Dipole-Stabilized Carbanions: Novel and Useful Intermediates

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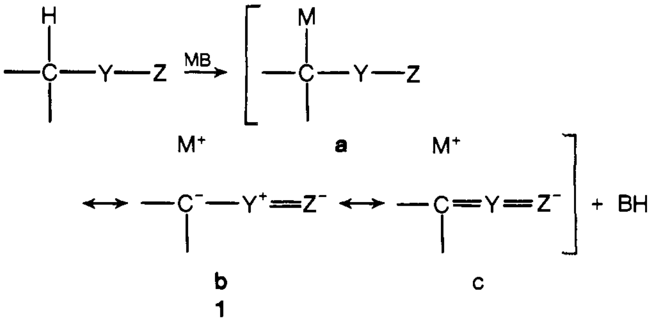
Contents

I. Introduction

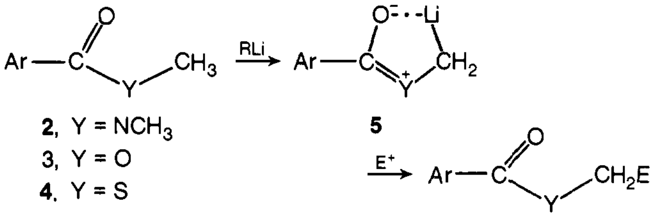
The removal of a proton from a carbon bearing a heteroatom to give an α-heteroatom organometallic is a synthetically useful and mechanistically interesting reaction. A number of investigators have suggested independently that formation of such organometallic species can be promoted by a local inductive effect when the heteroatom is the positive end of a dipole. In this review we will bring together cases which indicate that dipole stabilization can play an important role in the formation of formal α-heteroatom carbanions. This summary will illustrate the synthetic value of these novel species. Although the area is still developing, the concept of dipole stabilization of carbanions appears to be heuristically useful in the search for new reactions and in synthetic design.

SCHEME I



Y = NR, O, S

A general representation of a dipole-stabilized carbanion is provided by **1** in Scheme I where Y represents nitrogen, oxygen, or sulfur and Z is a group capable of inducing a formal positive charge on Y. If **1b** is a significant contributor to the hybrid, dipole stabilization is an important factor in the stability of **1** and, presumably, in the transition state leading to **1**. Specific examples of such reactions for nitrogen, oxygen, and sulfur are provided by the metalations on *N,N*-dimethyl-2,4,6-triisopropylbenzamide (**2**), methyl 2,4,6-triisopropylbenzoate (**3**), and methyl 2,4,6-triisopropylthiobenzoate (**4**) to give the intermediate **5** (Y = NCH_3, O, S) which can be subsequently trapped by electrophilic reagents, E^+.[1-3] The metalation of **4** is particularly pertinent, since it has been shown that **5** (Y = S) can be formed by proton transfer from **4** to lithiomethyl methyl sulfide,[3] a result which indicates that the carbonyl group does provide thermodynamic stabilization for the formal methyl carbanion adjacent to the heteroatom.



2, Y = NCH_3
3, Y = O
4, Y = S

Ar = 2,4,6-triisopropylphenyl

The long-standing mechanistic and theoretical interest in α-heteroatom carbanions has been well reviewed.[4] Inductive effects are discussed in terms of field, bond, polarization, and hybridization factors. Resonance stabilizations are usually considered to involve π–π or d–π delocalizations. A possible molecular orbital rationalization for the relative stability of formally dipole-stabilized systems could be constructed in terms of a lowering of the highest occupied molecular orbital of the carbanion due to its interaction with the lowest unoccupied molecular orbital of the heteroatom system. Other molecular orbital descriptions raise the possibility of stabilization by overlap of nonbonded orbitals[5] and electron pair interactions can be considered in terms of both local and delocalized effects to be stabilizing or destabilizing.[4,6] Although the order of organometallic stabilities appears to follow that intuitively expected for carbanions, quantitative separation of the factors affecting carbanion stability has not been generally achieved, and the present discussion of the stabilities of dipole-stabilized carbanions will be necessarily qualitative.[4,7,8] The question of whether dipole stabilization, in fact, contributes significantly to the stability of a given case will have to be individually evaluated on the basis of available information. The structures of most carbanionic intermediates in this review will be drawn as dipole stabilized, although the actual extent of that contribution generally remains to be determined.

Regardless of the mechanism of stabilization of **1**, the fact that such species can be formed from the corresponding carbon

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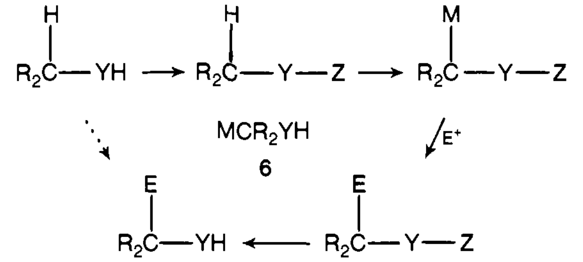
SCHEME II



acids and do undergo subsequent electrophilic substitution is of substantial synthetic interest. As illustrated in Scheme II, activation of the hydrogen adjacent to the heteroatom Y by addition of Z, followed by reaction with base, electrophilic attack on the anion, and removal of Z allows net electrophilic substitution of a hydrogen on the carbon adjacent to the heteroatom. In effect, the sequence provides a nucleophilic α-heteroatom synthon **6**. General methods for carrying out nucleophilic aminoalkylations, oxyalkylations, and thioalkylations would provide significant new pathways for the synthesis of many interesting compounds. Viewed alternatively, the novel electrophilic substitution of an amine, alcohol, or thiol by such a sequence has strategic implications for the design of syntheses. The reactions of Scheme II transform a carbon which would normally be susceptible to nucleophilic replacement to a center for electrophilic substitution, and the conversion is then of the reverse charge affinity, reverse polarity, or "umpolung" type.[9-11]

Although in principle any functional group which provides a dipole for a heteroatom may offer stabilization of the type illustrated for **1**, Z should not bear protons which would be more kinetically acidic than those adjacent to Y. Z should not be susceptible to nucleophilic attack or be involved in α or β elimination under the conditions required to generate the carbanions, yet Z should be readily removable. In addition, the carbanion **1** should be readily generated, persistent, and react nucleophilically with a wide variety of electrophiles. Despite these restrictions and the fact few cases have been studied for both synthetic potential and mechanistic understanding, a sufficient number of cases have been reported to suggest dipole-stabilized carbanions already form a class of useful intermediates.

This selective review will focus on cases for which dipole stabilization could be the major effect. Carbanionic intermediates in which resonance and hybridization could provide stabilization of the negative charge by well-established mechanisms will, with some exceptions, not be discussed. For example, the chemistry of α-metalated five-membered heteroaromatics has not been included, although inductive stabilization by a dipole is one of the mechanisms often cited in such species.[12,13] We will also be primarily concerned with cases in which chemical transformations have been effected and hydrogen–deuterium exchange[13] will be discussed only for cases in which direct guidance has been provided for subsequent chemistry.

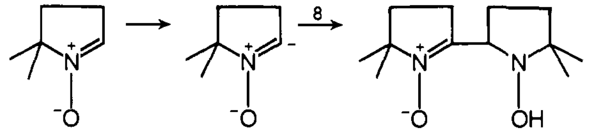
II. Dipole-Stabilized Carbanions Adjacent to Nitrogen

Formation of α-nitrogen dipole-stabilized carbanions **1**, Y = NR, from the corresponding carbon acids has been reported for a variety of functional groups. In particular, extensive work has been done on the α-nitrogen lithium reagents from isocyanides and nitrosamines, amides are receiving increasing attention, and efforts to discover and exploit new systems continue to appear. The α-nitrogen carbanionic synthon, **6**, Y = NR, would be particularly useful in a wide variety of syntheses.

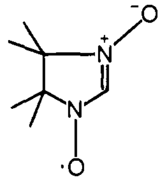
A. Amine Oxides and Nitro Compounds

One of the clearest indications that dipole stabilization can be an important factor in the kinetic acidity of an amine derivative is provided by the selective removal of a proton from a sp^2 carbon adjacent to the nitrogen of an amine oxide. Of a number of reports of base-catalyzed hydrogen-deuterium exchange at the 2 position of pyridine *N*-oxides, the work of Zoltewicz and Helmick is particularly important.[14,15] These workers resolved the problem of internal return and established that exchange in pyridine *N*-oxides, as well as in pyridinium ions, follows a linear free energy correlation with σ_1. This result establishes that inductive stabilization by the dipole can be of major importance in the transition state leading to the carbanion. In these cases delocalization of the sp^2 carbanion is structurally precluded and a complexing effect by the sodium ion seems unlikely to be important in the aqueous medium.

One of the earliest suggestions of a dipole-stabilized carbanion in a chemical transformation is that of **7** suggested by Brown et al., to explain the dimerization of the amine oxide **8** on treatment with soda amide in liquid ammonia to give **9** in 49% yield. A similar species has been suggested to rationalize the hydrogen–deuterium exchange of the olefinic hydrogen of the nitronyl-nitroxide radical **10** in deuterium oxide at pD 7–8.[17]



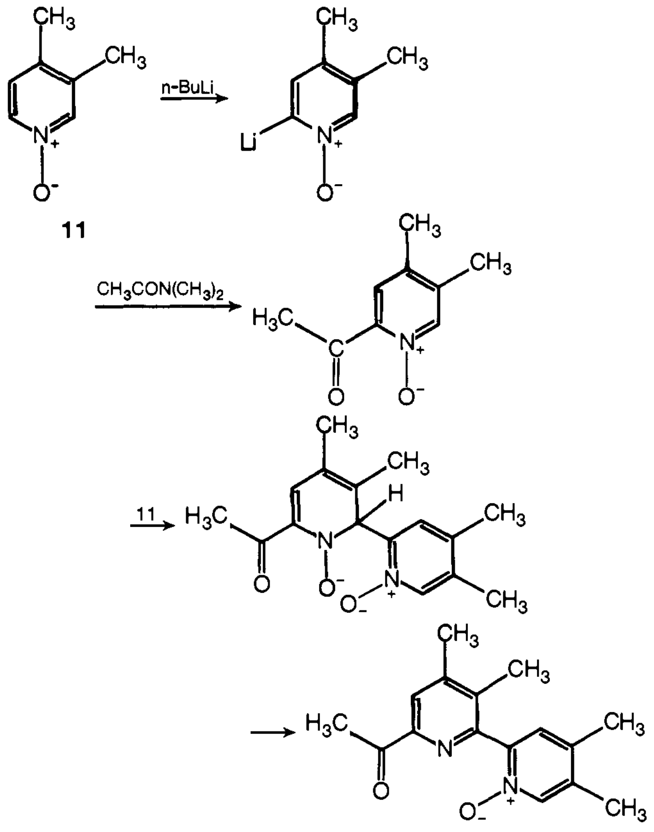
8 **7** **9**



10

The most extensive synthetic investigation of dipole-stabilized carbanions from amine oxides has been carried out by Abramovitch and co-workers who have shown a variety of 2-lithiopyridine *N*-oxides can be generated from the corresponding pyridine *N*-oxides and trapped in moderate yields by electrophiles.[18-20] Scheme III shows the general features of the reactions which are detailed in Table I. Chloro, methyl, and ethoxy substituents in the 3 and 4 positions do not interfere with the metalations. In the presence of a methyl at the 3 position, the incoming electrophile becomes attached to the 6 position. While some 2-lithiopyridine *N*-oxides undergo reaction with cyclohexanone to give either mono- or disubstitution, in most cases both products are formed. Trapping with carbon dioxide gives mono- and diacids. It has been suggested the disubstitution products could arise from the corresponding dianion, although alternative sequential reactions are also noted to be possible.[20] Reaction of the organometallic with oxygen or sulfur gives the corresponding *N*-hydroxythiopyridones and *N*-hydroxypyridones in low yields.[21] If the intermediate is trapped with bromine or chlorine the 2,6 dihalopyridine *N*-oxide is formed, although a 2,2′ dimer is also found on bromination.[21] Coupling also occurs with the organolithium produced from 3,4-dimethylpyridine *N*-oxide (**11**) on reaction with *N,N*-dimethylacetamide. Presumably, initial acylation is followed by nucleophilic addition to the 2 position of the adduct by a second molecule of the organometallic.[19] The diacylated product is also obtained. A similar reaction occurs between the intermediate from 4-chloro-3-methylpyridine *N*-oxide and benzonitrile.[19]

The selective removal of a proton from the 2 position of a 4-methyl-substituted pyridine-*N*-oxide, as illustrated by the conversion of **12** to **13** and **14**, is particularly interesting. The protons on methyl groups in the 2 and 4 positions of pyridine and pyridine *N*-oxide are relatively acidic and might be expected to



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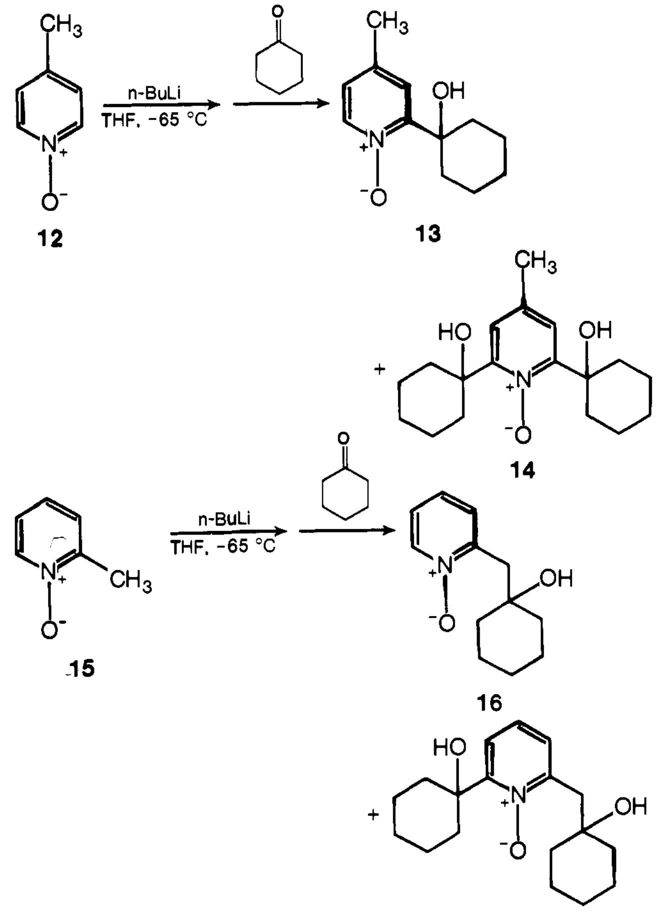


12

13

14

15

16

17

be removed by the base.[22] In fact, it is found that if lithium bis(trimethylsilyl)amide is used as the base for **11** in a similar sequence, approximately 3% of substitution on the C-4 methyl is observed to accompany the 4% yield of the 2-substituted product.[20] A similar metalation and substitution at both the 2 and the 2-methyl position is observed for the conversion of 2-methylpyridine *N*-oxide (**15**) to **16** and **17** in 4 and 20%, respectively. In this case a proximity effect in a complex formed between the oxygen of the amine oxide and the lithium of the base has been noted to be a possible factor in determining the site of metalation.

SCHEME III

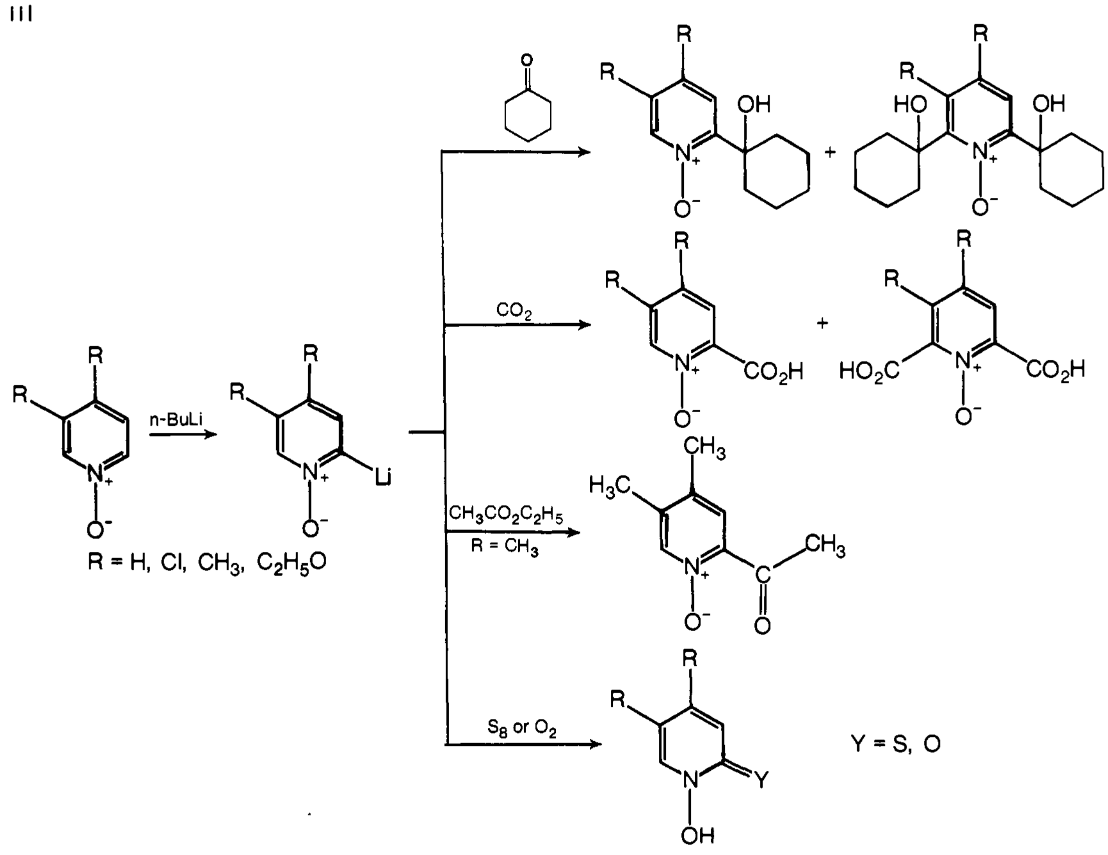
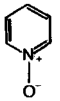
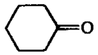
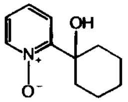
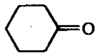
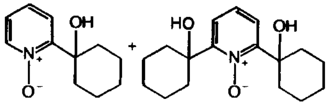
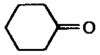
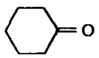
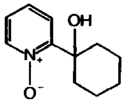
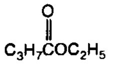
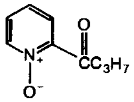
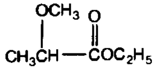
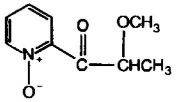
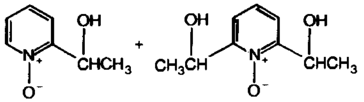
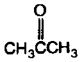
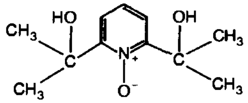
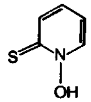
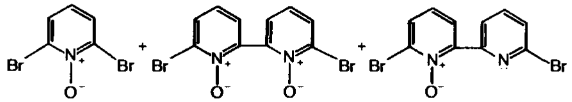
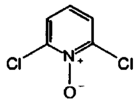
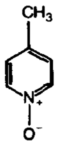
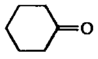
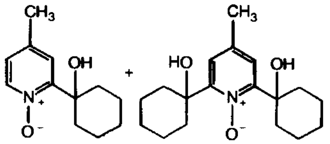


TABLE I. Formation and Reactions with Electrophiles of Lithiopyridine *N*-Oxides

Reactant	Base	Temp. °C	Solvent	Electrophile	Products	Yield, %	Ref
	*n*-BuLi	−65	Et_2O			7	20
	n-BuLi	−65	THF-Et_2O			5 + 15	20
	n-BuLi	Ambient	Et_2O		As above	12 + 36	20
	$[(CH_3)_3Si]_2NNa$	Reflux	C_6H_6			1	20
	n-BuLi	−65	THF	 $C_3H_7\overset{O}{\overset{\|}{C}}OC_2H_5$		55	19
	n-BuLi	−65	THF	 $CH_3\overset{OCH_3}{\overset{\mid}{C}}H—\overset{O}{\overset{\|}{C}}OC_2H_5$		56	19
	n-BuLi	−65	THF	CH_3CHO		36 + 30	20
	n-BuLi	−65	THF	 $CH_3\overset{O}{\overset{\|}{C}}CH_3$		18	20
	n-BuLi	−65	THF	S_8		8	21
	n-BuLi	−65	THF	Br_2		3 + 8 + 6	21
	n-BuLi	−65	Et_2O	Cl_2		5	21
	*n*-BuLi	−65	THF			21 + 27	20

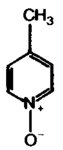
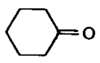
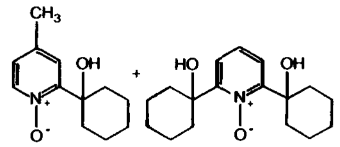
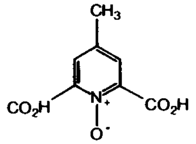
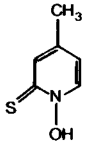
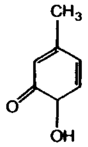
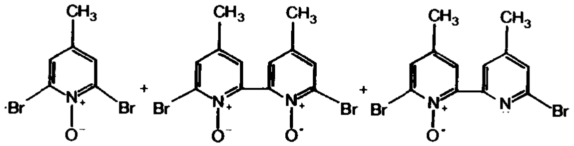
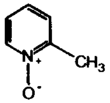
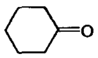
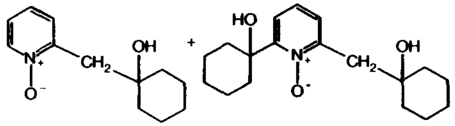
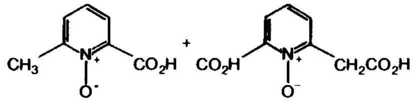
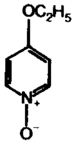
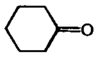
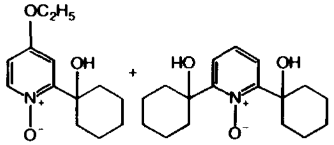
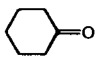
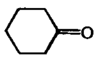
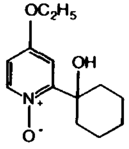
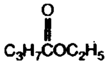
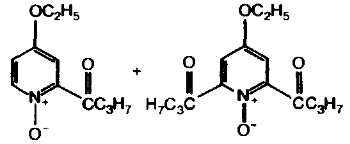
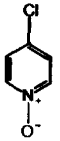
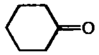
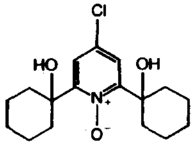
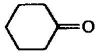
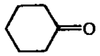
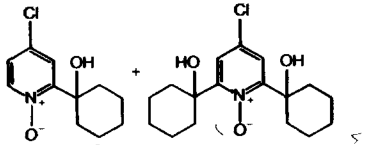
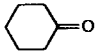
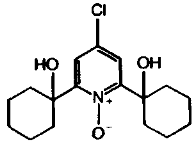
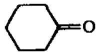
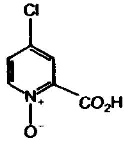
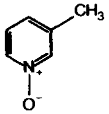
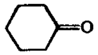
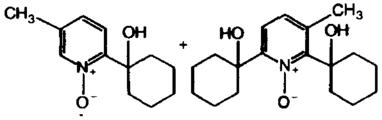
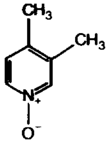
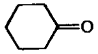
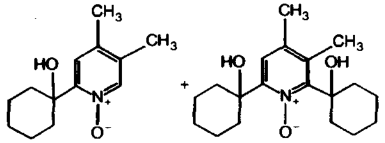
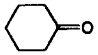
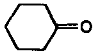
	*n*-BuLi	Ambient	Et_2O			20 + 25	20
	n-BuLi	−65	THF	CO_2		48	19
	n-BuLi	−65	THF	S_8		39	21
	n-BuLi	−65	THF	O_2		14	21
	n-BuLi	−65	THF	Br_2		5 + 13 + 18	21
	*n*-BuLi	−65	THF			4 + 20	20
	n-BuLi	−65	THF	CO_2		14 + 10	19
	*n*-BuLi	−65	Et_2O			4 + 12	20
	n-BuLi	−65	THF		As above	20 + 21	20
	NaH	Reflux	THF			8	20

