Lewis Acid Complexation of Tertiary Amines and Related Compounds: A Strategy for α-Deprotonation and Stereocontrol

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Received September 5, 1996 (Revised Manuscript Received December 30, 1996)

Contents

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Paramjit Singh was born in 1952 in Ropar district of Punjab, India. He received his Master's degree in chemistry in 1972 and Ph.D. degree in 1977 from Panjab University, Chandigarh, India, working on synthesis of isoquinoline and related alkaloids under the guidance of Professor Satinder V. Kessar. He joined the faculty of chemistry department of the same university as a teaching assistant in 1976 where he is at present a reader. He did a brief stint as a postdoctoral fellow with Professor J. F. Bunnett at University of California, Santa Cruz, during 1980–1981. His research interests include generation and reactions of intermediates like benzyne, α-oxoquinodimethane, and α-amino carbanion and photochemistry.

I. Introduction

In 1975, Seebach and Enders in their seminal article on umpolung of amine reactivity stated that no general procedure for reversible α-anionation of tertiary amines had yet become available.[1] This objective, as well as the development of a methodology for elaboration of tertiary amines through directly derived carbanions (**1** → **2** → **3**), remained unachieved for a decade and a half (Scheme 1). In contrast, during this period a large number of new procedures for generation of α-carbanions from primary and secondary amines were reported with considerable impact on the technology of amine synthesis.[2] In all these methods, α-deprotonation is facilitated by covalent attachment of an activator group to the nitrogen atom of the amine (**4** → **5** → **6**). The carbanion formed in this manner[3] is then reacted with an appropriate electrophile, and in the final step, the activating group is detached from the product. Functionalities which serve this purpose well, include nitrosoamines, amides, formamidines, oxazolidines, carbamates, and carbamate anions for secondary amines, and isonitriles, α-(nitrosoamino)-alkyl ethers and *tert*-butyldiphenylmethyl hydrazones for primary amines.[2] This approach has a limited scope in the case of tertiary amines because in the absence of a readily replaceable N−H bond, attachment−detachment of an activator is not easy.

S0009-2665(95)00082-3 CCC: $28.00

The *N*-oxide route explored by Barton's group is perhaps the solitary exception, and that too is limited to bridgehead nitrogen compounds (see section V).[4] In this context, the concept of tertiary amine activation by Lewis acid complexation was introduced through our laboratories in 1991.[5]

In essence, it was envisioned that deprotonation of a tertiary amine could be promoted by a Lewis acid as on forming a complex, a positive charge would develop on the nitrogen atom to inductively facilitate the removal of an α-proton. There was an obvious pitfall in this approach, i.e., the base used for deprotonation could attack the Lewis acid rather than the α-hydrogen. Nevertheless, if successful this methodology would be very advantageous because deprotonation, electrophilic reaction, and decomplexation could all be carried out in one pot. Moreover, it held promise of diastereo- and enantioselective transformations. The purpose of the present article is to review the progress of this idea and to assess its potential and limitations including applicability in heteroaromatic chemistry. In order to give a full perspective, other available methodologies for accessing tertiary amino carbanions are also discussed.

II. Acidity of C-α Hydrogens in Tertiary Amines

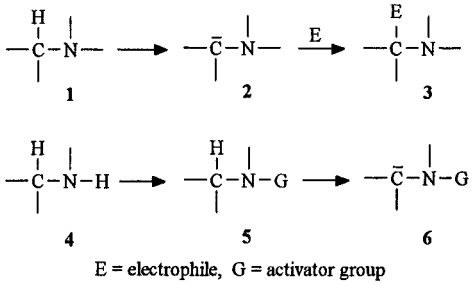
Many heteroatoms are known to increase the acidity of the hydrogens present on α-carbon atoms. Thus, compounds containing P, O, S, etc. can be regioselectively α-deprotonated by treatment with a strong base. The carbanions formed in this manner are stabilized by various factors, including the inductive effect of the heteroatom, its polarizability and its capacity to accept negative charge into low-lying empty orbitals.[2] The effect of a nitrogen atom on the acidity of α-hydrogens is somewhat ambiguous. Unlike S and P, it does not have high polarizability or low-energy empty orbitals, nor is its inductive effect as high as that of oxygen. On the other hand, the nitrogen lone pair generates a relatively strong repulsive interaction with the adjoining negative charge.[6a] However, this very lone pair can also provide stabilization to α-metalated amines by cation bridging—an effect which is expected to be more pronounced in case of lithium cations.[6b,c] Since quantitative data on the contribution of these factors and their net effect is not available, our main concern in this review will remain the experimental ease with which α-amino carbanions can be formed and reacted with electrophiles.

III. Direct Deprotonation of Tertiary Amines

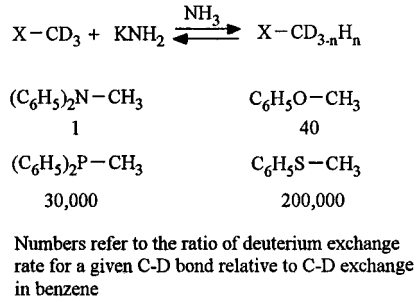
A measure of relative kinetic acidity of C-α hydrogens in compounds containing nitrogen, in comparison to other heteroatoms, is available from deuterium exchange studies.[7] From the values given in Scheme 2, it is evident that kinetic acidity of tertiary amines is several orders of magnitude lower than that of sulfides and phosphines, and even in ethers, deuterium exchange is about 40 times faster.

From a synthetic point of view, work on the problems associated with deprotonation of tertiary amines was initiated by Peterson.[8] He found that dodecyldimethylamine undergoes negligible metalation on prolonged treatment with t-BuLi (**7** → **8**), and the yields of substitution products, obtained on reaction with eletrophiles, are very poor. Around the same time, Lepley and Khan reported that treatment of a mixture of triethylamine and butyl iodide with n-BuLi affords the amine **9** in 25% yield (Scheme 3).[8c,d] It was shown that this reaction does not proceed through prior quaternization of the amine. But the authors also ruled out an amino carbanion pathway as their attempts to detect such an intermediate by addition of electrophiles, subsequent to exposure of the amine to the base, were unsuccessful. This inference is not necessarily valid, because it is possible that due to an unfavorable equilibrium the concentration of carbanions at any time is low but these get progressively formed as *in situ* trapping proceeds. Ahlbrecht and Dollinger also experienced considerable difficulty in deprotonation of *N*-methylpiperidine with a variety of strong bases.[9] Only the use of a combination of s-BuLi and KOt-Bu, the so called super base (SB),[10] in large excess of neat amine gave satisfactory results. It must be emphasized that attempts to carry out this reaction using 1 equiv of

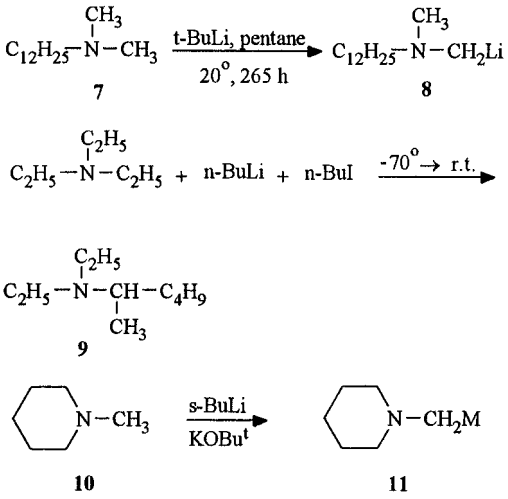
Scheme 1



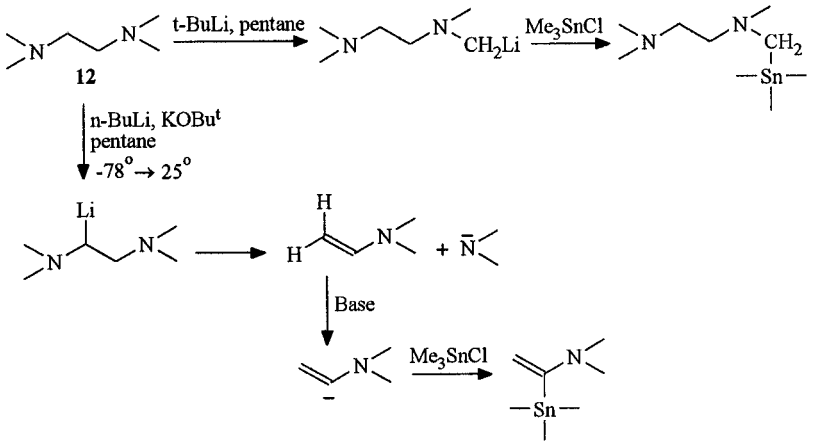
Scheme 2



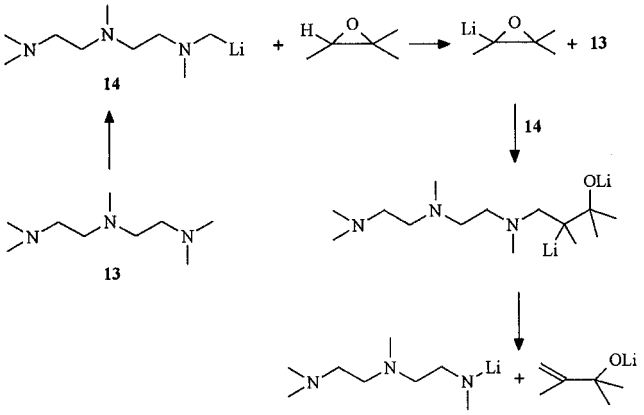
Scheme 3



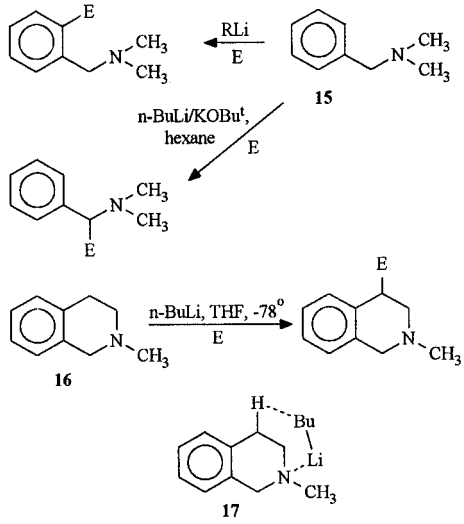
Scheme 4



Scheme 5



Scheme 6



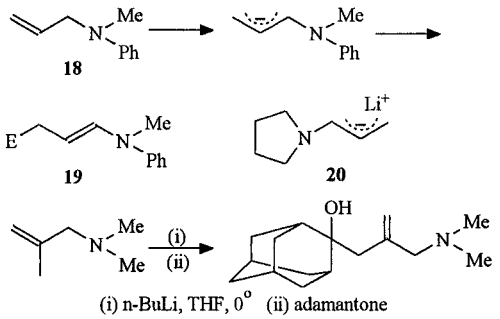
the amine in various solvents were unsuccessful which, for general synthetic purposes, is a serious disadvantage.

