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The Generation and Reactions of Non-stabilized α-Aminocarbanions

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1. Introduction

Reactions allowing the introduction of a substituent at an amino-substituted carbon atom are of great importance for the synthesis of many nitrogen-containing compounds of biological significance, including *inter-alia* alkaloids and amino acids. Such substitutions can occur *via* three different types of intermediates: (i) iminium ions,[1] (ii) amino-substituted radicals[2] and (iii) amino-substituted carbanions.[3-5] Each of these routes has been extensively investigated. α-Amino-substituted carbanions can be classified as stabilized and non-stabilized. Tsunoda *et al.*[6] defined stabilized α-aminocarbanions as including all of those with any stabilizing group (including vinyl or phenyl) on the anionic carbon or on the nitrogen atom (*e.g.* acyl group), restricting non-stabilized α-aminocarbanions to those containing solely alkyl or aralkyl groups. Our definition follows Tsunoda, including viewing those derived from allylic and benzylic amines as stabilized α-carbanions; however, we believe that α-aminocarbanions with solely a phenyl group connected to the nitrogen, should be viewed as non-stabilized.

Stabilized α-aminocarbanions are well known in synthetic organic chemistry and have been thoroughly studied.[3,4,7] By contrast, non-stabilized α-aminocarbanions have received much less attention, and only a few brief summaries of them are scattered in the comprehensive overviews which deal in detail with their stabilized counterparts[7-10] (see however, ref.[11]). Recent progress in the generation of non-stabilized α-aminocarbanions and their transformations have prompted us to compile a review on this topic which will hopefully stimulate further work on the use of non-stabilized α-aminocarbanions.

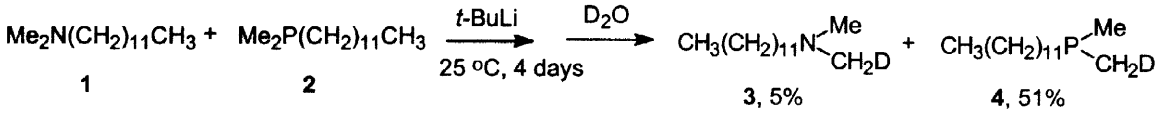
We restrict this report to non-stabilized α-aminocarbanions as defined above. We also exclude carbanions in which the nitrogen belongs to any functional group other than amino (*e.g.* nitro,[12] isocyanide[13] and isothiocyanate[14]) or to a heterocyclic ring.

2. Methods of Generation

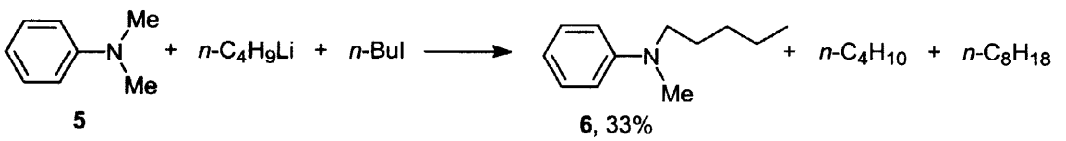
Up until the present, the use of non-stabilized α-aminocarbanions in organic synthesis has been limited, mainly due to the lack of appropriate methods for their generation. The main strategies, which have been applied to prepare non-stabilized α-aminocarbanions, are presented below.

2a. Lithiation by Proton Abstraction

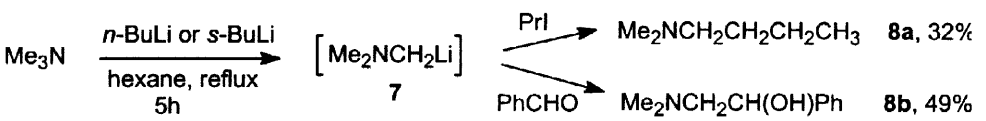
The direct deprotonation of simple alkyl amines is very difficult. Peterson and Hays obtained a small amount (5%) of α-deuterated dimethyldodecylamine (**3**) when amine **1**, together with dimethyldodecylphosphine (**2**), was treated with *t*-butyllithium in pentane for 4 days at 25 °C followed by quenching with D_2O.[15]



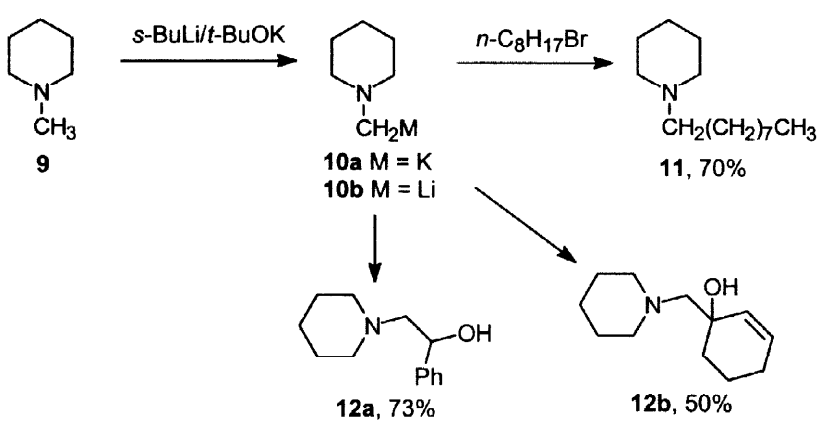
Lepley and Giumanini observed[16] the formation of *N*-methyl-*N*-(*n*-pentyl)aniline (**6**) from the reaction of *N,N*-dimethylaniline (**5**), 1-iodobutane and *n*-butyllithium in hexane. Their follow-up work revealed considerable carbanionic character at the α-position of the tertiary amine in the reaction transition state, but no evidence was found for an α-metallated species.[17-19]



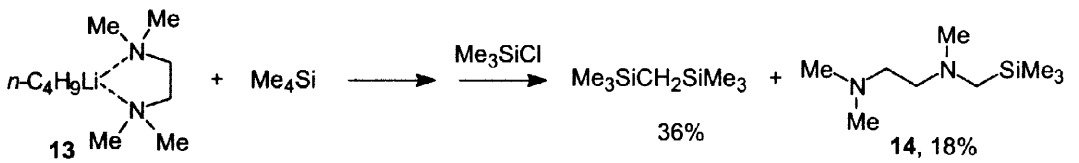
Smith studied the lithiation by *n*-BuLi or *s*-BuLi of *N*-methylpyrrolidine, *N*-methylpiperidine, triethylamine and trimethylamine in refluxing hexane.[20] Almost all of the BuLi was consumed in 0.5-6 h but in most cases only low yields of well-defined products from the lithiated amines were obtained, apparently due to the low stability of the intermediates. However, further reactions of lithiated trimethylamine (**7**) with iodopropane or benzaldehyde gave the corresponding products **8** in 32% and 49% yields, respectively.



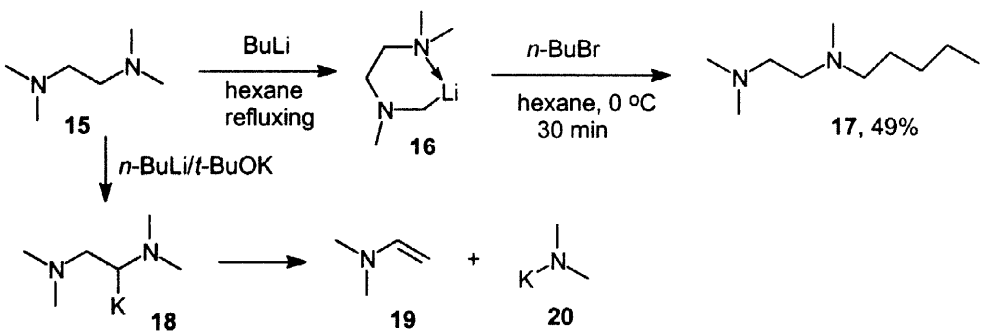
In 1984, Ahlbrecht and Dollinger reported direct observation of an α-metalated amino species, by using super base *s*-BuLi/*t*-BuOK.[21] Thus, *N*-methylpiperidine (**9**) was deprotonated at the methyl group and piperidinomethylpotassium (**10a**) was formed. After metal exchange, the resultant lithium reagent **10b** reacted with octyl bromide or carbonyl compounds to give *N*-nonylpiperidine (**11**) or β-hydroxy amines **12** in moderate to good yields.