TABLE I (*Continued*)

Reactant	Base	Temp, °C	Solvent	Electrophile	Products	Yield, %	Ref
	n-BuLi	−78	THF	 $C_3H_7\overset{O}{\overset{\|}{C}}OC_2H_5$		18 + 16	19
	*n*-BuLi	−100	Et_2O			11	20
	n-BuLi	−65	THF		As above	11	20
	n-BuLi	−65	Et_2O			36 + 21	20
	n-BuLi	−15	Et_2O			13	20
	n-BuLi	0	Et_2O		As above	7	20
	n-BuLi	−65	Et_2O	CO_2		49	19
	*n*-BuLi	−65	THF–Et_2O			25 + 8	20
	*n*-BuLi	−65	THF			39 + 12	20
	n-BuLi·TMEDA	−65	THF		As above	28 + 7	20
	CH_3Li	−65	THF		As above	47 + 9	20

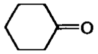
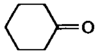
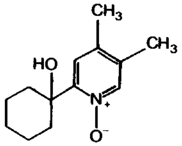
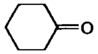
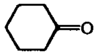
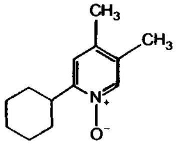
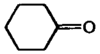
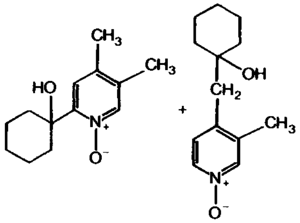
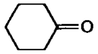
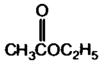
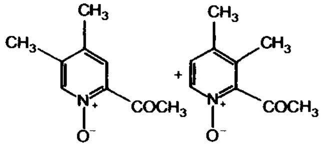
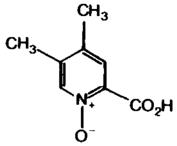
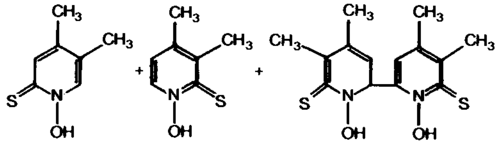
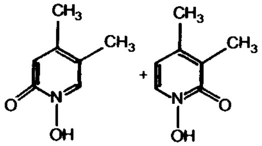
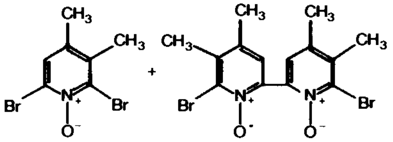
n-BuLi	−65	Et_2O		As above	56 + 16	20
$[(CH_3)_3Si]_2NNa$	Reflux	C_6H_6			2	20
$[(CH_3)_3Si]_2NNa$	Ambient	THF		As above	1	20
$[(CH_3)_3Si]_2NNa$	Reflux	THF			1	20
$[(CH_3)_3Si]_2NLi$	Ambient	Et_2O			4 + 3	20
$[(CH_3)_3Si]_2NLi$	Reflux	Et_2O		As above	5 + 3	20
n-BuLi	−78	THF	 $CH_3\overset{\overset{O}{\|}}{C}OC_2H_5$		20 + 6	19
n-BuLi	−65	THF	CO_2		18	19
n-BuLi	−65	THF	S_8		24 + 12 + 37	21
n-BuLi	−65	THF	O_2		14 + 10	21
n-BuLi	−65	THF	Br_2		13 + 4	21

TABLE I (*Continued*)

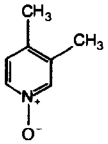
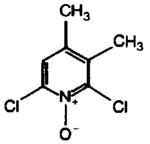
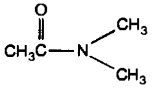
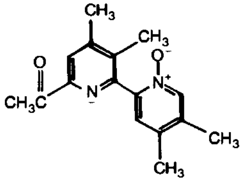
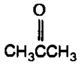
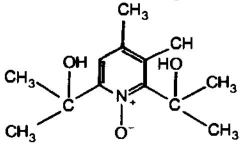
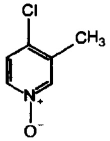
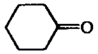
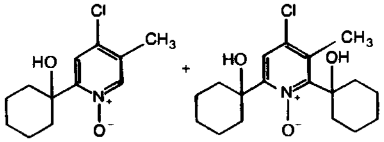
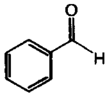
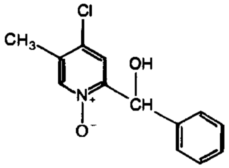
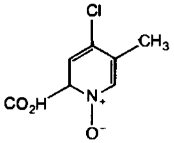
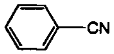
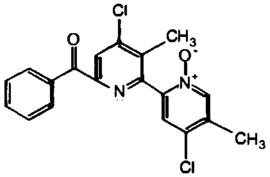
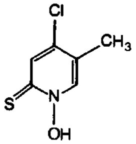
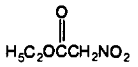
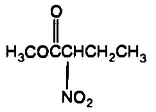
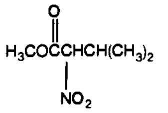
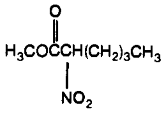
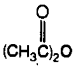
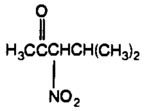
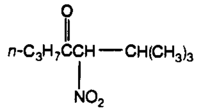
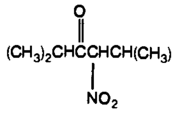
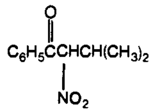
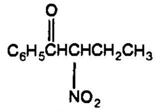
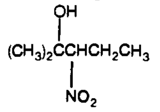
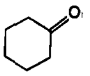
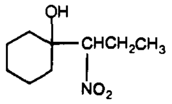
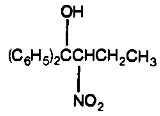
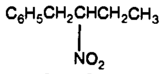
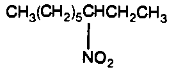
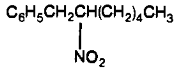
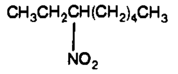
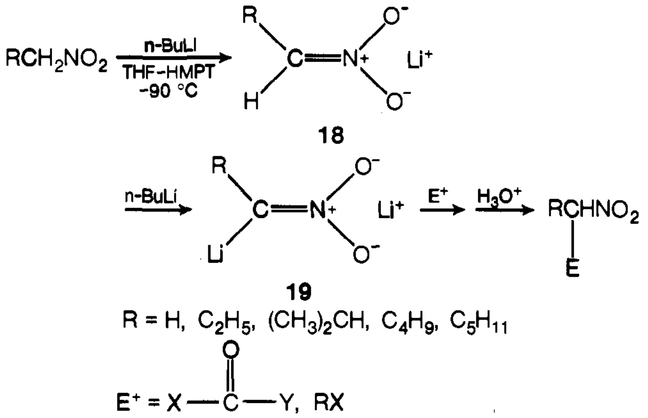
Reactant	Base	Temp, °C	Solvent	Electrophile	Products	Yield, %	Ref
	*n*-BuLi	−65	THF	Cl_2		9	21
	n-BuLi	−65	THF	 $CH_3C(=O)N(CH_3)_2$		13	19
	n-BuLi	−65	THF	 $CH_3C(=O)CH_3$		18	20
	*n*-BuLi	−65	Et_2O			44 + 5	20
	n-BuLi	−65	Et_2O			9	20
	n-BuLi	−65	Et_2O	CO_2		24	19
	n-BuLi	−78	THF			12	19
	n-BuLi	−65	THF	S_8		12	21

TABLE II. Formation and Reactions with Electrophiles of Dilithionitroalkanes

Reactant	Base	Temp, °C	Solvent	Electrophile	Product	Yield	Ref
CH_3NO_2	n-BuLi	−90	THF/HMPA	$(C_2H_5O)_2CO$	 $H_5C_2O\overset{\overset{O}{\|}}{C}CH_2NO_2$	65	23
$CH_3(CH_2)_2NO_2$	n-BuLi	−90	THF/HMPA	$(CH_3O)_2CO$	 $H_3CO\overset{\overset{O}{\|}}{C}\underset{\underset{NO_2}{|}}{C}HCH_2CH_3$	55	23
$(CH_3)_2CHCH_2NO_2$	n-BuLi	−90	THF/HMPA	CH_3OCOCl	 $H_3CO\overset{\overset{O}{\|}}{C}\underset{\underset{NO_2}{|}}{C}HCH(CH_3)_2$	65	23
$CH_3(CH_2)_4NO_2$	n-BuLi	−90	THF/HMPA	$(CH_3O)_2CO$	 $H_3CO\overset{\overset{O}{\|}}{C}\underset{\underset{NO_2}{|}}{C}H(CH_2)_3CH_3$	65	23
$(CH_3)_2CHCH_2NO_2$	n-BuLi	−90	THF/HMPA	 $(CH_3\overset{\overset{O}{\|}}{C})_2O$	 $H_3C\overset{\overset{O}{\|}}{C}\underset{\underset{NO_2}{|}}{C}HCH(CH_3)_2$	30	23
$(CH_3)_2CHCH_2NO_2$	n-BuLi	−90	THF/HMPA	$n\text{-}C_3H_7CO_2CH_3$	 $n\text{-}C_3H_7\overset{\overset{O}{\|}}{C}\underset{\underset{NO_2}{|}}{C}H\text{—}CH(CH_3)_3$	60	23
$(CH_3)_2CHCH_2NO_2$	n-BuLi	−90	THF/HMPA	$(CH_3)_2CHCO_2CH_3$	 $(CH_3)_2CH\overset{\overset{O}{\|}}{C}\underset{\underset{NO_2}{|}}{C}HCH(CH_3)_2$	75	23
$(CH_3)_2CHCH_2NO_2$	n-BuLi	−90	THF/HMPA	$C_6H_5CO_2CH_3$	 $C_6H_5\overset{\overset{O}{\|}}{C}\underset{\underset{NO_2}{|}}{C}HCH(CH_3)_2$	75	23
$CH_3(CH_2)_2NO_2$	n-BuLi	−90	THF/HMPA	C_6H_5CHO	 $C_6H_5\overset{\overset{O}{\|}}{C}H\underset{\underset{NO_2}{|}}{C}HCH_2CH_3$	80	23
$CH_3(CH_2)_2NO_2$	n-BuLi	−90	THF/HMPA	CH_3COCH_3	 $(CH_3)_2\overset{\overset{OH}{|}}{C}\underset{\underset{NO_2}{|}}{C}HCH_2CH_3$	40	23
$CH_3(CH_2)_2NO_2$	n-BuLi	−90	THF/HMPA			65	23
$CH_3(CH_2)_2NO_2$	n-BuLi	−90	THF/HMPA	$C_6H_5COC_6H_5$	 $(C_6H_5)_2\overset{\overset{OH}{|}}{C}\underset{\underset{NO_2}{|}}{C}HCH_2CH_3$	65	23
CH_3NO_2	n-BuLi	−90	THF/HMPA	$n\text{-}C_6H_{13}I$	$n\text{-}C_7H_{15}NO_2$	35	23
$CH_3(CH_2)_2NO_2$	n-BuLi	−90	THF/HMPA	$C_6H_5CH_2Br$	 $C_6H_5CH_2\underset{\underset{NO_2}{|}}{C}HCH_2CH_3$	53	23
$CH_3(CH_2)_2NO_2$	n-BuLi	−90	THF/HMPA	$n\text{-}C_6H_{13}I$	 $CH_3(CH_2)_5\underset{\underset{NO_2}{|}}{C}HCH_2CH_3$	51	23
$CH_3(CH_2)_5NO_2$	n-BuLi	−90	THF/HMPA	$C_6H_5CH_2Br$	 $C_6H_5CH_2\underset{\underset{NO_2}{|}}{C}H(CH_2)_4CH_3$	60	23
$CH_3(CH_2)_5NO_2$	n-BuLi	−90	THF/HMPA	C_2H_5I	 $CH_3CH_2\underset{\underset{NO_2}{|}}{C}H(CH_2)_4CH_3$	50	23

The synthetic use of 2-lithiopyridine *N*-oxides obtained by direct metalation is well established. If mono- and disubstitution can be controlled and if deoxygenation could be incorporated into a substitution sequence, this approach could prove generally very useful in pyridine synthesis.

A particularly interesting analogy to carbanion formation activated by the dipole of an adjacent amine oxide function is provided by the double deprotonation of nitroalkanes recently reported by Seebach and Lehr.[23] In this case, removal of the first proton presumably gives the intermediate **18** which has an sp^2 carbon bearing a hydrogen adjacent to the positive nitrogen of the dipole. Subsequent removal of the proton then gives the organometallic **19** in which the formal negative charge of the carbon-metal bond is in a sp^2 orbital orthogonal to the delocalized anion in the π system. Acylation and alkylation occurs on carbon in yields of 30–80% as shown in Table II. The avail-



18

19

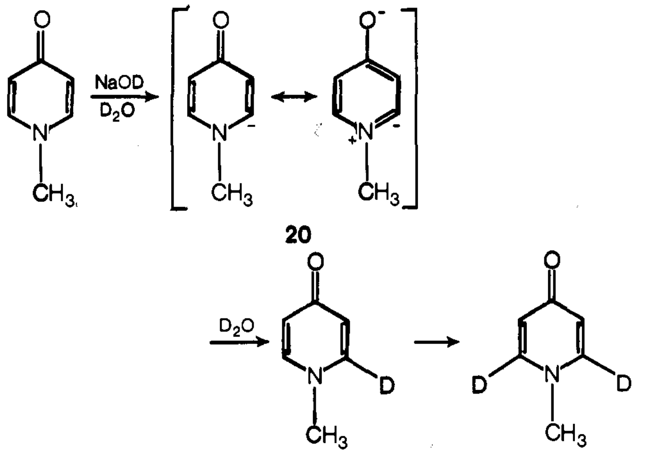
R = H, C_2H_5, $(CH_3)_2CH$, C_4H_9, C_5H_{11}

$E^+ = X—C(=O)—Y$, RX

able conversions of the nitro function to an amine by reduction or to a ketone by the Nef reaction suggests this approach may be particularly useful synthetically.

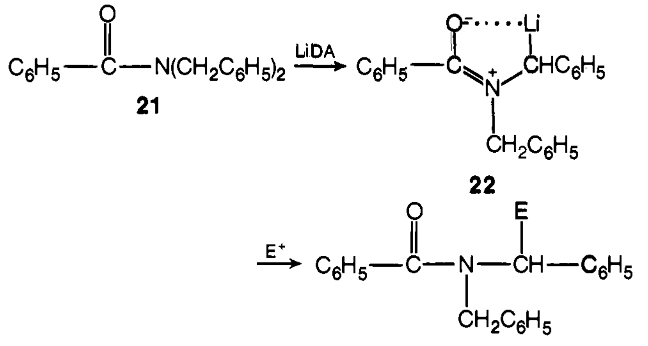
B. Amides

An early suggestion of the importance of stabilization of a carbanion by a dipole was the proposal that the base-catalyzed deuterium exchange of *N*-methyl-4-pyridone at the 2 and 6 positions involves **20**, termed at the time a "mesionic ylide".[24] The intermediacy of **20** was supported by kinetic and isotope effect studies, and similar species have been proposed in the exchange deuterations of *N*-methyl-2-pyridone,[25] some pyrimidones and the corresponding nucleosides,[26] and a vinylogous amide-sulfoxamide.[27] In support of the importance of dipole stabilization for **20**, it was shown that *N*-methylpyrrole is inert to the conditions of the reaction, while the 4-methoxy-*N*-methylpyridinium ion undergoes exchange of the 2 and 6 protons more readily than does *N*-methyl-4-pyridone. The structural limitations for delocalization of the sp^2 anion and the probability that the sodium ion does not play a role in the aqueous medium suggest the acidity of the exchangeable hydrogens stems from inductive and hybridization factors.[24]



20

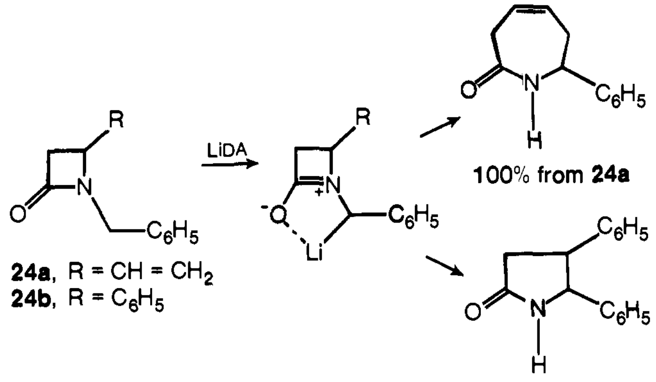
The first case in which a trappable α-amidoaza carbanion is formed was reported by Fraser et al. for *N,N*-dibenzylbenzamide (**21**).[28] Reaction of **21** with methyllithium or lithium diisopropylamide at −78 °C provides **22** which gives the products **23** in yields of 66–99%. A similar intermediate was proposed by Durst et al. to explain the ring enlargements of the benzyl β-lactams **24**.[29] In these cases, however, stabilization of the carbanion by delocalization into the aromatic ring could contribute significantly to the organolithium intermediates.



21

22

23, E = CH_3, CO_2H, $-COH(CH_3)_2$, CH_3CO-



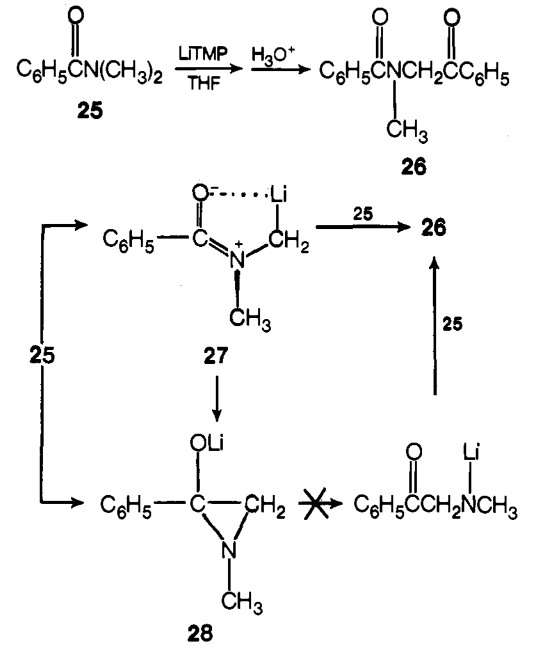
24a, R = CH = CH_2

24b, R = C_6H_5

100% from **24a**

93% from **24b**

A formal carbanion for which there is no stabilization beyond that provided by the amide function is **27**, the proposed intermediate in the conversion of *N,N*-dimethylbenzamide (**25**) to *N*-phenacylbenzamide (**26**) in 53% yield with lithium tetramethylpiperidide (LiTMP).[30] The possibility that the reaction involves formation and ring opening of a homoenolate anion **28** prior to reaction with **25** rather than the dipole-stabilized carbanion **27** was ruled out by a double-labeling experiment which revealed the carbon-nitrogen bonds of the reactant remained intact in the product.[30]



25

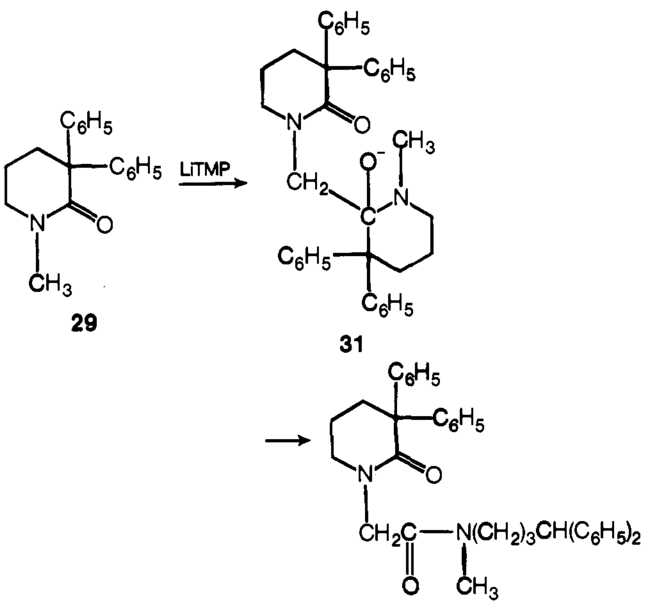
26

27

28

Reaction of the cyclic amide **29** to give **30** via **31** shows that the metalated methyl group can be syn to the carbonyl group. Moreover, because the reaction of **25** is lithium ion dependent, it has been suggested that the transition state leading to **27** has the base oriented toward the syn group in nitrogen because of prior complexation of the lithium of the LiTMP with the carbonyl oxygen.[30] Such an effect would also increase the positive charge on nitrogen in the transition state for proton removal.

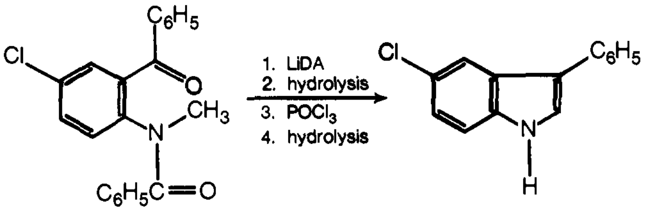
A synthetically useful sequence in which an analogous intermediate is probably involved is the conversion of the **32** to the indole **33** in 30% yield by a cyclization, hydrolysis, and dehydration.[31] The first step of the processes probably involves metalation of the amide methyl group by lithium diisopropylamide (LiDA).



29

31

30

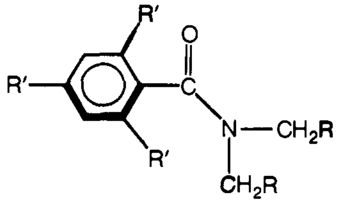


32

33

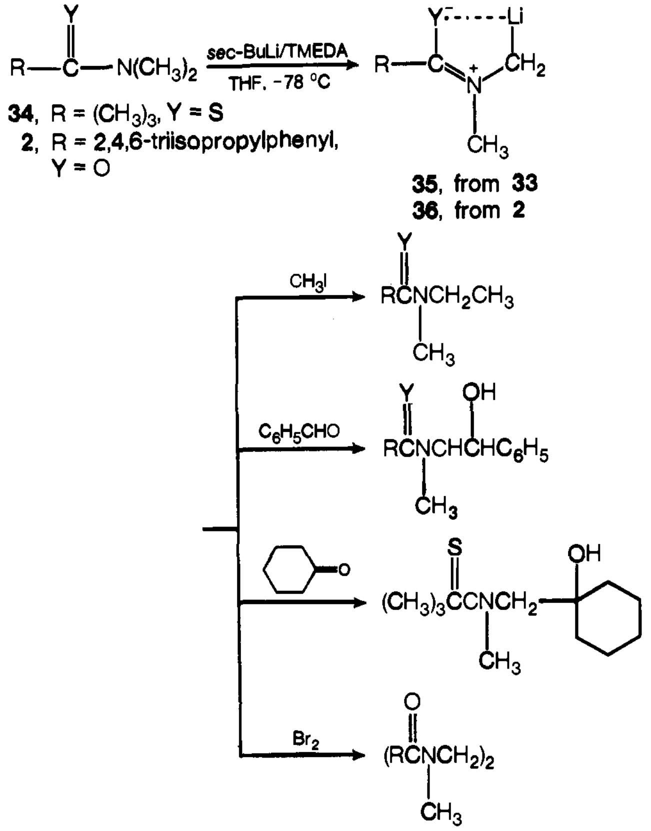
Recently a number of cases have been reported which involve a formally dipole-stabilized carbanion adjacent to the nitrogen of an amide, which can be trapped with a variety of subsequently added electrophiles. Seebach and Lubosch[32] have found that *N,N*-dimethylpivalthioamide (**34**) provides the intermediate **35**, and Beak, McKinnie, and Reitz[1,33] have reported that the benzamide **2** gives the intermediate **36**. Both **35** and **36** can be subsequently reacted with electrophiles as summarized in Scheme IV and detailed in Table III. In the latter case the ortho substitution was chosen to provide steric hindrance to the nucleophilic attack at the carbonyl which was observed with dimethylbenzamide (vide supra).[1] The substituents also block a position of potential acidity[34] and impose unfavorable strain in the possible transition states for benzylic proton removal.

