Metalation and Electrophilic Substitution of Amine Derivatives Adjacent to Nitrogen: α-Metallo Amine Synthetic Equivalents

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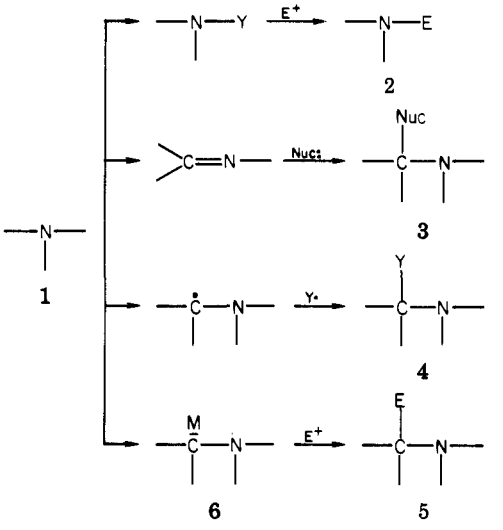
I. Introduction

The preparation and elaboration of amines is a matter of long-standing interest in organic synthesis. Most of the classical syntheses employ as the key step nucleophilic substitution either by nitrogen or by a nucleophile to a carbon adjacent to nitrogen. A sequence involving nucleophilic substitution by a nitrogen is shown in Scheme I for the transformation of 1 to 2, in which a masking or activating group Y often is needed in the first step. Methodology for achieving nucleophilic substitution adjacent to nitrogen is illustrated by the conversion of 1 to 3. Oxidative conversion of an amine to an imine, or more commonly, the formation of the imine from the condensation of 1 and an aldehyde or ketone, is followed by addition of a nucleophile to the α position in this approach. This sequence is effective with a wide variety of amines and nucleophiles and is probably the most widely used strategy for amine elaboration involving substitution at carbon.[1,2] Radical substitutions, shown for the conversion of 1 to 4 in Scheme I has also been achieved at the carbon adjacent to nitrogen of amines or derivatives and the synthetic utility of this approach is at a promising stage of development.[3]

SCHEME I



Classical syntheses of amines do not allow electrophilic substitution adjacent to nitrogen. The nonbonding electrons on nitrogen would be expected to interfere with direct substitution and the α-hydrogens of amines are not sufficiently acidic to be removed by strong bases except in systems which have additional activation. Thus the conversion of 1 to 5 either directly or via 6, as shown in Scheme I, has not been possible generally.

However, recent studies of a number of amine derivatives have shown that protons which are adjacent to a nitrogen bearing an electron-withdrawing group can be acidic. Thus α-metallo amine synthetic equivalents 6 can be prepared and conversion of an amine 1 to 5 in which the α-hydrogen of the amine is replaced by an electrophile, becomes possible. This approach provides a new general strategy for amine elaboration by charge affinity inversion or umpolung of the customary amine reactivity.[4]

II. Activating Groups

A general sequence for electrophilic substitution at the α-carbon of a secondary amine is illustrated in Scheme II. An activating group Z is added to the amine to afford a derivative 7. Subsequent removal of

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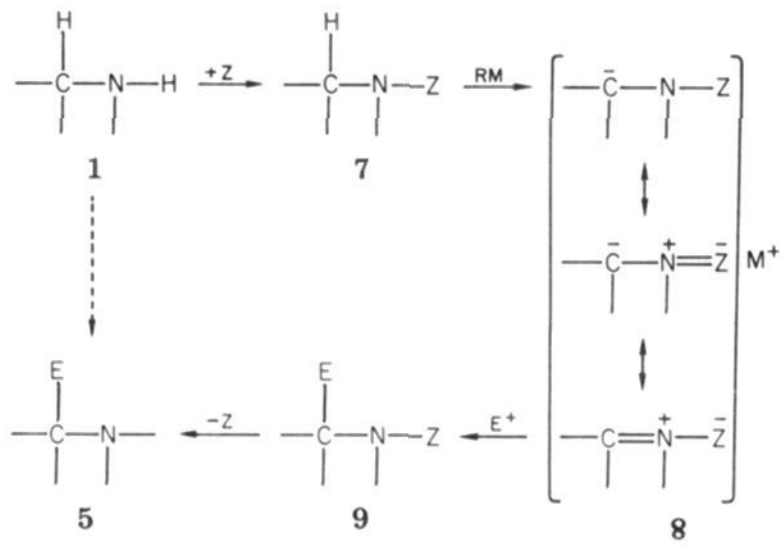
David B. Reitz received his B.S. degree from Kent State University in 1972 and his Ph.D. from the University of Illinois in 1977. His graduate work involved the investigation of dipole-stabilized carbanions from thio esters. He has a continuing interest in organometallic chemistry and in synthetic methodology. Dr. Reitz was a research chemist at the Proctor and Gamble Company in Cincinnati, Ohio from 1977 to 1979. He then moved to the Monsanto Agricultural Products Company in St. Louis, MO as a member of the synthesis section and he has recently transferred to the process development section.

SCHEME II

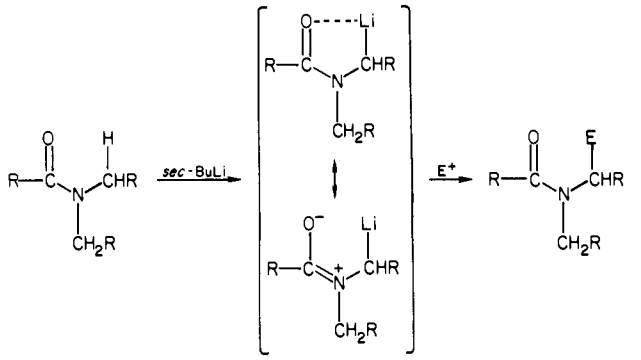


a proton adjacent to the nitrogen of **7** gives **8** which then is allowed to react with an electrophile to give the substituted derivative **9**. Removal of Z from **9** provides the α electrophilically substituted amine **5**. In this sequence the formation of **8**, an α-metallo amine synthetic equivalent, by deprotonation of **7** is the novel step. The ability of Z to provide stabilization for removal of the α-proton of **7** is the key to this methodology.

The group Z can provide stabilization in the transition state leading to **8** by complexation with the metal of the base, by dipole stabilization, and/or by resonance delocalization. Association in a preequilibrium complex can deliver the base to the α-proton and enhance the later contributions. Examples of each type of stabilization are known. Carbanions corresponding to **8** formed from amides and formamidenes are considered to be associated and dipole stabilized while the derivatives from nitrosoamines are resonance stabilized (vide infra). In addition to promoting the acidity of the *proton adjacent to nitrogen, the group Z, in order to be* synthetically useful, must not bear kinetically acidic protons, must be stable toward strongly basic reagents, must not interfere with the electrophilic substitution, and must be conveniently added in the first step and removed in the last step of the sequence.

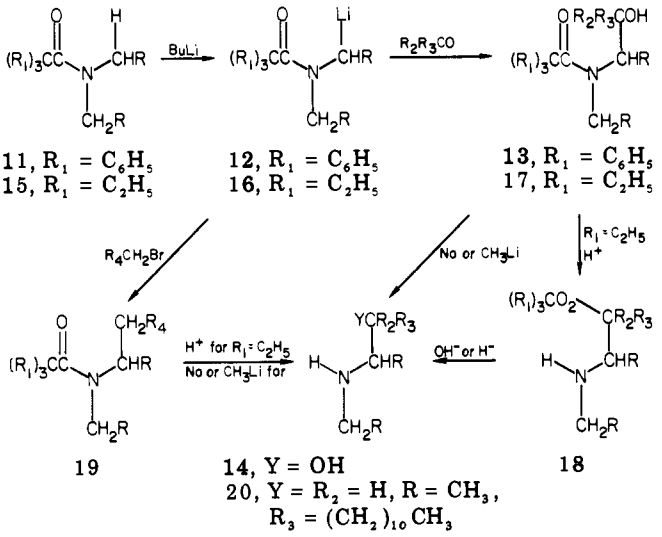
A number of groups which are useful in the sequence of Scheme II have been developed in recent years. In this report we will summarize the recent synthetic chemistry of these α-metallo amine synthetic equivalents. The review is organized on the basis of the type of functional groups and will not include much of the early work in this area which has been part of other summaries.[5,6] Specifically, material covered in our 1978 report on dipole-stabilized carbanions will be included only as needed for background in the present more prescribed coverage. All of the material in the tables and many of the synthetic developments which make this metholology generally useful postdate the earlier review. The schemes have generally been simplified for clarity and the tables should be consulted for details. The focus of the present review is on species in which the α-carbon of the amine derivative is activated primarily by the substituted nitrogen. Some examples which are of particular synthetic value and have an additional activating functional group, however, will be noted. The metalations and substitutions of nitro compounds, which can provide α-electrophically substituted amines by subsequent reduction of the nitro group, will not be included.[7]

SCHEME III



10

SCHEME IV[a]



11, $R_1 = C_6H_5$
15, $R_1 = C_2H_5$

12, $R_1 = C_6H_5$
16, $R_1 = C_2H_5$

13, $R_1 = C_6H_5$
17, $R_1 = C_2H_5$

19

14, Y = OH
20, Y = R_2 = H, R = CH_3, $R_3 = (CH_2)_{10}CH_3$

18

[a] R = H, alkyl.

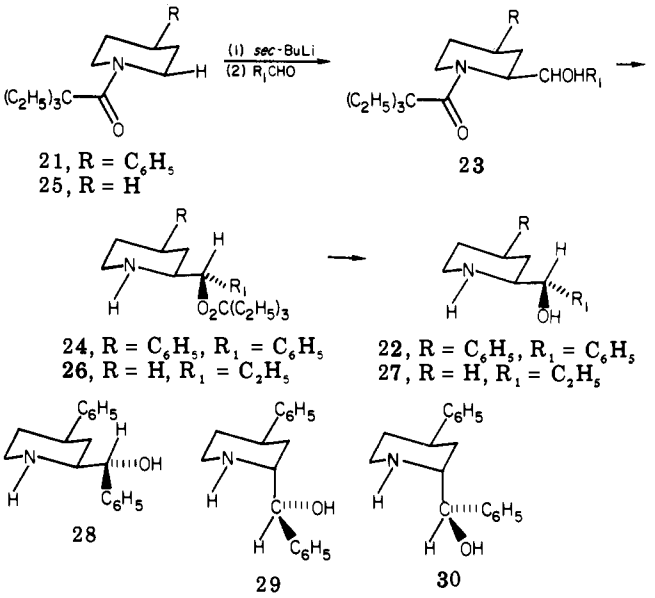
A. Amides (Z = C(=O)R)

The observation that dipole-stabilized carbanions **10** can be formed from amides and undergo electrophilic substitution as shown in Scheme III led to investigations of a number of systems in which the activating function Z contains a carbonyl group.[5,6,8] The conundrum which these studies face is the need for a carbonyl group which can be efficiently added to and cleaved from the amine while being resistant to nucleophilic addition by the alkyllithium base required to form the carbanionic intermediate **10**.

Two amide systems have been reported which allow electrophilic substitution of methyl and primary positions of unactivated amines as shown in Scheme IV. The triphenylacetamide system **11** can be lithiated to provide the intermediate **12** which reacts with nonenolizable aldehydes and ketones to give hydroxy amides **13** in useful yields (Table I).[9] However, at temperatures >0 °C transmetalation to an ortho position of one of the benzene rings followed by migration of the carbonyl group is observed. Hydrolysis of **13** is achievable with dissolving alkali metals/naphthalene or methyllithium to give the hydroxy amines **14** in moderate yields.

The diethylbutanamide system **15** can be lithiated to give **16** which reacts with aldehydes and ketones to give **17** in useful yields (Table I).[10] The amido alcohols **17** rearrange on treatment with acid to amino esters **18**

SCHEME V



21, $R = C_6H_5$
25, R = H

23

24, $R = C_6H_5$, $R_1 = C_6H_5$
26, R = H, $R_1 = C_2H_5$

22, $R = C_6H_5$, $R_1 = C_6H_5$
27, R = H, $R_1 = C_2H_5$

28

29

30

which subsequently can be hydrolyzed to the corresponding amino alcohols **14** in good yields. By these methodologies dimethylamine, diethylamine, and the piperidines have been substituted as shown in Scheme IV and detailed in Table II.

Alkylation is also possible; for example, the organolithium reagent **16** can effect nucleophilic displacement on primary halides and **12** reacts with benzyl halides (Table I). Reaction of **16** ($R_1 = C_2H_5$, R = CH_3) with dodecyl bromide gives **19** ($R_1 = C_2H_5$, R = CH_3, $R_4 = (CH_2)_{10}CH_3$) in 65% yield. When followed by strong acid hydrolysis this sequence provides *N*-(1-methyltridecyl)-*N*-ethylamine (**20**) in 79% yield. A similar alkylation of the 4-phenylpiperidinyl derivative provides 2-butyl-4-phenylpiperidine in 62% overall yield.[11]

The regiochemistry of substitution by aldehydes on piperidine rings has been determined with respect to both the configuration on the ring and at the carbon-oxygen bond as shown in Scheme V. From the 4-phenylpiperidinyl amide **21** the equatorial threo amino alcohol **22** is obtained in 76% yield in four steps. In this sequence a mixture of diasteromeric amido alcohols **23** is converted to only the threo amino esters **24** showing that the threo stereospecificity is achieved during the acid driven N-to-O acyl migration. The erythro amino alcohol **28** can also be obtained from the mixture **23**. A sequence of oxidation, equilibration, and reduction of **23** also provides the diastereomers **29** and **30**. In a similar sequence the piperidine derivative **25** was converted to the ester **26**, hydrolysis of which gives an epimer of conhydrin **27**.[11]

The success of the α-trisubstituted systems **11** and **15** in providing activation for metalation by a carbonyl group which is stable to the organolithium base while being sufficiently reactive for cleavage of the substituted amide is attributed to appropriate steric hinderance at the carbonyl. The advantages of ease of preparation and use of these systems is counterbalanced by the severe conditions required for the cleavage.

A number of amides have been studied in which additional activation for metalation is provided by carbon–carbon unsaturation. The dianion of *N*-benzylbenzamide (**31**), which can be generated from the amide

TABLE I. Formation of *N*-(α-Lithioalkyl) Trisubstituted Acetamides and Reactions with Electrophiles

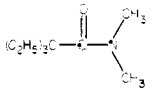
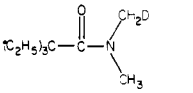
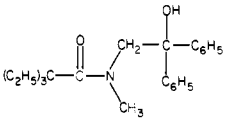
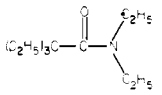
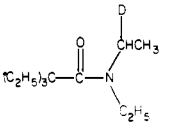
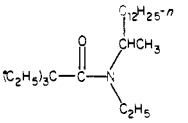
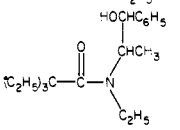
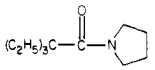
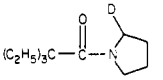
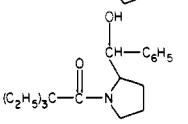
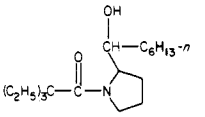
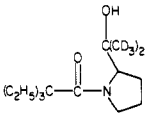
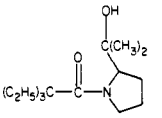
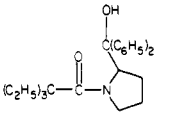
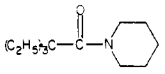
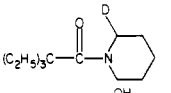
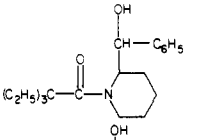
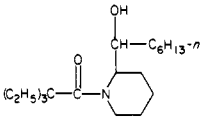
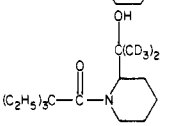
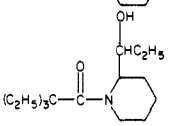
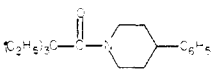
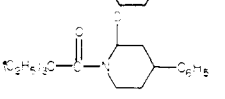
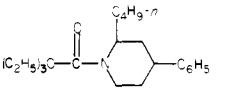
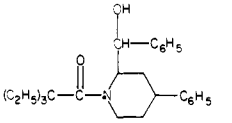
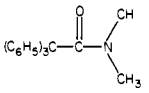
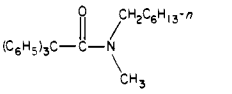
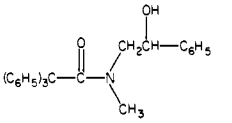
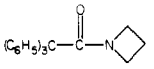
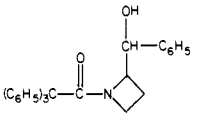
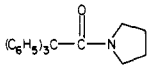
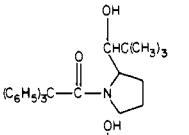
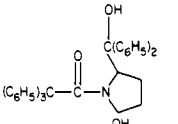
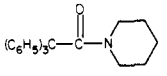
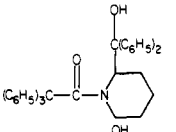
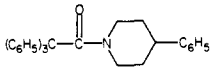
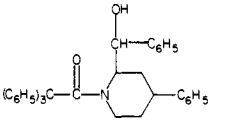
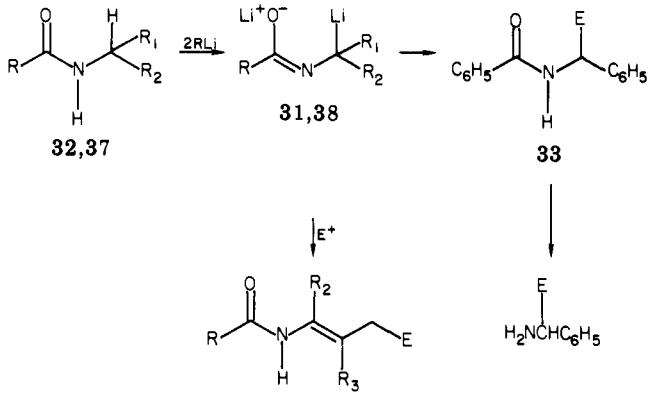
reactant	base	temp, °C	solvent	electrophile	product	yield, %	ref
	*sec*-BuLi·TMEDA	−78	THF	CH_3OD		90 (>95% d_1)	10
	sec-BuLi·TMEDA	−78	THF	$(C_6H_5)_2CO$		91	10
	*sec*-BuLi·TMEDA	−18 → 0	Et_2O	CH_3OD		91 (93% d_1)	11
	sec-BuLi·TMEDA	−18 → 0	Et_2O	n-$C_{12}H_{25}Br$		65	11
	sec-BuLi·TMEDA	−78	Et_2O	C_6H_5CHO		48	10
	*sec*-BuLi·TMEDA	−78	Et_2O	CH_3OD		94 (>92% d_1)	10
	sec-BuLi·TMEDA	−78	Et_2O	C_6H_5CHO		72	10
	sec-BuLi·TMEDA	−78	Et_2O	n-$C_6H_{13}CHO$		85	10
	sec-BuLi·TMEDA	−78	Et_2O	$(CD_3)_2CO$		69	10
	sec-BuLi·TMEDA	−78	Et_2O	$(CH_3)_2CO$		37	10
	sec-BuLi·TMEDA	−78	Et_2O	$(C_6H_5)_2CO$		35	10
	*sec*-BuLi·TMEDA	−18 → 0	Et_2O	CH_3OD		92 (>92% d_1)	11
	sec-BuLi·TMEDA	−78, −18 → 0	Et_2O	C_6H_5CHO		72	10, 11
	sec-BuLi·TMEDA	−78	Et_2O	n-$C_6H_{13}CHO$		67	10
	sec-BuLi·TMEDA	−78	Et_2O	$(CD_3)_2CO$		64	10
	sec-BuLi·TMEDA	−18 → 0	Et_2O	C_2H_5CHO		65	11
	*sec*-BuLi·TMEDA	−18 → 0	Et_2O	CH_3OD		87 (90% d_1)	11

TABLE I (Continued)

reactant	base	temp, °C	solvent	electrophile	product	yield, %	ref
	sec-BuLi·TMEDA	−18 → 0	Et_2O	*n*-C_4H_9I		69	11
	sec-BuLi·TMEDA	−18 → 0	Et_2O	C_6H_5CHO		78	11
	*sec*-BuLi	−40	THF	*n*-$C_6H_{13}I$		88	9a
	sec-BuLi	−40	THF	C_6H_5CHO		70	9a
	*t*-BuLi	−40 → 0	THF	C_6H_5CHO		62	9b
	*t*-BuLi	−40 → 0	THF	$(CH_3)_3CCHO$		38	9b
	sec-BuLi	−40 → 0	THF	$(C_6H_5)_2CO$		52	9b
	*t*-BuLi	−40 → 0	THF	$(C_6H_5)_2CO$		39	9b
	*t*-BuLi	−40 → 0	THF	C_6H_5CHO		13	9b

SCHEME VI

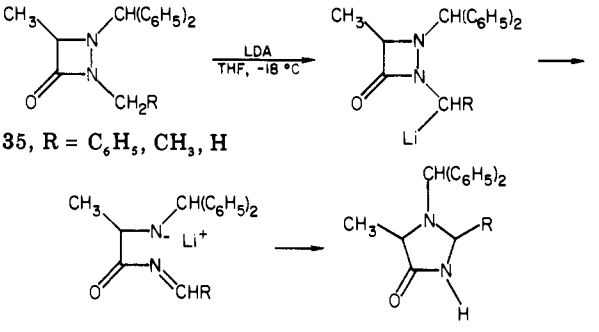


31, R = R_1 = C_6H_5, R_2 = H
32, R = R_1 = C_6H_5, R_2 = H
37, R = C_6H_5, $(CH_3)_3C$, R_1 = R_3C = CH_2, R_2 = H, C_6H_5
38, R = C_6H_5, $(CH_3)_3C$, R_1 = R_3C=CH_2, R_2 = H, C_6H_5

32, reacts with alkyl halides and aldehydes to produce **33** in 70–95% yields as shown in Scheme VI and Table III.[12] Hydrolysis to substituted benzylamines **34** is facile. Thus, **31** is a useful α-lithiobenzylamine synthon.[12a]

Benzyl activation may also supplement dipole stabilization in the formation of the intermediate in the ring expansion of diazetidines **35** to imidazolidines **36** shown in Scheme VII.[13] The reaction proceeds in somewhat better yield in the benzyl than in the unactivated cases.

SCHEME VII



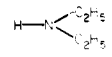
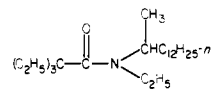
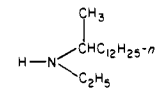
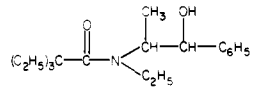
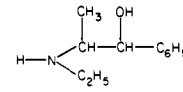
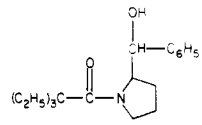
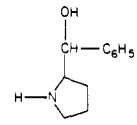
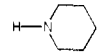
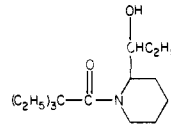
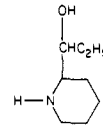
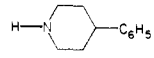
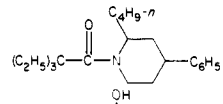
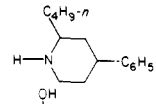
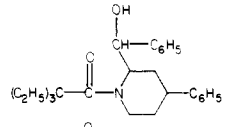
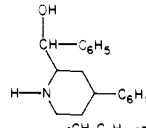
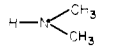
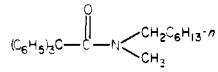
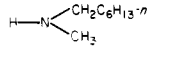
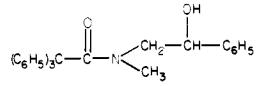
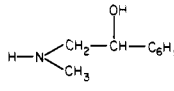
35, R = C_6H_5, CH_3, H

36, R = C_6H_5 (77%), CH_3 (61%), H (61%)

The dimetalation of *N*-allylamides **37** has also been investigated.[12b] Reaction of the intermediate organolithium reagent **38** with *n*-butyl iodide results in addition exclusively to the γ-position, affording enamide products as shown in Scheme VI in 75–99% yields (Table III). Since protonation of the intermediate occurs at the γ-position, migration of the double bond into conjugation with enamide nitrogen is achieved, thereby providing a useful procedure for the preparation of enamides.

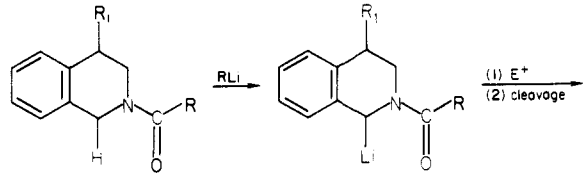
The pivalamide of tetrahydroisoquinoline **39a** as well as the amides **39b** and **39c** have been metalated to

TABLE II. Formation of α-Substituted Amines via Trisubstituted Acetamides

amine	electrophile	substituted amide	hydrolysis conditions[a]	product	yield,[b] %	ref
	n-$C_{12}H_{25}Br$		A		46	11
	C_6H_5CHO		B		40	11
	C_6H_5CHO		B		56	10
	C_2H_5CHO		B		61	11
	n-C_4H_9I		A		64	11
	C_6H_5CHO		B, C		76, 64	11
	n-$C_6H_{13}I$		D, E		45, 25	9a
	C_6H_5CHO		D		30	9a

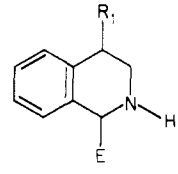
[a] A = 6N HCl, 72 h at reflux; B = CH_3OH/HCl (concd), 17 h at reflux and then $(CH_3)_3COK$ (6 equiv)/H_2O (2 equiv)/$(CH_3)_3COH$, 35 h at reflux; C = CH_3OH/HCl (concd), 17 h at reflux and then $LiAlH_4$; D = Na (4.5 equiv)/naphthalene (0.15 equiv)/THF, 2 h at ambient temp and then HCl (concd), 1 h at reflux; E = CH_3Li (6 equiv)/THF, 16 h at reflux. [b] From amine.