Lithiation at the α-methyl position of polyamines is comparatively easier. *N,N,N',N'*-Tetramethylethylenediamine (TMEDA), which is frequently used as a cosolvent and activating reagent for alkyllithium (RLi) in deprotonation reactions, is reported to be lithiated when the *n*-BuLi-TMEDA complex **13** is left to stand in heptane at room temperature.[22] Peterson also isolated an 18% yield of *N,N,N'*-trimethyl-*N'*-[(trimethylsilyl)methyl]ethylene diamine (**14**) from the following reaction.[23]



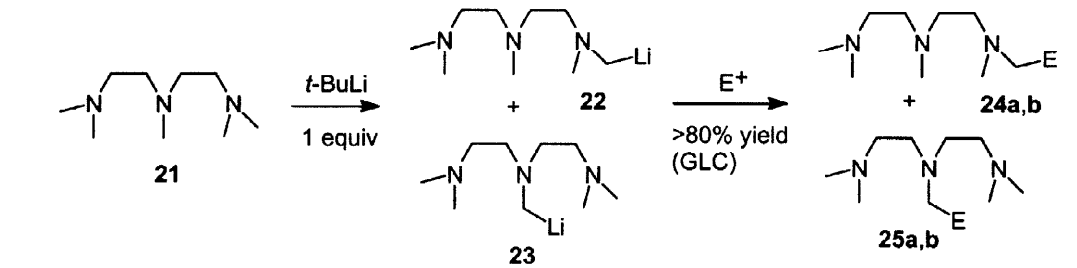
Smith systematically studied tertiary amine-organolithium complexes.[20] He found that TMEDA **15** can be lithiated completely within 1-3 h by *n*-BuLi or *s*-BuLi at 50 °C in hexane, and in 14 h by *t*-BuLi at 36 °C (refluxing pentane). No lithiation of TMEDA at the methylene carbons was observed. The use of *s*-BuLi in refluxing hexane gave good results in the lithiation of *N,N,N',N'*-tetramethyl-1,3-butanediamine and triethylenediamine, but not for *N,N'*-dimethyl-1,4-piperazine or *N,N,N',N'*-tetramethylmethylenediamine. Lithiated TMEDA **16** is reasonably stable in hexane at 35 °C (losing 0.52% of contained active material per day) and reacts with organic halides or carbonyl compounds to form the expected products (*e.g.* **16** → **17**) in 30-50% yields.

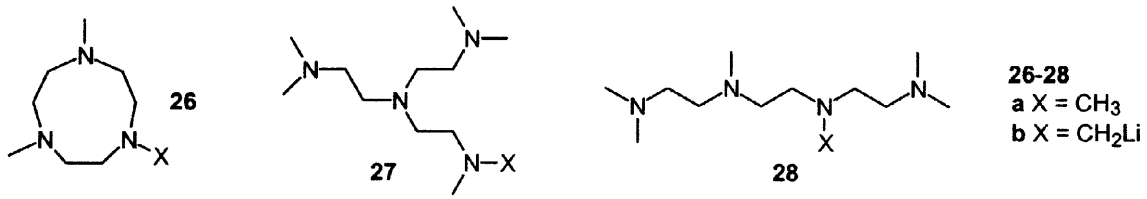


Köhler *et al.*[24] found that the regioselectivity of the metallation of TMEDA **15** could be altered by changing the conditions: *t*-BuLi attacks preferentially a methyl group whereas *n*-BuLi/*t*-BuOK deprotonates a methylene group. The methylene-metallated compound **18** is less stable and easily decomposes into dimethylvinylamine (**19**) and amide **20**. Harder and Lutz obtained the X-ray structure of a crystalline mixture of dilithiated 2-methyl-6-*t*-butylphenol, methyl-lithiated TMEDA and unreacted TMEDA.[25] Despite the instability of BuLi/TMEDA/hexane, this reagent can still be used as a powerful deprotonation reagent for the weak organic C-H acids. For example, benzene was lithiated in a hot benzene solution of *n*-BuLi/TMEDA to give, after trapping the phenyllithium intermediate, the expected products in high yield.[20,22]

N,N,N',N'',N''-Pentamethyldiethylenetriamine (PMDTA, **21**) was deprotonated easily at the *N*-methyl groups by butyllithiums.[26] The extent of lithiation at the terminal and central *N*-methyls depends on the nature

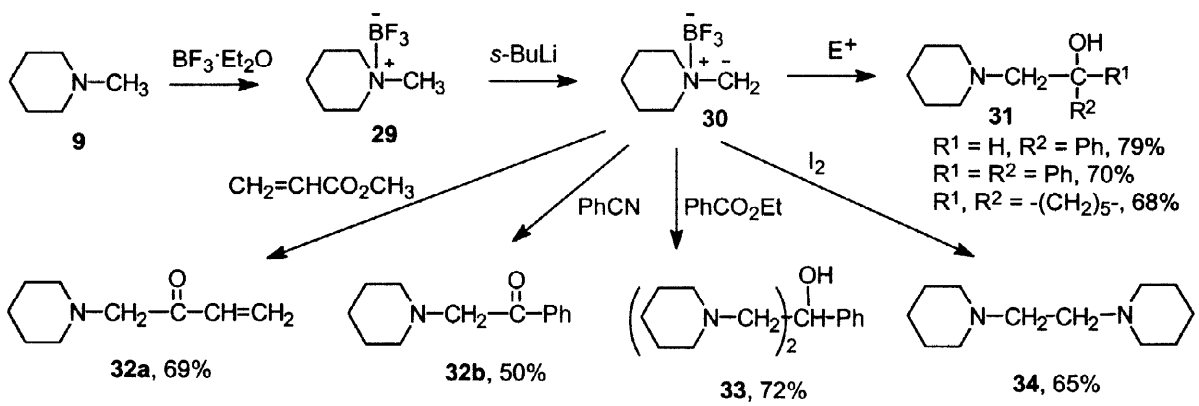
and amount of the lithium reagent used. Generally, terminal *N*-methyl is preferentially lithiated by *n*-, *s*-, and *t*-butyllithiums when only one equivalent of reagent was used (*cf.* **21** → **22** → **24**). The lithiation of other tri- **26** and tetra-amines **27**, **28** were also reported.[27]

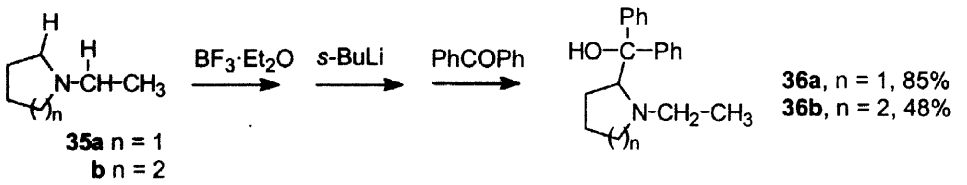




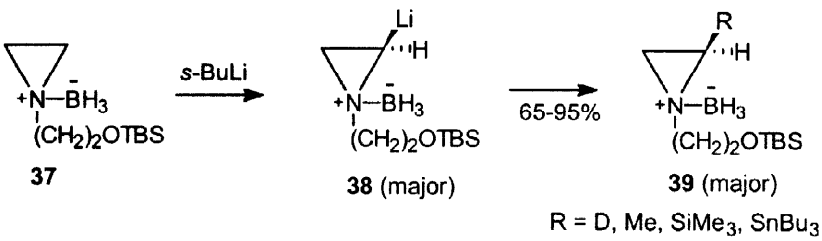
2b. Lithiation by Proton Abstraction of Amine-Lewis Acid Complexes

Due to the difficulties and limitations of their preparation by direct lithiation for simple amines, alternative methods to synthesis non-stabilized α-aminocarbanions have been developed over the past three decades. One protocol, first reported by Kessar *et al.*,[28] involves deprotonation of a preformed amine-Lewis acid complex.[11,29] Thus, *N*-methylpiperidine was treated with boron trifluoride etherate to form amine-Lewis acid complex **29**, which can be deprotonated readily at low temperature. The resulting carbanion **30** reacted with various electrophiles to produce β-hydroxyamines **31**, β-amino ketones **32**, β-hydroxydiamines **33**, and diamines **34** in good yields.[28] When no *N*-methyl group is present, ring deprotonation was observed in the cases of *N*-ethylpyrrolidine (**35a**) and *N*-ethylpiperidine (**35b**), quinuclidine and DABCO,[29] as shown by the formation of **36a,b**.



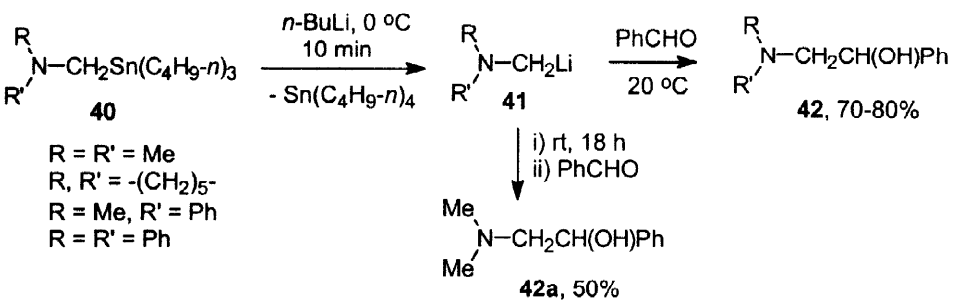


Later, Simpkins and coworkers found that borane (BH_3) could be used instead of BF_3 to form benzyl amine-Lewis acid complexes.[30] This methodology was applied to simple aziridines later.[31] In this case, the electrophile-incorporated amine-borane intermediate **39** can be isolated and the aziridine boranes can be cleaved by boiling ethanol.