Kohler has reported interesting results on deprotonation of tetramethylethylenediamine (TMEDA),[11] a reagent which is often used to promote deprotonation of carbon acids with alkyllithiums.[12] While t-BuLi removes a methyl proton of TMEDA, use of n-BuLi/KOt-Bu combination leads to deprotonation of a methylene site. In the latter case, deprotonation was followed by rapid amide ion elimination to give an enamine which, in turn, underwent further deprotonation (Scheme 4). The authors have not commented on the unexpected ease of α-deprotonation of this tertiary amine. A possible reason can be that association of the base cation with one nitrogen atom leads to an increase in the kinetic/thermodynamic acidity of hydrogens α to the other nitrogen, i.e., a complex induced proximity effect operates.[13] In fact, in the case of the related carbanion **14** which is readily derived from amine **13** and alkyllithiums, association of lithium cation with the two remote nitrogen atoms is supported by NMR data and MNDO calculations.[14] As a result of this chelation, **14** exists as a monomer even in hydrocarbon solvents and exhibits strong protophilicity and nucleophilicity. These properties have been utilized to develop a convenient route to alcohols from epoxides as shown in Scheme 5.

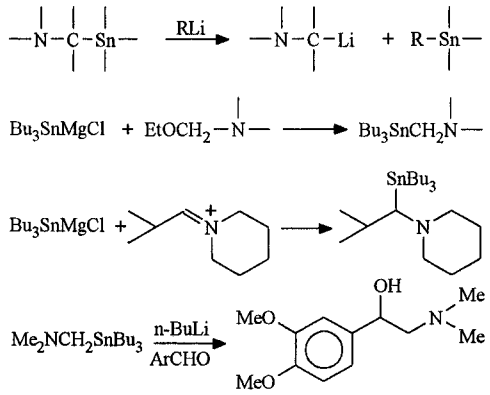
Generation of resonance-stabilized α-amino carbanions is relatively easy. For example, in contrast to earlier discussed *N*-methylpiperidine (**10**), α-deprotonation of *N*,*N*-dimethylbenzylamine (**15**) with n-BuLi/KOt-Bu mixture proceeds rapidly in hexane.[15] However, complications can arise due to competitive deprotonation of the ortho position when n-BuLi is used as the base. Similarly, reaction of *N*-methyl-1,2,3,4-tetrahydroisoquinoline (**16**) with n-BuLi in THF leads to lithiation at C-4 and this trend persists in the corresponding chromium carbonyl complex.[16] On the face of it, lithiation of the amine **16** at C-4, in preference to C-1, may be ascribed to an adverse effect of the adjoining nitrogen on the C-1 acidity. However, Davies has proposed a more subtle explanation.[16] It is suggested that complexation of n-BuLi with the nitrogen atom facilitates intramolecular abstraction of the C-4 proton through a bridged transition state as shown in **17** (Scheme 6).

Deprotonation of allyl tertiary amines with strong bases produces delocalized anions which react with electrophiles either exclusively or predominantly at the γ-position (**18** → **19**).[17] However, replacement of Li by Zn in **20** leads to almost exclusive α-addition of carbonyl compounds.[18a] Similarly, treatment of **20** with triethylaluminum followed by addition of trimethylsilyl chloride affords an α-silylated product.[18b] In the case of allylic tertiary amines carrying a methyl group on the double bond, deprotonation and subsequent electrophilic reaction take place at the methyl site (Scheme 7).[19]

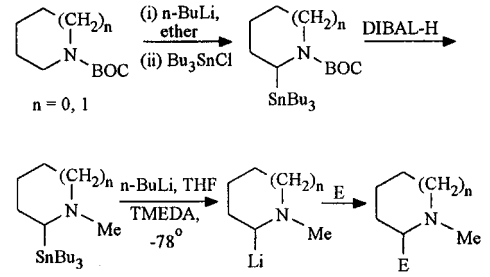
Scheme 7



Scheme 8



Scheme 9



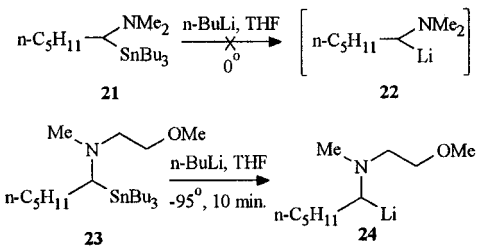
IV. Indirect Deprotonation of Tertiary Amines

The difficulties experienced in forming α-amino carbanions have led to the development of some indirect procedures to access these reagents. Out of these, transmetalation of α-aminostannanes, introduced by Peterson in 1970,[20] has been most widely used. With the development of better methods for the preparation of stannanes as shown in Scheme 8, this protocol has received further impetus.[21]

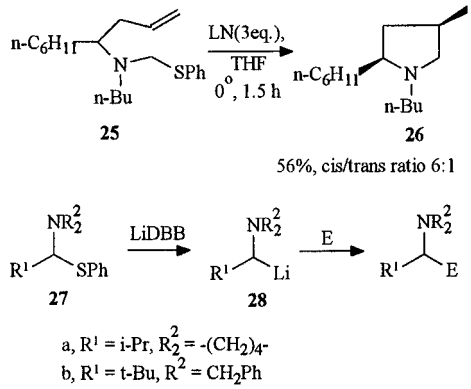
Transmetalation of α-aminostannanes has been used by Gawley to obtain 2-lithio-*N*-methylpiperidines and pyrrolidines which react well with a variety of electrophiles (Scheme 9).[22,23] He also showed that the lithiated amines derived from enantiomerically enriched stannanes exhibit remarkable configurational stability. The stannanes required in this work were obtained by reduction of N-BOC precursors which, in turn, can be readily secured by procedures developed by Beak.[24]

In contrast to cyclic secondary α-amino carbanions, the acyclic analogs do not seem to be available by transmetalation. For instance, Chong has reported that in the case of stannane **21** no observable reaction with n-BuLi occurred at low temperature (−78 °C, THF). At higher temperature (0 °C), **21** was consumed and tetrabutyltin was formed but no other products could be isolated from the reaction mixture.[25] Possibly, the intermediate secondary organolithium **22** is unstable at 0 °C and decomposes before it can be trapped with electrophiles. However, when a chelating alkoxy site is present in the amine side chain, Sn−Li exchange occurs readily (**23** → **24**, Scheme 10). The formed α-amino carbanion exhibits reasonably good configurational and chemical stability.[25]

Scheme 10



Scheme 11

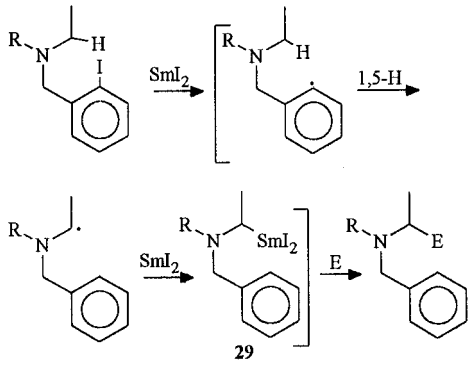


Reductive lithiation of α-amino sulfides constitutes another methodology for accessing α-amino carbanions. It is based on a technique developed by Cohen[26] and was first used by Broka and Shen[27] in their work on cyclization of homoallylic tertiary amines employing lithium naphthalenide for electron transfer. It was proposed that ring closure of **25** to **26** takes place via an α-amino carbanion. Even nonstabilized acyclic carbanions can be generated by this method. For example, addition of a 2 molar excess of lithium di-*tert*-butylbiphenyl radical anion (LiDBB) to a solution of **27** in THF at −75 °C results in instant formation of the dark red anion **28**. This anion is fairly stable at low temperatures and can be trapped with electrophiles, but it decomposes rapidly at 0 °C (Scheme 11).[28]

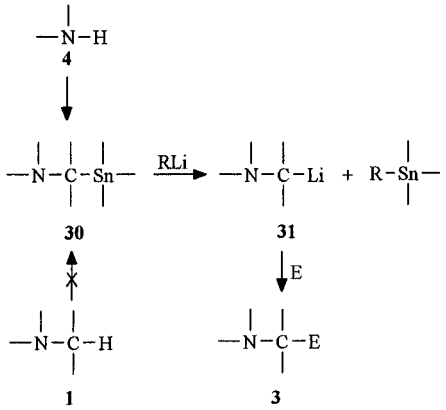
A procedure for introducing samarium metal at the α-position of tertiary amines has been reported briefly.[29a] The reaction course proposed for this transformation is shown in Scheme 12. Because samarium derivative **29** is unstable, electrophiles must be present in the reaction medium during its formation. Further, this procedure is restricted to tertiary amines with a pendant *o*-iodobenzyl group. An analogous reaction using Bu_3SnH instead of SmI_2 has also been described.[29b]

