Heteroatom-Facilitated Lithiations

Heinz W. Gschwend, Ciba-Geigy Corporation, Summit, New Jersey
Herman R. Rodriguez, Ciba-Geigy Corporation, Summit, New Jersey

1. Introduction

Some 25 years have elapsed since the topic of metalation reactions was reviewed by Gilman and Morton. (1) The intervening years have been notable for intensive explorations in this area, in part because many organolithium reagents are now commercially available. Specifically, research efforts have been characterized by the discovery of new functional groups that promote metalation, elaboration of novel heterocyclic and olefinic substrates as metalatable species, recognition of new types of lithiating agents, and the continuation of efforts to define accurately the mechanism of metalation. Accordingly, heteroatom-facilitated lithiation has become recognized as an increasingly important tool, not only in the elaboration of carbocyclic aromatic and heteroaromatic systems, but also in synthetic aliphatic chemistry. A few recent reviews have covered the topic in a more limited (2, 3) or less specific sense. (4-6) It is the purpose of this chapter to survey and classify the vast accumulation of heteroatom-facilitated lithiations recorded since the first coverage in *Organic Reactions*. (1)

As outlined by Gilman and Morton, the terms "metalation" in general and "lithiation" in particular denote any replacement of a hydrogen atom by metal or lithium. In this review, however, lithiation is defined as the exchange of a hydrogen atom attached to an sp^2-hybridized carbon atom by lithium to form a covalent lithium-carbon bond (Eq. 1). More specifically, discussion is limited to those metalations that, through the influence of a heteroatom, are characterized by rate enhancement and regioselectivity. In fact, lithiation reactions of this type are noted for an extraordinarily high degree of regioselectivity, metalation generally occurring on the sp^2-carbon atom closest to the heteroatom. Based on the relative position of the heteroatom, such lithiations are conveniently classified into two principal categories: alpha and beta (*ortho*) lithiations.

$$\begin{array}{c}\diagdown \\ \diagup\end{array}\!\!C\!-\!H \xrightarrow{\text{RLi}} \begin{array}{c}\diagdown \\ \diagup\end{array}\!\!C\!-\!Li \qquad\qquad (1)$$

In *alpha lithiations* the metalating agent deprotonates the sp^2-carbon atom *alpha* to the heteroatom to form a carbon—lithium bond (Eqs. 2 and 3). This

sp^2-carbon atom may be part of an olefinic or heteroaromatic π system (Eqs. 2 and 3, $X = \text{heteroatom}, Y = \text{heteroatom or } C_{sp^2}$).

(2)

(3)

In *beta lithiations* the metalating agent is directed to deprotonate the sp^2-carbon atom *beta* to the heteroatom-containing substituent (Eqs. 4 and 5, X = heteroatom and $n = 0 - 2$). The sp^2-carbon atom can be part of an aromatic (Eq. 4) or an olefinic (Eq. 5) π system. It should be noted that the designation "*ortho* metalation" is used specifically for the beta metalation of carbocyclic aromatic systems.

(4)

(5)

This chapter surveys all systems in which alpha and beta lithiations have been observed, with the exception of ferrocenes. (2, 3, 7)

2. Mechanism

Although numerous studies on the mechanism of heteroatom-facilitated lithiations have been undertaken, particularly those of alkyl aryl ethers, most of the current views are based more on speculation and hypothesis than on data. A major reason for this situation lies in the properties and/or characteristics of the traditional lithiating agents, *i.e.*, lithium alkyls and lithium aryls. These include high but variable reactivity and complexity (depending on solvent, concentration, and temperature) and instability. ([6], [8]) In recent years an additional dimension has been added through the utilization of new types of lithiating agents, particularly *n*-butyllithium/amine complexes and lithium dialkylamides.

An understanding of the mechanism of metalation can be facilitated by the recognition of the existence of *two* distinct types of metalating agents. Accordingly, before the actual mechanism is discussed, attention should be brought to the individual characteristics of these lithiating agents. The first type, lithium alkyls and lithium aryls, are oligomers of varying complexity in solution (see p. 8). In addition they are electron-deficient species, ([9], [10]) and therefore Lewis acids which can coordinate with Lewis bases such as ethers and amines ([6], [8]) with consequent depolymerization to varying extents. It is important to note that kinetically these reagents become more basic as the aggregate size diminishes; therefore, tetrahydrofuran is the solvent of choice for generating reactive species (see accompanying tabulation). The pK_a of *n*-butane is 45–50, ([11-13]) with that of other alkanes typically falling in the range 42–60. ([6], [11-13])

Lithiating Agent	Solvent	State of Aggregation	Reference
n-BuLi	hydrocarbon	hexameric	14
	ether	tetrameric	14
	tetrahydrofuran	dimeric (solvated)	15
n-BuLi/TMEDA[*]	hydrocarbon	monomeric	16
t-BuLi	hydrocarbon	tetrameric	17, 9
	tetrahydrofuran	dimeric (solvated)	15
C_6H_5Li	ether	dimeric	4, 18
	tetrahydrofuran	dimeric	19, 20

The distinguishing characteristic of the second type of lithiating agent is its negligible extent of Lewis-acid character relative to uncomplexed lithium alkyls and lithium aryls. Included in this category are *n*-butyllithium/amine complexes and lithium dialkylamides, the former being monomeric in hydrocarbon solution, whereas some evidence exists that the latter are dimeric aggregates in solution. (21) Another distinctive property of the lithium dialkylamides is their decreased thermodynamic basicity relative to the lithium alkyls, the pK_a's of secondary amines being approximately 30. (5)

Although an apparent contradiction in terms, it has often been noted (22-25) that lithium dialkylamides are generally more effective metalating agents than the thermodynamically more basic lithium alkyls and lithium aryls particularly vis-à-vis substrates with pK_a values < 30. The phenomenon of an increased kinetic basicity of heteroatom bases in general and lithium amides in particular may be rationalized by the availability of a free pair of electrons, which permits the formation of a four-membered transition state (Eq. 6). The intermediacy of a free carbanion is thus avoided. (22)

$$\begin{array}{c}\text{H}\text{...}\quad\text{R}\\ \diagdown\diagup\quad\diagdown\diagup\quad\diagup\\ \text{Li}-\text{N}\\ \quad\quad\text{R}\end{array}\longrightarrow \diagdown\diagup-\text{Li} + \text{HNR}_2 \tag{6}$$

It should be recognized that the deprotonation of an unsaturated carbon acid, such as benzene or ethylene (pK_a 36.5–37.0), (11-13) is thermodynamically feasible with lithium alkyls, as the $\triangle pK_a$ is greater than 5. Yet these metalations are exceedingly slow even in ethereal solvents; *e.g.*, benzene shows negligible lithiation with *n*-butyllithium in hexane after 3 hours at room temperature. (1, 26) Therefore, one phenomenon that must be explained by any mechanism concerning heteroatom-facilitated lithiation is the great rate enhancement; *e.g.*, anisole metalates to the extent of 30% with *n*-butyllithium in ether in 2 hours. (27) In addition the high degree of regioselectivity must be accounted for.

An example of rate enhancement in an intermolecular sense is the lithiation of benzene with *n*-butyllithium coordinated with TMEDA (3 hours/25°) *vs.* that of *n*-butyllithium alone (*vide supra*). (16, 26) The function of the TMEDA is the depolymerization of the normally hexameric *n*-butyllithium to the kinetically more reactive monomer via coordination of the nitrogen atoms of the bidentate ligand with the lithium atom. Analogously, as a working hypothesis it has been

assumed for many years that the initial step in heteroatom-facilitated lithiation reactions is the coordination of the electron-deficient metalating agent with the nonbonding electrons in the substrate heteroatom (with attendant depolymerization). (28) This coordination is then followed by a protophilic attack of the carbanionic portion of the lithiating agent on the adjacent hydrogen atom, leading to the metalated product. (29) Although this simplistic view of the mechanism is quite useful in explaining and predicting numerous experimental observations, other factors, particularly the inductive effects of heteroatoms or substituents, can play important roles in these reactions. It is the contention of these authors that the hydrocarbon acidity can become the sole determinant and that a new mechanism is indicated. Accordingly, it is postulated that there are, in fact, *two* limiting mechanisms:

1. "coordination only" mechanism
2. "acid–base" mechanism

Between these extremes there is a continuous spectrum of cases in which both effects simultaneously contribute in varying degrees to the observed phenomena. A full explication of these concepts is best presented through illustration.

2.1. Beta (*Ortho*) Lithiations

The best example of a "coordination only" mechanism is the *ortho* lithiation of N,N-dialkylbenzylamines. (30) Despite the fact that the benzylic methylene group (neglecting any effect of the basic nitrogen) has an inductive effect on the *ortho* position which actually decreases its acidity, lithiation occurs exclusively at position 2 as well as far more rapidly relative to benzene. (31, 32) Thus it has been assumed that the initial step in this reaction is the coordination of the metalating agent with the lone pair of the basic nitrogen atom. The nearest available proton in the *ortho* position then suffers a protophilic attack, leading to the internally chelated and isolable organolithium species (Eq. 7). (2, 3, 9) One may consider this an intramolecular version of the lithiation of benzene with the *n*-butyllithium/TMEDA complex alluded to earlier. This view is further supported by the observation that even with excess metalating agent only a monolithio species is formed, since the chelate no longer possesses Lewis-base character. (30, 33)

Most mechanistic studies of the *ortho* lithiation have been carried out with alkyl aryl ethers, where a combination of the two mechanistic determinants, *i.e.*, coordinative and inductive effects, is operative. Nmr data have shown that lithiation in hydrocarbon solvents results in the initial disruption of the oligomeric alkyllithium to yield a reactive complex with the substrate. (34) The stoichiometry of this complex depends on the structure of the ether. For anisole the whole process is generally and simplistically pictured in Eq. 8. (35) In the intermediate coordinated species the carbon - lithium bond of the metalating agent and the carbon - hydrogen bond of the substrate are polarized to a greater extent, thus rendering the proton to be removed more acidic by induction. The second step, namely the actual deprotonation (protophilic attack), is rate determining. Hydrogen–deuterium exchange studies clearly show the expected isotope effect (k_H/k_D) to be in the range 6–8. (36)

$$(8)$$

A pivotal example is the lithiation of *p*-methoxy-N,N-dimethylbenzylamine. (19) The acidity of the hydrogen atom at position 3 should be distinctly higher than at position 2 because of the inductive effect of the methoxyl group. (13, 31, 32) Nevertheless, metalation with a lithiating agent of high Lewis-acid character (*n*-butyllithium) occurs exclusively at position 2 as a result of the higher coordinative capacity of the basic nitrogen ("coordination only" mechanism). Alternatively, with the monomeric *n*-butyllithium/TMEDA complex whose Lewis-acid character has been considerably diminished via coordination (*vide supra*), the most *acidic* proton at position 3 is removed selectively ("acid–base" mechanism). (19)

2.2. Alpha Lithiations

For alpha metalations of π-excessive heterocycles, particularly those of thiophene, the precoordination of the metalating agent with the heteroatom has also been invoked as the initial step of the mechanism. (37, 38) However, it has been demonstrated that thiophene, like benzene, cannot be lithiated readily in hexane solution by *n*-butyllithium (23, 39, 40) but that lithiation does occur rapidly in ethereal solvents (see p. 35). This evidence suggests that the sulfur atom in thiophene does not in fact act as a Lewis base, as does the

oxygen atom in anisole, and therefore is unable to decrease the state of aggregation of the hexameric *n*-butyllithium (see p. 8) with consequent increase in its activity. Therefore the rate enhancement and regioselectivity of most alpha metalations can be attributed merely to the inherently higher acidity of the substrates. Consequently, alpha metalations can generally be considered to proceed by the "acid–base" mechanism.

There are few accurate pK_a measurements available for these substrates (*e.g.*, trichloroethylene, $pK_a = 18$, (12) thiophene (alpha position), $pK_a \gg 30$ (23)); however, ample evidence from base-catalyzed hydrogen exchange rates indicates that the kinetic acidity of the alpha position $(C_{sp^2}-H)$ is dramatically enhanced by the adjacent electronegative atom relative to ethylene or benzene (Eq. 9). This observation is corroborated by the fact that 2-thienyllithium can be generated to the extent of 50% with lithium diisopropylamide, a considerably weaker base than *n*-butyllithium. (23) It has similarly been established that the hydrogen exchange rate in the alpha position is greater by a factor of 2.5×10^5 than that in the beta position. (41, 42) Again, this observation explains the regioselectivity of the metalation without invoking precoordination.

$$\text{(9)}$$

Another example supportive of the "acid–base" mechanism hypothesis is the lithiation of pyrazoles. If precoordination were indeed an important factor, one would assume that N-substituted pyrazoles would lead to lithiation in the 3 position via coordination with the unshared pair of electrons of the nitrogen in the 2 position. Metalation, however, occurs exclusively at the more acidic 5 position (see p. 23).

