-trimethylpentan-2-yl)methanimine (*N*-(*tert*-octyl)methanimine, **35c**)



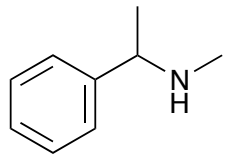
Paraformaldehyde (177 mg, 5.9 mmol) was suspended in methanol (3 mL) in a microwave vial. 2,4,4-trimethylpentan-2-amine (0.94 mL, 5.9 mmol) was added, followed by 3 Å

molecular sieves. The suspension was microwaved at 100 W, 80 ˚C for 15 minutes, and then filtered and concentrated to yield a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$, 298 K) δ 7.40 (d, *J* = 16.0 Hz, 1H, N＝C**H**$_2$), 7.30 (d, *J* = 16.0 Hz, 1H, N＝C**H**$_2$), 1.63 (s, 2H, C**H**$_2$), 1.21 (d, *J* = 0.6 Hz, 6H, (C**H**$_3$)$_2$), 0.93 (d, *J* = 0.6 Hz, 9H, (C**H**$_3$)$_3$).

^{13}C NMR (151 MHz, $CDCl_3$, 298 K) δ 147.7 (N＝**C**H_2), 62.3 (N**C**$(CH_3)_2$), 55.9 (**C**H_2), 32.2 (**C**$(CH_3)_3$), 31.8 ((**C**H_3)$_3$), 29.1 ((**C**H_3)$_2$).

N-methyl-1-phenylethylamine (**42**)

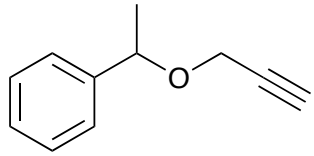


Produced as the major product from substitution procedure B when *N*-(1-phenylethyl)prop-2-yn-1-amine **20** is used and no heterocycle is added.

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.36 – 7.22 (m, 5H, *ortho*/*meta*/*para*-**H**), 3.64 (q, *J* = 6.6 Hz, 1H, PhC**H**N), 2.31 (s, 3H, NC**H**$_3$), 1.36 (d, *J* = 6.6 Hz, 3H, C(H)C**H**$_3$), 1.19 (broad s, 1H, N**H**).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ 145.6 (*ipso*-**C**), 128.6 (*meta*-**C**), 127.0 (*para*-**C**), 126.7 (*ortho*-**C**), 60.4 (Ph**C**HN), 34.7 (N**C**H_3), 24.1 (C(H)**C**H_3).

(1-phenylethyl)prop-2-yn-1-ylether (**45**)



Sodium hydride (60 % dispersion in oil, 1.0 g, 24 mmol) was suspended in tetrahydrofuran and cooled to 0 ˚C. Racemic 1-phenylethanol (2.4 mL, 20 mmol) was added, and the reaction warmed to room temperature and stirred for one hour. The reaction was cooled to 0 ˚C, and propargyl bromide (80 % in toluene, 2.7 mL, 24 mmol) was added. The suspension was heated to 50 ˚C for seven hours, and then allowed to cool to room temperature and stirred overnight. The reaction was quenched with saturated ammonium chloride solution, and then extracted

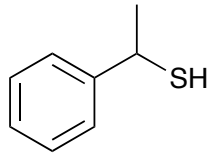
with diethyl ether. The residue was purified by column chromatography through silica gel (9:1 petroleum benzine : ethyl acetate) and then distilled to yield a colourless oil (1.17 g, 36 %).

B.p. 62-64 ˚C, 1×10^{-2} kPa.

^{1}H NMR (600 MHz, $CDCl_3$, 298 K) δ 7.38 – 7.32 (m, 4H, *ortho*/*meta*-**H**), 7.31 – 7.28 (m, 1H, *para*-**H**), 4.66 (q, *J* = 6.5 Hz, 1H, PhC**H**O), 4.09 (dd, *J* = 15.7, 2.4 Hz, 1H, OC**H**$_2$), 3.88 (dd, *J* = 15.7, 2.4 Hz, 1H, OC**H**$_2$), 2.41 (t, *J* = 2.4 Hz, 1H, C≡C**H**), 1.49 (d, *J* = 6.5 Hz, 3H, C**H**$_3$).

^{13}C NMR (151 MHz, $CDCl_3$, 298 K) δ 142.5 (*ipso*-**C**), 128.7 (*meta*-**C**), 128.0 (*para*-**C**), 126.6 (*ortho*-**C**), 80.2 (**C**≡CH), 76.8 (C≡**C**H), 74.2 (Ph**C**HO), 55.6 (O**C**H$_2$), 23.9 (**C**H$_3$).

1-phenylethane-1-thiol

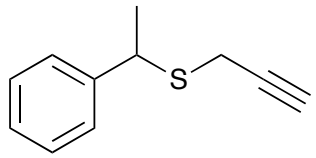


In a flask open to air, racemic 1-phenylethanol (6.0 mL, 50 mmol) was dissolved in 32 % hydrochloric acid (250 mL), and thiourea (5.7 g, 75 mmol) was added. The reaction mixture was heated to reflux overnight. The reaction was allowed to cool to room temperature, and sodium hydroxide pellets added carefully until the solution was basic, as determined by universal indicator paper (approximately 60 g). The solution was heated to reflux for a further three hours, cooled to room temperature, and then acidified with 32 % hydrochloric acid (20 mL). The reaction was extracted with diethyl ether, washed with water and brine, and then dried over magnesium sulfate. The solution was concentrated, and then distilled under vacuum to yield 1-phenylethane-1-thiol as a colourless (very smelly!) oil (2.93 g, 42 %).

B.p. 32-34 ˚C, 1×10^{-2} kPa.

^{1}H NMR (600 MHz, $CDCl_3$, 298 K) δ 7.40 – 7.34 (m, 2H, *ortho*-**H**), 7.34 – 7.30 (m, 2H, *meta*-**H**), 7.25 – 7.22 (m, 1H, *para*-**H**), 4.24 (qd, *J* = 7.0, 5.1 Hz, 1H, PhC**H**S), 1.99 (dd, *J* = 5.1, 0.6 Hz, 1H, S**H**), 1.68 (dd, *J* = 7.0, 0.6 Hz, 3H, C**H**$_3$).

(1-phenylethyl)prop-2-yn-1-ylthioether (**46**)



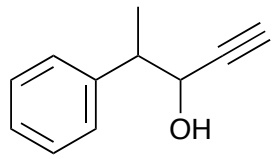
1-phenylethane-1-thiol (2.93 g, 21 mmol) was dissolved in degassed methanol (40 mL), and cooled to 0 ˚C. Potassium hydroxide (1.43 g, 25 mmol) was added, and the mixture stirred until the potassium hydroxide pellets disappeared. Propargyl bromide (80 % in toluene, 3.5 mL, 31 mmol) was then added at 0 ˚C and the reaction stirred overnight with slow warming to room temperature. The methanol was removed under vacuum, the residue dissolved in water, and the product extracted with diethyl ether. This solution was concentrated and the residue distilled under vacuum to yield a pale yellow oil (2.33 g, 63 %).

B.p. 80-84 ˚C, 1×10^{-2} kPa.

^{1}H NMR (600 MHz, $CDCl_3$, 298 K) δ 7.40 – 7.35 (m, 2H, *ortho*-**H**), 7.35 – 7.31 (m, 2H, *meta*-**H**), 7.27 – 7.24 (m, 1H, *para*-**H**), 4.21 (q, *J* = 7.2 Hz, 1H, PhC**H**S), 3.05 (dd, *J* = 16.9, 2.6 Hz, 1H, SC$\mathbf{H}_2$), 2.90 (dd, *J* = 16.9, 2.6 Hz, 1H, SC$\mathbf{H}_2$), 2.24 (t, *J* = 2.6 Hz, 1H, C≡C**H**), 1.62 (d, *J* = 7.2 Hz, 3H, C$\mathbf{H}_3$).

^{13}C NMR (151 MHz, $CDCl_3$, 298 K) δ 143.0 (*ipso*-**C**), 128.7 (*meta*-**C**), 127.5 (*ortho*-**C**), 127.5 (*para*-**C**), 80.4 (**C**≡CH), 71.0 (C≡**C**H), 43.6 (Ph**C**HS), 21.8 (S**C**H_2), 19.0 (**C**H_3).

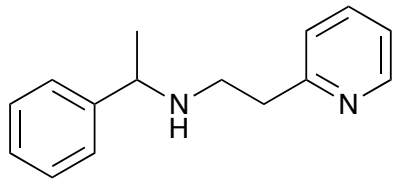
4-phenylpent-1-yn-3-ol (**47**)



Produced as a mixture of diastereomers from substitution procedure A using *n*-butyllithium and (1-phenylethyl)prop-2-yn-1-ylether (**45**).

^{1}H NMR (600 MHz, $CDCl_3$, 298 K) δ 7.36 – 7.06 (m, 5H, aromatic-**H**), 4.50 (d, *J* = 5.4 Hz, 1H, C**H**OH), 4.45 (dd, *J* = 7.0, 1.9 Hz, 1H, C**H**OH), 3.08 (qd, *J* = 6.8, 5.2 Hz, 1H, PhC**H**), 3.04 (p, *J* = 6.9 Hz, 1H, PhC**H**), 2.51 (d, *J* = 2.1 Hz, 1H, C≡C**H**), 2.46 (d, *J* = 2.2 Hz, 1H, C≡C**H**), 1.78 (s, 1H, O**H**), 1.43 (d, *J* = 7.1 Hz, 3H, C$\mathbf{H}_3$).

N-(1-phenylethyl)-2-(pyridin-2-yl)ethylamine (**51**)



Compound **51** was synthesised according to the literature procedure:[4]

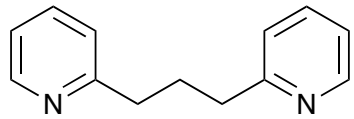
In a flask open to air, 2-vinylpyridine (20 mmol) and 1-phenylethylamine (20 mmol) were dissolved in methanol (30 mL), and acetic acid (20 mmol) was added. The reaction mixture was heated to reflux for 16 hours, neutralised with saturated sodium carbonate solution, and extracted with toluene. The organic layer was dried over magnesium sulfate, and then the solvent was removed under vacuum. Distillation yielded a colourless oil (1.2 g, 27 %).

B.p. 142-144 ˚C, 6×10^{-2} kPa.

^{1}H NMR (600 MHz, $CDCl_3$, 298 K) δ 8.51 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H, pyr-**H6**), 7.56 (td, *J* = 7.7, 1.9 Hz, 1H, pyr-**H4**), 7.36 – 7.27 (m, 4H, *ortho*/*meta*-**H**), 7.25 – 7.19 (m, 1H, *para*-**H**), 7.12 (dt, *J* = 7.8, 1.1 Hz, 1H, pyr-**H3**), 7.10 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H, pyr-**H5**), 3.80 (q, *J* = 6.6 Hz, 1H, PhC**H**N), 2.97 – 2.81 (m, 4H, (C**H**$_2$)$_2$), 1.64 (broad s, 1H, N**H**), 1.34 (d, *J* = 6.6 Hz, 3H, C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ 160.5 (pyr-**C2**), 149.4 (pyr-**C6**), 145.7 (*ipso*-**C**), 136.4 (pyr-**C4**), 128.5 (*meta*-**C**), 127.0 (*para*-**C**), 126.7 (*ortho*-**C**), 123.3 (pyr-**C5**), 121.3 (pyr-**C3**), 58.4 (Ph**C**HN), 47.4 (N**C**H$_2$), 38.7 (N(CH$_2$)**C**H$_2$), 24.5 (**C**H$_3$).

1,3-di(pyridin-2-yl)propane (**53**)

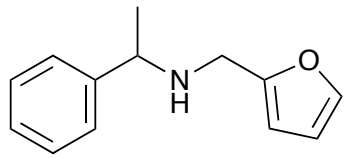


Produced from substitution procedure A using 2-picolyllithium and *N*-(1-phenylethyl)prop-2-yn-1-amine (**20**).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 8.52 (ddd, *J* = 4.9, 1.9, 1.0 Hz, 2H, **H6**), 7.57 (td, *J* = 7.6, 1.8 Hz, 2H, **H4**), 7.15 (dt, *J* = 7.8, 1.1 Hz, 2H, **H3**), 7.09 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 2H, **H5**), 2.86 (t, *J* = 7.7 Hz, 4H, (pyr)-C**H**$_2$), 2.24 – 2.14 (m, 2H (CH$_2$)C**H**$_2$(CH$_2$)).

ESI MS *m/z*: 199.1 (M^+, 100 %).

N-(1-phenylethyl)-furan-2-ylmethyl-1-amine (**55**)

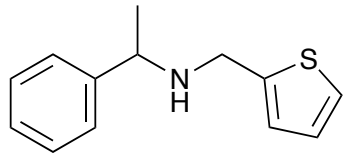


Produced from substitution procedure B using furan and *N*-(1-phenylethyl)prop-2-yn-1-amine (**20**).