In summary, it may be inferred that efficient α-deprotonation of tertiary amines is generally not feasible in the absence of carbanion stabilizing groups or an additional chelating site. This is, perhaps, a

Scheme 12



Scheme 13



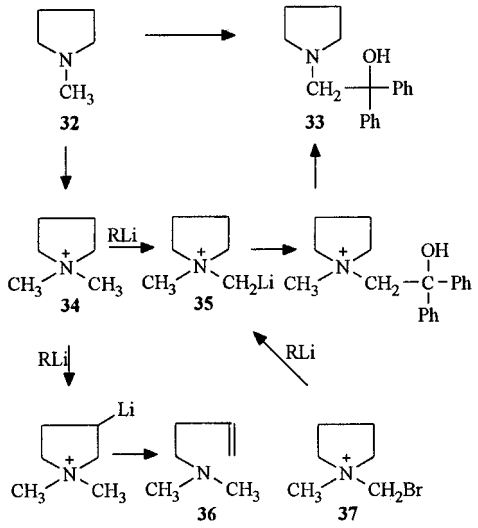
consequence of low kinetic acidity because, as mentioned in the above section, α-amino carbanions can be generated effectively by indirect methods, e.g., transmetalation of stannanes (**30** → **31**, Scheme 13). It has also been shown that once these carbanions are formed they display considerable stability. However, as far as synthetic elaboration of tertiary amines (**1** → **3**) is concerned transmetalation is of little value because the required α-stannanes cannot be obtained directly from tertiary amines (**1** ↛ **30**). Thus, the utility of these indirect methods is generally confined to synthetic sequences starting with secondary amines (**4** → **30** → **31** → **3**).

V. Deprotonation of Quaternary Ammonium Compounds and N-Oxides

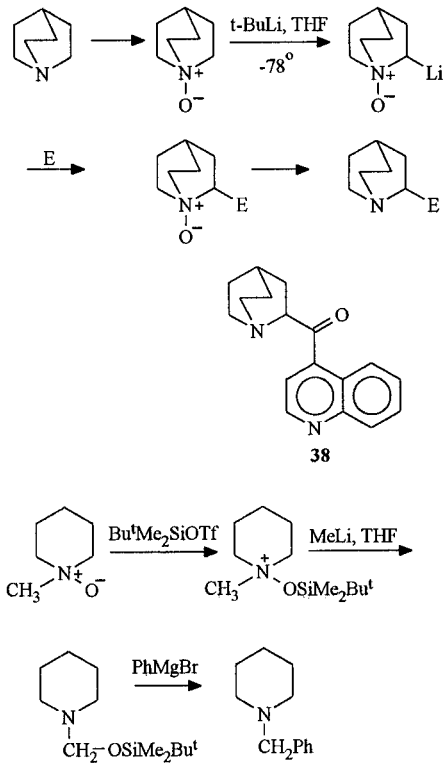
In their review on umpolung of amine reactivity, Seebach and Enders mentioned that ammonium ylides and amine oxides could provide a route for generation of α-carbanions from tertiary amines.[1] A conceptual conversion of 1-methylpyrrolidine (**32**) into the amino alcohol **33** was also given (Scheme 14). Most of the envisaged steps are well precedented and only the deprotonation of **34** is problematic. In fact, from the work of Wittig it is clear that treatment of **34** with n-BuLi results in Hofmann elimination to give the homoallylic amine **36**.[30] For effective generation of **35**, these workers had to resort to the bromo precursor **37**. Tetramethylammonium compounds are an exception in this regard and give stable α-carbanions.[31]

Pyridine *N*-oxides are known to undergo deprotonation to afford carbanions which can be reacted with a variety of electrophiles. Since the products can be

Scheme 14



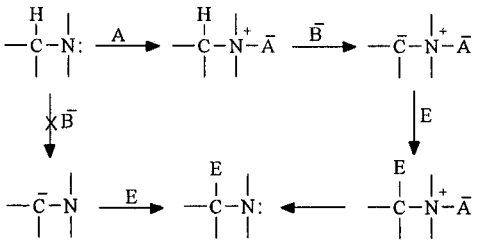
Scheme 15



readily deoxygenated, this approach provides a convenient synthesis of 2-substituted pyridines, although the overall yields are often modest.[32]

As mentioned earlier, metalation of sp^3 carbon atoms attached to an *N*-oxide moiety has been reported by Barton and co-workers.[5] Thus, treatment of quinuclidine *N*-oxide with t-BuLi followed by reaction with D_2O, aldehydes and esters gave products which could be conveniently deoxygenated with triphenylphosphine. Following this procedure, the ketone **38** was prepared in four steps. The *N*-oxide methodology is suitable only for tertiary amines in which the nitrogen atom is located at a bridgehead. Otherwise, the reaction course seems to get diverted by a rapid elimination of LiOH (see section VII). This problem is obviated in the Okazaki procedure using O-silylation of *N*-oxides as shown in Scheme 15.[33]

Scheme 16



A = Lewis acid; B = base; E = electrophile

VI. Lewis Acid Activation of Tertiary Amines

1. The Concept

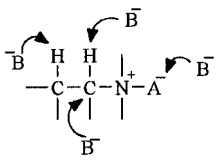
A.

α-Deprotonation of a tertiary amine may be promoted by forming a complex with a Lewis acid, because the positive charge developed on coordination of the nitrogen lone pair should inductively facilitate this process. If the Lewis acid carries a ligand capable of chelating the cation of the base used for deprotonation, further increase in the kinetic or thermodynamic acidity of α-protons may occur. The carbanion formed in this manner can be reacted with an electrophile to get, after decomplexation, an elaborated tertiary amine. Compared to the conventional methodologies involving covalent bond formation between the nitrogen and the activating group, attachment/detachment of a Lewis acid should be easy and a one-pot operation feasible.

B.

Besides facilitating deprotonation, complex formation may also be used to alter the course of subsequent reactions including their diastereo- or enantioselectivity. The spatial bias, in comparison to the uncomplexed α-amino carbanions, may arise from a change in the size or the nature of the amino moiety, or from a stereogenic center originally present in the Lewis acid or generated upon complex formation (Scheme 16).

The concept might sound a bit fanciful as reaction between the Lewis acid and the deprotonating base comes to mind immediately. However, when complexed to an amine the Lewis acid acquires a high negative charge and may not be as prone to attack by a base as when it is bare or is less strongly complexed. This reaction course could also be suppressed by introducing a steric or softness−hardness mismatch between the Lewis acid and the base.[34] In any case, there was evidence in literature that trifluoroboron etherate (BF_3 -etherate) can coexist with alkyllithiums at low temperatures.[34,35] Admittedly, the desired deprotonation of the complex could also be plagued by other side reactions. In fact, analogies for all four reaction pathways shown in **39**



39

exist in heteroatom chemistry,[30,34−36] and there is no *a priori* way of predicting which one will prevail in the case of complexed amines. It is relevant to note that Miller observed an enhancement of acidity of carboxyl-activated methylene protons in *N*,*N*-dimethylglycinatoborane.[36c] On the other hand, in one known example involving an unactivated tertiary amine, i.e., in the reaction of *N*-alkylaziridine−BF_3 complex with alkyllithium cuprates, predominant attack on the α-carbon had been observed.[36d] However, this could be only a reflection of the strain present in aziridine or the nucleophilicity of cuprates.

2. Synthetic Applications

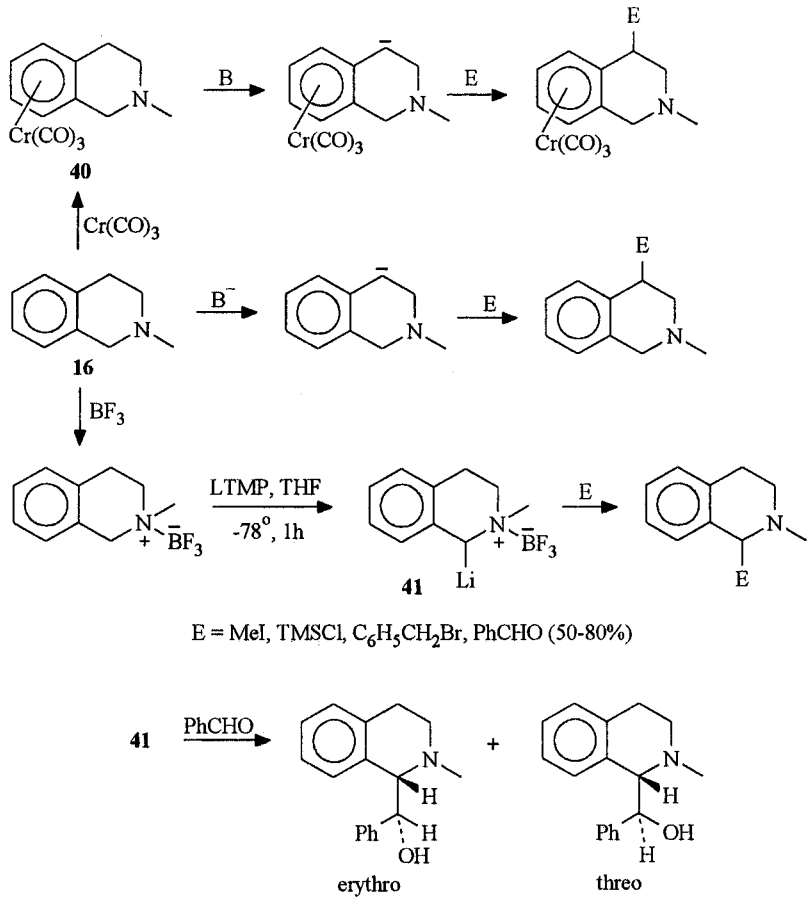
A. Benzylic α-Amino Carbanions

The workability of the Lewis acid activation of tertiary amines was first established through α-deprotonation of **16**—a rather well-explored model. As described in section III, **16** on treatment with n-BuLi gets deprotonated at the benzylic carbon away from the nitrogen atom, and this trend persists in its chromium carbonyl complex **40**.[16] Addition of 1 equiv of BF_3-etherate, prior to exposure of **16** to the base, caused a complete reversal of the regioselectivity of deprotonation. The α-amino carbanion **41** generated in this manner readily furnished 1-substituted products (Scheme 17).[5] In these reactions some starting material (∼10%) was always recovered but no 4-substituted isomers could be isolated. In the reaction of **41** with benzaldehyde erythro and threo alcohols were formed in a ratio of 6:1. This may be compared with the lack of diastereoselectivity observed by Seebach in the corresponding reaction of 1-lithiated *N*-pivaloyl-1,2,3,4-tetrahydroisoquinoline.[37] However, in the latter case, erythro products can be secured almost exclusively by transmetalation of the carbanion with $MgBr_2$. Similar transmetalation had little effect on the reaction of **41** with benzaldehyde.