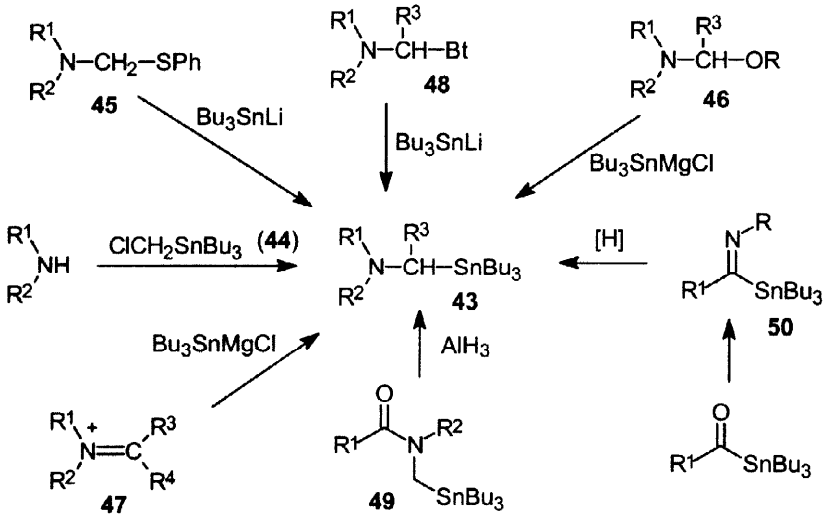
2c. Lithiation by Lithium-Metal Exchange

In the 1970's, Peterson developed a mild and high yielding transmetalation method to prepare non-stabilized α-aminocarbanions.[32,33] (*N,N*-Disubstituted-aminomethyl)tributyltins **40** were cleanly transformed in hexane or hexane-THF at 0 °C into the corresponding aminocarbanions **41**, which could be trapped with benzaldehyde in 70-80% yields.[33] The authors found that (*N,N*-dimethylamino)methyllithium is substantially more stable than (*N*-methyl-*N*-phenylamino)methyllithium.



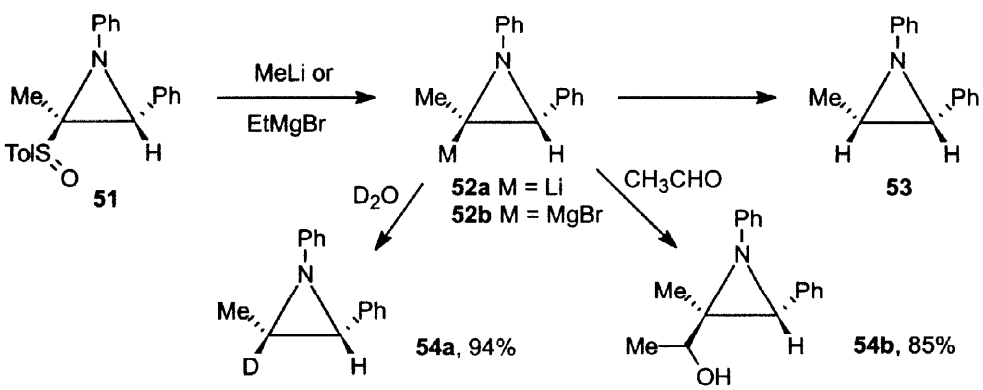
This transmetallation protocol has become the method of choice for many synthetic applications, due to its facile and site-specific generation of the required non-stabilized α-aminocarbanions. Many routes have been reported for the synthesis of α-aminomethyltin reagents **43**, such as (i) the reaction between amines with halomethylorganostannanes (**44**);[34,35] (ii) reactions of Bu_3SnM (M = Li, MgCl) with R_2NCH_2SR' (**45**),[33,36] R_2NCH_2OR' (**46**),[37] iminium salts **47**[38] or R_2NCH_2Bt (**48**) (Bt = benzotriazol-1-yl and/or benzotriazol-2-yl);[39,40] and (iii) reductions of the corresponding tin-substituted amides **49**[41] or imines **50**.[42] However, this method

method from the tin reagent has its own disadvantages: difficulties in starting material synthesis, byproduct Bu_4Sn separation, the toxicity of tin. Furthermore, it is not applicable in the generation of unchelated, acyclic secondary non-stabilized α-aminocarbanions[6,43] or tertiary carbanions.



2d. Metal-Sulfoxide Exchange

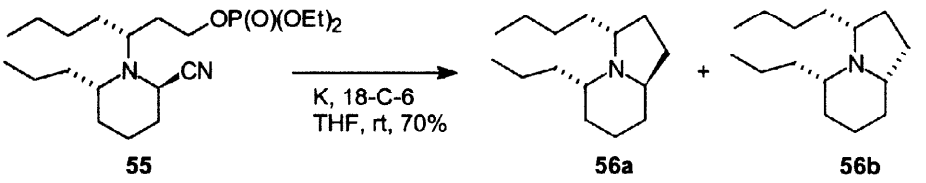
Yamakawa and co-workers reported[44] the preparation of metalated aziridines **52a,b** by a metal exchange reaction involving the displacement of the sulfinyl group from sulfinylaziridines **51**. They found the lithiated aziridine **52a** cannot survive the reaction conditions and forms protonated aziridine **53** immediately, but the aziridine Grignard reagent **52b** was relatively stable and can be trapped by D_2O and acetaldehyde to give **54**.



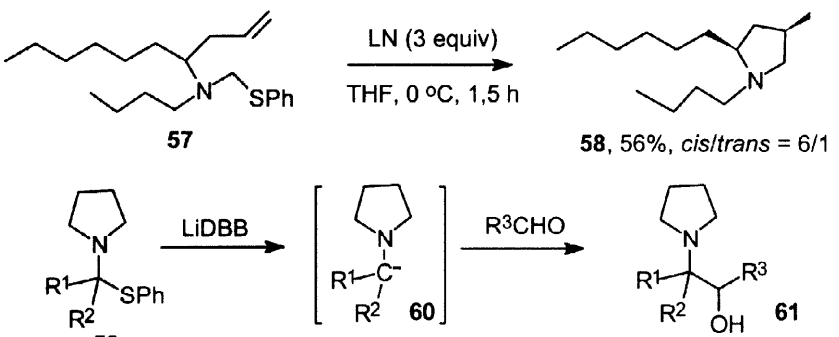
2e. Reductive Cleavage

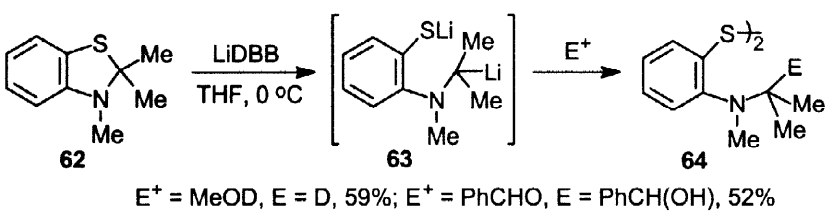
Reductive decyanation of α-aminonitriles has been known for long time and α-aminocarbanions are considered to be the transient intermediates;[45,46] however, the reactive intermediate had only been captured

with water, until 1988 when Zeller and Grierson reported their ring closure reaction of α-aminonitriles (*e.g.* **55**).[45,47]

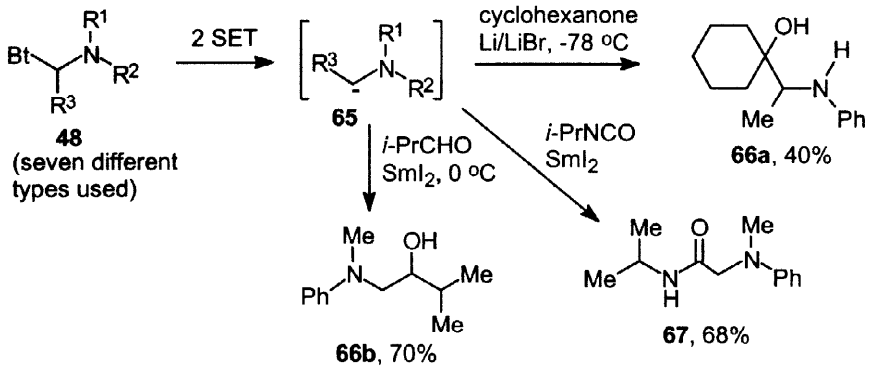


α-Aminosulfides (*e.g.* **57**, **59**, **62**) were demonstrated to be the useful precursors for the generation of α-amino-primary,[48] -secondary[6] and -tertiary[6,49] carbanions by selective C-S bond scission. Lithium naphthalenide (LN) or lithium 4,4'-di-*t*-butylbiphenylide (LDBB) were used as the reducing reagents, and the reactive α-aminocarbanions (*e.g.* **60**, **63**) were trapped *in situ* by alkenes in intramolecular cyclizations to give **58**[48] and intermolecularly by the usual electrophiles, such as aldehydes, ketones, MeOD and Bu_3SnCl to give **61** and **64**.[6,49]