^{1}H NMR (600 MHz, $CDCl_3$, 298 K) δ 7.36 – 7.31 (m, 5H, *ortho*/*meta*-**H**, furyl-**H5**), 7.27 – 7.24 (m, 1H, *para*-**H**), 6.30 (dd, *J* = 3.2, 1.8 Hz, 1H, furyl-**H4**), 6.10 (dq, *J* = 3.2, 0.8 Hz, 1H, furyl-**H3**), 3.79 (q, *J* = 6.6 Hz, 1H, PhC**H**N), 3.67 (d, *J* = 14.6 Hz, 1H, NC$\mathbf{H}_2$), 3.58 (d, *J* = 14.5 Hz, 1H, NC$\mathbf{H}_2$), 1.68 (broad s, 1H, N**H**), 1.37 (d, *J* = 6.6 Hz, 3H, C$\mathbf{H}_3$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ 154.0 (furyl-**C2**), 144.4 (*ipso*-**C**), 141.8 (furyl-**C5**), 128.5 (*meta*-**C**), 127.1 (*para*-**C**), 126.8 (*ortho*-**C**), 110.1 (furyl-**C4**), 106.8 (furyl-**C3**), 57.1 (Ph**C**HN), 44.0 (N**C**H_2), 24.3 (**C**H_3).

N-(1-phenylethyl)-thiophen-2-ylmethyl-1-amine (**56**)

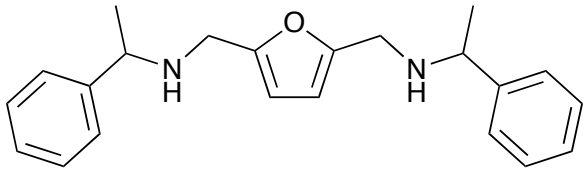


Produced from substitution procedure B using thiophene and *N*-(1-phenylethyl)prop-2-yn-1-amine (**20**).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.40 – 7.30 (m, 4H, *ortho*/*meta*-**H**), 7.32 – 7.21 (m, 1H, *para*-**H**), 7.20 (dd, *J* = 5.1, 1.2 Hz, 1H, thienyl-**H5**), 6.94 (dd, *J* = 5.1, 3.4 Hz, 1H, thienyl-**H4**), 6.86 (dq, *J* = 3.3, 1.0 Hz, 1H, thienyl-**H3**), 3.87 (q, *J* = 6.6 Hz, 1H, PhC**H**N), 3.86 (dd, *J* = 14.2, 1.0 Hz, 1H, NC$\mathbf{H}_2$), 3.81 (dd, *J* = 14.2, 0.8 Hz, 1H, NC$\mathbf{H}_2$), 1.69 (broad s, 1H, N**H**), 1.38 (d, *J* = 6.6 Hz, 3H, C$\mathbf{H}_3$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ 145.2 (*ipso*-**C**), 144.4 (thienyl-**C2**), 128.6 (*meta*-**C**), 127.1 (*para*-**C**), 126.8 (*ortho*-**C**), 126.7 (thienyl-**C4**), 124.9 (thienyl-**C3**), 124.3 (thienyl-**C2**), 57.1 (Ph**C**HN), 46.1 (N**C**H_2), 24.4 (**C**H_3).

N,*N*'-(furan-2,5-diylbis(methylene))bis(1-phenylethan-1-amine) (**57**)

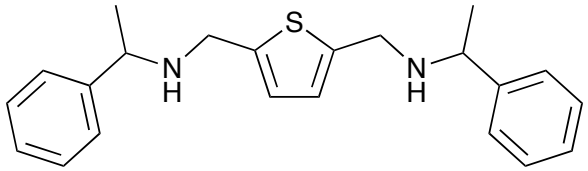


Produced from substitution procedure B using furan and *N*-(1-phenylethyl)prop-2-yn-1-amine (**20**).

^{1}H NMR (600 MHz, $CDCl_3$, 298 K) δ 7.36 – 7.31 (m, 8H, *ortho*/*meta*-**H**), 7.27 – 7.24 (m, 2H, *para*-**H**), 6.00 (s, 2H, furyl-**H**), 3.78 (q, *J* = 6.6 Hz, 2H, PhC**H**N), 3.64 (d, *J* = 14.4 Hz, 2H, NC$\mathbf{H}_2$), 3.55 (d, *J* = 14.4 Hz, 2H, NC$\mathbf{H}_2$), 1.68 (broad s, 2H, N**H**), 1.36 (d, *J* = 6.6 Hz, 6H, C$\mathbf{H}_3$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ 153.2 (furyl-**C2,5**), 145.1 (*ipso*-**C**), 128.5 (*meta*-**C**), 127.1 (*para*-**C**), 126.8 (*ortho*-**C**), 107.5 (furyl-**C3,4**), 57.1 (Ph**C**HN), 44.1 (N**C**H_2), 24.2 (**C**H_3).

N,*N*'-(thiophene-2,5-diylbis(methylene))bis(1-phenylethan-1-amine) (**58**)

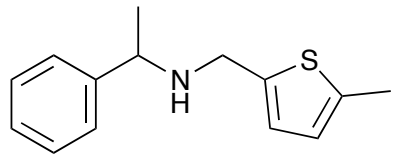


Produced from substitution procedure B using thiophene and *N*-(1-phenylethyl)prop-2-yn-1-amine (**20**).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.40 – 7.30 (m, 8H, *ortho*/*meta*-**H**), 7.32 – 7.21 (m, 2H, *para*-**H**), 6.67 (s, 2H, thienyl-**H**), 3.87 (q, *J* = 6.6 Hz, 2H, PhC**H**N), 3.79 (d, *J* = 14.0 Hz, 2H, NC$\mathbf{H}_2$), 3.74 (d, *J* = 14.0 Hz, 2H, NC$\mathbf{H}_2$), 1.69 (broad s, 2H, N**H**), 1.37 (d, *J* = 6.6 Hz, 6H, C$\mathbf{H}_3$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ 145.2 (*ipso*-**C**), 143.3 (thienyl-**C2,5**), 128.6 (*meta*-**C**), 127.1 (*para*-**C**), 126.8 (*ortho*-**C**), 124.4 (thienyl-**C3,4**), 57.1 (Ph**C**HN), 46.4 (N**C**H_2), 24.4 (**C**H_3).

N-(1-phenylethyl)-(5-methylthiophen-2-yl)methyl-1-amine (**59**)

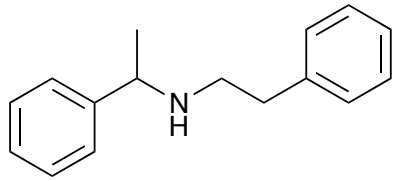


Produced from substitution procedure B using 2-methylthiophene and *N*-(1-phenylethyl)prop-2-yn-1-amine (**20**).

^{1}H NMR (600 MHz, $CDCl_3$, 298 K) δ 7.37 – 7.29 (m, 4H, *ortho*/*meta*-**H**), 7.28 – 7.24 (m, 1H, *para*-**H**), 6.63 (dt, *J* = 3.4, 0.9 Hz, 1H, thienyl-**H3**), 6.57 (dq, *J* = 3.4, 1.2 Hz, 1H, thienyl-**H4**), 3.87 (q, *J* = 6.6 Hz, 1H, PhC**H**N), 3.77 (d, *J* = 14.1 Hz, 1H, NC**H**$_2$), 3.71 (d, *J* = 14.1 Hz, 1H, NC**H**$_2$), 2.46 (d, *J* = 1.2 Hz, 3H, thienyl-C**H**$_3$), 1.57 (broad s, 1H, N**H**), 1.37 (d, *J* = 6.7 Hz, 3H, PhCC**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ 145.4 (*ipso*-**C**), 142.1 (thienyl-**C2**), 138.8 (thienyl-**C5**), 128.6 (*meta*-**C**), 127.1 (*para*-**C**), 126.8 (*ortho*-**C**), 124.7 (thienyl-**C3**), 124.6 (thienyl-**C4**), 57.0 (Ph**C**HN), 46.3 (N**C**H$_2$), 24.5 (PhC(H)**C**H$_3$), 15.5 (thienyl-**C**H$_3$).

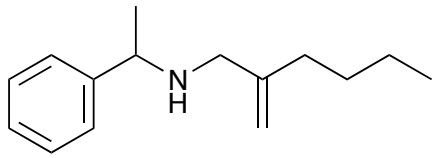
N-(2-phenylethyl)-1-phenylethylamine (**60**)



Benzylpotassium (130 mg, 1 mmol) was suspended in hexane (10 mL), and *N*-(1-phenylethyl)prop-2-yn-1-amine (**20**) was added at room temperature. After 4.5 hours, the reaction was poured into saturated sodium hydrogen carbonate, and then extracted three times with diethyl ether. The combined extracts were washed with water and brine, dried over magnesium sulfate, and then concentrated to yield a cloudy orange oil.

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.42 – 7.12 (m, 10H, aromatic-**H**), 3.77 (q, *J* = 6.6 Hz, 1H, PhC**H**N), 2.82 – 2.66 (m, 4H, N(C**H**$_2$)$_2$), 1.32 (d, *J* = 6.6 Hz, 3H, C**H**$_3$).

2-methylene-*N*-(1-phenylethyl)hexan-1-amine (**61**)



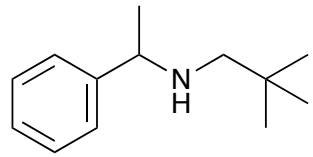
Produced from substitution procedure A using di-*n*-butylmagnesium and *N*-(1-phenylethyl)prop-2-yn-1-amine (**20**) in hexane.

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.35 – 7.29 (m, 4H, *ortho*/*meta*-**H**), 7.28 – 7.20 (m, 1H, *para*-**H**), 4.89 – 4.87 (m, 1H, =C**H**$_2$), 4.83 – 4.81 (m, 1H, =C**H**$_2$), 3.77 (q, *J* = 6.6 Hz, 1H, PhC**H**N), 3.03 (t, *J* = 1.1 Hz, 2H, NC**H**$_2$), 2.02 (t, *J* = 7.6 Hz, 2H, =CC**H**$_2$), 1.36 (d, *J* = 6.6 Hz, 3H, PhCC**H**$_3$), 1.42 – 1.21 (m, 4H, (C**H**$_2$)$_2$), 0.89 (t, *J* = 7.1 Hz, 3H, $(CH_2)_3$C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ 148.5 (**C**=CH_2), 145.9 (*ipso*-**C**), 128.5 (*meta*-**C**), 126.9 (*para*-**C**), 126.8 (*ortho*-**C**), 109.5 (=**C**H_2), 57.6 (Ph**C**HN), 52.3 (N**C**H_2), 34.3 (=C**C**H_2), 30.1 (CH_2)**C**$H_2(CH_2)$, 24.5 (PhC(H)**C**H_3), 22.6 $((CH_2)_2$**C**H_2), 14.1 $(CH_2)_3$**C**H_3).

ESI MS *m/z*: 218 (M^+, 21 %), 105 (100).

N-(1-phenylethyl)-2,2-dimethylpropylamine

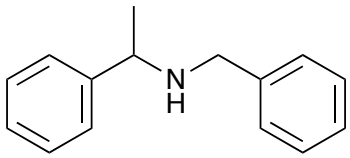


Produced from substitution procedure A using *t*-butyllithium and *N*-(1-phenylethyl)prop-2-yn-1-amine (**20**).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.36 – 7.30 (m, 4H, *ortho*/*meta*-**H**), 7.26 – 7.20 (m, 1H, *para*-**H**), 3.70 (q, *J* = 6.6 Hz, 1H, PhC**H**N), 2.27 (d, *J* = 11.2 Hz, 1H, NC**H**$_2$), 2.14 (d, *J* = 11.3 Hz, 1H, NC**H**$_2$), 1.33 (d, *J* = 6.6 Hz, 3H, PhCC**H**$_3$), 0.89 (s, 9H, (C**H**$_3)_3$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ 146.5 (*ipso*-**C**), 128.4 (*meta*-**C**), 127.0 (*para*-**C**), 126.7 (*ortho*-**C**), 60.2 (N**C**H_2), 59.0 (Ph**C**HN), 31.5 (**C**$(CH_3)_3$), 27.9 ((**C**$H_3)_3$), 25.0 (PhC(H)**C**H_3).

N-(1-phenylethyl)benzylamine

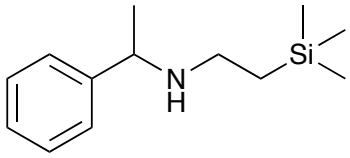


Produced from substitution procedure A using phenyllithium and *N*-(1-phenylethyl)-3-(trimethylsilyl)prop-2-yn-1-amine (**22**).

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 7.37 – 7.19 (m, 10H, aromatic-**H**), 3.81 (q, *J* = 6.6 Hz, 1H, PhC**H**N), 3.66 (d, *J* = 13.1 Hz, 1H, PhC**H**$_2$N), 3.59 (d, *J* = 13.2 Hz, 1H, PhC**H**$_2$N), 1.34 (d, *J* = 6.6 Hz, 3H, C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ 145.5 (*ipso*-**C**), 140.6 (*ipso*-**C**), 128.4 (*meta*-**C**), 128.3 (*meta*-**C**), 128.1 (*ortho*-**C**), 126.9 (*para*-**C**), 126.8 (*para*-**C**), 126.7 (*ortho*-**C**), 57.5 (N**C**H), 51.6 (N**C**H$_2$), 24.5 (**C**H$_3$).

N-(1-phenylethyl)-2-(trimethylsilyl)ethanamine

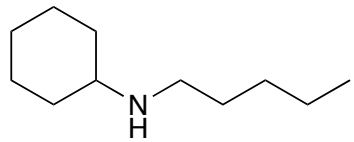


Produced from substitution procedure A using (trimethylsilyl)methyllithium and *N*-(1-phenylethyl)-3-(trimethylsilyl)prop-2-yn-1-amine (**22**).