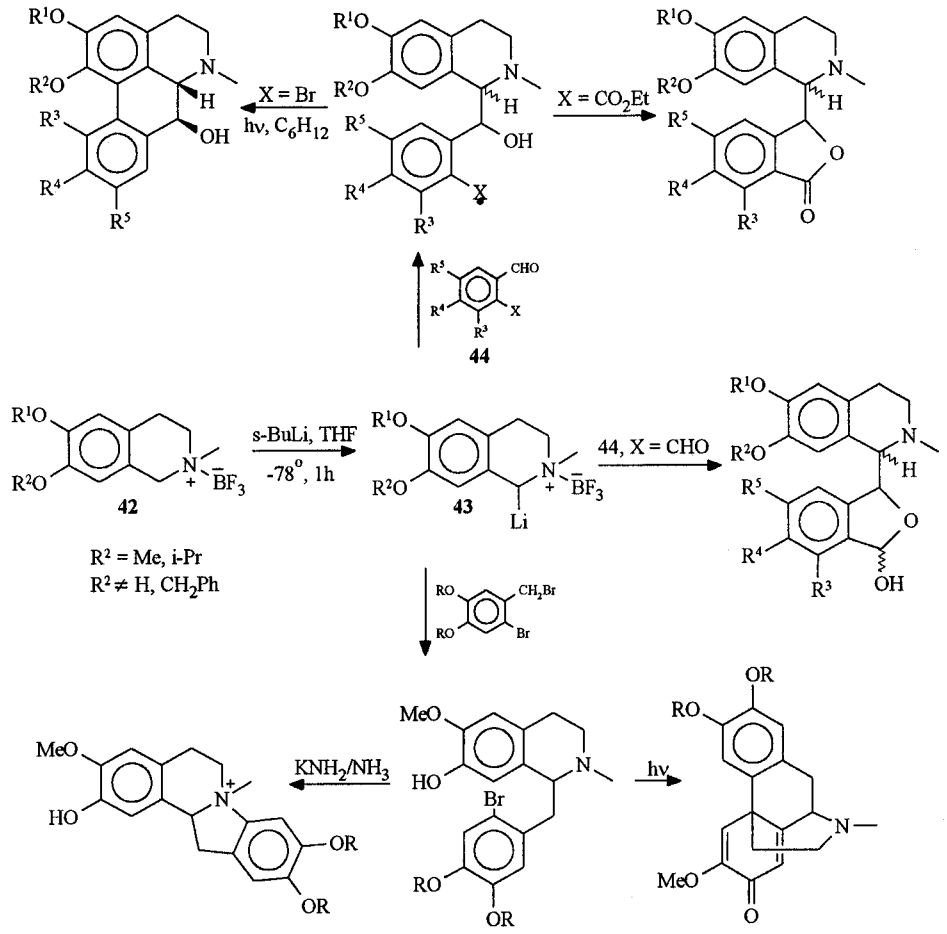
Success in C-1 deprotonation of **16** and subsequent benzylation opens up a versatile route to precursors of isoquinoline alkaloids having a variety of structural frameworks (Scheme 18).[38] A few points that merit attention in this connection are (a) A stronger base is required when alkoxy substituents are present on the aromatic ring, e.g., in the case of **42** use of s-BuLi is essential, whereas n-BuLi, or even lithium tetramethylpiperidide (LTMP), is effective for deprotonation of the unsubstituted amine **16**; and (b) protection of any phenolic functions present in the substrate is necessary and for this purpose isopropyl group is preferable as the conventional benzyl group introduces a competing acidic site.[38e]

Synthesis of spiro alkaloids from *N*-methyltetrahydroisoquinolines has some features of special interest. As shown in Scheme 18, reaction of carbethoxybenzaldehyde **44** with the carbanion **43** affords phthalide isoquinoline alkaloids in a straightforward manner. However, if the aldehyde function of **45** is protected by internal acetal formation (**46**), then addition of the carbanion **43** occurs at the carbethoxy end and leads to a spiro structure.[38d] Further, photorearrangement of **45** gives the acetal **47** in which the oxidation levels of the carbon atoms attached to the benzene ring are reversed. Its reaction with the carbanion **43** affords

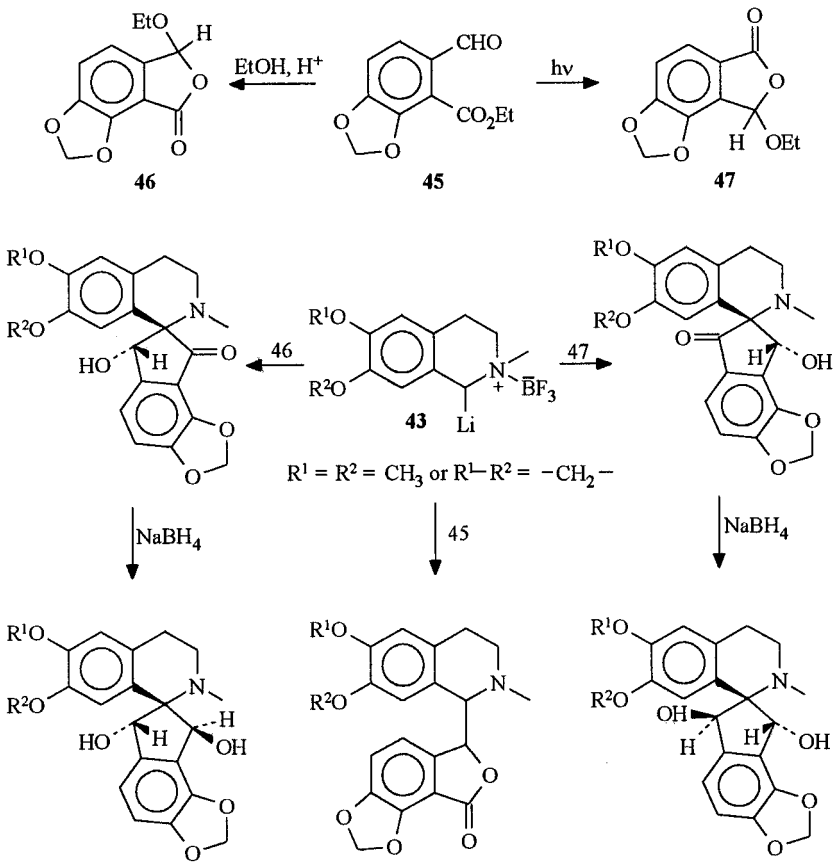
Scheme 17



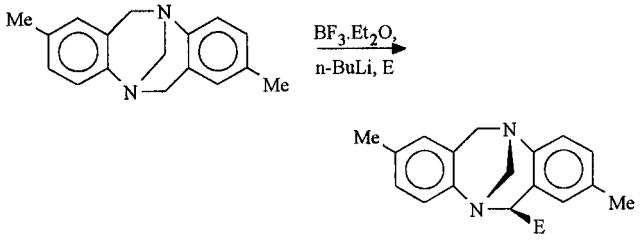
Scheme 18



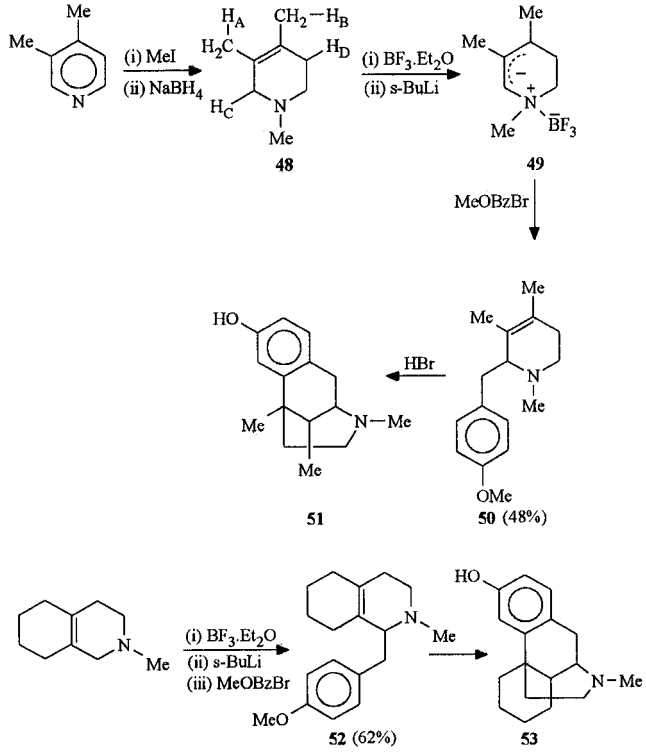
Scheme 19



Scheme 20



Scheme 21



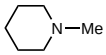
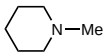
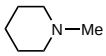
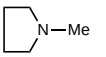
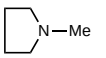
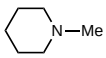
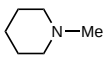
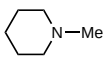
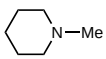
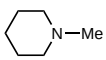
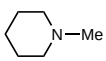
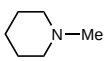
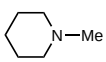
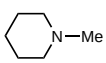
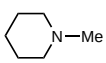
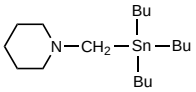
spiro alkaloids having a different stereochemistry. Thus, three types of alkaloids can be accessed from the same pair of carbethoxybenzaldehyde and *N*-methyltetrahydroisoquinoline (Scheme 19).