SCHEME VIII



39a R = $C(CH_3)_3$, R_1 = H
39b R = $C(C_6H_5)_3$, R_1 = OH
39c R = $COH(CH_3)_2$, R_1 = H

40



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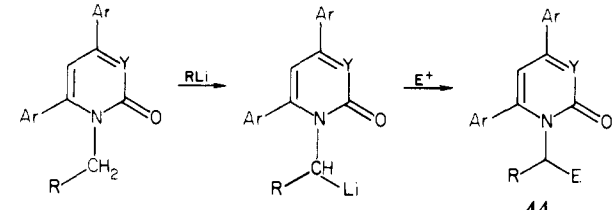
provide the α-amido carbanions **40** which react remarkably well with alkyl halides, aldehydes, ketones, trimethylchlorosilane, and tributyltin chloride to give substituted amide products in yields of 56–94% as shown in Scheme VIII and Table IV.[14] Conversion of **39a** to the amine **41a** can be achieved with strong base or aluminate reduction as summarized in Table V. This appears to be a unique example of pivalamide utility, since the aromatic ring seems necessary for the preparation of **40** as a stable intermediate. *N*-*N*-Dimethylpivalamide itself has been found to undergo extensive self-condensation upon metalation[15a,b] as does *N*,*N*-dimethyl-1-adamantane carboxamide.[15c]

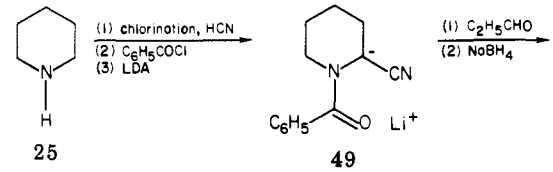
Other examples of α-amido carbanions at activated positions of heteroaromatic rings are provided by the metalations of the *N*-benzylpyridone **42** (Y = CH, Ar = C_6H_5) and *N*-benzylpyrimidone **43**, (Y = N, Ar = C_6H_5) as shown in Scheme IX.[16] Lithiation and reaction with carbonyl compounds provides substituted products **44** in yields of 12–85% as summarized in Table VI. With *N*-alkylpyridones **45** lower yields of electrophilic substitution products are obtained upon additions to aldehydes and ketones.[16a,c]

SCHEME IX



42, R = Ar, Y = CH
43, R = Ar, Y = N
45, R = H, alkyl, Y = CH

SCHEME X



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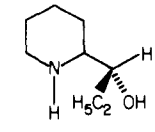
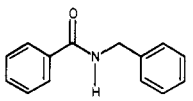
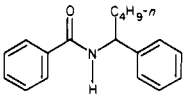
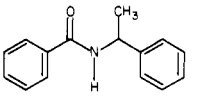
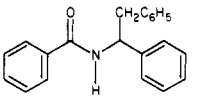
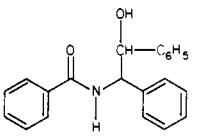
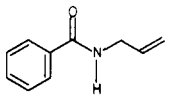
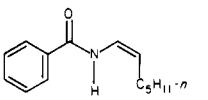
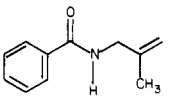
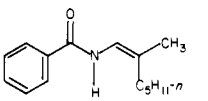
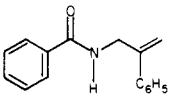
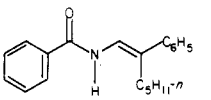
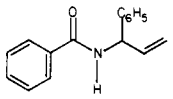
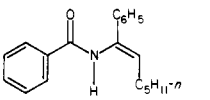
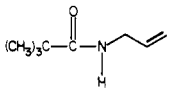
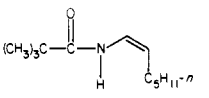
49



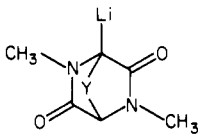
dl-conhydrine

TABLE III. Formation of *N*-(α-Lithio) Amides with Carbon–Carbon Unsaturation and Reactions with Electrophiles

reactant	base	temp, °C	solvent	electrophile	product	yield, %	ref
	LDA, LiTMP, or *n*-BuLi[a]	−78	diglyme	*n*-C_4H_9I		95	12a
	LDA, LiTMP, or *n*-BuLi[a]	−78	diglyme	CH_3I		79	12a
	LDA, LiTMP, or *n*-BuLi[a]	−78	diglyme	$C_6H_5CH_2Cl$		79	12a
	LDA, LiTMP, or *n*-BuLi[a]	−78	diglyme	C_6H_5CHO		71	12a
	LDA or *n*-BuLi[b]	−78	diglyme	*n*-C_4H_9I		91	12b
	LDA or *n*-BuLi[b]	−78	diglyme	*n*-C_4H_9I		77	12b
	LDA or *n*-BuLi[b]	−78	diglyme	*n*-C_4H_9I		75	12b
	LDA or *n*-BuLi[b]	−78	diglyme	*n*-C_4H_9I		99	12b
	LDA or *n*-BuLi[b]	−78	diglyme	*n*-C_4H_9I		88	12b

[a] 2.5 equiv. [b] 2 equiv.

Interesting new cases in which dipole stabilization of a bridgehead α-amino carbanion may be supplemented by the effects of other substituents are the formations of **46**,[17] **47**,[18] and **48**.[19] These organolithium reagents

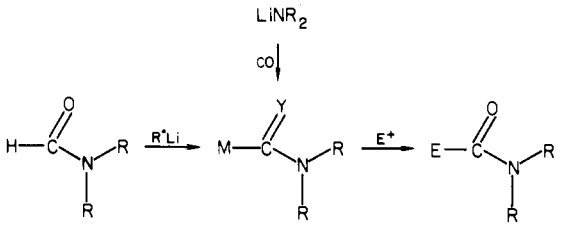


46, Y = S–SCHR
47, Y = CH_2=$C(CH_2)_3O$
48, Y = $(CH_2)_n$, *n* = 2, 3

undergo alkylation and acylation in useful yields. The systems **48** demonstrate that the carbanionic center need not be sp^2 hydridized and that stabilization by nitrogen and a carbonyl group is sufficient for stabilization of the formal carbanion.[19]

Although, in general, activated cases will not be covered in this review there are approaches to electrophilic substitution adjacent to amino nitrogen in which dipole stabilization by an amide supplements a more well-recognized carbanionic stabilization by another group. An example of this methodology is the substitution of a nitrile α to an amine, followed by formation of the amide, lithiation, reaction with an electrophile, and reductive cleavage. In this way piperidine has been converted to *erythro*-2-(α-hydroxypropyl)piperidine

SCHEME XI



50, R = alkyl **51**, Y = O, M = Li, Cu; **57**, Y = O, R = *n*-C_3H_7, R = $N(n\text{-}C_3H_7)_2$; **63**, Y = S **52**, E = CR'_2OH, $C(=O)R'$, R'

(*dl*-conhydrine) as illustrated in Scheme X.[20] The use of **49** as an α-lithioalkylamine synthetic equivalent is stereochemically complimented by the conversion of **25** to *threo*-2-(α-hydroxypropyl)piperidine discussed above.

It is possible to achieve not only the removal of a proton from the carbon adjacent to the nitrogen of an amide but also from the acyl carbon itself. Thus, as shown in Scheme XI, reaction of a number of formamides **50** with alkyllithium reagents provides **51**, a true acyl anion which reacts with the usual electrophiles to give α-hydroxyl amides, α-keto amides, and homologated amides **52** (Table VII).[5,21] Extension of this approach to the optically active formamide **53** provides the chiral organolithium reagent **54** which reacts with acetophenone, phenyl isopropyl ketone, and 3,3-dimethyl-2-butanone to give diastereomeric hydroxy ketones **55** in 70–80% yields. Separation of the diaste-

TABLE IV. Formation of *N*-(α-Lithio) Amides of Tetrahydroisoquinolines and Reactions with Electrophiles

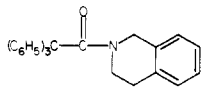
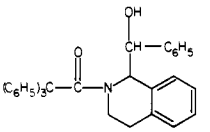
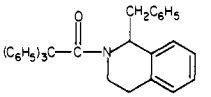
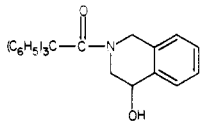
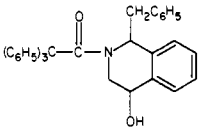
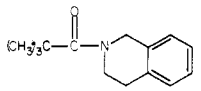
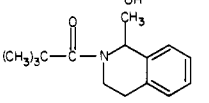
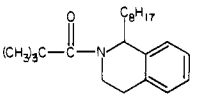
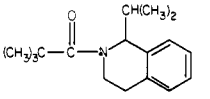
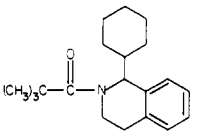
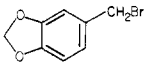
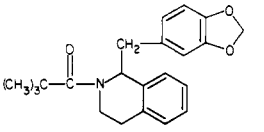
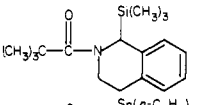
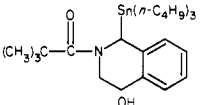
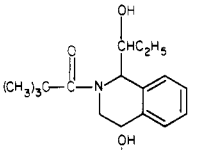
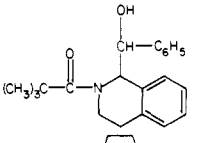
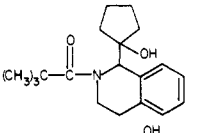
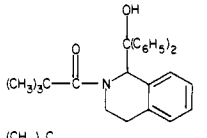
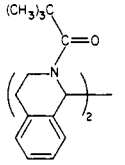
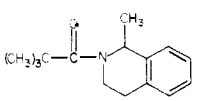
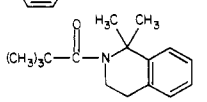
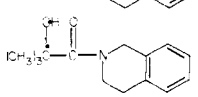
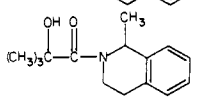
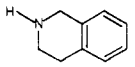
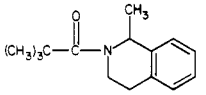
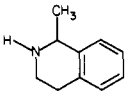
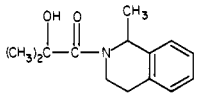
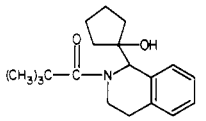
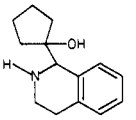
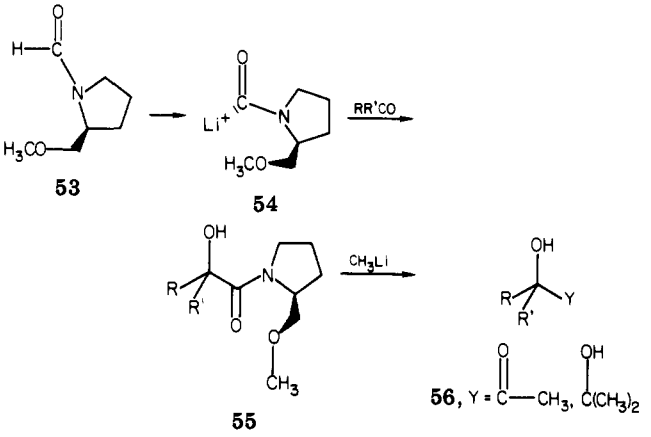
reactant	base	electrophile	product	yield, %	ref
	*sec*-BuLi	C_6H_5CHO		71	9b
	sec-BuLi	$C_6H_5CH_2Br$		64	9b
	*sec*-BuLi (2 equiv)	$C_6H_5CH_2Br$		66	9b
	*t*-BuLi	CH_3I		94	14, 119
	t-BuLi	n-$C_8H_{17}Cl$ n-$C_8H_{17}Br$ n-$C_8H_{17}I$		85 85 86	14, 119
	t-BuLi	$(CH_3)_2CHI$		90	14, 119
	t-BuLi			89	14, 119
	t-BuLi			77	14, 119
	t-BuLi	$(CH_3)_3SiCl$		88	14, 119
	t-BuLi	$(n$-$C_4H_9)_3SnCl$		84	14, 119
	t-BuLi	C_2H_5CHO		69	14
	t-BuLi	C_6H_5CHO		78	14
	t-BuLi			75	14, 119
	t-BuLi	$(C_6H_5)_2CO$		83	14, 119
	t-BuLi	I_2		45	14
	*t*-BuLi	CH_3I		59	14, 119
	*t*-BuLi (2 equiv)	CH_3I		56	14

TABLE V. Formation of α-Substituted Tetrahydroisoquinolines via Amides

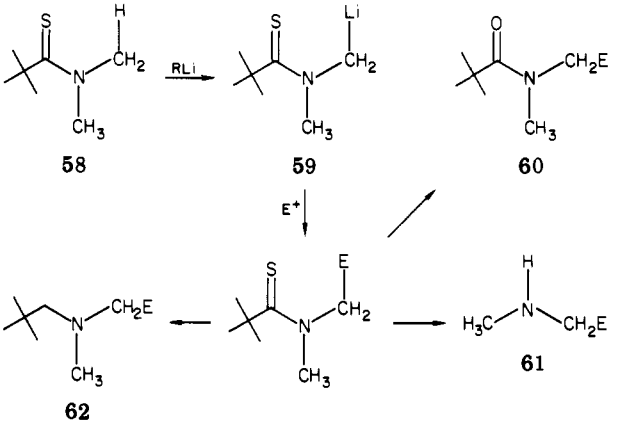
amine	electrophile	substituted amide	hydrolysis conditions[a]	product	yield, %	ref
	CH_3I		A		72	14
	CH_3I		B		40	14
			A		66	14

[a] A = Exactly 1.0 equiv of $Na[AlH_2(OCH_2CH_2OCH_3)_2]$ in benzene at 20–80 °C; B = KOH in methanol at reflux.

SCHEME XII



SCHEME XIII



reomeric mixtures and treatment with excess methyllithium leads to enantiomerically pure mixtures of α-hydroxy ketones and 1,2-diols **56**[22] as shown in Scheme XII and Table VII.

An alternative generation of the acyl anion **51** from a lithium dialkylamine and carbon monoxide provides another method of elaborating dialkyl amines to **52**, although α-keto amides arising from a second addition of carbon monoxide prior to electrophilic addition are also obtained.[23] Analogously, reaction of bis(*N*,*N*-diethylcarbamoyl)cuprate **51** with methyl iodide, phenyl iodide, allyl bromides, acyl halides, or methyl vinyl ketone affords substituted products **52** (R = C_2H_5) in 10–65% yields, based on starting diethylamine (Table VIII).[24] Carbonylation of lithium tri-*n*-propylhydrazide has been reported to provide **57** (Scheme XI) which undergoes reaction with aldehydes or ketones to give hydroxy carbonyl hydrazines which can be reductively cleaved to substituted-propyl amides in useful yields.[25] Lithium (*N*,*N*-dimethylcarbamoyl)nickel carbonylate has also been shown to effect carbamoylation of vinylic and aromatic halides.[26] Since reductions of these amide products to tertiary amines should be possible with hydride reagents the organometallics **51** are potential tertiary α-lithioamine synthetic equivalents (See Addendum).

B. Thioamides (Z = C(=S)R)

The use of *N*,*N*-dimethylthiopivalamide (**58**) to provide **59**, the synthetic equivalent of (α-lithiomethyl)-methylamine and (α-lithiomethyl)methylneopentylamine, has been developed as shown in Scheme XIII.[27]

Reaction of **59** with alkyl halides, aldehydes, or ketones gives the expected products in 12–82% yields (Table IX). The substituted thioamides can be hydrolyzed to pivalamides **60** or secondary amines **61**, or reduced to neopentylamines **62**. Substituted products could not be obtained from *N*-methyl-*N*-benzyl-, *N*-methyl-*N*-phenyl-, *N*,*N*-diethyl-, or *N*,*N*-pentamethylenepivalthioamides. The α-azo metalation of a wide variety of *N*,*N*-dialkyl thioamides with palladium dichloride has also been recently reported, and further development of such transition-metal species can be expected.[28] The formyl proton of *N*,*N*-dialkylthioformamides can be removed to provide an acyl anion **63** (Scheme XI), which reacts with aldehydes and ketones to afford substituted thioamide products in yields of 10–83% (Table X), analogous to the reactions of **51**.[29]

C. Imides (Z = (RC(=O))$_2$)

The use of a tetrasubstituted *N*-methylsuccinimide to provide the α-lithiomethylamine synthetic equivalent has been reported and reviewed.[5,30]

D. Ureas (Z = $R_2NC(=O)$)

The problem of achieving cleavage of electrophilically substituted derivatives of α-lithio amides, thioamides, and imides has generally been addressed by using forcing conditions for hydrolyses and reductions. A more imaginative approach has been reported using fragmentation of methyl and activated urea derivatives by Seebach and co-workers. They have found that the *N*,*N*-dimethylureas **64** and **65**, as shown in Scheme XIV

TABLE VI. Formation of α-Amido Exocyclic Carbanions of Heterocycles and Reactions with Electrophiles

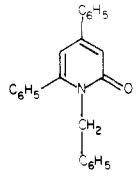
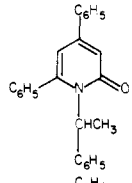
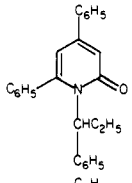
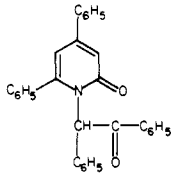
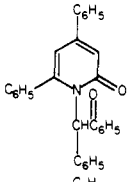
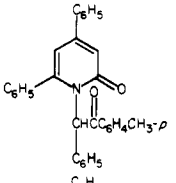
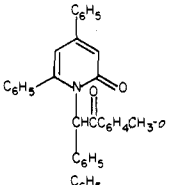
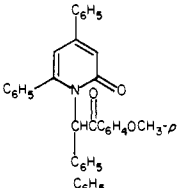
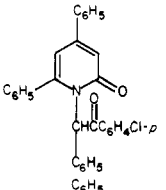
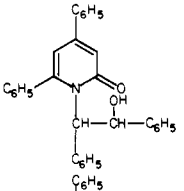
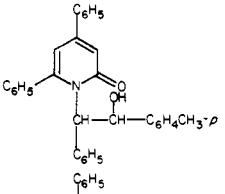
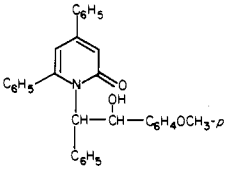
reactant	electrophile	procedure[a]	reaction time, h	product	yield, %	ref
	CH_3I	A	1.5		76	16b
	C_2H_5I	B	3		20	16b
	C_6H_5COCl	A	3		71	16b
	$C_6H_5CO_2CH_3$	B	6		12	16b
	p-$CH_3C_6H_4COCl$	A	3		67	16b
	o-$CH_3C_6H_4COCl$	A	3		39	16b
	p-$CH_3OC_6H_4COCl$	A	3		56	16b
	p-ClC_6H_5COCl	A	3		38	16b
	C_6H_5CHO	A	2.5		78	16b
	p-$CH_3C_6H_4CHO$	A	2.5		85	16b
	p-$CH_3OC_6H_4CHO$	A	2.5		50	16b

TABLE VI (Continued)

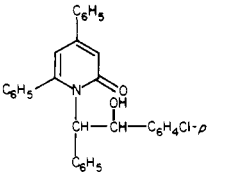
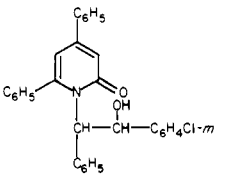
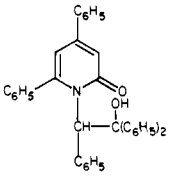
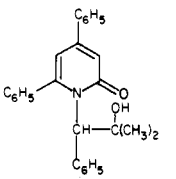
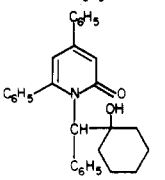
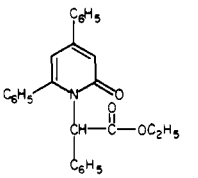
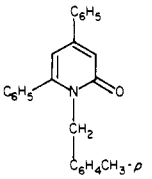
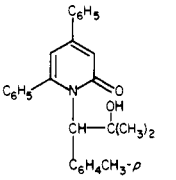
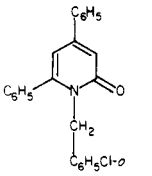
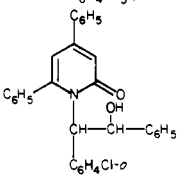
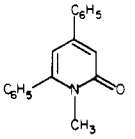
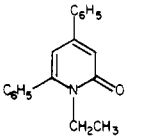
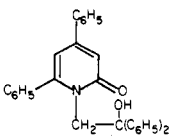
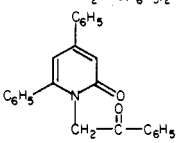
reactant	electrophile	procedure[a]	reaction time, h	product	yield, %	ref
	p-ClC_6H_4CHO	A	2.5		65	16b
	m-ClC_6H_4CHO	A	2.5		60	16b
	$(C_6H_5)_2CO$	A	2.5		72	16b
	$(CH_3)_2CO$	A	2.5		60	16b
		A	2		75	16b
	$ClCO_2C_2H_5$	A	4		84	16b
	$(CH_3)_2CO$	A	3		78	16b
	C_6H_5CHO	A	2.5		68	16b
	CH_3I	A	10		25	16c
	$(C_6H_5)_2CO$	A	12		67	16c
	$C_6H_5CO_2C_2H_5$	B	12		25	16c

TABLE VI (Continued)

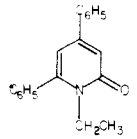
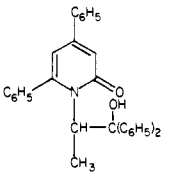
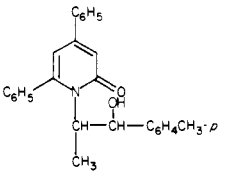
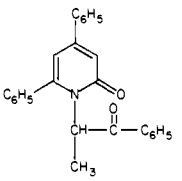
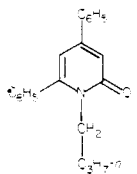
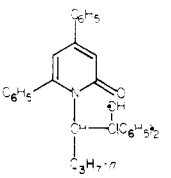
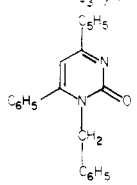
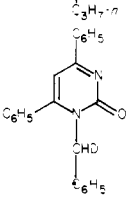
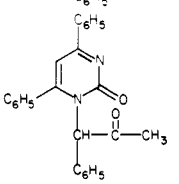
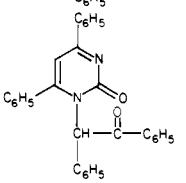
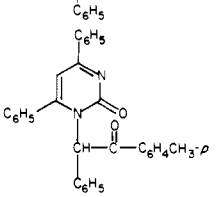
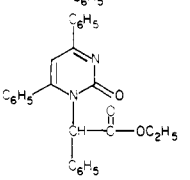
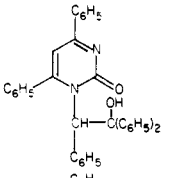
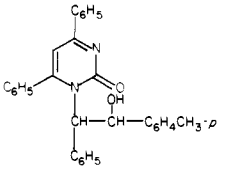
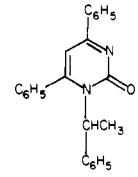
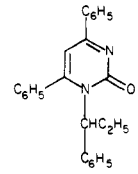
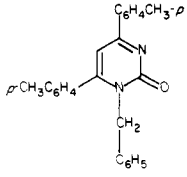
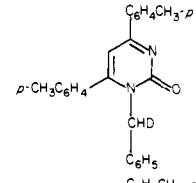
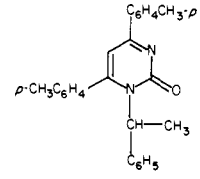
reactant	electrophile	procedure[a]	reaction time, h	product	yield, %	ref
	$(C_6H_5)_2CO$	A	8		48	16c
	p-$CH_3C_6H_4CHO$	A	10		44	16c
	$C_6H_5CO_2CH_3$	B	4		12	16c
	$(C_6H_5)_2CO$	A	10		64	16c
	D_2O	A	10		90	16d
	CH_3COCl	A	10		48	16d
	C_6H_5COCl	A	10		52	16d
	p-$CH_3C_6H_4COCl$	A	10		54	16d
	$ClCO_2C_2H_5$	A	10		35	16d
	$(C_6H_5)_2CO$	A	10		20	16d
	p-$CH_3C_6H_4CHO$	A	10		40	16d

TABLE VI (Continued)

reactant	electrophile	procedure[a]	reaction time, h	product	yield, %	ref
	CH_3I	A	10		40	16d
	C_2H_5I	A	10		33	16d
	D_2O	A	10		85	16d
	CH_3I	A	10		95	16d

[a] A = Reactant added to a THF solution of LDA at −78 °C, the electrophile was subsequently added; B = LDA was added to a THF solution of reactant and electrophile at −78 °C.

and Table XI, undergo lithiation to give **66** which adds readily to aldehydes, ketones, and alkyl halides to give **67**.[31] Derivatives of **65** undergo hydrolysis to the substituted amines **61** under the usual strong conditions. The hydrolysis of derivatives of **64**, however, can be driven by a retro-Mannich fragmentation to ethylene glycol, acetone, and ammonia under milder conditions.

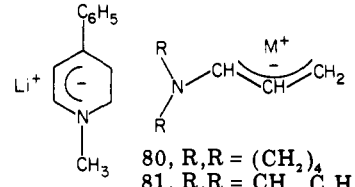
The same strategy has been used to achieve lithiation, substitution, and cleavage of the *N*-allyl-*N*-methylurea **68**. In this case reaction of the intermediate organolithium reagent **69** with alkyl halides, ketones, or aldehydes provides mixtures of α- and γ-substituted products, **70** and **71**. With a change in the counterion from lithium to magnesium, γ substitution is favored.[32] These results are summarized in Scheme XIV and Table XII.