In synopsis, it can be stated that lithiating agents with little or no Lewis-acid character generally lead to thermodynamic products derived from deprotonation at the most acidic position. In contrast, coordinatively unsaturated metalating agents, such as *n*-butyllithium in hydrocarbons or ethers, produce kinetic products derived from deprotonation at the atom closest to the most effective ligand.

3. Scope and Limitations

3.1. Nature and Reactivity of the Lithiated Species

Few reports describe the physical properties or the relative reactivity of alpha- or beta-lithiated species. The most complete information is available on *o*-lithio-N,N-dimethylbenzylamine, which can actually be isolated as a pure solid. (9) In this case there is good evidence for strong intra- and/or intermolecular lithium–nitrogen interactions (9, 43) and, that by virtue of the latter, a solvent- and concentration-dependent aggregation occurs. Because of this type of internal chelation and/or the acidifying inductive effect of electron-withdrawing directors, heteroatom-stabilized lithioorganics appear to be both somewhat less reactive (23, 24, 44) and weaker Lewis acids. The decrease in these parameters is dependent on the nature and strength of the internal chelation and inductive effects. It is this very decrease in Lewis–acid character that permits the isolation of such lithiated reagents, notably *o*-lithio-N,N,-dimethylbenzylamine, free of ethereal solvents. (9)

3.2. Influence of Other Substituents

In carbocyclic aromatic, heteroaromatic, and olefinic systems, the presence or absence of substituents other than the one arbitrarily considered to be the directing functionality is of considerable importance, since several factors in the lithiation of a particular substrate will be affected. These can be classified into the following categories: effects on rates, regioselectivity, and compatibility.

3.2.1.1. Effects on Rates

Substituents clearly affect the rates of lithiation in a particular π system. These effects are largely inductive in nature and are reflected in an increased or decreased kinetic acidity of a particular proton. Although various substrates readily lend themselves to kinetic studies under carefully controlled conditions, the rate-enhancing effects of substituents have been quantitatively studied only for bromobenzene derivatives. (32) These studies on the kinetics of aryne formation from substituted bromobenzenes, in which the *ortho* lithiation is considered to be the rate-determining step, probably represent the best basis for the assessment of these substituent effects. By applying the data to *ortho* lithiations in general (X = any *ortho*-directing group), the effect of the substituent R on the rate of metalation should decrease as indicated in Eqs. 10-12.

Effect of R on a *meta* position:

k_m (R)

R = F > CF$_3$, Cl* > OCH$_3$, H > CH$_3$ > N(CH$_3$)$_2$

(10)

Effect of R on a *meta* position:

k_m (R)

R = F > CF$_3$, Cl* > OCH$_3$, H > CH$_3$ > N(CH$_3$)$_2$

(11)

Effect of R on an *ortho* position:

k_o (R)

R = F > OCH$_3$ > Cl, CF$_3$* > N(CH$_3$)$_2$ > H > CH$_3$

(12)

One interesting aspect of these data is the unusual position occupied by the methoxyl and dimethylamino groups in 1,3-disubstituted benzenes. Although both groups exhibit a smaller acidifying effect on an *ortho* position than does chlorine or the trifluoromethyl group, (31) their rate-enhancing effect, particularly that of the methoxyl group, is greater than that shown by the trifluoromethyl group. This phenomenon is ascribed to the enhanced coordinative involvement of these two moieties, (32) as discussed in the mechanistic section. Accordingly, in 1,3-disubstituted benzenes the rate enhancement of R is determined not only by its inductive effect but also by its coordinative potential.

These relative directing effects are corroborated in several other systems, as judged by the rough estimates of the degree of *ortho* lithiation determined by deuteration. For example, from the studies of N,N-dimethylbenzylamines, (24,

45) N-methylbenzamides, (23, 24) and 2-aryloxazolines, (46) it can be stated that a chlorine in a *para* position has a rate-enhancing effect, whereas a methoxyl group has a small, if any, rate-decreasing effect relative to hydrogen. These effects run parallel to the relative rate factors *f* of the potassium amide–catalyzed hydrogen–deuterium exchange in liquid ammonia for substituted benzenes. (31, 47)

In alpha lithiations the situation is rather similar. Any substituent in a position beta to the facilitating heteroatom increases the rate of metalation if it exerts an inductive effect that increases the acidity of the alpha proton. The reverse inductive effect, of course, has the opposite effect. This is true for both olefins and π-excessive, five-membered heterocycles. Specifically, this rate-enhancing or -decreasing effect is shown, for example, in the thiophene series: 3-bromothiophene > thiophene > 3-methylthiophene. (48)

3.2.1.2. Regioselectivity

Since a large number of functional groups and atoms possess an inherent directing effect on the metalation of π-systems, their presence in a substrate, together with the dominant directing group, can have a pronounced effect on the regioselectivity of the metalation. For benzenoid systems, when a substituent (Y) is present in either a 1,2 or 1,4 relationship to the dominant *ortho*-directing group or atom (X), the general rule is that the higher degree of lithiation occurs *ortho* to the more powerful directing group. The strength of the director, however, is interdependent on the nature of the lithiating agent utilized (see p. 49 and pp. 77–80).

When X and Y are in a 1,3 relationship, even if the directing effect of Y is weak, lithiation occurs predominantly or exclusively in the position *ortho* to both the beta-directing group X and the substituent Y. The degree of regioselectivity depends on the relative inductive and coordinative capacities of Y. Known exceptions to this phenomenon are those in which X = Y = CF_3 (49, 50) and X = Y = $CONHC_4H_9$. (24, 51) Analogously, in π-excessive five-membered heterocycles, the general effect of Y in the 3 position (studied most extensively in the thiophene series) (52) is to provide selective or specific lithiation in the 2 position.

Whereas most substituents exert some beta-directing effect, some groups cannot coordinate, and these influence the regioselectivity in a different sense. For Y = alkyl, for instance, metalation occurs preferably *not* in the position *ortho* to both substituents in 1,3-disubstituted benzenoid systems but, rather *para* to Y, whereas in π -excessive, five-membered heterocycles position 5 is preferred.

3.2.1.3. Compatibility
As a generalization, any substituent that does not react with the lithiating agent used to effect a metalation is considered compatible. Most of the knowledge concerning such compatibility is based on data available for benzene and thiophene systems. It should be emphasized that for any particular example the compatibility of a substituent with the lithiation conditions depends both on the facility of metalation of the substrate and on the lithiating agent itself. Whether or not a given substituent is compatible, therefore, is often a question of competing reactions, *i.e.*, nucleophilic attack of the lithiating agent on the substituent *vs.* the actual metalation. Accordingly, it should be noted that substituents often considered incompatible in the metalation of carbocyclic aromatic systems are quite compatible in the more facile alpha lithiations. In addition the use of the non-nucleophilic lithium dialkylamides renders compatibility to certain electrophilic substrates in isolated instances. The following summary lists those functional groups that are generally considered incompatible, except where noted. These substituents conveniently fall into three categories: electrophiles, acidic groups, and halogens.

3.2.1.3.1. Electrophiles
Included in this category are nitro groups, aldehydes, ketones, acids, esters, nitriles, and, in most instances, primary and tertiary amides. (53, 54) Low-temperature lithiations of *m*-chlorobenzonitrile, (24) hindered tertiary benzamides, (55, 56) and β -aminoacrylic acid derivatives, 57a–c however, are known.

3.2.1.3.2. Acidic Groups
This category encompasses alkylmercapto, (1, 58, 59) alkyl sulfinyl, alkylsulfonyl, (60) and *ortho* alkyl groups. The acidic character of these groups usually precludes their presence in substrates. However, the alkylmercapto groups are perfectly acceptable in heterocyclic or olefinic systems. Alkyl substituents are generally quite compatible under the usual lithiating conditions. If, however, such alkyl groups, particularly methyl, are located in an *ortho* position with respect to the directing group, deprotonation of the alkyl group can be either a side reaction, as for *o*-alkoxytoluenes (61, 62) or *o*-toluidines, (63) or the exclusive pathway, as for *o*-toluamides, (64, 65) *o*-tolylsulfonamides, (66) *o*-tolyloxazolines, (46) and *o*-methylbenzylamines

(67) (Eq. 13). This type of reaction is synthetically rather useful but, since it lies beyond the defined scope of this chapter, it is not discussed in detail.

$$\text{(benzene with X and CH}_3\text{)} \xrightarrow{\text{RLi}} \text{(benzene with X···Li and CH}_2\text{)} \qquad (13)$$

3.2.1.3.3. Halogens

Whereas metal–halogen exchange of chlorine and fluorine usually is not a problem, aryne formation can become the predominant reaction if the lithium enters *ortho* or beta with respect to the halogen. The use of lithium amides generally increases the rate of aryne formation. (25) This eliminative pathway can be suppressed at low temperatures. In bromine- or iodine-containing substrates metal–halogen exchange is usually the preferred reaction. In the readily lithiatable heterocyclic systems, however, even in the presence of bromine and, in a few cases, iodine metalation proceeds normally, and little if any halogen–metal exchange is observed. (48, 68) A few exceptions are known in which metalation is preferred in bromo-substituted benzenoid systems. (69)

3.3. Alpha Lithiation

Alpha metalations are deprotonations of olefinic, aromatic, or other π systems at the sp^2-hybridized carbon that is alpha to a heteroatom X, as illustrated by Eq. 14. Alpha lithiations occur primarily in families of

$$Y = C \begin{smallmatrix} H \\ \diagdown \\ X \end{smallmatrix} \xrightarrow{\text{RLi}} Y = C \begin{smallmatrix} Li \\ \diagdown \\ X \end{smallmatrix} \qquad \begin{array}{l} Y = \text{C, O, S, --N} \\ X = \text{OR, SR, NRR', halogen} \end{array} \qquad (14)$$

five-membered heterocycles that have one or more heteroatoms. More recently, the metalation of simple heterosubstituted olefins has been developed into a synthetically useful tool (*vide infra*). One common feature of alpha lithiations is the rapidity with which they proceed in comparison to beta lithiations.

3.3.1. Alpha Activators and Their Relative Activating Ability

The inductive effect of an alpha activator greatly increases the acidity of the adjacent carbon - hydrogen bond, thus making alpha lithiations very facile. The following heteroatoms are known to lead to alpha metalations: nitrogen, oxygen, sulfur, selenium, tellurium, fluorine, chlorine, and bromine. In the series of five-membered heterocycles–thiophene, furan, and N-alkylpyrroles–competitive metalation studies have revealed that under

thermodynamic conditions the rate of metalation is greatest with sulfur, resulting in the following rank order: sulfur > oxygen > N-alkyl. (70) The fact that sulfur is the best alpha activator is explained by the (d –σ) overlap, which apparently outweighs the inductive effect of the more electronegative oxygen and nitrogen atoms. (42, 70) It appears that this (d – σ) overlap is a major factor in the enhancement of the thermodynamic stability of such anions adjacent to sulfur. (71, 72) Conversely, the more rapid lithiation of furan under kinetic conditions points to the superior ability of oxygen to act as a ligand. (40) Accordingly, under kinetic conditions the order becomes
oxygen > sulfur > N-alkyl.

By inference from the available experimental facts the following additional conclusions can be drawn:

1. Alpha metalations occur more readily on a carbon bearing two heteroatoms (Eq. 14, X and Y = heteroatom).
2. The rate of alpha metalation increases with an increasing number of heteroatoms present in five-membered heterocycles. (71, 73)
3. Alpha metalations of olefins occur most readily, usually at temperatures below –70°. The relative activating potency of the heteroatom under thermodynamic conditions appears to be
halogen > sulfur > oxygen > nitrogen.