The barrier to rotation about the carbon-nitrogen bond is raised by the ortho substituents to the point that the isomers do not equilibrate on the laboratory time scale.[35] From the chemical shifts of the substituents on nitrogen it can be established that metalation and electrophilic substitution occur only on the methyl of **2** which is syn to the carbonyl oxygen.[33,36] That result can be taken to further support the chelate structure assigned to **36**.



2, R = H; R′ = CH(CH$_3$)$_2$
37, R = CH$_3$; R′ = CH(CH$_3$)$_2$

SCHEME IV

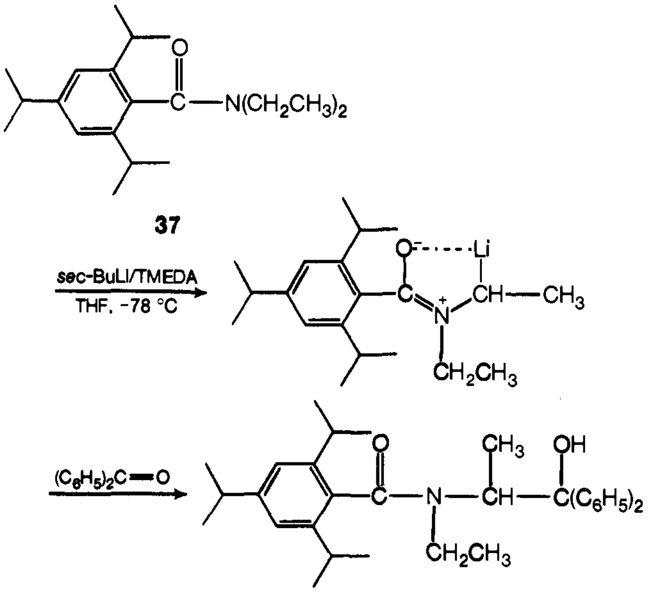


34, R = (CH$_3$)$_3$, Y = S
2, R = 2,4,6-triisopropylphenyl, Y = O

35, from **33**
36, from **2**

Derivatives of the thioamide **34** may be hydrolyzed to secondary amines and reduced to neopentylamines. This case appears then synthetically useful as optimal in Scheme II. The benzamides derived from **36**, however, are not easily hydrolyzed. The fact that *N,N*-diethyl-2,4,6-triisopropylbenzamide (**37**) undergoes metalation to give a dipole-stabilized species which can be trapped by benzophenone in 55% yield is particularly interesting and suggests further study is warranted.

The generation and trapping of the α-aza carbanions **38** from the imides **39a–d** have been reported by Schlecker and Seebach.[37] In cases **38a**, **38b**, and **38c** there is substantial self-condensation, although some deuteration can be achieved. With **38d** steric hindrance again seems to be important and trapping with a variety of electrophiles is possible although the products are also accompanied by the product of self-trapping as summarized in Table III. The equilibration of **38d** with diphenyl-



37

TABLE III. Formation of Lithioalkylamides, Lithiomethylthioamides, and Lithiomethylsuccinimides and Reactions with Electrophiles

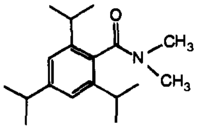
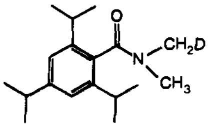
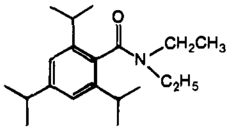
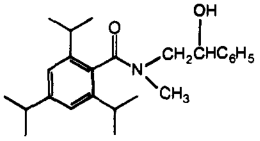
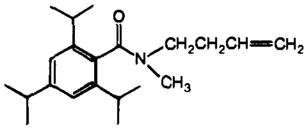
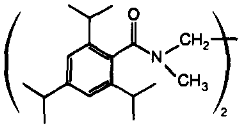
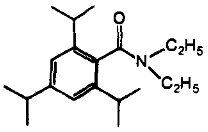
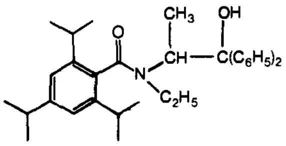
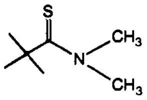
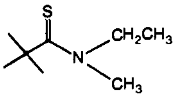
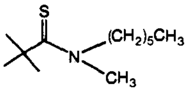
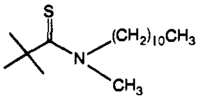
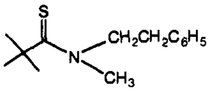
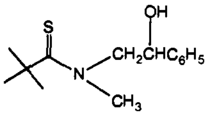
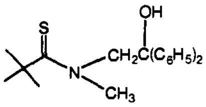
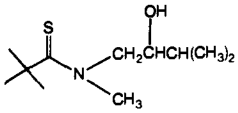
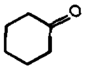
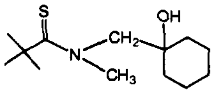
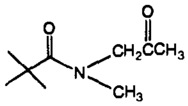
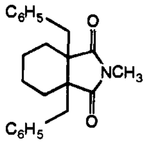
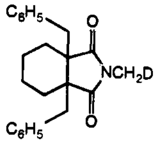
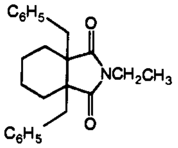
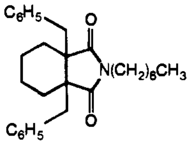
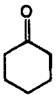
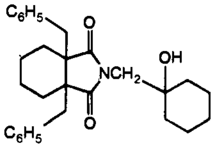
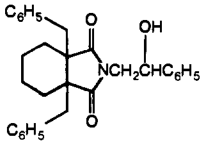
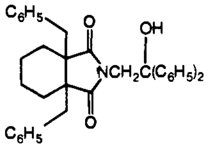
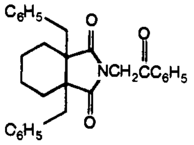
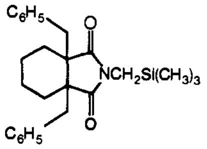
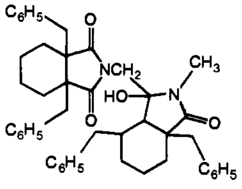
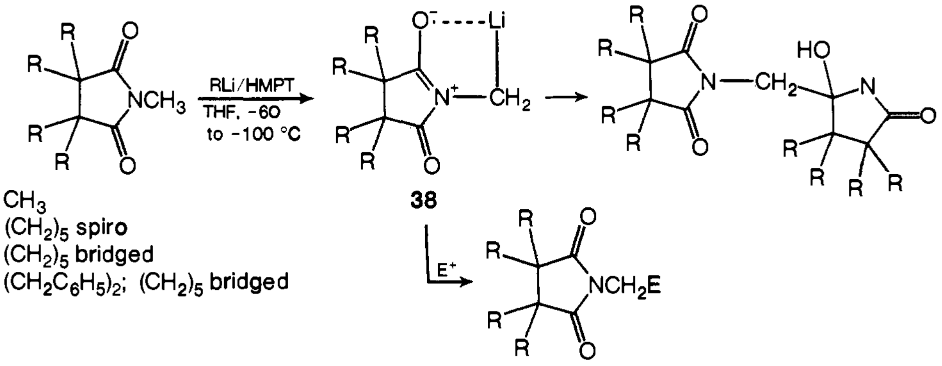
Reactant	Base	Temp, °C	Solvent	Electrophile	Products	Yield, %	Ref
	sec-BuLi·TMEDA	−78	THF	CD_3OD		82	1
	sec-BuLi·TMEDA	−78	THF	CH_3I		77	1
	sec-BuLi·TMEDA	−78	THF	C_6H_5CHO		75	1
	sec-BuLi·TMEDA	−78	THF	$BrCH_2CH{=}CH_2$		58	1
	sec-BuLi·TMEDA	−78	THF	Br_2		57	1
	sec-BuLi·TMEDA	−45	THF	$(C_6H_5)_2CO$		55	1
	sec-BuLi·TMEDA	−78	THF	CH_3I		80	32
	sec-BuLi·TMEDA	−78	THF	n-$C_5H_{11}I$		82	32
	sec-BuLi·TMEDA	−78	THF	n-$C_{10}H_{21}Br$		79	32
	sec-BuLi·TMEDA	−78	THF	$C_6H_5CH_2Br$		44	32
	sec-BuLi·TMEDA	−78	THF	C_6H_5CHO		70	32
	sec-BuLi·TMEDA	−78	THF	$(C_6H_5)_2CO$		63	32
	sec-BuLi·TMEDA	−78	THF	$(CH_3)_2CHCHO$		23	32
	sec-BuLi·TMEDA	−78	THF			17	32
	sec-BuLi·TMEDA	−78	THF	$CH_3CON(CH_3)_2$		33	32

TABLE III. (*Continued*)

Reactant	Base	Temp, °C	Solvent	Electrophile	Products	Yield, %	Ref
	*sec*-BuLi	−100	THF/HMPA	D_2O		80[a]	37
	sec-BuLi	−100	THF/HMPA	CH_3I		57[a]	37
	sec-BuLi	−100	THF/HMPA	n-$C_6H_{13}I$		47[a]	37
	sec-BuLi	−100	THF/HMPA			73[a]	37
	sec-BuLi	−100	THF/HMPA	C_6H_5CHO		54[a]	37
	sec-BuLi	−100	THF/HMPA	$(C_6H_5)_2CO$		43[a]	37
	sec-BuLi	−100	THF/HMPA	$C_6H_5CO_2CH_3$		42[a]	37
	sec-BuLi	−100	THF/HMPA	$ClSi(CH_3)_3$		30[a]	37

[a] The dimer  was produced in ~20% yield.



39a, R = CH$_3$
39b, R = (CH$_2$)$_5$ spiro
39c, R = (CH$_2$)$_5$ bridged
39d, R = (CH$_2$C$_6$H$_5$)$_2$; (CH$_2$)$_5$ bridged

TABLE IV. Formation of Carbamoyllithium and Thiocarbamoyllithium Reagents and Reactions with Electrophiles

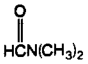
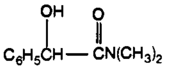
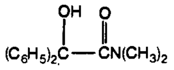
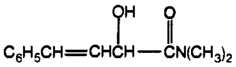
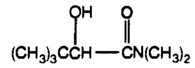
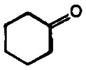
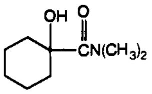
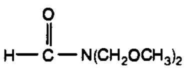
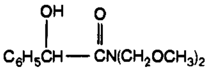
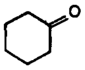
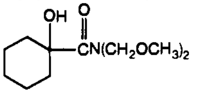
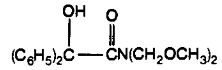
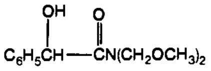
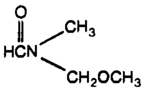
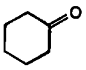
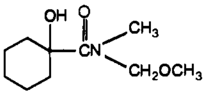
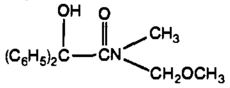
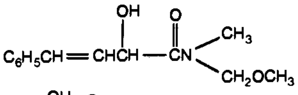
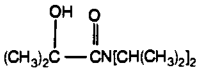
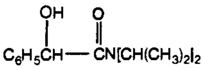
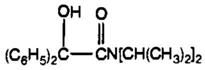
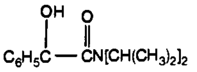
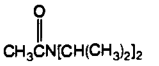
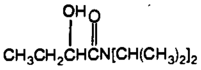
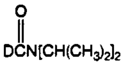
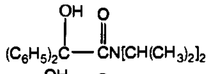
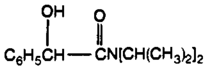
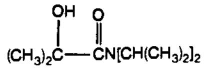
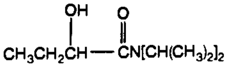
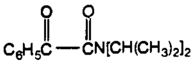
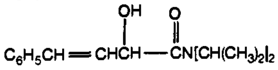
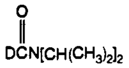
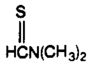
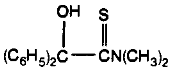
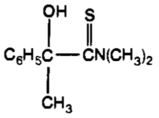
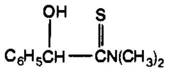
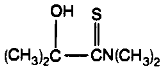
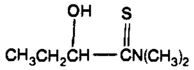
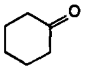
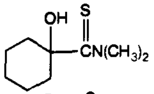
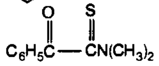
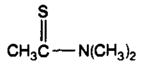
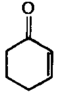
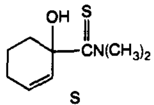
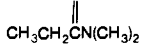
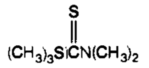
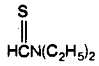
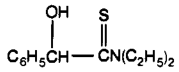
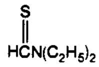
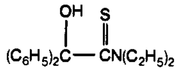
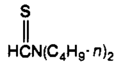
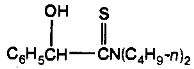
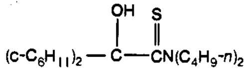
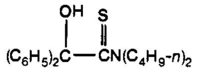
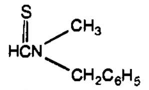
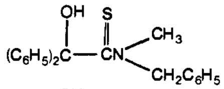
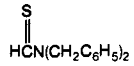
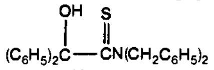
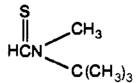
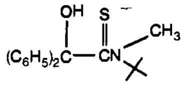
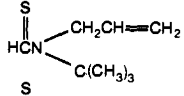
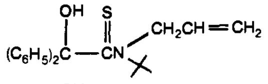
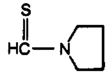
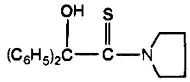
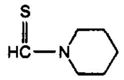
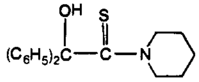
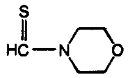
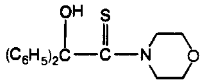
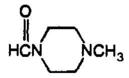
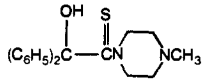
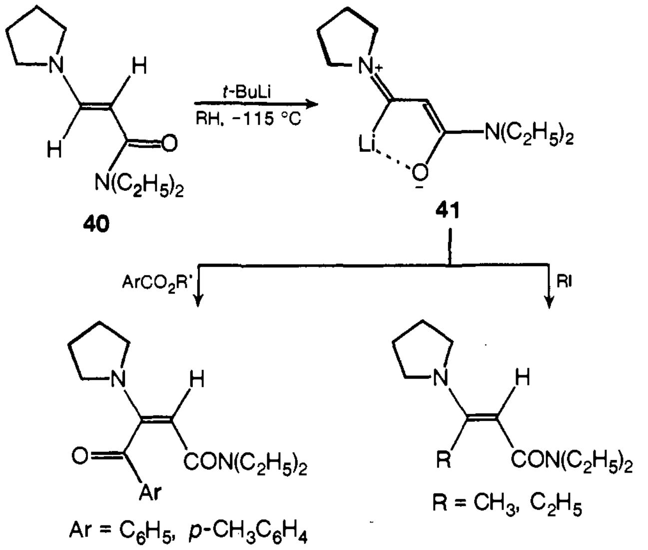
Reactant	Base	Temp, °C	Solvent	Electrophile	Product	Yield, %	Ref
 $H\overset{O}{\overset{\|}{C}}N(CH_3)_2$	LIDA	−78	THF/Et$_2$O	C_6H_5CHO	 $C_6H_5\overset{OH}{\overset{\|}{C}}H-\overset{O}{\overset{\|}{C}}N(CH_3)_2$	45	40
	LIDA	−78	THF/Et$_2$O	$(C_6H_5)_2CO$	 $(C_6H_5)_2\overset{OH}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}N(CH_3)_2$	85	40
	LIDA	−78	THF/Et$_2$O	$C_6H_5CH{=}CHCHO$	 $C_6H_5CH{=}CH\overset{OH}{\overset{\|}{C}}H-\overset{O}{\overset{\|}{C}}N(CH_3)_2$	89	40
	LIDA	−78	THF/Et$_2$O	$(CH_3)_3CCHO$	 $(CH_3)_3C\overset{OH}{\overset{\|}{C}}H-\overset{O}{\overset{\|}{C}}N(CH_3)_2$	66	40
	LIDA	−78	THF/Et$_2$O			62	40
 $H-\overset{O}{\overset{\|}{C}}-N(CH_2OCH_3)_2$	LIDA	−75	THF	C_6H_5CHO	 $C_6H_5\overset{OH}{\overset{\|}{C}}H-\overset{O}{\overset{\|}{C}}N(CH_2OCH_3)_2$	74	40
	LIDA	−75	THF			44	40
	LIDA	−75	THF	$(C_6H_5)_2CO$	 $(C_6H_5)_2\overset{OH}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}N(CH_2OCH_3)_2$	88	40
	LIDA	−75	THF	C_6H_5CHO	 $C_6H_5\overset{OH}{\overset{\|}{C}}H-\overset{O}{\overset{\|}{C}}N(CH_2OCH_3)_2$	76	40
	LIDA	−75	THF			39	40
	LIDA	−75	THF	$(C_6H_5)_2CO$		85	40
	LIDA	−75	THF	$C_6H_5CH{=}CHCHO$		40	40
	LIDA	−78	THF	$(CH_3)_2CO$	 $(CH_3)_2\overset{OH}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}N[CH(CH_3)_2]_2$	30	42
	LIDA	−78	THF	C_6H_5CHO	 $C_6H_5\overset{OH}{\overset{\|}{C}}H-\overset{O}{\overset{\|}{C}}N[CH(CH_3)_2]_2$	51	42
	LIDA	−78	THF	$(C_6H_5)_2CO$	 $(C_6H_5)_2\overset{OH}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}N[CH(CH_3)_2]_2$	92	42
	LIDA	−78	THF	$C_6H_5CO_2C_2H_5$	 $C_6H_5\overset{OH}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}N[CH(CH_3)_2]_2$	45	42
	LIDA	−78	THF	CH_3I	 $CH_3\overset{O}{\overset{\|}{C}}N[CH(CH_3)_2]_2$	20	42
	LIDA	−78	THF	CH_3CH_2CHO	 $CH_3CH_2\overset{OH}{\overset{\|}{C}}H\overset{O}{\overset{\|}{C}}N[CH(CH_3)_2]_2$	41	42
	LIDA	−78	THF	D_2O	 $D\overset{O}{\overset{\|}{C}}N[CH(CH_3)_2]_2$	70	42
	t-BuLi	−95	THF/Et$_2$O	$(C_6H_5)_2CO$	 $(C_6H_5)_2\overset{OH}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}N[CH(CH_3)_2]_2$	85	43
	t-BuLi	−95	THF/Et$_2$O	C_6H_5CHO	 $C_6H_5\overset{OH}{\overset{\|}{C}}H-\overset{O}{\overset{\|}{C}}N[CH(CH_3)_2]_2$	80	43
	t-BuLi	−95	THF/Et$_2$O	$(CH_3)_2CO$	 $(CH_3)_2\overset{OH}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}N[CH(CH_3)_2]_2$	81	43
	t-BuLi	−95	THF/Et$_2$O	CH_3CH_2CHO	 $CH_3CH_2\overset{OH}{\overset{\|}{C}}H-\overset{O}{\overset{\|}{C}}N[CH(CH_3)_2]_2$	62	43
	t-BuLi	−95	THF/Et$_2$O	$C_6H_5CO_2C_2H_5$	 $C_6H_5\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}N[CH(CH_3)_2]_2$	70	43
	t-BuLi	−95	THF/Et$_2$O	$C_6H_5CH{=}CHCHO$	 $C_6H_5CH{=}CH\overset{OH}{\overset{\|}{C}}H-\overset{O}{\overset{\|}{C}}N[CH(CH_3)_2]_2$	68	43

TABLE IV (*Continued*)

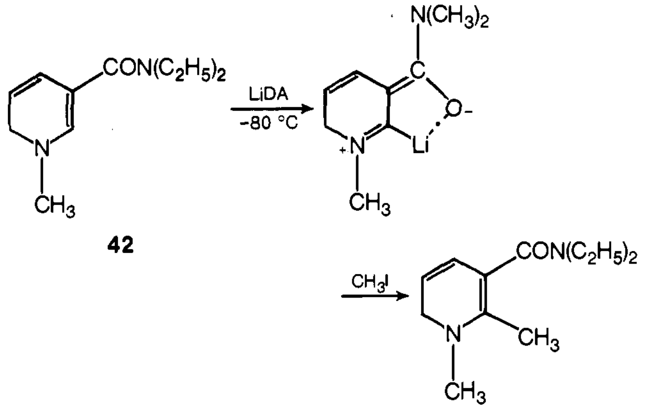
Reactant	Base	Temp, °C	Solvent	Electrophile	Product	Yield, %	Ref
	t-BuLi	−95	THF/Et$_2$O	D$_2$O	 $D\overset{O}{C}N[CH(CH_3)_2]_2$	70	43
 $H\overset{S}{C}N(CH_3)_2$	LIDA	−100	THF	$(C_6H_5)_2CO$	 $(C_6H_5)_2\overset{OH}{C}-\overset{S}{C}N(CH_3)_2$	85	41
	LIDA	−100	THF	$C_6H_5COCH_3$	 $C_6H_5\underset{CH_3}{\overset{OH}{C}}-\overset{S}{C}N(CH_3)_2$	65	41
	LIDA	−100	THF	C_6H_5CHO	 $C_6H_5\overset{OH}{C}H-\overset{S}{C}N(CH_3)_2$	75	41
	LIDA	−100	THF	$(CH_3)_2CO$	 $(CH_3)_2\overset{OH}{C}-\overset{S}{C}N(CH_3)_2$	85	41
	LIDA	−100	THF	CH_3CH_2CHO	 $CH_3CH_2\overset{OH}{C}H-\overset{S}{C}N(CH_3)_2$	80	41
	LIDA	−100	THF			65	41
	LIDA	−100	THF	$C_6H_5CO_2CH_3$	 $C_6H_5\overset{O}{C}-\overset{S}{C}N(CH_3)_2$	85	41
	LIDA	−100	THF	CH_3I	 $CH_3\overset{S}{C}-N(CH_3)_2$	50	41
	LIDA	−100	THF			50	41
	LIDA	−100	THF	C_2H_5I	 $CH_3CH_2\overset{S}{C}N(CH_3)_2$	48	41
	LIDA	−100	THF	$(CH_3)_3SiCl$	 $(CH_3)_3Si\overset{S}{C}N(CH_3)_2$	36	41
 $H\overset{S}{C}N(C_2H_5)_2$	LIDA	−100	THF	C_6H_5CHO	 $C_6H_5\overset{OH}{C}H-\overset{S}{C}N(C_2H_5)_2$	70	41
 $H\overset{S}{C}N(C_2H_5)_2$	LIDA	−100	THF	$(C_6H_5)_2CO$	 $(C_6H_5)_2\overset{OH}{C}-\overset{S}{C}N(C_2H_5)_2$	83	41
 $H\overset{S}{C}N(C_4H_9\text{-}n)_2$	LIDA	−100	THF	C_6H_5CHO	 $C_6H_5\overset{OH}{C}H-\overset{S}{C}N(C_4H_9\text{-}n)_2$	45	41
	LIDA	−100	THF	$(c\text{-}C_6H_{11})_2CO$	 $(c\text{-}C_6H_{11})_2-\overset{OH}{C}-\overset{S}{C}N(C_4H_9\text{-}n)_2$	62	41
	LIDA	−100	THF	$(C_6H_5)_2CO$	 $(C_6H_5)_2\overset{OH}{C}-\overset{S}{C}N(C_4H_9\text{-}n)_2$	10	41
 $H\overset{S}{C}N(CH_3)(CH_2C_6H_5)$	LIDA	−100	THF	$(C_6H_5)_2CO$	 $(C_6H_5)_2\overset{OH}{C}-\overset{S}{C}N(CH_3)(CH_2C_6H_5)$	79	41
 $H\overset{S}{C}N(CH_2C_6H_5)_2$	LIDA	−100	THF	$(C_6H_5)_2CO$	 $(C_6H_5)_2\overset{OH}{C}-\overset{S}{C}N(CH_2C_6H_5)_2$	70	41
 $H\overset{S}{C}N(CH_3)C(CH_3)_3$	LIDA	−100	THF	$(C_6H_5)_2CO$		55	41
 $H\overset{S}{C}N(CH_2CH{=}CH_2)C(CH_3)_3$	LIDA	−100	THF	$(C_6H_5)_2CO$		54	41
	LIDA	−100	THF	$(C_6H_5)_2CO$		77	41
	LIDA	−100	THF	$(C_6H_5)_2CO$		79	41
	LIDA	−100	THF	$(C_6H_5)_2CO$		68	41
	LIDA	−100	THF	$(C_6H_5)_2CO$		60	41

methane has been observed, and the pK of **39**d has been estimated on the basis of deuterium trapping experiments to be in the range of 31–35.[37]

Vinylogous α-amido carbanions analogous to **20** have been recently reported by Schmidt and Talbiersky from the metalation of β-acylenamines. The reaction of *N*,*N*-diethylpyrrolidinoacrylamide (**40**) with *tert*-butyllithium at −115 °C is reported to give an intermediate **41** which can be subsequently benzylated or alkylated in good yields.[38] It is especially interesting that metalation is reported to occur α to nitrogen rather than α to the carbonyl group of **40**. The same laboratory has also reported the lithiations, deuterations, and methylations of 3-cyano- and 3-amidodihydropyridines.[39] For example, **42** can be lithiated at the 2 position followed by methylation to give 81% **43**.