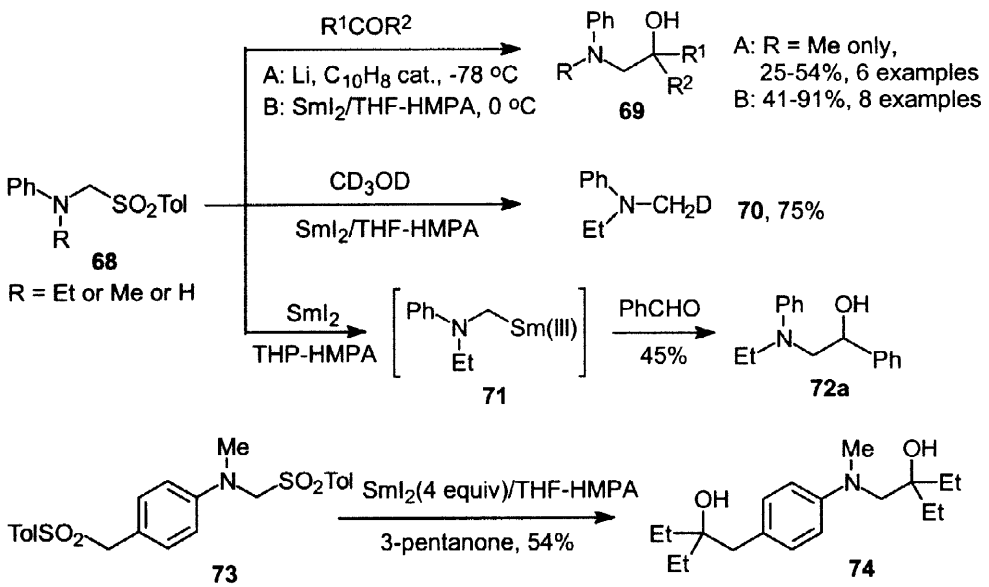




Recently, our group has developed a new protocol to form non-stabilized α-aminocarbanions,[50] based on selective C-N bond scission[51] of N-C-Bt reagents. Either lithium metal or samarium diiodide can be used for the reduction, and these reagents complement each other to provide a general route to various types of α-aminocarbanions **65**, which reacted *in situ* with ketones or aldehydes and with isocyanates to afford β-hydroxyamines (*e.g.* **66**) and amino acid derivatives (*e.g.* **67**), respectively.



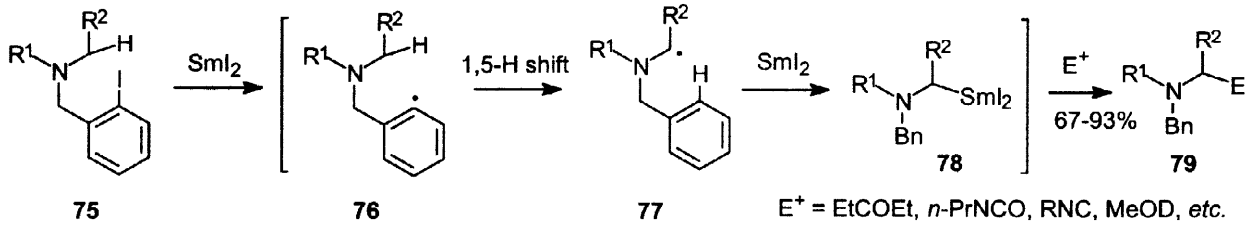
α-Tosylmethylamines **68** were recently shown to be good precursors for some non-stabilized α-aminocarbanions.[52,53] Yus and co-workers[52] employed a large excess of lithium as the reductant with naphthalene as catalyst (**68** → **69**, Method A). We found that samarium diiodide can work under milder conditions: reactions between ketones and α-tosylmethylamines **68** then generally gave excellent yields (80-98%) of β-hydroxyamines **69**.[53] A successful two-step procedure suggested that the reaction involved an α-amino organosamarium intermediate **71**. Moreover, dicarbanion equivalents can be formally generated using our method (*cf.* **73** → **74**).[53]



2f. Other Methods

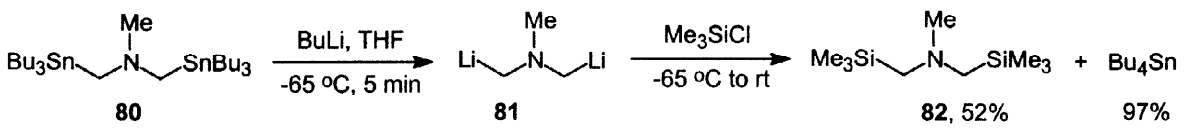
Ito *et al.* published an interesting approach for the generation of non-stabilized α-amino organosamarium reagents **78** by treatment of a tertiary amine **75**, bearing a pendant *o*-iodobenzyl group at the nitrogen atom, with SmI_2.[54,55] The reaction proceeds by the formation of a radical center followed by a second electron transfer from SmI_2/tetrahydopyran (THP)-HMPA to the intermediate radical **77** forming the key intermediate α-amino organosamarium **78**, which can be reacted with various electrophiles to furnish new carbon-carbon

bonds.[54] Acyclic and a variety of cyclic amines could be used in this process, according to their report;[54,55] however, Booth *et al.* found that only 3-pentanone can be used as the electrophile and indicated that seven- and eight-membered ring cyclic amines substrates gave low yields of products.[56]

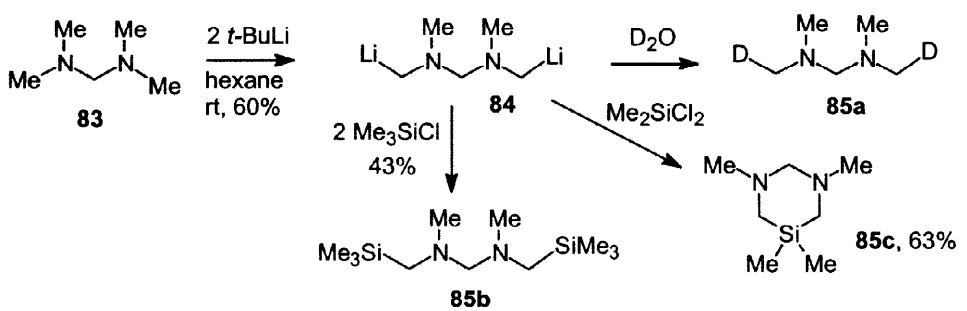


2g. Methods for the Formation of Dianion Equivalents

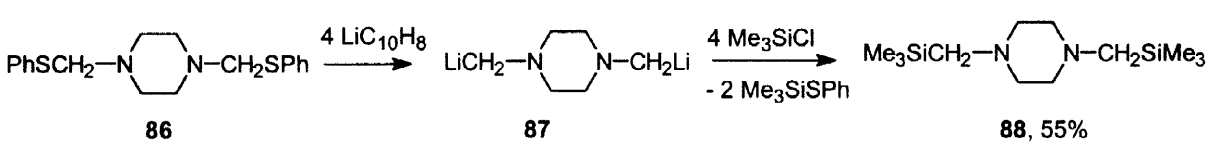
The first α,α′-dilithiated amine **81** was reported by Peterson and Ward.[36] The tin compound **80** was transmetalated and the resulting dianion reacted easily with chloromethylsilane to produce bis(*N*-trimethylsilylmethyl)methylamine (**82**).



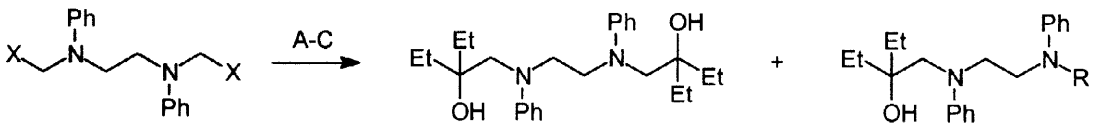
Karsch reported a doubly lithiated diamine and identified the structure as **84** by elemental analysis and further reactions.[57] Compound **84** is a white and highly pyrophoric solid, it reacted with D_2O and with chlorosilanes to produce di-deuterated or -silylated products **85**, respectively.[57]



Strohmann and Abele also described an example of a dilithiated nonstabilized (lithiomethyl)amine **87** from reductive cleavage of bis(α-thioamine) **86**.[58]



Our attempts[59] to transform **89a** into a formal dicarbanion using SmI_2 gave a mixture of the expected product **90**, from dicarbanion intermediate, and **91a**. Byproduct **91a** obviously came from one C-N(Ph) bond cleavage of the starting **89a** due to the presence of two C-N bonds.[50] When bis(α-sulphonyamine) **89b** was used instead of **89a**, its reaction with 3-pentanone in the presence of SmI_2/THF-HMPA yielded 24% bis(α-amino alcohol) **90** and 23% diamino alcohol **91b**. Byproduct **91b** was eliminated and **90a** obtained in 31% yield by employing SmI_2/THP-HMPA, because of the avoidance of the proton abstraction of the intermediate radical from THF.[50]



89a X = Bt
89b X = SO_2Tol

90

91a R = H
91b R = Me

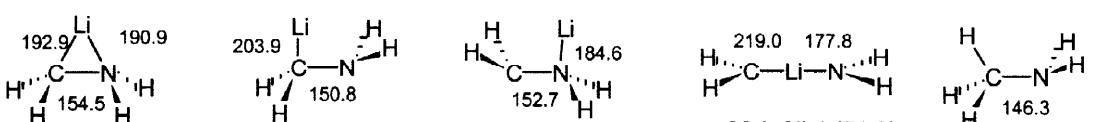
A: **89a**, 3-pentanone, SmI_2/THF-HMPA, 0 °C
B: **89b**, 3-pentanone, SmI_2/THF-HMPA, 0 °C
C: **89b**, 3-pentanone, SmI_2/THP-HMPA, -20 °C

3. Physical Properties - Structure and Stability

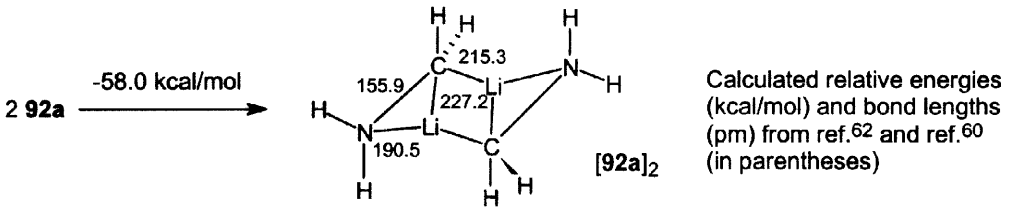
The structure and stability of non-stabilized α-aminocarbanions have been studied by a number of different approaches, such as theoretical calculations, NMR, X-ray crystallography, and chemical transformations.