3.3.2. Nitrogen as an Alpha-Activating Atom

3.3.2.1. Enamines

The alpha lithiation of enamines has received only scant attention, being limited to special cases. N,N-Diethyl-3-(1-pyrrolidinyl)acrylamide, for instance, can be metalated at –115° to produce the corresponding α -lithio species. (57a) The latter reacts with methyl iodide, for instance, to give the analogous crotonamide in high yield. The facility of this metalation is probably a result of both the alpha-activating ability of the pyrrolidine group and the acidifying and directing effects of the beta-directing carboxamide function. It should be noted that at higher temperatures 1,4 addition of the lithiating agent prevails. (57a)

Alpha lithiation of ethyl 3-(1-pyrrolidinyl)acrylate proceeds equally well at low temperatures. (57b) However, a different picture emerges on the

(95%)

metalation of 3-(1-pyrrolidinyl)acrylonitrile. Reaction with lithium diisopropylamide at temperatures lower than –105° results in the kinetically controlled deprotonation of the expected position, *i.e.*, alpha to the enamine group, to give the lithio species **1**. When warmed above –100°, however, this intermediate (**1**) slowly rearranges to the thermodynamically more stable beta-lithiated isomer **2a**, which is mesomeric with the imine anion **2b**. Both lithiated species **1** and **2a,b** can be reacted selectively with electrophiles to produce, after treatment with methyl iodide, *e.g.*, 3-(1-pyrrolidinyl)crotonitrile and 2-methyl-3-(1-pyrrolidinyl)-acrylonitrile, respectively. (57c)

Deuterium incorporation has shown that the dihydropyridine **3** undergoes alpha metalation. (74)

(82%)

3.3.2.2. *Vinyl Isocyanides*

Functionally, vinyl isocyanides may be considered derivatives of enamines. The strong acidifying character of the isocyanide group on sp^3 carbons is well known. (75) Apparently, this electron-withdrawing effect is also sufficiently operative on sp^2 carbons to permit alpha lithiation of certain types of vinyl isocyanides. Styryl isocyanide, for instance, is readily deprotonated at low temperatures to give α -lithio styryl isocyanide. (76) This reacts readily with various electrophiles; reaction with carbon dioxide, for example, gives a high yield of lithio α-isocyanocinnamate. With aldehydes and ketones, *e.g.*, acetone, the initial adduct is in equilibrium with the lithiated oxazoline (see p. 31), which in turn can further react to give a diadduct. The ratio of mono- and diadduct appears to depend on the character of the carbonyl reactant. (76) In view of the limited thermal stability of vinyl isocyanides, these reactions are clearly only of theoretical interest.

3.3.2.3. Formamides and Thioformamides

Deprotonation of dialkylformamides is essentially instantaneous even at −100°, (77) and there seem to be very few limitations to the nature of the N-alkyl substituent (Eq. 15). Alpha-lithiated formamides represent a novel type of acyl anion equivalent or, more specifically, a highly reactive one-carbon synthon with the oxidation state of cyanide. The synthetic potential of lithio dialkylformamides is documented by their excellent reactivity with numerous electrophiles. (77, 78)

$$\tag{15}$$

The deprotonation of dimethylformamide can be carried out with lithium diisopropylamide at −78°; subsequent reaction with pivalaldehyde, for example, gives a good yield of the hydroxyamide **4**. (78) A variant of this technique using N-methoxymethyl substituents gives access to adducts such as **5** and **6**, which upon deprotection give either secondary or primary amides. (79) An interesting facet of this reaction is that the lithiated species need not be preformed, for a 1:1 mixture of dimethylformamide and a substrate, *e.g.*, cyclohexanone, can be treated with lithium diisopropylamide at −78° to form the corresponding

hydroxyamide in 62% yield. (78) This observation certainly attests to the kinetic acidity of the formamide proton relative to those of cyclohexanone.

$$HCON(CH_3)_2 \xrightarrow[\text{2. } t\text{-C}_4\text{H}_9\text{CHO}]{\text{1. LDA}} t\text{-C}_4\text{H}_9\text{CH(OH)CON(CH}_3)_2$$
$$\textbf{4} \quad (76\%)$$

$$HCONR_1R_2 \xrightarrow[\text{2. } (C_6H_5)_2CO]{\text{1. LDA}} (C_6H_5)_2C(OH)CONR_1R_2$$

5 $R_1 = CH_3, R_2 = CH_2OCH_3$ (85%)
6 $R_1 = R_2 = CH_2OCH_3$ (88%)

The reported lithiation of N,N-dimethylthioformamide (77, 80) is carried out at –100° to form the desired anion within 3 minutes. Reaction of the anion with methyl benzoate gives an 85% yield of the corresponding α -ketothioamide. (77)

3.3.2.4. Pyrroles and Indoles

Compared with the oxygen and sulfur isosteres, furan and thiophene, pyrroles are lithiated only poorly in their alpha position. In fact, pyrrole itself undergoes only deprotonation of the nitrogen atom, even with excess reagent. (81) N-Alkyl- and N-arylpyrroles, however, do undergo the expected alpha lithiation, baut higher temperatures or longer reaction times are needed. Markedly increased rates of metalation can be achieved, however, by the use of reactive alkyllithium/TMEDA complexes. (40, 68, 82) This is illustrated by the transformation of N-methylpyrrole into N-methylpyrrole-2-carboxylic acid in good yield, (68) whereas the same reaction with *n*-butyllithium alone provides only a 42% yield of the acid. (81) With excess *n*-butyllithium and TMEDA products derived from 2,5-dilithio-N-methylpyrrole can be isolated, whereas in the absence of TMEDA the 2,4-dilithio species predominates. (40) N-Arylpyrroles can also be considered as tertiary anilines and, in fact, products of both alpha *and ortho* lithiation are isolated, as illustrated by the formation of the tricyclic ketone **7**. (81)

The metalation of indoles follows a similar pattern. N-Unsubstituted indoles are transformed into their lithium salts only, whereas N-alkylindoles are metalated in their alpha positions. (83) The rate of lithiation

is moderate; however, as for the metalation of pyrroles, the rate can be enhanced by using tetrahydrofuran as solvent. (84) The modest reactivity of indoles, particularly in comparison with benzofuran, is documented by the results observed in the lithiation of 5-methoxy-1-methylindole. After reaction with pyridine-2-carboxaldehyde, all three possible products (8–10) are formed, indicating that the *ortho*-directing effect of the methoxyl group is as strong as the alpha-activating effect of the indole nitrogen. (84)

The alpha lithiation of indoles can be facilitated by using methoxymethyl (85) or arylsulfonyl (84) protecting groups, *i.e.*, functionalities that have a beta-directing influence of their own. The cumulative directing effect of both the indole nitrogen and the protecting group is now sufficient, for instance, to lead exclusively to alpha lithiation, with 5-methoxy-1-(phenylsulfonyl)indole producing the 2-substituted derivative **11** in very good yield. (84) The presence of the methoxymethyl group has a similar rate-enhancing effect, as illustrated by the high yields achieved in the preparation of the acid **12**. (85) A potential

advantage in the use of protected indoles lies, of course, in the possibility of removing the protecting group.

11 (84%)

12 (80%)

3.3.2.5. Pyrazoles

1-Substituted pyrazoles are metalated in the 5 position. 3-Methyl-1-propylpyrazole, for instance, is alpha lithiated rapidly and essentially quantitatively to produce the carbinol **13**. (86) Although N-unsubstituted pyrazoles are reported to undergo metalation in the 5 position, the yields are poor. (87) The generation of a 1,2 dianion may be responsible for this phenomenon. Again, an alternative is to use an

13 (95%)

appropriate protecting group. The tetrahydropyranyl ether **14** is metalated under mild conditions, allowing very good yields of the 5-substituted products, as documented by the isolation of the thioether **15**. (23)

Two interesting side reactions can be observed in the metalation of certain pyrazoles. The first is a relatively facile deprotonation of the

14 → **15** (80%)

1. n-BuLi
2. (C$_6$H$_5$S)$_2$

N-alkyl substituent, particularly when it is a methyl group. Lithiation of 1,3-dimethylpyrazole, for instance, results not only in the formation of the expected alpha-metalated heterocycle **16**, but also appreciable amounts of the species **17**. Subsequent reaction with benzaldehyde yields

n-BuLi

C$_6$H$_5$CHO

16

(60%) R = CH(OH)C$_6$H$_5$

C$_6$H$_5$CHO

17

(30%)

the corresponding carbinols. (86) It appears that the two anions are interconvertible. It should therefore be possible to run such reactions under conditions permitting the trapping of only the kinetic deprotonation product. The second example pertains to 1-phenylpyrazoles, where, aside from the normal alpha lithiation, *ortho* metalation of the phenyl ring is observed because of chelation with the imine nitrogen, giving rise to two acids **18** and **19**. (88) This type of side reaction becomes predominant when organomagnesium halides are utilized as metalating agents. (89)

3.3.2.6. Imidazoles and Condensed Imidazoles
As with other π-excessive, five-membered heterocycles with two heteroatoms in a 1,3 arrangement, lithiation of 1-substituted imidazoles occurs between the nitrogen atoms when the position is available. If the 2 position is occupied by an alkyl group, deprotonation may occur either at the 5 position or on the alkyl

18 (39%)

19 (10%)

group, depending on its nature. Although 1,2-dimethylimidazole is reported to lithiate at position 5, (90) a more recent investigation clearly demonstrates that the products of such reactions are derived exclusively from deprotonation of the relatively acidic 2-methyl group, (91) as illustrated by the isolation of the carbinol **20**.

1. n-BuLi
2. 2-Pyridinecarboxaldehyde

20 (66%)

Alpha lithiation between the nitrogen atoms is extremely facile, occurring even in the presence of a bromine substituent otherwise liable to undergo halogen–metal exchange. This is illustrated by the preparation of the carbinol **21**. (92)

1. n-BuLi
2. CH_3CHO

21 (50%)

Lithiation of 1-substituted benzimidazoles proceeds analogously with great facility and leads to 2-lithiated species. 1-Methylbenzimidazole can thus be silylated in high yield to give **22**. (93)

22 (91%)

Imidazo[1,2-*a*]pyridine, a condensed imidazole with a blocked 2 position, undergoes alpha metalation as expected to produce, after quenching with dimethylformamide, the aldehyde **23**. (94)

23 (24%)

3.3.2.7. Triazoles and Tetrazoles
1,2,3-Triazoles (95) and 1,2,4-triazoles (96) are lithiated with extreme rapidity in their respective alpha positions. It should be noted, however, that 5-lithio-1,2,3-triazoles are only stable at low temperatures. Above –40° they display a tendency to undergo a cycloreversion with loss of nitrogen and formation of an N-substituted ketenimine anion. (97) Nevertheless, low-temperature lithiation of 1-phenyl-1,2,3-triazole followed by reaction with methyl iodide gives an excellent yield of the 5-methyl derivative **24**. (95) Under similar conditions, followed by quenching with benzophenone, 1-benzyl-3-phenyl-1,2,4-triazole gives an equally high yield of the alcohol **25**. (96)

Tetrazoles are probably among the most readily lithiatable heterocycles because they contain the maximum number of four electronegative ring atoms. (73) The acidity of the only available ring hydrogen must be appreciable. N-Methyltetrazole, for instance, can thus be converted to the thiol **26**. (98)

3.3.2.8. Pyridines, Condensed Pyridines, and Pyridine N-Oxides

Alpha metalation of pyridines and condensed pyridines is not a practical reaction, largely because these compounds are susceptible to nucleophilic attack. However, what may appear to be a direct lithiation can be achieved through use of lithium diisopropylamide and hexamethylphosphoramide as a cosolvent. Under these conditions only dimeric products (2,2′-bipyridines) can be isolated. (99) Comparatively stable 2-lithiopyridines (or quinolines) are, nevertheless, readily available via halogen–metal exchange. (100)

Direct metalation of pyridine N-oxides with *n*-butyllithium is feasible, although the yields are generally modest to poor.* This is accounted for by the fact that addition competes with alpha deprotonation. (101) Although the lithiation proceeds alpha to the nitrogen atom, one has to assume a good deal of *ortho*-directing effect on the part of the oxygen atom. Thus a comparison with the *ortho* lithiation of phenol[1] (an equally poor process) may be suggested. The reactivity of the 2-lithio derivatives is not high enough to permit reactions with epoxides. (102) However, it is not uncommon for products derived from 2-lithiopyridine N-oxides to be highly electrophilic and therefore subject to

additions of unreacted metalated species to the remaining azomethine linkage. (101) The reaction thus has only a limited synthetic potential.