40 **41**

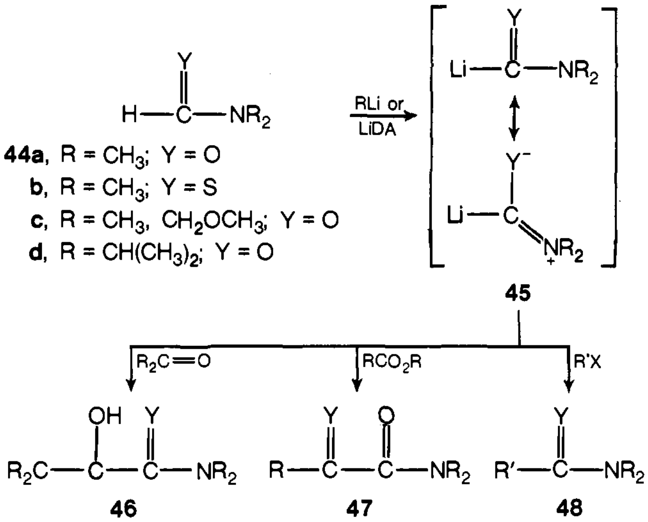


42 **43**

Formal acyl anions have proven very useful synthetically. These species usually are produced in masked form and discussed as synthetic equivalents. However, direct removal of a formyl proton from the formamide **44** gives **45**, an acyl anion in unmasked form.[40–43] Table IV provides the details of the conversions of **45** to α-hydroxy amides **46**, α-keto amides **47**, and amides **48** shown in Scheme V. Reduction of the α-hydroxythioamides **46**, Y = S, gives β-amino alcohols; for example, *N*,*N*-dimethylthioformamide can be converted to 1,1-diphenyl-2-dimethylaminoethanol in 66% yield by this sequence. Thus **44** can be used to achieve the nucleophilic amino alkylation of a ketone in two steps.

An interesting prospectively dipole-stabilized carbanion is the synthetically useful bridgehead species **50** formed by metalation of **49**. The anion has been used by Kishi et al. in elegant syntheses of dehydroliotoxin, gliotoxin, and sporidesmin A.[44] Although the importance of the α-sulfur (vide infra) and the inductive effect of the carbonyl should not be discounted, analogy to the above cases suggests dipolar stabilization by the positive nitrogen could also be important in the formation and stability of **50**. If that is accepted, it can be speculated that the differences noted in the acidities of the bridgehead hydrogens of **49** might be attributable to torsional differences in the transition states leading to **50**. Differential twisting, which could be induced by the different relationship of the amide bonds to the dithione ring, could result in different degrees of positive charge on nitrogen and the resulting different acidities. It is clear that complexation of the amide in the same manner as suggested above is not possible in this case and it appears difficult to distinguish this effect from the suggested geometrical dependence of p-d overlap with sulfur.[44]

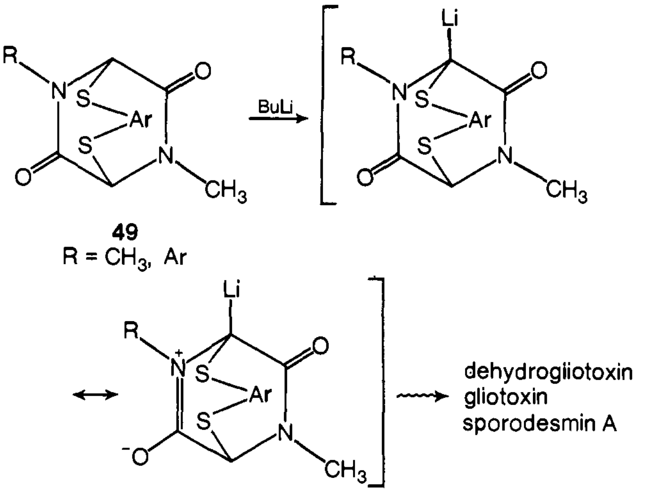
SCHEME V



44a, R = CH_3; Y = O
b, R = CH_3; Y = S
c, R = CH_3, CH_2OCH_3; Y = O
d, R = $CH(CH_3)_2$; Y = O

45

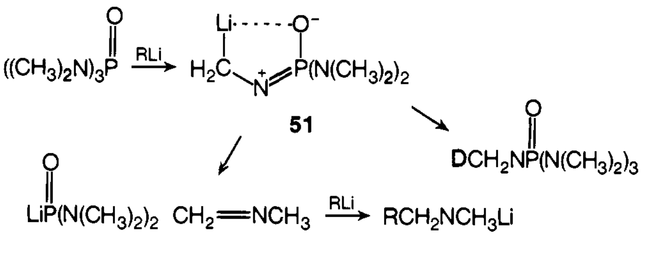
46 **47** **48**



49
R = CH_3, Ar

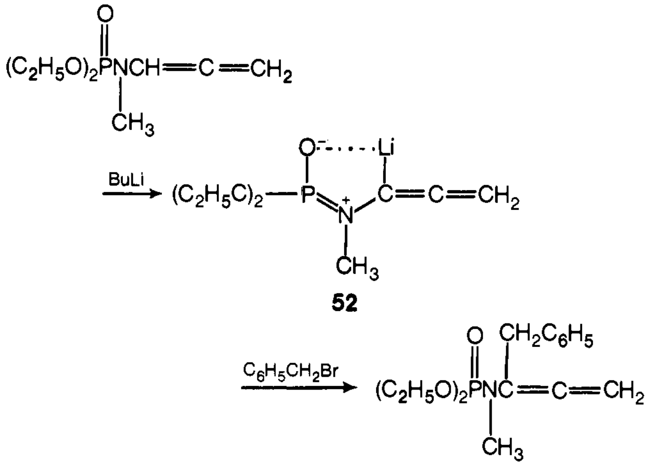
50

There are indications that formally dipole-stabilized carbanions can be formed adjacent to the nitrogen of a phosphoramide. Although hexamethylphosphoramide (HMPA) is a superior solvent for strong bases, Normant and co-workers did note some hydrogen-deuterium exchange of the *N*-methyl groups of HMPA in the presence of strong bases and suggested the intermediate **51**, drawn here as a dipole-stabilized carbanion.[45] The same type of species could be involved in the reaction of HMPA with



51

methyllithium to give methane and in the cleavage of HMPA by organolithiums to give N-methylformimine which subsequently undergoes further addition.[46-48] Savignac et al. have shown stable carbanions **52** can be formed and reacted with electrophiles if the position is benzylic, allenic, or vinylic.[49] The case is illustrated for alkylation of the allenic system to give the benzyl product in 80% yield.

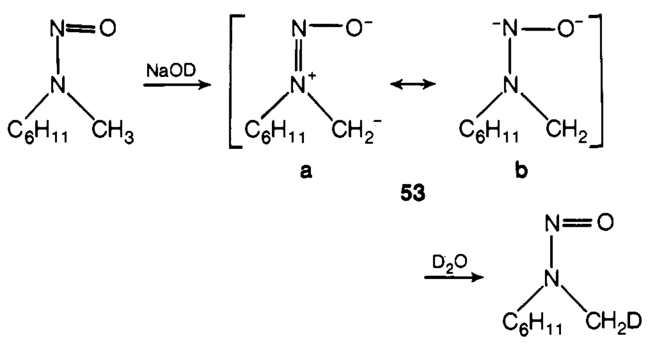


52

Overall, there appears to be considerable evidence that the nitrogen of an amide can provide substantial stabilization for removal of a proton α to the nitrogen. Questions about the importance of complexation of the metal ion, the extent of dipolar stabilization, and the use of such species in syntheses are open, but the area seems promising.

C. Nitrosoamines

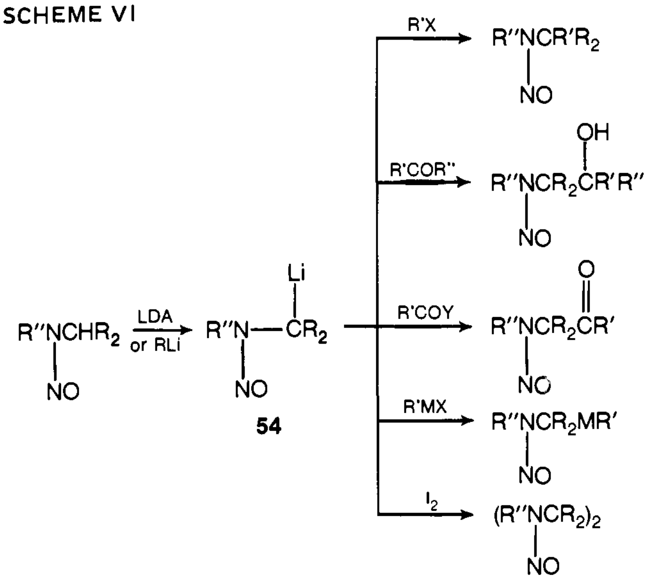
The most generally useful α-aza carbanions from secondary amines which might be dipole stabilized are those obtained by deprotonation of nitrosoamines. The seminal discoveries made by Keefer and Fodor and by Rademacher and Lüttke are the base-catalyzed hydrogen-deuterium exchanges of methylene and methyl groups adjacent to a nitroso-substituted nitrogen and the methylation of dimethyl-N-nitrosoamine on carbon in low yield on treatment with sodium hydride and methyl iodide.[50] The exchange of cyclohexylmethylnitrosoamine illustrates the formal qualifications of intermediate **53** as a dipole-stabilized, **53a**, and/or resonance-stabilized, **53b**, carbanion.



53

The possible importance of dipole stabilization in this system seems consistent with the rotational barriers of 20–25 kcal/mol established for nitrosoamines. Such a high barrier requires an appreciable nitrogen-nitrogen double bond and thereby a substantial positive charge on nitrogen.[51] However, Fraser and co-workers (vide infra) have carefully and convincingly established the preferred stereochemistry of deprotonation-protonation of the nitrosoamines is consistent with stabilization by delocalization.[52] Although it now appears that dipole stabilization is not of major importance for the carbanions from nitrosoamines, their synthetic value and the evidence on the nature of their stabilization are instructive. Accordingly, a discussion of some of these species will be included.

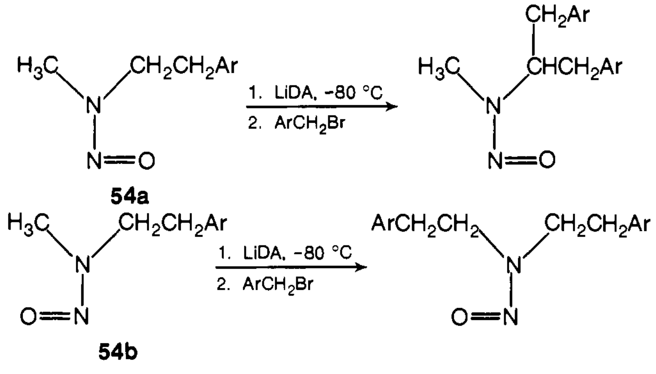
SCHEME VI



Seebach and Enders have demonstrated that carbanions analogous to **53** are synthetically useful species which can be generated from a variety of nitrosoamines with lithium diisopropylamide (LiDA) at low temperatures.[53,54] Much of the important developments on the synthetic use of these species has been carried out by Seebach and co-workers.[55] They have found that these α-aza carbanions can be generated at methyl, primary, secondary, and tertiary centers on reaction with lithium amides or organolithium reagents and that the metalated nitrosoamines react on carbon with a variety of electrophiles. Typical reactions are presented in Scheme VI, and Table V is a more extensive compilation. A summary by Seebach and Enders has appeared.[55] The nitrosation of amines and denitrosation of products can be carried out in situ to avoid contact with the carcenogenic nitrosoamines.

Alkylations of the α-nitroso organolithium reagents take place in 40 to 95% yield with readily displaceable halides.[56] Acylation, additions to aldehydes and ketones, heterosubstitution, and coupling have been reported.[55-57] It has been noted that additions occur at the α position of allyl derivatives, but for carbonyl compounds the additions can be reversible.[58] More than 50 examples have been reported of the reactions of primary, secondary, and tertiary derivatives with aldehydes and ketones to give β-hydroxynitrosoamines in good yields. Hydrolyses of the adducts from reactions with aromatic aldehydes give 2-amino-1-arylethanols, compounds which are of considerable interest in pharmacology.[59]

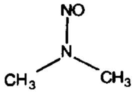
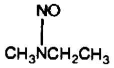
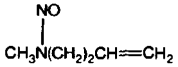
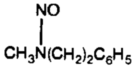
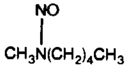
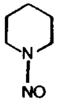
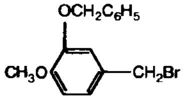
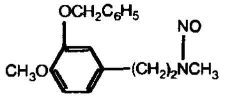
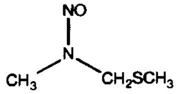
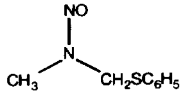
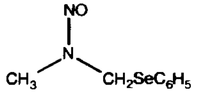
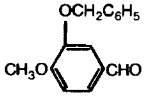
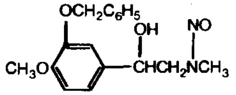
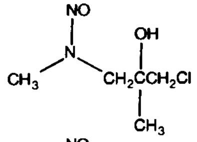
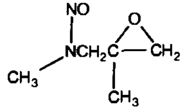
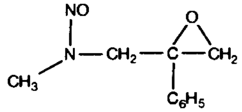
With most unsymmetrical nitrosoamines the hydrogen appears to be abstracted from the least substituted carbon unless the more substituted carbon bears an anion-stabilizing group. However, the regioselectivity of the proton abstraction appears to be controlled by the stereochemistry of the nitrosoamine. Barton and co-workers have shown that the isomers **54a** and **54b**



54a

54b

TABLE V. Formation of α-Lithionitrosamines and Reactions with Electrophiles

Reactant	Base	Temp, °C	Solvent	Electrophile	Product	Yield, %	Ref
	LiDA	−80	THF	CH_3I	 $CH_3N(NO)CH_2CH_3$	60	56
	LiDA	−80	THF	$CH_2{=}CHCH_2Br$	 $CH_3N(NO)(CH_2)_2CH{=}CH_2$	80	56
	LiDA	−80	THF	$C_6H_5CH_2Br$	 $CH_3N(NO)(CH_2)_2C_6H_5$	95	56
	LiDA	−80	THF	$CH_3(CH_2)_3I$	 $CH_3N(NO)(CH_2)_4CH_3$	65	56
	LiDA	−78	THF/HMPA	1. $Br(CH_2)_3I$ 2. LiDA		54	57
	LiDA	−80				84	60
	LiDA	−78	THF	CH_3SSCH_3		85	59
	LiDA	−78	THF	$C_6H_5SSC_6H_5$		83	59
	LiDA	−78	THF	$C_6H_5SeSeC_6H_5$		67	59
	LiDA	−80	THF			94	60
	LiDA	−80	THF	1. CH_3COCH_2Cl 2. H_2O at −80°		90	55
	LiDA	−80	THF	1. CH_3COCH_2Cl 2. H_2O at −20°		80	55
	LiDA	−80	THF	1. $C_6H_5COCH_2Br$ 2. H_2O at −20°		85	55

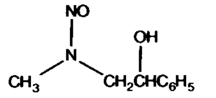
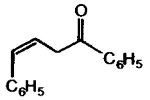
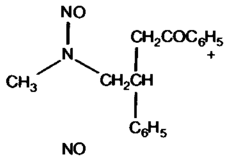
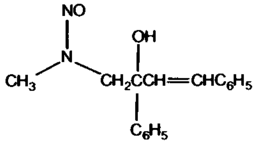
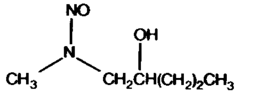
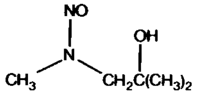
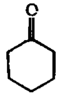
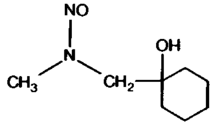
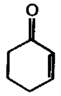
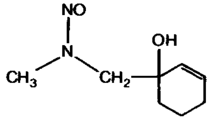
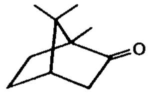
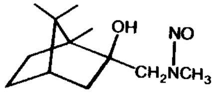
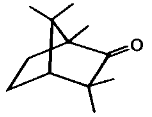
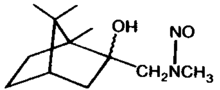
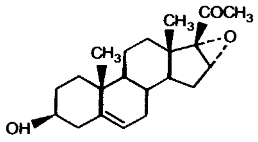
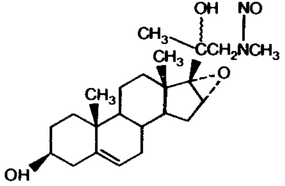
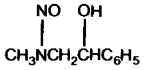
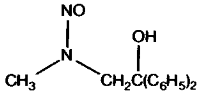
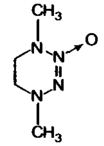
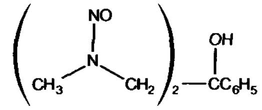
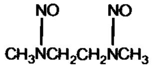
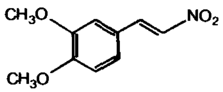
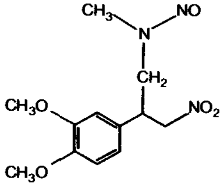
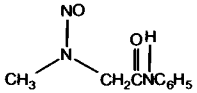
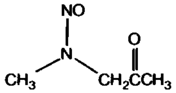
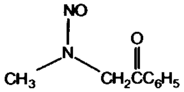
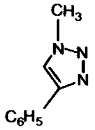
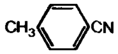
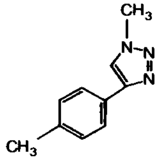
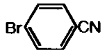
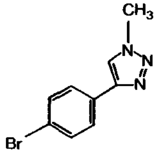
KOC(CH$_3$)$_3$	—	THF	C$_6$H$_5$CHO (in situ)	 $CH_3N(NO)CH_2CH(OH)C_6H_5$	95	55
LiDA	−80	THF		 $CH_3N(NO)CH_2CH(C_6H_5)CH_2COC_6H_5$ +	55, 45	55
				 $CH_3N(NO)CH_2C(OH)(C_6H_5)CH{=}CHC_6H_5$		
LiDA	−80	THF	CH$_3$(CH$_2$)$_2$CHO	 $CH_3N(NO)CH_2CH(OH)(CH_2)_2CH_3$	65	56
LiDA	−80	THF	(CH$_3$)$_2$CO	 $CH_3N(NO)CH_2C(OH)(CH_3)_2$	60	56
LiDA	−80	THF			75	56
LiDA	−80	THF			75	56
LiDA	−80	THF			55	56
LiDA	−80	THF			71	56
LiDA	−80	THF			80	56
LiDA	−80	THF	C$_6$H$_5$CHO	 $CH_3N(NO)CH_2CH(OH)C_6H_5$	85	56
LiDA	−80	THF	(C$_6$H$_5$)$_2$CO	 $CH_3N(NO)CH_2C(OH)(C_6H_5)_2$	71	56

TABLE V (*Continued*)

Reactant	Base	Temp, °C	Solvent	Electrophile	Product	Yield, %	Ref
	LiDA	>−80	THF	—		30–45	61
	LiDA	−80	THF	C_6H_5COCl		70	54
	LiDA	−80	THF	I_2	 $\mathrm{CH_3\overset{NO}{N}CH_2CH_2\overset{NO}{N}CH_3}$	95	54
	LiDA	−80	THF			75	55
	LiDA	−80	THF	$C_6H_5N{=}C{=}O$		85	55
	LiDA	−80	THF	CH_3COCl		40–50	55
	LiDA	−80	THF	C_6H_5COCl		40–50	55
	LiDA	−80	THF	C_6H_5CN		83	55
	LiDA	−80	THF			57	55
	LiDA	−80	THF			84	55

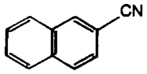
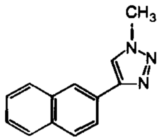
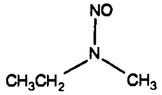
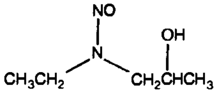
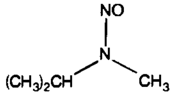
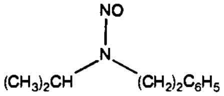
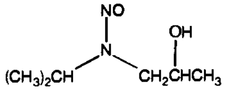
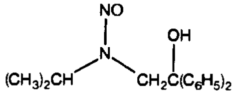
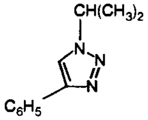
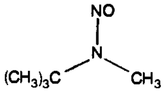
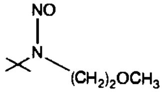
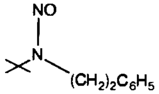
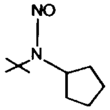
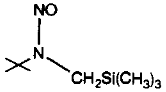
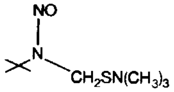
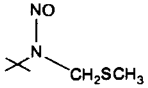
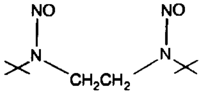
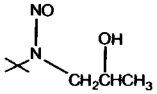
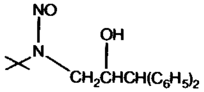
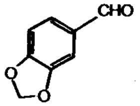
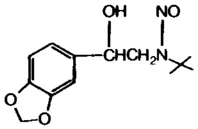
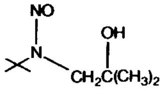
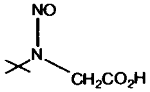
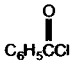
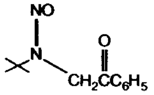
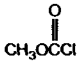
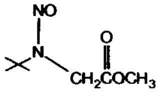
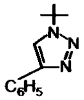
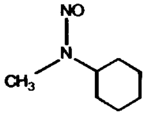
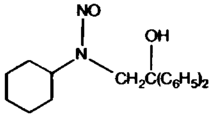
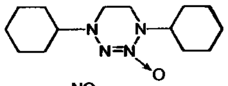
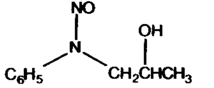
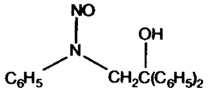
	LiDA	−80	THF			80	55
	LiDA	−80	THF	CH_3CHO		76	56
	LiDA	−80	THF	$C_6H_5CH_2Br$		90	56
	LiDA	−80	THF	CH_3CHO		77	56
	LiDA	−80	THF	$(C_6H_5)_2CO$		70	56
	LiDA	−80	THF	C_6H_5CN		90	55
	LiDA	−80	THF	$ClCH_2OCH_3$		70	56
	LiDA	−80	THF	$C_6H_5CH_2Br$		95	56
	LiDA	−78	THF	1. $Cl(CH_2)_4I$ 2. LiDA		80	57
	LiDA	−78	THF	$(CH_3)_3SiCl$		80	59
	LiDA	−78	THF	$(CH_3)_3SNCl$		95	59
	LiDA	−78	THF	CH_3SSCH_3		90	59
	LiDA	−78	THF	I_2		50	55