3a. Calculations

Computational calculations have employed the simplest α-aminocarbanion $LiCH_2NH_2$ for the structure study and stability comparison with the parent molecule CH_3NH_2.[60-62] First Schleyer and coworkers used the relatively small basis set MP2/6-31G(*d*)//3-21G.[60,63] Boche *et al.* later recalculated with the bigger basis sets MP2/6-311 + + G(*d,p*)//MP2/6-311 + + G(*d,p*) + ZPE.[62] These calculations all reached very similar results, predicting that isomer **92a** in which lithium bridges the anionic carbon and the nitrogen atoms is 13.7 kcal/mol more stable than the next most stable isomer **92b**, in which the Li-N bond is broken. The results show that the bond lengths of C-N in $LiCH_2NH_2$ of all isomers **92a-d** are longer than the corresponding C-N in CH_3NH_2. The calculation also revealed that the dimerization of **92a** is favored by 58.0 kcal/mol, and that such dimerization occurs along the C-Li bonds.



92a, 0.0 **92b**, 13.7 (14.3) **92c**, 15.0 (18.1) **92d**, 65.4 (71.3)



Pross *et al.*[61] emphasized that $LiCH_2NH_2$ shows a small stabilization (3.3-5.6 kcal/mol, depending on the basis set used) compared to CH_3NH_2, due to the σ-accepting nature of NH_2 group. They also predicted the difficulty to generate such aminocarbanions.

3b. NMR Spectra

Klumpp *et al.* found that *N*-lithiomethyl-*N*,*N*',*N*'',*N*''-tetramethyldiethylenetriamine (**22**) is a rare monomeric alkyllithium in hydrocarbon solvents,[64] presumably due to steric hindrance of aggregation and to intramolecular Li-N coordination. At low temperature (*ca.* -78 °C), the monomer has two different forms, as its ^6Li, ^1H and ^{13}C NMR show two sets of peaks for CH_2Li: δ_{Li} 1.75 and 1.35 ppm; δ_H 1.63, 1.19, 0.67, and 0.30 (all d, $^2J_{HH}$ = 10.4 Hz); and δ_C 51.0 and 52.9 (both t, $^1J_{C\text{-}Li}$ = 13.9 Hz). At higher temperature (≥ -8 °C), these two sets of peaks coalesce and the ^{13}C-^6Li couplings vanish at 2 °C.[64]

^1H and ^{13}C NMR were also used to study the structure of non-stabilized α-aminocarbanions from simple amines.[65] The chemical shifts (δ_H and δ_C) of the carbanion carbon and its proton are listed in the Table. Interestingly, these carbanions ^1H chemical shifts are located upfield and the ^{13}C chemical shifts downfield from the corresponding amines.

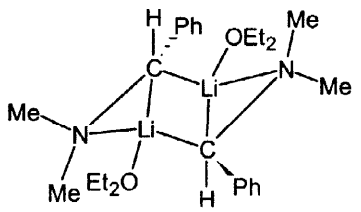
Table. The chemical shifts of the carbanion carbon and its proton of a few non-stabilized α-aminocarbanions

Compound	δ_H [a]	δ_C [a]
Me_2NCH_2Li	0.94	57.0
$(CH_2)_5NCH_2Li$	0.98	55.9
$Ph_2NCH_2Li{\cdot}THF$	2.59	46.1
$\{[Li(OEt_2)]_2Ni(CH_2NMe_2)_4\}$	1.32	61.4
$\{[Li(OEt_2)]_2Ni[CH_2N(CH_2)_5]_4\}$	1.39	59.0

[a] All NMR measured in THF-d_8 solvent and from ref.[65]; Chemical shifts in ppm.

3c. X-ray Crystallography

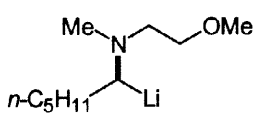
A few X-ray structures have been reported for non-stabilized α-aminocarbanions.[62,65] A simplified X-ray structures is presented below for $Me_2NCH(Li)Ph{\cdot}Et_2O$.[62,66] The calculated structure corresponds exactly to a dimer along the C-Li bonds.[62]



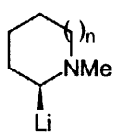
A simplified X-ray structure of $Me_2NCH(Li)Ph{\cdot}Et_2O$ (a dimer)

3d. Configurational Stability

The configurational stability of non-stabilized α-aminocarbanions has been investigated.[43,67] Chong and co-workers[43] found that acyclic α-aminocarbanions (*e.g.* from **93**) with a chelating methoxyethyl group are chemically and configurationally stable for a short time at low temperatures (-90 °C). Gawley and Zhang[67-69] demonstrated that unchelated cyclic α-aminocarbanions **94** as 2-lithio-*N*-methylpiperidines and pyrrolidines are configurationally stable for 45 min at -40 °C in the presence of TMEDA. They attribute this exceptional stability to the lithium-carbon-nitrogen bridge, amine ring, and non-chelating group.[67]



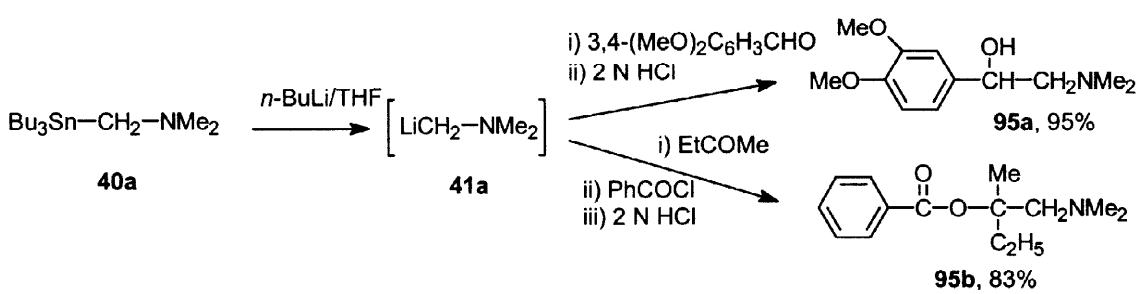
93



94, n = 0, 1

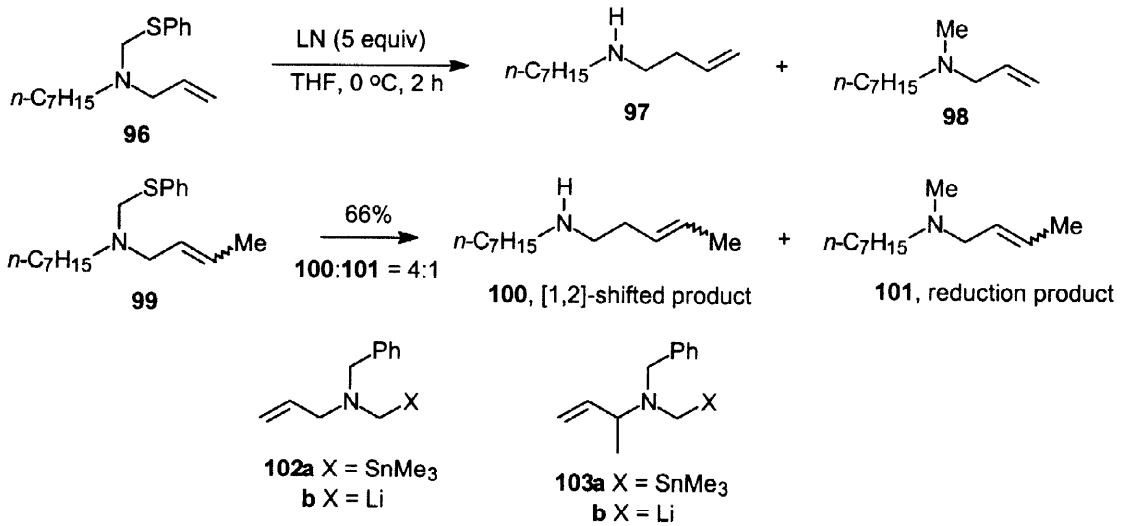
4. Synthetic Applications

Non-stabilized α-aminocarbanions have obvious application in the synthesis of β-hydroxyamines (*e.g.* **8**, **12**, **31**, **42**) and β-amino acids and their derivatives (*e.g.* **67**),[50,53,54] as already demonstrated in Section 2. The synthesis of a few specially interesting β-hydroxy amines, such as the alkaloids macromerine **95a** and stovaine **95b** are shown.[37] Alkaloids **95a,b** were prepared from α-aminocarbanions generated by transmetalation.