E. Carbamates (Z = ROC(=O))

The 2,4,6-tri-*tert*-butylphenoxyl moiety has also been demonstrated to provide sufficient steric protection of the carbonyl of **72** to allow deprotonation to afford **66** which reacts with alkyl halides, aldehydes, and ketones to provide **67** in moderate yields as shown in Scheme XIV and Table XIII.[33] The substituted tertiary dimethylamine **73** can be obtained by reduction, while reaction with aluminum chloride affords a phenyl carbamate which can be hydrolyzed to **61**.[31]

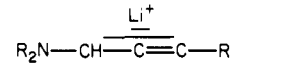
Allyl activation has been used in the carbamate as well as the urea systems. The carbamate **74a** derived from 3-pyrroline and the vinylogous carbamate **74b** in Scheme XV have been shown to undergo lithiation on the pyrrolidine ring. The carbamate **74a** is particularly useful and has been shown by Armande and Pandit[34] to undergo metalation to give an α-azo carbanion which reacts with alkyl halides to afford **75a**. Macdonald has shown that sequential lithiation and alkylation generates *trans*-2,5-dialkylpyrrolines **76** with high regio- and stereoselectivity.[35] For example, the ant poison **77** was prepared in 38% yield from **74a** by this methodology.[35] Olefin reduction, hydrolysis, and cyclization were employed in the synthesis of indolizidine and pyrrolizidine alkaloids; thus, the ant trail phermone **78** was prepared from **74a** in 15% overall yield. These results and those with related systems are summarized in Table XIV (See Addendum).

It should be noted that allyl and/or benzyl activation, by itself can be sufficient to allow the direct preparation of synthetically useful α-lithio amines. For example **79**,[36a] **80**,[36b] **81**,[36c] and **82**[36d] have been reported. Such



79

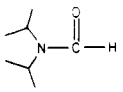
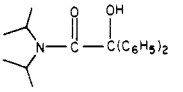
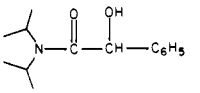
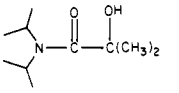
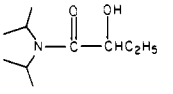
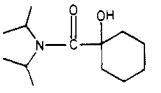
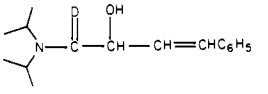
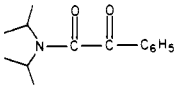
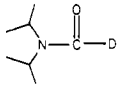
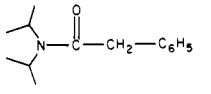
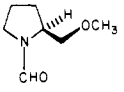
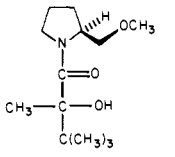
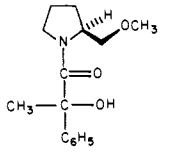
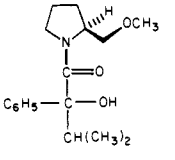
80, R,R = $(CH_2)_4$
81, R,R = CH_3, C_6H_5



82, R = $(CH_2)_5$ or R = $(CH_2)_2O(CH_2)_2$

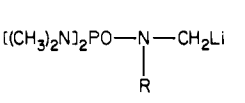
species however, are more commonly used as homoenolate synthetic equivalents, as illustrated by the conversion of **83** to **84** via **81** and **85** in Scheme XVI, than for amine elaboration. It appears that these organolithium reagents could be exploited as α-lithio amine synthetic equivalents in conjunction with reductions or reactions of the enamines.[36a]

TABLE VII. Formation of Acyl Anions from Formamides and Reactions with Electrophiles

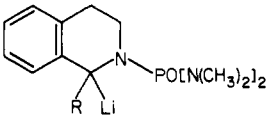
reactant	base	temp, °C	solvent	electrophile	product	yield, %	ref
	*t*-BuLi	−95	THF/ether	$(C_6H_5)_2CO$		85	21
	t-BuLi	−95	THF/ether	C_6H_5CHO		80	21
	t-BuLi	−95	THF/ether	$(CH_3)_2CO$		81	21
	t-BuLi	−95	THF/ether	C_2H_5CHO		62	21
	t-BuLi	−95	THF/ether			83	21
	t-BuLi	−95	THF/ether	$C_6H_5CH{=}CHCHO$		68	21
	t-BuLi	−95	THF/ether	$C_6H_5CO_2C_2H_5$		70	21
	t-BuLi	−95	THF/ether	D_2O		70	21
	t-BuLi	−95	THF/ether	$C_6H_5CH_2Br$		68	21
	LiTMP	−100	THF	$CH_3COC(CH_3)_3$		80	22
	LiTMP	−100	THF	$C_6H_5COCH_3$		71	22
	LiTMP	−100	THF	$C_6H_5COCH(CH_3)_2$		77	22

F. Phosphoramides (Z = P(=O)(NR$_2$)$_2$)

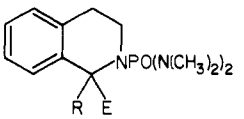
There have been several reports of the formation of a carbanion adjacent to the nitrogen of a phosphoramide. Activated benzylic, allenic, or vinylic phosphoramides have been shown to form stable α-azo carbanionic intermediates which undergo addition to alkyl halides and carbonyl compounds (Table XV).[37] Hexamethylphosphoric triamide can be lithiated to give **86** which also adds efficiently to the usual electrophiles. The organolithium reagents **87a** and **87b** available from tetrahydroisoquinoline react readily with alkyl halides, alkehydes, ketones, and epoxides to give substituted phosphoramides which are susceptible to acid hydrolysis to the corresponding amines as summarized in Tables XVI and XVII. It is notable that dialkylation of **87a** to provide **88** and phenylation of **87b** to provide **89** has been achieved.[38]



86



87a, R = CH_3
87b, R = H



88, R = E = CH_3
89, R = H, E = C_6H_5

G. Nitrosoamines (Z = NO)

The discovery, development, analysis, and use of α-azo carbanions from nitrosoamines has been reviewed.[5,39] It has been shown that primary, secondary,

TABLE VIII. Formation of Acyl Anions from Lithium Amides and Carbon Monoxide and Reactions with Electrophiles

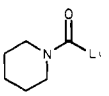
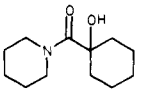
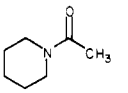
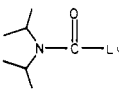
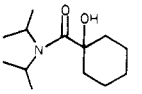
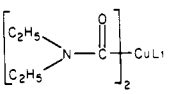
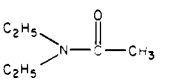
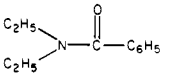
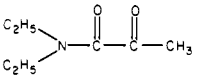
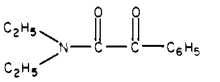
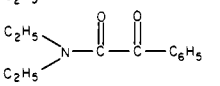
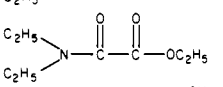
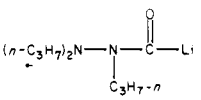
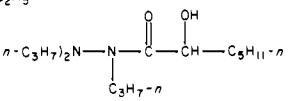
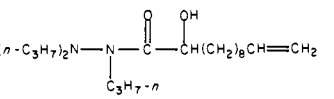
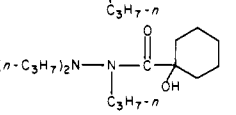
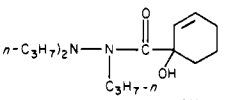
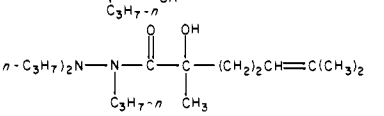
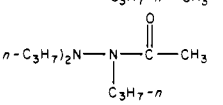
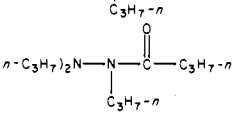
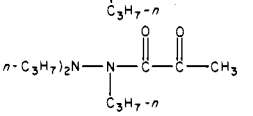
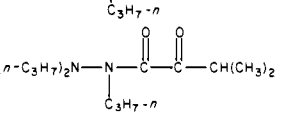
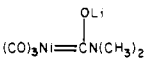
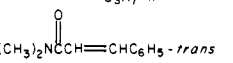
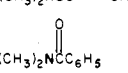
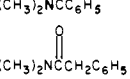
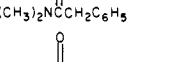
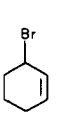
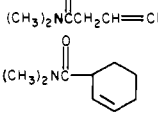
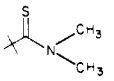
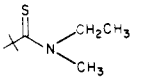
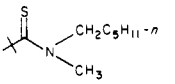
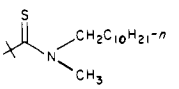
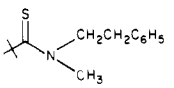
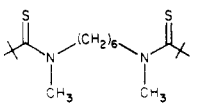
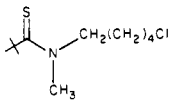
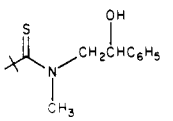
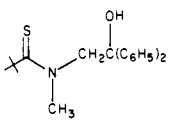
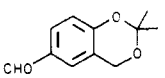
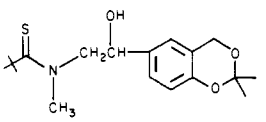
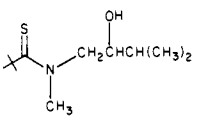
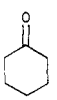
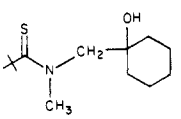
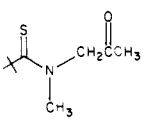
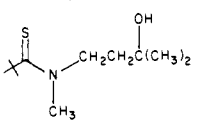
acyl anion	solvent	temp, °C	electrophile	product	yield, %	ref
	DME/THF	−75			ca. 68	23
	DME/THF	−75	CH_3I		ca. 33	23
	DME/THF	−75			ca. 50	23
	THF/HMPA	80	CH_3I		10	24
	THF/HMPA	80	C_6H_5I		49	24
	THF/HMPA	−78 → ambient, 80	CH_3COBr		70, 65	24
	THF/HMPA	−78 → ambient, 60	C_6H_5COBr		64, 74	24
	THF/HMPA	−78 → ambient, 80	C_6H_5COCl		23, 60	24
	THF,HMPA	60	$ClCO_2C_2H_5$		36	24
	THF	−75	n-$C_5H_{11}CHO$		60–85	25
	THF	−75	$CH_2{=}CH(CH_2)_8CHO$		60–85	25
	THF	−75	 #r		60–85	25
	THF	−75	 #t		60–85	25
	THF	−75	$CH_3CO(CH_2)_2CH{=}C(CH_3)_2$		60–85	25
	THF	−75	CH_3I		ca. 60	25
	THF	−75	n-C_3H_7I		ca. 30	25
	THF	−75	$CH_3CO_2C_2H_5$		ca. 35	25
	THF	−75	$(CH_3)_2CHCO_2C_2H_5$		ca. 55	25
	ether	ambient	$trans$-$C_6H_5CH{=}CHBr$		96	26
	ether	ambient	C_6H_5I		98	26
	ether	ambient	$C_6H_5CH_2Br$		65	26
	ether	ambient	$CH_2{=}CHCH_2Br$		36	26
	ether	ambient			99	26

TABLE IX. Formation of *N*-(α-Lithiomethyl)-*N*-methylthiopivalamide and Reaction with Electrophiles

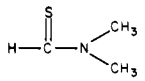
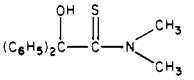
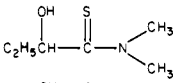
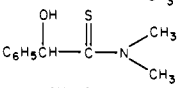
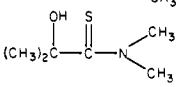
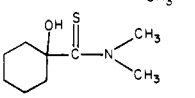
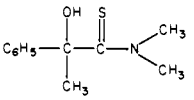
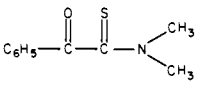
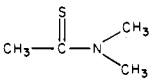
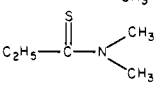
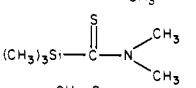
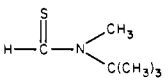
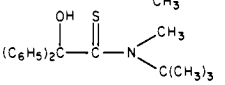
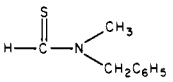
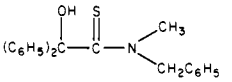
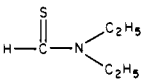
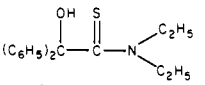
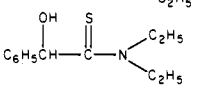
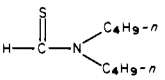
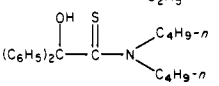
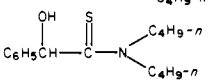
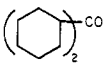
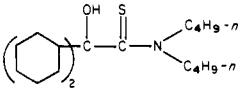
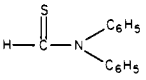
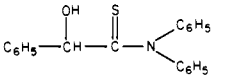
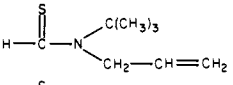
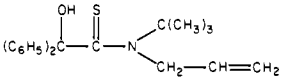
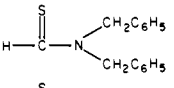
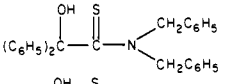
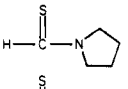
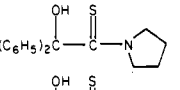
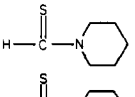
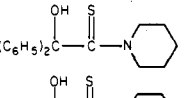
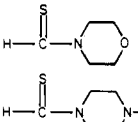
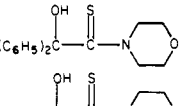
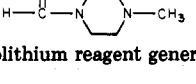
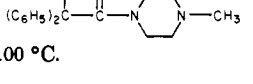
reactant[a]	electrophile	product	yield, %	ref
	CH_3I		80	27
	n-$C_5H_{11}I$		82	27
	n-$C_{10}H_{21}Br$		79	27
	$C_6H_5CH_2Br$		44	27
	$I(CH_2)_4I$		67	27
	$Br(CH_2)_4Cl$		65	27
	C_6H_5CHO		70	27
	$(C_6H_5)_2CO$		63	27
			48	27
	$(CH_3)_2CHCHO$		23	27
			17	27
	$CH_3CON(CH_3)_2$		32	27
			12	27

[a] Metalated with *sec*-BuLi-TMEDA in THF at −78 °C.

and tertiary positions adjacent to the nitrogen of nitrosoamines (**90–92**) can be metalated with lithium diisopropylamine or alkyllithium bases at low temperatures to form the intermediate **93**, which reacts with electrophiles to yield **94** as shown in Scheme XVII. Useful electrophiles include alkyl and allyl halides,[40] ketones and aldehydes,[39-41] cyanides,[42] acyl halides,[39] and sulfur, tin, selenium, and silyl heteroatom electrophiles.[43] The substituted nitrosoamines **94** generally are produced in moderate to excellent yields, and denitrosation to substituted amines **95** can be achieved with gaseous hydrogen chloride or under reducing conditions with Raney Nickel.[39,44] A "one-pot" procedure, designed to minimize contact with the potentially carcenogenic nitrosoamines has been reported; it involves $LiAlH_4$ reduction of the nitrosoamine to the corresponding hydrazine prior to Raney Nickel reduction.[45] As α-lithioalkyl alkylamine synthetic equivalents the α-lithioalkyl nitrosoamines represented by **93** appear to have advantages over alternatives; however, because of the potentially hazardous nature of nitrosoamines they have been less widely used than their utility might warrant.

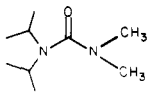
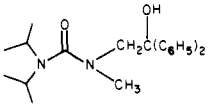
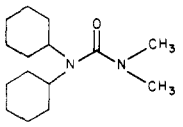
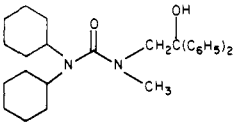
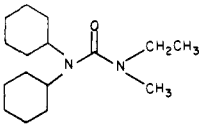
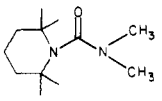
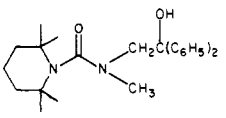
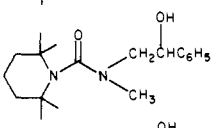
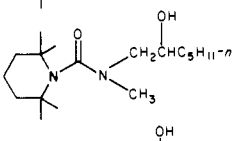
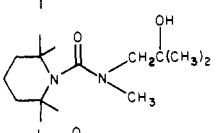
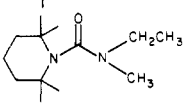
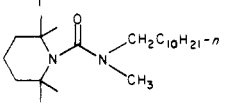
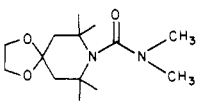
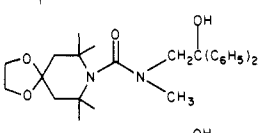
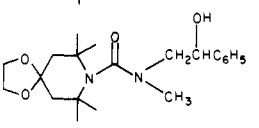
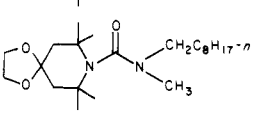
In view of the previous reviews[5,39] the present discussion will focus on recent work. Seebach et al. have noted that nitrosoamines can be metalated rapidly with

TABLE X. Formation of Lithiothioformamides and Reactions with Electrophiles

reactant[a]	electrophile	product	yield, %	ref
	$(C_6H_5)_2CO$		80	29a
	C_2H_5CHO		65	29a
	C_6H_5CHO		65	29a
	$(CH_3)_2CO$		75	29a
			50	29a
	$C_6H_5COCH_3$		50	29a
	$C_6H_5CO_2CH_3$		75	29a
	CH_3I		45	29a
	C_2H_5I		48	29a
	$(CH_3)_3SiCl$		36	29a
	$(C_6H_5)_2CO$		55	29a
	$(C_6H_5)_2CO$		79	29a
	$(C_6H_5)_2CO$		83	29a
	C_6H_5CHO		70	29a
	$(C_6H_5)_2CO$		10	29a
	C_6H_5CHO		45	29a
			62	29a
	C_6H_5CHO		20	29a
	$(C_6H_5)_2CO$		54	29a
	$(C_6H_5)_2CO$		70	29a
	$(C_6H_5)_2CO$		77	29a
	$(C_6H_5)_2CO$		79	29a
	$(C_6H_5)_2CO$		68	29a
	$(C_6H_5)_2CO$		60	29a

[a] Organolithium reagent generated by the action of LDA in THF at −100 °C.

TABLE XI. Formation of *N*-(α-Lithiomethyl) Ureas and Reactions with Electrophiles

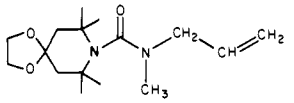
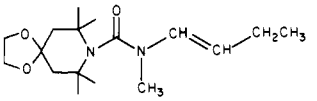
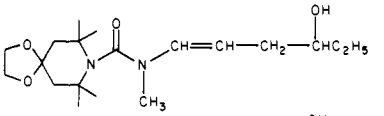
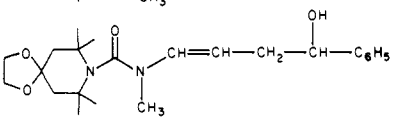
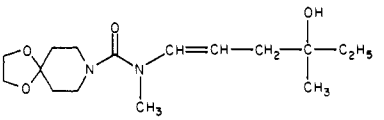
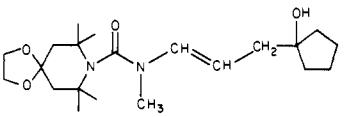
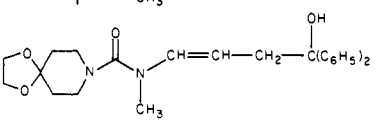
reactant	reaction conditions[a]	electrophile	product	yield, %	ref
	A	$(C_6H_5)_2CO$		23	31
	A	$(C_6H_5)_2CO$		43	31
	A	CH_3I		60	31
	B	$(C_6H_5)_2CO$		81	31
	B	C_6H_5CHO		89	31
	B	n-$C_5H_{11}CHO$		75	31
	B	$(CH_3)_2CO$		52	31
	B	CH_3I		78	31
	B	n-$C_{10}H_{21}Br$		68	31
	B	$(C_6H_5)_2CO$		70	31
	B	C_6H_5CHO		78	31
	B	n-$C_8H_{17}I$		72	31

[a] A = *sec*-BuLi·TMEDA in THF at −80 °C for 6 h; B = *sec*-BuLi·TMDDA in THF at 0 °C for 1.5 h.

potassium *tert*-butoxide/*n*-butyllithium/diisopropylamine, and that substituted nitrosoamines **94** are produced in high yields upon subsequent reaction with electrophiles.[46] The synthesis of α-stannylnitrosoamines **96** from methyl nitrosoamines is useful because these compounds undergo thermal addition to aryl aldehydes to give stannyl ethers which can be hydrolyzed to *N*-methyl-β-aryl hydroxyl nitrosoamines. The yields of acylated nitrosoamines **97** from methyl nitrosoamines have been improved by the use of acyl cyanides instead of acyl halides or esters as electrophiles.[46] The carbomethoxylation of **93** with methyl chloroformate occurs selectively at the least substituted carbon of an unsymmetrical nitrosoamine unless the more substituted carbon bears an anion stabilizing group. Yields in the formations of acyl nitrosoamines ranged from 60 to 95%.[47] Although alkylations and α-hydroxyalkylations of benzyl methyl nitrosoamines can provide thermodynamically or kinetically controlled product mixtures depending on reaction conditions,[39,48] carbomethoxylation occurs exclusively at the benzylic position.

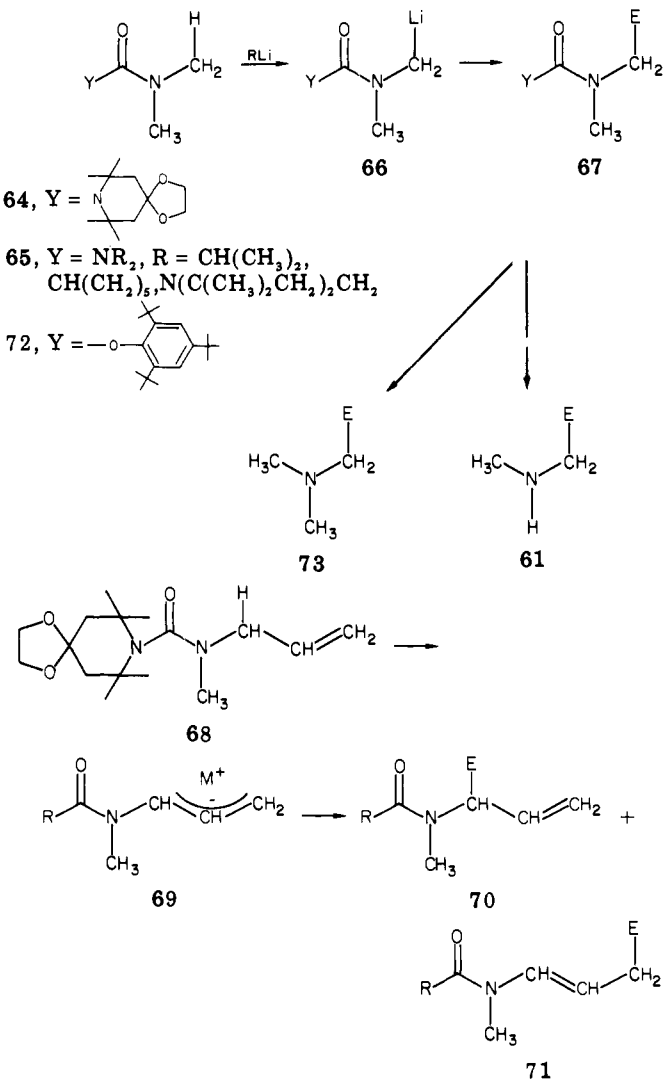
Metalated nitrosoamines have been used in the synthesis of tetrazines,[49] triazoles,[50] the hemlock alkaloids **98** and **99**,[44b] and a constituent of fire ant venom **100**.[51] In the case of **100** a mixture of cis/trans isomers was produced; the previously discussed carbamate synthesis of a 1,5-disubstituted pyrrolidine **75** provided only the trans isomer. Stereochemical studies have shown the

TABLE XII. Formation of a Metalated Allylurea and Reaction with Electrophiles

reactant[a]	electrophile	product	yield, %	ref
	CH_3I		80	32
	C_2H_5CHO		83	32
	C_6H_5CHO		85	32
	$C_2H_5COCH_3$		54	32
			87	32
	$(C_6H_5)_2CO$		63	32

[a] The lithium derivative was generated with *n*-BuLi in THF at −80 °C; after 1.5 h, $MgBr_2 \cdot OEt_2$ was added and the mixture was warmed until the precipitate was completely dissolved. The anion was recooled to −80 °C prior to the addition of the electrophile.

SCHEME XIV

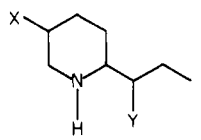


64, Y =

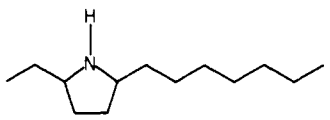
65, Y = NR_2, R = $CH(CH_3)_2$, $CH(CH_2)_5$, $N(C(CH_3)_2CH_2)_2CH_2$

72, Y =

66 67 73 61 68 69 70 71



98, X = H, Y = H or OH
99, X = OH, Y = H



100

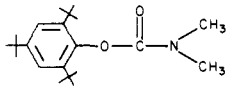
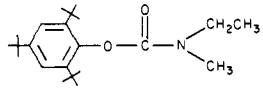
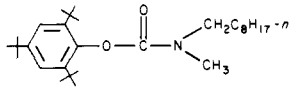
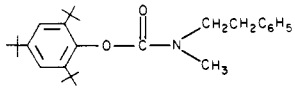
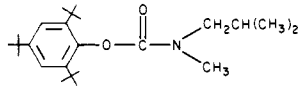
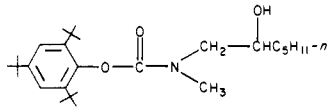
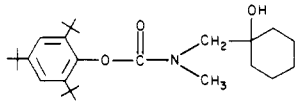
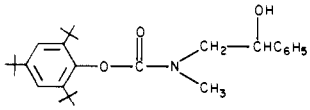
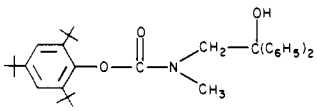
intermediate to be a π-anion which reacts with expected stereochemistry.[52] For example, *N*-nitrosopiperidine upon metalation and substitution gives an axial product.[52] It is notable that this is different from the equatorial substitution obtained with the piperidine amides (vide supra).