3.3.2.9. Pyrimidines

Unlike imidazoles, pyrimidines apparently are not metalated by alkyllithiums in the 2 position, *i.e.*, between the nitrogen atoms, because of the known propensity of the pyrimidine nucleus to suffer nucleophilic attack at one of the azomethine linkages by nucleophilic organometallic reagents. One report, however, describes a successful metalation in the 4 position of 5-methylpyrimidine by using the non-nucleophilic lithium diisopropylamide. On quenching with benzophenone a modest but nonetheless significant yield of the carbinol **27** is isolated. (99)

27 (30%)

3.3.3. Oxygen as an Alpha-Activating Atom

3.3.3.1. Alkyl Vinyl Ethers and Allenic Ethers

The synthetic potential of alpha-metalated vinyl ethers is substantial because they represent acyl anion equivalents, a type of synthon that has only recently become available (see p. 90). Although numerous enol ethers have been metalated, (103) methyl vinyl ether has been explored most thoroughly. (104) It is readily lithiated by *t*-butyllithium in tetrahydrofuran at low temperatures, reacting with essentially any electrophile to give good to excellent yields of the primary products. These in turn may then be hydrolyzed to ketones and elaborated further. The conversion of methyl vinyl ether into the ketone **28** is but one example of this useful type of reaction. (104) α -Methoxyvinyllithium undergoes 1,2 addition exclusively on α , β -unsaturated systems, (104) but 1,4 addition can be effected by conversion to the corresponding copperlithium reagent. (105, 106)

28 (70%)

An interesting and potentially useful variant of this reaction is the *in situ* preparation of an enol ether via tautomerization of a protected allylic alcohol. Thus the tetrahydropyranyl ether of allyl alcohol is isomerized to the enol ether **29**, which in turn is readily metalated to the lithio species **30**. Subsequent reaction with methyl iodide produces a very good yield of the enol ether **31**. (107) It is likely that the oxygen of the protecting group of **30** provides additional chelation and stability to such reagents.

31 (83%)

Metalation of enol ether systems was first realized with alkoxyallenes. (108a) If the higher metalation temperature in the reaction between methoxyallene and

n-butyllithium is any indication, it would appear that the resulting anion **32** has a greater stability than simple lithiated vinyl ethers. The product yields are generally good (108a) to excellent, (23) as illustrated by the formation of the allenic ether **33**. (108a) The accessibility and facility of metalation of allenic ethers, combined with their high reactivity toward a broad spectrum of electrophiles, make species like **32** very valuable synthons indeed.

$$CH_2{=}C{=}CHOCH_3 \xrightarrow{\text{n-BuLi}} CH_2{=}C{=}C\overset{OCH_3}{\underset{Li}{\big<}} \xrightarrow{C_6H_5CH_2Br}$$

32

$$CH_2{=}C{=}C\overset{OCH_3}{\underset{CH_2C_6H_5}{\big<}}$$

33 (64%)

Interestingly, metalation of hindered allenic ethers, such as *t*-butoxyallene, with lithium dicyclohexylamide occurs predominantly at the gamma position (*ca.* 80%). (108b) Similarly, lithiation of alpha-substituted allenic ethers with *n*-butyllithium takes place at the gamma position. (108b)

Higher alkoxycumulenes are apparently metalated equally well. Treatment of 1-methoxy-4-methyl-1,2,3-pentatriene with *n*-butyllithium provides the lithiated derivative **34**, (109) which can also be prepared from 1,4-dimethoxy-4-methyl-2-pentyne via *in situ* elimination and metalation. (110, 111) It reacts with electrophiles such as cyclohexanone to give the expected products, *e.g.*, the alcohol **35**, in good yields.

$$(CH_3)_2C{=}C{=}C{=}CHOCH_3 \xrightarrow{\text{n-BuLi}}$$

$$(CH_3)_2C{=}C{=}C\overset{OCH_3}{\underset{Li}{\big<}} \xleftarrow{2\,\text{n-BuLi}} (CH_3)_2\underset{OCH_3}{\overset{}{C}}C{\equiv}CCH_2OCH_3$$

34

| Cyclohexanone

$$(CH_3)_2C{=}C{=}C\overset{OCH_3}{\underset{HO}{\big<}}\bigcirc$$

35 (90%)

3.3.3.2. Furans and Condensed Furans

The alpha metalation of furans can be compared with the lithiation of vinyl ethers, since furan is itself a cyclic divinyl ether. Accordingly, the reaction of furan with *n*-butyllithium, although considerably less facile, does proceed in high yield in refluxing ether, as shown by the isolation of the carbinol **36**. (112) Dilithiation of furan can be achieved efficiently with *n*-butyllithium/TMEDA in refluxing hexane, as indicated by the isolation (90%) of dimethyl furan-2,5-dicarboxylate. (40) With a substituent in the 2 position, metalation occurs equally well in the free 5 position. As is discussed in more detail in regard to the thiophene series, a 3 substituent with a beta-directing capacity permits a regioselective metalation in the 2 position. Furan-3-carboxaldehyde ethylene ketal, for instance, leads to the 2-lithio species **37**, which can be quenched with various electrophiles to produce, after hydrolysis, 2-substituted-3-carboxaldehydes (113) such as the boronic acid **38**. (114, 115)

Condensed furans such as benzofuran undergo alpha metalation in the 2 position rather than *ortho* lithiation in the 7 position, which, at least in principle, could be considered an alternate pathway. The fact that alpha metalation is achieved far more readily than *ortho* metalation at any of the three possible sites (4, 6, or 7) of 5-methoxybenzofuran is documented by the reaction with *n*-butyllithium, followed by ethylene oxide, to obtain only the 2-substituted ethanol **39**. (116) The result is additional evidence that alpha metalation proceeds more readily in furans than pyrroles, for the analogous 1-methyl-5-methoxyindole gives a mixture of products, (84) as indicated on p. 22.

3.3.3.3. Isoxazoles

In contrast to the isothiazoles (p. 39) the lithiation of isoxazoles does not lead to the expected products. Still, metalation does occur next to the more electronegative oxygen atom when the 3 position is occupied, as illustrated for 3,4-diphenylisoxazole, but the lifetime of the lithiated species is very short and it suffers fragmentation into benzonitrile and a deprotonated phenyl ketene which can be trapped with electrophiles. (117)

3.3.3.4. Oxazoles and Oxazolines

Oxazoles can be readily lithiated in the 2 position. Unlike their nitrogen analogs, the imidazoles, the ambireactive character of their lithiated species indicates that they are in equilibrium with the enolate of a β -ketoisonitrile. Lithiation of 4,5-diphenyloxazole, for instance, produces the carbinol **40** on reaction with benzaldehyde, whereas reaction with chlorotrimethylsilane leads exclusively to the O-silyl ether **41**. (118)

2-Oxazolines can be metalated in a similar manner, leading to an equilibrium mixture of alpha-lithiated species and isonitrile. (119, 120) Lithiated 4,5-diphenyl-2-oxazoline, for example, is acylated on oxygen with acetic anhydride, whereas reaction with benzaldehyde produces the dihydro derivative of **40**. (120)

3.3.4. Sulfur as an Alpha-Activating Atom
3.3.4.1. Vinyl Sulfides and Allenic Thioethers

Vinyl sulfides undergo rapid alpha metalation with lithium alkyls under carefully controlled conditions, and thus provide yet another acyl anion equivalent. (121) However, a possible side reaction in these alpha lithiations is a Michael-type addition of the metalating agent to the olefinic bond, leading to a saturated carbanion stabilized by the ($sp^3 - d$) overlap. (59, 122) The reaction is fairly general with respect to the nature of the substitution on sulfur; *i.e.*, both alkyl and aryl groups are permissible. Allyl or benzyl sulfides are excluded, however, because of their known propensity for deprotonation of the sp^3-bound hydrogen, as is the case with allyl vinyl sulfide. (123) The metalation of phenyl vinyl sulfide can be effected readily with lithium diisopropylamide, (124, 125) as well as with *n*-butyllithium/TMEDA, (126) without incurring addition of the metalating agent (see pp. 98–99). The vinyl sulfide anions react readily with aldehydes, ketones, epoxides, and alkyl halides. For example, alkylation of lithiated ethyl vinyl sulfide with *n*-octyl bromide, followed by mercuric ion-catalyzed hydrolysis of the primary product gives 2-decanone in excellent yield. (121)

An interesting situation arises with 2-alkoxy-1-(alkylthio)ethylenes where alpha lithiation is, in principle, possible at either of the two sp^2-carbon atoms. Paralleling the observations made in the rates of lithiation of thiophene and furan under thermodynamic conditions, metalation of 2-ethoxy-1-(pentylthio)ethylene proceeds exclusively at the position alpha to sulfur. (127) The reactivity of the resulting anion appears to be comparable to that of the simple α-alkylthiovinyllithium species, and reaction with various electrophiles is possible. As shown, reaction with ethylene oxide produces the alcohol **42** in good yield. (127) The ethoxy group quite likely provides an additional beta-directing or at least an acidifying effect. One aspect worthy of note in this reaction is the apparent absence of elimination of lithium alkoxide. Similarly, lithiated (Z)-1,2-bis(diethylthio)ethylene (128) is stable at low temperatures, whereas the correspondingly metalated 1,2-bis(phenylthio)ethylenes (Z or E) undergo elimination at higher temperatures. (129)

In contrast to the vinyl sulfides discussed thus far, the amine **43** is unique in that the beta-directing nitrogen ligand serves to depolymerize the metalating agent and to chelate the resulting alpha-lithiated species. Despite the stability of the anion at ice-bath temperature, it is still reactive enough to undergo addition to a variety of electrophiles, as illustrated by the reaction with dimethyl disulfide to produce the basic ketene-S-acetal **44**. (23)

The alpha lithiation of allenic thioethers is facile, but in contrast to the oxygen congeners (see p. 29), the reactivity of the metalated species is more complex because of an increased stability of the propargylic anions. Thus metalation of the allene **45** followed by reaction with formaldehyde leads to a mixture of the two alcohols **46** and **47**. (130) This ambireactive character can be changed in favor of the products derived from alpha-lithiated allenic thioethers by using lithium amide and ammonia as the metalating system. 131a,b

3.3.4.2. Vinyl Sulfoxides

Alpha metalation of alkenyl aryl sulfoxides is particularly facile and occurs at very low temperatures with lithium diisopropylamide. One noteworthy feature observed in the lithiation of E/Z mixtures of such substrates is the preferential formation of E-products which must be accounted for by an isomerization of the intermediate anion. Thus lithiation of a 1:1 mixture of (E)- and (Z)-3-methoxypropenyl phenyl sulfoxide followed by alkylation with methyl iodide leads almost exclusively to the E-product. (132) The yield of products is even higher in alkenyl 2-pyridyl sulfoxides. It appears that the metalation of propenyl 2-pyridyl sulfoxide is greatly facilitated by the presence of the pyridine nitrogen, which serves as a ligand to stabilize the resulting species via a

five-membered chelate. The methylated product, 1-methylpropenyl 2-pyridyl sulfoxide, is isolated in almost quantitative yield. (132)

3.3.4.3. Thiophenes and Condensed Thiophenes

Thiophene is metalated very readily, and under appropriate conditions even 2,5-dilithiothiophene can be generated. (40) Competitive lithiations between furan and thiophene have revealed (4, 41, 133) that under thermodynamic conditions the product ratio is 96:4 in favor of thiophene, whereas under kinetic conditions furan is metalated faster (40) (see p. 18). The calculated relative activities for the two heterocycles indicate that the alpha position in thiophene is 500 times more reactive than that in furan. (41) In addition, the greater stability of 2-thienyllithium is explained by d-orbital participation.

The lithiation of thiophene and numerous substituted derivatives has been extensively studied and reviewed. (38, 40, 42, 134) From the wealth of data available the following generalizations can be made for the lithiation of thiophene derivatives:

1. Because of the great facility with which thiophene itself can be metalated in its alpha position, 2-substituted derivatives in general give exclusive metalation in the 5 position. Two exceptions are discussed (p. 77).

2. A 3-substituted thiophene whose 3 substituent has any beta-directing ability (either inductive or coordinative) gives rise to exclusive or predominant 2 lithiation.

3. 3-Substituted thiophenes whose substituent has *no* beta-directing capability, such as 3-alkyl or arylthiophenes, are lithiated in both the 2 and predominantly in the 5 positions, depending on the degree of steric hindrance.

4. 3,4-Disubstituted thiophenes are lithiated beta to the stronger directing group.

5. Metalation of 2,5-disubstituted thiophenes is governed by the relative effectiveness of the beta-directing substituents (see p. 43).