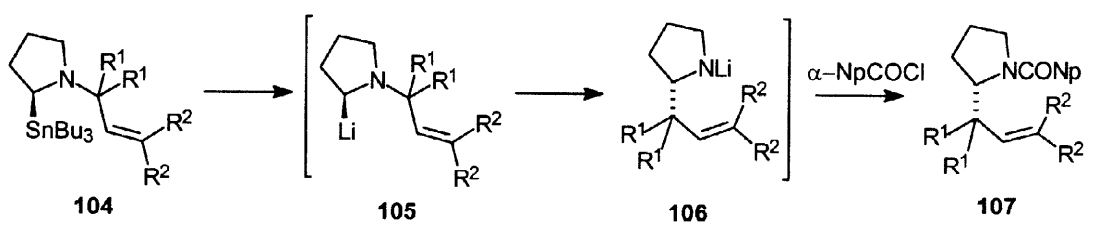


Reactions of α-aminocarbanions with equivalent amounts of methyl acrylate and benzonitrile gave the corresponding β-amino ketones **32**.[28] Both esters[28] and acyl chloride[38] can react with α-aminocarbanions to form α,α'-diamino alcohols **33**.

The aza-Wittig rearrangement of non-stabilized α-aminocarbanions has been studied by a few groups,[48,70-72] though its mechanism was unclear until Gawley's report appeared.[72] Broka and Shen explained their results on the basis of a postulated [2,3]-rearrangement (**96** → **97**),[48] but Murata and Nakai concluded that is a [1,2]-shift reaction, according to that only [1,2]-shifted product **100** and reduction product **101** were obtained from aminosulfide **99**.[70] Coldham observed both the [1,2]-rearrangement from **102b** and [2,3]-rearrangement from **103b**;[71] however, definition of the rearrangement mechanism awaits further evidence.



More recently Gawley *et al.* clarified the rearrangement of *N*-allyl-2-lithiopyrrolidine **105**.[72] By using regioselectively deuterated substrates **104a,b**, they found the rearrangement involves both [1,2]- and [2,3]-mechanisms [**104a/104b** (7:1) → **107a/107b** (4.3:1)], but only the [1,2]-rearrangment was observed for **104c**, due to steric factors. These results suggest that [2,3]-rearrangement cannot be ruled out in Broka and Shen's reaction,[48] and that steric influences are important in the aza-Wittig rearrangement of non-stabilized α-aminocarbanions.

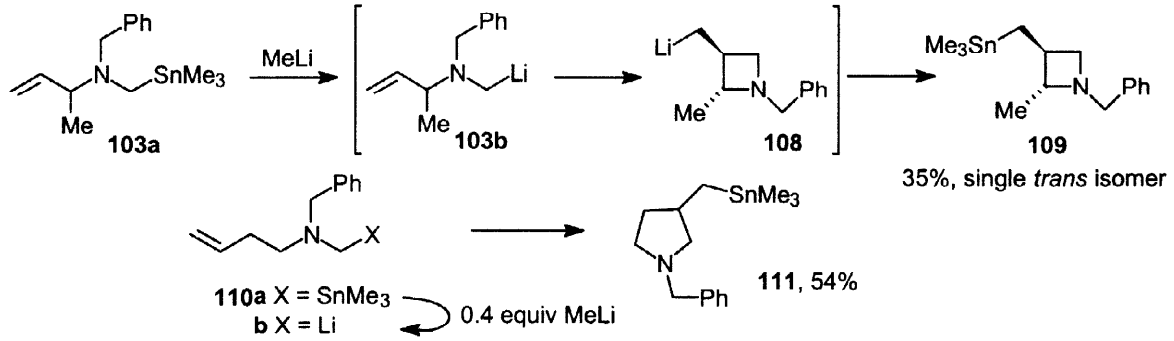


104 105 106 107

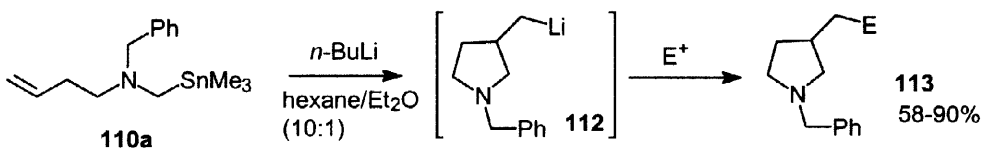
104, 105a R^1 = D, R^2 = H
b R^1 = H, R^2 = D
c R^1 = H, R^2 = Me

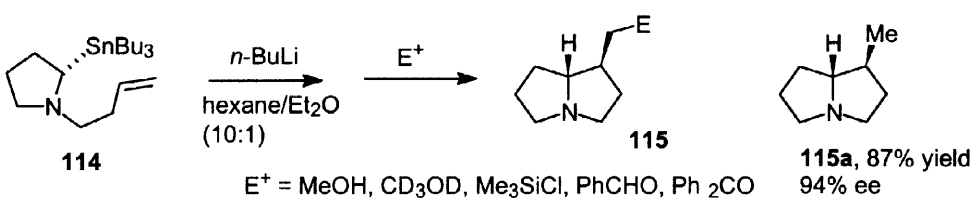
106, 107a R^3 = D, R^4 = H
b R^3 = H, R^4 = D
c R^3 = H, R^4 = Me

By contrast to intermolecular cyclization, intramolecular cyclization reactions of non-stabilized α-aminocarbanions are of both synthetic interest and useful.[73,74] Non-stabilized α-aminocarbanion **103b** and **110b**, generated from transmetalation, cyclize to form the azetidine **109** and pyrrolidine **111**, respectively.[71] The trimethylstannyl group was reincorporated into the cyclized products. Noteably high stereoselectivity was observed, as only the *trans*-azetidine **109** was isolated. Further studies showed that the cyclization reactions depend on the reaction solvent and temperature.[73]

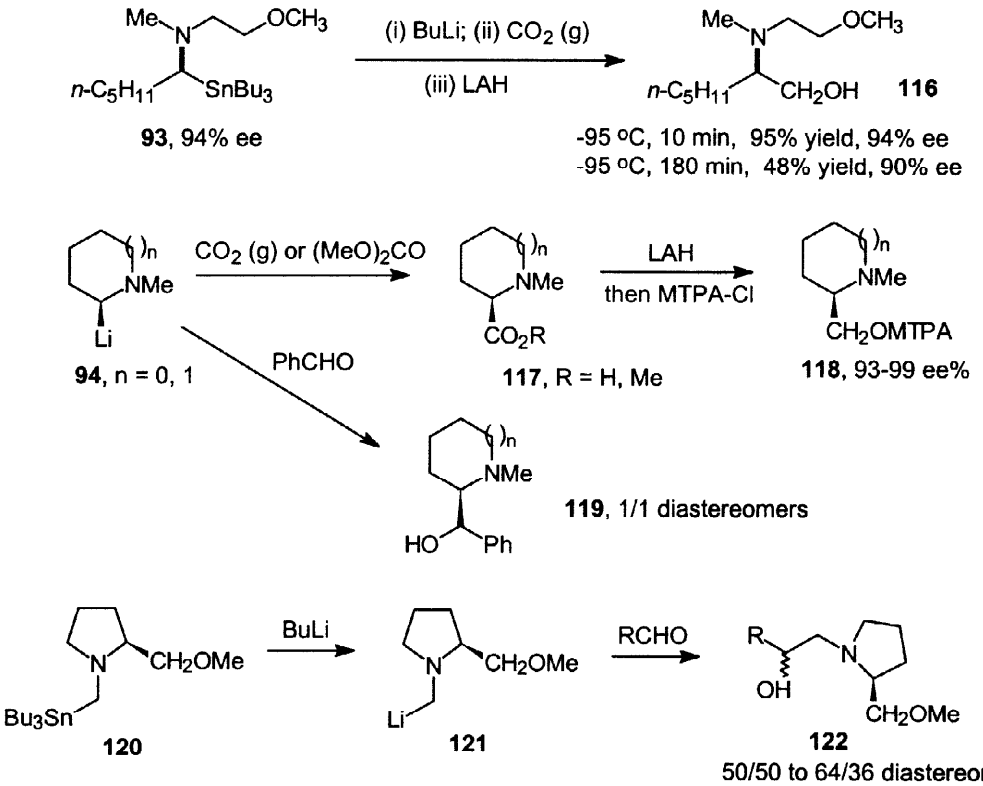


A second electrophile can be introduced in a one-pot two-step procedure (**110a** → **112** → **113**).[54] The anionic cyclization process was proven to be stereospecific: a single diastereomer of pyrrolidine alkaloid (+)-pseudoheliotriadane **115a** was obtained with full stereochemical control.[54] Other derivatives of pseudoheliotridane were similarly prepared in high optical purity (**114** → **115**).