TABLE V (*Continued*)

Reactant	Base	Temp. °C	Solvent	Electrophile	Product	Yield. %	Ref
	LiDA	−78	THF	CH_3CHO		90	56
	LiDA	−80	THF	$(C_6H_5)_2CHCHO$		80	56
	LiDA	−80	THF			83	56
	LiDA	−80	THF	$(CH_3)_2CO$		80	56
	LiDA	−80	THF	CO_2		80	55
	LiDA	−80	THF	 $C_6H_5C(=O)Cl$		40–50	55
	LiDA	−80	THF	 $CH_3OC(=O)Cl$		95	55
	LiDA	−60	THF	C_6H_5CN		99	55
	LiDA	−80	THF	$(C_6H_5)_2CO$		93	56
	LiDA	>−80	THF	—		30–45	61
	LiDA	−80	THF	CH_3CHO		45	56
	LiDA	−80	THF	$(C_6H_5)_2CO$		95	55

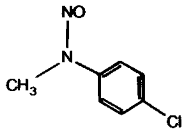
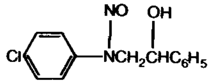
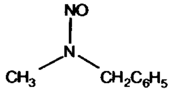
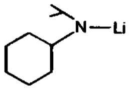
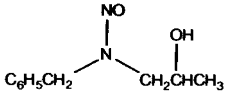
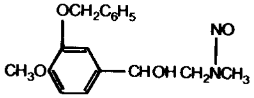
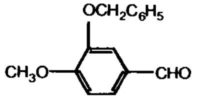
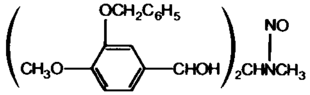
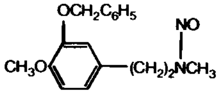
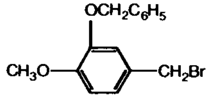
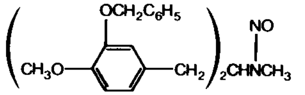
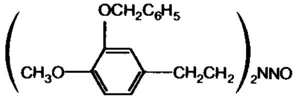
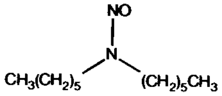
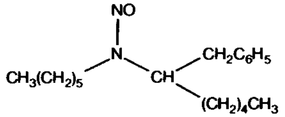
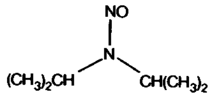
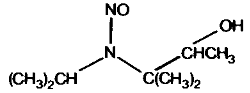
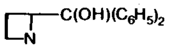
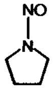
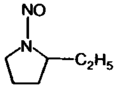
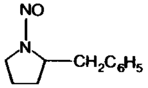
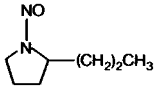
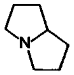
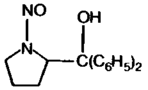
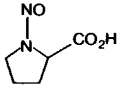
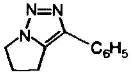
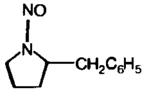
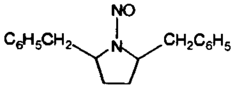
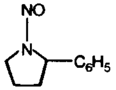
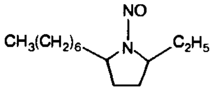
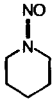
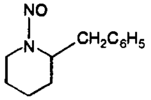
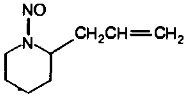
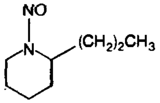
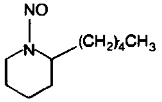
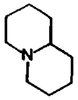
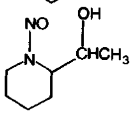
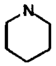
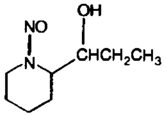
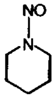
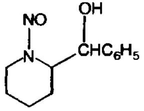
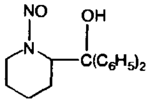
	$KOC(CH_3)_3$	—	THF	C_6H_5CHO (in situ)		69	55
		−110	THF	CH_3CHO		60	55
	LiDA	−80	THF			12	60
	LiDA	−80	THF			93	60
	$((CH_3)_3Si)_2NNa$	−80	THF	As above		94	60
	LiDA	−80	THF	$C_6H_5CH_2Br$		95	53
	LiDA	−80	THF	CH_3CHO		40	54
	LiDA	−78	THF	$(C_6H_5)_2CO$		65	57
	LiDA	−95	THF	C_2H_5I		64	62
	LiDA	−78. −95	THF	$C_6H_5CH_2Br$		75. 95	57. 62
	LiDA	−78	THF	$CH_3(CH_2)_2I$		52	57
	LiDA	−78	THF	1. $Cl(CH_2)_3I$ 2. denitrosation 3. base		46	57
	LiDA	−78	THF	$(C_6H_5)_2CO$		85	57
	LiDA	−80	THF	CO_2		20	53

TABLE V (*Continued*)

Reactant	Base	Temp, °C	Solvent	Electrophile	Product	Yield, %	Ref
	LiDA	−80	THF	C_6H_5CN		40–60	55
	LiDA	−95	THF	$C_6H_5CH_2Br$		85	62
	LiDA	−95	THF	$CH_3(CH_2)_6I$		65	62
	LiDA	−78	THF	$C_6H_5CH_2Br$		60	57
	LiDA	−78	THF	$CH_2{=}CHCH_2Br$		58	57
	LiDA	−78	THF	$CH_3(CH_2)_2I$		49	57
	LiDA	−78	THF	$CH_3(CH_2)_4I$		46	57
	LiDA	−78	THF/HMPA	1. $Cl(CH_2)_4I$ 2. denitrosation 3. base		18	57
	LiDA	−78	THF	CH_3CHO		85	57
	LiDA	−78	THF	CH_3CH_2CHO		78	57
	LiDA	−78	THF	C_6H_5CHO		53	57
	$KOC(CH_3)_3$	—	THF	C_6H_5CHO (in situ)	As above	80	55
	LiDA	−78	THF	$(C_6H_5)_2CO$		32	57

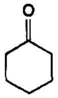
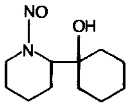
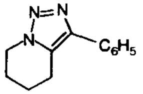
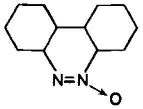
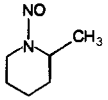
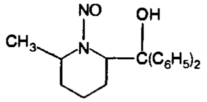
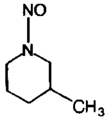
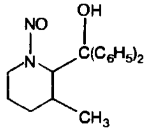
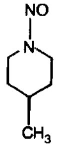
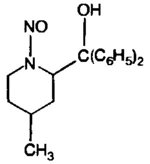
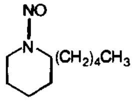
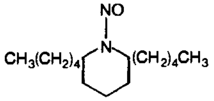
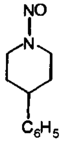
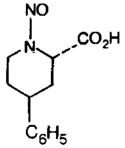
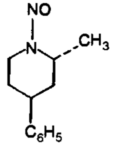
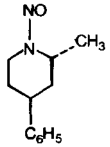
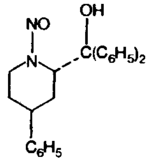
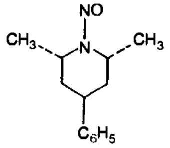
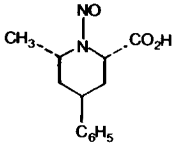
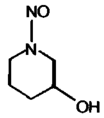
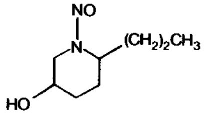
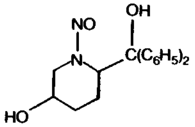
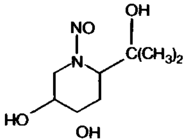
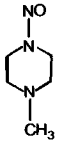
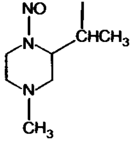
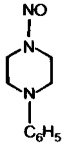
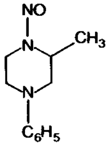
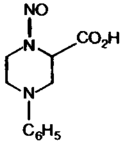
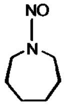
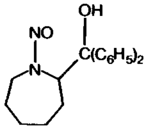
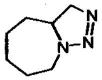
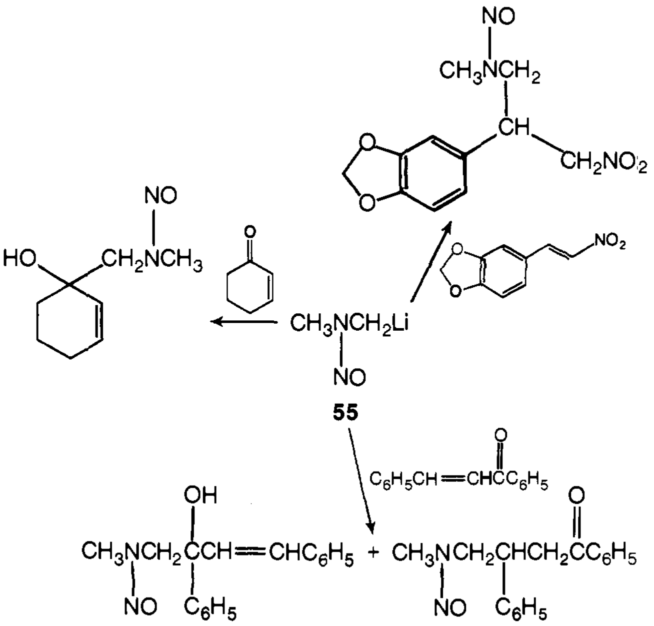
	LiDA	−78	THF			63	57
	LiDA	−80	THF	C_6H_5CN		40–60	55
	LiDA	>−80	THF	—		30–45	61
	LiDA	−78	THF	$(C_6H_5)_2CO$		33	65
	LiDA	−78	THF	$(C_6H_5)_2CO$		35	65
	LiDA	−78	THF	$(C_6H_5)_2CO$		30	65
	LiDA	−78	THF	$CH_3(CH_2)_4I$		71	65
	LiDA	−78	THF	CO_2		76	63
	LiDA	−78	THF	CH_3I		79	63
	LiDA	−78	THF	$(C_6H_5)_2CO$		72	63
	LiDA	−78	THF	CH_3I		62	63

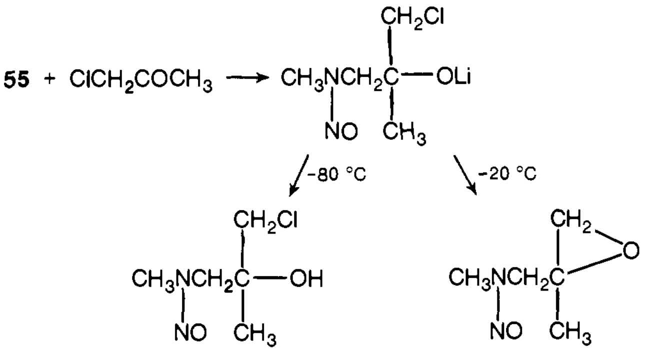
TABLE V (*Continued*)

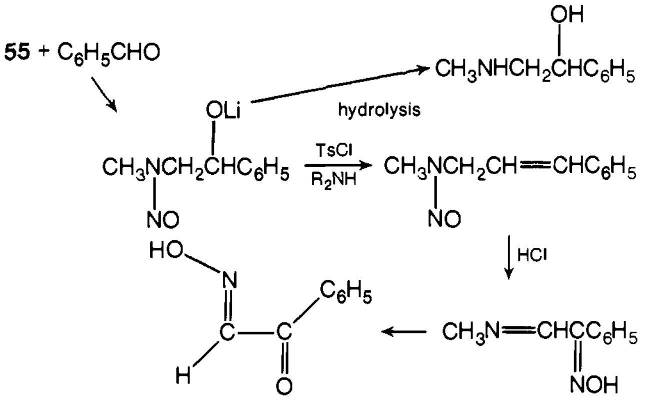
Reactant	Base	Temp, °C	Solvent	Electrophile	Product	Yield, %	Ref
	LiDA	−78	THF	CO_2		33	63
	LiDA	−78	THF/HMPA	$CH_3(CH_2)_2I$		52	65
	LiDA	−78	THF/HMPA	$(C_6H_5)_2CO$		33	65
	LiDA	−78	THF/HMPA	$(CH_3)_2CO$		50	55
	LiDA	−96	THF	CH_3CHO		45	57
	LiDA	−78	THF	CH_3I		46	52
	LiDA	−78	THF	CO_2		73	52
	LiDA	−78	THF	$(C_6H_5)_2CO$		85	57
	LiDA	−80	THF	C_6H_5CN		40–60	55

give products of substitution at the carbon syn to the nitroso oxygen.[60]

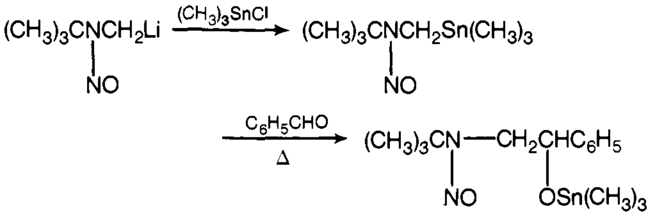
The regiochemistry of the reaction on the electrophile appears to be a function of the substrate. Cyclohexenone reacts with **55**, the organolithium reagent from dimethylnitrosoamine, at the carbonyl carbon, but benzalacetophenone gives almost equal amounts of 1,2 and 1,4 additions on reaction with **55**, and a nitrostyrene gives only 1,4 addition.[56] Reaction of α-chloroacetone with **55** gives the adduct at the carbonyl carbon at −80 °C or formation of an epoxide at higher temperatures.[56] Another example of a useful synthetic conversion which occurs after initial addition is provided by the elimination and rearrangement of the product from **55** and benzaldehyde to give the oxime of phenylglyoxal.





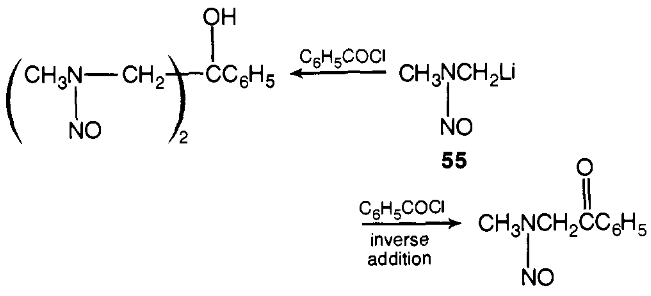


A mild procedure has been devised for reaction with electrophiles which could be sensitive to strong base.[59] The trialkyltin derivative can be prepared and allowed to react with the electrophile under neutral conditions. The reaction is illustrated for the case of *tert*-butyltrialkyltin methylnitrosoamine and benzaldehyde. Sulfur, selenium, and silicon derivatives also are directly preparable.[59]

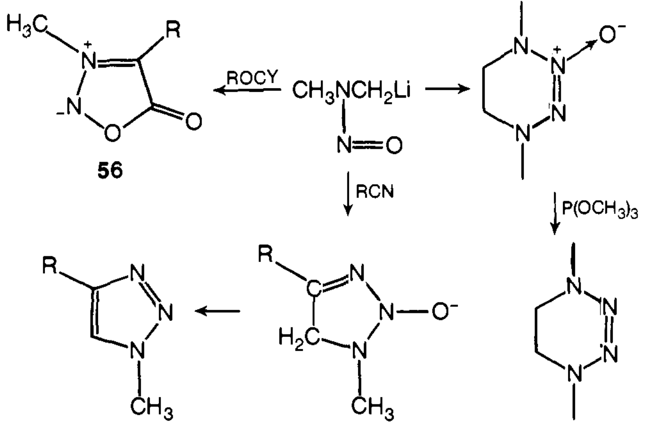


$$\underset{NO}{(CH_3)_3CNCH_2Li} \xrightarrow{(CH_3)_3SnCl} \underset{NO}{(CH_3)_3CNCH_2Sn(CH_3)_3} \xrightarrow[\Delta]{C_6H_5CHO} \underset{NO}{(CH_3)_3CN}\text{—}\underset{OSn(CH_3)_3}{CH_2CHC_6H_5}$$

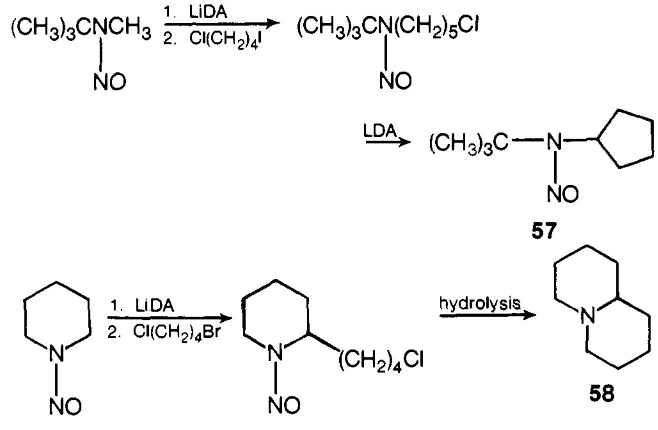
Acylations can be carried out in moderate yields although reverse addition is necessary to avoid formation of diadducts. Acid chlorides, esters, carbon dioxide, and isocyanates are effective electrophiles.

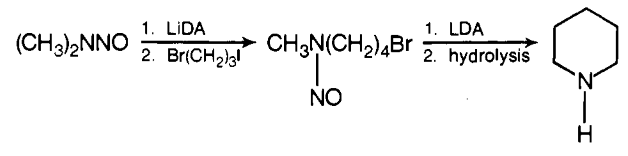


The organolithium reagents from nitrosoamines are also useful in heterocyclic syntheses. Thus coupling, cyclization, and reduction give the novel *v*-tetrazines **56** in moderate yields.[61] Reaction of **55** or its derivatives[57] with nitriles gives the triazines in good yields, and cyclization of acylated intermediates can provide the sydnones (**56**).



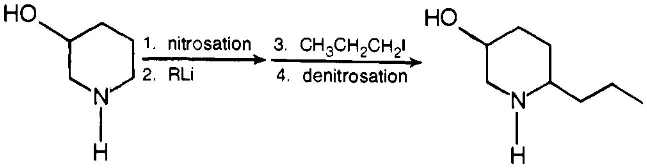
The synthetic versatility of these intermediates has been nicely demonstrated by Seebach et al. for the three types of ring formations illustrated by the syntheses of **57**–**59**. In these cases cyclizations occur at: (1) the carbon initially substituted, **57**, (2) at nitrogen, **58**, and (3) at the remote carbon of the nitrosoamine **59**.[57]



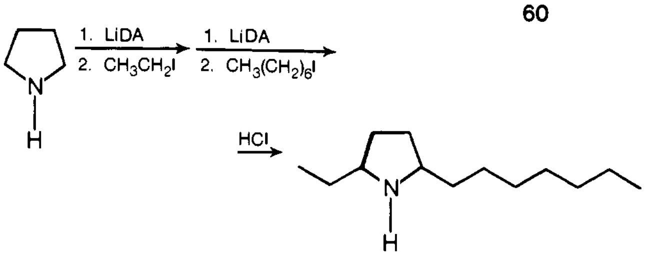


59

This sequence, which allows electrophilic substitution adjacent to nitrogen, holds particular promise for alkaloid synthesis. Syntheses of ψ-conhydrine[55] (**60**) and **61**, a constituent of fire ant venom,[62] are shown. These reactions illustrate the masking, activation, substitution, and demasking sequence suggested by Scheme II.

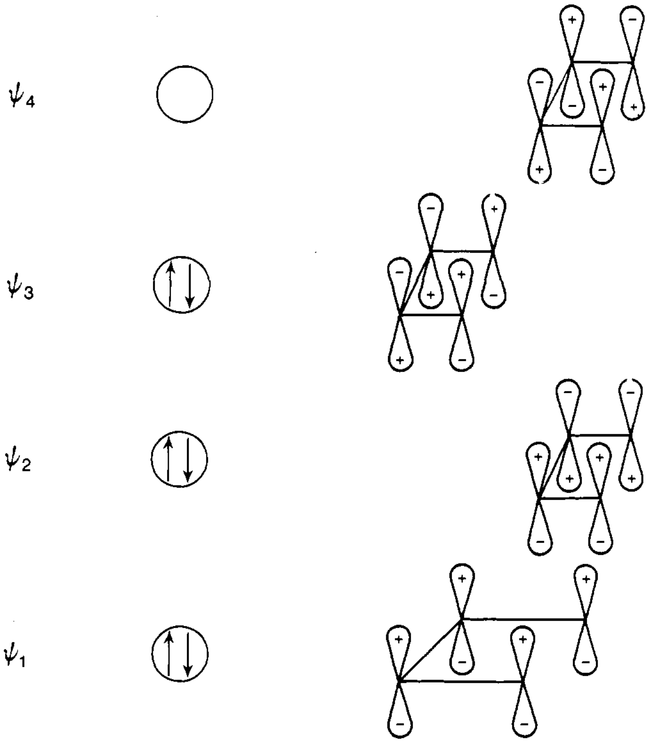


60

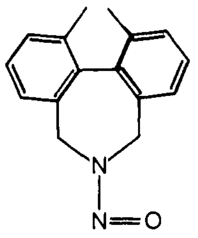


61 (cis-trans mixture)

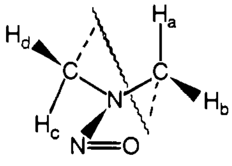
Although Keefer and Fodor[50a] suggested that the dipole of the nitrosoamine (**53a**) could play an important role in providing stabilization for the formal carbanion **53**, studies by Fraser et al. suggest that delocalization (**53b**) is the dominant factor. The principal line of evidence is that stereochemical preferences in formation and reaction are observed which are explained by favorable overlap of the orbital on carbon with the π system of the nitroso function. In the extreme, this can be viewed as a 6π-electron, 4-atom system, in which the antibonding orbital ψ_3 (psi = ψ) is occupied, as shown below. While it is also possible to allow the orbital on carbon to bear some s character, to represent differential overlap in the orbitals by different-sized lobes, the symmetry arguments and the "through-space" overlap favoring "syn" orientation of the nitroso function and the carbon bearing the negative charge, are adequately represented by ψ_3.

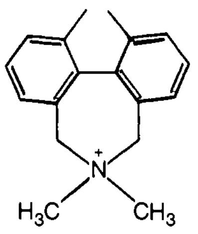


The first system studied in stereochemical detail was the nitrosodibenzazepine **62**, which has four chemically distinct protons adjacent to nitrogen. The different sites are respectively, syn axial (H_a); syn equatorial (H_b); anti axial (H_c); and anti equatorial (H_d) with respect to the azepine ring. In a careful investigation of metalations and trapping of **63** which included consideration of internal return and concomitant rotation about the N–N bond, Fraser and Ng found the ratio of rates of hydrogen-deuterium exchange with potassium *tert*-butoxide in *tert*-butyl alcohol-*d* to be $10^5:10^2:10^3:1$, with $H_a > H_b > H_c > H_d$. The axial hydrogens exchange more readily than the equatorial hydrogens by a factor of 100 ($H_a > H_b$ and $H_c > H_d$) while the syn hydrogens exchange faster than the anti hydrogens by a factor of 1000 ($H_a > H_c$ and $H_b > H_d$). On the basis of this result Fraser and Ng suggested the molecular orbital rationale cited above for both the syn and axial preference.[52] Their position that the intermediate can be described as a free ion is supported by the fact the reaction is insensitive to the presence of crown ether. Moreover, the importance of a dipolar contribution is discounted by the observation that the ammonium ion **63** does not undergo base-catalyzed exchange on heating at 100 °C for 24 h whereas the half-life of H_a of **62** is 20 min at 35 °C under comparable conditions. An intriguing question which remains, however, is why the syn equatorial hydrogen at **62** undergoes exchange at all and, in particular, why it is faster than the anti equatorial hydrogen.