The most intriguing aspect of the alpha metalation of thiophenes is the sheer inability of almost any beta-directing group to compete with the alpha lithiation. Although the sulfonamide, sulfone, and dimethylaminomethyl groups are among the strongest beta directors, when present as 2 substituents in thiophenes, their effect is completely over-shadowed by a selective alpha lithiation in the 5 position, as illustrated by the exclusive formation of the products **48**, (135) **49**, (69) and **50**. (134) In the presence of excess *n*-butyllithium, however, 3,5-dilithio species can be generated. For example, the diacid **51** can be isolated after an exhaustive metalation of *t*-butyl 2-thienyl sulfone. (136) In fact, the only beta-directing functionality capable of competing with an alpha activator is the imine moiety inherent in pyridine nuclei (137, 138) and oxazolines. (139) These results are discussed in more detail in the competitive metalations section (p. 77).

48 (82%)

49 (42%)

50 (88%)

51 (68%)

The regioselectivity provided by a 3 substituent with beta-directing ability, however, weak it may be, is quite striking. With the exception of 3-(alkylseleno)thiophenes, (140) alpha metalation in the 2 position is the predominant or exclusive process. 3-Alkoxy substituents provide a very high degree of regioselectivity and, in contrast to the carbocyclic aromatic systems, even a bulky *t*-butoxy group gives access to a high yield of the 2-methylated product **52**. (141) The dimethylaminomethyl group gives regioselective metalation in the 2 position, as evidenced by the isolation of the aldehyde **53**. (43, 134) A methoxymethyl group in the 3 position has a similar effect. (43, 134, 142)

52 (87%)

53 (75%)

Such selective metalations are utilized in the preparation of condensed thiophenes, *e.g.*, the acid **54**. The reported overall yield in this multistep

transformation is impressive. (143) 3,3′-Thiodithiophene can be dilithiated in the 2 and 2′ positions to give, after copper-catalyzed coupling, the trithienyl system **55**. (144)

54 (94%)

55 (52%)

3-Alkyl- or -arylthiophenes give varying amounts of 2- and predominantly 5-metalated products, depending on the steric and/or inductive effects of these groups. These effects are best illustrated by comparing the relative amounts of lithiation in the respective positions, as determined by the isolation of various products. (20, 145, 146)

			R	Yield (%)
22	:	78	CH_3	87
—		100	C_4H_9-t	72
44	:	56	C_6H_5	72

3,4-Disubstituted thiophenes are lithiated in the alpha position that is beta to the more effective directing group. Thus 3-*t*-butoxy-4-methylthiophene gives exclusively the 2-substituted product **56**. (147) Likewise, the intermediate **57**, derived from 3-*t*-butoxy-4-lithiothiophene and dimethylformamide, is metalated selectively next to the more strongly beta-directing dimethylaminomethyl group leading, after reaction with dimethylformamide, to the dialdehyde **58**, (148)

56 (79%)

57

58 (60%)

Lithiation of benzothiophenes proceeds readily and exclusively at the alpha position to provide high yields of 2-substituted derivatives. Thus, on reaction of 2-lithiobenzothiophene with perchloryl fluoride a good yield of the 2-fluorobenzothiophene is obtained, (149) whereas quenching with tributyl borate followed by oxidative workup leads to the thiolactone **59**. (150, 151) When a free alpha (2) position is available, metalation never occurs in the benzene ring *ortho* to the sulfur atom, as is the case with dibenzothiophene(see p. 69). (1, 152) The intermediacy of a 2,7-dilithio species, however, has been observed with excess metalating agent. (40) 3-Substituted benzothiophenes are metalated equally well, as documented by the quantitative deuteration of the amine **60**. (153) In

59 (76%)

60

contrast to N,N-dimethylphenethylamine (p. 52), no benzylic deprotonation is observed.

3.3.4.4. Isothiazoles
The activating influence of the two heteroatoms in isothiazoles permits a facile lithiation in the 5 position at very low temperatures, making this reaction

preparatively useful, as demonstrated by the formation of isothiazole-5-carboxaldehyde. (154) However, at higher temperatures metalation can be complicated by fragmentations that occur either via nucleophilic attack of the lithiating agent at sulfur (155) or by other mechanisms. (154, 155)

(75%)

3.3.4.5. Thiazoles and Benzothiazoles

Thiazoles have two possible sites for metalation, namely, the 2 and the 5 positions. As with imidazoles, metalation in the 2 position is favored for derivatives lacking a 2 substituent, as illustrated for the preparation of thiazole-2-carboxylic acid. (156) 2-Substituted thiazoles such as 2-chlorothiazole, (157) undergo metalation exclusively in the 5-position. If the 2 substituent is a methyl group, however, lithiation in the 5 position, while still the major pathway, is accompanied by a lateral deprotonation of the relatively acidic methyl group. (158, 159) This side reaction normally amounts to as much as 10% of the product mixture, as evinced by the two alkylated products **61** and

(40%)

62. (159) In comparison to the corresponding imidazoles, this side reaction is less pronounced, as would be expected from the higher alpha-activating ability of the sulfur atom.

Benzothiazole undergoes rapid metalation in the 2 position, as illustrated by the formation of the silane **63**. (160)

63 (77%)

3.3.5. Selenium and Tellurium as Alpha-Activating Atoms

3.3.5.1. Vinyl Selenides

In comparison to the vinyl sulfides (p. 32) phenyl vinyl selenide can react with metalating agents via three different pathways. In diethyl ether, *n*-butyllithium adds in a Michael-type fashion (A), whereas in tetrahydrofuran attack is at selenium (B), followed by cleavage of the phenyl-Se bond. It is only through the use of lithium diisopropylamide that alpha lithiation can be achieved (C) as illustrated by the isolation of 1-methyleneundecyl phenyl selenide. (161) Tetraselafulvalene on the other hand, which is a more complex cyclic vinyl selenide, can be alpha metalated with *n*-butyllithium. (162)

3.3.5.2. Selenophenes and Tellurophenes

Like their oxygen and sulfur analogs, selenophene (163) and tellurophene can be alpha-metalated effectively to give, for example, 2-methyltellurophene in very good yield. (164) In unsymmetrically substituted derivatives the directing influence of an ether

functionality provides for regioselectivity in very much the same way as for the thiophenes, as illustrated by the formation of 3-methoxyselenophene-2-carboxaldehyde. (165)

3.3.6. Halogen as Alpha-Activating Atoms

3.3.6.1. Haloalkenes

The alpha metalation of haloalkenes, or chloroalkenes in particular, has been extensively studied and reviewed. (166) Unlike all other alpha-lithiated species reported thus far, α-lithio haloalkenes can add to electrophilic substrates (E) as well as undergo an alpha elimination of lithium halide to form carbenoid species (Eq. 16). The stability of

$$(16)$$

α -lithio haloalkenes is generally lower than that of other alpha-metalated species, and their generation must often be carried out at temperatures below –100°. Vinyl chloride, for instance, can be metalated and carboxylated quantitatively at –115° to produce α-chloroacrylic acid. (167, 168) The presence of one or two phenyl substituents tends to increase the stability of the alpha-lithiated species. Thus β -chlorostyrene can be metalated at –80°, and carboxylation gives a high yield of (E)-2-chlorocinnamic acid. (169) Even more stable is the trisubstituted species **64**, which can be prepared at –43°. (170) Carboxylation at that temperature leads to formation of the acid **66**. At higher temperatures, such as –12°, the lithio derivative **65** undergoes a Fritsch–Buttenberg–Wiechell rearrangement which is quite general for various *gem*-diaryl derivatives of this type. (166, 170, 171)

C_6H_5

$\xrightarrow{\text{1. } n\text{-BuLi}/-80° \quad \text{2. } CO_2}$

Cl

C_6H_5 CO_2H

Cl

(90%)

Ar—Cl / Ar (**64**)

$\xrightarrow{n\text{-BuLi} \atop -43°}$

Ar—Cl / Ar—Li (**65**)

$\xrightarrow{CO_2}$

Ar / Cl / Ar CO_2H

66 (88%)   Ar = p-ClC$_6$H$_4$

$\xrightarrow{-12°}$ Ar—C≡C—Ar

(61%)

As with other appropriately 1,2-disubstituted olefins, beta elimination can also be a problem. For example, lithiation of (Z)-1,2-dichloroethylene followed by carboxylation leads via elimination of lithium chloride to chloropropiolic acid. It should be noted, however, that the (E) isomer gives the normal product of alpha lithiation, namely (E)-2,3-dichloroacrylic acid, in essentially quantitative yield. (167, 168)

Cl / Cl

$\xrightarrow{\text{1. } n\text{-BuLi}/-100° \quad \text{2. } CO_2}$

Cl / CO_2H / Cl

(99%)

The alpha metalation of fluoroalkenes (172, 173) and bromoalkenes, 174a,b although feasible, has received only scant attention.

3.4. Beta (*Ortho*) Lithiation

As defined in the introduction, beta (*ortho*) lithiation consists in the replacement of a C_{sp^2}-bound hydrogen atom by lithium at the position beta to a functional group with nonbonding electrons. The designation "ortho lithiation," which is a type of beta lithiation, is used in this chapter exclusively to denote the deprotonation of the position adjacent to the directing atom or functional group attached to carbocyclic aromatic systems. The reaction itself is characterized by its high degree of regioselectivity, as with very few exceptions no other carbon atoms are deprotonated. The reaction is shown in Eqs. 17 and 18, where X represents a heteroatom and *n* may vary from 0 to 2. Metalations of this type are observed with a wide variety of groups in which X may be nitrogen, oxygen, sulfur, halogen, selenium, or phosphorus.

$$\text{(structure)} \xrightarrow{\text{RLi}} \text{(structure)} + \text{RH} \quad \text{beta lithiation} \qquad (17)$$

$$\text{(structure)} \xrightarrow{\text{RLi}} \text{(structure)} + \text{RH} \quad \textit{ortho} \text{ lithiation} \qquad (18)$$

3.4.1. Beta (Ortho)-Directing Groups and Their Relative Directing Ability

An attempt to classify all directing groups based on their inductive electron-withdrawing or electron-donating and coordinative properties leads to the following categories:

3.4.1.1. Coordination Only

Heteroatoms that are attached to a π system (carbocyclic aromatic, heteroaromatic, olefinic) by one or at the most two saturated carbon atoms can lead to a beta metalation only via the coordinative mechanism if the effect of the saturated carbon(s) is considered neutral. The most effective groups are basic amines, *e.g.*, $\geq CNR_1R_2$, $-CR_1(O^-)NR_2R_3$, and $\geq CCH_2NR_1R_2$. Considerably less efficient as *ortho* directors are alkoxides, ethers, acetals, and ketals, *e.g.*, $\geq CO^-$, $\geq COR$, and $\geq C(OR)_2$. The latter groups, however, provide excellent beta-directing effects in the lithiation of more readily metalated systems, such as π-excessive, five-membered heterocycles.

3.4.1.2. Electron-Withdrawing Groups

Electron-withdrawing groups with little or no coordinative capacity are effective beta directors because of their ability to markedly increase the hydrocarbon acidity of adjacent positions. Groups that have shown beta-directing properties include $>CO, CF_3, F$, Cl, Br, and I.

3.4.1.3. Electron-Withdrawing Groups with Moderate Coordination Potential

A common feature of these functionalities is a moderate capacity for coordination with the lithiating agent. Their inherent effect on the beta position is electron withdrawing by induction. On coordination with the metalating agent this effect is enhanced. Such groups are, in order of decreasing effect:
$$SO_2\text{-aryl}, \quad SO_2NR_1R_2 > OR > SR > SeR > .$$

3.4.1.4. Electron-Withdrawing Groups with Pronounced Coordination Potential

These functional groups exhibit the ideal features for facile beta metalations, *i.e.*, a high capacity for effective coordination with the lithiating agent via the nonbonding pair of electrons of their sp^2-hybridized nitrogen atoms, and the ability to inductively acidify adjacent hydrogens through their electron-withdrawing properties. Some of these functionalities are

$-CONR_1R_2$, 2-oxazolines, 2-pyridines, and $>C{=}NNR_1R_2$.

Each individual group has its own distinct beta-directing ability. Thus the establishment of a ranking system is not only of theoretical but certainly of considerable practical interest for π systems bearing more than one directing group. Various research groups have addressed themselves to this problem. (1, 2, 19, 23, 24) Their results, combined with additional inferential interpretations, permit the following generalizations:

1. Under kinetic lithiation conditions, the strongest beta-directing groups combine both an electron-withdrawing effect *and* the properties of a good ligand.

2. Among the groups in which the directing heteroatom is separated from the π system by a saturated carbon atom, thus providing no electron-withdrawing effect, a basic nitrogen atom is the most powerful director.