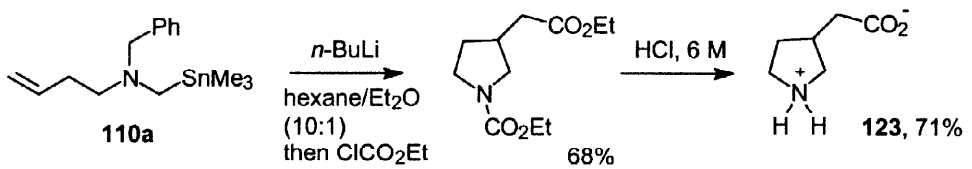




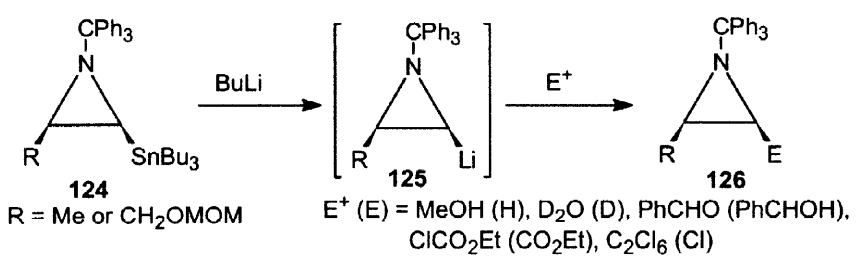
As already discussed in Section 3d, many unstabilized α-aminocarbanions are configurationally stable, and their reactions with some electrophiles give products with retention of steoreochemistry at the anionic carbon (*eg.* **93** → **116**;[43] **94** → **118** [67]). However, all attempts to use these chiral lithium compounds to induce diastereoselectivity proved to be unsuccessful (**94** → **119**,[69] **121** → **122** [75]).

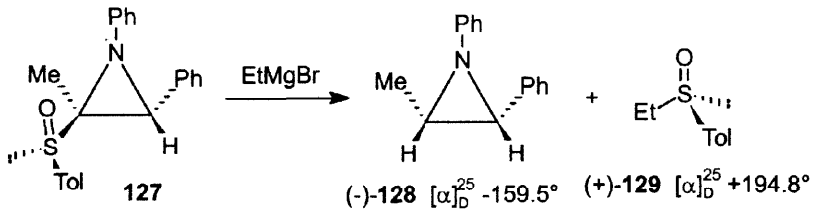


A known GABA uptake inhibitor **123** was easily prepared in four steps from commercially available 4-bromobut-1-ene.[76]

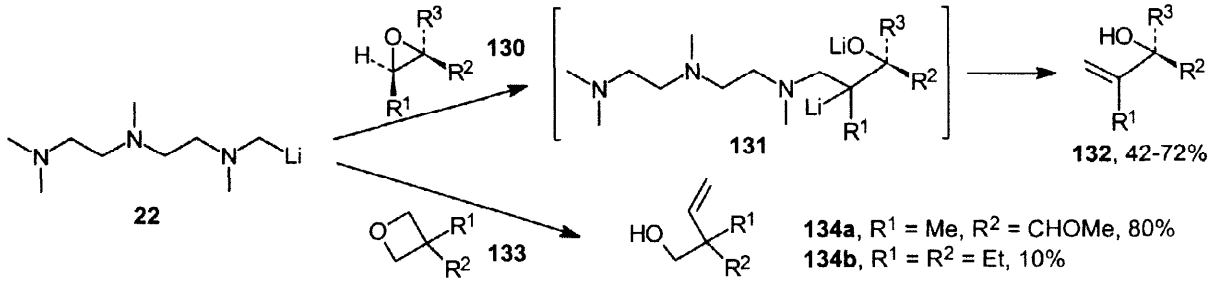


The synthesis of substituted aziridines (*e.g.* **54, 126, 128**) were reported from unstabilized aziridinylmetals (**52, 125**).[44,77] The intermediates **125** and **52** were prepared from Li-Sn exchange[77] and alkylmetals desulfinylation,[44] respectively. By using optically active sulfoxides **127**, optically active aziridines **128** were synthesized.

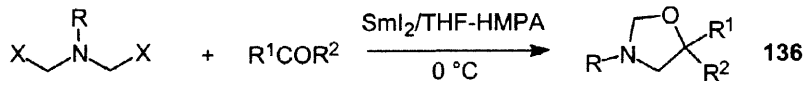




The use of α-aminocarbanion from polyamines in the synthesis of allylic **132** and homoallylic alcohols **134**, from epoxides **130** and oxetanes **133**, has been reported.[78]



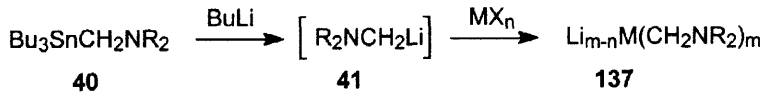
We found[57] that substituted oxazolidines (**136**) can be prepared from the reactions of *N,N*-bis(benzotriazolylmethyl)amines **135a,b** or *N,N*-bis(tosylmethyl)benzylamine **135c** with carbonyl compounds, in the presence of SmI_2/THF-HMPA. Apparently, compounds **136a-c** were formed from the reaction of an unstabilized α-aminocarbanion intermediate with ketones followed by intramolecular cyclization.



135a R = $PhCH_2$, X = Bt
135b R = Ph, X = Bt
135c R = $PhCH_2$, X = SO_2Tol

135a to **136a** R = $PhCH_2$, $R^1 = R^2$ = Et, 47% GC/MS
135b to **136b** R = Ph, $R^1 = R^2$ = Et, 30% GC/MS
135c to **136a** R = $PhCH_2$, $R^1 = R^2$ = Et, 90% isolated
135c to **136c** R = $PhCH_2$, R^1, R^2 = $-(CH_2)_5-$, 43% isolated

Many other unstabilized α-aminometals **137** have been synthesized by transmetallation between lithium and trasitional metal halides.[65,79,80]



137a $Li_2\{Co[CH_2N(CH_2)_5]_4\}\cdot 2THF$
b $Li_2\{Cr[CH_2N(CH_2)_5]_4\}\cdot 2THF$
c $Li_2\{Cr_2[CH_2N(CH_2)_5]_6\}$
d $Li_2\{Fe[CH_2N(CH_2)_5]_4\}\cdot 2THF$
e $Li_2\{Fe[CH_2N(CH_2)_5]_4\}\cdot 2$ dioxane
f $Li_2\{Mn[CH_2N(CH_2)_5]_4\}\cdot 2$ dioxane
g $Li_2\{Ni[CH_2N(CH_2)_5]_4\}\cdot 2$ ether
h $V[CH_2N(CH_2)_5]_4$

5. Summary

α-Aminocarbanions are important synthetic intermediates in modern organic synthesis. Due to the difficult generation of the non-stabilized α-aminocarbanions, stabilized α-aminocarbanions have been employed in the most synthetic applications. However, in many cases, two steps (protection and deprotection) could be saved by using non-stabilized α-aminocarbanions for the same process. This report discussed important recent progress in the generation of the non-stabilized α-aminocarbanions, and will hopefully stimulate the further use of non-stabilized α-aminocarbanions in synthesis. The physical properties and reactivities of non-stabilized α-aminocarbanions were also presented.

References

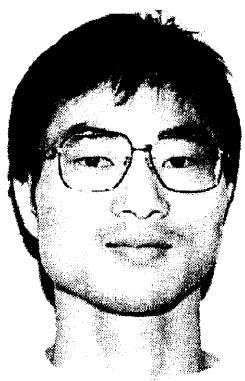
1. Kleinman, E. F. in *Comprehensive Organic Synthesis: Selectivity, Strategy and Efficiency in Modern Organic Chemistry*; Trost, B. M.; Fleming, I. Eds.; Pergamon Press: Oxford, 1991; Vol 2, pp. 893-915.
2. Renaud, P.; Giraud, L. *Synthesis* **1996**, 913-926.
3. Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552-560.
4. Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471-523.
5. Gawley, R. E.; Rein, K. in *Comprehensive Organic Synthesis: Selectivity, Strategy and Efficiency in Modern Organic Chemistry*; Trost, B. M.; Fleming, I. Eds.; Pergamon: Oxford, 1991; Vol 3, pp. 65-83.
6. Tsunoda, T.; Fujiwara, K.; Yamamoto, Y.-i.; Itô, S. *Tetrahedron Lett.* **1991**, *32*, 1975-1978.
7. Gray, M.; Tinkl, M. and Snieckus, V. in *Comprehensive Organometallic Chemistry II*; Abel, E. W.; Stone, F. G. A. and Wilkinson, G. Eds.; Pergamon: Oxford, 1995; Vol 11, pp. 15-21.
8. Edwards, G. L. in *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R.; Meth-Cohn, O.; Rees, C. W. Eds.; Pergamon: New York, 1995; Vol 1, pp. 147-156.
9. Steele, J.; Gough, M. J. in *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R.; Meth-Cohn, O.; Rees, C. W. Eds.; Pergamon: New York, 1995; Vol 4, pp. 526-534.
10. Lindell, S. D. in *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R.; Meth-Cohn, O.; Rees, C. W. Eds.; Pergamon: New York, 1995; Vol 2, pp. 1001-1003.
11. Kessar, S. V.; Singh, P. *Chem. Rev.* **1997**, *97*, 721-737.
12. Klebe, G.; Böhn, K. H.; Marsch, M.; Boche, G. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 78-79.
13. Schöllkopf, U. *Pure Appl. Chem.* **1979**, *51*, 1347-1355.
14. Brandsma, L.; Nedolya, N. A.; Verkruijsse, H. D.; Trofimov, B. A. *Synthesis* **1997**, 423-424.
15. Peterson, D. J.; Hays, H. R. *J. Org. Chem.* **1965**, *30*, 1939-1942.
16. Lepley, A. R.; Giumanini, A. G. *Chem. Ind. (London)* **1965**, 1035-1036.
17. Lepley, A. R.; Giumanini, A. G. . *J. Org. Chem.* **1966**, *31*, 2055-2060.