^{1}H NMR (600 MHz, $CDCl_3$, 298 K) δ 7.35 – 7.29 (m, 4H, *ortho*/*meta*-**H**), 7.25 – 7.21 (m, 1H, *para*-**H**), 3.77 (q, *J* = 6.6 Hz, 1H, PhC**H**N), 2.55 (td, *J* = 11.4, 5.3 Hz, 1H, NC**H**$_2$), 2.49 (td, *J* = 11.4, 5.7 Hz, 1H, NC**H**$_2$), 1.35 (d, *J* = 6.6 Hz, 3H, PhCC**H**$_3$), 0.79 (ddd, *J* = 14.0, 11.4, 5.3 Hz, 1H, C**H**$_2$Si), 0.72 (ddd, *J* = 14.0, 11.4, 5.7 Hz, 1H, C**H**$_2$Si), -0.1 (s, 9H, Si(C**H**$_3$)$_3$).

^{13}C NMR (151 MHz, $CDCl_3$, 298 K) δ 146.0 (*ipso*-**C**), 128.5 (*meta*-**C**), 126.9 (*para*-**C**), 126.7 (*ortho*-**C**), 58.3 (Ph**C**HN), 43.7 (N**C**H$_2$), 24.4 (PhC(H)**C**H$_3$), 18.5 (**C**H$_2$Si), -1.3 (Si(**C**H$_3$)$_3$).

N-cyclohexylpentanamine

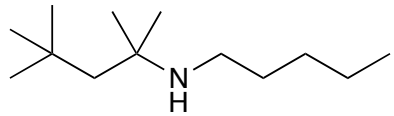


Produced from substitution procedure A using *n*-butyllithium and *N*-(cyclohexyl)prop-2-yn-1-amine.

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 2.59 (t, *J* = 7.3 Hz, 2H, NC**H**$_2$), 2.38 (tt, *J* = 10.5, 3.8 Hz, 1H, NCH), 1.90 – 1.82 (m, 2H, cyclohexyl-**H2,6**), 1.76 – 1.67 (m, 2H, cyclohexyl-**H3,5**), 1.64 – 1.57 (m, 1H, cyclohexyl-**H4**), 1.51 – 1.42 (m, 2H, N(CH_2)C**H**$_2$), 1.35 – 1.10 (m, 8H), 1.10 – 0.98 (m, 2H, cyclohexyl-**H2,6**), 0.89 (t, *J* = 6.9 Hz, 3H, C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ 57.1 (N**C**H), 47.2 (N**C**H_2), 33.8, 30.4, 29.8, 26.4, 25.3, 22.8, 14.2.

N-(2,4,4-trimethylpentan-2-yl)pentan-1-amine

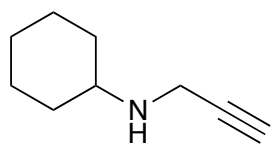


Produced from substitution procedure A using *n*-butyllithium and *N*-(2,4,4-trimethylpentan-2-yl)prop-2-yn-1-amine.

^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 2.52 (t, *J* = 7.3 Hz, 2H, NC**H**$_2$), 1.43 (s, 2H, CC**H**$_2$C), 1.50 – 1.37 (m, 2H, NCH_2C**H**$_2$), 1.36 – 1.25 (m, 4H, N(CH_2)$_2$(C**H**$_2$)$_2$), 1.13 (s, 6H, (C**H**$_3$)$_2$), 1.01 (s, 9H, (C**H**$_3$)$_3$), 1.50 – 1.37 (m, 3H, N(CH_2)$_4$C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ 54.3 (**C**(CH_3)$_2$), 53.1 (C**C**H_2C), 42.2 (NCH_2), 31.9 ((**C**H_3)$_3$), 31.8 (**C**(CH_3)$_3$), 31.0 (NCH_2**C**H_2), 30.0 (N(CH_2)$_2$**C**H_2), 29.2 ((**C**H_3)$_2$), 22.8 (N(CH_2)$_3$**C**H_2), 14.2 (N(CH_2)$_4$**C**H_3).

N-(cyclohexyl)prop-2-yn-1-amine



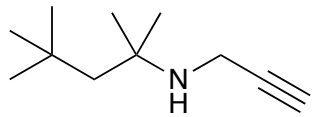
In a flask open to air, potassium carbonate (60 mmol) was suspended in acetonitrile (200 mL) and cooled to 0 ˚C. Cyclohexylamine (150 mmol) was added, followed by addition of propargyl bromide (80 % in toluene, 50 mmol) dissolved in an extra 10 mL of toluene. The addition of propargyl bromide was done dropwise over 10 minutes in order to supress formation of tertiary dipropargylamine. The reaction was allowed to warm slowly to room temperature overnight, and then filtered to remove potassium carbonate, and concentrated. The residue was distilled to isolate a colourless oil (excess cyclohexylamine was captured in the cold trap) (5.69 g, 83 %).

B.p. 32 ˚C, 6×10^{-2} kPa.

^{1}H NMR (600 MHz, $CDCl_3$, 298 K) δ 3.46 (d, *J* = 2.5 Hz, 2H, NC**H**$_2$), 2.65 (tt, *J* = 10.5, 3.8 Hz, 1H, cyclohexyl-**H**1), 2.19 (t, *J* = 2.4 Hz, 1H, C≡C**H**), 1.94 - 1.77 (m, 3H, cyclohexyl-**H2,6**, N**H**), 1.76 - 1.70 (m, 2H, cyclohexyl-**H3,5**), 1.66 - 1.59 (m, 1H, cyclohexyl-**H4**), 1.33 - 1.23 (m, 2H, cyclohexyl-**H3,5**), 1.21 - 1.12 (m, 1H, cyclohexyl-**H4**), 1.12 - 1.03 (m, 2H, cyclohexyl-**H2,6**).

^{13}C NMR (151 MHz, $CDCl_3$, 298 K) δ 82.8 (**C**≡CH), 71.0 (C≡**C**H), 55.1 (cyclohexyl-**C1**), 35.3 (N**C**H$_2$), 33.2 (cyclohexyl-**C2,6**), 26.3 (cyclohexyl-**C4**), 25.0 (cyclohexyl-**C3,5**).

N-(2,4,4-trimethylpentan-2-yl)prop-2-yn-1-amine



In a flask open to air, potassium carbonate (27 mmol) was suspended in acetonitrile (100 mL) and cooled to -30 ˚C. 2,4,4-trimethylpentan-2-amine (50 mmol) was added, followed by addition of propargyl bromide (80 % in toluene, 20 mmol) dissolved in 10 mL of acetonitrile. The addition of propargyl bromide was done dropwise over 10 minutes in order to supress formation of tertiary dipropargylamine. The reaction was allowed to warm slowly to room temperature overnight, and then filtered to remove potassium carbonate, and concentrated to yield an oil. Excess 2,4,4-trimethylpentan-2-amine was removed by distillation. The concentrated product should be handled carefully, as 2,4,4-trimethylpentan-2-amine crytsallises quickly upon exposure to the air, apparently due to formation of an amine hydrate. The residue was purified by column chromatography through silica gel (neat ethyl

acetate). The resulting oil was distilled under high vacuum to yield the product, which was stored under a nitrogen atmosphere.

^{1}H NMR (600 MHz, $CDCl_3$, 298 K) δ 3.37 (d, *J* = 2.5 Hz, 2H, NC**H**$_2$), 2.17 (t, *J* = 2.5 Hz, 1H, C≡C**H**), 1.42 (s, 2H, CC**H**$_2$C), 1.16 (s, 6H, (C**H**$_3$)$_2$), 1.29 (bs, 1H, N**H**), 1.01 (s, 9H, (C**H**$_3$)$_3$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ 83.7 (**C**≡CH), 70.7 (C≡**C**H), 54.8 (**C**(CH$_3$)$_2$), 52.9 (C**C**H$_2$C), 31.8 ((**C**H$_3$)$_3$), 31.8 (**C**(CH$_3$)$_3$), 31.7 (N**C**H$_2$), 29.0 ((**C**H$_3$)$_2$).

Chapter 3

General procedures

Unless otherwise stated, all reactions were performed using Schlenk technique under an inert argon or nitrogen atmosphere. Tetrahydrofuran, diethyl ether, toluene, and hexane were purified using the MBraun SPS-800 solvent purification system and stored over 4 Å molecular sieves, or freshly distilled from sodium/benzophenone. TMEDA, PMDETA, and 2,2,6,6-tetramethylpiperidine were dried by reflux over calcium hydride, distilled under vacuum, and stored over 4 Å molecular sieves. Diisopropylamine was distilled from calcium hydride and stored over 4 Å molecular sieves. *n*-Butylpotassium and benzylpotassium were synthesised according to the literature procedure from the reaction of *n*-butyllithium with potassium *tert*-butoxide in hexane or toluene.[1] (Trimethylsilyl)methylpotassium and potassium 2,2,6,6-tetramethylpiperidide were synthesised by the same procedure using (trimethylsilyl)methyllithium or lithium 2,2,6,6-tetramethylpiperidide. (Trimethylsilyl)methyllithium was purchased from Sigma-Aldrich and used as received, or the solvent was removed under vacuum and the residue dissolved to 0.5 M in hexane. C_6D_6, d_8-toluene, and d_8-THF were degassed by three freeze-pump-thaw cycles, and stored over 4 Å molecular sieves. All other reagents were purchased from commercial suppliers and used without further purification. ^{1}H, ^{7}Li, ^{11}B, ^{13}C, and ^{27}Al NMR spectra were recorded on a Bruker DRX 400 or 600 MHz spectrometer, with chemical shifts referenced internally to C_6D_6, d_8-toluene, or d_8-THF. Molecular weight determinations were performed via DOSY NMR, and calculated using the calibration curves provided by Stalke,[5,6] with 1,2,3,4-tetraphenylnaphthalene as an internal reference.

Crystallographic data for compound **70** were obtained on a Bruker X8 APEXII CCD diffractometer equipped with an Oxford Cryosystems 700 Cryostream and cooled to 123(2) K. Data were collected with monochromatic (graphite) Mo Kα radiation (λ = 0.710 73 Å) and processed using the Bruker Apex2 v2012.2.0 software; Lorentz, polarization, and absorption corrections (multiscan, SADABS[2]) were applied. The crystals were mounted in Krytox GPL-107 perfluorinated oil. The structure was solved by standard methods and refined by full matrix least-squares using the SHELX-97 program.[3] Non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms attached to C were placed in calculated positions using a riding model with C−H distances of 0.99 Å and $U_{iso}(H) = 1.2 \times U_{eq}(C)$.

General synthetic procedure for potassium aluminates

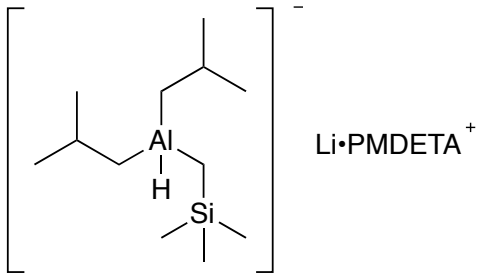
The organopotassium reagent was suspended in hexane, and cooled to -89 ˚C (isopropanol/liquid nitrogen). Diisobutylaluminium hydride (1.0 M in hexanes, 1 equivalent) was added dropwise, before addition of a Lewis donor, either at -89 ˚C or at room temperature. Removal of the solvent under vacuum, or cooling the solution followed by careful removal of the solvent by syringe, allowed for the isolation of a colourless oil.

General procedure for catalytic hydroboration

In an inert atmosphere dry box, the substrate to be hydroborated was dissolved in C_6D_6 in a J. Young valve NMR tube, and mesitylene added, followed by pinacolborane (1.1 equivalents) and then the catalyst. The tube was sealed, and the reaction progress monitored by ^{1}H and ^{11}B NMR spectroscopy.

Synthesis and characterisation

Lithium (diisobutyl)(trimethylsilylmethyl)hydridoaluminate *N*,*N*,*N'*,*N''*,*N''*-pentamethyldiethylenetriamine complex (**68**)



(Trimethylsilyl)methyllithium (0.5 M in hexane, 1 equivalent) was diluted to approximately 0.1 M in hexane. PMDETA (1 equivalent) was added, forming a precipitate upon addition of 0.5 equivalents, which redissolved upon complete addition. This solution was slowly added at -78 ˚C to a solution of diisobutylaluminium hydride (0.1 M in hexane, 1 equivalent), forming a white precipitate, which was washed at -78 ˚C with cold hexane. The solid was carefully isolated by filtration using a filter canula. Excess solvent was removed under vacuum while allowing to warm slowly to room temperature to yield a crystalline white solid (80 %).

^{1}H NMR (400 MHz, C_6D_6, 298 K) δ 2.75 (broad s, 1H, hydride-**H**), 2.24 (t-hept, *J* = 7.1, 6.6 Hz, 2H, isobutyl-C**H**), 1.96 (s, 3H, PMDETA-NC**H**$_3$), 1.93 (s, 12H, PMDETA-N(C**H**$_3$)$_2$), 1.77 (s, 8H, PMDETA-(C**H**$_2$)$_2$), 1.34 (d, *J* = 6.6 Hz, 12H, isobutyl-(C**H**$_3$)$_2$), 0.38 (s, 9H, Si(C**H**$_3$)$_3$), 0.27 (d, *J* = 7.0 Hz, 4H, isobutyl-C**H**$_2$), -0.79 (s, 2H, C**H**$_2$Si).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ 57.1 (PMDETA-**C**H_2), 53.4 (PMDETA-**C**H_2), 45.6 (PMDETA-N(**C**H_3)$_2$), 44.4 (PMDETA-N**C**H_3), 29.6 (isobutyl-(**C**H_3)$_2$), 29.6 (isobutyl-**C**H), 29.0 (**C**H_2Si), 28.9 (isobutyl-**C**H_2), 3.9 (Si(**C**H_3)$_3$).