3. In the presence of non-Lewis-acid metalating agents, the rank order of the directing groups is determined largely by their inductive or acidifying effect.

In the lithiation of carbocyclic aromatic systems with coordinatively unsaturated metalating agents, the following order of beta-directing potential can be established. The list includes only those groups that either have been studied in competitive experiments or for which assumptions can be made based on the wealth of data available:

$$SO_2NR_1R_2, ^*SO_2\text{-aryl}^{23} > 2\text{-oxazolines} > CONHR, CSNHR^{2,24} > CH_2N(CH_3)_2$$
$$> CR(O^-)CH_2N(CH_3)_2^{175} > OCH_3 > O\text{-aryl} > NH\text{-aryl}^{176}$$
$$> S\text{-aryl}^{177,178} > NR\text{-aryl} > N(CH_3)_2 > CR_1R_2O^-$$

(The lack of comparative data precludes an exact ranking of the halogens.)

3.4.2. Nitrogen as a Beta (Ortho)-Directing Atom

3.4.2.1. Mono-, Di-, and Triarylamines

The nitrogen atoms in N,N-disubstituted anilines rate among the poorest *ortho*-directing groups. This observation may be attributed to the fact that their nitrogen lone pairs are not readily available for coordination with the lithiating agent because they are strongly engaged in the resonance of the π system to which they are attached. N,N-Dimethylaniline is lithiated in refluxing hexane in 55% yield, as shown by the isolation of an *ortho*-substituted product. (179, 180) The inferiority of a tertiary aromatic amine as a directing group is clearly exemplified by the metalation of N,N-dimethyl-*p*-anisidine (**67**), which is lithiated exclusively (85%) *ortho* to the methoxyl group. (19) The observation that the *meta* isomer is lithiated in the position *ortho* to both directing groups (**68**, 80%) underscores the fact that the anilino nitrogen nevertheless possesses a distinct, albeit weak, *ortho*-directing ability. (19) The use of *n*-butyllithium/TMEDA greatly facilitates the otherwise sluggish metalation of anilines, as evinced by the lithiation of N,N-dimethyl-*p*-toluidine (80%). (63) The predominant deprotonation of the methyl group in N,N-dimethyl-*o*-toluidine is characteristic of this general alternative pathway (see p. 16). (63)

No successful *ortho* lithiations of N-alkyl or N-unsubstituted anilines have been reported. One way to achieve the latter goal (see p. 48) is exemplified by the dilithiation of pivalanilide where the oxygen or nitrogen atom of the monodeprotonated species can serve as a ligand for the metalating agent. The method is general and the reaction of the dilithio species proceeds in very good yield, as illustrated by the isolation of *o*-(methylthio)pivalanilide. (181a)

An example of the lithiation of a diarylamine is that of 2-anilinonaphthalene, which occurs predominantly in the 3 position of the naphthalene nucleus. (181b) Conversely, 1-anilinonaphthalene is metalated almost exclusively in the 8 position to give, after treatment with carbon dioxide, good yields of the products **69** and **70**. (181b) Thus, when there is a choice between a four- or five-membered cyclometalated intermediate, the latter is clearly favored, and lithiation takes place in a position formally gamma rather than beta with respect to the nitrogen ligand.

69 (56%)

70 (25%)

71

72 (80%)

In the more complex system **71**, where there is a choice of three metalatable sites, namely positions 1, 6, and 13, lithiation at carbon 1 via a five-membered cyclometalated species is again clearly the preferred pathway. Carboxylation produces the acid **72** in excellent yield. (182)

Another interesting observation was made with the phenothiazines. N-Unsubstituted derivatives are lithiated more readily and regioselectively than are the N-alkylated homologs. Lithiation of N-methylphenothiazine leads to a mixture of about equal amounts of products **73** and **74**, (177, 183a) indicating the approximate equivalence of sulfur and nitrogen as *ortho*-directing atoms. However, phenothiazine itself is lithiated exclusively *ortho* to nitrogen to give **76**. (178) If it is indeed the relative unavailability of the nitrogen lone pair for

chelation with the lithiating agent that makes the tertiary nitrogen of N-methylphenothiazine a poorer *ortho* director, one rationale is the following: As the formal negative charge of the monoanion generated by N-deprotonation of phenothiazine is delocalized over the entire π -system (75), the nonbonding pair of electrons of the nitrogen atom, now coplanar with the tricyclic system, becomes available for chelation with the lithiating agent. This phenomenon is not limited to phenothiazines, but has also been observed with benzo- and dibenzophenothiazines where the exclusive site of metalation is *ortho* to the (NH) group. (176, 182-183b)

The unusual *meta* lithiation of triphenylamine was explained in terms of steric hindrance by Gilman and Morton (1) in the latest review on this subject. An alternate rationalization may also be the unavailability of the nitrogen lone pair for coordination. A reexamination of these results confirms the preponderance of a rather sluggish *meta* metalation. (23)

3.4.2.2. α -Lithio(N-alkylidene)arylamines (Aryl Isocyanides)
As discussed previously (p. 20), the activating influence of the isocyanide group promotes alpha lithiation at very low temperatures, with little or no attendant addition of the lithiating agent to the electrophilic isocyanide carbon. In contrast, the isocyanide group is only a very poor *ortho* director, and therefore the initial step in the attempted *ortho* lithiation of phenyl isocyanide with *t*-butyllithium is addition of the metalating agent to form α -lithio(N-neopentylidene)aniline. The latter in turn can now be metalated in its *ortho* position by a second equivalent of *t*-butyllithium to form the dilithio species, α ,2-dilithio(N-neopentylidene)aniline. (184) Formally, therefore, one is not dealing with an *ortho* lithiation of an arylisocyanide but rather with an *ortho* metalation of an α-lithio(N-alkylidene)arylamine. It should be noted that the metalation conditions (*t*-butyllithium/TMEDA) are critical, and in the

absence of the chelating amine no ring deprotonation occurs. (184) This finding is indicative of the weak *ortho*-directing influence of the intermediate metallo aldimine group. Nevertheless, under the conditions indicated generation of the dilithio species proceeds in high yield, as illustrated by the reaction products with methyl iodide and dimethylgermanium dichloride. (184)

From a synthetic point of view the reaction permits in effect an *ortho* lithiation of a primary aromatic amine since the initial products (ketimines) can readily be hydrolyzed to the respective anilines. It should be pointed out that generally both carbon-lithium bonds in the dilithio species react with the electrophile, which may prove to be a limitation in certain instances.

3.4.2.3. Aralkylamines

The dialkylaminomethyl group is the most powerful non-electron-withdrawing *ortho* director (see p. 43). This group has served to metalate variously substituted benzene rings, (30, 33, 45) naphthalenes, (185) thiophenes, (134) isoxazoles, (186) and vinyl sulfides (23) (Eq. 19). Although the nitrogen substituents may be varied, the dimethylamino function has received the broadest attention. Nevertheless, other cases have been studied, e.g., benzylmorpholine. (187)

$$(19)$$

Even the metalation of secondary amines is feasible, proceeding to give good yields of products. The use of *n*-butyllithium/TMEDA, however, is essential to attain appreciable amounts of the required dilithio species **77a,b**. (188) In N-benzylaniline the superiority of the $CH_2NR_1R_2$ group over the anilino function with respect to their *ortho*-directing abilities (see p. 45) is documented by the isolation of the alcohol **78a**. (188) The benzylic position may be fully substituted without affecting the degree of *ortho* lithiation, (33) or it may even be joined with the nitrogen atom to form a ring, as in **79**. (24) The excellent yield of **80** formed after reaction of the lithiated species with methyl iodide clearly indicates the broad applicability of this reaction.

The presence of an *ortho*-methyl group, as in o-methyl-N,N-dimethylbenzylamine, leads exclusively to removal of the sp^3-bound hydrogen, as discussed earlier (p. 16). (67) The strength of the benzylamino group relative to other *ortho*-directing functions is illustrated by the observation that p-methoxy-N,N-dimethylbenzylamine is metalated exclusively *ortho* to the nitrogen functionality under kinetic lithiation conditions to give the alcohol **81** after quenching with benzophenone. (19, 45, 180) An interesting reversal of this result can be achieved by lithiating with the monomeric *n*-butyllithium/TMEDA complex. In this case the major (thermodynamic) product **82** is derived from lithiation *ortho* to the methoxyl group, with only a minor amount (7%) of **81** being formed. (19) By analogy with the anisidines, *m*-methoxy-N,N-dimethylbenzylamine is lithiated exclusively in the position *ortho* to both directing groups. (19, 45, 189) Further insight into the chelating ability of nitrogen and oxygen with organolithium compounds is provided by o-methoxy-N,N-dimethylbenzylamine. The predominant lithiation *ortho* to the methoxyl group (58% yield of **84**) is postulated to occur because the substrate serves as a bidentate ligand to convert, as does TMEDA, the

tetrameric *n*-butyllithium (in ether) into the monomeric species **83**. This in turn would then serve as the actual lithiating agent and thus, like the *n*-butyllithium/TMEDA complex, preferentially lead to metalation at the most acidic position, that is, *ortho* to the methoxyl group. (19) Alternatively, of course, it could be postulated that the nitrogen lone pair in **83** is no longer available for coordination.

Benzylamines with halogen substituents (F, Cl, CF$_3$) in an *ortho* or *para* position are lithiated *ortho* to the nitrogen director to give, *e.g.*, the metalated species **85** and **86**. (23, 24) For the *meta*-trifluoromethyl derivative **87** lithiation occurs as expected in the position *ortho* to both substituents (**87**). (45) *meta*-Fluoro and *meta*-chloro derivatives lead to benzyne formation, and are therefore not suitable as substrates under the conditions reported. (45) However, at lower temperatures successful lithiations may be anticipated.

The facile alpha deprotonation of the thiophene nucleus precludes a successful competition of the dimethylaminomethyl group. However, by blocking the 5 position, as in **88**, lithiation proceeds normally beta to the

85 **86** **87**

1. n-BuLi
2. $(C_6H_5)_2CO$

88 **89** (65%)

nitrogen function, *i.e.*, in the 3 position, to give the carbinol **89** in good yield. (43, 134)

In the 1-substituted naphthalene **90** lithiation occurs with surprising selectivity in the 8 position (185, 190) to give the alcohol **91** with only a minor amount of the 2-substituted isomer. (191) This finding parallels the results with 1-alkoxynaphthalenes (192) (p. 63) and 1-anilinonaphthalenes 181 (p. 46). In the 2-substituted naphthalene **92** metalation occurs both in the 1 and 3 positions, as reflected by the isolation of approximately equal amounts of products **93** and **94**. (185, 191)

1. n-BuLi
2. $(C_6H_5)_2CO$

$R = C(C_6H_5)_2OH$

90 **91** (73%)

1. n-BuLi
2. $(C_6H_5)_2CO$

92 **93** (34%)

+

94 (45%)

3.4.2.4. Arylethylamines

The phenethylamine **95a** can be lithiated in minimal yield in the *ortho* position, (193, 194) although there are conflicting reports. (195) The predominant pathway is benzylic deprotonation followed by beta elimination. By blocking the benzylic position, as in **95b**, *ortho* metalation can be achieved in poor yield. (195) A more interesting and potentially rather useful way to circumvent the elimination problem is illustrated by the lithiation of the phenethanolamine **96**, in which the alkoxide prevents benzylic deprotonation. Thus *ortho*-substituted derivatives such as the silane **97**, can be isolated in moderate to good yields. (175)

Moving the basic nitrogen still further from the aromatic nucleus as in N,N-dimethyl-3-phenylpropylamine prevents *ortho* metalation, and benzylic deprotonation becomes the exclusive pathway of the reaction. (19, 195) This is not unexpected in view of the fact that the lithium at the benzylic position can form the favored five-membered ring through chelation with the basic nitrogen.