Two recent reports of the achievement of asymmetric induction in the addition of an α-lithionitrosamine to benzaldehyde in chiral media have appeared (Scheme XVIII). Seebach et al. reported the synthesis of halostanine (**101**) in 15% optical purity by the addition of **102** to benzaldehyde using (+)-2,3-dimethoxy-*N*,*N*,*N*′,*N*′-tetramethyl-1,4-butanediamine as a chiral media.[53] Soai and Mukaiyama have obtained an optical purity of 25% for the same reaction by employing (2*S*,2′*S*)-2-hydroxymethyl-1-[(1-methyl-2-pyrrolidinyl)methyl]pyrrolidine as the chiral media.[54]

The synthesis of (+)-macrostomine (**103**) has been reported via the nitrosoamine as shown in Scheme XIX.[55] Metalation, and subsequent reaction with 3,4-(methylenedioxy)benzyl bromide, followed by denitrosation afforded **104**, a key intermediate in the sequence, in 80% yield.

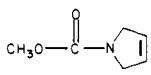
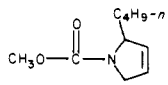
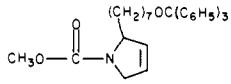
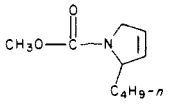
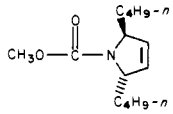
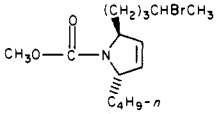
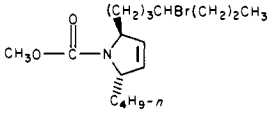
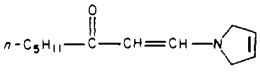
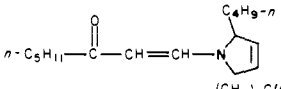
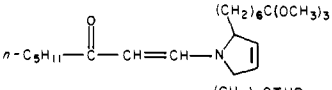
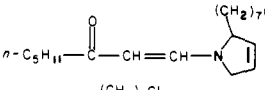
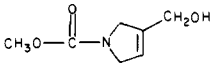
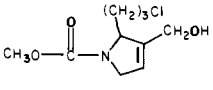
Reversibility of the regio- and stereochemistry of the addition of the alkyl α-metalloallyl nitrosamine **105** to aldehydes and ketones has been demonstrated as illustrated in Scheme XX. It is found that the α adduct **106** formed at low temperatures is converted to the γ adduct **107** at high temperatures. Initial formation of a mixture of threo and erythro isomers from α addition

TABLE XIII. Formation of a *N*-(α-Lithiomethyl)carbamate and Reaction with Electrophiles

reactant[a]	electrophile	product	yield, %	ref
	CH_3I		71	33
	n-$C_8H_{17}I$		87	33
	$C_6H_5CH_2Br$		35	33
	$(CH_3)_2CHI$		32	33
	n-$C_5H_{11}CHO$		80	33
			63	33
C_6H_5CHO			50	33
$(C_6H_5)_2CO$			61	33

[a] Metalated with *sec*-BuLi-TMEDA in THF at 0 °C.

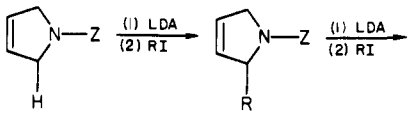
TABLE XIV. Formation of *N*-(α-Lithio) Carbamates and (α-Lithio) Vinylogous Carbamates and Reactions with Electrophiles

reactant	base	temp, °C	solvent	electrophile	product	yield, %	ref
	LDA	−78, −40	THF	n-C_4H_9Br		62, 65	34a, 35
	LDA	−78	THF	$(C_6H_5)_3CO(CH_2)_7I$		35	34a
	LDA	−78	THF	n-C_4H_9Br		21	34a
	LDA	−40	THF	$Br(CH_2)_3CHBrCH_3$		71	35
	LDA	−40	THF	$Br(CH_2)_3CHBr(CH_2)_2CH_3$		78	35
	LDA	−78	THF	n-C_4H_9Br		58	34a
	LDA	−78	THF	$I(CH_2)_6C(OCH_3)_3$		74	34a
	LDA	−78	THF	$I(CH_2)_7OTHP$		43	34b
	LiTMP (2 equiv)	−78	THF	$Br(CH_2)_3Cl$		48	121

of **105** to aldehydes is also found to similarly revert to the threo isomer and related cases have been reported.[46]

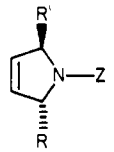
The base-induced fragmentation of β-hydroxy nitrosoamines to give an aldehyde or ketone and a smaller

SCHEME XV

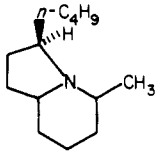


74a, Z = CO_2CH_3
74b, Z = $CH{=}CHCO\text{-}n\text{-}C_5H_{11}$

75

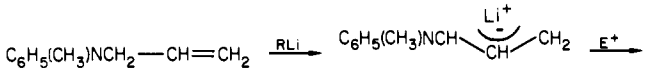


76, Z = CO_2CH_3
77, R = $n\text{-}C_4H_9$, R′ = $n\text{-}C_5H_{11}$, Z = H

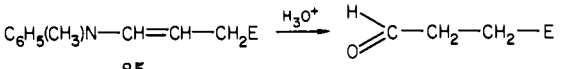


78

SCHEME XVI

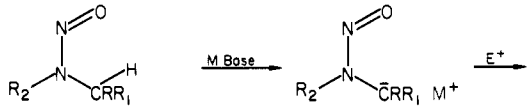


83 81



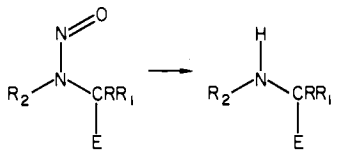
85 84

SCHEME XVII



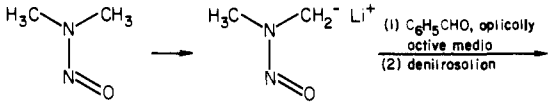
90, R = R_1 = H
91, R = H, R_1 = alkyl
92, R = R_1 = alkyl

93

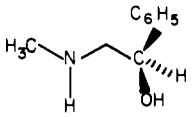


94 95
96, E = SnR_3
97, E = COR

SCHEME XVIII



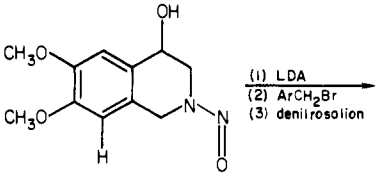
102

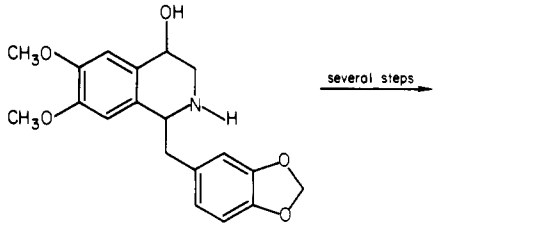


101

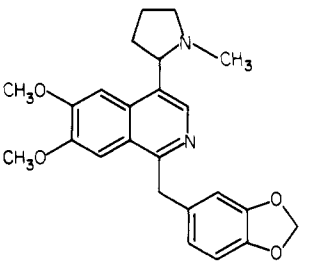
alkylnitrosoamine has been studied recently by Loeppky.[56a] The reaction is found to be subject to control by the stereochemical orientation of the *N*-nitroso function; fragmentation for the *Z* isomer **108Z** is much more rapid than for the *E* isomer **108E**. Loeppky et al.[56b] note that this is due to the greater stability of the incipient syn α-nitrosoamino carbanion and provide rate data to support a mechanism in which the *E* isomer isomerizes to the *Z* isomer prior to fragmentation, as shown in Scheme XXI.

SCHEME XIX



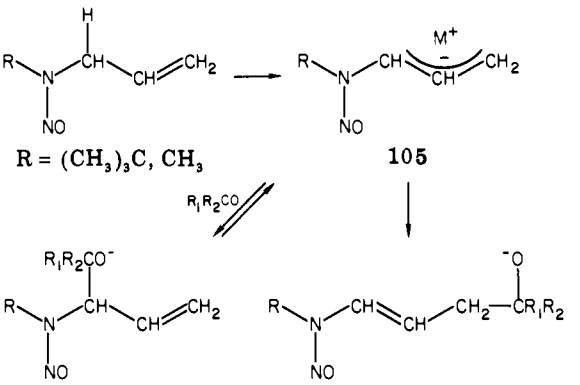


104



103

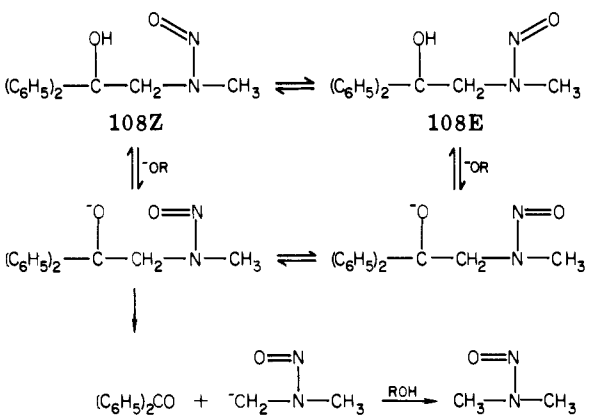
SCHEME XX



R = $(CH_3)_3C$, CH_3

105 106 107

SCHEME XXI



108Z 108E

H. Isocyanides (Z = ≡C)

Fifteen years ago, Schöllkopf and Gerhart discovered that methyl isocyanide can be metalated to give an

TABLE XV. Formation of *N*-(α-Lithio) Phosphoramides and Reactions with Electrophiles

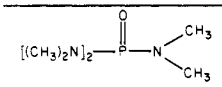
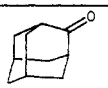
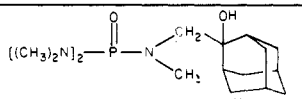
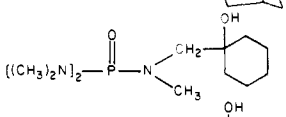
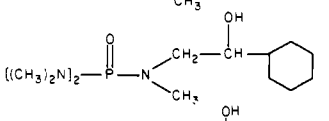
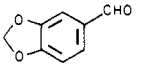
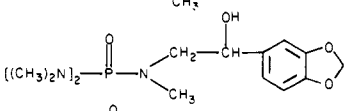
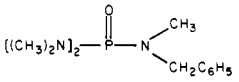
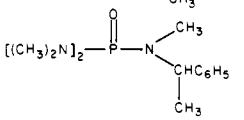
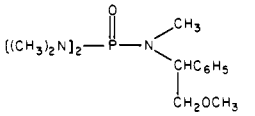
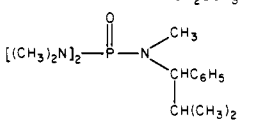
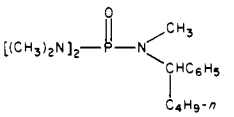
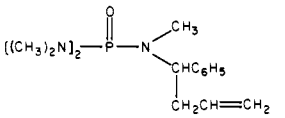
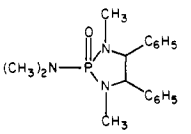
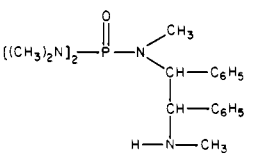
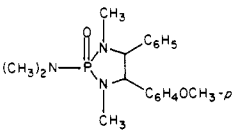
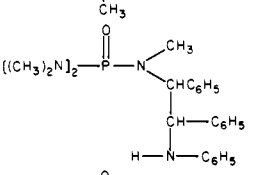
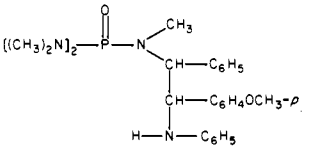
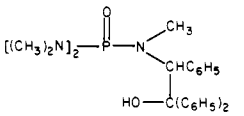
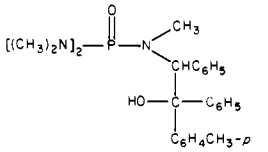
reactant	base	temp, °C	solvent	electrophile	product	yield, %	ref
	*sec*-BuLi	−78	DME			80	37e
	sec-BuLi	−78	DME			80	37e
	sec-BuLi	−78	DME			83	37e
	sec-BuLi	−78	DME			50	37e
	*n*-BuLi	−78	THF	CH_3I		100	37b
	n-BuLi	−78	THF	CH_3OCH_2Cl		100	37b
	n-BuLi	−78	THF	$(CH_3)_2CHI$		80	37b
	n-BuLi	−78	THF	n-C_4H_9I		80	37b
	n-BuLi	−78	THF	$CH_2{=}CHCH_2Br$		80	37b
	n-BuLi	−78	THF	$C_6H_5CH{=}NCH_3$[a]		46	37b
	n-BuLi	−78	THF	$C_6H_5CH{=}NCH_3$[b]		40	37b
	n-BuLi	−78	THF	p-$CH_3OC_6H_4CH{=}NCH_3$[a]		49	37b
	n-BuLi	−78	THF	$C_6H_5CH{=}NC_6H_5$[c]		80	37b
	n-BuLi	−78	THF	p-$OCH_3C_6H_4CH{=}NC_6H_5$[c]		92	37b
	n-BuLi	−78	THF	$(C_6H_5)_2CO$		86	37b
	n-BuLi	−78	THF	p-$CH_3C_6H_4COC_6H_5$		82	37b

TABLE XV (Continued)

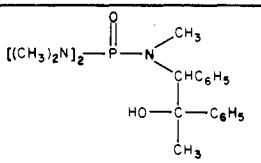
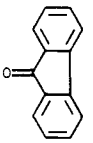
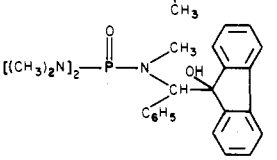
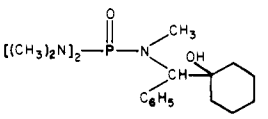
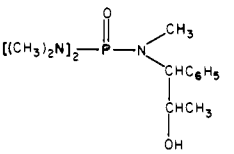
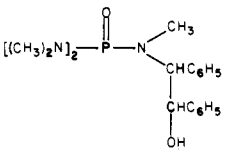
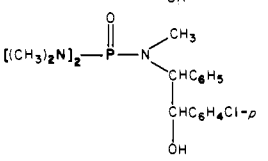
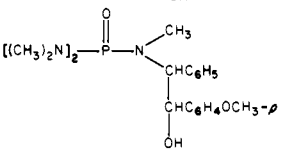
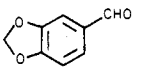
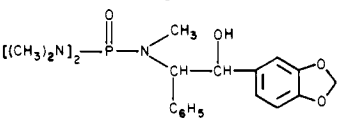
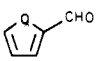
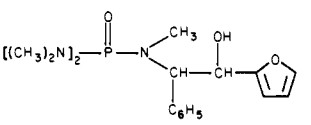
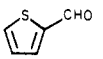
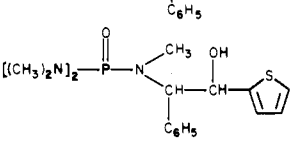
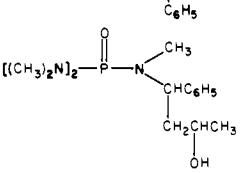
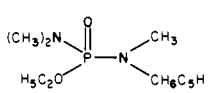
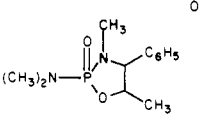
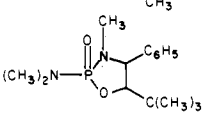
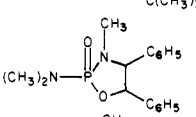
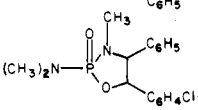
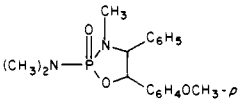
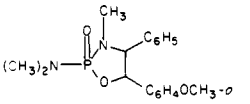
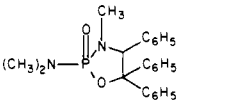
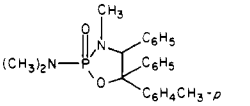
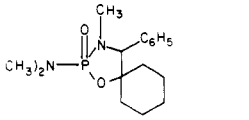
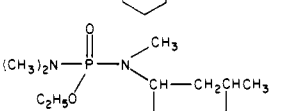
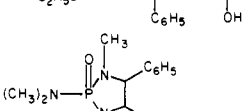
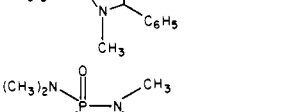
reactant	base	temp, °C	solvent	electrophile	product	yield, %	ref
	n-BuLi	−78	THF	$C_6H_5COCH_3$		49, 50	37b, 37c
	n-BuLi	−78	THF			60	37b
	n-BuLi	−78	THF			55	37b
	n-BuLi	−78	THF	CH_3CHO		76	37b
	n-BuLi	−78	THF	C_6H_5CHO		89	37b
	n-BuLi	−78	THF	*p*-ClC_6H_4CHO		87	37b
	n-BuLi	−78	THF	*p*-$CH_3OC_6H_4CHO$		83	37b
	n-BuLi	−78	THF			83	37b
	n-BuLi	−78	THF			70	37b
	n-BuLi	−78	THF			81	37b
	n-BuLi	−78	THF			91	37b
	*n*-BuLi	−78	THF	CH_3CHO		78	37b
	n-BuLi	−78	THF	$(CH_3)_3CCHO$		65	37b
	n-BuLi	−78	THF	C_6H_5CHO		68	37b
	n-BuLi	−78	THF	*p*-ClC_6H_4CHO		70	37b

TABLE XV (Continued)

reactant	base	temp, °C	solvent	electrophile	product	yield, %	ref
	n-BuLi	-78	THF	*p*-$CH_3OC_6H_4CHO$		39	37b
	n∞BuLi	-78	THF	*o*-$CH_3OC_6H_4CHO$		38	37b
	n-BuLi	-78	THF	$(C_6H_5)_2CO$		80	37b
	n-BuLi	-78	THF	*p*-$CH_3C_6H_4COC_6H_5$		69	37b
	n-BuLi	-78	THF			41	37b
	n-BuLi	-78	THF			85	37b
	n-BuLi	-78	THF	$C_6H_5CH{=}NCH_3$[a]		60	37b
	n-BuLi	-78	THF	$C_6H_5CH{=}NC_6H_5$[d]		75	37b

[a] 20 h at -50 °C. [b] 20 h at -78 °C. [c] 3 h at -20 °C. [d] 2 h at -30 °C and then 3 h at 0 °C.

α-azo carbanionic intermediate **109** which reacts with a wide variety of electrophiles to give a number of useful adducts.[57] As shown in Scheme XXII, the product **110** can be hydrolyzed to substituted primary amines **111**. Reaction of **109** with polar multiple bonds gives heterocycles **112**. Several reviews of this chemistry have appeared and only a general outline and a summary of recent work will be given.[58]

The organolithium **109** is a versatile α-lithiomethyl methylamine synthetic equivalent. Reaction of **109** with aldehydes or ketones, followed by alkaline workup gives 2-oxazolines while acidic workup provides 2-isocyano alcohols which can be hydrolyzed to the corresponding 1,2-amino alcohols. Addition of **109** to aryl carbonyl compounds provides methylenation while reaction with imines give dihydroimidazoles.[58c] Addition of **109** to nitrones gives dihydroimidazolones **113** via **114** as shown in Scheme XXIII and Table XVIII.[59] Oxazoles can be obtained by reaction of **109** with acid chlorides, amides, or esters,[60] while 5-(alkylthio)thiazoles can be obtained by reaction with carbon disulfide.[61] Addition of **109** to carbonates and chloroformates gave α-amino esters.[62] Electrophilic substitution of **109** has also been reported with alkyl and allyl halides and epoxides. In addition **109** has been used in the synthesis of ellipticine.[63,64]

Recent studies have focused on the chemistry of metalated isocyanides activated by the presence of carbonyl, nitrile, aryl, phosphonyl, or sulfonyl groups on the α-carbon. These species are of synthetic value and have been used in the synthesis of a wide variety of compounds including oxazoles,[65] imidazoles,[59] quinolines,[66] pyrroles,[67] α-isocyano phosphates,[68] and 2-isocyanoacrylates.[69] Thiazoline derivatives produced from α-isocyano acetate esters have been converted to β-lactones.[70]

An activated isocyanide which has been remarkably useful is tosylmethyl isocyanide (**115**), known as TosMIC. Van Leusen and co-workers have demonstrated that olefinic ketones, esters, and nitriles are subject to attack by metalated tosylmethyl isocyanide to afford substituted pyrroles by processes analogous to the formation of **111** from **109**. The TosMIC anion can be mono- or dialkylated and this intermediate also adds to isothiocyanates to yield thiazoles. Dilithiated TosMIC affords imidazoles.[71] Although TosMIC has been widely used in the conversion of ketones to nitriles or α-hydroxy aldehydes,[72] perhaps its most general application has been as an acyl dianion equivalent. Symmetrical and unsymmetrical ketones can be readily synthesized using the TosMIC anion by this approach in yields ranging from 40 to 80%.[73]

Alkenyl isocyanides **116** have been metalated at the α-vinyl carbon by alkyllithium to afford the α-azo carbanionic intermediate **117** which reacts with alkyl halides and carbonyl compounds to yield **118** as shown in Scheme XXIV and Table XIX.[74]

Primary alkyl isocyanides **119** can be substituted to give **120** in low yields if the lithiation can be carried out in the presence of an electrophile.[60,63] With the ex-

TABLE XVI. Formation of 1-Substituted-2-[bis(dimethylamino)phosphinoyl]tetrahydroisoquinolines

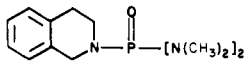
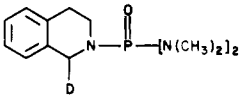
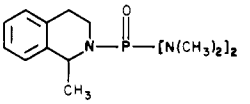
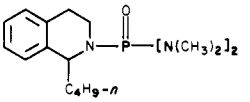
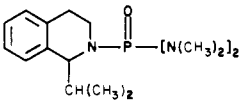
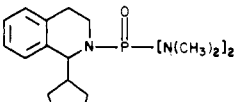
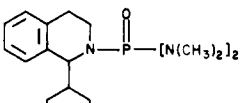
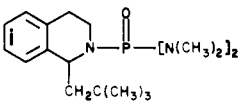
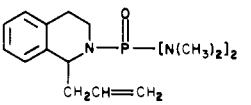
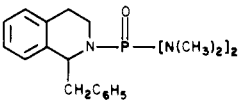
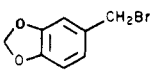
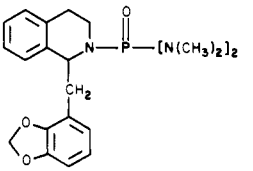
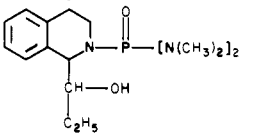
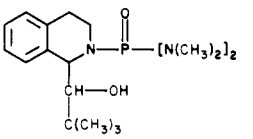
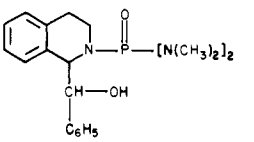
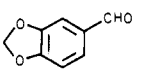
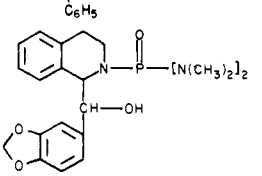
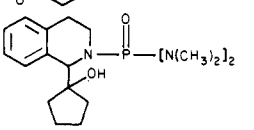
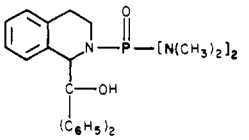
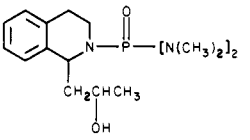
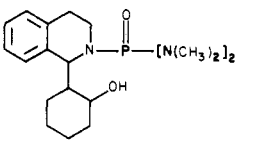
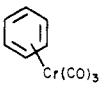
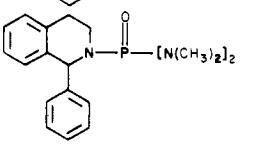
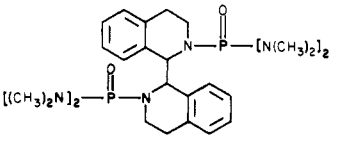
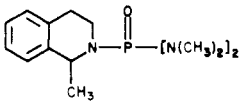
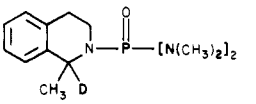
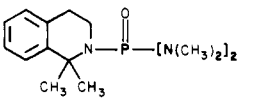
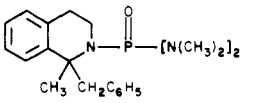
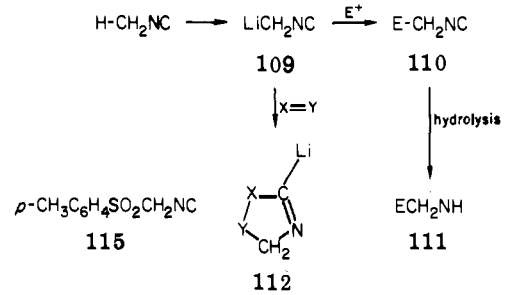
reactant[a]	electrophile	product	yield,[b] %	ref
	D_2O		>95	38, 119
	CH_3I		89, 66	38, 119
	n-C_4H_9Cl		>95, 86	38, 119
	$(CH_3)_2CHI$		86, 78	38, 119
			52	38
			35	119
	$(CH_3)_3CCH_2Br$		60, 39	38, 119
	$CH_2{=}CHCH_2Cl$		>95, 87	38, 119
	$C_6H_5CH_2Cl$		>95, 91	38, 119
			63	38
	C_2H_5CHO		>95	38
	$(CH_3)_3CCHO$		90	38
	C_6H_5CHO		81	38
			>95	38
			64, 73	38, 119

TABLE XVI (Continued)

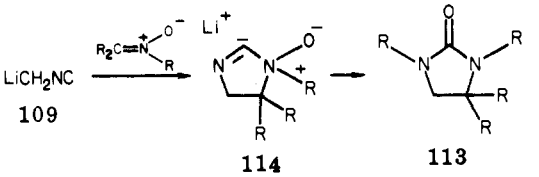
reactant[a]	electrophile	product	yield,[b] %	ref
	$(C_6H_5)_2CO$		>95, 74	38, 119
			>95	38
			>95	38
			57, 45	38, 119
	I_2		66	38
	D_2O		65	119
	CH_3I		56, 19	38, 119
	$C_6H_5CH_2Cl$		>95, 40	38, 119

[a] 2-[Bis(dimethylamino)phosphinoyl-1-lithiotetrahydroisoquinolines were generated by the action of *n*-BuLi in THF at −78 °C. [b] Yields were determined spectroscopically by NMR from nonpurified crude materials.