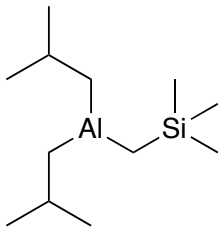
^{7}Li NMR (156 MHz, C_6D_6, 298 K) δ 0.49.

^{27}Al NMR (104 MHz, $CDCl_3$, 298 K) δ 147.4.

Hexakis((*E*)-(phenyl((1-phenyl-2-(trimethylsilyl)vinyl)amino)methylene)amido)-bis(trimethylsiloxy)-peroxido decalithium (**70**)

Crystal Data for **70**: $C_{114}H_{144}Li_{10}N_{12}O_4Si_8$; M_r = 2040.57; triclinic; space group: P-1; *a* = 14.8719(12), *b* = 15.6021(12), *c* = 16.7264(13); α = 110.431; β = 94.442(4); γ = 109.160(4); *V* = 3353.7(5) Å^3; *Z* = 1, reflections collected/unique: 54909/13207 (Rint = 0.2523); R_1 values ($I > 2\sigma(I)$) = 0.0839; $wR(F^2)$ values ($I > 2\sigma(I)$) = 0.1970; R_1 values (all data) = 0.2296; $wR(F^2)$ values (all data) = 0.2814; GOF = 0.941.

(Diisobutyl)(trimethylsilyl)methylaluminium (**73**)



Diisobutylaluminium chloride (1 equivalent) was dissolved in hexane, and cooled to -89 ˚C (isopropanol/liquid nitrogen). (Trimethylsilyl)methyllithium (1.0 M in pentane, 1 equivalent) was added, forming a white suspension, which was allowed to warm to room temperature. The suspension was filtered, and solvent removed from the filtrate under vacuum, before being distilled under high vacuum to yield an extremely pyrophoric colourless oil.

^{1}H NMR (400 MHz, C_6D_6, 298 K) δ 1.96 (t-hept, *J* = 7.1, 6.6 Hz, 3H, isobutyl-C**H**), 1.02 (d, *J* = 6.6 Hz, 18H, isobutyl-(C**H**$_3$)$_2$), 0.28 (d, *J* = 7.1 Hz, 6H, isobutyl-C**H**$_2$).

^{13}C NMR (101 MHz, $CDCl_3$, 298 K) δ 28.4 (isobutyl-(**C**H_3)$_2$), 26.7 (isobutyl-**C**H_2), 26.3 (isobutyl-**C**H).

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ORGANOMETALLICS

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Loss of Chirality through Facile Lewis Base Mediated Aza-enolate Formation in Na and K (*S*)-*N*-(α-Methylbenzyl)methallylamides

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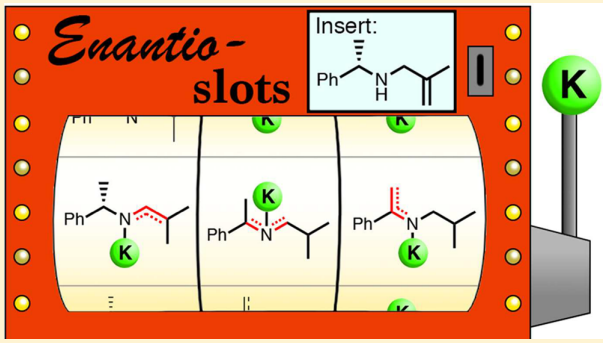
Supporting Information

ABSTRACT: Metalation of (*S*)-*N*-(α-methylbenzyl)-methallylamine with *n*BuM (M = Li, Na, or K) in hexane leads to the allylic metal amides [(*S*)-PhCH(CH$_3$)N(CH$_2$C{CH$_3$}=CHLi)Li]$_6$, **1**, [(*S*)-PhCH(CH$_3$)N(CH$_2$C{CH$_3$}=CH$_2$)Na]$_n$, and [(*S*)-PhCH(CH$_3$)N(CH$_2$C{CH$_3$}=CH$_2$)K]$_n$, respectively. The addition of any Lewis base (here THF, TMEDA, or PMDETA) to the Na and K amides promotes rapid anion rearrangement to the aza-enolate complexes [PhC(=CH$_2$)N(CH$_2$CH{CH$_3$}$_2$)Na]$_\infty$, **2**, [PhC(=CH$_2$)N-(CH$_2$CH{CH$_3$}$_2$)Na·TMEDA]$_n$, **3**, [PhC(=CH$_2$)N(CH$_2$CH-{CH$_3$}$_2$)Na·PMDETA]$_n$, **4**, and [PhC(=CH$_2$)N(CH$_2$CH-{CH$_3$}$_2$)K]$_n$, **5**, resulting in loss of chirality. In contrast, the addition of benzene leads exclusively to the 1-aza-allyl complexes [(*S*)-PhCH(CH$_3$)N(CH=C{CH$_3$}$_2$)Na]$_n$, **6**, and [(*S*)-PhCH(CH$_3$)N(CH=C{CH$_3$}$_2$)K]$_n$, **7**, both of which are not observed in the presence of Lewis donors. Doping a benzene solution of **7** with THF gives the first observation of reorganization to the intermediate 2-aza-allyl anion. All seven complexes have been characterized by NMR spectroscopy, with complexes **1** and **2** also being characterized by single-crystal X-ray diffraction. Rearrangement to the aza-enolates **2** and **3** is unprecedented under the conditions employed.



INTRODUCTION

Chiral lithium amides have been extensively used in asymmetric synthesis, as powerful bases for the deprotonation of prochiral compounds and as chiral auxiliaries.[1−5] The high synthetic value of these reagents has prompted many studies into their structural chemistry in attempts to better understand their complex and often highly selective behavior.[1,6−10]

Davies and co-workers have produced an expansive catalogue of reactions utilizing the conjugate addition of lithium amide derivatives of α-methylbenzylamine to α,β-unsaturated esters.[2,3] Many of these reactions employ benzyl, methylbenzyl, or allyl moieties as the second N-bound group on the amide since these can be easily and selectively removed from the resultant β-amino ester through hydrogenolysis or deallylation. (*R*/*S*)-*N*-(α-Methylbenzyl)allylamine ((*R*/*S*)-*N*-α-mba) and some higher substituted derivatives have also been utilized in tandem addition/cyclization reactions that employ the allyl moiety to form a five-membered nitrogen heterocycle.[11,12] This approach has also been combined with the use of azides to form bicyclic compounds with high enantioselectivity, which can be reacted further to form α,β,γ-triamino acid derivatives.[13]

Our previous studies into the structural characterization of alkali metal complexes of (*R*/*S*)-*N*-α-mba have shown that three distinct anion forms can form: allyl-amide, 1-aza-allyl, and aza-enolate (Figure 1).

The allyl-amide results from simple deprotonation of the parent amine; however, the only lithium complex whose solid-state structure has been authenticated in this anionic isomer is that coordinated with the monodentate donor HMPA (hexamethylphosphoramide).[14] However, retention of the allyl-amide structure in the presence of a monodentate O-donor is consistent with the synthetic outcomes when generating and using the lithium allyl-amide in THF or Et$_2$O solvent in conjugate addition reactions.[15−17] Heating the HMPA complex in solution to 90 °C prompts a 1,3-sigmatropic rearrangement of the anion to the 1-aza-allyl form, a rearrangement that is observed at room temperature when employing the bidentate donor TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine), with either lithium or sodium.[18,19] The use of the tridentate donor PMDETA (*N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine) prompts a further internal anion rearrangement to the aza-enolate, with an accompanying loss of chirality within the complex.[18] Highlighting the influence of the metal on anion isomerization, metalation of (*R*)-*N*-α-mba with potassium in the presence of THF alone leads to the aza-enolate form of the anion.[20]

These anion rearrangements can clearly affect the outcome of any reaction in which the amide base is employed to provide high enantioselectivity. *Ab initio* calculations, which focused on the interplay of the metal and Lewis donor denticity in influencing anion rearrangements, suggested that it is the

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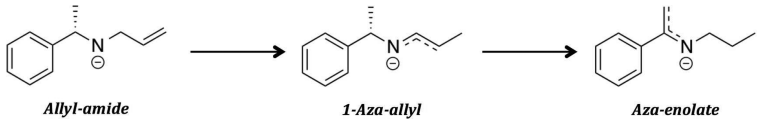


Figure 1. Anion rearrangements observed in (*S*)-*N*-(α)-mba.

separation of metal cation and the amido-anion that is key to allowing the thermodynamically favored bonding rearrangements to occur.[18] What is less studied is how the degree of substitution in the amine impacts the propensity for these rearrangements to occur. To date, the only amines studied have been (*S*)-*N*-(α)-mba and (*S*)-*N*-(α-methylbenzyl)-3-phenylprop-2-enamine ((*S*)-*N*-(α)-mbpa). Thus, we have been seeking to broaden the scope of amines under examination and have turned to the more highly branched (*S*)-*N*-(α-methylbenzyl)-methallylamine ((*S*)-*N*-(α)-mbma) to explore the effect of the presence of a methyl group on the β position of the allyl moiety.

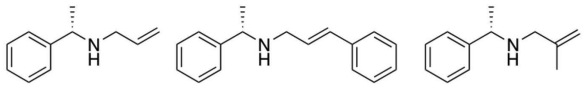


Figure 2. Three different homoallylic amines studied in the context of anion rearrangements.

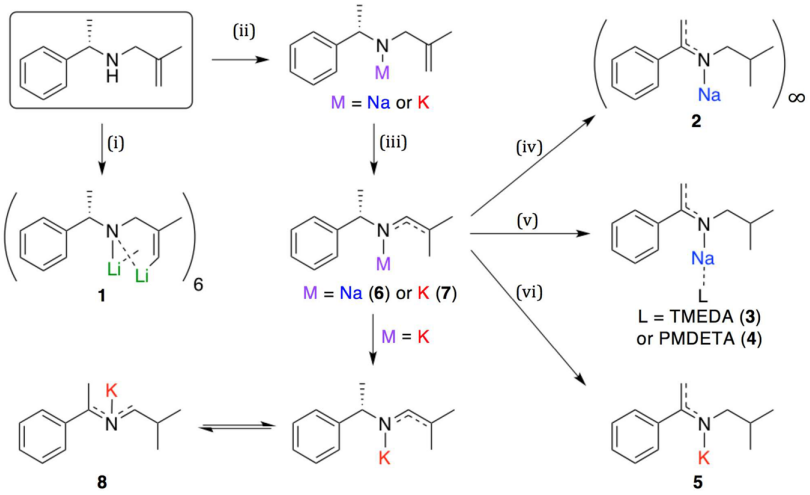
This paper describes the synthesis and characterization of eight new complexes resulting from the metalation of (*S*)-*N*-(α)-mba in the presence of various Lewis donors, namely, $[(S)\text{-PhCH(CH}_3\text{)N(CH}_2\text{C\{CH}_3\text{\}=CHLi)Li]}_6$, **1**, $[\text{PhC(=CH}_2\text{)N(CH}_2\text{CH\{CH}_3\text{\}}_2\text{)Na]}_\infty$, **2**, $[\text{PhC(=CH}_2\text{)N(CH}_2\text{CH\{CH}_3\text{\}}_2\text{)Na·TMEDA]}_n$, **3**, $[\text{PhC(=CH}_2\text{)N(CH}_2\text{CH\{CH}_3\text{\}}_2\text{)Na·PMDETA]}_n$, **4**, $[\text{PhC(=CH}_2\text{)N(CH}_2\text{CH\{CH}_3\text{\}}_2\text{)K]}_n$, **5**, $[(S)\text{-PhCH(CH}_3\text{)N(CH=C\{CH}_3\text{\}}_2\text{)Na]}_n$, **6**, $[(S)\text{-PhCH(CH}_3\text{)N(CH=C\{CH}_3\text{\}}_2\text{)K]}_n$, **7**, and $[\text{PhC(CH}_3\text{)N(=CHCH\{CH}_3\text{\}}_2\text{)K]}_n$, **8**. Complexes **1**–**7** have been analyzed and characterized using solution NMR spectroscopic studies and elemental analysis, with compounds **1** and **2** additionally structurally characterized via single-crystal X-ray diffraction studies. Complex **8** has so far been observed only in solution and was identified by NMR spectroscopy.

RESULTS AND DISCUSSION

The syntheses of compounds **1**–**8** are summarized in Scheme 1. Attempts to synthesize a monolithiated amide of (*S*)-*N*-(α)-mbma resulted only in isolation of the dilithiated complex $[(S)\text{-PhCH(CH}_3\text{)N(CH}_2\text{CH\{CH}_3\text{\}=CHLi)Li]}_6$, **1**. Attempts at using lithium diisopropylamide (LDA) to selectively monolithiate only returned the unreacted amine. Synthesis of **1** was optimized by reacting (*S*)-*N*-(α)-mbma with one equivalent of *n*BuLi in hexane at −60 °C, followed by the addition at −10 °C of one equivalent of *t*BuLi. After warming to room temperature and stirring for 1 h, filtration of the mixture yielded a solution that at room temperature deposited yellow crystals overnight.