In a program on construction of new chiral ligands and auxiliaries for asymmetric processes, Harmata has investigated α-functionalization of Troeger's base by the Lewis acid activation approach (Scheme 20).[39] Reaction with various halides and carbonyl compounds proceeded stereoselectively to afford products in 60−85% yield. If complexation of the base with BF_3 was omitted, deprotonation was less efficient, e.g., in the benzylation reaction the yield came down from 62 to 14%.

B. Allylic α-Amino Carbanions

The regioselectivity observed in deprotonation of allylic tertiary amines, and in the reactions thereof, was discussed in section III. Complexation of such amines with BF_3 prior to treatment with base gives very interesting and useful results. For example, *N*-methyl-3,4-dimethyl-1,2,5,6-tetrahydropyridine (**48**) has four allylic protons (H_{A-D}) and on the basis of the observations of Fitt,[19] deprotonation of H_A or H_B should predominate in this case. However, treatment of a BF_3 complex of **48** with s-BuLi results in preferential removal of H_C.[5] Further, as shown in Scheme 21, the formed carbanion **49** gets alkylated at the α-position which, again, is contrary to what is

Table 1. Reaction of Deprotonated BF_3-Complexed *N*-Methylamines

entry	amine	reactant	product	yield,[a] %	ref
1		PhCH=O	**58**, $R^1-R^2 = -(CH_2)_5-$, $R^3 = C_6H_5$, $R^4 = H$	79	5
2		$Ph_2C=O$	**58**, $R^1-R^2 = -(CH_2)_5-$, $R^3 = R^4 = C_6H_5$	70	5
3			**58**, $R^1-R^2 = -(CH_2)_5-$, $R^3-R^4 = (CH_2)_5$	68	5
4		PhCH=O	**58**, $R^1-R^2 = -(CH_2)_4-$, $R^3 = C_6H_5$, $R^4 = H$	68	5
5		$Ph_2C=O$	**58**, $R^1-R^2 = -(CH_2)_4-$, $R^3 = R^4 = C_6H_5$	65	5
6		PhCOOEt	**59**, $R^1-R^2 = -(CH_2)_5-$, $R = C_6H_5$	72	5
7		PhCN	**54**, $R^1-R^2 = -(CH_2)_5-$, $R = C_6H_5$	50	5
8		$CH_2=CHCOOEt$	**54**, $R^1-R^2 = -(CH_2)_5-$, $R = -CH=CH_2$	69	5
9		PhCH=CHCOPh	**55**, $R^1-R^2 = -(CH_2)_5-$, $R^3 = R^6 = Ph$, $R^4 = R^5 = H$	69	41
10		I_2	**60**, $R^1-R^2 = -(CH_2)_5-$	65	5
11		MeI	**61**, $R^1-R^2 = -(CH_2)_5-$, $R = Me$	51	5
12		n-BuBr	**61**, $R^1-R^2 = -(CH_2)_5-$, $R = -(CH_2)_3CH_3$	–	41
13		n-BuOTf	**61**, $R^1-R^2 = -(CH_2)_5-$, $R = -(CH_2)_3CH_3$	40	41
14		CsF/n-BuBr	**61**, $R^1-R^2 = -(CH_2)_5-$, $R = -(CH_2)_3CH_3$	37	41
15		Bu_3SnCl	**61**, $R^1-R^2 = -(CH_2)_5-$, $R = Bu_3Sn$	94	41
16		s-BuLi/n-BuBr	**61**, $R^1-R^2 = -(CH_2)_5-$, $R = -(CH_2)_3CH_3$	70[b]	41

[a] Yields are pure products isolated after chromatography/crystallization. [b] Combined yield of **61** from entries 15 and 16 is 66%.

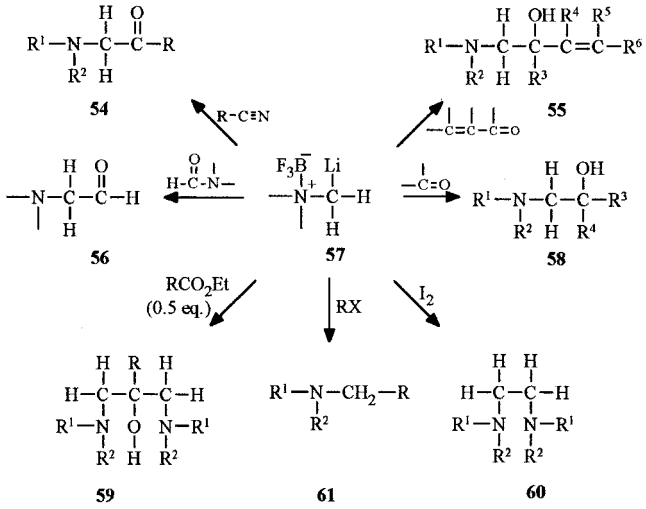
observed in the case of uncomplexed allylic amines.

The amines **50** and **52**, obtained as shown in Scheme 21, can be easily converted through a Grewe cyclization into metazocine **51** and dextrophan **53**.[40,41] These drugs had been synthesized earlier by Meyers group using their formamidine procedure.[42] The BF_3 activation approach is considerably shorter but, unlike the Meyers methodology, it affords only racemic products.

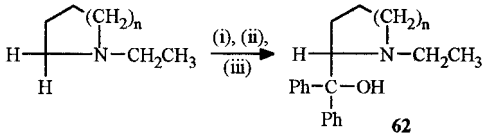
C. Unstablized sp³ Carbanions

From deprotonation of BF_3 complexes of amines **16** and **48**, it is clear that benzylic and allylic protons get removed in preference to other types of α-protons. Next in terms of ease of removal are the *N*-methyl protons, e.g., deprotonation of *N*-methylpiperidine–BF_3 complex can be readily effected with s-BuLi in THF at −78 °C. A number of examples of *N*-methyl deprotonation and subsequent reaction with electrophiles are represented in Scheme 22 and Table 1. It can be seen that whereas carbonyl electrophiles and tin halides react well with such unstabilized α-amino carbanions, reaction with *n*-butyl bromide proceeds poorly (entry 12, Table 1). Moderate yields of alkylated products can be obtained by use of more reactive alkyl triflates (cf. entry 13 with 12, Table 1) or through prior treatment with CsF (entry 14, Table 1). It seems that exposure to CsF removes the BF_3 from the nitrogen and the uncomplexed α-amino

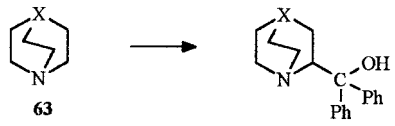
Scheme 22



Scheme 23



(i) $BF_3.Et_2O$, (ii) s-BuLi/KOBu^t, (iii) Ph_2CO



a, X = CH; b, X = N

carbanions react better with alkyl halides. In fact, best yields of alkylation products are obtained if the amine is converted, through deprotonation of BF_3 complex, into an α-stannane which is then, in a separate step, lithiated and reacted with the alkyl halide (entries 15 and 16, Table 1).[43]

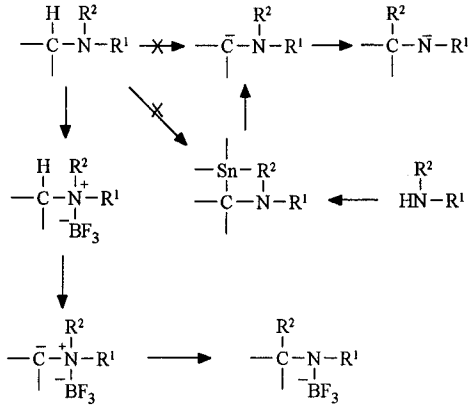
Deprotonation of a secondary ring carbon in cyclic amines, specially piperidine, has been considered to be a demanding test for any deprotonation methodology.[2f] Attempted deprotonation of a BF_3 complex of *N*-ethylpiperidine with s-BuLi was, indeed, unsuccessful. However, the use of a super base (s-BuLi/KOt-Bu) led to ring metalation as shown by reaction with benzophenone (**62**, 48%, $n = 2$; 85%, $n = 1$; Scheme 23).[41] It seems that the ease of removal of protons from secondary carbon atoms of BF_3-complexed cyclic amines is in the order 5-ring > 6-ring > exocyclic, as has been observed earlier with derivatized secondary amines.[2f] BF_3-promoted deprotonation has also been extended to quinuclidine (**63a**) and DABCO (**63b**), two tertiary amines having the nitrogen atom in a bridgehead position.[41]

D. Anionic Rerrangements of Complexed N-Allyl and Benzyl Amines

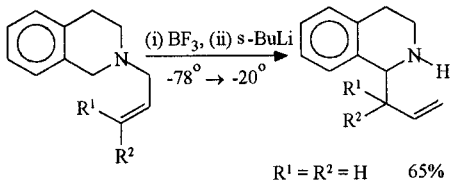
Anionic rearrangements of ethers have been investigated extensively but analogous isomerizations with tertiary amines have been reported only in a few isolated instances.[44a] The recent work of Anderson et al. shows that the main difficulty lies not in the rearrangement step but in the regioselective generation of α-amino carbanions.[44b] These intermediates when generated indirectly, i.e., by displacement reaction on α-stannanes, undergo facile anionic rearrangements (Scheme 24).

Lewis acid complexation of tertiary amines should not only facilitate deprotonation but should also promote subsequent rearrangement because of the driving force of charge neutralization. The carbanion derived from BF_3-complexed *N*-allyltetrahydroisoquinoline indeed undergoes a facile 2,3-sigmatropic rearrangement around −20 °C. The corresponding *N*-benzylamines rearrange at slightly higher temperatures, and the yields depend upon the substituent present on the migrating aromatic moiety (Scheme 25).[45] No rearrangement was observed in case of *N*-alkylamines, indicating that the migratory aptitudes are in the order allyl > benzyl > alkyl.