SCHEME XXII



SCHEME XXIII



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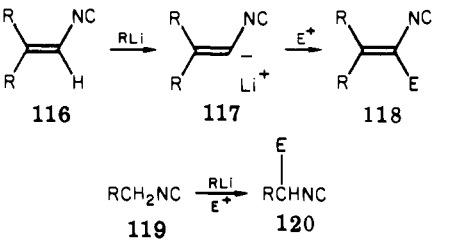
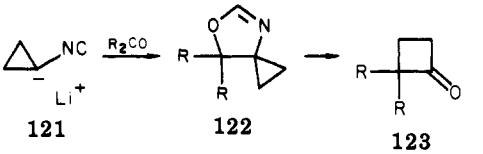


SCHEME XXV

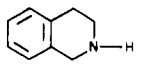
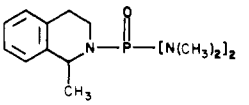
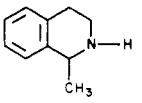
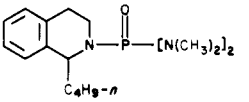
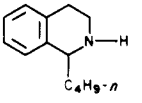
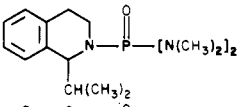
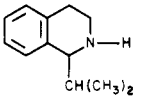
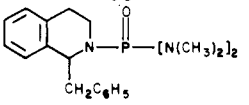
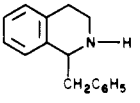
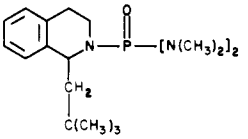
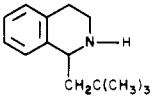
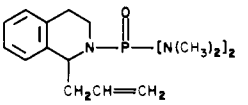
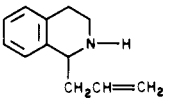
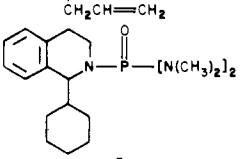
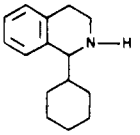
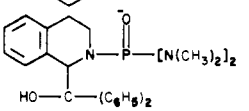
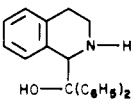
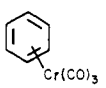
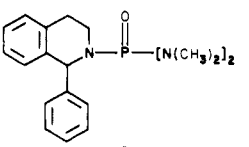
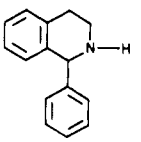
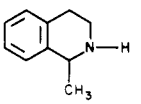
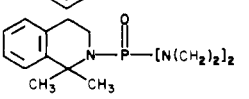
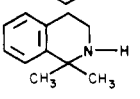
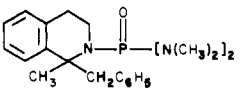
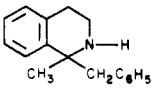


ception of cyclopropyl and cyclobutyl isocyanides,[63,75] secondary alkyl isocyanides do not metalate efficiently. However, the product of lithiation of cyclopropyl isocyanide provides an organolithium reagent **121** which is useful in the synthesis of cyclobutanones. Reaction of **121** with carbonyl compounds gives 2-oxazoline-4-spirocyclopropanes **122** which can be hydrolyzed and rearranged to cyclobutanones **123** as shown in Scheme XXV and Table XX.[76]

Walborsky and Periasamy have found that isocyanocyclopropyl carbanions are configurationally stable at low temperatures which is interpretable as evidence for dipole stabilization.[77]

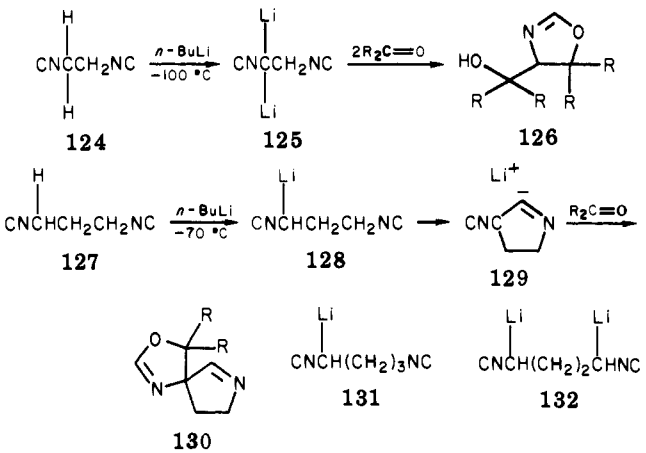
The terminally disubstituted isocyanides of the simple alkanes provide interesting organolithium reagents.

TABLE XVII. Formation of α-Substituted Tetrahydroisoquinolines via Phosphoramides

amine	electrophile	substituted phosphoramide	product[a]	yield, %	ref
	CH_3I			54, 61	38, 119
	n-C_4H_9Cl			63, 72	38, 119
	$(CH_3)_2CHI$			61, 65	38, 119
	$C_6H_5CH_2Cl$			60, 69	38, 119
	$(CH_3)_3CCH_2Br$			29	119
	CH_2=$CHCH_2Cl$			65	119
				23	119
	$(C_6H_5)_2CO$			38	119
				36	119
	CH_3I			36, 14	38, 119
	$C_6H_5CH_2Cl$			36	119

[a] Hydrolysis conditions: aqueous methanolic hydrochloric acid (1.0–5.0 M) at reflux.

SCHEME XXVI



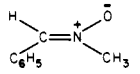
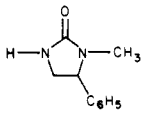
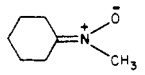
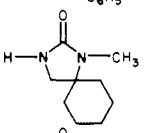
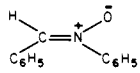
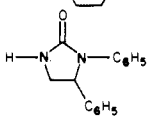
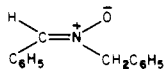
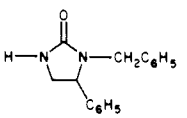
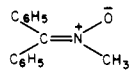
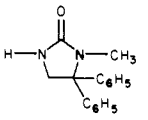
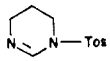
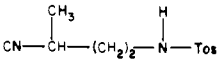
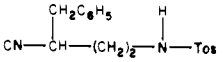
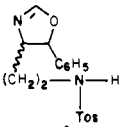
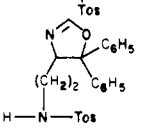
Reaction of ethylene diisocyanide (124) with n-butyllithium at −100 °C is reported to provide the unusual dilithiated species 125 which adds to aldehydes and ketones to provide 126.[60b] At −70 °C, the corresponding propane derivative 127 gives a monolithio intermediate 128, which cyclizes to 129 and on addition of an aldehyde or ketone provides 130. The terminally diisocyano-substituted butane can be lithiated to give either the mono- or dilithiated species 131 or 132, respectively, as shown in Scheme XXVI and Table XXI.[60b]

A potential competing reaction in the metalation of isocyanides is nucleophilic addition to carbon. Indeed, if the α-azo carbon is trisubstituted, addition of an organolithium reagent occurs exclusively to produce the α-lithiated aldimine 133 which can be reacted with various electrophiles and subsequently hydrolyzed to afford a substituted ketone 134.[78] Thus 133 is an acyl anion equivalent as shown in Scheme XXVII.

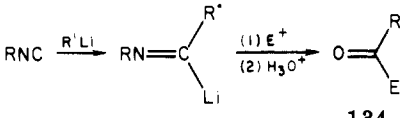
I. Formamidines (Z = CH(=NR))

In the last two years the formamidine group has emerged as a potent group for activation of a carbon–

TABLE XVIII. Formation of *N*-(α-Lithio) Isocyanides and Reactions with Electrophiles

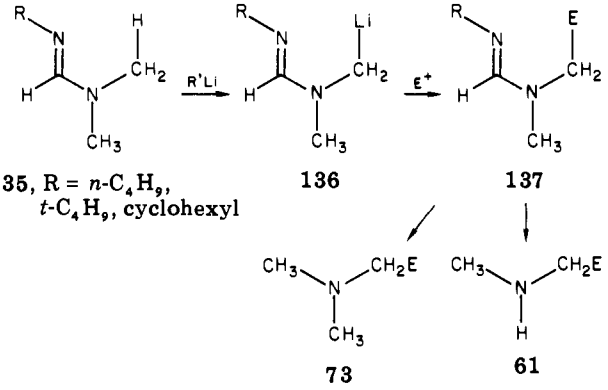
reactant	base	temp, °C	solvent	electrophile	product	yield, %	ref
CH_3NC	*n*-BuLi	−60 to −70	THF			22	59
	n-BuLi	−60 to −70	THF			20	59
	n-BuLi	−60 to −70	THF			46	59
	n-BuLi	−60 to −70	THF			50	59
	n-BuLi	−60 to −70	THF			45	59
	*n*-BuLi (2 equiv)	−78	THF	CH_3I		52	60
	n-BuLi (2 equiv)	−78	THF	$C_6H_5CH_2Br$		64	60
	n-BuLi (2 equiv)	−78	THF	C_6H_5CHO		47	60
	n-BuLi (2 equiv)	−78	THF	$(C_6H_5)_2CO$		49	60

SCHEME XXVII



133 134

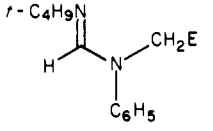
SCHEME XXVIII



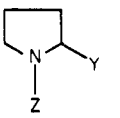
135, R = *n*-C_4H_9, *t*-C_4H_9, cyclohexyl

136 137 73 61

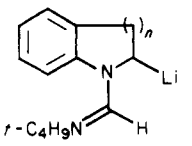
hydrogen bond adjacent to nitrogen in the sequence of Scheme II. Meyers et al. initially found that the *N,N*-dimethylformamidines **135** can be metalated with *sec*-butyl- or *tert*-butyllithium to afford the α-azo carbanion **136** shown in Scheme XXVIII. This dipole-stabilized organolithium reagent reacts with alkyl halides, ketones, and aldehydes to provide the substituted amidines **137**. A particular advantage of formamidines for this methodology is the facile cleavage of the activating group. Hydrolysis with acidic aqueous methanol provides the secondary amines **61** while hydride reduction gives an *N*-methyl tertiary amine.[79] Overall yields of substituted amines range from 40 to 77% as shown in Table XXII. Formamidines derived from phenylmethylamine were also metalated and found to react with alkyl iodides to give formamidines **138**, a result which suggests the utility of this approach for unsymmetrical systems.[80]



138



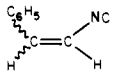
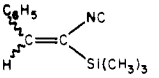
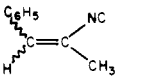
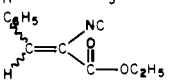
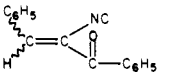
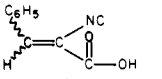
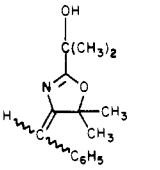
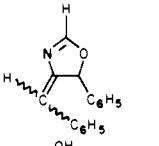
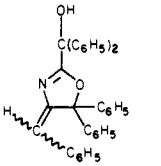
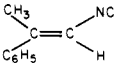
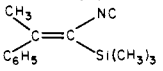
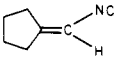
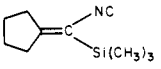
139, Z = $HC{=}NC_6H_5$, Y = Li
140, Z = H, Y = C_6H_5CHOH



141, *n* = 2
142, *n* = 1

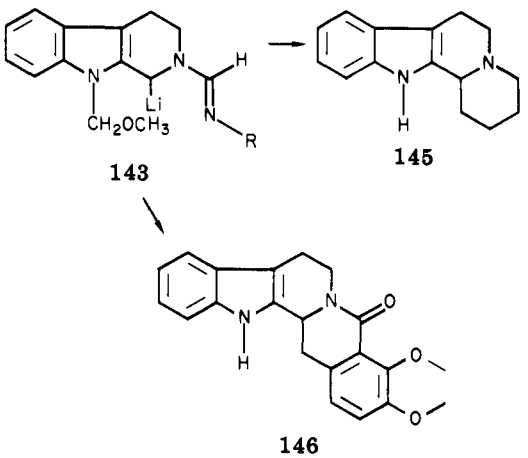
An important feature of the formamidine group is that it is sufficiently activating to allow lithiation at secondary centers. The pyrrolidine formamidine has been converted via **139** to the β-hydroxy amine **140** by the sequence of lithiation, addition to benzaldehyde, and hydrolysis.[79] Analogously, the formamidines of tetrahydroquinoline and indoline have been metalated

TABLE XIX. Formation of *N*-(α-Lithioalkenyl) Isocyanides and Reactions with Electrophiles

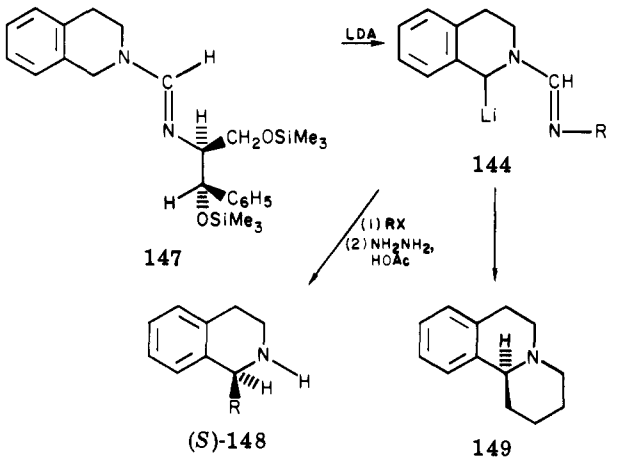
reactant	base	temp, °C	solvent	electrophile	product	yield, %	ref
	*n*-BuLi	−70	THF	$ClSi(CH_3)_3$		53	74
	n-BuLi	−70	THF	CH_3I		75	74
	n-BuLi	−70	THF	$ClCO_2C_2H_5$		ca. 70[a]	74
	n-BuLi	−70	THF	C_6H_5COCl		ca. 94[a]	74
	n-BuLi	−70	THF	CO_2, H^+		ca. 95[a]	74
	n-BuLi	−78	THF	$(CH_3)_2CO$		77	74
	n-BuLi	−78	THF	C_6H_5CHO		36	74
	n-BuLi	−78	THF	$(C_6H_5)_2CO$			74
	*n*-BuLi	−78	THF	$ClSi(CH_3)_3$		78	74
	*n*-BuLi	−78	THF	$ClSi(CH_3)_3$		53	74

[a] Yield was determined spectroscopically by NMR from nonpurified crude material.

SCHEME XXIX



SCHEME XXX

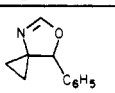
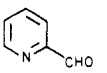
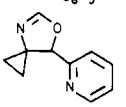
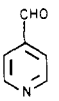
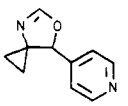
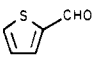
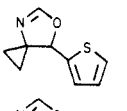
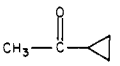
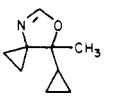
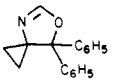
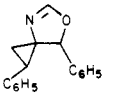
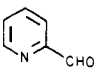
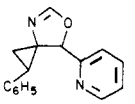
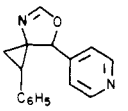
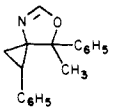


to provide **141** and **142**, respectively. Subsequent reaction of these organolithium reagents with alkyl iodides and benzaldehyde give substituted products in useful yields (Table XXII).[80]

Formamidines derived from tetrahydrocarboline and tetrahydroisoquinoline also can be lithiated to afford **143** and **144**, respectively, which undergo electrophilic substitution at the activated methylene position to give the expected products in 52–67% yields as shown in Table XXIII.[81] The metalated formamidine **143** has been successfully used in the synthesis of indole alkaloid derivatives as illustrated in Scheme XXIX for the indolo[2,3-*a*]quinolizidine **145** and the yohimbane indole skeleton **146**.[82] Both syntheses illustrate a general strategy for alkaloid syntheses in which the originally activating nitrogen can participate in a nucleophilic cyclization following removal of the activating group.[35,39]

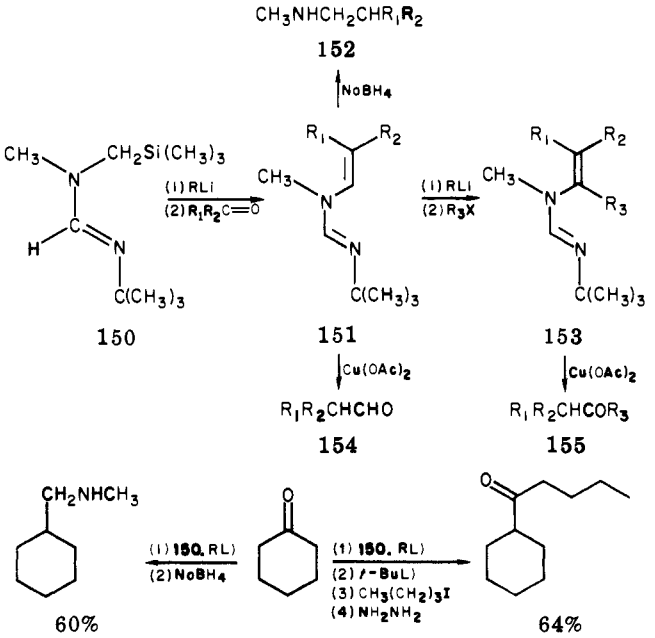
Recent work establishes that formamidines are exceptionally useful as α-lithio amine synthetic equivalents for asymmetric induction. Thus, the formation

TABLE XX. Formation of *N*-(α-Lithiocyclopropyl) Isocyanides and Reactions with Electrophiles

reactant	base	temp, °C	solvent	electrophile	product	yield, %	ref
	*n*-BuLi	−70	THF	C_6H_5CHO		89	76
	n-BuLi	−70	THF			75	76
	n-BuLi	−70	THF			62	76
	n-BuLi	−70	THF			78	76
	n-BuLi	−70	THF			89	76
	n-BuLi	−70	THF	$(C_6H_5)_2CO$		61	76
	*n*-BuLi	−70	THF	C_6H_5CHO		35	76
	n-BuLi	−70	THF			90[a]	76
	n-BuLi	−70	THF			40	76
	n-BuLi	−70	THF	$C_6H_5COCH_3$		85[a]	76

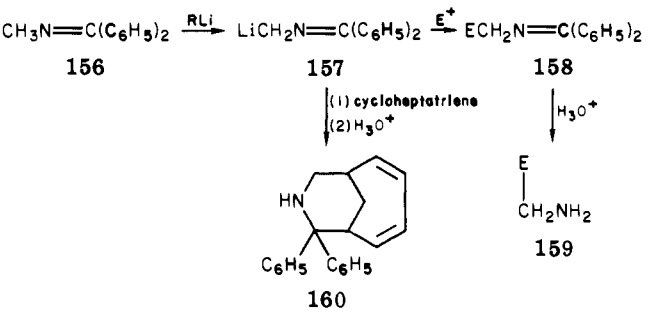
[a] Yield was determined spectroscopically by NMR from nonpurified crude material.

SCHEME XXXI



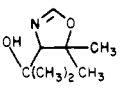
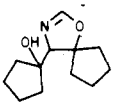
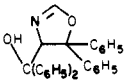
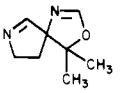
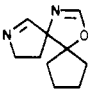
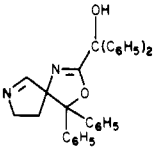
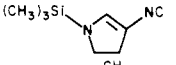
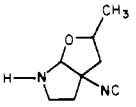
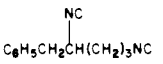
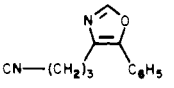
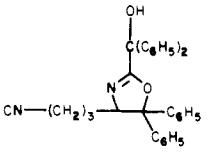
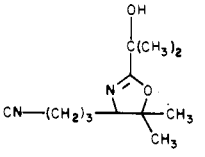
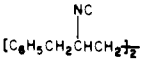
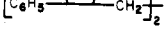
of 144 (R = 1(*S*),2(*S*)-(+)-1-phenyl-2-amino-1,3-bis-(trimethylsiloxy)-2-propyl) from 147 with lithium diisopropylamide when followed by addition to alkyl halides and hydrolysis gives chiral 1-substituted tetrahydroquinolines 148 in yields of 65–68% with enantiomeric excesses of the *S* configuration greater than 90% as shown in Scheme XXX and Table XXIV.[83] This sequence has been used to prepare the benzoquinolizine 149 in 70% yield and 90% enantiomeric excess. The chiral amine is regenerated upon hydrolysis.

SCHEME XXXII



The lithiated formamidine 136 is useful in a variety of syntheses. Reaction with trimethylsilyl chloride gives 150 which on lithiation and addition to carbonyl compounds provides the enamidine 151 as shown in Scheme XXXI. This species in turn can be reduced to an amine 152, subjected to further metalation and electrophilic substitution to the enamine 153, or hydrolyzed to the aldehyde 154.[84] The enamine 153 can be hy-

TABLE XXI. Formation of Mono- and Di-*N*-(α-Lithioalkyl) Isocyanides and Reactions with Electrophiles

reactant	base	temp, °C	solvent	electrophile	product	yield, %	ref
$CN(CH_2)_2NC$	*n*-BuLi (2 equiv)	−100	THF	$(CH_3)_2CO$		80	60b
	n-BuLi (2 equiv)	−100	THF	 #b		68	60b
	n-BuLi (2 equiv)	−100	THF	$(C_6H_5)_2CO$		78	60b
$CN(CH_2)_3NC$	*n*-BuLi	−70	THF	$(CH_3)_2CO$		68	60b
	n-BuLi	−70	THF	 #f		46	60b
	n-BuLi	−70	THF	$(C_6H_5)_2CO$		76	60b
	n-BuLi	−70	THF	$ClSi(CH_3)_3$		67	60b
	n-BuLi	−70	THF			30	60b
$CN(CH_2)_4NC$	*n*-BuLi	−100	THF	$C_6H_5CH_2Br$		78	60b
	n-BuLi	−100	THF	$C_6H_5CON(C_2H_5)_2$		66	60b
	n-BuLi	−100	THF	$(C_6H_5)_2CO$		64	60b
	n-BuLi	−100	THF	$(CH_3)_2CO$		40	60b
	n-BuLi (2 equiv)	−100	THF	$C_6H_5CH_2Br$		83	60b
	n-BuLi (2 equiv)	−100	THF	$C_6H_5CON(C_2H_5)_2$		47	60b

drolyzed to the carbonyl derivative **155** while reduction to an amine should also be possible. Specific uses of this approach for aminomethylation and reductive acylation are illustrated for cyclohexanone at the bottom of Scheme XXXI. Related results are compiled in Table XXV.