In the synthesis of $[\text{PhC(=CH}_2\text{)N(CH}_2\text{CH\{CH}_3\text{\}}_2\text{)Na]}_\infty$, **2**, (*S*)-*N*-(α)-mbma was added to a stirring suspension of one equivalent of *n*BuNa in hexane at −60 °C. The suspension was allowed to warm slowly to room temperature, and THF added to form an orange suspension. On filtering, this gave a clear red solution, from which yellow plate crystals grew. $[\text{PhC(=CH}_2\text{)N(CH}_2\text{CH\{CH}_3\text{\}}_2\text{)Na·TMEDA]}_n$ (**3**) was synthesized in a similar manner with THF being replaced by an equimolar amount of TMEDA. Synthesis of $[\text{PhC(=CH}_2\text{)N(CH}_2\text{CH\{CH}_3\text{\}}_2\text{)Na·PMDETA]}_n$ (**4**) was accomplished by the same addition of (*S*)-*N*-(α)-mbma to one equivalent of *n*BuNa, followed by one equivalent of PMDETA, which formed a red solution, from which orange needle crystals deposited at 4 °C overnight. Addition of (*S*)-*N*-(α)-mbma to a stirring suspension of one equivalent of *n*BuK, followed by the addition of an

Scheme 1. Synthesis of Compounds 1–8[a]



[a]Reaction conditions: (i) *n*BuLi, hexane, −60 to −10 °C, then *t*BuLi, −10 °C to rt; (ii) *n*BuNa or *n*BuK, hexane, −60 °C to rt; (iii) d_6-benzene doped with 5% d_8-THF; (iv) THF; (v) 1 equiv of TMEDA or PMDETA (vi) THF, TMEDA, or PMDETA.

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excess of THF and filtration of the resulting suspension, gave a dark brown solution, from which dark brown crystals of $[PhC(=CH_2)N(CH_2CH\{CH_3\}_2)K]_n$ (**5**) deposited overnight. Reaction of (*S*)-*N*-*α*-mbma with *n*BuNa in hexane at −78 °C resulted in the formation of a bright yellow powder, which was identified by NMR spectroscopy as $[(S)\text{-}PhCH(CH_3)N(CH{=}C\{CH_3\}_2)Na]_n$ (**6**). Substitution of *n*BuNa for *n*BuK gave the corresponding potassium complex $[(S)\text{-}PhCH(CH_3)N(CH{=}C\{CH_3\}_2)K]_n$ (**7**) as a light brown powder, which when dissolved in d_6-benzene or d_8-THF rearranges to form $[PhC(CH_3)N(=CHCH\{CH_3\}_2)K]_n$ (**8**) in equilibrium with **7**.

Of particular note is the preference of complex **2** for an aza-enolate bonding arrangement, and while THF is used as a cosolvent, it is not incorporated into the solid-state structure of the complex itself. Our previous reactivity studies involving Na and (*S*)-*N*-mba showed that in order to access the aza-enolate anion it was necessary to use the tridentate donor PMDETA (cf. monodentate THF for **2**).[18] This was part of a broader study into the metal-mediated (Li, Na, or K) anion rearrangements in complexes of (*S*)-*N*-mba and (*S*)-*N*-mbpa. DFT calculations support the experimental observations that the 1-aza-allyl and aza-enolate anions are of comparable stability. However, as the denticity of the donor is increased (Et_2O/THF < TMEDA < PMDETA), the aza-enolate anion becomes increasingly more favorable and stable.[18−21]

The introduction here of the additional C atom on the allyl moiety of (*S*)-*N*-*α*-mbma appears to buck this trend in generating even lower energy pathways through to the aza-enolate isomer and is independent of the denticity of the Lewis base employed.

Structural Studies. Of the five complexes synthesized, complexes **1** and **2** were successfully analyzed by single-crystal X-ray diffraction studies. Crystals of **4** and **5** proved too reactive under both the mineral and perfluorinated oils to provide diffraction data of a suitable quality. A summary of the crystallographic data for **1** and **2** is provided in the Experimental Section.

Yellow needle crystals of **1** were obtained from a hexane solution at room temperature, with X-ray studies revealing them to be the cyclic dilithiated hexamer $[(S)\text{-}PhCH(CH_3)N(CH_2C\{CH_3\}{=}CHLi)Li]_6$ (**1**), the asymmetric unit of which is shown in Figure 3. Complex **1** is isostructural with the previously reported dilithio allyl-amide complex $[(S)\text{-}PhCH(CH_3)N(CH_2CH{=}CHLi)Li]_6$[21] (**9**), derived from (*S*)-*N*-*α*-mba and differing only by the additional methyl group on the allylic chain (Figure 4).

In the asymmetric unit of **1** (Figure 3) there are four Li cations and two dianionic amide ligands deprotonated at N(1)/N(2) and the terminal allylic positions C(12)/C(24). The bond lengths within the methallyl moiety indicate retention of the vinylic double bond rather than formation of a delocalized anionic system [N(1)−C(9), 1.4579(18); C(9)−C(10), 1.5216(19); C(10)−C(12), 1.350(2) Å], which is essentially identical to that seen in isostructural **9**.[21] All four Li cations are located in high coordination environments, forming a range of covalent and electrostatic/agostic contacts with either the amide N atoms, allylic C atoms, and/or the *ipso* and *ortho* C atoms of the phenyl rings. The Li−N bond lengths range from 2.002(3) to 2.157(3) Å for Li(4)−N(2) to Li(2)′−N(2), while the longer Li−C allylic bonds range from 2.163(3) to 2.706(3) Å for Li(3)−C(24) to Li(4)−C(10), respectively, which lie in the same range as those seen in **9**.[21]

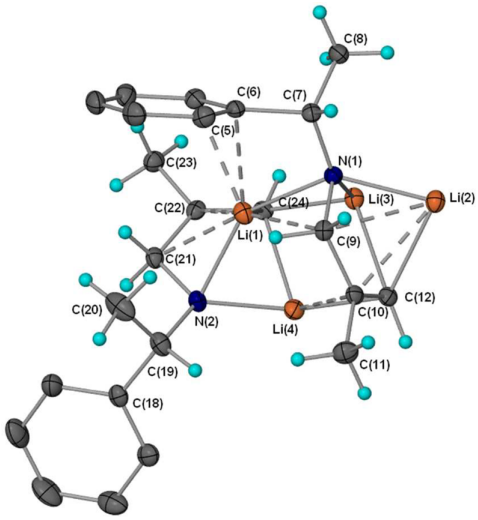

Figure 3. Asymmetric unit of the molecular structure of $[(S)\text{-}PhCH(CH_3)N(CH_2C\{CH_3\}{=}CHLi)Li]_6$ (**1**) showing thermal ellipsoids at 45% probability. Hydrogen atoms (except vinyl ones) have been omitted for clarity. Selected bond lengths (Å): Li(1)−N(1), 2.135(3); Li(1)−N(2), 2.094(3); Li(1)−C(5), 2.538(3); Li(1)−C(6), 2.648(3); Li(1)−C(9), 2.445(3); Li(1)−C(21), 2.453(3); Li(1)−C(22), 2.457(3); Li(1)−C(24), 2.251(3); Li(2)−N(1), 2.111(3); Li(2)−C(9), 2.533(3); Li(2)−C(10), 2.533(3); Li(2)−C(12), 2.227(3); Li(3)−N(1), 2.046(3); Li(3)−C(12), 2.408(3); Li(3)−C(24), 2.163(3); Li(4)−N(2), 2.002(3); Li(4)−C(10), 2.706(3); Li(4)−C(12), 2.261(3); Li(4)−C(24), 2.364(3).

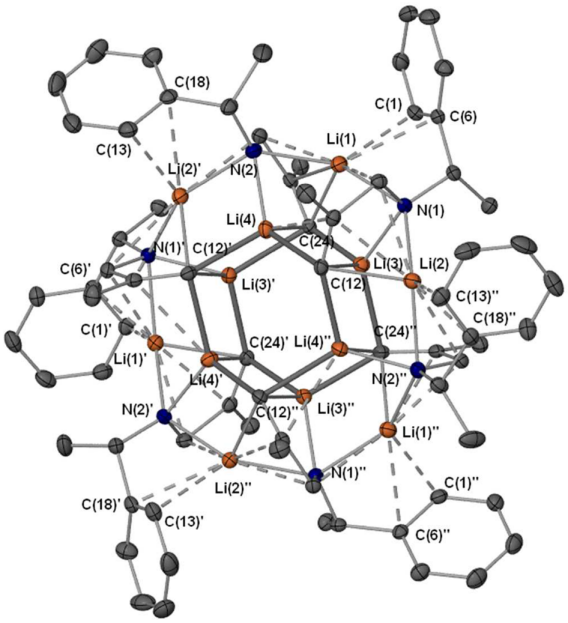

Figure 4. Molecular structure of **1** with selected atom labeling and thermal ellipsoids at 45% probability. Hydrogen atoms are omitted for clarity. The hexameric central core has been highlighted. Symmetry operator: ′ = 1−*y*, *x*−*y*, *z*; ″ = 1−*x*, *y*, 1−*x*, *z*. Selected bond lengths (Å): Li(2)′−N(2), 2.157(3); Li(2)′−C(13), 2.568(3); Li(2)′−C(18), 2.613(3); Li(2)′−C(21), 2.565(3); Li(2)−N(2)″, 2.157(3); Li(3)′−C(24), 2.274(3); Li(4)″−C(12), 2.152(3).

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Similar to **9**, as well as $[(t\mathrm{Bu})(\mathrm{Me})_2\mathrm{SiN}(\mathrm{CH_2CH{=}CHLi})\text{-}\mathrm{Li}]_6$,[22] complex **1** forms a hexamer in its full aggregation state, having the gross structural features of a paddlewheel with a prismatic hexagonal core (Figure 4). The inner core is composed of alternating short and long Li−C bonds [Li(3)−C(24),C(24)′, 2.163(3), 2.274(3) Å and Li(4)−C(12),C(12)′, 2.152(3), 2.261(3) Å] that make up two Li_3C_3 hexagonal rings that sit on top of each other in a slightly eclipsed fashion. The two rings are joined by more Li−C bonds, which make up the "rungs" of the core, again showing distinct short [Li(4)−C(24), 2.364(3) Å] and long bond character [Li(3)−C(12)′, 2.408(3) Å]. The outer "paddles" of the hexamer are composed of six five-membered $NLiC_3$ rings, made up of the deprotonated methallyl group of (*S*)-*N*-mbma. These five-membered rings alternate with the methylbenzyl group around the outside of the core, giving the complex its final composition.

Moving to sodium, very air sensitive[23] light yellow plate crystals, grown from a hexane/THF solution, were analyzed by X-ray crystallography, revealing the complex to be $[\mathrm{PhC(=CH_2)N(CH_2CH\{CH_3\}_2)Na}]_\infty$, **2**. Figure 5 depicts the

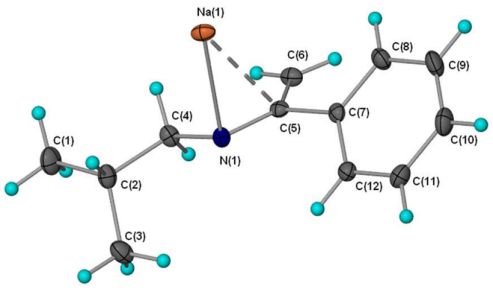

Figure 5. Mononuclear fragment of the molecular structure of $[\mathrm{PhC(=CH_2)N(CH_2CH\{CH_3\}_2)Na}]_\infty$ (**2**) showing thermal ellipsoids at 45% probability and selected atom labeling. Selected bond lengths (Å): Na(1)−N(1), 2.4914(9); N(1)−C(5), 1.3440(13); N(1)−C(4), 1.4499(12); C(4)−C(2), 1.5219(15); C(2)−C(3), 1.5195(17); C(2)−C(1), 1.5186(15); C(5)−C(6), 1.3825(14).

mononuclear section of **2**, while Figure 6 shows a longer section of its polymeric composition. Complex **2** has rearranged to the η^1-*N*-aza-enolate containing a new double bond [C(5)−C(6), 1.3825(14) Å] at the previous benzylmethyl moiety, with loss of chirality at C(5) and saturation of the former methallyl group [C(4)−C(2), 1.5219(15); C(2)−C(1), 1.5186(15); C(2)−C(3), 1.5195(17) Å].