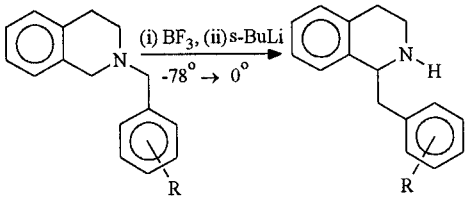
Scheme 24



Scheme 25

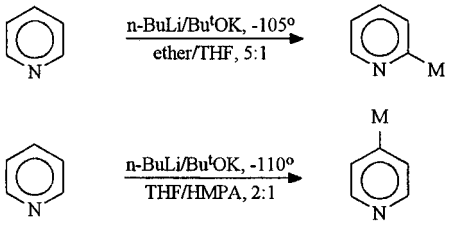


$R^1 = R^2 = H$ 65%
$R^1 = R^2 = Me$ 70%
$R^1 = H, R^2 = Me$ 76%



R = H 41%
R = 2-Me 57%
R = 4-Me 56%
R = 4-OMe 25%
R = 4-NO_2 0%

Scheme 26

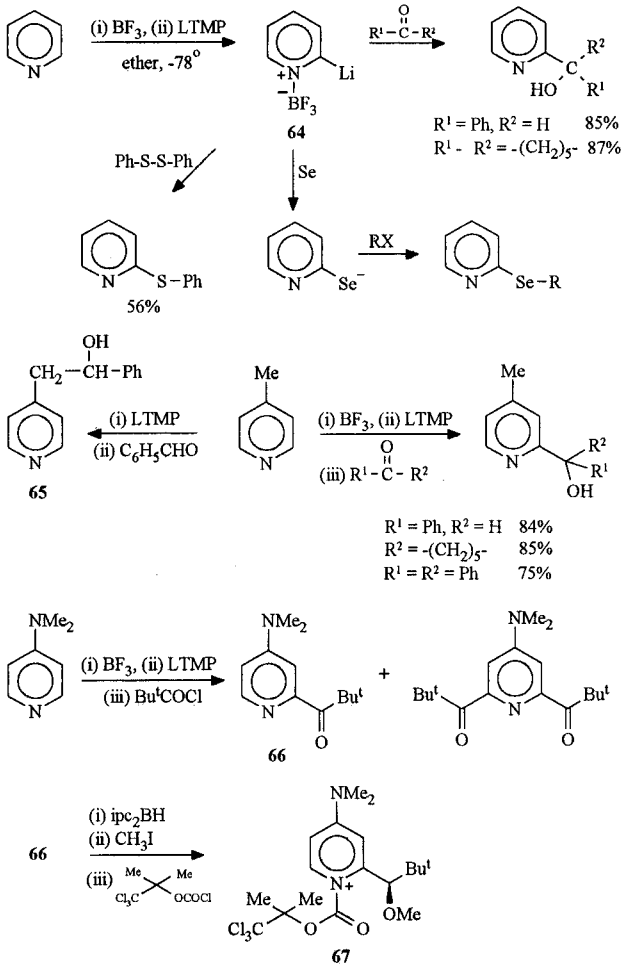


E. α-Pyridyl Carbanions

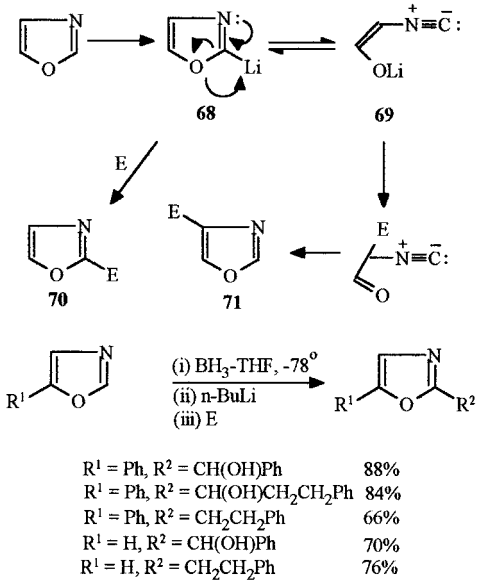
The metalation of π-excessive nitrogen heterocycles, like the azoles, occurs readily,[46] whereas removal of an α-proton of pyridine poses problems because the common deprotonating agents tend to add to the azomethine double bond or cause dimer formation.[47] However, addition to the C=N bond is a temperature-dependent phenomenon and working at low temperatures and employing a super base, regioselective metalation of pyridine is feasible (Scheme 26).[48] Nevertheless, this method is a bit cumbersome for orthometalation of pyridines because it requires use of excess base which has to be selectively destroyed before reaction with the electrophile.

The strategies developed for indirect metalation of pyridine include halogen exchange,[49] deprotonation

Scheme 27



Scheme 28



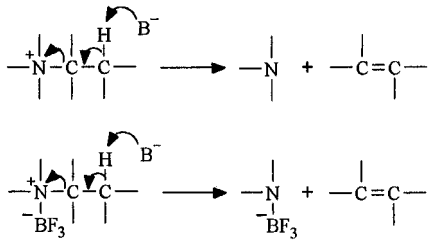
of pyridine *N*-oxides,[50] complexation with chromium(0) carbonyl,[51] and adduct formation with hexafluoroacetone,[52] and these have been reviewed.[46] A useful innovation in this area is the activation of nitrogen heterocycles by forming a complex with a boron Lewis acid.[53] In case of pyridine, good results are obtained using BF_3 in diethyl ether. LTMP is the most suitable deprotonating base but yields with less expensive LDA are only slightly inferior. However, use of an alkyllithium is complicated by addition reactions. In subsequent reactions of carbanions derived from Lewis acid-complexed pyridines, yields with ketones and aldehydes are very good but are modest with electrophiles like selenium metal and disulfides.[54] However, in the reaction with butyl bromide no alkylation product could be obtained from **64**, directly or after Cu transmetalation. The effectiveness of this procedure for securing α-pyridyl alcohols becomes evident when relatively acidic benzylic protons are also present in the substrate. For example, deprotonation of γ-picoline with LTMP followed by reaction with benzaldehyde affords the side-chain alcohol **65** in good yield. Addition of 1 equiv of BF_3-etherate, prior to treatment with base, has a dramatic effect and the corresponding α-pyridyl alcohol becomes the sole isolable product (Scheme 27). Vedejs has recently used this procedure to obtain ketone **66** for conversion to the pyridinium salt **67**—an effective reagent for enantioselective acylation of secondary alcohols.[55]

Recently, another very useful application of Lewis acid complexation to promote α-deprotonation of nitrogen heterocycles has been reported.[56] As mentioned in section VI.E, azoles can be readily deprotonated and reacted with electrophiles. Oxazoles, however, are an exception as complications arise due to facile equilibration between valence bond tautomers **68** and **69**.[57] Thus, reaction of metalated oxazole **68** with benzaldehyde affords only 2% of **70** along with 20% of 4-substituted oxazole **71** and other side products.[58] Vedejs and Monahan argued that the undesired electocyclic ring opening can be prevented if the crucial electron pair of the oxazole nitrogen could be locked in place by complexation with a Lewis acid.[56] Complexation was also expected to activate the C_2−H bond for metalation. Supression of the electrocyclic pathway was indeed achieved by forming a BH_3 complex and C-2 functionalized oxazoles **72** were obtained in good yields (Scheme 28). No complications due to nucleophilic addition to the iminium bond were experienced. Specially noteworthy is the good yield in which 2-phenethyloxazoles are obtained by reaction with $Ph(CH_2)_2OSO_2CF_3$.

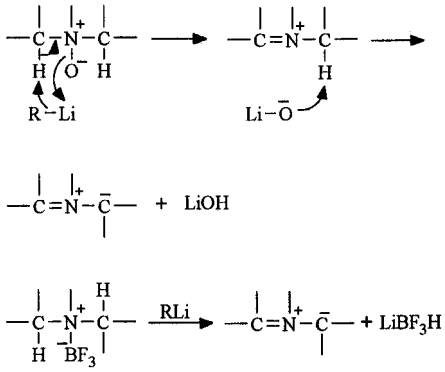
VII. Structure and Reactivity of Lewis Acid Complexed Amino Carbanions

By virtue of its preparation in 1809 by Gay-Lussac and in 1812 by Davy,[59a,b] H_3NBF_3 has been referred to as the first known coordination compound.[59c] The structure of this archetypal donor−acceptor complex has been the subject of many experimental and theoretical studies.[59c,d] These show the distance *r*(N−B) to be around 1.6 Å which is considerably longer than C−C bond length (~1.5 Å) in the isoelectronic molecule H_3CCF_3.[59c] As far as the charge on the nitrogen atom is concerned, BF_3−amine complexes fall in between neutral amines and quaternary ammonium compounds. These complexes are essentially dipolar in nature and an upper limit of 0.45 electron for charge transfer from N to B has been proposed on the basis of NQR studies.[60] It is, perhaps, this midway position of the complexed amines which confers on the derived carbanions, a

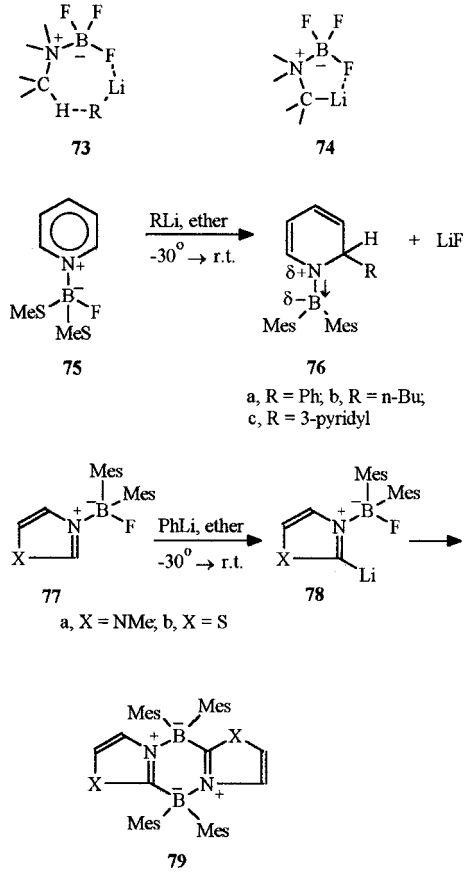
Scheme 29



Scheme 30



Scheme 31



unique mix of stability and reactivity. On one hand, such carbanions can be trapped efficiently with electrophiles at −78 °C and on the other, facile migrations of allyl and benzyl groups occur in the −20 to 0 °C range. The difference in the charge on the nitrogen atom in the quaternary ammonium compounds and the Lewis acid complexes of amines may also be responsible for the fact that the latter do not undergo rapid Hofmann elimination. As shown in Scheme 29, in the case of quaternary ammonium compounds this reaction involves expulsion of a neutral amine molecule.[61] A corresponding fragmentation of an amine Lewis acid complex would require loss of a charged $>N-BF_3$ moiety, i.e., of a comparatively poor nucleofuge.