3.4.2.5. α -Alkoxidobenzylamines

α -Alkoxidobenzylamines of type **98**, obtained by the addition of an

organolithium reagent to a tertiary amide, can be successfully used as *ortho*-directing groups. The sequence, as outlined in Eq. 20, permits a one-pot transformation of an organolithium reagent and a tertiary carboxamide into an *ortho*-substituted aryl ketone **100**. The basic nitrogen in the tetrahedral intermediate **98** is assumed to be responsible for directing the subsequent lithiation into the *ortho* position to produce the dilithiated species **99**. The process is another example of *ortho* metalation of an α -*gem*-disubstituted

benzylamine. The versatility of the reaction is indicated by the transformation of p-chloro-N,N-dimethylbenzamide into 4-chloro-2-methylacetophenone and to the benzophenone **101**. (196) The latter example is quite interesting in that there are two possible sites for *ortho* metalation, namely, in the chlorinated and in the unsubstituted phenyl rings. The known rate-enhancing effect of the *para*-chloro substituent (p. 14) provides good regioselectivity, and no detectable lithiation is observed in the unsubstituted ring. (196)

(20)

Lithiation of the selenophene intermediate **102** exemplifies the superiority of an α-alkoxidoamine over a t-butoxy group (under kinetic conditions) in terms of their beta-directing ability, as illustrated by the formation of 4-t-butoxyselenophene-2,3-dicarboxaldehyde. (148)

3.4.2.6. Arylcarboxamides and Thioamides

Deprotonated secondary carboxamides unlike their carboxylate analogs, (197) are essentially inert toward nucleophilic attack by organolithium reagents. (54) In addition, they possess not only electron-withdrawing, but also chelating characteristics. The combination of these properties has led to the development of the selective *ortho* functionalization of arylcarboxamides by lithiation (Eq. 21).

$$\underset{\text{CONHR}}{\text{(ring)}} \xrightarrow{\text{R'Li}} \underset{}{\text{(ring)}} \xrightarrow{\text{R'Li}} \underset{}{\text{(ring)}} \tag{21}$$

Primary benzamides fail to undergo *ortho* lithiation even with an excess of *n*-butyllithium. (54) Certain tertiary amides, however, can successfully be metalated, particularly if the metalation is facilitated by additional factors, such as the influence of an alpha activator, as in N,N-diethyl-3-thiophenecarboxamide (134) or β -aminoacrylamides, (57a) or by the careful selection of conditions. (55, 56) For instance, N,N-diethylbenzamide can be lithiated with *s*-butyllithium/TMEDA at low temperatures and subsequently treated with various electrophiles. Reaction with methyl iodide, for example, gives a good yield of N,N-diethyl-*o*-toluamide. (56) In general, however, tertiary benzamides suffer nucleophilic attack by the lithiating agent (54, 196) (see p. 53) for the practical use made of this fact), and it is the secondary arylcarboxamides that are synthetically more useful. The nature of the nitrogen substituent does not appear to influence the outcome of the lithiation to any noticeable extent, and both alkyl or aryl groups are feasible. The use of the *t*-butyl group permits a later transformation into primary amides or nitriles. (24) There are few substituents (see p. 16) that affect this rather general reaction in a negative manner, and the directing potency of the carboxamide group virtually assures regioselective metalation in its *ortho* position. The reactions generally proceed in good yield, as illustrated by the lithiation of N-methylbenzamide and the isolation of the carbinol **103**. (54, 198)

$CON(C_2H_5)_2$ → [1. s-BuLi/TMEDA/−78° 2. CH$_3$I] → ortho-CH$_3$ $CON(C_2H_5)_2$ (75%)

$CONHCH_3$ → [1. 2 n-BuLi 2. (C$_6$H$_5$)$_2$CO] → ortho $CONHCH_3$, $C(C_6H_5)_2OH$

103 (81%)

It should be noted that certain primary products are relatively unstable, particularly those derived from addition of the lithiated amide to aldehydes, ketones, nitriles, and epoxides. The tendency of these adducts to form cyclic products is rather high, and only under carefully controlled conditions can the intermediates be isolated. (199) This may in fact be one of the reasons for the relatively modest yields often cited for isolation of primary products. Alternatively, if the resulting heterocycles are desired, the method is well suited for obtaining bicyclic products, such as phthalides **104**, (200) phthalimidines **105**, (24) **106**, (201) or isocoumarins **107**. (202) The first **(104)** and last examples **(107)** also illustrate the superiority of the carboxamide function over a fluorine and a methoxyl group as an *ortho* director. Numerous additional studies have confirmed this fact. (19)

104 (45%)

105 (86%)

106 (62%)

107 (35%)

For N-alkyl-*o*-toluamides the exclusive pathway of the lithiation reaction is again deprotonation of the relatively acidic *ortho*-methyl group (64) (see p. 16).

Secondary thiobenzamides can also be utilized for regioselective *ortho* metalation. (65) The formation of the thioether **108** illustrates this reaction. Although the tendency of primary adducts of this type to form cyclic products is apparently no less than that of the carboxamides, the thioamide function may nevertheless prove useful for further synthetic elaboration via sulfur alkylation and extrusion. (65)

108 (91%)

3.4.2.7. 2-Aryloxazolines and 2-Aryloxazines

The azomethine linkage has long been recognized as an excellent ligand. (203) This property, combined with a strong electron-withdrawing effect, makes this functionality one of the most powerful beta directors known to date. 4,4-Dimethyl-2-oxazolines and 1,3-oxazines constitute synthetically useful directing groups that contain this common structural element. The *ortho* lithiation of 2-aryloxazolines proceeds readily even at low temperatures. The *ortho*-metalated intermediates react with numerous electrophiles. (46, 204-206) For example, the method can be used to prepare 2,6-dideuterated benzoic acids. (204) For the *para*-methoxyl derivative **109** lithiation occurs, not unexpectedly, regioselectively in the position *ortho* to the oxazoline ring, as the aldehyde **110** is the only product isolated. (46) In fact, the directing capacity of the oxazoline group is so high that it can compete successfully

with the alpha metalation of the thiophene nucleus, one of the more readily lithiated substrates known. (139) Moreover, despite the susceptibility of the pyridine nucleus to attack by nucleophilic metalating agents, the oxazoline derived from pyridine-4-carboxylic acid can successfully be lithiated in the 3 position. (207)

Thus far the following limitations of this reaction have been observed: *ortho*-methoxyl 208a,b (**111a**) and *ortho*-fluoro derivatives (208c) (**111b**) suffer clean nucleophilic displacement of the methoxyl or fluoro groups in preference to *ortho* metalation, whereas *ortho*-tolyl derivatives undergo the familiar deprotonation at the methyl group, (46) quite analogous to the *o*-toluamides (p. 16). (64) It should be noted that in certain cases nucleophilic substitution can be suppressed in favor of *ortho* lithiation by the use of *n*-butyllithium/TMEDA. (23) Interestingly, treatment of 2,2′-*m*-phenylenebis(4, 4-dimethyloxazoline) with alkyl or aryl lithium reagents leads to addition of the metalating agent to the aromatic ring. (208d) Normal *ortho* lithiation at the 2 position, however, can be effected with lithium diisopropylamide/TMEDA.

111 a: Y = OCH₃
b: Y = F

3.4.2.8. Arylcarbimines

The synthetic utility of carbimines as *ortho*-directing groups is limited by the propensity of the azomethine linkage in such substrates to suffer attack by a nucleophilic lithiating agent or to facilitate alpha deprotonation. (209, 210) Nevertheless, in systems where neither of these two side reactions can or does occur, the C=N group again proves to be a very powerful *ortho*-directing functionality.

Imines of alkyl aryl ketones clearly undergo deprotonation of the rather acidic alpha position. Nevertheless, *ortho* metalation can also be observed, (211) although it is of little synthetic value. For aryl carboxaldimines, which lack acidic alpha protons, nucleophilic attack is the generally observed reaction, even with N-*t*-butylimines. (24) In special cases, such as in the cyclohexylimine **112**, where *ortho* metalation is facilitated by the

112

113 (60%)

additional directing effect of an ether function, good yields of *ortho*-substituted products such as **113** are observed. (212)

3.4.2.9. 2-Arylpyridines

Although pyridines generally are susceptible to nucleophilic attack by the metalating agent on the azomethine linkage, some can serve as powerful *ortho*-directing groups. Metalation of the arylpyridine **114** followed by

deuteration indicates that the kinetic product **115** arises from an *ortho* lithiation and slowly equilibrates to the thermodynamic product **116**. (213, 214) When viewed in the light of the rather facile lateral deprotonation of picolines, (215) the successful *ortho* lithiation of **114** clearly underscores the marked directing ability of the pyridine nucleus. In 2-(2-thienyl)quinoline the *ortho*-directing ability of the quinoline nitrogen leads to predominant metalation in the 3 position of

the thiophene nucleus and only a small amount of alpha metalation, as reflected by the isolation of the silanes **117** and **118**. (138) The significance of this result becomes apparent in the discussion of the competitive *ortho vs.* alpha lithiations (p. 77).

3.4.2.10. Hydrazones
Although the N,N-dialkylhydrazones of alkyl aryl ketones suffer from the same alpha deprotonation as imines, a good degree of *ortho* metalation is nevertheless observed. (23) Thus metalation of the hydrazone **119** followed by reaction with dimethyl disulfide produces the bisthioether **120** in good yield. (23) N,N-Dimethylhydrazones of diaryl ketones, on the other hand, appear to be promising substrates for *ortho* metalations, as indicated by the formation of the thioether **121**. (23)

3.4.2.11. 3-Arylpyrazoles

1-Alkyl-3-arylpyrazoles incorporate the same functional array of nitrogen atoms as hydrazones. Unlike the diaryl hydrazones, however, such pyrazoles offer two additional sites of deprotonation, both of which are attacked, (23) namely, the 5 position of the pyrazole nucleus and the N-alkyl substituent (see p. 24). (86) Both side reactions can be suppressed by a bulky tertiary nitrogen substituent, such as the methoxyisopropyl protecting group in the pyrazole **122**. Metalation now proceeds predominantly at the *ortho* position. After removal of the protecting group the ketone **123** can be isolated in fair yield. (23)

3.4.2.12. 2-Arylimidazolines

2-Arylimidazolines are metalated in their *ortho* position in a manner reminiscent of the 2-aryloxazolines. Thus lithiation of 2-phenylimidazoline

followed by reaction with *p*-chlorobenzaldehyde produces the alcohol **124**. (216)

124

3.4.2.13. Nitriles

The use of a nitrile as an *ortho* director is limited because of its highly electrophilic character. One report describes the low temperature alpha metalation of 3-cyanothiophene, which evidently is kinetically favored over nucleophilic addition. (217) The predominant formation of 3-cyano-2-thiophenecarboxylic acid attests to the directing influence of the cyano group. An interesting example is *m*-chlorobenzonitrile. The basicity of the non-nucleophilic lithium tetramethylpiperidide is apparently sufficient to metalate the position *ortho* to both substituents. The stability of the lithiated species at low temperatures permits reaction with electrophiles. For example, the thioether **125** can be isolated in moderate yield. (24)

125 (32%)

126 (37%)

For α , β -unsaturated nitriles beta metalation can be achieved under carefully selected conditions, as shown by the deuteration of the dihydropyridine **126**. (218) The analogous lithiation of β -aminoacrylonitriles is more complex (see p. 19). (57c)

3.4.3. Oxygen as a Beta (Ortho)-Directing Atom

3.4.3.1. Alkyl Vinyl Ethers

Lithiations in the beta position of vinyl ethers, unassisted by additional directing groups, have not been reported. However, when the anion is further activated by the presence of an adjacent chlorine, such as in (E)-2-chlorovinyl ethyl ether, metalation occurs at low temperatures, as indicated by the quantitative conversion to the acid **127**. (174a) Conversely, when the same conditions are applied to (Z)-2-chlorovinyl ethyl ether, the corresponding acid is produced in only 40% yield. (174a) This may be a result of both the absence of a chelating effect by the ether oxygen and the fact that the lithiated species can undergo a *trans* beta elimination. Similar observations were made with the corresponding (E/Z)-2-bromovinyl ethyl ethers. (174b)

3.4.3.2. Alkyl Aryl Ethers

Alkyl aryl ethers are by far the most widely studied group of compounds, not only in terms of the scope of the metalation, but also with respect to the mechanism of the reaction. A recent study gives a systematic account of the relative *ortho*-directing ability of the methoxyl group in relation to other functionalities. (19)

Most lithiations of alkyl aryl ethers are carried out in diethyl ether as solvent, largely because the original reports call for it. (1) More recently, however, it was realized that, as with diaryl ethers, the use of tetrahydrofuran accelerates the metalation considerably and greatly improves the yields of products. Of the numerous examples studied in carbocyclic aromatic systems, a few deserve special attention. 1,3-Dimethoxybenzene illustrates a characteristic common to most other directing groups, namely, the highly selective lithiation in the position *ortho* to both methoxyl groups. The extent of metalation in that position is 96–97%. (36, 50) As illustrated, reaction with 1,6-dibromohexane gives an excellent yield of the diarylhexane **128**. (219) Interesting aspects of the metalation of the bromoether **129** are its regioselectivity and, quite obviously, the absence of any appreciable metal–halogen exchange (220, 221) (p. 17). The use of phenyllithium, rather than *n*-butyllithium, in the preparation of **130** should be noted. Another example of regioselectivity is the lithiation of chlorotrimethoxybenzene (**131**), which is extremely facile, being complete within 3 minutes at –70°. The major product **132** is derived from metalation

between the methoxyl group and the chlorine, with formation of only a minor amount of the isomer **133**. (222, 223) Although