To appreciate the full coordination environment around the Na cation, it is necessary to look at the extended polymeric aggregation of **2** (Figure 6). In its simplest form the complex can be described as a polymer of repeating dimeric units. Each dimer is composed of a central $(\mathrm{NaN})_2$ ring and two deprotonated (*S*)-*N*-*α*-mbma ligands, which show distinct short [Na(1)−N(1)′, 2.3994(9) Å] and long [Na(1)−N(1), 2.4914(9) Å] Na−N_{amide} bond lengths. The Na cation further engages in a short electrostatic interaction with the aza-enolate moiety [Na(1)−C(5), 2.768(1) Å] and makes a longer *π*-interaction with a neighboring aromatic carbon [Na(1)−C(12)′, 3.0003(11) Å]. The Na−N_{amide} bond lengths in **2** lie in the same range as those seen in other Na dimers, $[\mathrm{Na(HMDS)\cdot THF}]_2$,[24] $[\mathrm{Na(TMP)\cdot TMEDA}]_2$,[25] $[\mathrm{Na\{N(Ph)\text{-}iPr\}}]_2$,[26] and $[\mathrm{Na(NPh_2)\cdot THF_2}]$.[26]

The formation of the final polymeric chain is achieved through a short vinylic Na−C electrostatic interaction

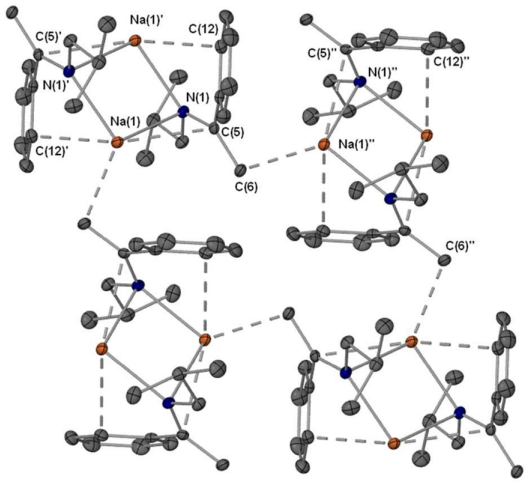

Figure 6. Molecular structure of $[\mathrm{PhC(=CH_2)N(CH_2CH\{CH_3\}_2)Na}]_\infty$ (**2**) showing thermal ellipsoids at 45% probability and selected atom labeling. Hydrogen atoms are omitted for clarity. Symmetry operators: ′ = 1−*x*, −*y*, −*z*; ″ = *x*, −*y*−1/2, 1/2+*z*. Selected bond lengths (Å) and angles (deg): Na(1)″−C(6), 2.5792(11); Na(1)−C(12)′, 3.0003(11); Na(1)−N(1)−Na(1)′, 79.69(3); N(1)−Na(1)−N(1)′, 100.31(3); Na(1)′−N(1)−C(5), 125.49(7); Na(1)′−N(1)−C(4), 122.26(6); C(5)−N(1)−C(4), 112.24(8).

[Na(1)″−C(6), 2.5792(11) Å], giving an overall coordination number of five for each Na cation. Interestingly, despite an excess of THF being added to the reaction mixture, there is no coordination of any THF molecules in the molecular structure of **2**. This would suggest that the electrostatic interactions between the Na cation and the aza-enolate functionality are sufficiently strong enough to exclude THF from its coordination sphere.[27]

Solution Studies. All eight complexes were characterized by multinuclear NMR spectroscopy (^{1}H, ^{13}C, COSY, and HSQC, as well as ^{7}Li for **1**) in d_6-benzene and d_8-THF alone or in a d_6-benzene solution doped with d_8-THF.

^{1}H NMR spectroscopy shows that the structure of **1** is preserved in the solution state, with the signals at 6.38, 3.78, and 2.09 ppm corresponding to the vinylic, methylene, and methyl protons, respectively. All of the signals are shifted downfield relative to the free amine, except for the *cis*- and amine protons, which are absent.

The ^{1}H NMR spectra of compounds **2**−**5** all show the presence of the aza-enolate configuration in solution. This is characterized by the disappearance of the doublet and quartet corresponding to the methyl and benzylic protons (PhC*H*-($C\mathit{H}_3$)), respectively, and in particular by the appearance of a septet at ca. 1.9 ppm resulting from the formation of the isobutyl moiety.

A comparison of the chemical shifts for each compound **2**−**5** shows little variation between different Lewis donors and metals (see Supporting Information, Table S2). All three sodium complexes display essentially identical signal frequencies, while a small shift to lower frequency of some signals is observed in the potassium complex.

TMEDA and PMDETA are observed in the NMR spectra of **3** and **4**, respectively; however THF is not observed in **2** or **5**, despite both being crystallized from a hexane/THF mixture. Synthesizing **5** in the presence of TMEDA or PMDETA had no effect on the reaction product, with neither donor appearing in

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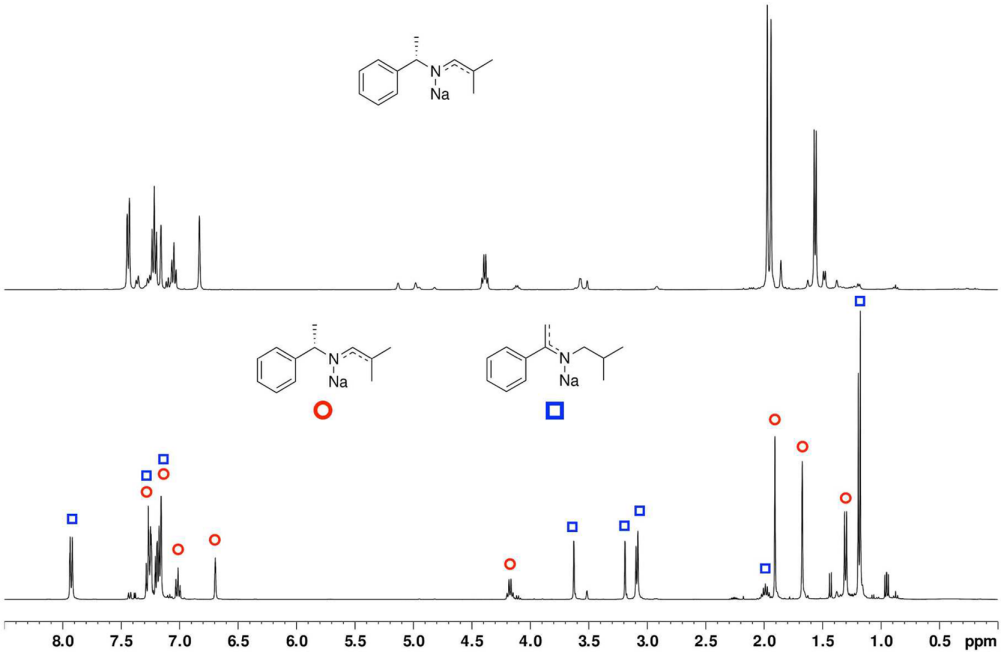

Figure 7. ^{1}H NMR spectrum of **6** in d_6-benzene doped with d_8-THF (top) and the same sample 10 days later (bottom). Signals belonging to the 1-aza-allyl anion (red circles) are shifted slightly, presumably due to changes in aggregation state and interactions with other species in solution.

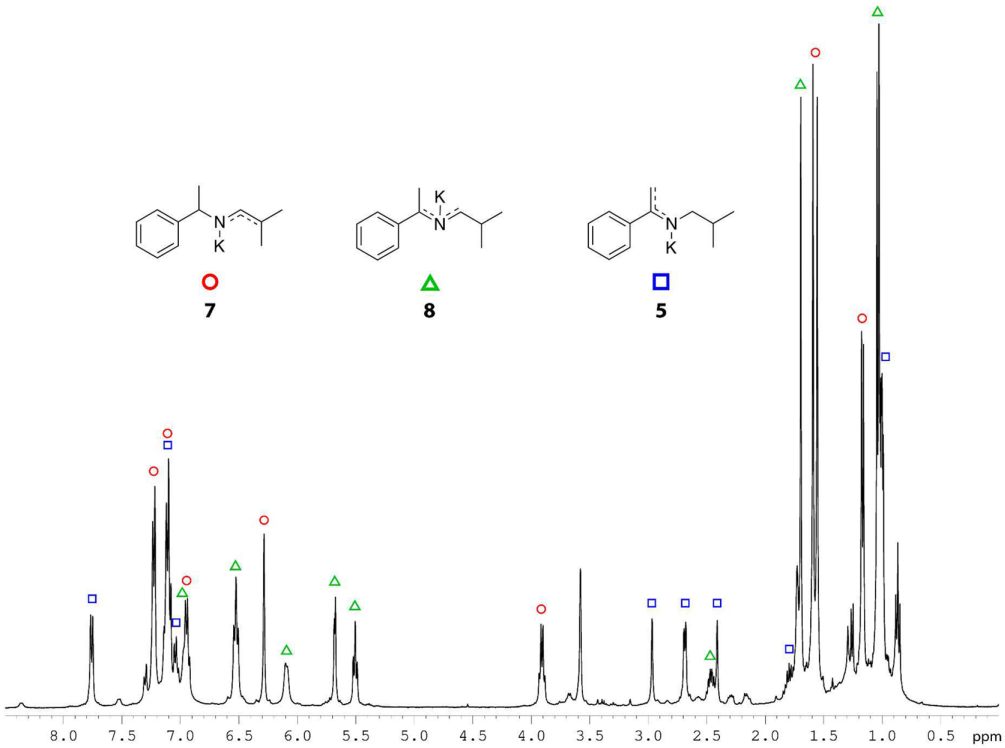

Figure 8. ^{1}H NMR spectrum of **7** 5 days after dissolution in d_8-THF.

the product after washing with hexane, suggesting that the potassium has enough electrostatic interactions with the ligand to exclude any Lewis donors. This is an established phenomenon, previously reported for example in the cases of $[PhC(=CH_2)N(CH_2CH_2CH_2Ph)K]_\infty$[20] and $[(Ph\{Me\}N)_4K_2Ca]_\infty$,[28] which both exclude donor solvents despite being synthesized in THF.

This is the first system in which we have observed the aza-enolate species being formed so readily, where both sodium and potassium complexes form the aza-enolate anion in the presence of only THF, compared with (*S*)-*N*-*α*-mba, which

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requires the presence of PMDETA for the sodium complex to rearrange to the aza-enolate form.

In order to determine what effect the absence of Lewis donors would have upon the rearrangement of the allyl-amide, an NMR spectrum was obtained in d_6-benzene. However, the complexes proved to be insoluble without the presence of a small amount of Lewis donor being present. Therefore, the yellow powder **6** was dissolved in d_6-benzene doped with approximately 5% d_8-THF. Immediately after preparing the sample, analysis showed that a 1,3-sigmatropic rearrangement to the 1-aza-allyl form had occurred, as indicated by the disappearance of the methylene proton signals as well as the vinylic proton signals, replaced by a new vinylic proton signal at 6.75 ppm and two signals at 1.85 and 1.91 ppm, corresponding to two terminal methyl groups. Analysis of the same sample 10 days later showed that a further rearrangement had occurred, with approximately half of the sample having transformed to the aza-enolate species (Figure 7).

The same experiment was performed with **7** and also showed a 1,3-sigmatropic rearrangement; however the absence of both vinylic and methylene proton signals indicates that no rearrangement to the aza-enolate form occurred. Instead, the gradual appearance of a different set of signals was observed, which have been attributed to the formation of a 2-aza-allyl anion of $[PhC(CH_3)N(=CHCH\{CH_3\}_2)K]_n$ (**8**). The signal shifts and splitting closely resemble those reported for $[PhC(CH_3)(NMe_2)K]_n$ and $[PhCH(NMe_2)K]_n$.[29] Dissolving **7** in neat d_8-THF resulted in formation of the 1-aza-allyl anion, which rearranged over the course of 5 days to a mixture of the 1-aza-allyl (42% of total compound by integration), 2-aza-allyl (34%), and aza-enolate (24%) forms (Figure 8).

CONCLUSION

A detailed solid- and solution-state structural study on the metalation (Li, Na, and K) of (*S*)-*N*-(α-methylbenzyl)-methallylamine demonstrates that anion rearrangements to the 1-aza-allyl and aza-enolate isomers occur more readily than in the analogous allylic amides derived from (*S*)-*N*-α-mba (= methylbenzylallylamine) and (*S*)-*N*-α-mbpa (= methylbenzyl-3-phenylprop-2-enamine). The significant differences are that the amide to 1-aza-allyl form occurs for Na and K complexes simply by the presence of benzene and that the addition of any standard Lewis base promotes facile transition to the aza-enolate isomer irrespective of the denticity of the Lewis base used. The facile transition to the aza-enolate isomer destroys the chiral center and limits their role in any enantioselective reactions.

In total eight complexes were observed by solution NMR, with two (**1** and **2**) being structurally authenticated by single-crystal diffraction. Complex **1**, $[(S)\text{-}PhCH(CH_3)N(CH_2C\{CH_3\}=CHLi)Li]_6$, is dilithiated and forms a typical hexameric paddlewheel structure. Reaction with *n*BuNa followed by addition of a Lewis donor gave complexes **2**−**4**, all of which have undergone an anion rearrangement to the aza-enolate form. The polymeric solid-state structure of **2**, $[PhC(=CH_2)N(CH_2CH\{CH_3\}_2)Na]_\infty$, indicates that the THF solvent, which assists the anion rearrangement, is not incorporated into the crystal structure. The potassium complex $[PhC(=CH_2)N(CH_2CH\{CH_3\}_2)K]_n$ (**5**) also excludes any donor solvents, favoring instead internal electrostatic interactions. Minimizing the use of donor solvents allowed for the characterization of **6** and **7**, which shows that the complexes undergo a 1,3-sigmatropic rearrangement from the allyl-amide to the 1-aza-allyl form and continue to rearrange over time. Complex **6** rearranges to the aza-enolate form, while no evidence of this rearrangement was found to occur in **7**, instead giving evidence of a rearrangement to the previously unobserved 2-aza-allyl form in solution.