The lithiation of formamidines bearing additional activation due to ester substitution at the α-carbon provides an enolate which reacts with alkyl and allyl halides to afford substituted amino acids in useful yields. Subsequent hydrolysis to provide substituted products in 60–80% yields have been reported (See Addendum).[85]

J. Imines (Z = CR_2)

Aldimines and ketimines from methylamine or amines bearing additional electron-withdrawing substituents in the α-positions have been shown to metalate readily to give α-aminoallylic carbanionic species.[86] For example, Kauffmann's demonstration that the methylimine of benzophenone **156** can be metalated to give **157** has led to investigation of the addition of **157** to alkyl halides, ketones, and aldehydes, to give **158** as shown in Scheme XXXII.[87,88] Subsequent hydrolysis to an electrophilically substituted methylamine **159** is achieved by heating in aqueous acid in yields of 17–70% as shown in Table XXVI.[87] The anion **157** also reacts with cycloheptatriene to give the [6 + 4] cycloaddition product **160** in 47% yield.[89] The anion **161** derived from the metalation of benzylidenebenzylamine **162** reacts analogously with alkyl halides, ketones, alkenes, carbon dioxide, and isocyanates to give substituted products

TABLE XXII. α-Substituted Amines via Dipole-Stabilized Carbanions from Formamidines

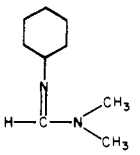
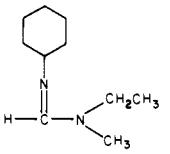
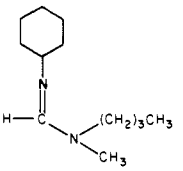
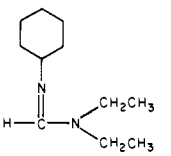
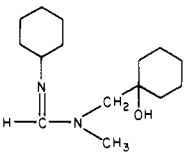
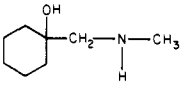
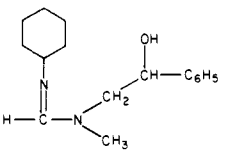
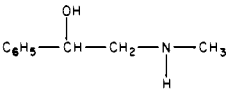
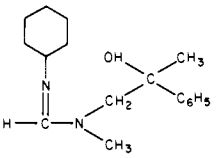
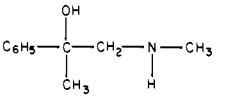
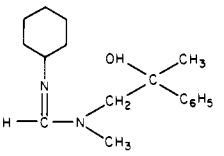
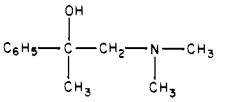
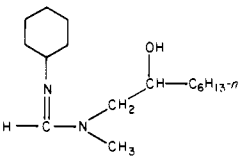
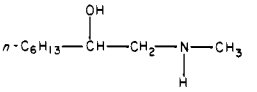
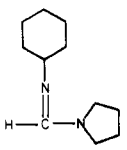
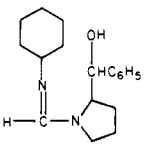
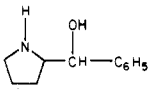
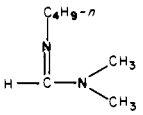
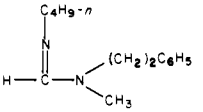
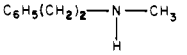
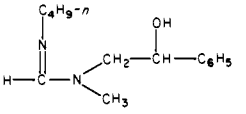
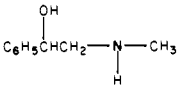
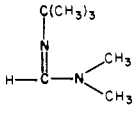
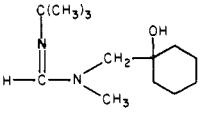
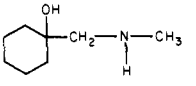
reactant[a]	electrophile	α-substituted formamidine	yield, %	α-substituted amine	yield, %	ref
	CH_3I		85			79
	n-C_3H_7I		82			79
	CH_3I (sequence repeated)		88			79
					45[b]	79
	C_6H_5CHO				77[b]	79
	$C_6H_5COCH_3$				64[b]	79
	$C_6H_5COCH_3$				67[c]	79
	n-$C_6H_{13}CHO$				40[b]	79
	C_6H_5CHO				57[b]	79
	$C_6H_5CH_2Br$				54[d]	79
	C_6H_5CHO				71[b]	79
					40[b]	79

TABLE XXII (Continued)

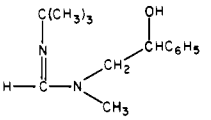
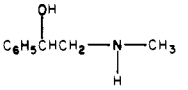
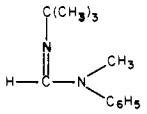
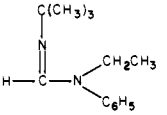
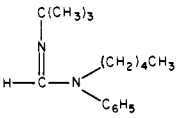
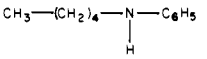
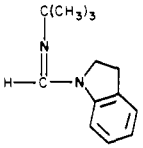
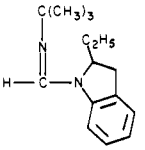
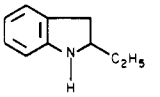
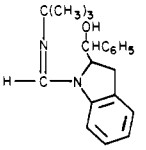
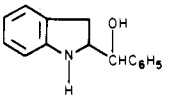
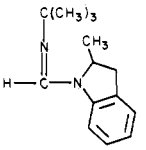
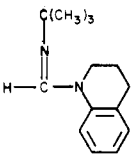
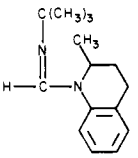
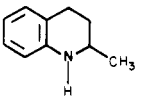
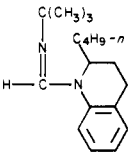
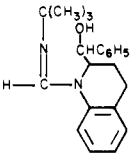
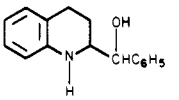
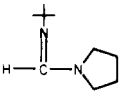
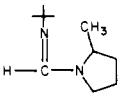
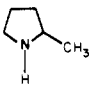
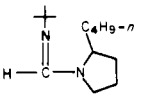
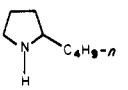
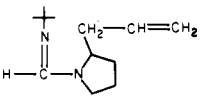
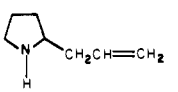
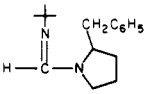
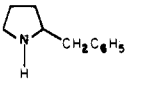
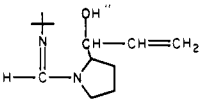
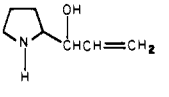
reactant[a]	electrophile	α-substituted formamidine	yield, %	α-substituted amine	yield, %	ref
	C_6H_5CHO				76[b]	79
	CH_3I		90			80
	n-C_4H_9I				68[e]	80
	C_2H_5I				66[e]	80
	C_6H_5CHO				73[e]	80
	CH_3I		83			80
	CH_3I				65[e]	80
	n-C_4H_9I		84			80
	C_6H_5CHO				64[e]	80
	CH_3I		63,[f] 73[g]		87,[h] 85[b]	126
	n-C_4H_9Br		75[f]		70[h]	126
	$CH_2{=}CHCH_2Br$		30–40		80[b]	126
	$BrCH_2C_6H_5$		20–30		90[b]	126
	$CH_2{=}CHCHO$		62		61[c]	126

TABLE XXII (Continued)

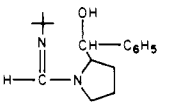
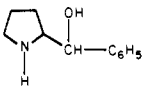
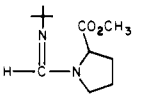
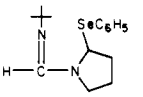
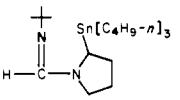
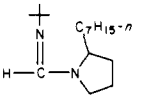
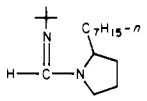
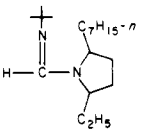
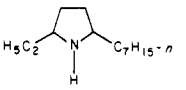
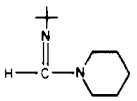
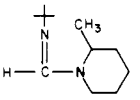
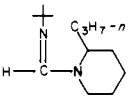
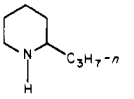
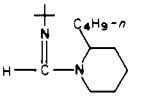
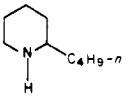
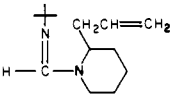
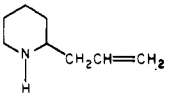
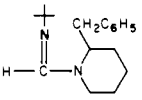
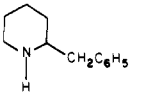
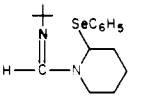
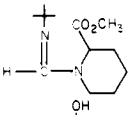
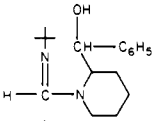
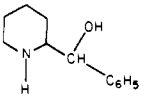
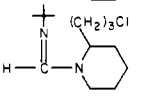
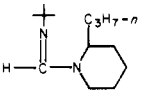
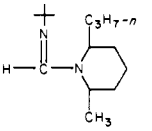
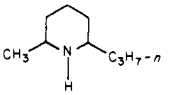
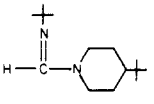
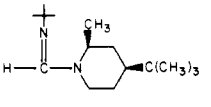
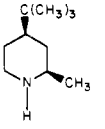
reactant[a]	electrophile	α-substituted formamidine	yield, %	α-substituted amine	yield, %	ref
	C_6H_5CHO		74		89[c]	126
	$ClCO_2CH_3$		85			126
	$(C_6H_5Se)_2$		70			126
	$(n\text{-}C_4H_9)_3SnCl$		95			126
	$n\text{-}C_7H_{15}Br$		78			126
	BrC_2H_5		80		87[h]	126
	CH_3I		18, 81[g]			126
	$n\text{-}C_3H_7I$		<5, 80[g]		83[b]	126
	$n\text{-}C_4H_9I$		13, 81[g]		92[b]	126
	$CH_2{=}CHCH_2Br$		30, 81[g]		85[b]	126
	$C_6H_5CH_2Br$		20, 55[g]		87[b]	126
	$(C_6H_5Se)_2$		90			126
	$ClCO_2CH_3$		87			126
	C_6H_5CHO		93		77[c]	126
	$Br(CH_2)_3Cl$		0, 76[g]			126
	CH_3I				71[b]	126
	CH_3I				50–70[e]	126

TABLE XXII (Continued)

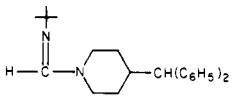
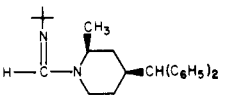
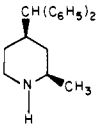
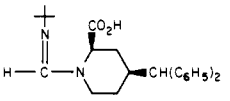
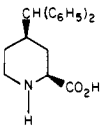
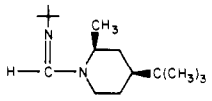
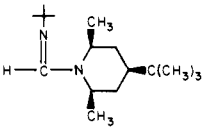
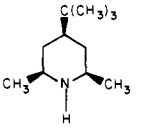
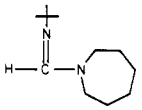
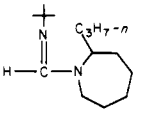
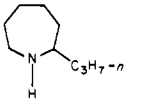
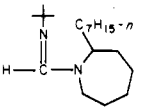
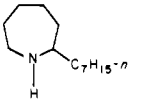
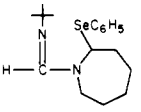
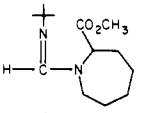
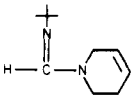
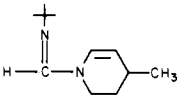
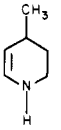
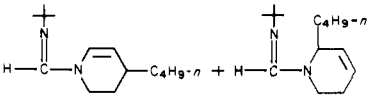
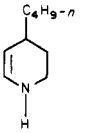
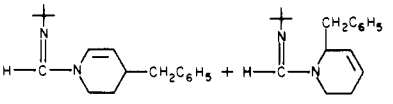
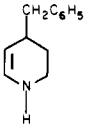
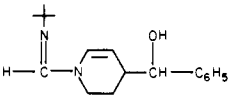
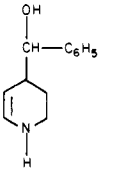
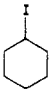
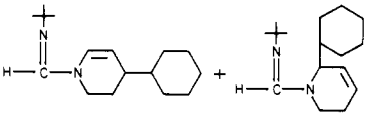
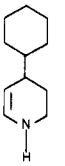
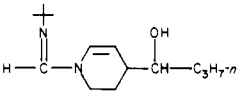
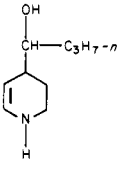
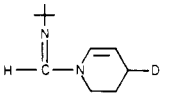
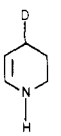
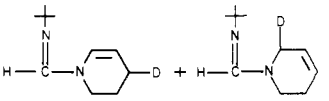
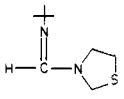
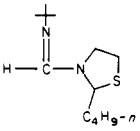
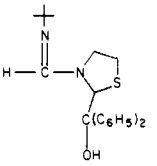
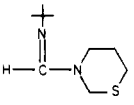
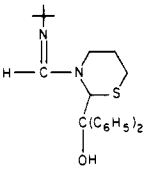
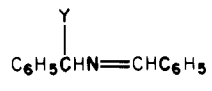
reactant[a]	electrophile	α-substituted formamidine	yield, %	α-substituted amine	yield, %	ref
	CH_3I				50–70[e]	126
	CO_2, H^+					126
	CH_3I					126
	n-C_3H_7I		79			126
	n-$C_7H_{15}I$		80			126
	$(C_6H_5Se)_2$		81			126
	$ClCO_2CH_3$		91			126
	CH_3I				58[h]	126
	n-C_4H_9Br				60[h]	126
	$C_6H_5CH_2Cl$				63[h]	126
	C_6H_5CHO				66[h]	126
					40[h]	126
	n-C_3H_7CHO				71[h]	126

TABLE XXII (Continued)

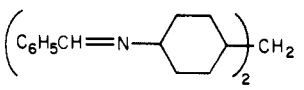
reactant[a]	electrophile	α-substituted formamidine	yield, %	α-substituted amine	yield, %	ref
	D_2O				95[h]	126
	CH_3OD			mixture	95[h]	126
	n-C_4H_9Br		50–55			126
	$(C_6H_5)_2CO$		50–55			126
	$(C_6H_5)_2CO$		50			126

[a] Metalation was accomplished quantitatively by t-BuLi in THF at −78 °C; the anion was allowed to warm to −25 °C for 1 h prior to the addition of the electrophile. [b] Hydrolyzed with KOH (5 equiv) in CH_3OH/H_2O (2:1) at reflux for 18 h. [c] Product after treating the N-formyl derivative with $LiAlH_4$. [d] Hydrolyzed with $HCl/H_2O/CH_3OH$. [e] Hydrolysis conditions not specified. [f] HMPA added prior to electrophile. [g] Pentynylcopper added prior to electrophile. [h] Hydrolyzed with NH_2NH_2.

163 in yields ranging from 20 to 92%.[87,68,90] Similar α-azoallylic anions are involved in the isomerization of



161, Y = Li
162, Y = H
163, Y = E



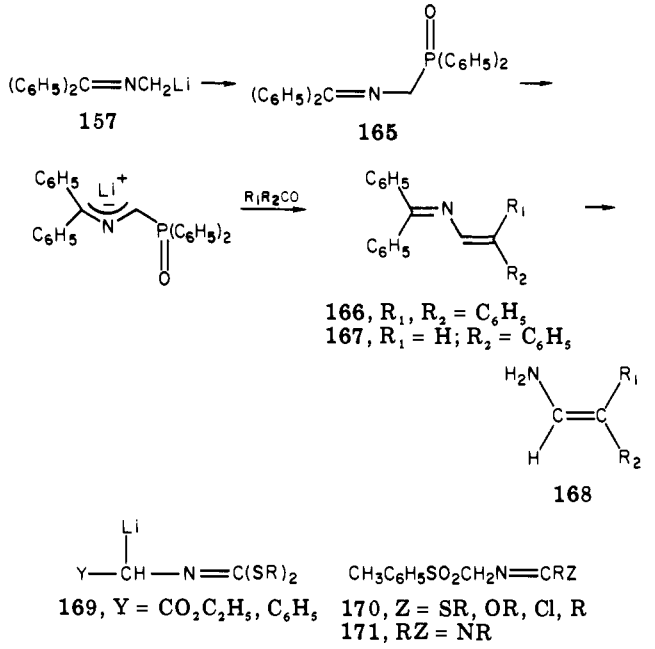
164

164 from *cis,cis*-bis(benzaldimines) to the thermodynamically favored trans,trans isomer in greater than 90% yields, upon treatment with potassium *tert*-butoxide.[91]

The anion **157** has also been useful for the synthesis of enamines. Activation towards further metalation is achieved by conversion to the phosphonyl derivative **165** which undergoes lithiation and addition to benzophenone or benzaldehyde to give **166** and **167** in 92 and 56% yields, respectively. Hydrolysis of these imines provides the enamines **168** shown in Scheme XXXIII.[92] Related imine derivatives in which dominant activation for carbanion formation is provided by an adjacent carbonyl group have been useful in the synthesis of penicillin[93] and amino acid[94] derivatives. In addition, imino derivatives of lithiodithiocarbonates undergo facile metalation to **169** and subsequent substitution occurs adjacent to the activating group.[93] The sulfonate derivatives **170** and **171** have also been shown to react similarly.[94]

Finally, (1-phenyl-1,2-diazaallyl)lithium **172** has been generated and allowed to react with aldehydes and ketones to yield α-hydroxy aldehyde phenylhydrazones as shown in Scheme XXXIV.[95]

SCHEME XXXIII



157 **165**

166, R_1, R_2 = C_6H_5
167, R_1 = H; R_2 = C_6H_5

168

169, Y = $CO_2C_2H_5$, C_6H_5

170, Z = SR, OR, Cl, R
171, RZ = NR

K. Isothiocyanates (Z = C═S)

Methyl isothiocyanate has been reported to give the imidazoline derivative **173** under metalation conditions. The formation of **173** can occur via addition of the transient α-metallo isothiocyanate **174** to methyl isothiocyanate. Indeed **174** can be generated from the trimethylsilyl derivative of methyl isothiocyanate and trapped in situ by carbonyl electrophiles to give oxa-

TABLE XXIII. α-Substituted Amines via α-Amino Carbanions from Formamidines

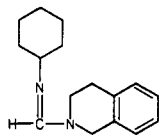
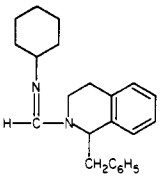
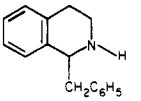
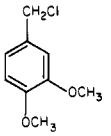
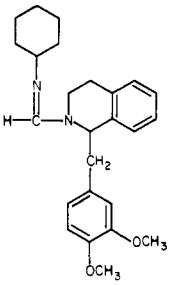
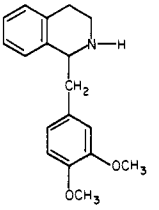
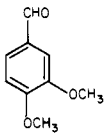
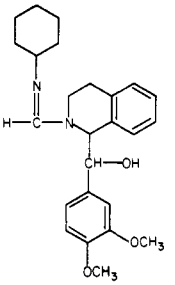
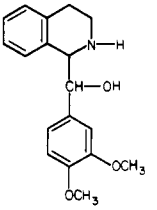
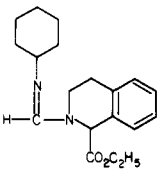
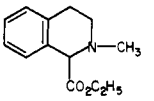
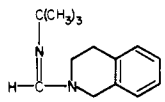
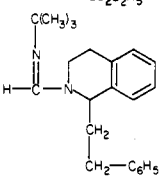
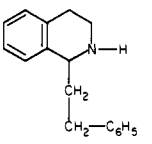
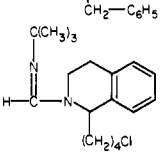
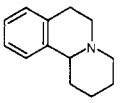
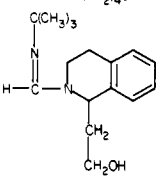
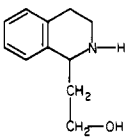
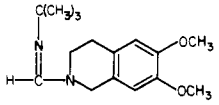
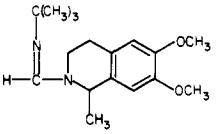
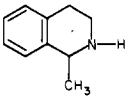
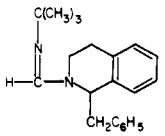
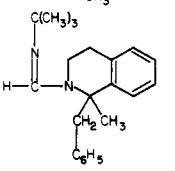
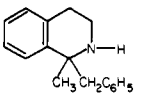
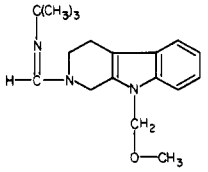
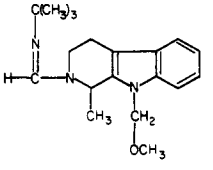
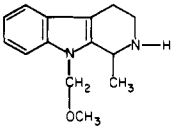
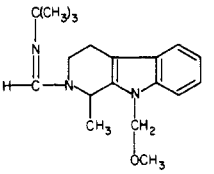
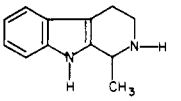
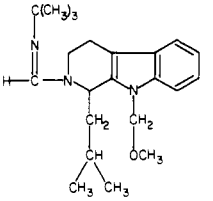
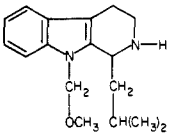
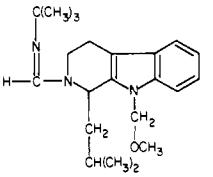
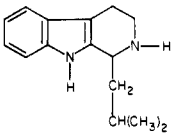
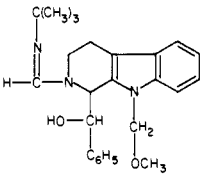
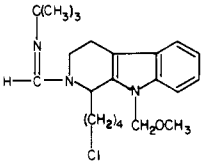
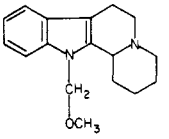
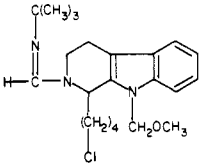
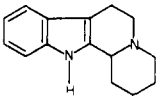
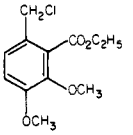
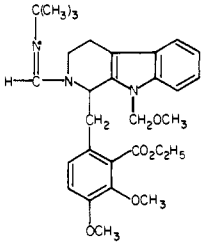
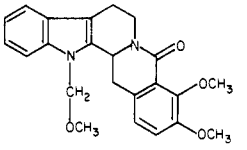
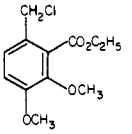
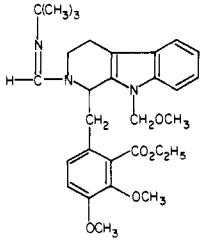
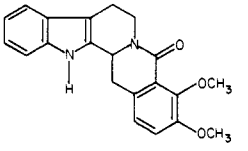
reactant	metalation conditions[a]	electrophile	α-substituted formamidine	yield, %	α-substituted amine	yield,[b] %	ref
	A	$C_6H_5CH_2Br$				52[c]	81
	A					52[c]	81
	A					53[c]	81
	A	$ClCO_2C_2H_5$				62[d]	81
	A	$C_6H_5CH_2CH_2Br$				61[e]	81
	A	$Br(CH_2)_4Cl$				71[f]	81
	A					67[e]	81
	A	CH_3I				52[c]	81
	A	CH_3I				53[f]	81
	B	CH_3I		84		68[c]	82

TABLE XXIII. (Continued)

reactant	metalation conditions[a]	electrophile	α-substituted formamidine	yield, %	α-substituted amine	yield,[b] %	ref
	B	CH_3I		84		77[g]	82
	B	$(CH_3)_2CHCH_2I$		87		91[c]	82
	B	$(CH_3)_2CHCH_2I$		87		78[h]	82
	B	C_6H_5CHO		89			82
	B	$Cl(CH_2)_4Br$				68[c]	82
	B	$Cl(CH_2)_4Br$				77[h]	82
	B			89		83[c]	82
	B			89		75[i]	82

[a] A = LDA in THF at −78 °C for 2–3 h or *sec*-BuLi in THF at −78 °C for ~45 min; B = *t*-BuLi in THF at −25 °C for ~45 min (the electrophile was added at −78 °C). [b] Cleavage conditions: [c] 95% $NH_2NH_2/CH_3CO_2H/C_2H_5OH$ (aq) (1:1.6:10) at 53 °C overnight. [d] Al–Hg reagent described by A. I. Meyers and J. R. Durandetta, *J. Org. Chem.*, **40**, 2021 (1975). [e] 10% KOH/CH_3OH (1:1) heated to reflux for 24 h. [f] $LiAlH_4$ (3 equiv Li) in THF at reflux for 16 h. [g] Stirred for 15 min with 3 N HCl, neutralized to pH 10 with NaOH, stirred for 1 h at 25 °C. [h] Heated at 60–65 °C for 1 h in 3 N HCl/THF (1:1), neutralized to pH > 11, two layers stirred overnight. [i] Same conditions as in *h* except heating was continued for 5.5 h.

zoline-2-thiones **175a** in 25–75% yield as summarized in Scheme XXXV and Table XXVII.[96] Derivatives in which stabilization for a carbanion is provided by additional substitution, shown as **176**, have been used to produce **175b**, dialkyl-α-isothiocyanoacrylates, **177**, and substituted esters.[97,98]

TABLE XXIV. Asymmetric Alkylations of Chiral α-Amino Carbanions from Formamidines

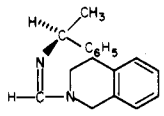
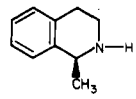
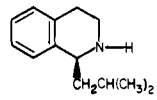
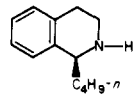
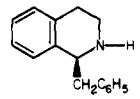
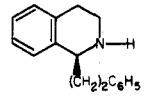
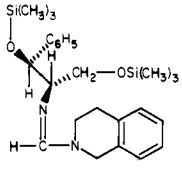
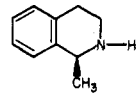
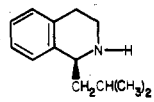
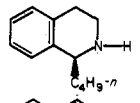
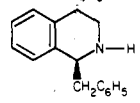
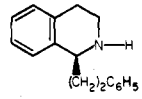
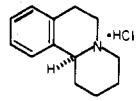
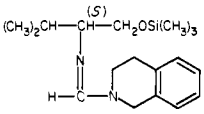
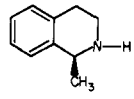
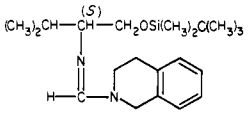
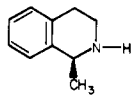
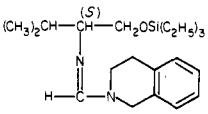
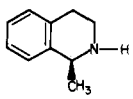
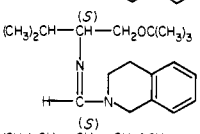
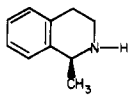
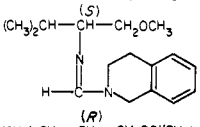
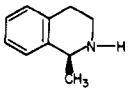
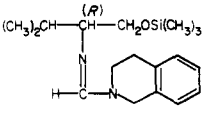
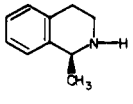
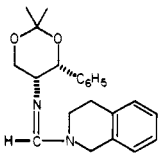
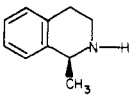
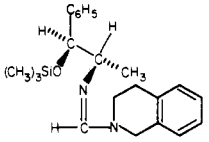
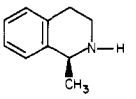
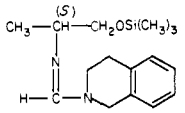
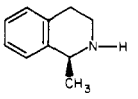
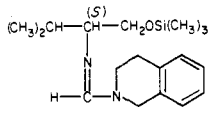
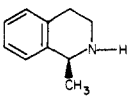
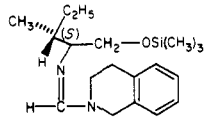
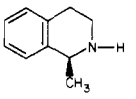
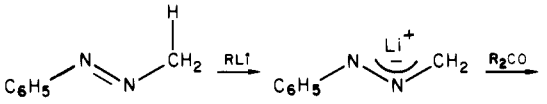
reactant	metalation conditions[a]	electrophile	α-substituted chiral amine	chemical yield,[b] %	ee, %	configuration	ref
	A	CH_3I		85	10	*R*	83
	A	$(CH_3)_2CHCH_2Br$		84	27	*R*	83
	A	*n*-C_4H_9Br		93	19	*R*	83
	A	$C_6H_5CH_2Br$		97	35	*R*	83
	A	$C_6H_5CH_2CH_2Br$		89	52	*S*	83
	A,B	CH_3I		80, 79	80, >99	*S*	83
	B	$(CH_3)_2CHCH_2Br$		85	91	*S*	83
	B	*n*-C_4H_9Br		80	91	*S*	83
	B	$C_6H_5CH_2Br$		70	93	*S*	83
	B	$C_6H_5(CH_2)_2Br$		65	>99	*S*	83
	B	$Br(CH_2)_4Cl$		70[c]	90	*S*	83
	B	CH_3I		52	88	*S*	125
	B	CH_3I		74	75	*S*	124
	B	CH_3I		70	74	*S*	124
	B	CH_3I		90	86	*S*	124
	B	CH_3I		46[d]	84	*S*	124
	B	CH_3I		73	93	*R*	124

TABLE XXIV (Continued)

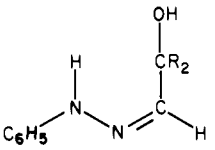
reactant	metalation conditions[a]	electrophile	α-substituted chiral amine	chemical yield,[b] %	ee, %	configuration	ref
	B	CH_3I		77	12	*R*	124
	B	CH_3I		74	39	*R*	124
	B	CH_3I		60	50	*S*	124
	B	CH_3I		71	93	*S*	124
	B	CH_3I		71	90	*S*	124

[a] A = LDA in THF at −78 °C; B = LDA in THF at −78 °C, electrophile added at −100 °C. [b] Hydrazinolysis was accomplished by treatment of formamidine with hydrazine/acetic acid. [c] Catalyzed during hydrazinolysis. [d] Low yield due to methoxy elimination during the metalation step.