18. Lepley, A. R.; Khan, W. A. *J. Org. Chem.* **1966**, *31*, 2061-2064.
19. Lepley, A. R.; Khan, W. A. *J. Chem. Soc., Chem. Commun.* **1967**, 1198-1199.
20. Smith, W. N. *Adv. Chem. Ser.* **1974**, *130*, 23-55.
21. Ahlbrecht, H.; Dollinger, H. *Tetrahedron Lett.* **1984**, *25*, 1353-1356.
22. Langer, A. W. Jr. *Trans. N. Y. Acad. Sci.* **1965**, *27*, 741-747.
23. Peterson, D. J. *J. Organomet. Chem.* **1967**, 9, 373-374.
24. Köhler, F. H.; Hertkorn, N.; Blümel, J. *Chem. Ber.* **1987**, *120*, 2081-2082.
25. Harder, S.; Lutz, M. *Organomettallics* **1994**, *13*, 5173-5176.
26. Schakel, M.; Aarnts, M. P.; Klumpp, G. W. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 305-306.
27. Luitjes, H.; Schakel, M.; Aarnts, M. P.; Schmitz, R. F.; de Kanter, F. J. J.; Klumpp, G. W. *Tetrahedron* **1997**, *53*, 9977-9988.
28. Kessar, S. V.; Singh, P.; Vohra, R.; Kaur, N. P.; Singh, K. N. *J. Chem. Soc., Chem. Commun.* **1991**, 568-570.
29. Kessar, S. V. *Pure Appl. Chem.* **1996**, *68*, 509-514.
30. Ebden, M. R.; Simpkins, N. S.; Fox, D. N. A. *Tetrahedron Lett.* **1995**, *36*, 8697-8700.
31. Vedejs, E.; Kendall, J. T. *J. Am. Chem. Soc.* **1997**, *119*, 6941-6942.
32. Peterson, D. J. *J. Organomet. Chem.* **1970**, *21*, P63-P64.
33. Peterson, D. J. *J. Am. Chem. Soc.* **1971**, *93*, 4027-4031.
34. Kostyanovskii, R. G.; Prokof'ev, A. K. *Izv. Akad. Nauk. SSSR* **1965**, 175-178.
35. Abel, E. W.; Rowley, R. J. *J. Organomet. Chem.* **1975**, *97*, 159-165.
36. Peterson, D. J.; Ward, J. F. *J. Organomet. Chem.* **1974**, *66*, 209-217.
37. Quintard, J.-P.; Elissondo, B.; Jousseaume, B. *Synthesis* **1984**, 495-498.
38. Elissondo, B.; Verlhac, J.-B.; Quintard, J.-P.; Pereyre, M. *J. Organomet. Chem.* **1988**, *339*, 267-275.
39. Pearson, W. H.; Stevens, E. P. *Synthesis* **1994**, 904-906.
40. Katritzky, A. R.; Chang, H.-X.; Wu, J. *Synthesis* **1994**, 907-908.
41. Burchat, A. F.; Chong, J. M.; Nielsen, N. *J. Org. Chem.* **1996**, *61*, 7627-7630.
42. Ahlbrecht, H.; Baumann, V. *Synthesis* **1994**, 770-772.
43. Burchat, A. F.; Chong, J. M.; Park, S. B. *Tetrahedron Lett.* **1993**, *34*, 51-54.
44. Satoh, T.; Sato, T.; Oohara, T.; Yamakawa, K. *J. Org. Chem.* **1989**, *54*, 3973-3978.
45. Zeller, E.; Sajus, H.; Grierson, D. S. *Synlett* **1991**, 44-46.
46. Bonin, M.; Romero, J. R.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1982**, *23*, 3369-3372.
47. Zeller, E.; Grierson, D. S. *Heterocycles* **1988**, *27*, 1575-1578.
48. Broka, C. A.; Shen, T. *J. Am. Chem. Soc.* **1989**, *111*, 2981-2984.
49. Florio, S.; Capriati, V.; Gallo, A.; Cohen, T. *Tetrahedron Lett.* **1995**, *36*, 4463-4466.
50. Katritzky, A. R.; Qi, M.; Feng, D.; Nichols, D. A. *J. Org. Chem.* **1997**, *62*, 4121-4124.

51. Katritzky, A. R.; Qi, M. *J. Org. Chem.* **1997**, *62*, 4116-4120.
52. Alonso, D. A.; Alonso, E.; Nájera, C.; Ramón, D. J.; Yus, M. *Tetrahedron* **1997**, *53*, 4835-4856.
53. Katritzky, A. R.; Feng, D.; Qi, M. *J. Org. Chem.* **1997**, *62*, 6222-6225.
54. Murakami, M.; Hayashi, M.; Ito, Y. *J. Org. Chem.* **1992**, *57*, 793-794.
55. Murakami, M.; Hayashi, M.; Ito, Y. *Appl. Organomet. Chem.* **1995**, *9*, 385-397.
56. Booth, S. E.; Benneche, T.; Undheim, K. *Tetrahedron* **1995**, *51*, 3665-3674.
57. Karsch, H. H. *Chem. Ber.* **1996**, *129*, 483-484.
58. Strohmann, C.; Abele, B. C. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2378-2380.
59. Katritzky, A. R.; Feng, D.; Qi, M. unpublished results.
60. Clark, T.; Schleyer, P. v. R.; Houk, K. N.; Rondan, N. G. *J. Chem. Soc., Chem. Commun.* **1981**, 579-581.
61. Pross, A.; DeFrees, D. J.; Levi, B. A.; Pollack, S. K.; Radom, L.; Hehre, W. J. *J. Org. Chem.* **1981**, *46*, 1693-1699.
62. Boche, G.; Marsch, M.; Harbach, J.; H-arms, K.; Ledig, B.; Schubert, F.; Lohrenz, J. C. W.; Ahlbrecht, H. *Chem. Ber.* **1993**, *126*, 1887-1894.
63. Schleyer, P. v. R.; Clark, T.; Kos, A. J.; Spitznagel, G. W.; Rohde, C.; Arad, D.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1984**, *106*, 6467-6475.
64. Klumpp, G. W.; Luitjes, H.; Schakel, M.; Kanter, F. J. J.; Schmitz, R. F.; Hommes, N. J. R. van E. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 633-635.
65. Steinborn, D.; Becke, F.; Boese, R. *Inorg. Chem.* **1995**, *34*, 2625-2628.
66. This molecule actually should be viewed as a stabilized α-aminocarbanion. We put it here because it is very close to non-stabilized one and corresponds exactly with the calculated structure.
67. Gawley, R. E.; Zhang, Q. *J. Am. Chem. Soc.* **1993**, *115*, 7515-7516.
68. Gawley, R. E.; Zhang, Q. *Tetrahedron* **1994**, *50*, 6077-6088.
69. Gawley, R. E.; Zhang, Q. *J. Org. Chem.* **1995**, *60*, 5763-5769.
70. Murata, Y.; Nakai, T. *Chem. Lett.* **1990**, 2069-2072.
71. Coldham, I. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1275-1276.
72. Gawley, R. E.; Zhang, Q.; Campagna, S. *J. Am. Chem. Soc.* **1995**, *117*, 11817-11818.
73. Coldham, I.; Hufton, R. *Tetrahedron Lett.* **1995**, *36*, 2157-2160.
74. Coldham, I.; Hufton, R.; Snowden, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 5322-5323.
75. Coldham, I.; Holman, S.; Lang-Anderson, M. M. S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1481-1485.
76. Coldham, I.; Hufton, R. *Tetrahedron* **1996**, *52*, 12541-12552.
77. Vedejs, E.; Moss, W. O. *J. Am. Chem. Soc.* **1993**, *115*, 1607-1608.
78. Schakel, M.; Luitjes, H.; Dewever, F. L. M.; Scheele, J.; Klumpp, G. W. *J. Chem. Soc., Chem. Commun.* **1995**, 513-514.
79. Steinborn, D. *Z. Chem.* **1976**, *16*, 328.
80. Steinborn, D. *Z. Chem.* **1977**, *17*, 347-348.

Biographical sketch

Alan R. Katritzky



Ming Qi

Alan R. Katritzky taught, administered and researched successively at the Universities of Oxford, Cambridge, and East Anglia, in the UK before transferring to the University of Florida in 1980 when he is Kenan Professor and Director of the Florida Institute for Heterocyclic Compounds. His interests comprise heterocyclic chemistry, synthetic methodology and QSPR. During 1997, recognitions for his work included the Heyrowsky Medal of the Czech Academy of Sciences and an honorary D.Sc from St. Petersburg State University in Russia. Information about his present research group, group reports for 1995 and 1996, news of some 600 ex-group members now working and living all over the world, information about future opportunities for work in his group, and a publications list are all available on the World Wide Web at "http:\\ufark12.chem.ufl.edu".

Ming Qi, born in 1967, received his Ph.D. in 1994 at the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences. He then joined Kenan Professor Alan R. Katritzky at the University of Florida as a postdoctoral research associate, and later a group leader. His research interests include organic synthesis, particularly nonstabilized α-aminocarbanions, heterocycles and asymmetric synthesis, and combinatorial chemistry.