EXPERIMENTAL SECTION

Unless otherwise stated, all reactions were carried out using Schlenk techniques under a nitrogen atmosphere. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX 400 MHz spectrometer, with chemical shifts referenced internally to C_6D_6 or d_8-THF. Water and oxygen were removed from hexane and THF using the MBraun SPS-800 solvent purification system and stored over 4 Å molecular sieves. TMEDA and PMDETA were dried by reflux over CaH_2 and stored over 4 Å molecular sieves. *n*BuLi (1.6 M in hexanes) and *t*BuLi (1.7 M in pentane) were purchased from Sigma-Aldrich, and (*S*)-α-methylbenzylamine and 3-bromo-2-methylpropene were purchased from Alfa Aesar and Matrix Scientific, respectively, and used without further purification. *n*BuNa[30] and *n*BuK[30] were synthesized according to the literature. Elemental analysis for compounds **1**−**5** was performed by CMAS, Melbourne, Australia.

Single-crystal X-ray data for compound **1** was collected at 123 K using an Oxford Gemini Ultra CCD with Cu Kα (phase 1) radiation. The diffraction images were processed using the CrysAlisPro software package.[31] Crystallographic data for compound **2** were obtained on a Bruker X8 APEXII CCD diffractometer equipped with an Oxford Cryosystems 700 Cryostream and cooled to 123(2) K. Data were collected with monochromatic (graphite) Mo Kα radiation (λ = 0.710 73 Å) and processed using the Bruker Apex2 v2012.2.0 software; Lorentz, polarization, and absorption corrections (multiscan, SADABS[32]) were applied. Both compounds' crystals were mounted in Krytox GPL-107 perfluorinated oil. All structures were solved by standard methods and refined by full matrix least-squares using the SHELX-97 program.[33] Non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms attached to C were placed in calculated positions using a riding model with C−H distances of 0.99 Å and $U_{iso}(H) = 1.2 \times U_{eq}(C)$. CCDC reference numbers 1436016 and 1436017 contain supplementary crystallographic data for this paper.

Synthesis and Characterization. *(S)-N-(α-Methylbenzyl)-methallylamine.* (*S*)-α-Methylbenzylamine (6.06 g, 50 mmol) was dissolved in 40 mL of THF, followed by addition of *n*BuLi (31 mL [1.6 M solution in hexanes], 50 mmol) at −78 °C. The solution was stirred for 2 h while warming to 0 °C. 3-Bromo-2-methylpropene (6.75 g, 50 mmol) was then added dropwise, and the resultant solution allowed to warm to room temperature and stirred overnight. The resultant orange solution was quenched with water (50 mL) and THF, evaporated *in vacuo*, and then extracted with diethyl ether (3 × 40 mL). The organic phase was washed with brine and dried over Na_2SO_4, and then the solvent removed *in vacuo* to yield a pale yellow liquid. This was distilled *in vacuo* to produce the title compound as a colorless oil, which was stored under N_2 over 4 Å molecular sieves (7.84 g, 89%). Bp: 40 °C/0.1 mmHg. ^1H NMR (400 MHz, C_6D_6, 30 °C): δ 7.29 (2H, m, *ortho*-H), 7.20 (2H, m, *meta*-H), 7.10 (1H, m, *para*-H), 4.97 (1H, s, $CH_2C(CH_3)=CH_2$trans), 4.83 (1H, s, $CH_2C(CH_3)=CH_2$cis), 3.59 (1H, q, ^3J = 6.6 Hz, $PhC(H)CH_3$), 2.94 (1H, d, ^2J = 14.4 Hz, $CH_2C(CH_3)=CH_2$), 2.92 (1H, dd, ^3J = 14.4 Hz, $CH_2C(CH_3)=CH_2$), 1.63 (3H, s, $CH_2C(CH_3)=CH_2$), 1.19 (3H, d, ^3J = 6.6 Hz, $PhC(H)CH_3$), 1.00 (1H, br s, NH). ^{13}C NMR (100 MHz, C_6D_6, 30 °C): δ 146.5 (*ipso*-C), 144.9 ($CH_2C(CH_3)=CH_2$), 128.7 (*meta*-C), 127.1 (*para*-C), 127.0 (*ortho*-C), 110.5 ($CH_2C(CH_3)=CH_2$), 57.9 ($PhC(H)CH_3$), 53.9 ($CH_2C(CH_3)=CH_2$), 25.0 ($PhC(H)CH_3$), 20.9 ($CH_2C(CH_3)=CH_2$)

[(S)-PhCH(CH$_3$)N(CH$_2$C{CH$_3$}=CHLi)Li]$_6$, 1. (*S*)-*N*-(α-Methylbenzyl)methallylamine (0.35 g, 2 mmol) was dissolved in hexane (8 mL) and cooled to −60 °C, and *n*BuLi (1.25 mL [1.6 M solution in hexanes], 2 mmol) was added dropwise. The solution was allowed to warm slowly to −10 °C, followed by the dropwise addition of *t*BuLi (1.2 mL [1.7 M solution in pentane], 2 mmol), before the

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solution was allowed to warm to room temperature. After stirring for 1 h, the solution was filtered through a filter cannula and stored at 20 °C. After several days, a large crop of yellow needle crystals deposited (0.31 g, 86%). Mp: 186−187 °C (dark brown melt). ^{1}H NMR (400 MHz, C_6D_6, d_8-THF (5% v/v) 30 °C): δ 7.50 (2H, d, ^3J = 7.4 Hz, *ortho*-H), 7.29 (2H, t, ^3J = 7.5 Hz, *meta*-H), 7.13 (1H, t, ^3J = 7.3 Hz, *para*-H), 6.39 (1H, s, $CH_2C(CH_3)$=C*H*Li), 4.16 (1H, q, ^3J = 6.3 Hz, PhC(*H*)CH_3), 3.85 (1H, d, ^2J = 17.4 Hz, $CH_2C(CH_3)$=CHLi), 3.73 (1H, d, ^2J = 17.4 Hz, $CH_2C(CH_3)$=CHLi), 2.10 (3H, s, $CH_2C(CH_3)$=CHLi), 1.62 (3H, d, ^3J = 6.3 Hz, PhC(H)CH_3). ^{13}C NMR (100 MHz, C_6D_6, d_8-THF (5% v/v), 30 °C): δ 159.1 ($CH_2C(CH_3)$=CHLi), 153.2 (*ipso*-C), 151.3 ($CH_2C(CH_3)$=CHLi), 128.2 (*meta*-C), 127.5 (*ortho*-C), 125.6 (*para*-C), 64.3 (PhC(H)CH_3), 63.4 ($CH_2C(CH_3)$=CHLi), 29.4 ($CH_2C(CH_3)$=CHLi), 23.1 (PhC(H)CH_3). ^{7}Li NMR (156 MHz, C_6D_6, d_8-THF (5% v/v), 30 °C): δ 1.75. Anal. Calcd for $Li_{12}N_6C_{72}H_{90}$: C, 77.02; H, 8.08; N, 7.48. Found: C, 76.98; H, 8.45; N, 7.32.

Crystal Data for ***1****.* $Li_{12}N_6C_{72}H_{90}$; M_r = 1122.78; trigonal; space group: *r*3; *a* = 25.7286(5) Å, *b* = 25.7286(5) Å, *c* = 8.9644(2) Å; α = 90°; β = 90°; γ = 120°; *V* = 5139.06(18) Å^3; *Z* = 3, reflections collected/unique 18 469/4001 (R_{int} = 0.0274); R_1 values ($I > 2\sigma(I)$) = 0.0305; $wR(F^2)$ values ($I > 2\sigma(I)$) = 0.0812; R_1 values (all data) = 0.0314; $wR(F^2)$ values (all data) = 0.0821; GOF = 1.055.

[PhC(=CH$_2$)N(CH$_2$CH{CH$_3$}$_2$)Na]$_\infty$, ***2****.* To a stirring suspension of *n*BuNa (0.16 g, 2 mmol) in hexane (10 mL) at −60 °C was added (*S*)-*N*-(α-methylbenzyl)methallylamine (0.35 g, 2 mmol). The suspension was allowed to warm slowly to room temperature and stirred overnight, forming a yellow suspension. An orange suspension was formed upon addition of THF (2.5 mL), which was filtered to isolate a red solution. From this solution, a large crop of yellow plate crystals deposited overnight (0.29 g, 74%). Mp: 251−252 °C (dark brown melt). ^{1}H NMR (400 MHz, d_8-THF, 30 °C): δ 7.68 (2H, d, ^3J = 7.9 Hz, *ortho*-H), 7.10 (2H, t, ^3J = 7.4 Hz, *meta*-H), 7.01 (1H, t, ^3J = 7.2 Hz, *para*-H), 2.86 (1H, d, ^2J = 1.7 Hz, C=C*H*$_2$), 2.75 (2H, d, ^3J = 6.6 Hz, $CH_2CH(CH_3)_2$), 2.48 (1H, d, ^2J = 1.7 Hz, C=C*H*$_2$), 1.74 (1H, septet, ^3J = 6.6 Hz, $CH_2CH(CH_3)_2$), 0.99 (6H, d, ^3J = 6.5 Hz, $CH_2CH(CH_3)_2$). ^{13}C NMR (100 MHz, d_8-THF, 30 °C): δ 164.2 (C=CH_2), 152.4 (*ipso*-C), 128.0 (*meta*-C), 127.5 (*ortho*-C), 125.6 (*para*-C), 63.2 ($CH_2CH(CH_3)_2$), 60.7 (C=CH_2), 31.6 ($CH_2CH(CH_3)_2$), 22.8 ($CH_2CH(CH_3)_2$). Anal. Calcd for $Na_2N_2C_{24}H_{32}$: C, 73.07; H, 8.18; N, 7.10. Found: C, 69.98; H, 8.30; N, 6.89.

Crystal Data for ***2****.* $Na_2N_2C_{24}H_{32}$; M_r = 394.50; monoclinic; space group *P*2(1)/*c*; *a* = 11.4543(6) Å, *b* = 11.3694(7) Å, *c* = 8.8489(5) Å; α = 90°; β = 103.044(4)°; γ = 90°; *V* = 1122.64(11) Å^3; *Z* = 2, reflections collected/unique 10 457/3178 (R_{int} = 0.0175); R_1 values ($I > 2\sigma(I)$) = 0.0413; $wR(F^2)$ values ($I > 2\sigma(I)$) = 0.1096; R_1 values (all data) = 0.0461; $wR(F^2)$ values (all data) = 0.1137; GOF = 1.048.

[PhC(=CH$_2$)N(CH$_2$CH{CH$_3$}$_2$)Na·TMEDA]$_n$, ***3****.* To a stirring suspension of *n*BuNa (0.16 g, 2 mmol) in hexane (32 mL) at −60 °C was added (*S*)-*N*-(α-methylbenzyl)methallylamine (0.35 g, 2 mmol). After gently warming to ambient temperature, TMEDA (0.30 mL, 2 mmol) was added, which caused dissolution of the yellow precipitate and formation of a dark brown solution. THF (1 mL) was added, and the solution was stored at room temperature. After several days a large crop of yellow crystals deposited (0.42 g, 67%). Mp: 253−254 °C (dark brown melt). ^{1}H NMR (400 MHz, d_8-THF, 30 °C): δ 7.69 (2H, d, ^3J = 7.8 Hz, *ortho*-H), 7.09 (2H, t, ^3J = 7.5 Hz, *meta*-H), 7.00 (1H, t, ^3J = 7.2 Hz, *para*-H), 2.87 (1H, s, C=C*H*$_2$), 2.77 (2H, d, ^3J = 6.6 Hz, $CH_2CH(CH_3)_2$), 2.50 (1H, s, C=C*H*$_2$), 2.30 (4H, s, CH_2-TMEDA), 2.15 (12H, s, CH_3-TMEDA), 1.75 (1H, septet, ^3J = 6.6 Hz, $CH_2CH(CH_3)_2$), 0.99 (6H, d, ^3J = 6.6 Hz, $CH_2CH(CH_3)_2$). ^{13}C NMR (100 MHz, d_8-THF, 30 °C): δ 164.0 (C=CH_2), 152.7 (*ipso*-C), 127.9 (*meta*-C), 127.6 (*ortho*-C), 125.6 (*para*-C), 63.3 ($CH_2CH(CH_3)_2$), 60.7 (C=CH_2), 59.1 (CH_2-TMEDA), 46.4 (CH_3-TMEDA), 31.7 ($CH_2CH(CH_3)_2$), 22.9 ($CH_2CH(CH_3)_2$). Anal. Calcd for $NaN_3C_{18}H_{32}$: C, 68.97; H, 10.29; N, 13.41. Found: C, 68.97; H, 10.29; N, 13.53.