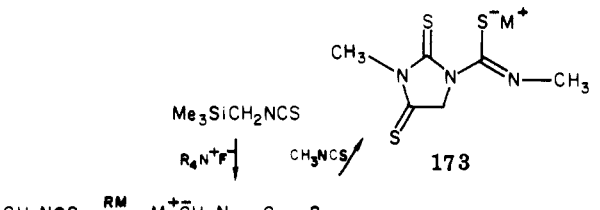
SCHEME XXXIV



172

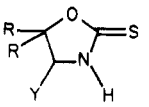


SCHEME XXXV

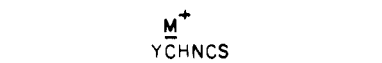


173

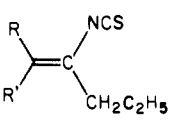
174



175a, Y = H
175b, Y = $CO_2C_2H_5$, C_6H_5, $CH{=}CH_2$



176, Y = $CO_2C_2H_5$, C_6H_5, $CH{=}CH_2$



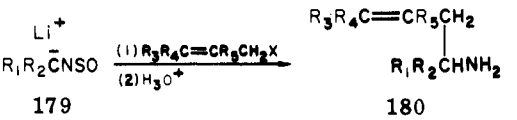
177

L. N-Sulfinylamines (Z = SO)

Interesting examples of the formation of an α-azo carbanion have been reported by Schell for the lithiation of *N*-sulfinylamines **178** with lithium triphenylmethide to give **179** as shown in Scheme XXXVI.[99] The organolithium reagent **179** reacts with allyl halides

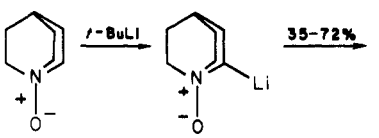
SCHEME XXXVI

178a, $R_1 = R_2 = n\text{-}C_3H_7$
178b, $R_1 = H$, $R_2 = n\text{-}C_5H_{11}$
178c, $R_1R_2 = (CH_2)_5$

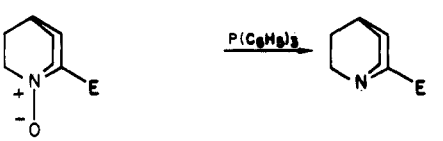


179 180

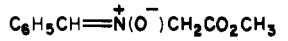
SCHEME XXXVII



181

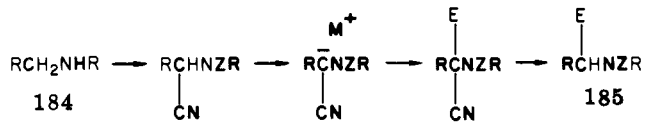


182, E = D, $COHR_1R_2$, COR'



183

SCHEME XXXVIII



184 185

TABLE XXV. Homologation of Carbonyls to Amines, Aldehydes, and Ketones via Dipole-Stabilized Carbanions from Formamidines

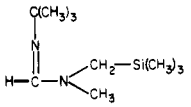
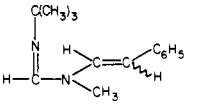
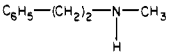
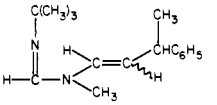
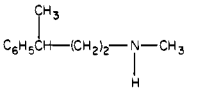
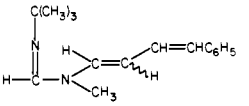
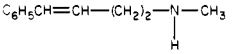
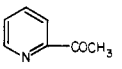
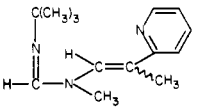
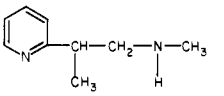
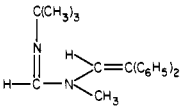
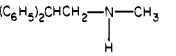
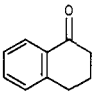
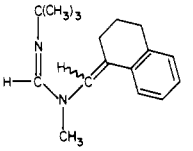
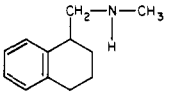
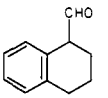
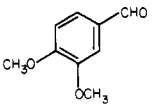
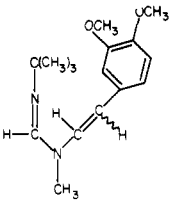
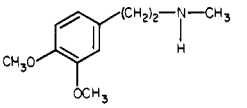
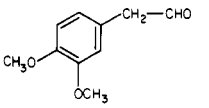
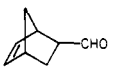
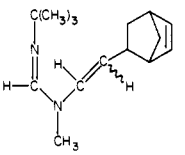
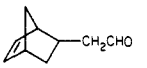
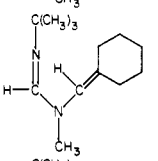
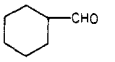
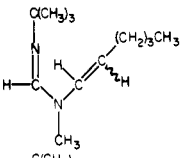
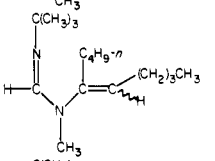
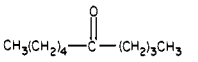
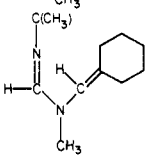
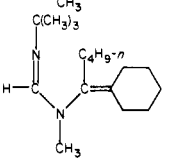
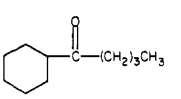
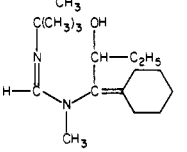
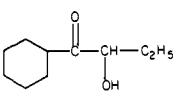
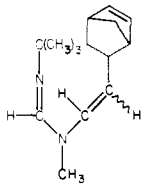
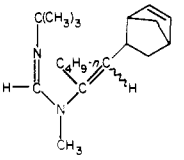
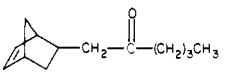
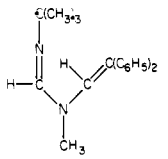
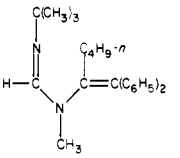
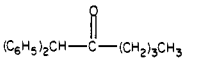
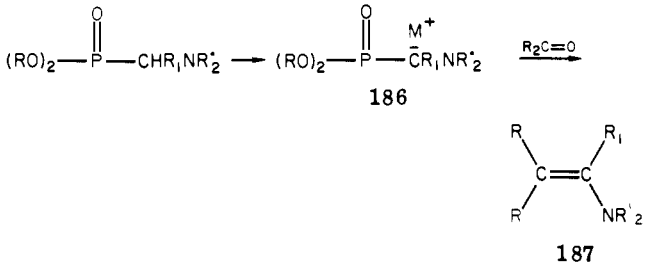
reactant	metalation conditions[a]	electrophile	enamidine	product	yield, %	ref
	A	C_6H_5CHO			66[b]	84
	A				61[b]	84
	A	$C_6H_5CH{=}CHCHO$			52[b]	84
	A				70[b]	84
	A	$(C_6H_5)_2CO$			65[b]	84
				$(C_6H_5)_2CHCHO$	84[c]	84
	A				66[b]	84
					60[c]	84
	A				67[b]	84
					55[c]	84
	A				72[c]	84
	A				62[c]	84
	B	n-C_4H_9I			71[c]	84
	B	n-C_4H_9I			64[c]	84
	B	C_2H_5CHO			50[c]	84

TABLE XXV (Continued)

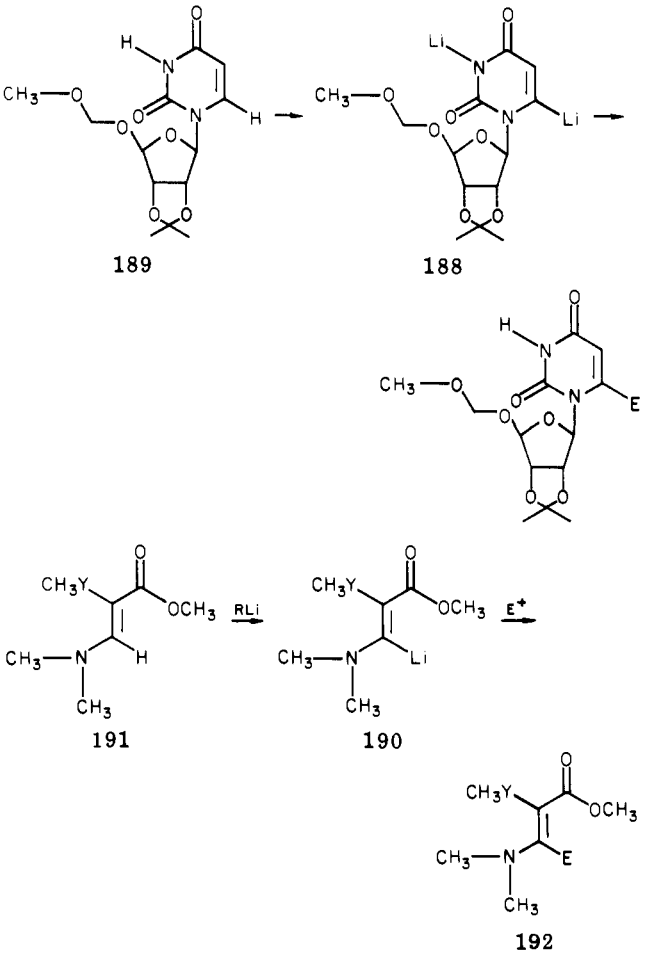
reactant	metalation conditions[a]	electrophile	enamidine	product	yield, %	ref
	B	n-C_4H_9I			74[c]	84
	B	n-C_4H_9I			61[c]	84

[a] A = n-BuLi in THF at −78 °C; B = t-BuLi in THF at −78 °C. [b] The formamidine was treated with $NaBH_4$ in ethanol at −10 °C while maintaining the pH at 6; the aminal thus produced was hydrolyzed with dilute acid. [c] Hydrazinolysis with hydrazine or dimethylhydrazine/acetic acid/ethanol/water followed by treatment with aqueous $Cu(OAc)_2$ gave the aldehyde or ketone.

SCHEME XXXIX



SCHEME XL



to give the corresponding α-substituted amines **180** in moderate yields after acidic hydrolysis as shown in Table XXVIII. If this reaction has an appreciable scope it could be a very useful approach to α-lithio amine synthetic equivalents.

M. Amine Oxides (Z = $-O^-$)

Pyridine N-oxides are well known to undergo lithiation to give dipole-stabilized carbanions which are subject to electrophilic substitutions. In conjunction with deoxygenation this approach could provide a useful synthesis of 2-substituted pyridines. The area has been reviewed.[5,100]

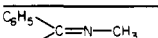
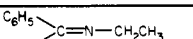
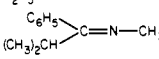
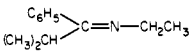
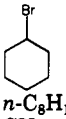
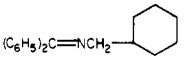
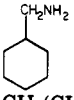
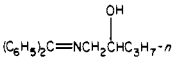
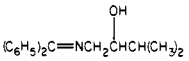
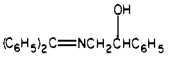
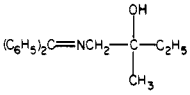
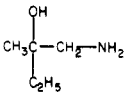
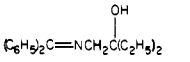
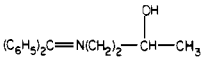
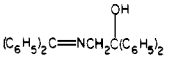
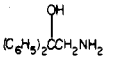
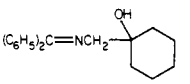
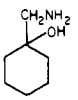
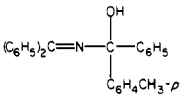
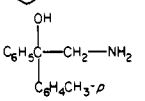
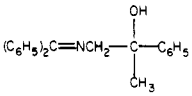
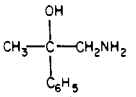
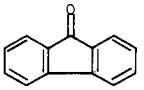
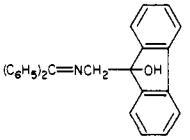
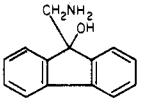
Metalation of an sp^3 carbon stabilized by an N-oxide moiety has been reported for quinuclidine N-oxide.[101] Lithiation with *tert*-butyllithium to give **181** followed by reaction with D_2O, aldehydes, and esters gives **182** which can be deoxygenaated with triphenylphosphine to give α-substituted quinuclidines as shown in Scheme XXXVII in synthetically useful yields. Dipole-stabilization appears to be an important factor in the formation of **181** in this case although complexation could also be involved. An amine oxide system which bears additional activation for anion formation adjacent to nitrogen is methyl N-benzylidine-α-aminoacetate N-oxides (**183**). This system has been metalated and subsequently allowed to react with alkyl halides to give mono- and disubstituted products.[102]

III. Systems with Additional Activation

In the preceding discussion some systems which bear additional activating groups on the carbon-bearing nitrogen have been mentioned. Such systems can be useful as general α-lithio amine synthetic equivalents if the activating group can be easily removed subsequently to electrophilic substitution.

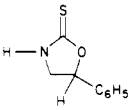
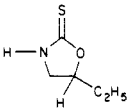
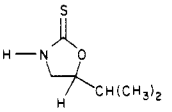
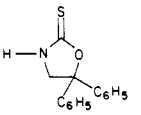
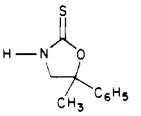
The use of α-amino nitriles has been generally useful and the deprotonation of α-amino nitriles derived from aldehydes has been shown to give organometallics which have been converted to amino nitriles (80–94%),[103,104] α,β-unsaturated nitriles (40–70%),[105] enamines,[104] or substituted ketones (70–90%)[106] as illustrated for the conversion of **184** to **185** shown in Scheme XXXVIII. A specific example of this approach is the conversion of piperidine to *dl*-conhydrine by Stork et al. shown in

TABLE XXVI. α-Substituted Methylamines via α-Amino Carbanions from Imines

reactant	metalation conditions[a]	electrophile	α-substituted imine	yield, %	α-substituted methylamine	yield,[b] %	ref
	A	CH_3I		18[c]			87d
	A	CH_3I		17[c]			87d
$(C_6H_5)_2C{=}NCH_3$	B	n-C_3H_7Cl	$(C_6H_5)_2C{=}N(CH_2)_3CH_3$	81			87a
	B, C	n-C_3H_7Br	$(C_6H_5)_2C{=}N(CH_2)_3CH_3$	81, 63			87a
	B	n-$C_7H_{15}Br$	$(C_6H_5)_2C{=}N(CH_2)_7CH_3$	76			87a
	B	$(CH_3)_2CHCH_2Br$	$(C_6H_5)_2C{=}N(CH_2)_2CH(CH_3)_2$	69			87a
	B	$C_6H_5CH_2Cl$	$(C_6H_5)_2C{=}N(CH_2)_2C_6H_5$	64	$C_6H_5(CH_2)_2NH_2$	48	87a
	B	$(CH_3)_2CHBr$	$(C_6H_5)_2C{=}NCH_2CH(CH_3)_2$	84			87a
	B, D	$CH_3CH(Br)C_2H_5$	$(C_6H_5)_2C{=}NCH_2CH(CH_3)C_2H_5$	18, 70			87a
	B	$CH_3CH(Br)C_3H_7$-n	$(C_6H_5)_2C{=}NCH_2CH(CH_3)C_3H_7$-$n$	43			87a
	D	$CH_3CH(Br)C_6H_{13}$-n	$(C_6H_5)_2C{=}NCH_2CH(CH_3)C_6H_{13}$-$n$	6			87a
	B, D, E			34, 54, 22		40, 40, 51	87a, 87a, 87c
	E	n-$C_8H_{17}Br$	$(C_6H_5)_2C{=}N(CH_2)_8CH_3$	64	$CH_3(CH_2)_8NH_2$	70	87c
	C, E	$CH_2{=}CHCH_2Br$	$(C_6H_5)_2C{=}N(CH_2)_2CH{=}CH_2$	19, 58	$CH_2{=}CH(CH_2)_2NH_2$	–, 17	87a, 87c
	E	$BrCH_2CH_2Br$	$[(C_6H_5)_2C{=}NCH_2]_2$	31			87c
	C	C_2H_5Br	$(C_6H_5)_2C{=}N(CH_2)_2CH_3$	88			87a
	C	$BrCH(CH_3)C_2H_5$	$(C_6H_5)_2C{=}NCH_2CH(CH_3)C_2H_5$	66			87a
	C	$BrCH(CH_3)C_3H_7$-n	$(C_6H_5)_2C{=}NCH_2CH(CH_3)C_3H_7$-$n$	40			87a
	C	$ClSi(CH_3)_3$	$(C_6H_5)_2C{=}NCH_2Si(CH_3)_3$	51			87a
	C	$ClSi(C_6H_5)_3$	$(C_6H_5)_2C{=}NCH_2Si(C_6H_5)_3$	58			87a
	E	n-C_3H_7CHO		50			87a
	E	$(CH_3)_2CHCHO$		60			87a
	E, F	C_6H_5CHO		63, 34			87a
	E	$CH_3COC_2H_5$		78		40	87a
	E	$(C_2H_5)_2CO$		85			87a
	E			75			87a
	E, F, G	$(C_6H_5)_2CO$		62, 14, 42		59, 59, 78	87a, 87a, 87c
	E, G			76, 49		69, 70	87a, 87c
	E, G	$C_6H_5COC_6H_4CH_3$-p		78, 32		69, 78	87a, 87c
	H	$CH_3COC_6H_5$		52		80	86
	H			32		48	86

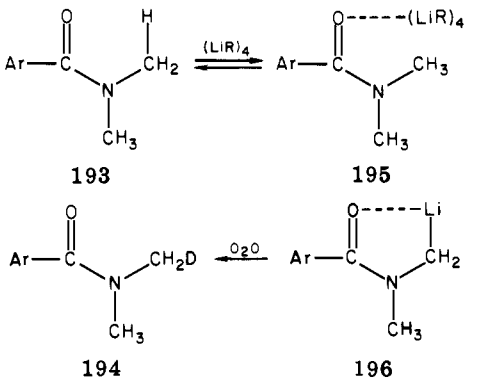
[a] A = LDA in Et_2O at 0 °C; B = $LiN(C_2H_5)_2$ in THF at −70 °C; C = n-BuLi in THF at −78 °C; D = $LiN(C_2H_5)_2$ in THF/HMPT at −70 °C; E = n-BuLi in THF/HMPT at −78 °C; F = n-BuLi in Et_2O/HMPT at −78 °C; G = LDA in THF at −60 °C; H = LDA in THF/Et_2O at −45 °C. [b] Imine was hydrolyzed with 2–3 N HCl. [c] Other products were also formed.

TABLE XXVII. Preparation of Oxazolidine-2-thiones from Methyl Isothiocyanate

reactant[a]	electrophile	oxazolidine-2-thione	yield, %	ref
$(CH_3)_3SiCH_2NCS$	C_6H_5CHO		74	96
	C_2H_5CHO		63	96
	$(CH_3)_2CHCHO$		67	96
	$(C_6H_5)_2CO$		25	96
	$C_6H_5COCH_3$		35	96

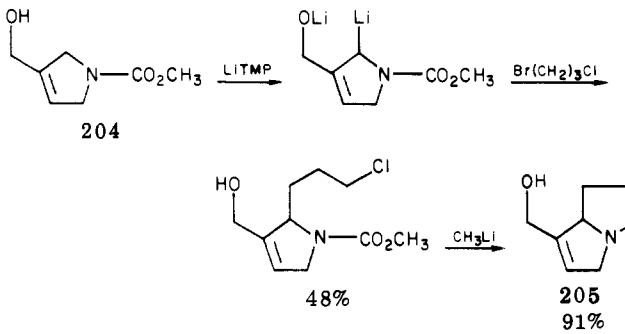
[a] The isothiocyanate was allowed to react with the carbonyl compound in the presence of a catalytic amount of $(n\text{-}C_4H_9)_4NF$.

SCHEME XLI



193 195 194 196

SCHEME XLII

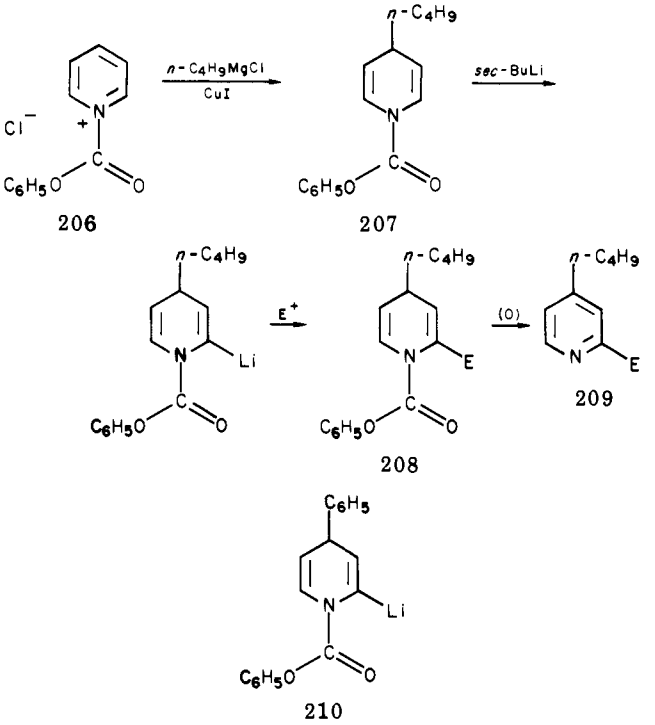


204 48% 205 91%

Scheme X (vide supra). α-Metalated amino nitriles also have been successfully employed in the synthesis of 6-aryl-3(2*H*)-pyridazinones,[107] mysomine,[108] nornicotine,[108] and labeled shihunine precursors.[109] In a similar sequence (diethylamino)acetonitrile serves as an excellent latent formaldehyde anion, thus permitting the transformation of alkyl halides to homologous aldehydes.[103a]

Another example is provided by the α-amino carbanions **186** generated from α-amino phosphinic acid esters and used in the synthesis of enamines **187** shown in Scheme XXXIX. The phosphorus function can be removed to form **187** which subsequently can be converted to aldehydes, ketones, or to molecules with spiroannelated five- and six-membered rings in synthetically useful yields.[110] Similar substitutions have been reported for phosphinyl derivatives,[111] and for the substitution of nitrogen of an imine.[112]

SCHEME XLIII



206 207 208 209 210

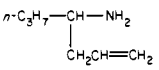
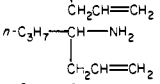
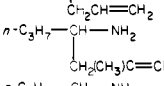
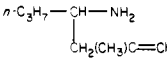
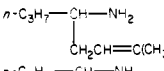
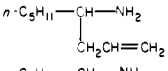
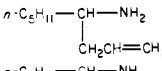
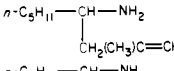
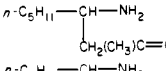
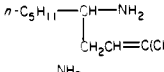
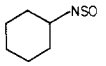
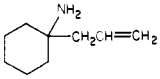
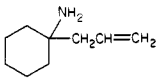
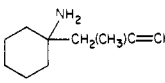
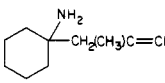
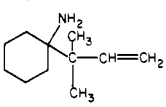
In addition to the vinyl α-azo carbanions discussed in the preceding section there are a number of such systems which have synthetic value in special cases. Thus, the 6-lithiopyrimidone **188** has been prepared by deprotonation of the corresponding nucleotide **189**.[113] Structurally these species are similar to intermediates in the deuteration of *N*-methyl-4-pyridone[5] and to the system **190** produced from **191** which was converted to **192** by Schmidt and Betz.[114] The substitutions of these systems are summarized in Scheme XL and Table XXIX. Other examples of similar systems have been reported.[5]

IV. Comparison of α-Lithio Amine Synthetic Equivalents

Thirteen functionally different amine derivatives which can be metalated adjacent to nitrogen have been reported in the literature. Succinimides, pivalthioamides, and carbamates have been useful only for the substitution of *N*-methyl or *N,N*-dimethylamine. Benzamides, pivalamides, ureas, phosphoramides, imines, and carbamates have been shown to allow metalation of a variety of activated methyl groups. While cyclopropyl, cyclobutyl, 2-dimethylamino and 2-methoxy, and diisocyano isocyanides have been metalated, secondary organometallic reagents have not been formed in high yield from simple alkyl isocyanides. The isocyanides are exceptionally useful, however, for metalation of methyl or additionally activated sites.