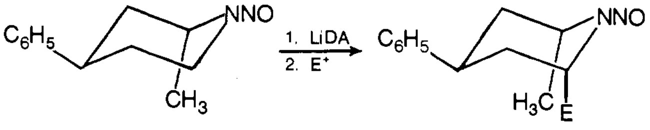
62





63

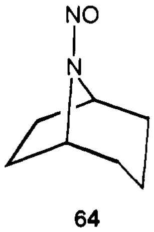
The reactions of **54a** and **54b** (vide supra) also reveal the importance of syn geometry in controlling the nature of the carbanion. The carbanions formed from substituted *N*-nitrosopiperidines also show a preference for syn axial reactions on deuterium exchange or on lithiation–electrophilic substitution,[55,63,64,65] which is sufficiently large to be synthetically useful and mechanistically informative. 4-Phenyl-*N*-nitrosopiperidine on lithiation and reaction with carbon dioxide, methyl iodide, and benzophenone gives axial products in yields of 76, 79, and 72% with less than 1% of the equatorial isomers present. These stereochemical preferences are greater than for alkylations of the corresponding enolates or eneamines.[63] Unfavorable 1,3-diaxial interactions are not sufficient to change the stereochemical result. Similar reactions of 2-methyl-4-phenyl-*N*-nitrosopiperidine gives the diaxial products of methylation and carboxylation in 62 and 33% yields with less than 2% of the equatorial isomers being present.[63] Careful analyses of the conformational energies for these and related systems have led Fraser to conclude that a substantial stereoelectronic effect is



E = CH_3, CO_2H

operative in the transition state for these processes. Similar conclusions have been reached by Lyle, who has investigated the 4-*tert*-butyl-*N*-nitrosopiperidine system[64] and also follow from Barton's studies of the acyclic systems **54**.[60]

Additional support for the conclusion of Fraser that delocalization is an important factor in the metalation of nitrosoamines comes from the recent report that **64** does not metalate.[56] In this case, overlap of the anion would require an unfavorable bridgehead double bond, and the failure of **63** to react can be understood as a reflection of the high energy of that species.



64

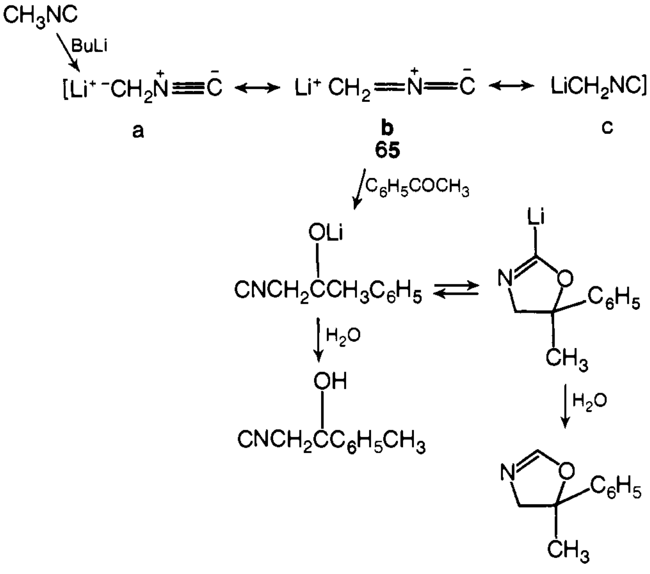
The stereochemical results then provide strong evidence for the importance of delocalization in providing stabilization for the carbanions adjacent to the nitrogen of a nitrosoamine. The question of whether an effect of dipole stabilization also contributes seems presently moot.

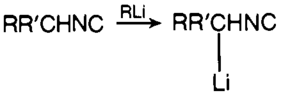
D. Isocyanides

The most useful α-aza carbanions formally derived from primary amines are those obtained by metalation of isocyanides. The initiating discovery of the metalation of methyl isocyanide, reported by Schöllkopf and Gerhart, is shown in Scheme VII to produce **65**.[66] Schöllkopf and Hoppe have suggested that inductive stabilization by the dipole of the isocyanide group is very important[67,68] in the formation of **65**, and Walborsky has recently presented evidence in support of that position.[69] The unique potential of these species for nucleophilic aminoalkylation and heterocyclic synthesis is exemplified in Scheme VII for the reaction of **65** with acetophenone to give β-hydroxyamine or oxazoline derivatives. Synthetic use of this reaction is particularly important for species which have additional stabilizing groups attached to carbon; such cases have been recently reviewed and will not be covered here.[67,68]

With the exception of cyclopropyl and cyclobutyl isocyanide, secondary alkyl isocyanides do not undergo efficient metalation. However, in the initial report it was shown that the ethyl isocyanide could be metalated in situ to generate **66a** in the presence of a trapping agent. Subsequent reports have cited the generation of analogs of **66** with R, R′ = H, $CH{=}CHC_6H_5$,[68] R, R′ = CH_3, CH_3,[70] R, R′ = $-(CH_2)_5-$,[70] R, R′ = H, $CH_2CH_2N(CH_3)_2$,[68,71] R, R′ = H, $CH_2CH_2OCH_3$.[70,71] Reactions of these species are summarized in Table VI. Reactions involving **66f** and **66g** proceed in better yields than for **66a–d**, suggesting that stabilization by intramolecular complexation of lithium is a factor.[68,71,72] If a potentially complexing atom is located in the position, however, elimination results.[70]

SCHEME VII



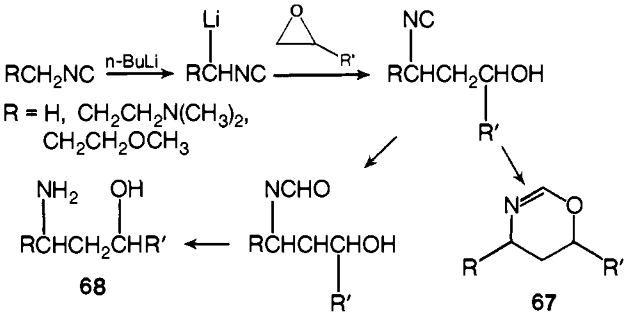


$$\mathrm{RR'CHNC} \xrightarrow{\mathrm{RLi}} \mathrm{RR'\underset{\displaystyle Li}{C}HNC}$$

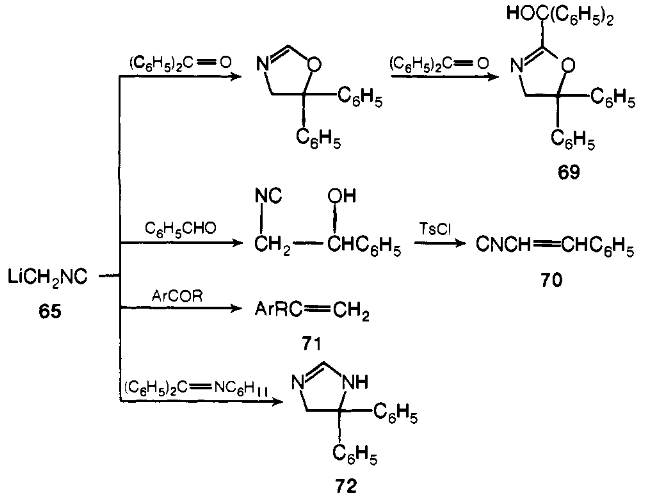
66

a, R, R′ = H, CH_3
b, R, R′ = H, $CH{=}CHC_6H_5$
c, R, R′ = CH_3, CH_3
d, R, R′ = $-(CH_2)_4-$
e, R, R′ = $-(CH_2)_5-$
f, R, R′ = H, $CH_2CH_2N(CH_3)_2$
g, R, R′ = H, $CH_2CH_2OCH_3$

The organolithium reagents **65** and **66d** undergo alkylation with alkyl iodides or bromides.[68] Alkylation of metalated isocyanides by epoxides provides a route to γ-amino isocyanides, compounds which can be converted 5,6-dihydro-4*H*,1,3-oxazines (**67**) or to γ-amino alcohol (**68**) in useful yields.



Reactions of metalated isocyanides with aldehydes and ketones generally give oxazolines and β-amino alcohols in good yields (Table VI).[68,70,73] In some cases, however, further reactions are possible. At higher reaction temperatures, the intermediate from **65** and benzophenone undergoes cyclization and further reaction with the ketone to give **69**. Another pathway of reaction of these intermediates is shown by the reaction of **65** with benzaldehyde to provide the vinyl isocyanide **70**. Reactions of **65** with other aryl or vinyl carbonyl compounds gives the methylene derivatives **71**. Addition of **65** to an imine gives the dihydridoimidazole **72**.[68]



Since the β-amino alcohols prepared by these additions are subject to subsequent rearrangement on treatment with nitrous acid, an aminomethylation–ring expansion sequence is possible. This is illustrated for the conversion of cyclohexanone to cycloheptanone in 34% yield.[74]

TABLE VI. Formation of α-Lithioisocyanides and Reactions with Electrophiles

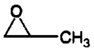
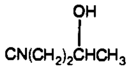
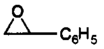
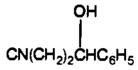
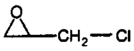
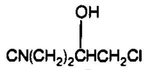
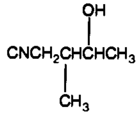
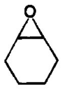
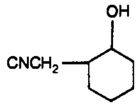
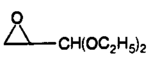
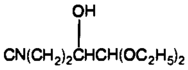
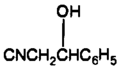
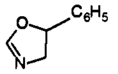
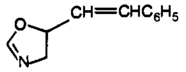
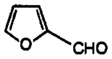
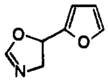
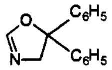
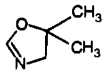
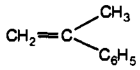
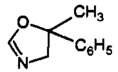
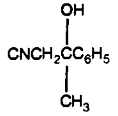
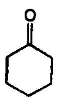
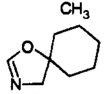
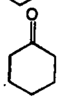
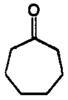
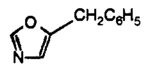
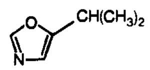
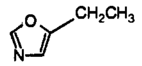
Reactant	Base	Temp, °C	Solvent	Electrophile	Product	Yield, %	Ref
CH_3NC	*n*-BuLi	−70	THF	$CH_2{=}CHCH_2Br$	$CH_2{=}CH(CH_2)_2NC$	27	80
	n-BuLi	−70	THF	$C_6H_5CH{=}CHCH_2Br$	$C_6H_5CH{=}CH(CH_2)_2NC$	41	80
	n-BuLi	−70	THF	$CH_3CH{=}CHCH_2Br$	$CH_3CH{=}CH(CH_2)_2NC$	70	80
	n-BuLi	−70	THF	$CH_3(CH_2)_2Br$	$CH_3(CH_2)_3NC$	39	80
	n-BuLi	−70	THF		$CN(CH_2)_3OH$	42	71
	n-BuLi	−70	THF		 $CN(CH_2)_2\overset{OH}{\overset{\mid}{C}}HCH_3$	78	71
	n-BuLi	−70	THF		 $CN(CH_2)_2\overset{OH}{\overset{\mid}{C}}HC_6H_5$	74	71
	n-BuLi	−70	THF		 $CN(CH_2)_2\overset{OH}{\overset{\mid}{C}}HCH_2Cl$	48	71
	n-BuLi	−70	THF		 $CNCH_2\underset{\overset{\mid}{CH_3}}{C}H\overset{OH}{\overset{\mid}{C}}HCH_3$	48	71
	n-BuLi	−70	THF			85	71
	n-BuLi	−70	THF		 $CN(CH_2)_2\overset{OH}{\overset{\mid}{C}}HCH(OC_2H_5)_2$	49	71
	n-BuLi	−70	THF	C_6H_5CHO	 $CNCH_2\overset{OH}{\overset{\mid}{C}}HC_6H_5$	80	73
	n-BuLi	−70	THF	C_6H_5CHO		77	70
	n-BuLi	65	THF	$C_6H_5CH{=}CHCHO$	$C_6H_5CH{=}CHCH{=}CH_2$	28	66
	n-BuLi	−70	THF	$C_6H_5CH{=}CHCHO$		58	70
	n-BuLi	−70	THF			44	66
	n-BuLi	−75	THF	$(C_6H_5)_2CO$	$CH_2{=}C(C_6H_5)_2$	40	66
	n-BuLi	−70	THF	$(C_6H_5)_2CO$		83	70
	n-BuLi	−70	THF	$(CH_3)_2CO$		31	66
	n-BuLi	65	THF	$C_6H_5COCH_3$		65	66
	n-BuLi	−70	THF	$C_6H_5COCH_3$		80	70
	n-BuLi	−70	THF	$C_6H_5COCH_3$	 $CNCH_2\underset{\overset{\mid}{CH_3}}{\overset{OH}{\overset{\mid}{C}}}C_6H_5$	75	73
	n-BuLi	−70	THF			57	70
	n-BuLi	−70	THF	1. 2. HNO$_2$		35	74
	n-BuLi	−70	THF	$C_6H_5CH_2CON(CH_3)_2$		41	75
	n-BuLi	−70	THF	$(CH_3)_2CHCON(CH_3)_2$		55	75
	n-BuLi	−70	THF	$CH_3CH_2CON(CH_3)_2$		48	75

TABLE VI (*Continued*)

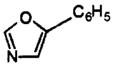
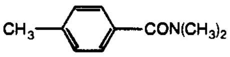
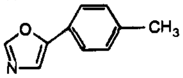
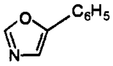
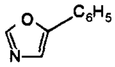
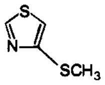
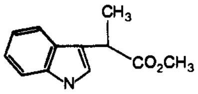
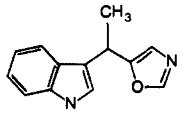
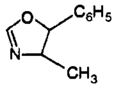
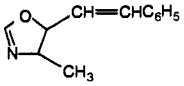
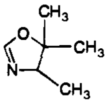
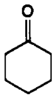
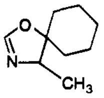
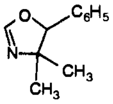
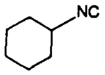
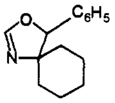
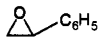
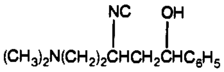
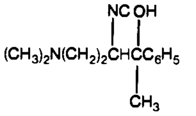
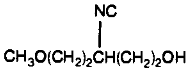
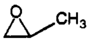
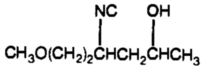
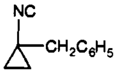
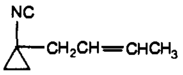
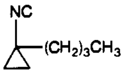
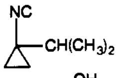
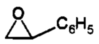
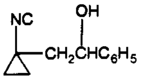
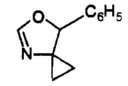
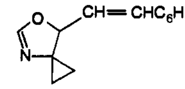
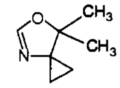
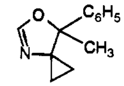
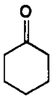
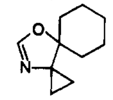
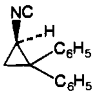
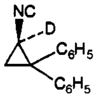
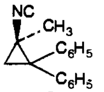
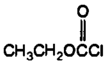
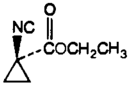
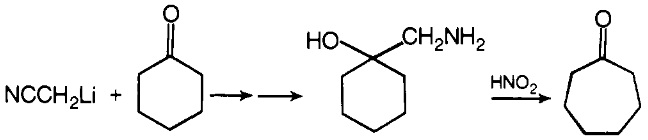
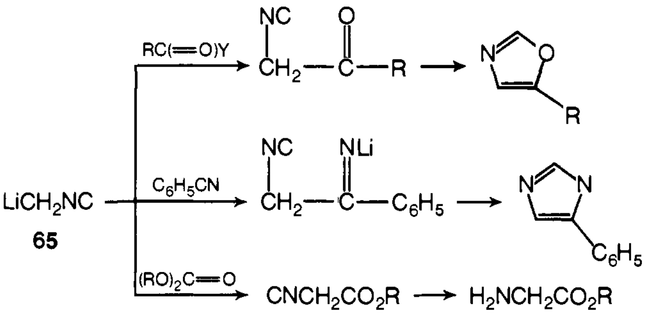
Reactant	Base	Temp. °C	Solvent	Electrophile	Product	Yield, %	Ref
	n-BuLi	−70	THF	$C_6H_5CON(CH_3)_2$		67	75
	n-BuLi	−70	THF			85	75
	n-BuLi	−70	THF	C_6H_5COCl		72	75
	n-BuLi	−70	THF	$C_6H_5CO_2C_2H_5$		72	75
	n-BuLi	−70	THF	$(CH_3CH_2)_2CO_3$	$CNCH_2CO_2CH_2CH_3$	35	77
	n-BuLi	−70	THF	1. CS_2 2. CH_3I		34	78
	n-BuLi	−70	THF			80	79
CH_3CH_2NC	LiTMP	−70	THF	C_6H_5CHO		50	70
	LiTMP	−70	THF	$C_6H_5CH{=}CHCHO$		46	70
	LiTMP	−70	THF	$(CH_3)_2CO$		40	70
	LiTMP	−70	THF			40	70
$(CH_3)_2CHNC$	LiTMP	−70	THF	C_6H_5CHO		5	70
	LiTMP	−70	THF	C_6H_5CHO		6	70
$(CH_3)_2N(CH_2)_3NC$	*n*-BuLi	−70	THF		 $(CH_3)_2N(CH_2)_2CH(NC)CH_2CH(OH)C_6H_5$	70	71
$(CH_3)_2N(CH_2)_3NC$	*n*-BuLi	−70	THF	$C_6H_5COCH_3$	 $(CH_3)_2N(CH_2)_2CH(NC)C(OH)(CH_3)C_6H_5$	75	73
$CH_3O(CH_2)_3NC$	*n*-BuLi	−70	THF		 $CH_3O(CH_2)_2CH(NC)(CH_2)_2OH$	82	71
	n-BuLi	−70	THF		 $CH_3O(CH_2)_2CH(NC)CH_2CH(OH)CH_3$	76	71
	*n*-BuLi	−70	THF	$C_6H_5CH_2Br$		76	80
	n-BuLi	−70	THF	$CH_3CH{=}CHCH_2Br$		65	80
	n-BuLi	−70	THF	$CH_3(CH_2)_3Br$		33	80
	n-BuLi	−70	THF	$(CH_3)_2CHBr$		27	80
	n-BuLi	−70	THF			75	71

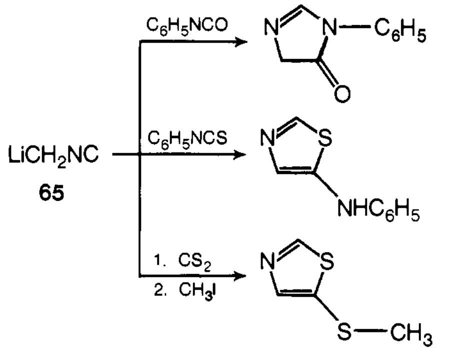
TABLE VI (*Continued*)

Reactant	Base	Temp, °C	Solvent	Electrophile	Product	Yield, %	Ref
	n-BuLi	−70	THF	C_6H_5CHO		89	70
	n-BuLi	−70	THF	$C_6H_5CH{=}CHCHO$		83	70
	n-BuLi	−70	THF	$(CH_3)_2CO$		61	70
	n-BuLi	−70	THF	$C_6H_5COCH_3$		69	70
	n-BuLi	−70	THF			75	70
	LiDA	−72	THF	CH_3OD		70	69
	$NaOC(CH_3)_3$	−72	THF	CH_3OD	As above	78	69
	$KOC(CH_3)_3$	−72	THF	CH_3OD	As above	90	69
	LiDA	−72	THF	CH_3I		96	69
	LiDA	−72	THF	 $CH_3CH_2O\overset{O}{\overset{\|}{C}}Cl$		44	69

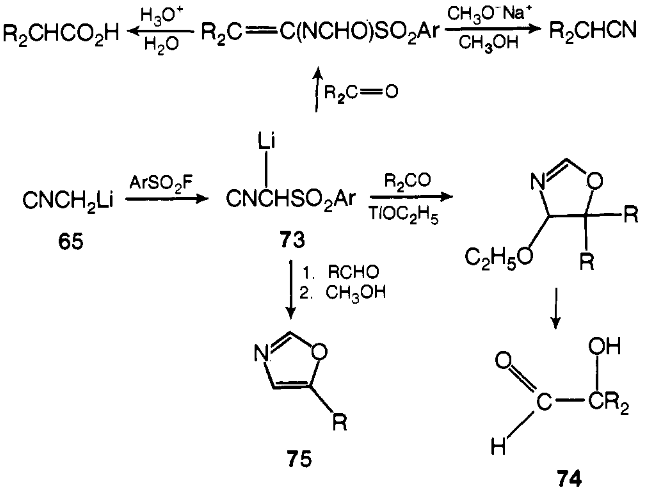


Acylation of metalated isocyanides usually proceeds smoothly. For example, reaction of **65** with acid chlorides, amides, or esters gives oxazoles in 40–70% yields,[75,76] and reaction with benzonitrile gives 5-phenylimidazole in 40% yield.[76] The organolithium reagent **65** also undergoes reaction with carbonates or chloroformates to give esters of α-amino acids after hydrolysis.[77] Reactions of **65** with isocyanates, thioisocyanates, and carbon disulfide are also useful in producing azoles in moderate yields.[68,76,78]

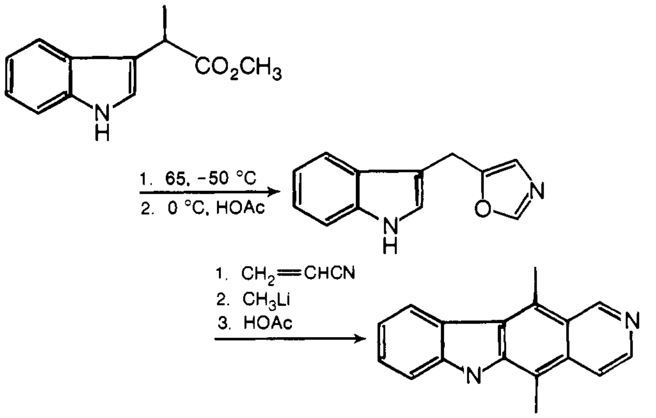




The dipole-stabilized carbanion **65** is especially useful as a precursor for substituted isocyanides which are in turn useful for a variety of syntheses. The sequence is illustrated for preparation of the lithiated arylsulfonyl isocyanides **73** and its subsequent use in one carbon homologation of a ketone to an acid, a nitrile, an α-hydroxy aldehyde **74**, or oxazole **75**. Use of lithiated isocyanides esters has been reported for syntheses of amino acid derivatives.[68] Although the reactions of activated isocyanides is not covered in this review, the considerable value of these species indicates the important role α-heterocarbanions can play in synthetic design.



An example of the use of metalated methyl isocyanide (**65**) in the synthesis of elliptione is shown.[79] The use of these or-



ganolithium reagents in chain elongation of amines has also been investigated and is illustrated for a sequence involving **65** and a readily displaceable organohalide.[80]

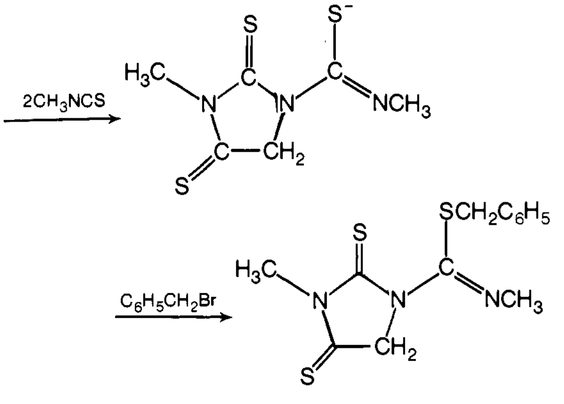
$$CH_3NH_2 \rightarrow CH_3NC \rightarrow \underset{\textbf{65}}{LiCH_2NC} \xrightarrow{RX} RCH_2NC \rightarrow RCH_2NH_2$$

Although α-alkyl-substituted isocyanides do undergo metalation with lithium tetramethylpiperidide, the reaction proceeds in low yield.[67,68] The use of alkyl lithium reagents for metalation has been obviated by the more facile nucleophilic additions to the carbon of the isocyanide function.[81]

Dipole stabilization appears to make a major contribution to the stability of the metalated isocyanides as illustrated for **65a** in Scheme VII. The principal evidence on this point comes from Walborsky's studies of the configurational stability of the (+)-(*S*)-1-isocyano-2,2-diphenylcyclopropyl carbanion (**76**) at low temperature.[69,82] If stabilization of **76** is achieved by a π–π delocalization, the anion would be expected to be planar and the asymmetry would be lost, in contrast to the observation. The failure of cyclopropylnitriles and cyclopropylacetylenes corresponding to **76** to maintain configurational stability establishes experimentally that such delocalization does lead to loss of configuration. It is important to note that the configurational stability of **76** is not affected by a change of the counterion from lithium to sodium or potassium, by change in the solvent, or by the presence of crown ethers, triglyme, or hexamethylphosphoramide. The species appears to maintain its geometry whether it is a contact ion pair, a solvent-separated ion pair, or a free ion pair. Walborsky also notes that electron pair repulsions in the planar transition state for delocalization and racemization may play a role in the configurational stability of **76**.