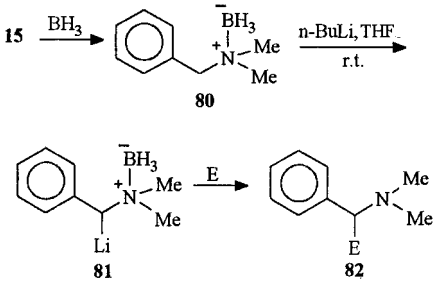
It is interesting to compare the stability of carbanions derived from Lewis acid-complexed amines with those from *N*-oxides. As mentioned earlier, unless the *N*-oxide nitrogen is present in a bridgehead position, the carbanion formed on deprotonation undergoes rapid LiOH elimination. In fact, the azomethine ylides derived in this manner can be usefully trapped with dienophiles to get a variety of nitrogen heterocycles.[62,63] However, as far as the utilization of the carbanions by reaction with electrophiles is concerned, this is a wasteful pathway. The elimination mechanism proposed by Roussi[62] is shown in Scheme 30, and a one- or two-step process for the loss of LiOH can be envisaged. A similar reaction course does not ingress in case of carbanions derived from Lewis acid-complexed amines, probably because loss of $LiBF_3H$ is not as facile as that of LiOH.

In lithiation of BF_3−amine complexes an element of lithium fluorine chelation may be involved as shown in **73** and **74** (Scheme 31). If so, it can influence the ease of deprotonation or the stability and reactivity of the formed carbanions. No experimental evidence on this point is available as yet, but occurrence of similar association of Li with covalently bonded fluorine has been supported in other cases by X-ray diffraction and NMR spectroscopic data.[64] In connection with the structure of α-metalated Lewis acid complexes of amines, attention is also drawn to the work of Okada et al.[65] The investigators found that the complex of pyridine and dimesitylfluoroborane gives adduct **76** on reaction with alkyl- or aryllithiums. In contrast, similar complexes of azoles **77a** and **77b** undergo α-lithiation and subsequent self-condensation at room temperature. For the product formed in this manner, novel 1,4-diazonia-2,5-diboralacyclohexa-3,6-diene structure (**79**) was proposed on the basis of NMR and X-ray evidence.[65] Similar dimer formation in case of the carbanions derived from BF_3 complexes of pyridine, and even those of tertiary amines, remains a possibility. Finally, Lewis acid shifts from the nitrogen to the adjoining carbanion center can also occur, especially at higher temperatures.

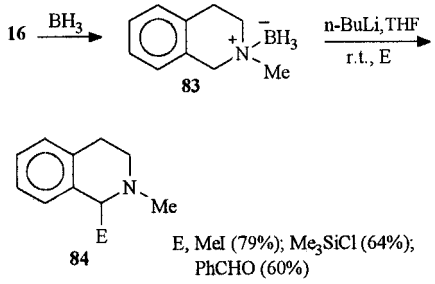
VIII. Amine Activation by BH_3 and Other Lewis Acids

Besides BF_3, other boron Lewis acids which have been used for α-deprotonation include BH_3,[5,56,66,68] dimesitylfluoroborane,[65] diisopinocamphenylborane,[53] and phenyldifluoroborane.[74] Simpkins has studied the deprotonation of *N*,*N*-dimethylbenzylamine−borane **80**.[66] As mentioned in section III, treatment of amine **15** itself with n-BuLi in ether leads to ortho deprotonation. The regioselectivity of deprotonation gets reversed on forming a BH_3 complex and a number of α-substituted benzylamines have been synthesized in this manner (Scheme 32).[66] Simpkins

Scheme 32



Scheme 33



also found that both borane and chloroborane react with **15** to give stable analytically pure adducts whilst other boranes, such as $BCl(C_6H_{11})_2$ and BCl_2-Ph, formed adducts (TLC) which were not stable to work up and purification. On the whole, BH_3 complexes were considered to be more amenable to amine substitution chemistry and best results were obtained when 2 equiv of n-BuLi in THF at room temperature were used for deprotonation. It was not necessary to isolate the complex **80** and a one-pot reaction also worked well.[66] The yields given in Scheme 32 are for such a conversion of **15** to **82**.

The borane activation method was extended by Simpkins to *N*-methyltetrahydroisoquinoline, with the results shown in Scheme 33.[66] The yields obtained in the conversion of the isolated complex **83** to **84** are very good. However, if the complex-forming step is taken into account, the overall yields are comparable to those reported using BF_3 as a Lewis acid.[5]

In the preliminary communication describing the concept of Lewis acid activation of tertiary amines, we had indicated that BCl_3, BH_3, and Me_3Al give inferior results as compared to BF_3.[5] It is true that for deprotonation of benzylic amines like **15** and **16**, BH_3 functions as well as BF_3 and has the advantage of isolable complexes as pointed out by Simpkins. Further, the utility of BH_3 complexation in deprotonation of oxazole has also been established.[58] However, in our experience borane activation is not as effective for generation of unstablized sp^3 carbanions. For example, exposure of an *in situ*-formed complex of BH_3 and *N*-methylpiperidine to s-BuLi followed by treatment with benzophenone did not afford the desired alcohol **58** and the starting material was recovered almost quantitatively.[41] Under identical conditions, BF_3 activation of *N*-methylpiperidine affords **58** in 70% yield (entry 2, Table 1). In fact, it is not clear that the BH_3-induced change in regiochemistry of deprotonation of benzylic amine **15** can be wholly ascribed to α-proton activation. In the complex, the lone pair on the nitrogen is not available for association with the cation of the base. Therefore, cation chelation effects which presumably facilitate ortho metalation of **15** are absent. As such, "abnormal" metalation of complex **80** as well as **83** could, at least in part, be a reflection of the suppression of deprotonation at the otherwise competing sites. In any case, BF_3 seems to be a more powerful activator than BH_3. In this context it is relevant to note that although the distance r(B−N) is virtually identical in BH_3 and BF_3 complexes of Me_3N, thermochemical data and NMR studies suggest that BF_3 is more strongly bound.[67a−c] Also, the B−N force constant is larger in BF_3 adducts, indicating a stronger acid−base interaction.[67d,e] On the other hand, quantum mechanical calculations and NQR studies indicate that nitrogen is not more positively charged in R_3NBF_3 than in R_3NBH_3.[60] This seemingly anomalous situation has been rationalized by pointing out that stronger electron withdrawl by BF_3 than by BH_3 is compensated by a greater flow of charge from R groups to nitrogen in the former case. Thus, a more effective facilitation of α-deprotonation by BF_3 can be expected. Whether it is solely due to variation in complexing strength or fluorine lithium chelation also plays a role, as mentioned in section VII, is not clear.

IX. Diastereo- and Enantioselective Transformation

As stated in section VI, Lewis acid activation of amines has potential for effecting diastereo- and enantioselective transformations. In fact, such an effect was observed in the reaction of **41** with benzaldehyde. More recently, Lewis acid complexation has been ingeniously used to influence syn/anti ratio in aldol reaction of some glycinates (Scheme 34).[68] Ferey et al. have observed that the enolate derived from the ester **85** and LDA adds to a variety of aldehydes to afford the corresponding aldols with a high syn/anti ratio. These reactions were carried out in THF at −78 °C, although allowing the reaction mixture to warm up to 0 °C, before the work up, had no effect on the syn/anti ratio. In contrast, the enolate derived from the borane complex **86** exhibited no diastereoselectivity in the aldol reaction at −78 °C. However, if the reaction mixture was allowed to warm up to 0 °C, there was a dramatic shift in favor of the anti isomer (Table 2). The investigators suggest that at 0 °C, equilibration takes place in favor of the more stable anti aldolate **90**. A similar equilibration does not occur in case of aldolates derived from the free amine **85** because of the stabilization arising out of intramolecular chelation between the nitrogen lone pair and the lithium cation. For effecting enantioselective transformations with carbanions, the usual strategies involve either enantioselective deprotonation or creation of a chirotopic environment around the carbanion prior to its reaction with the electrophile.[69−72] These approaches may be applicable to the carbanions derived from complexed amines also. In addition, there are other features of interest which are conse-