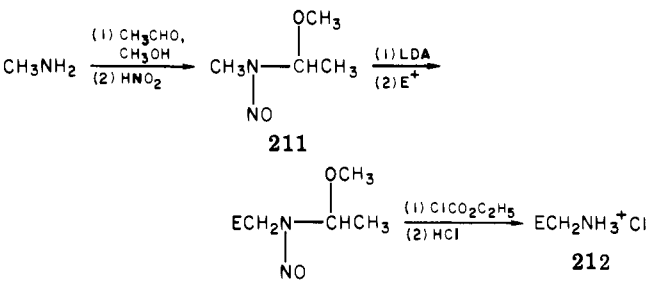
The nitrosamines, *N,N*-dialkyltriphenylacetamides, *N,N*-dialkyl-2,2-diethylbutanamides, and *N,N*-dialkylformamidines at present appear to be the most

TABLE XXVIII. Formation of *N*-(α-Lithioalkyl)-*N*-Sulfinylamines and Reaction with Alkyl Halides

reactant	base	temp, °C	solvent	electrophile	product	yield,[a] %	ref
n-$C_3H_7CH_2NSO$	$LiC(C_6H_5)_3$	−78	THF	CH_2=$CHCH_2Br$		65	99
	$KOC(CH_3)_3$	0	DME	CH_2=$CHCH_2Br$		46	99
	$LiC(C_6H_5)_3$	−78	THF	CH_2=$C(CH_3)CH_2Cl$		40	99
	$KOC(CH_3)_3$	0	DME	CH_2=$C(CH_3)CH_2Cl$		58	99
	$KOC(CH_3)_3$	0	DME	$(CH_3)_2C$=$CHCH_2Cl$		47	99
n-$C_5H_{11}CH_2NSO$	$LiC(C_6H_5)_3$	−78	THF	CH_2=$CHCH_2Br$		32	99
	$KOC(CH_3)_3$	0	DME	CH_2=$CHCH_2Br$		56	99
	$LiC(C_6H_5)_3$	−78	THF	CH_2=$C(CH_3)CH_2Cl$		31	99
	$KOC(CH_3)_3$	0	DME	CH_2=$C(CH_3)CH_2Cl$		42	99
	$KOC(CH_3)_3$	0	DME	$(CH_3)_2C$=$CHCH_2Cl$		50	99
	$LiC(C_6H_5)_3$	−78	THF	CH_2=$CHCH_2Br$		33	99
	$KOC(CH_3)_3$	0	DME	CH_2=$CHCH_2Br$		53	99
	$LiC(C_6H_5)_3$	−78	THF	CH_2=$C(CH_3)CH_2Cl$		23	99
	$KOC(CH_3)_3$	0	DME	CH_2=$C(CH_3)CH_2Cl$		56	99
	$KOC(CH_3)_3$	0	DME	$(CH_3)_2C$=$CHCH_2Cl$		28	99

[a] On aqueous acid workup the *N*-sulfinyl group is hydrolyzed to the corresponding amine.

SCHEME XLIV



211

212

generally useful intermediates as α-lithioalkyl alkylamine synthetic equivalents. Of these the nitrosamines have the broadest scope. The nitrosamines undergo metalation at primary, secondary, and tertiary centers under moderate conditions. Yields on alkylation and addition to carbonyl compounds are high in most cases although tertiary centers appear not to have been added to carbonyl electrophiles and substitution yields are moderate with cyclic systems. Regio- and stereochemical information is available for a number of cases. The difficulty with the use of nitrosamines appears to lie in the denitrosation and in concern about their potential carcinogeneity. A procedure for carrying out all the reactions in the substitution sequence in one pot has been reported.[45]

The *N*,*N*-dialkyltriphenylacetamides are useful but give moderate yields when reacted with a number of electrophiles. Cleavage, which to date has been reported only for substituted methylamines, requires exposure to sodionaphthalene. The *N*,*N*-dialkyl-2,2-diethylbutanamides can be formed, metalated, and reacted with electrophiles fairly effectively and stereochemical information is available for piperidine systems. Cleavage of the amide however requires exposure to strong acid and lithiation of tertiary positions has not been achieved.

Lithiation of formamidines appears to be very promising. The formamidines can be readily prepared, metalated, electrophilically substituted, and reduced or cleaved to the substituted amines. Moreover, this approach has been shown to give exceptional asymmetric control. However, as with the amides, lithiation of a tertiary position has not been reported (See Addendum).

V. Mechanism of Metalation

At the outset of this review it was noted that the activating group Z could provide stabilization for metalation of the organometallic species 8 in Scheme II by complexation, inductive, and/or resonance interactions.

TABLE XXIX. Formation of Vinyl α-Azo Carbanions and Reactions with Electrophiles

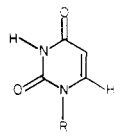
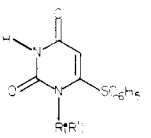
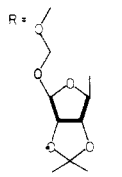
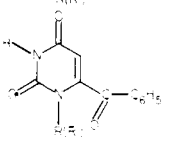
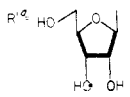
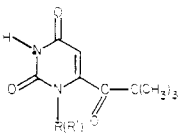
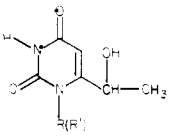
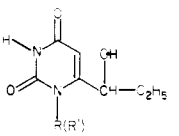
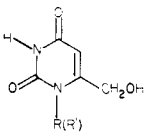
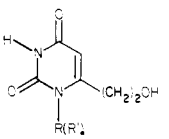
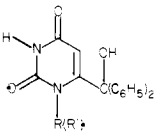
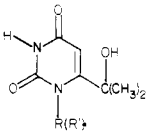
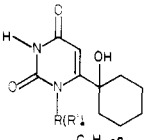
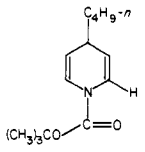
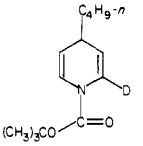
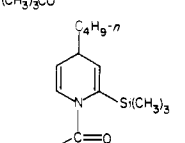
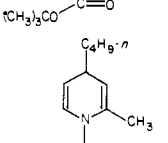
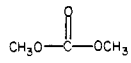
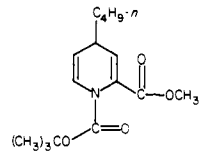
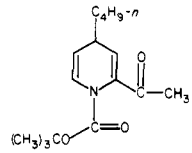
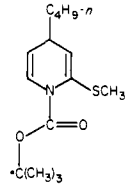
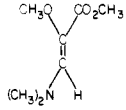
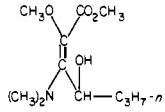
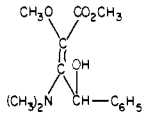
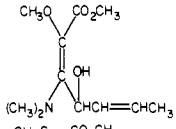
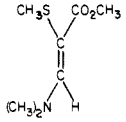
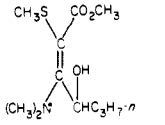
reactant	base	solvent	temp, °C	electrophile	product	yield, % R(R')[a]	ref
	LDA[b]	THF	<−70	$[C_6H_5S]_2$		83 (77)	113
	LDA[b]	THF	<−70	C_6H_5COCl		88 (84)	113
	LDA[b]	THF	<−70	$(CH_3)_3CCOCl$		72 (95)	113
	LDA[b]	THF	<−70	CH_3CHO		77	113
	LDA[b]	THF	<−70	C_2H_5CHO		76	113
	LDA[b]	THF	<−70	$HCO_2C_2H_5$		66[c] (73)	113
	LDA[b]	THF	<−70			26	113
	LDA[b]	THF	<−70	$(C_6H_5)_2CO$		74 (87)	113
	LDA[b]	THF	<−70	$(CH_3)_2CO$		19 (88)	113
	LDA[b]	THF	<−70			30 (85)	113
	*sec*-BuLi	THF	−42	D_2O		85	122
	sec-BuLi	THF	−42	$(CH_3)_3SiCl$		85	122
	sec-BuLi	THF	−42	CH_3I		72	122

TABLE XXIX (Continued)

reactant	base	solvent	temp, °C	electrophile	product	yield, % R(R')[a]	ref
	sec-BuLi	THF	−42			89	122
	sec-BuLi	THF	−42			70	122
	sec-BuLi	THF	−42	CH_3SSCH_3		83	122
	LDA	THF	−100	*n*-C_3H_7CHO		56	114
	LDA	THF	−100	C_6H_5CHO		64	114
	LDA	THF	−100	$CH_3CH{=}CHCHO$		60	114
	LDA	THF	−100	*n*-C_3H_7CHO		72	114

[a] Deprotection was accomplished by treatment with 50% aqueous CF_3CO_2H at ambient temperature. [b] 2.5 equiv was used. [c] After reduction with $NaBH_4$.

Stereochemical investigations of nitrosoamine carbanions have been useful in defining the nature of the anions, and these results have been reviewed.[48,52] Careful investigation by Fraser et al. has established that π-delocalization is the dominant factor in stabilizing the anion of *N*-nitroso-6,7-dihydro-1,11-dimethyl-5*H*-dibenz[*c*,*e*]azepine which is formed by the stereoselective removal of the syn-axial proton. Fraser's work ruled out dipole stabilization or metal ion complexation as dominant contributors to the transition state for carbanion formation.

For the lithiation of amides, syn substitution, demonstrated for the conversion of **193** to **194** in Scheme XLI has been taken to indicate complexation plays a major role in the reaction.[5,8,115,116] Infrared observation of the lithiation of **193** in a stopped-flow spectrometer recently has revealed the existence of a complex **195** in equilibrium with **193** which is converted to **196**, the precursor for the syn deuterated product **194**. A possible mechanism for lithiation is conversion of **195** to **196** directly but alternatives exist and more information will be required to decide the mechanism. The direct observation of **195** provides evidence for the importance of complexation by lithium in the sequence.

Evidence for dipole stabilization by the amide comes for the equatorial substitution noted for the conversion of **21** to **23** and the bridgehead substitution of **48**. This result is taken to imply that lithiation and substitution occur via an sp^3 hybridized intermediate. It should be noted that the species illustrated for purposes of this review as carbanions are probably aggregated organolithium species with a carbon–lithium bond. Both complexation and dipole stabilization of the α′-amido organolithium species are supported by calculations.[8] Recently Bach et al. have carried out calculations which explain the orthogonal stereochemistry of these species in terms of 4-electron HOMO–HOMO repulsions of the alternative orbitally parallel π species.[117] Reactions of the α-lithiated species from *N*,*N*-dialkylformamides has been discussed in terms of the importance of solvent dissociating from the lithium in a complex.[118]

VI. Summary

The present review summarizes 5 years of progress in the development of methodology to effect elaboration of amines via α metalloorganic amine synthetic equivalents. The conversion of **1** to **5** via **6** in Scheme I is now feasible for a wide variety of amines. This new strategy provides approaches to amine elaboration which frequently is more efficient than the classical

TABLE XXX. Formation of α-Lithiated *N*-Alkylpyrazoles and Reactions with Electrophiles

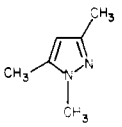
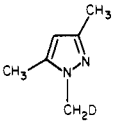
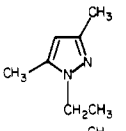
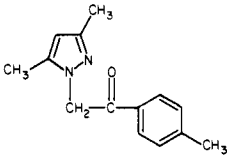
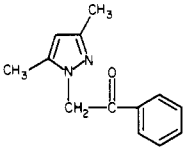
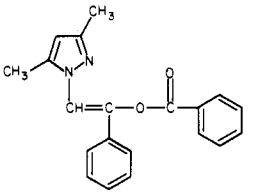
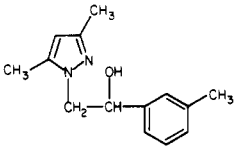
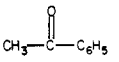
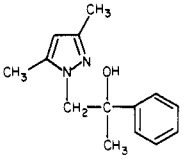
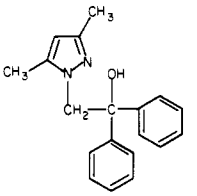
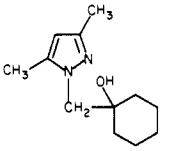
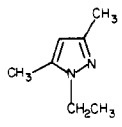
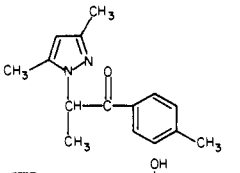
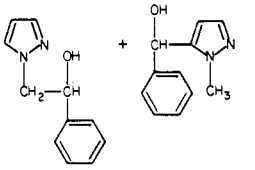
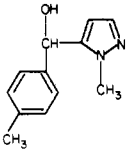
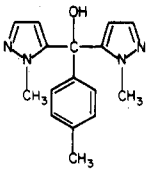
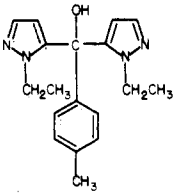
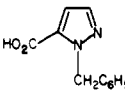
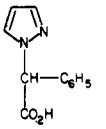
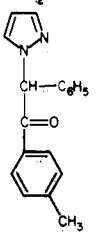
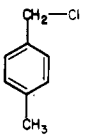
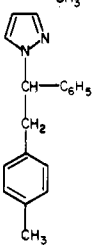
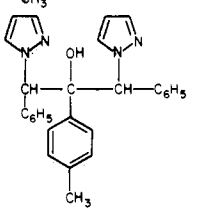
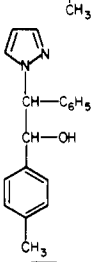
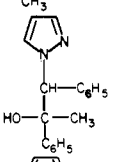
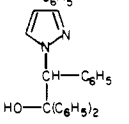
reactant	base	temp, °C	solvent	electrophile	product	yield, %	ref
	*n*-BuLi	−78	THF	D_2O		99	127
	n-BuLi	−78	THF	CH_3I		52	127
	n-BuLi	−78	THF	*p*-$CH_3C_6H_4COCl$		92	127
	n-BuLi	−78	THF	C_6H_5COCl		22	127
	n-BuLi	−78	THF	C_6H_5COCl (excess)		85	127
	n-BuLi	−78	THF	*m*-$CH_3C_6H_4CHO$		84	127
	n-BuLi	−78	THF			78	127
	n-BuLi	−78	THF	$(C_6H_5)_2CO$		80	127
	n-BuLi	−78	THF			65	127
	*t*-BuLi	−78	THF	*p*-$CH_3C_6H_4CO_2CH_3$		22	127
	*n*-BuLi	−78 → 0	THF	C_6H_5CHO		57	127
	n-BuLi	−78 → 0	THF	*p*-$CH_3C_6H_4CHO$		68	127

TABLE XXX (Continued)

reactant	base	temp, °C	solvent	electrophile	product	yield, %	ref
	n-BuLi	−78	THF	*p*-$CH_3C_6H_4CO_2CH_3$		21	127
	*t*-BuLi	−78	THF	*p*-$CH_3C_6H_4CO_2CH_3$		21	127
	*n*-BuLi	−78 → 23	THF	CO_2, H^+		35	127
	n-BuLi	−78	THF	CO_2, H^+		32	127
	n-BuLi	−78	THF	*p*-$CH_3C_6H_4CO_2CH_3$		29	127
	n-BuLi	−78	THF			42	127
	n-BuLi	−78	THF	*p*-$CH_3C_6H_4COCl$		73	127
	n-BuLi	−78	THF	*p*-$CH_3C_6H_4CHO$		54	127
	n-BuLi	−78	THF	$C_6H_5COCH_3$		62	127
	n-BuLi	−78	THF	$(C_6H_5)_2CO$		85	127

routes shown in the first two entries in Scheme I. In many cases combinations of two of these general strategies provides exceptionally useful methodology (See Addendum).

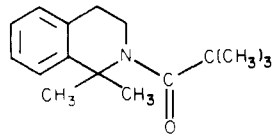
VII. Addendum

After the submission of this review a number of pertinent articles which amplify and significantly ex-

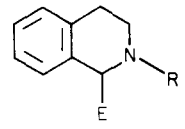
tend earlier reports appeared. Those reports are presented in this addendum, classified by activating group, and the new information is included in the Tables.

Amides. The tetrahydroisoquinoline nucleus continues to attract attention.

A full report on the 2-pivaloyltetrahydroisoquinoline **39a**, including a summary and perspective on the methodology, has appeared.[119] The nucleophilicity of



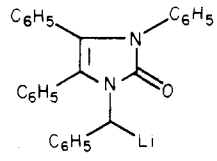
197



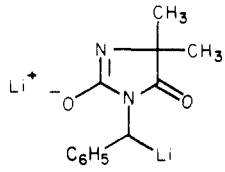
198, R = $CH_2C(CH_3)_3$
199, R = H

40a is notable as is the fact substitutions can be carried out sequentially at the 1-position. In the case of methyl iodide as the electrophile the amide **197** is provided in two steps. Cleavage of the pivalamide group however, is difficult, requiring strongly reducing conditions and providing the neopentyl derivative **198** in addition to the secondary amines **199**.

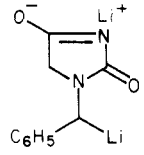
Further work on heteroaromatic amides has appeared.[120] Thus **200** can be formed by reaction of LDA with the corresponding imidazolene; it reacts with the usual electrophiles to give substituted products in 60–85% yields. The corresponding 1-ethyl compound undergoes metalation on the aromatic ring. The dianions **201**, **202**, and **203** have also been reported.[120]



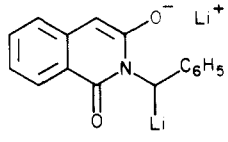
200



201



202



203

Carbamates. The use of derivatives of the carbamate **74** for the synthesis of $\Delta^{1,2}$-pyrrolizidine alkaloids has been reported and is shown in Scheme XLII.[121] Reaction of the readily available pyrrole derivative **204** with 2 equiv of lithium tetramethylpiperidide followed by alkylation, cleavage of the carbonate group, and spontaneous cyclization gives supinidine (**205**) in good yield. This approach again demonstrates the value of a bifunctional electrophile in ring formation at carbon and nitrogen of an α-lithio amine synthetic equivalent.

A recent case of carbamate activation of a vinyl position has been provided by Comins for 1,4-dihydropyridine systems.[122] The latter is obtained by addition of *n*-butylmagnesium chloride in the presence of copper iodide to the 1-(phenoxycarbonyl)pyridinium chloride **206** as shown in Scheme XLIII. Treatment of **207** with *sec*-butyl lithium and electrophiles provide **208** which can be oxidized to the pyridine **209**. An interesting feature of this system is removal of a vinyl hydrogen even in the presence of a benzylic proton; thus **210** is provided from the corresponding 1,4-dihydropyridine.

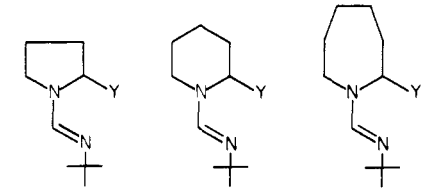
Phosphonamides. The phsophonamide tetrahydroisoquinoline **87b** is readily available although somewhat less nucleophilic than the corresponding pivalamide **39a**. The advantage of the phosphonamide system lies in its ready hydrolysis to provide the substituted tetrahydroisoquinoline in high yield.[119]

Nitrosoamines. An approach to the preparation of a primary α-lithio amine synthetic equivalent has been provided by Saavedra and is illustrated in Scheme XLIV.[123] Thus the α-(nitrosoamino)alkyl ether **211**, prepared from methylamine and acetaldehyde, methanol, and nitrous acid, can be metalated, allowed to react with an electrophile, and hydrolyzed to the substituted primary amine **212**. The approach should be readily extendable to more highly substituted amines.

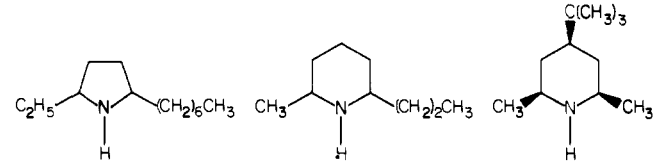
Formamidines. The details of the enantioselective syntheses using the α'-lithio tetrahydroisoquinoline formamidine **144** which is optically active and its derivatives have been reported.[124] Improved procedures for the preparation of the formamidines and alkylations which provide enantiomeric excesses greater than 90% from **144** are notable. The use of enantiomeric formamidines in asymmetric induction is illustrated by the use of (*S*)- and (*R*)-valinol derivatives to provide the (*S*)-**148** and (*R*)-**148** as shown in Scheme XLV.

In other work Meyers and Fuentes have observed that deuteration of **144a** gives **213**-d_1 which in subsequent lithiation followed by reaction with methyl iodide gives (*S*)-**148** containing only 10% deuterium.[125] A reasonable explanation of these results is that the dipole-stabilized species **144a** has association of the nitrogen and oxygen of the formamidine groups with a pseudoequatorial lithium. The important role of lithium ion is suggested by the observation that if metalation is carried out with potassium diisopropylamide the product is obtained with less than 10% ee.

A full report on the use of formamidines for synthesis of α-lithio amine synthetic equivalents of unactivated cyclic systems has been given.[126] The *tert*-butylformamidines have proved useful for the formation of **214**, **215**, **216**, with *sec*-butyl- or *tert*-butyllithium and the subsequent alkylation to **217**, **218**, and **219**, respectively, can be achieved in good yields under appropriate conditions as shown in the Tables. Cleavage to free the



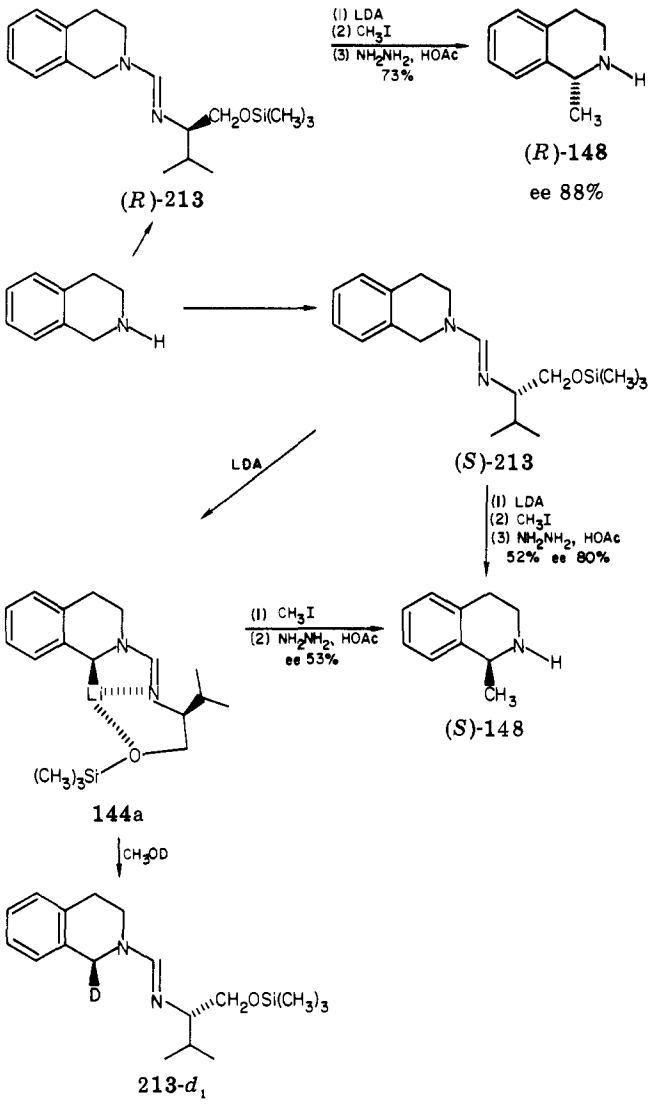
214, Y = H 215, Y = H 216, Y = H
217, Y = R 218, Y = R 219, Y = R



220 221 222

substituted amine with hydrazine and acetic acid is an especially mild procedure, although reductive and base

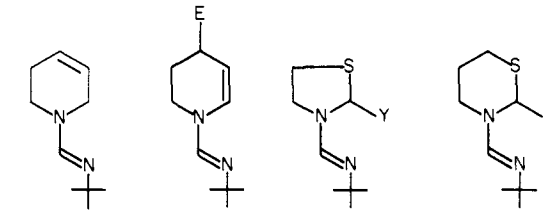
SCHEME XLV



procedures are also available. Alkylation of **214**, **215**, and **216** occurs in good yields if the lithiation is followed by addition of pentynylcopper prior to reaction with the alkyl halide. Alternatively, alkylation of **214** and **216** can be achieved in the presence of hexamethyl phosphorous triamide (HMPA). In the absence of pentynylcopper or HMPA, oxidation occurs with **214**, **215**, and **216**. The authors suggest for **215** that it involves formation of an axial carbon–lithium bond which promotes electron transfer. In the piperidine case substitution of the 4-position with *tert*-butyl or benzhydryl groups provides an α-lithio intermediate which undergoes alkylation with methyl iodide without the pentynylcopper or HMPA.

Disubstitution of the amines has also been achieved by Meyers' group. Thus **214**, **215**, and a 4-*tert*-butylpiperidine derivative have been converted in a two-step procedure to **220**, **221**, and **222**, respectively. The amine **220**, a fire ant venom, is obtained as a 60:40 mixture, while **221** is a 1:1 mixture of cis and trans isomers. The product **222** on the other hand is only the cis,cis isomer consistent with the equatorial assignment to the organolithium intermediate.

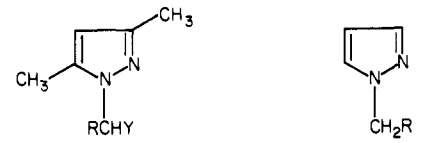
The formamidine activating group is also useful in systems which possess additional activation for deprotonation. Thus the tetrahydropyridine derivative **223**, the thiazole **224**, and thiazene **225** derivatives are readily lithiated by *n*-butyllithium and react with electrophiles to give **226**, **227**, and **228**, respectively. Electrophilic



223, Y = H **226** **224**, Y = H **225**, Y = H
227, Y = E **228**, Y = E

substitution of the organolithium from **223** occurs mainly at the 4-position and the products can be reduced and cleaved to 4-substituted piperidines. Thus this methodology can be used for synthesis of 2- and 4-substituted piperidines. The thiazoles and thiazenes behave normally on electrophilic substitution and, as the authors note, may prove to be useful in antibiotic syntheses.

Systems which are formally vinylogous formamidines, the pyrazoles **229** and **230** are reported to undergo lithiation with *n*-butyllithium at −78 °C to give **231** and **232**, respectively,[127] and are presented in Table XXX.



229, R = H, Y = H
230, R = CH_3, Y = H
231, R = H, Y = Li
232, R = CH_3, Y = Li

233, R = C_6H_5
234, R = H
235, R = Li

The apparent kinetic acidity of this position, instead of lithiation on the methyl at the 3-position, is notable. The pyrazole **233** undergoes initial metalation at the benzyl group at −78 °C and electrophilic substitutions are possible; however, that species rearranges to the 5-lithio derivative on warming. The 1-methylpyrazole (**234**) gives a mixture of **235** and the 5-lithio derivative on treatment with *n*-butyllithium.

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