The carbanion **76** does undergo racemization at −5 °C. Moreover, an acyclic isocyanide, (+)-(*R*)-1-phenyl-2-isocyanopropane, does racemize on treatment with base at −70 °C.

$$CH_3NCS \xrightarrow{LiTMP} \underset{\textbf{78}}{LiCH_2NCS}$$



77

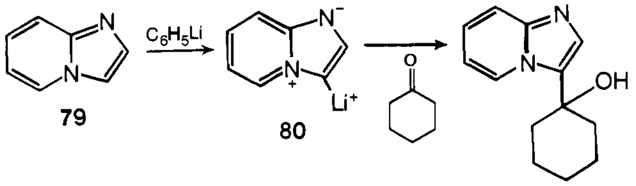
Accordingly, the possibility exists that the mechanism of stabilization of **76** is special for the small ring and that **76** is not a suitable model for **65.** Nonetheless, **76** would appear to provide clear evidence for dipole stabilization and that effect should be considered important for metalated isocyanides until more definitive experiments on other systems are available.

E. Imines

The metalation of activated isocyanates, reported by Hoppe a few years ago, has recently been extended to the reaction of methyl isothiocyanate with LiTMP to give **77.**[83,84] A reasonable mechanism for the reaction involves the formally dipole-stabilized intermediate **78.**

F. Polyazaindenes

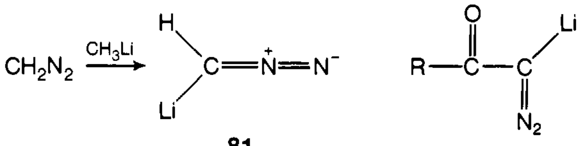
Base-catalyzed hydrogen–deuterium exchange of the protons α to nitrogen in imidazo[1,2-*a*]pyridine (**79**) has been observed to occur preferentially at the 3 position.[85] Paudler and Shin have shown that **79** and its derivatives can be metalated at the same position and that substitution occurs as expected on reaction with cyclohexanone in yields of 15–30%.[86] Dipolar stabilization is illustrated as a factor contributing to the stability of the intermediate **80.**



79 **80**

G. Diazo Compounds

The metalation of diazomethane to give **81** has been reported by Müller et al.[87] Although the species **81** appears too hazardous for general synthetic use, its existence does suggest that dipole stabilization, in addition to hybridization and/or delocalization, could be a factor which favors the formation of the synthetically useful α-lithioacyldiazomethanes **82.**[88]



81 **82**

H. Synthetic Alternatives

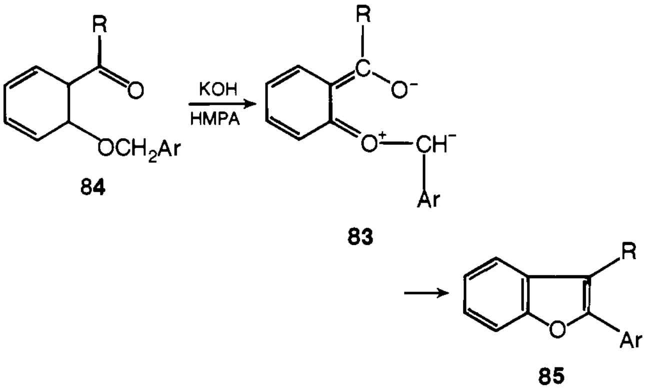
Alternative methods of generating α-nitrogen organometallics exist. From a synthetic point of view the generation of an α-amino organolithium reagent from the corresponding tin derivatives reported by Peterson and Ward appears to be the most convenient and general, although it does require an α-substituted amino precursor.[89] Direct metalation of amines, while possible,[4,90] does not appear useful. However, azaallylic anions are known[91] and have been shown, particularly by Kauffmann, to be synthetically useful. The products from reaction of azaallylic anions and electrophiles can be subjected to hydrolysis to provide overall nucleophilic aminomethylations and the anions are also useful in cycloadditions.[92]

III. Dipole-Stabilized Carbanions Adjacent to Oxygen

The direct formation of stable carbanions α to oxygen is not a facile process. In fact, the effect of an ether oxygen on a prospective carbanion appears to be deactivating with respect to proton removal, due to electron pair repulsions overcoming a favorable inductive effect.[4,93] Such destabilization might provide some of the driving force for the Wittig rearrangements[67,94] and α- and β-eliminations[95] observed for reactions in which α-oxo carbanions are possible intermediates. However, if stabilization of an α-oxo carbanion is provided by unsaturation either for the formation of formally sp^2 carbanions or for delocalization of the carbanion, stable synthetically useful species can be obtained by direct metalation. Cases which have received recent attention are vinyl ethers[96] and allyl ethers.[97]

A. Esters

Although it is possible that some dipole stabilization is provided by the vinylogous ester function in the intermediate **83** in the cyclizations of **84** to the benzofuran **85**,[98] the possibility that



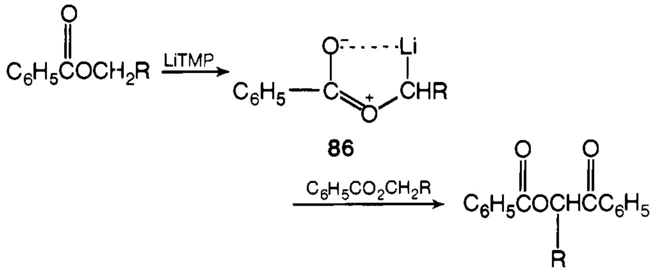
84

83

85

R = H, CH_3

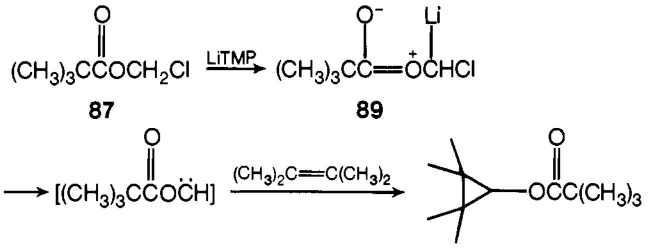
stabilization be delocalization into the phenyl ring is the dominant factor cannot be discounted. The nature of the stabilization of the intermediates **86** involved in the self-condensations of benzyl benzoate, allyl benzoate, and vinyl benzoate is similarly ambiguous.[99]



86

R = C_6H_5, CH=CH$_2$

A transient α-acyloxy carbanion may be involved in the formation of cyclopropyl esters from α-acyloxy carbenoids as illustrated for the conversion of **87** to **88** via **89**. The synthetic



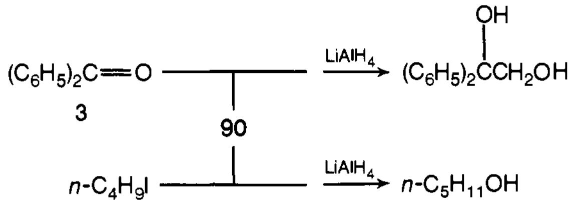
87

89

value of the reaction as well as the interesting idea that the intermediate could be cyclized to a novel 6π dioxane aromatic system has been discussed by Olofson, Lotts, and Barber.[100]

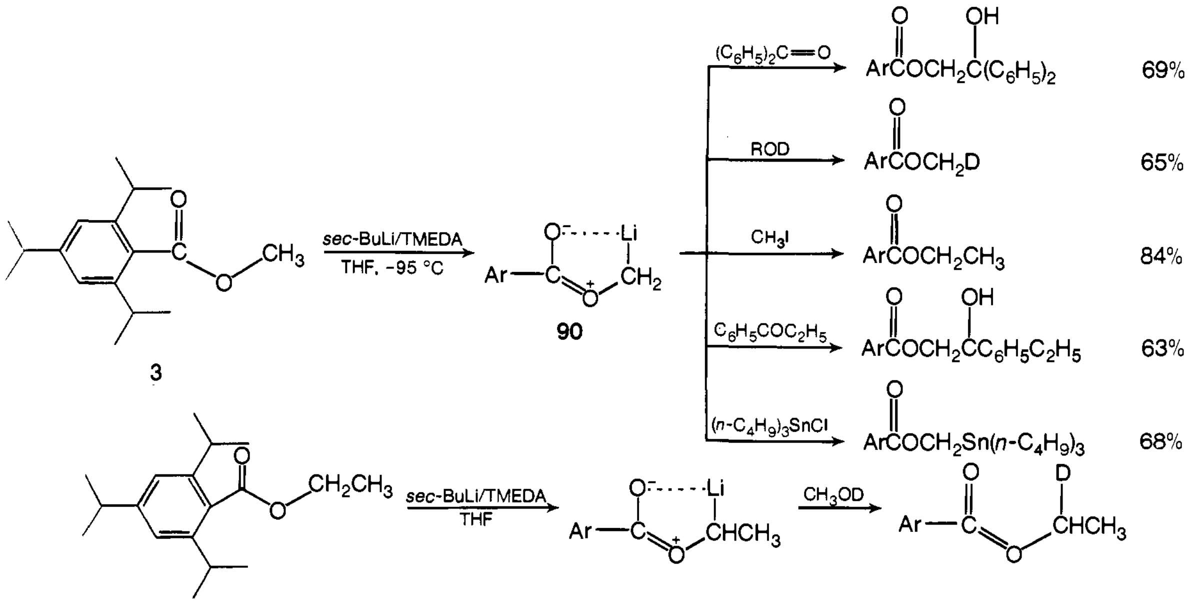
The first case of metalation of an unactivated ester adjacent to the acyl oxygen has been recently reported.[2] The reaction of methyl 2,4,6-triisopropylbenzoate (**3**) with *sec*-butyllithium/tetramethylethylenediamine (TMEDA) at −78 and −95 °C gives the organolithium **90** which can be trapped in acceptable yields as indicated in Scheme VIII. An interesting feature of this system is that a primary alcohol derivative also undergoes metalation. Thus reaction of ethyl 2,4,6-triisopropylbenzoate under the same conditions followed by treatment with methanol-*d* gives 57% deuteration.

When the metalation and electrophilic substitution of these esters is combined with an ester cleavage step, the requirements of Scheme II for an α-heteroatom carbanionic synthon are fulfilled. For example, formation of **90** from **3** when followed by reaction with benzophenone and reduction with lithium aluminum hydride gives 1,1-diphenylethane-1,2-diol. Reaction of **90** with *n*-butyl iodide followed by a similar reductive cleavage gives 1-pentanol.



The formation of **90** by the metalation of **3** provides formation of a formally dipole-stabilized carbanion α to oxygen in a system

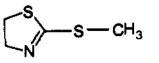
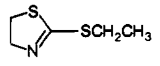
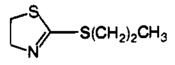
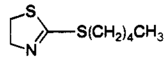
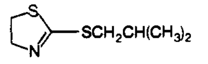
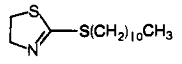
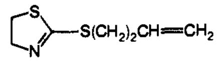
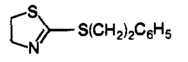
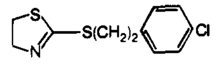
SCHEME VIII



3

90

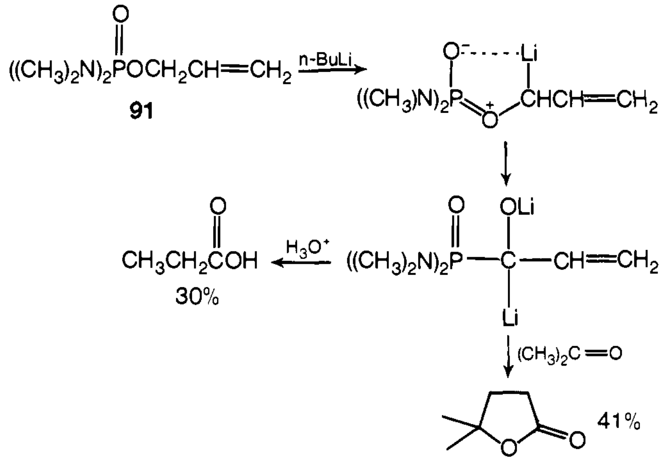
TABLE VII. Formation of 2-Thio(lithiomethyl)thiazoline and Reaction with Alkylating Agents

Reactant	Base	Temp, °C	Solvent	Electrophile	Product	Yield, %	Ref
	*n*-BuLi	−20	THF	CH_3I		60	105
	n-BuLi	−20	THF	C_2H_5Br		45	105
	n-BuLi	−20	THF	*n*-C_4H_9Br		50	105
	n-BuLi	−20	THF	$(CH_3)_2CHBr$		25	105
	n-BuLi	−20	THF	*n*-$C_{10}H_{21}Br$		21	105
	n-BuLi	−20	THF	$CH_2{=}CHCH_2Br$		40	105
	n-BuLi	−20	THF	$C_6H_5CH_2Cl$		80	105
	n-BuLi	−20	THF	*p*-$ClC_6H_4CH_2Br$		70	105

where additional stabilization by convential resonance or hybridization effects seem unlikely. On the other hand, the role of the metal ion and a more quantitative determination of the stability of **90** relative to a species in which the dipole is absent is needed before definitive evidence for dipole stabilization should be claimed.

B. Phosphates

Metalation α to the oxygen of a phosphate is considered to be the first step in the rearrangement of these species to phosphorates.[101] Sturtz et al. have recently reported the interesting rearrangement of such a system to a dianion which can be hydrolyzed to an acid or allowed to react with a carbonyl compound to provide a lactone.[97] The conversions are illustrated for **91** to **92**.



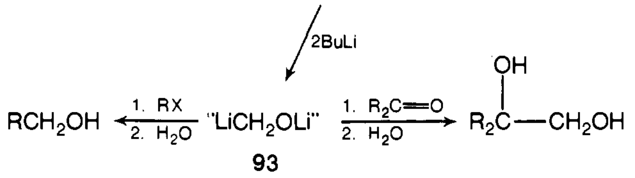
91

92

C. Synthetic Alternatives

Synthetically α-oxo carbanions can be formed by halogen-metal interchange of α-halo ethers[102] or by reduction of formaldehyde.[103] The latter route involves initial reduction to a tin derivative of methanol magnesium chloride which is subsequently cleaved to **93**, which, like **90**, is equivalent to the α-oxomethylene carbanion synthon.

$$CH_2O + Bu_3SnMgCl \longrightarrow Bu_3SnCH_2OMgCl$$



$$\downarrow 2BuLi$$

$$RCH_2OH \xleftarrow[2.\ H_2O]{1.\ RX} \text{"}LiCH_2OLi\text{"} \xrightarrow[2.\ H_2O]{1.\ R_2C{=}O} R_2C(OH){-}CH_2OH$$

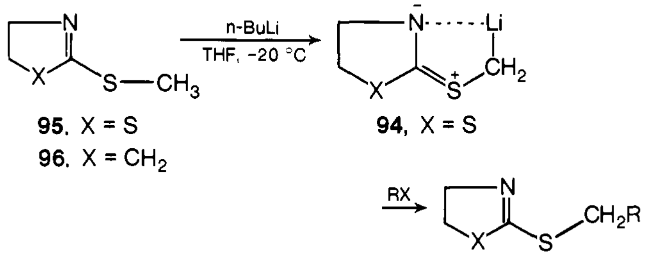
93

IV. Dipole-Stabilized Carbanions Adjacent to Sulfur

The fact that sulfur provides stabilization for a negative charge on an adjacent carbon is well known, although rationalization of this phenomenon in terms of polarization, d-orbital expansion, or other electron acceptance by sulfur is a matter of continuing discussion.[4,6,104] In any case, these mechanisms are reinforced if sulfur bears a positive charge. Accordingly, there are now a number of cases of α-sulfur carbanions which are formally dipole stabilized.

A. Thioimidates

One of the earliest cases of a trappable formally dipole-stabilized carbanion is the organolithium **94**, obtained by metalation of 2-thiomethylthiazoline (**95**).[105] Hirai and Kishida found **94** could be alkylated by primary halides in yields of 68–75% and later reported that the thioimidate **96** was less effective than **95** in this sequence.[106] The difference between **95** and **96** might reflect the importance of an initial complexation of the substrate with a lithium base aggregate, an equilibrium which should be more favorable for **95** than for **96**. The metalations and subsequent electrophilic trapping of a number of the imidates are collected in Table VII.



95, X = S
96, X = CH₂

94, X = S

The work of Meyers[107] and Johnson[108] has revealed a unique synthetic use for **94** and the related organolithiums **97** and **98**. Reaction of these organolithiums with aldehydes and ketones produces thiiranes in yields generally greater than 60% as shown in Table VIII. Conversions of the thiiranes to olefins can be achieved in good yields with phosphines or phosphates. The sequence and the mechanism of the reaction are illustrated in

TABLE VIII. Formation of Thiiranes and Chiral Thiiranes from Dipole-Stabilized Organolithiums

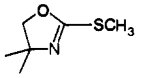
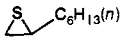
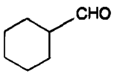
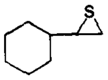
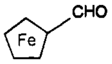
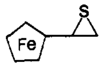
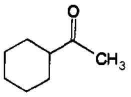
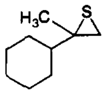
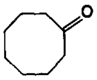
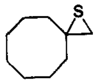
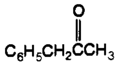
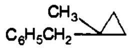
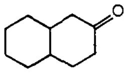
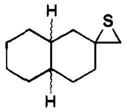
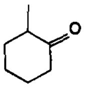
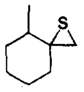
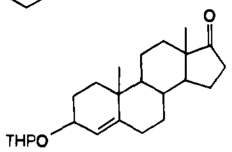
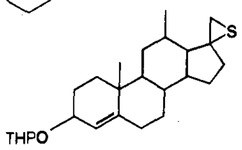
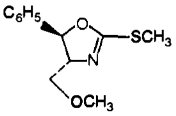
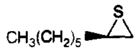
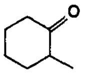
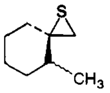
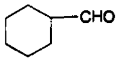
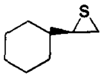
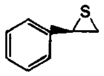
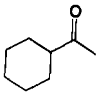
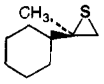
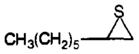
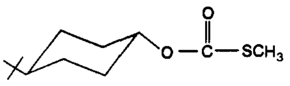
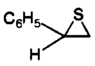
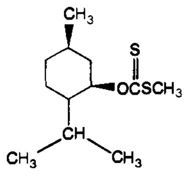
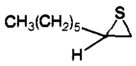
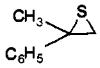
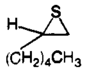
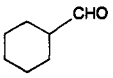
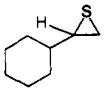
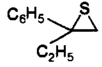
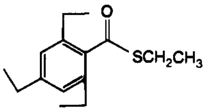
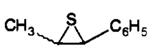
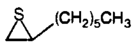
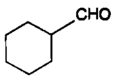
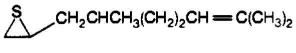
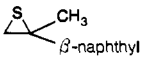
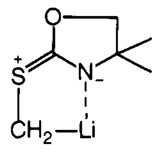
Reactant	Base	Temp, °C	Solvent	Electrophile	Product	Yield,[a] %	Ref
	*n*-BuLi	−78	THF	$CH_3(CH_2)_5CHO$		73	107
	n-BuLi	−78	THF			78	107
	n-BuLi	−78	THF			68	107
	n-BuLi	−78	THF			66	107
	n-BuLi	−78	THF			61	107
	n-BuLi	−78	THF	 $C_6H_5CH_2\overset{O}{\overset{\|}{C}}CH_3$		62	107
	n-BuLi	−78	THF			61	107
	n-BuLi	−78	THF			61	107
	n-BuLi	−78	THF			70	107
	LiDA	−95	THF	$CH_3(CH_2)_5CHO$		53 (21)	107
	LiDA	−95	THF			67	107
	LiDA	−95	THF			64 (32)	107
	LiDA	−95	THF	C_6H_5CHO		48 (19)	107
	LiDA	−95	THF			70	107
	LiDA	−78	THF	$CH_3(CH_2)_5CHO$		71	108
	LiDA	−78	THF	C_6H_5CHO		55 (5)	108
	LiDA	−78	THF	$CH_3(CH_2)_5CHO$		63 (1.5)	108
	LiDA	−78	THF	$C_6H_5COCH_3$		61	108
	LiDA	−78	THF	$CH_3(CH_2)_4CHO$		61	108
	LiDA	−78	THF			77 (9)	108
	LiDA	−78	THF	$C_6H_5COC_2H_5$		64	108

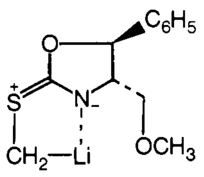
TABLE VIII (*Continued*)

Reactant	Base	Temp, °C	Solvent	Electrophile	Product	Yield,[a] %	Ref
	*sec*-BuLi· TMEDA	−95	THF	1. C_6H_5CHO 2. NaH, THF		71	3
$CH_3N{=}CS(CH_3)_2$	LiDA	−78	THF	1. $CH_3(CH_2)_5CHO$ 2. $NaOC_2H_5$, C_2H_5OH		92	111
	LiDA	−78	THF	1.  2. $NaOC_2H_5$, C_2H_5OH		82	111
	LiDA	−78	THF	1. $(CH_3)_2C{=}CH(CH_2)_2CH_3CHCH_2CHO$ 2. $NaOC_2H_5$, C_2H_5OH		88	111
	LiDA	−78	THF	1. β-Naphthyl methyl ketone 2. $NaOC_2H_5$, C_2H_5OH		45	111

[a] Value in parentheses is enantiomeric excess.[9]



97

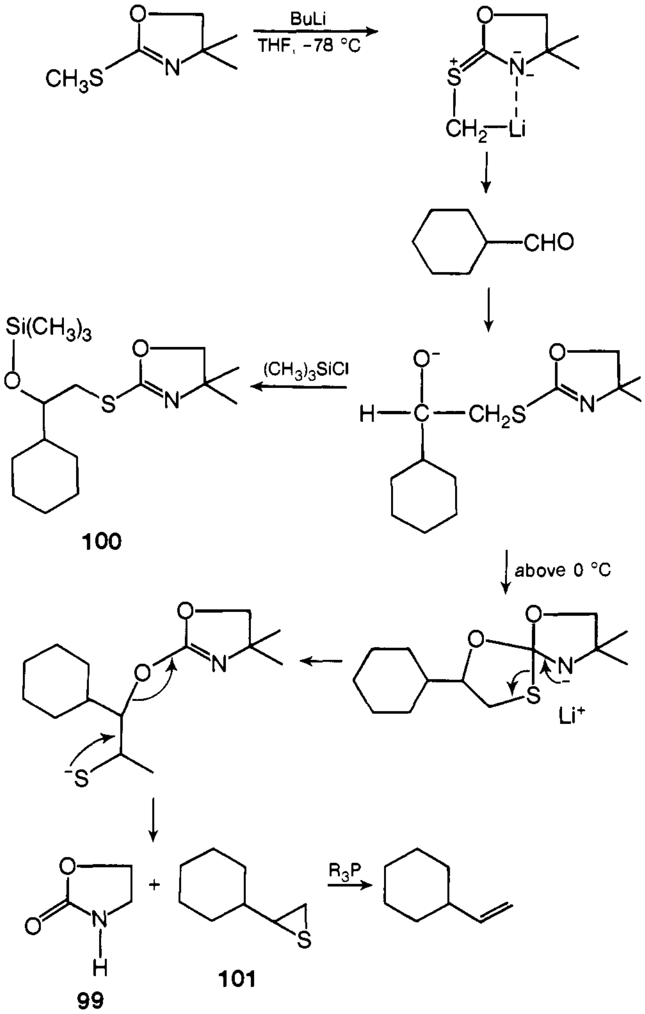


98

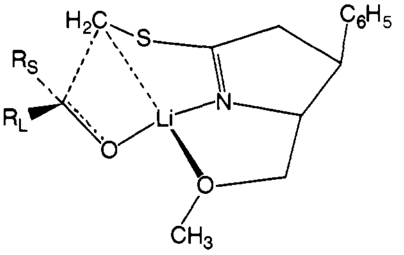
Scheme IX for the reaction of **97** with cyclohexanecarboxaldehyde.