Scheme 34

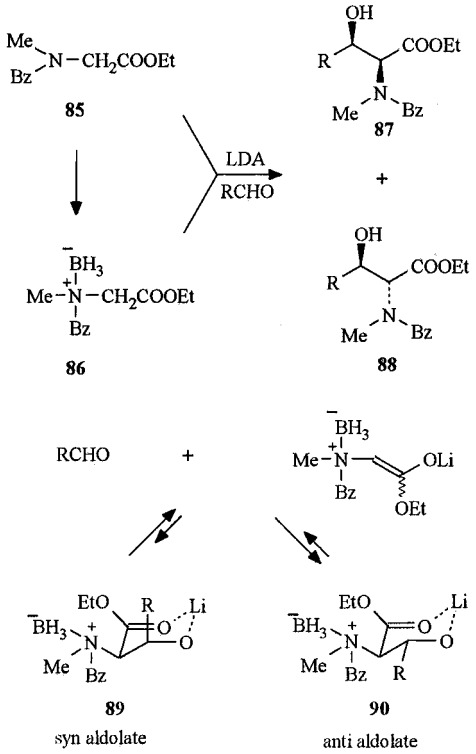
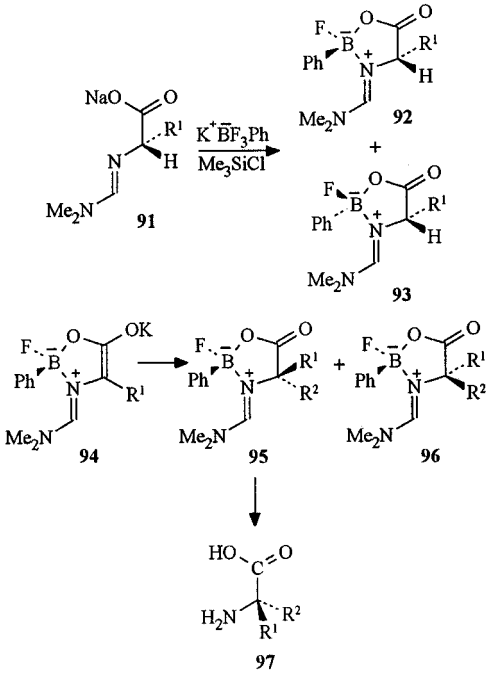


Table 2. Aldol Reaction of 85 and 86

	amine **85**		complex **86**	
R	syn/anti ratio	yield, %	syn/anti ratio	yield, %
phenyl	66:34	76	6:94	63
4-nitrophenyl	57:43	73	6:94	52
(*E*)-pent-1-enyl	75:25	82	7:93	62
pentyl	84:16	66	21:79	67
cyclohexyl	75:25	78	17:83	48
tert-butyl	82:18	61	−	−

quent upon complex formation. Firstly, a chiral ligand present on the Lewis acid may impart an enantiofacial bias to the reactions of the derived carbanion. Thus, the Lewis acid can serve as a lightly attached chiral auxillary.[73] A more subtle aspect is that in boron−amine complexes new stereogenic centers can arise if the three substituents present on the nitrogen or the boron atom are different (**92** and **93**). Exploitation of these transitory chiral centers for enantioselective transformations of the complex derived carbanion is an exciting prospect. Of course, enantioselective creation of these chiral centers would require ingenious approaches as there is not much precedent to go by. Vedejs has made a beginning in this direction in his work on chiral amino acid enolate equivalents (Scheme 35).[74] On formation of a complex of an enantiomer of the α-amidino carboxylate **91** with $PhBF_2$, generated *in situ* by action of Me_3SiCl on $K^+ {}^-BF_3Ph$, a new stereogenic center arises at the boron atom. Its formation is influenced by the chiral center already present in **91**. Thus, diastereomers **92** and **93** were formed in a ratio of 3.5:1 when R^1 was an isopropyl group. Crystallization of this mixture under conditions in which the two diastereomers were equilibrating, probably through reversible B−N bond dissociation, resulted in a solid in which **92** to **93** ratio

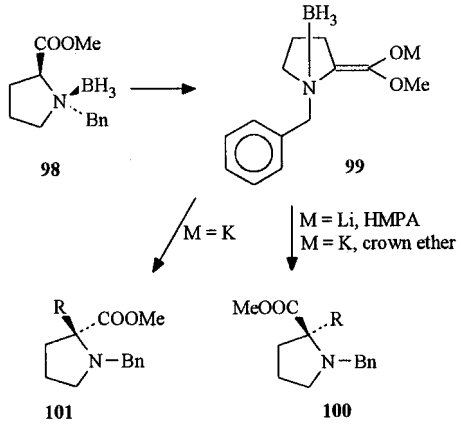
Scheme 35



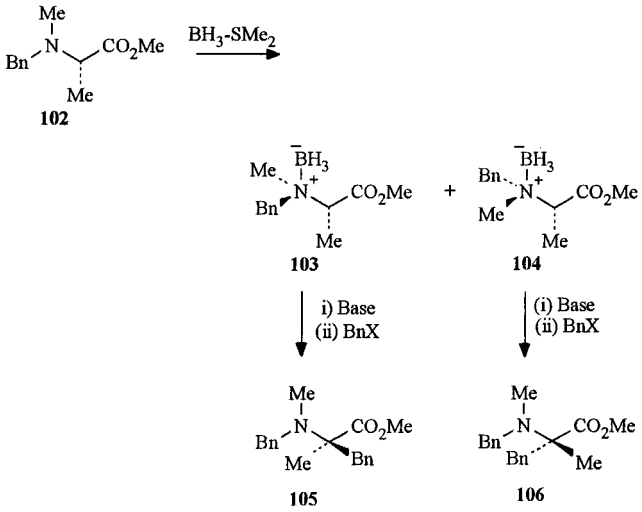
was >150:1. Thus, making use of a "order" asymmetric transformation (AT),[75] almost pure **92** could be obtained. Reaction of the enolate **94**, derived from **92**, with allyl and benzyl bromides occurred with preferential C−C bonding at the less hindered face (syn to fluorine), giving **95** with excellent diastereoselection. Slightly lower stereoselection was observed if R^1 = Ph, probably because of some epimerization at boron prior or subsequent to enolate formation. Lewis acid cleavage of oxazaborolidinones to give enantiomerically enriched disubstituted amino acids occurs under mild conditions (refluxing ethanol + ethylenediamine). Thus, this methodology not only demonstrates the power of AT technique and the concept of asymmetric memory,[76] but also brings out the potential of new stereogenic centers which arises on complexation of amines with Lewis acids.

Chirality transfer through the quaternary nitrogen center, generated on formation of an amine complex with a boron Lewis acid, has also been achieved recently.[77−79] Treatment of methyl ester of (*S*)-*N*-benzylproline with borane afforded a complex, as a single diastereomer, in which the boranato group was cis to the carboxylate function (**98**, Scheme 36). Its lithium enolate (**99**, M = Li) was unreactive toward benzyl bromide but when 3 equiv of HMPA was added prior to the electrophile, the product **100** was obtained in 74% yield (88% ee). In contrast, the potassium enolate (**99**, M = K) reacted without the need of additive to give the other enantiomer **101** (66% yield, 54% ee). However, addition of 1 equiv of 18-crown-6 reversed the enantioselectivity of the potassium enolate and **100** was obtained in 74% yield with 80% ee. To account for this result, it has been suggested that the O−K bond in the enolate lies out of its plane and the crown ether associates on the side of the smaller boranato group thus preventing approach to this side by the incoming electrophile. A similar course is envisioned for the reaction of the lithium enolate−HMPA complex.

Scheme 36



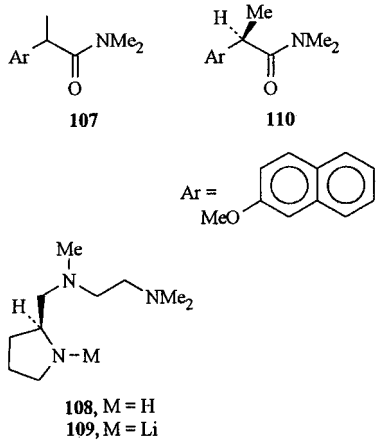
Scheme 37



Mioskowski's group has also achieved enantioselective alkylation of open chain enolates.[78] The diastereomeric mixture obtained on formation of BH_3 complex of L-alanine ester **102** was separated by column chromatography or crystallized selectively (AT).[80] Deprotonation of **103** or **104** followed by alkylation afforded corresponding products with ee's in the 36−82% range (Scheme 37). The results can be explained on the basis of Felkin model of the transition state,[81] keeping the negatively charged boranato and carboxylate functions far from each other.

Finally, mention may be made of Vedejs' work on Lewis acid-induced internal proton return in enolates complexed with chiral amines, although it involves transfer of an NH proton.[82] It was found that addition of BF_3-etherate to a mixture of a secondary amine and an enolate results in transfer of a proton from the amine to the enolate. This may be attributed to an increase in NH acidity on formation of a Lewis acid complex of the amine. Compared to quenching with an external proton source, where both direct protonation and internal proton return can occur,[83] this procedure makes possible proton transfer totally within a chirotopic environment. Thus, treatment of a 1:1:1 mixture of enolate derived from **107**, amine **108**, and lithium amide **109** with $BF_3 \cdot Et_2O$ affords naproxen amide **110** with an enantiomeric excess of 77% (79% yield, Scheme 38).

Scheme 38



X. Future Prospects and Challenges

Generation and utilization of α-carbanions from amines continues to be an active area of research. With the emergence of the Lewis acid activation concept, formation of new bonds at the α-carbon atom has become feasible for many tertiary amines which were not otherwise amenable to direct elaboration. To further enlarge the scope of this methodology, it is desirable to find or develop new Lewis acid/base combinations which allow stereo- and enantioselective transformations, and furnish α-amino carbanions with improved reactivity, particularly toward alkyl halides. Also, there is need for economical reagents and reaction conditions which are suitable for industrial applications, including the possibility of Lewis acid turn over in a catalytic cycle. Lastly, this concept can, perhaps, be extended to other heteroatom compounds, like ethers, to achieve deprotonation under milder conditions and for diastereo- or enantioselective transformations.

XI. Acknowledgments

We express sincere appreciation of students and co-workers who made our work in this field possible. The financial support by the department of Science and Technology, Government of India, is gratefully acknowledged. We also thank Professor Vedejs for sending yet unpublished material and Vijay K. Kaul for valuable help in preparation of this manuscript.

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CR950082N