[PhC(=CH$_2$)N(CH$_2$CH{CH$_3$}$_2$)Na·PMDETA]$_n$, ***4****.* To a stirring suspension of *n*BuNa (0.16 g, 2 mmol) in hexane (20 mL) at −60 °C was added (*S*)-*N*-(α-methylbenzyl)methallylamine (0.35 g, 2 mmol). After warming to 0 °C, PMDETA (0.42 mL, 2 mmol) was added, which caused dissolution of the yellow precipitate and formation of a bright red solution, which was filtered and left standing at room temperature. A dark red oil deposited, and storage at 4 °C yielded a crop of orange needle crystals. ^{1}H NMR (400 MHz, d_8-THF, 30 °C): δ 7.70 (2H, m, *ortho*-H), 7.11 (2H, t, ^3J = 7.2 Hz, *meta*-H), 7.01 (1H, t, ^3J = 7.2 Hz, *para*-H), 2.88 (1H, s, C=C*H*$_2$), 2.77 (2H, d, ^3J = 6.7 Hz, $CH_2CH(CH_3)_2$), 2.51 (1H, s, C=C*H*$_2$), 2.38 (6H, m, CH_2-PMDETA), 2.28 (6H, m, CH_2-PMDETA), 2.13 (17H, s, CH_3-PMDETA), 2.11 (5H, s, CH_3-PMDETA), 1.73 (1H, septet, ^3J = 6.6 Hz, $CH_2CH(CH_3)_2$), 1.01 (6H, d, ^3J = 6.6 Hz, $CH_2CH(CH_3)_2$). ^{13}C NMR (100 MHz, d_8-THF, 30 °C): δ 163.5 (C=CH_2), 152.3 (*ipso*-C), 127.7 (*meta*-C), 127.2 (*ortho*-C), 125.4 (*para*-C), 62.9 ($CH_2CH(CH_3)_2$), 60.1 (C=CH_2), 58.4 (CH_2-PMDETA), 56.7 (CH_2-PMDETA), 45.9 (CH_3-PMDETA), 43.1 (CH_3-PMDETA), 31.7 ($CH_2CH(CH_3)_2$), 22.5 ($CH_2CH(CH_3)_2$).

[PhC(=CH$_2$)N(CH$_2$CH{CH$_3$}$_2$)K]$_n$, ***5****.* To a stirring suspension of *n*BuK (0.19 g, 2 mmol) in hexane (10 mL) at −60 °C was added (*S*)-*N*-(α-methylbenzyl)methallylamine (0.35 g, 2 mmol). The suspension was allowed to warm slowly to room temperature and stirred overnight. Addition of THF (3 mL) resulted in a cloudy brown solution, which was filtered to isolate a dark brown solution. After standing at room temperature for several days, a large crop of brown crystals had formed (0.13 g, 30%). Mp: 271−272 °C (black melt). ^{1}H NMR (400 MHz, d_8-THF, 30 °C): δ 7.66 (2H, d, ^3J = 6.9 Hz, *ortho*-H), 7.10 (2H, t, ^3J = 7.3 Hz, *meta*-H), 7.02 (1H, t, ^3J = 7.2 Hz, *para*-H), 2.91 (1H, d, ^2J = 1.0 Hz, C=C*H*$_2$), 2.58 (2H, d, ^3J = 6.6 Hz, $CH_2CH(CH_3)_2$), 2.38 (1H, d, ^2J = 1.0 Hz, C=C*H*$_2$), 1.65 (1H, septet, ^3J = 6.6 Hz, $CH_2CH(CH_3)_2$), 0.95 (6H, d, ^3J = 6.6 Hz, $CH_2CH(CH_3)_2$). ^{13}C NMR (100 MHz, d_8-THF, 30 °C): δ 164.0 (C=CH_2), 151.2 (*ipso*-C), 128.0 (*meta*-C), 127.5 (*ortho*-C), 125.8 (*para*-C), 63.2 ($CH_2CH(CH_3)_2$), 58.7 (C=CH_2), 31.7 ($CH_2CH(CH_3)_2$), 22.8 ($CH_2CH(CH_3)_2$). Anal. Calcd for $KNC_{12}H_{16}$: C, 67.55; H, 7.56; N, 6.56. Found: C, 67.44; H, 7.50; N, 6.66.

[(S)-PhCH(CH$_3$)N(CH=C{CH$_3$}$_2$)Na]$_n$, ***6****.* To a stirring suspension of *n*BuNa (0.16 g, 2 mmol) in hexane (10 mL) at −60 °C was added (*S*)-*N*-(α-methylbenzyl)methallylamine (0.35 g, 2 mmol). The suspension was allowed to warm slowly to room temperature and stirred overnight. The resulting bright yellow powder was washed with two 10 mL volumes of hexane and dried under vacuum (0.15 g, 39%). Mp: 234−242 °C (dark brown melt). ^{1}H NMR (400 MHz, d_6-benzene with 5% d_8-THF, 30 °C): δ 7.44 (2H, d, ^3J = 7.5 Hz, *ortho*-H), 7.22 (2H, t, ^3J = 7.5 Hz, *meta*-H), 7.05 (1H, t, ^3J = 7.2 Hz, *para*-H), 6.83 (1H, s, C*H*=C), 4.39 (1H, q, ^3J = 6.7 Hz, PhC*H*(CH_3)), 1.96 (6H, d, ^3J = 12.5 Hz, = C(CH_3)$_2$), 1.56 (3H, d, ^3J = 6.7 Hz, PhCH(CH_3)). ^{13}C NMR (100 MHz, d_6-benzene with 5% d_8-THF, 30 °C): δ 153.3 (*ipso*-C), 148.5 (CH=C), 128.7 (*meta*-C), 126.7 (*ortho*-C), 125.6 (*para*-C), 81.2 (CH=*C*), 64.4 (PhCHCH$_3$), 25.9 (PhCH*C*H$_3$), 24.5 (=C*C*H$_3$), 18.2 (=CC*H*$_3$).

[(S)-PhCH(CH$_3$)N(CH=C{CH$_3$}$_2$)K]$_n$, ***7****.* To a stirring suspension of *n*BuK (0.19 g, 2 mmol) in hexane (10 mL) at −60 °C was added (*S*)-*N*-(α-methylbenzyl)methallylamine (0.35 g, 2 mmol). The suspension was allowed to warm slowly to room temperature and stirred overnight. The resulting light brown powder was washed with two 10 mL volumes of hexane and dried under vacuum (0.18 g, 42%). Mp: 100−103 °C (black melt). ^{1}H NMR (400 MHz, d_6-benzene with 5% d_8-THF, 30 °C): δ 7.29 (2H, d, ^3J = 7.5 Hz, *ortho*-H), 7.21 (2H, t, ^3J = 7.6 Hz, *meta*-H), 6.99 (1H, t, ^3J = 7.2 Hz, *para*-H), 6.58 (1H, s, C*H*=C), 4.03 (1H, q, ^3J = 6.5 Hz, PhC*H*(CH_3)), 2.03 (3H, s, =C(CH_3)$_2$), 1.86 (3H, s, =C(CH_3)$_2$), 1.44 (3H, d, ^3J = 6.6 Hz, PhCH(CH_3)). ^{13}C NMR (100 MHz, d_6-benzene with 5% d_8-THF, 30 °C): δ 152.4 (*ipso*-C), 149.1 (CH=C), 129.0 (*meta*-C), 125.8 (*ortho*-C), 125.4 (*para*-C), 75.8 (CH=*C*), 67.5 (PhCHCH$_3$), 25.4 (PhCH*C*H$_3$), 24.3 (=C*C*H$_3$), 18.1 (=CC*H*$_3$).

[PhC(CH$_3$)N(=CHCH{CH$_3$}$_2$)K]$_n$, ***8****.* Complex **8** has been observed only as part of a solution equilibrium. ^{1}H NMR (400 MHz, d_8-THF, 30 °C): δ 6.97 (1H, br s, *ortho*-H), 6.52 (2H, t, ^3J = 7.4 Hz, *meta*-H), 6.09 (1H, d, ^3J = 5.8 Hz, *ortho*′-H), 5.68 (1H, d, ^3J = 4.1 Hz, N=C*H*), 5.50 (1H, t, ^3J = 6.7 Hz, *para*-H), 2.46 (1H, q, ^3J = 6.6 Hz, 4.9 Hz, $CH(CH_3)_2$), 1.70 (3H, s, PhC(CH_3)), 1.04 (6H, d, ^3J = 6.8 Hz,

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$CH(CH_3)_2$). ^{13}C NMR (100 MHz, d_8-THF, 30 °C): δ 144.7 (*ipso*-C), 129.2 (*meta*-C), 120.0 (N=CH), 112.8 (*ortho*-C), 112.6 (*ortho*′-C), 105.6 (*para*-C), 94.6 ($PhCCH_3$), 34.7 ($CH(CH_3)_2$), 23.7 ($CH(CH_3)_2$), 12.1 ($PhCCH_3$).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.6b00445.

Crystallographic data (CIF)

Summary of crystallographic data for complexes **1** and **2** and NMR spectroscopy data for compounds **1**−**8** (PDF)

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Notes

The authors declare no competing financial interest.

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

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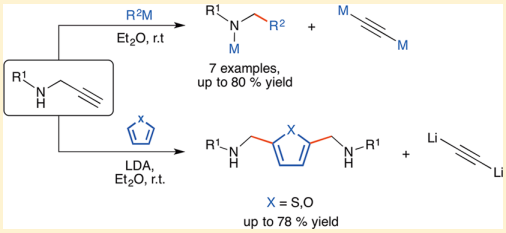
Supporting Information

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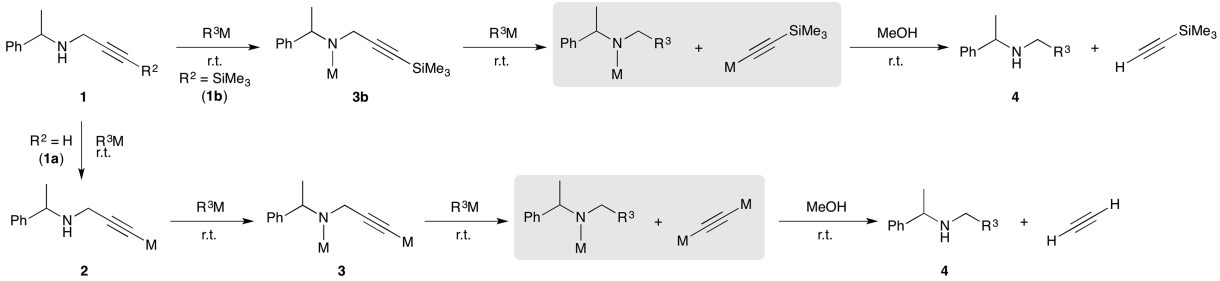
Scheme 1. Metal Acetylide Elimination during the Transformation of Propargyl Amines 1 to Methanediylamines 4[a]

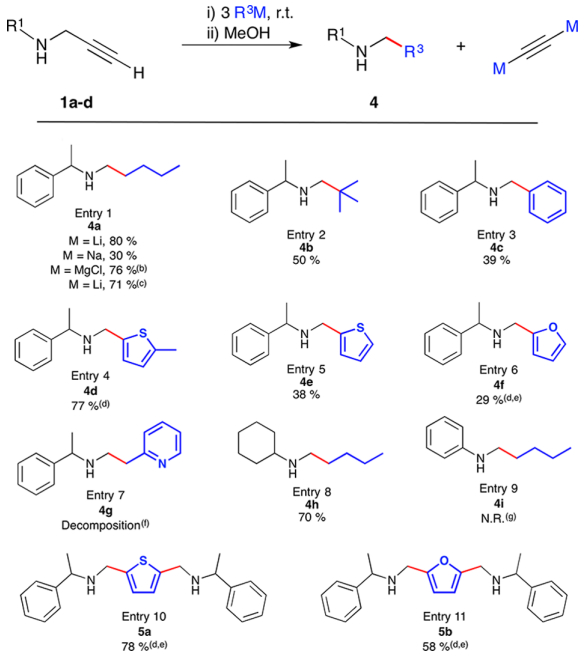


[a]R^3M = *n*-BuLi, *n*-BuNa, *n*-BuMgCl, *t*-BuLi, PhLi, furyllithium, thienyllithium, 5-methylthienyllithium.

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).

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

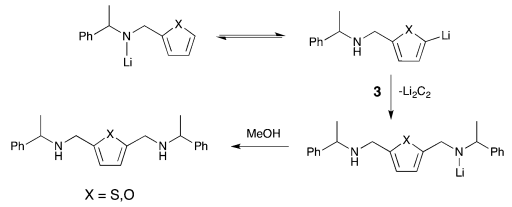


[a]Isolated yields after aqueous workup, calculated by NMR where impurities remained. [b]The reaction was conducted in THF solvent at reflux. [c]The internal alkyne **1b** was used instead of **1a**. [d]The organolithium R^3Li was generated in situ with LDA. [e]A 2:1 ratio of amine to heterocycle was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

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).

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



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.

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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]

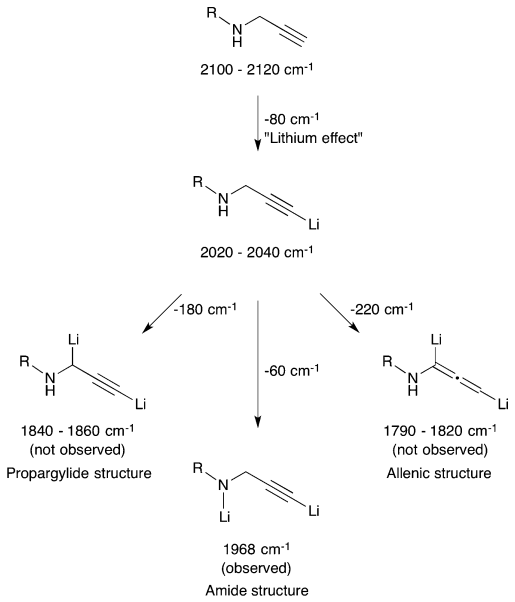

Figure 1. Comparison of expected and observed IR bands for plausible dilithiated intermediates.

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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