The key step is the intramolecular rearrangement of the oxazoline from sulfur to oxygen. Evidence for the scheme comes from detection of the oxazolidinone **99** as a product[107] and trapping of the initial adduct by trimethylsilyl chloride as **100**. Cases in which the methyl was further substituted by allyl or benzyl groups were found to give predominantly *E* isomers. That result can be rationalized in terms of a transition state for nucleophilic addition to the carbonyl which minimizes steric interactions.[109]

SCHEME IX

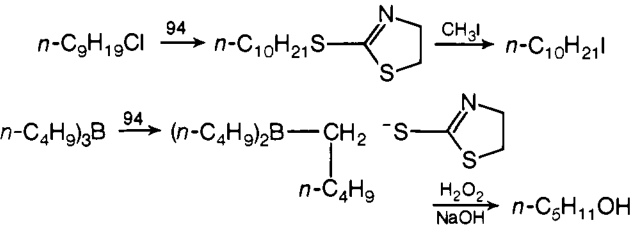


A most imaginative use of this sequence provides optically active thiiranes and olefins of established absolute configuration in optical yields up to 32%.[107,108] For example, reaction of **98** and cyclohexanecarboxaldehyde gives the thiirane (*R*) − **101** in 64% yield and 32% enantiomeric purity. Reaction of **98** with 2-methylcyclohexanone in the sequence of Scheme IX provides 2-methylmethylenecyclohexane in 69% yield and 30% enantiomeric purity.[107] The available results on thiirane synthesis by this route are summarized in Table VIII. Asymmetric induction by **98** may be understood in terms of the transition state depicted as **102** where R_L and R_S represent the large and small groups on the carbonyl carbon. In this view the steric interactions are minimized for a transition state in which the carbonyl oxygen is associated with the complexing site of a four-coordinate lithium atom which is also complexed to the nitrogen, oxygen, and the carbon of the reagent.[107] Analogy with the asymmetric reactions of chiral oxazolines seems particularly pertinent.[109] This indication that the metal ion plays an important role in the reaction of a formally dipole-stabilized carbanion provides circumstantial support for the importance of the metal ion in the structure of such species.



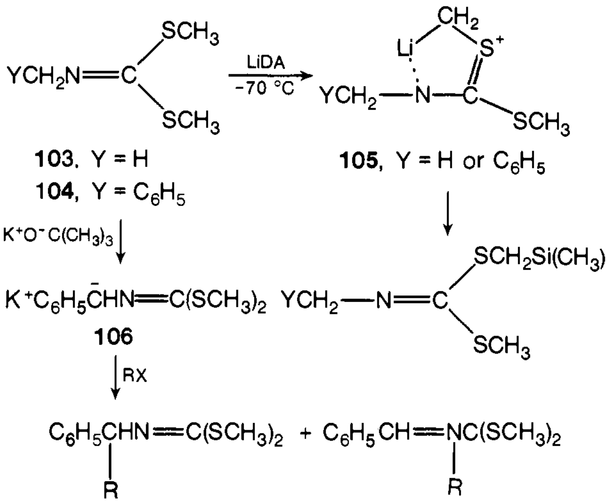
102

Two interesting uses of the organolithium **94** in homologative



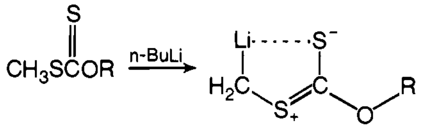
transformations have appeared. Hira and Kishida have reported a homologation–iodation of alkyl halides as illustrated for *n*-nonyl chloride.[105] Negishi et al. have reported **94** can be used in the conversions of organoboranes to alcohol homologs as shown for tri-*n*-butylborane.[110]

A case in which complexation is suggested to be important has been reported by Hoppe.[111] Reaction of the iminodithiocarbonate **103** with lithium diisopropylamide at −70 °C gives the carbanions **105** which can be trapped with chlorotrimethylsilane. Reaction of **104** under similar conditions gives two products from **105** and **106** in an 85:15 ratio. However, if **104** is allowed to react with potassium *tert*-butoxide, the anion **106** is produced, as indicated by the products of alkylation. The direction of metalation is considered to be controlled by chelation of the lithium with the imino nitrogen. Hoppe has also shown that **105** can be used to provide thiiranes with carbonyl compounds.[111]



B. Dithiocarbonates

Johnson and co-workers have reported that dithiocarbonates can be metalated α to sulfur to provide synthetically useful organolithium reagents. The reactions of **107** are similar to those of **94**. For example, cyclohexanecarboxaldehyde and **107** (R = menthyl) provide the thiirane **101** in 77% yield and 9% enantiomeric excess.[108]

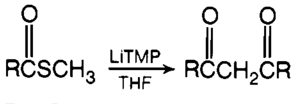


107

R = *trans*-4-*t*-Bu cyclohexyl, Me

C. Thioesters

A dipole-stabilized carbanion has been postulated as an intermediate for the conversion of methyl thiobenzoate to dibenzoylmethane by lithium 2,2,6,6-tetramethylpiperidide.[30] That reaction provides a model for the synthesis of other β-diketones from methyl thioesters in yields of 60–82%. The reaction is

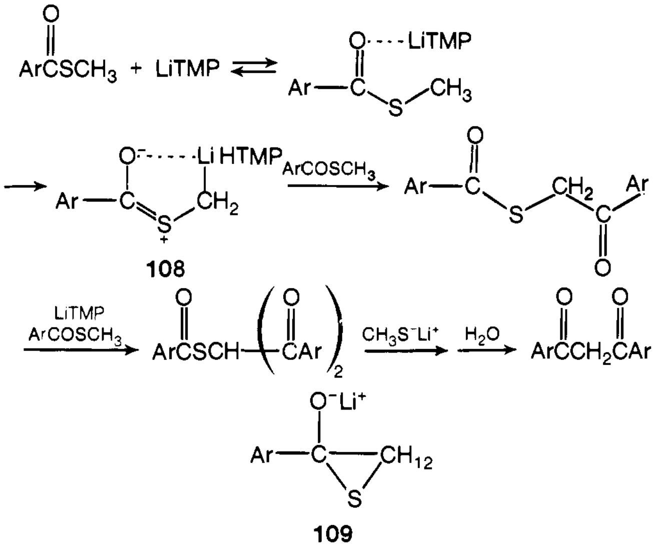


$$\mathrm{R\overset{O}{\overset{\|}{C}}SCH_3 \xrightarrow[THF]{LiTMP} R\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}R}$$

R = C_6H_5, *p*-$CH_3OC_6H_4$, *p*-ClC_6H_4, $(CH_3)_3C$

restricted to cases in which the thioester does not bear an acidic hydrogen on the carbon adjacent to the carbonyl group. The conversion of ethyl thiobenzoate to methyldibenzoylmethane proceeds in 28% yield and 2-mercaptoprophiophenone is also formed. If the reaction is carried out at −98 °C, however, 2-thiobenzylpropiophenone is the only product isolated.[3]

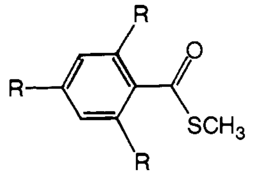
SCHEME X



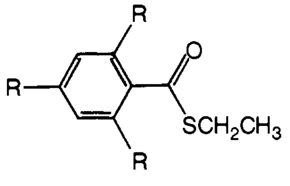
The mechanism proposed for the formation of the β-diketones from the methyl thioesters is considered to involve initially a dipole-stabilized carbanion **108** which can react by intra- or intermolecular paths to give the observed β-diketone as shown in Scheme X. At −98 °C the reaction of ethylthiobenzoate has proceeded to the point that the proposed 2-thiobenzoyl propiophenone intermediate can be observed. The initial formation of a complex as shown is based on the fact the reaction appears to be lithium ion dependent. A double-labeling experiment rules out pathways involving the homoenolate **109**, for the reaction of ethyl thiobenzoate, and, by analogy, for the other cases also.[3]

Consideration of the proposed mechanism shows that if nucleophilic addition of **108** to the thioester were suppressed, formation of a trappable lithiomethyl thioester might be possible. Chronologically, achievement of this objective by the use of methyl 2,4,6-triethylthiobenzoate (**110**) as the substrate preceded the successful use of this strategy with the amide **2** and the ester **3** (vide supra).

Reaction of **110** with *n*-butyllithium provided the organolithium reagent **111** which could be allowed to react with a wide variety of subsequently added electrophiles as shown in Scheme XI.[1] Similar metalations have been carried out with the methyl and ethyl thioesters **4, 112,** and **113.**[3] The latter are particularly interesting as attempts to metalate the ethyl group of a 2-thioethylthiazoline were not successful. The case is illustrated for metalation of **113b** to give **114** and subsequent reaction with benzophenone.[1]



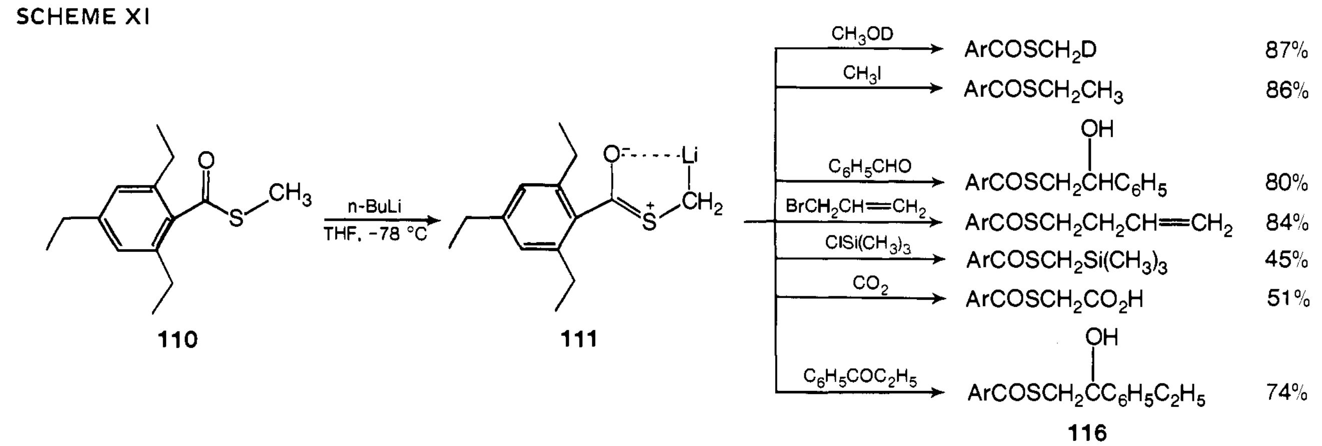
112, R = CH_3, $C(CH_3)_3$



113a, R = C_2H_5
b, R = $CH(CH_3)_2$

The use of **111** and **114a** (Ar = $Ph(C_2H_5)_3$) as α-lithiomethanethiol and α-lithioethenethiol synthons is illustrated for the conversion of benzyl bromide to 2-phenylethylmercaptan and 2-mercapto-1-phenylpropene in **77** and 81% yields,[1] respectively. Another synthetic use of **111** and **114** is in the synthesis of thiiranes and olefins. For example, **115**, the product of **114** and benzaldehyde, gives 2-methyl-3-phenylthiirane upon treatment with sodium hydride in THF at ambient temperature,

SCHEME XI



$\mathbf{110} \xrightarrow[\text{THF, -78 °C}]{\text{n-BuLi}} \mathbf{111}$

$\xrightarrow{\mathrm{CH_3OD}} \mathrm{ArCOSCH_2D}$ 87%

$\xrightarrow{\mathrm{CH_3I}} \mathrm{ArCOSCH_2CH_3}$ 86%

$\xrightarrow{\mathrm{C_6H_5CHO}} \mathrm{ArCOSCH_2CH(OH)C_6H_5}$ 80%

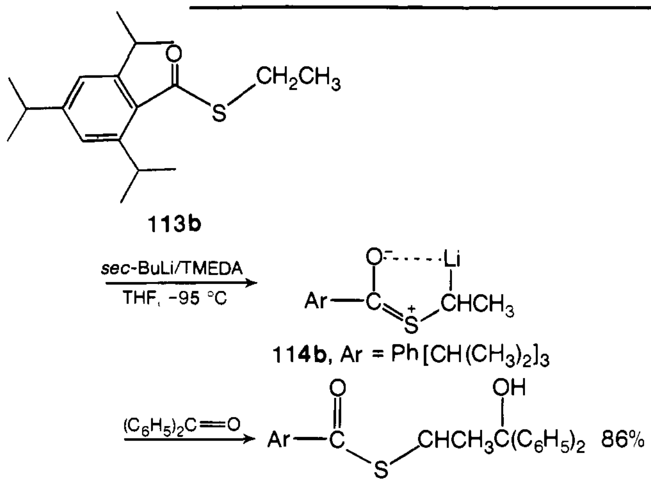
$\xrightarrow{\mathrm{BrCH_2CH{=}CH_2}} \mathrm{ArCOSCH_2CH_2CH{=}CH_2}$ 84%

$\xrightarrow{\mathrm{ClSi(CH_3)_3}} \mathrm{ArCOSCH_2Si(CH_3)_3}$ 45%

$\xrightarrow{\mathrm{CO_2}} \mathrm{ArCOSCH_2CO_2H}$ 51%

$\xrightarrow{\mathrm{C_6H_5COC_2H_5}} \mathrm{ArCOSCH_2C(OH)C_6H_5C_2H_5}$ 74%

116

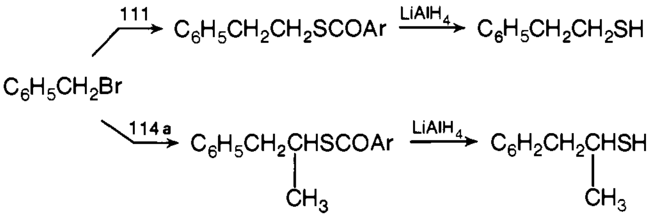


113b

$\xrightarrow[\text{THF, -95 °C}]{sec\text{-BuLi/TMEDA}}$

114b, Ar = Ph[CH(CH$_3$)$_2$]$_3$

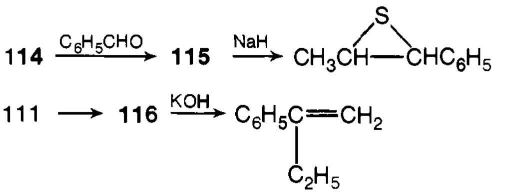
$\xrightarrow{\mathrm{(C_6H_5)_2C{=}O}} \mathrm{Ar{-}C(O){-}S{-}CHCH_3C(OH)(C_6H_5)_2}$ 86%



$\mathrm{C_6H_5CH_2Br} \xrightarrow{\mathbf{111}} \mathrm{C_6H_5CH_2CH_2SCOAr} \xrightarrow{\mathrm{LiAlH_4}} \mathrm{C_6H_5CH_2CH_2SH}$

$\mathrm{C_6H_5CH_2Br} \xrightarrow{\mathbf{114a}} \mathrm{C_6H_5CH_2CH(CH_3)SCOAr} \xrightarrow{\mathrm{LiAlH_4}} \mathrm{C_6H_2CH_2CH(CH_3)SH}$

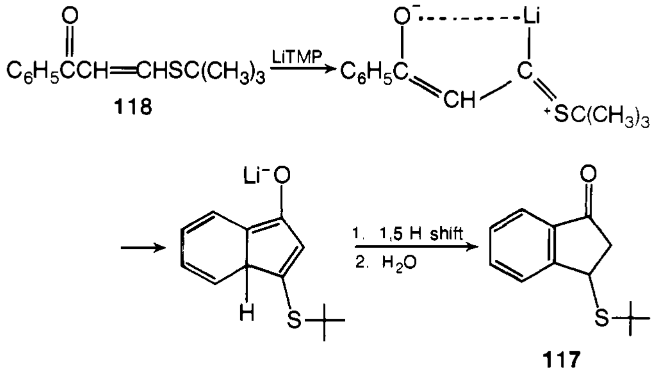
and **116** gives α-ethylstyrene on being heated with potassium hydroxide in ethanol.[3]



$\mathbf{114} \xrightarrow{\mathrm{C_6H_5CHO}} \mathbf{115} \xrightarrow{\mathrm{NaH}}$

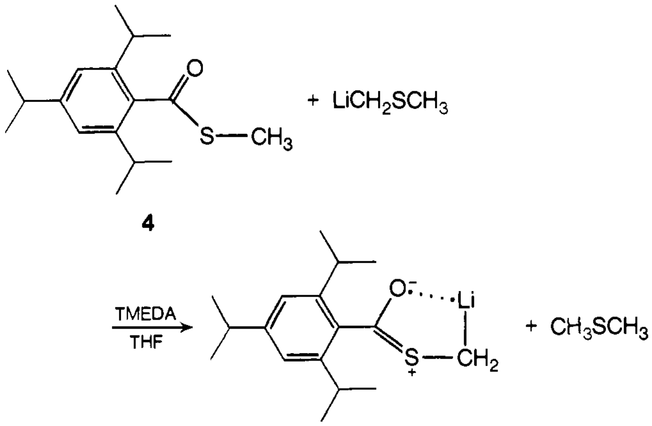
$\mathbf{111} \longrightarrow \mathbf{116} \xrightarrow{\mathrm{KOH}} \mathrm{C_6H_5C(C_2H_5){=}CH_2}$

A reaction in which a vinylic dipole-stabilized carbanion could be involved is illustrated by the synthesis of the tetralone **117** from the vinylogous thioester **118**. Reaction is presumed to involve the intermediate α-lithiothio species rather than an ortho-lithiated species because the corresponding oxygen compound does not undergo cyclization.[112]



$\mathrm{C_6H_5C(O)CH{=}CHSC(CH_3)_3}$ **118** $\xrightarrow{\mathrm{LiTMP}}$ $\xrightarrow[\text{2. H}_2\text{O}]{\text{1. 1,5 H shift}}$ **117**

It has also been shown that the presence of the carbonyl group stabilizes an α-lithiocarbon bond with respect to a thioether. Thus, the equilibrium between **4** and lithiomethyl methyl sulfide has been shown to lie far on the product side by direct observation of an equilibrated solution by NMR.[3] While that result is consistent with dipole stabilization, any of the other mechanisms by which sulfur provides stabilization for an adjacent negative charge could also be enhanced by the presence of a carbonyl function. Indeed, definitive tests for dipole stabilization by sulfur appear to be less available than for nitrogen and oxygen.



4

$+ \mathrm{LiCH_2SCH_3} \xrightarrow[\text{THF}]{\text{TMEDA}} \; + \mathrm{CH_3SCH_3}$

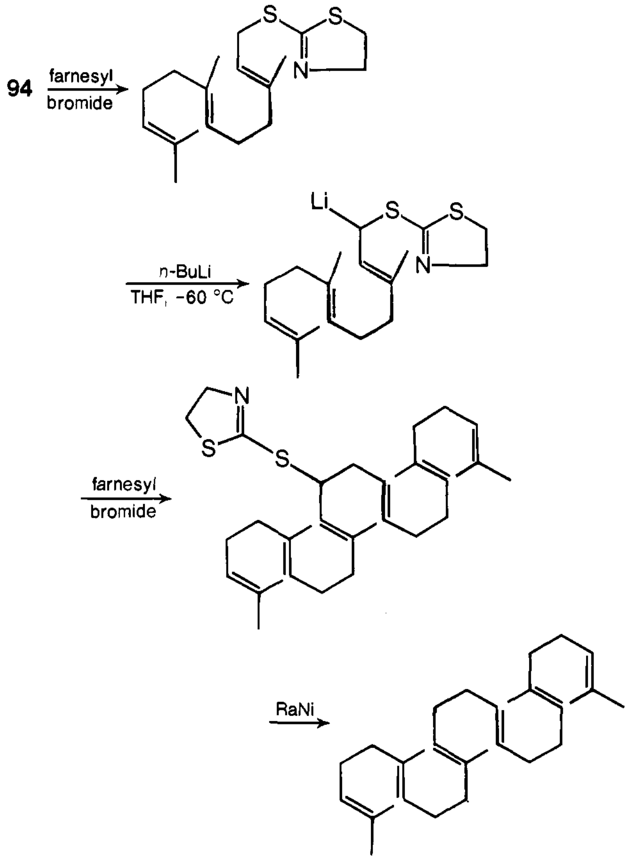
D. Activated Cases

Although cases with additional activation are beyond the scope of this review, the use of a bis(dithiocarbonate) as an acyl anion equivalent has been claimed to have advantages in ease of cleavage over the more well-explored dithiane route.[113] More generally the use of allyl derivatives of thioimidate and thiocarbonate derivatives has proved exceedingly useful in natural product syntheses. An example is shown in Scheme XII of the synthesis of squalene. Other examples include the efficient synthesis of α-*cis*-bergamotene,[114] nuciferal,[10,115] and alkenol pheromones.[116] Regiospecific α-alkylation is notable in these cases as is the utilization of sigmatropic rearrangements. Such reactions are useful in making *E* α,β-unsaturated aldehydes from allyl dithiocarbonates and *E* γ,δ-unsaturated esters from allyl dithioesters.[117]

E. Synthetic Alternatives

Dimethyl sulfide and thioanisole can be metalated and trapped with electrophiles, but the products are not readily converted to mercaptans.[118,119] Anions from sulfoxides and sulfones are readily formed and easily undergo electrophilic reactions, but

SCHEME XII



a reductive step would be required to return sulfur to the mercaptan level.

V. Overview

The preceding review shows that there are a number of functional derivatives of nitrogen, oxygen, and sulfur in which the heteroatom is the positive end of a dipole and from which an α heteroatom carbanion can be formed by loss of a proton to a strong base. In many cases the organometallics thus produced have proven of synthetic value.

The hypothesis that organometallics can be dipole stabilized appears to be useful, although substantial questions remain to be addressed. Quantitative measures of the extent of dipole stabilization should be attempted.[8] The role of the metal ion, the stereochemistry of the intermediates, and the more extensive synthetic use of these species in syntheses need to be investigated. The field appears to hold opportunities for new discoveries and advances in understanding which would be of complementary synthetic and mechanistic interest, and it is hoped this review will stimulate such further work.

VI. Addendum

The generation and synthetic utilization of species which can be described as dipole-stabilized carbanions is continuing in a number of laboratories. This section includes those cases which have appeared in the last few months.

II.B Amides

Reaction of the metalated vinylogous amide derivatives **41** with phenones and conversions of the products to lactones and ketones has been recently reported.[120] A detailed report of the metalation and electrophilic trapping of *N,N*-diisopropylformamide has appeared.[121] The novel dimetalation and selective electrophilic substitution of dilithiobenzylbenzamide on the benzylic carbon have been communicated.[122]

Metalations of **2** and electrophilic trapping of **36** have been independently reported. Important additional results include the demonstration that methylation of **36** to give *N*-ethyl-*N*-methyl-2,4,6-triisopropylbenzamide (**2**) followed by metalation and reaction with benzaldehyde occurs on the ethyl group and that *N,N*-dimethyltriphenylacetamide can be metalated, electrophilically substituted, and subsequently cleaved by reduction and hydrolysis.[123] The former provides further support for the preference of metalation syn to the carbonyl group of amides and the latter the lithiomethylamine synthetic equivalent.

II.D. Isocyanides

The metalation and electrophilic trapping of vinyl isocyanides have been reported.[124] Reaction of **68** with a variety of imines has appeared.[125]

III.A. Esters

Metalation and alkylation of the methyl group of methyl 2,4,6-tri-*tert*-butylbenzoate have been reported.[123]

III.C. Synthetic Alternative

A new and general method of synthesis of α-alkoxy organolithiums has been achieved by addition of tributylstannyllithium to an aldehyde followed by reaction with α-chloroethyl ethyl ether and then *n*-butyllithium. The subsequent reaction of the α-oxoorgano lithiums with electrophiles and cleavage of the ether function provides the carbinyl carbanion equivalent.

IV.C. Thioesters

The metalation of the methyl group of some vinylogous methyl thioesters is the initial step of the reactions of these species with lithium amides.[127]

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