128 (93%)

129   **130** (33%)

131   **132** (79%)   **133** (16%)

134 (94%)

chlorine is known to be a less effective *ortho* director for coordinatively unsaturated metalating agents than the methoxyl group, the apparent inconsistency can be accounted for by the greater *acidifying* effect of the chlorine, (31, 32) since for each lithiatable position the necessity for coordination of the metalating agent is satisfied by either *single* methoxyl group. Metalation of 1,2,3-trimethoxybenzene in tetrahydrofuran proceeds rapidly to produce the deuterated product **134** in excellent yield. (224)

The side reaction common to most *ortho* lithiations, namely, the deprotonation of an *ortho*-methyl group, is also apparent in *o*-methylanisole, albeit to a lesser extent (1, 61) (see p. 16). Cyclic alkyl aryl ethers such as **135** can be metalated as expected in the position *ortho* to the oxygen function to give upon carbonation the acid **136** in respectable yield. (225)

135 → **136** (73%)

The controversy concerning the lithiation of 1-methoxynaphthalene was apparently caused not only by divergent interpretations but also by differing reaction conditions. (226, 227) The conditions indeed play an important role, particularly with respect to the lithiating agent and its origin. A thorough investigation of the various factors affecting the ratio of isomeric products indicates that under carefully controlled conditions either one of the isomers **137** and **138** can be obtained essentially as the exclusive product. (192) These results imply that metalation in the 2 position, which is achieved exclusively with *n*-butyllithium/TMEDA, is strictly an acid–base reaction (see p. 10), whereas in hydrocarbon solvents the precoordination of the lithiating agents leads to the more favorable five-membered cyclometalated intermediate. The regioselective metalation in the 8 position can formally be compared to the recently reported

R = *n*-Bu/ether, hexane	73 : 27	(28% total)
n-Bu/hexane, TMEDA	>99.3:<0.3	(60% total)
t-Bu/cyclohexane	1 : 99	(35% total)

ortho lithiation of α-silyloxystyrenes in which, in fact, an enol ether serves as the directing group. (228) Here again, the ring size of the cyclometalated intermediate is five rather than four as for anisoles. The analogous observation is made in the case of 1-anilinonaphthalenes (p. 46). The metalation of 2-methoxynaphthalenes also depends on the conditions. In tetrahydrofuran the 3-lithiated species is formed almost exclusively, as indicated by the isolation of the imine **139**, whereas other conditions lead to a mixture of 1- and 3-substituted products with the latter predominating. (17, 229, 230)

139 (90%)

In five-membered, π-excessive heterocycles the alkoxy group can provide regioselectivity for alpha metalations as outlined earlier (p. 37). In the absence of any free alpha protons, as in 2-methoxy-5-methylthiophene, the beta-directing effect of the ether function leads to metalation in the 3 position to give the carboxylic acid **140**. (231) In the isoxazole **141** metalation facilitated by the methoxyl group occurs in the only available position, and the iodo derivative **142** is obtained in high yield. (232)

140 (50%)

141   **142** (88%)

3.4.3.3. Alkoxyalkyl Aryl Ethers

Free phenols can be metalated in their *ortho* position, (1, 233) but the yields of products are too low to be of preparative interest. Considerably more valuable is the metalation of protected phenols such as methoxymethyl or tetrahydropyranyl ethers. The yields in the metalation of these derivatives are generally good to excellent, as illustrated by the preparation of the aldehyde **143** (234) using the methoxymethyl protecting group, and the alcohol **144**, (235) where the tetrahydropyranyl ether is utilized.

143 (85%)

144 (70%)

3.4.3.4. Diaryl Ethers and Condensed Diaryl Ethers

The ability of *n*-butyllithium to deprotonate the *ortho* position of dibenzofuran in particular and diaryl ethers in general was recognized as early as 1934. ([1])
This observation constitutes the discovery of the heteroatom-facilitated metalations discussed in this chapter. Competitive experiments show that the ethers have a greater *ortho*-directing effect than either sulfides or amines. ([1])
This differential directing ability is best documented by the lithiation of phenoxathiine, in which monometalation occurs exclusively adjacent to oxygen.
Even dimetalation, using excess *n*-butyllithium, takes place predominantly in the two positions *ortho* to oxygen and only to a smaller extent at position 1.
([236], [237]) Likewise, N-ethylphenoxazine is metalated adjacent to oxygen exclusively to give the acid **145** (p. 66). ([238])

The lithiation of diaryl ethers is used extensively to prepare not only specifically *ortho*-substituted derivatives, but also condensed tricyclic systems.
Dimetalation of diphenyl ether, for example, followed by reaction with a dichlorosilane gives reasonable yields of phenoxasilins ([239-242]) such as **146** or, with tetrachlorosilane, the spirosilane **147**. ([239])

In asymmetrically substituted diaryl ethers the rate-increasing or -decreasing influence of substituents can be used to provide regioselective

ortho lithiation. Thus *p*-chlorophenyl phenyl ether is lithiated in the substituted ring to give the silane **148**. (243)

3.4.3.5. Alkyl Aralkyl Ethers and Aralkyl Alcohols

Ortho lithiation of alkyl benzyl ethers is generally not feasible because of their well-known propensity to undergo benzylic deprotonation, followed by Wittig rearrangement. (244a) Nevertheless, alkoxymethyl groups possess a proven beta-directing effect and are extensively used to provide regioselectivity in the alpha metalation of π-excessive, five-membered heterocycles. The most commonly encountered functionalities are the methoxymethyl group and the

acetals and ketals of carbonyl compounds. Thus 3-(methoxymethyl)thiophene is metalated exclusively in the 2 position to give a high yield of the acid **149**. (142) This is in distinct contrast to the random metalation of 3-methylthiophene (p. 38). Furan-3-carboxaldehyde ethylene ketal is not only metalated more rapidly than furan itself but also regioselectively in the 2 position, as illustrated by the isolation of the ketone **150**. (113) For 1-(methoxymethyl)indole the methoxymethyl group provides a more rapid and clean lithiation in the 2 position than is observed for 1-alkylindoles (85) (p. 23).

149 (89%)

150 (61%)

In carbocyclic aromatic systems, where benzylic ethers can generally not serve as *ortho*-directing groups, benzylic alcohols may be used instead. The hydroxyalkyl group is by itself a poor *ortho* director, as evinced by the low-yielding metalation of benzyl alcohol. (1) Under forcing conditions, however, lithiation can be effected remarkably well. (244b) In addition, it can be successfully utilized to provide a desired regioselectivity in more complex aromatic templates with additional *ortho*-directing functionalities. In the octahydrophenanthrene system **151**, for example, lithiation proceeds with a high degree of regioselectivity in the position *ortho* to both the methoxyl and hydroxyalkyl groups to produce, after carboxylation, the tetracyclic lactone **152**. (245)

151

152 (80%)

3.4.3.6. Arylcarboxylic Acids, Esters, and Diaryl Ketones

In contrast to arylcarboxamides, the direct *ortho* lithiation of arylcarboxylic acids is generally not feasible because of the increased electrophilicity of the carboxylate group. Thus treatment of lithium benzoate with an additional equivalent of an organolithium reagent leads to addition rather than metalation, providing useful ketone syntheses. (197) However, lithiations in the position *ortho* to the carbonyl groups of acids and ketones are reported in a few special cases. For example, the use of the non-nucleophilic lithium dialkylamides is successful with thiophene-3-carboxylic acid. (246) Alternatively, metalation can be achieved even with alkyllithium reagents if, because of additional activation, the rate of deprotonation is faster than the rate of addition of the lithiating agent to the carboxylate carbonyl group. For example, the bromo compound **153** is prepared in good yield from 3-methylisothiazole-4-carboxylic acid. (154) Similar reactions, albeit of little synthetic value because of self-condensations, are reported for arylcarboxylic esters and diaryl ketones. (53) For example, the phthalan **154** can be obtained in high yield. (53)

3.4.4. Sulphur as a Beta (Ortho)-Directing Atom

3.4.4.1. Alkyl Aryl Sulfides

The ability of a thioether to facilitate *ortho* lithiation is intermediate between that of ethers and anilines. The lithiation of thioanisole is, in contrast to that of anisole, more complex because of an equilibration of the kinetic ring metalation product and the thermodynamic sidechain-metalated species (Eq. 22). (1, 58) Hence this *ortho*

(22)

functionalization is of little preparative value. However, the lateral deprotonation, which can be made the exclusive reaction, has received considerable attention. (247) The reason for this competitive reaction must be the additional anion stabilization by the *d* shells of sulfur. (59) Such a stabilizing effect is clearly not available for anisole.

Thioethers, however, do provide high regioselectivity in the alpha metalation of π -excessive, five-membered heterocycles. Evidently, in such substrates deprotonation of the alkylmercapto group is not a problem, possibly because of the greater thermodynamic stability of the alpha-metalated species. 3-(Methylthio)thiophene is lithiated regioselectively in the 2 position to give a good yield of the corresponding acid. (248) For the isoxazole **155** the thioether function allows rapid *ortho* lithiation to produce the carboxylic acid **156** in good yield. (232)

3.4.4.2. Diaryl Sulfides and Condensed Diaryl Sulfides

Diaryl or condensed diaryl sulfides can be metalated without occurrence of the side reaction reported for alkyl aryl sulfides. Dibenzothiophene is lithiated as expected, *ortho* to sulfur. (1, 152) The use of tetrahydrofuran as solvent greatly facilitates this reaction, as indicated by the good yield of 4-bromodibenzothiophene. (152, 249) The reported yields for the lithiation of thianthrene seem rather low, as exemplified by the preparation of the boronic acid **157**. (250) It is conceivable that the use of tetrahydrofuran could be equally beneficial here.

As already discussed, the metalation of N-alkylphenothiazines leads to approximately equal amounts of products derived from lithiation *ortho* to both sulfur and nitrogen, (177) whereas in phenoxathiins the oxygen is clearly the dominant directing group. (236, 237)

The lithiation of diphenyl sulfide is reported to give a moderate yield of products derived from *ortho* metalation. (1, 251) However, a more recent

(77%)

157 (22%)

investigation indicates that the crude metalation products are 9:1 mixtures of *ortho* and *meta* isomers. (252)

3.4.4.3. Sulfones

The potential of the sulfone group as an *ortho* director is limited to diaryl and *t*-alkyl aryl sulfones for reasons outlined earlier (p. 16). An additional limiting factor is the propensity of aryl sulfones, in particular naphthyl sulfones, to undergo conjugate addition of the lithiating agent. (253) Nevertheless, the sulfone is a powerful directing group, and clean *ortho* metalation can be achieved at low temperatures. Thus *t*-butyl 1-naphthyl sulfone is metalated exclusively at the 2 position at −70° to give the acid **158**, whereas conjugate addition occurs at the reflux temperature of ether, leading to the *trans*-substituted dihydronaphthalene **159**. (253) The increased directing effect as compared with the ether function is evinced by the dilithiation of phenoxathiin-10,10-dioxide, which is metalated exclusively at the positions *ortho* to the sulfonyl group to produce the diacid **160**. (236) This is in contrast to phenoxathiin itself, where the ether function is the dominant directing group.

A unique example is the metalation of *m*-bromophenyl phenyl sulfone, which occurs at the position *ortho* to both directing groups, leading to the

158 (47%)   **159** (57%)

160 (52%)

161 (54%)

acid **161**. (69) The example is remarkable insofar as there is neither any appreciable metal–halogen exchange nor any benzyne formation. The *para* isomer is also metalated *ortho* to the sulfone with less than 2% metal–halogen exchange. (69) These results attest not only to the powerful directing influence of the sulfone group but also to the thermodynamic stability of the resulting anion.

3.4.4.4. Arylsulfonamides

Secondary and tertiary sulfonamides are the strongest *ortho*-directing groups known to date, at least in carbocyclic aromatic systems. (2, 19) Unlike the tertiary arylcarboxamides, (56) tertiary arylsulfonamides can be lithiated without any special conditions, *e.g.*, N,N-dimethylbenzenesulfonamide is metalated cleanly in its *ortho* position, and the imine **162** can be isolated in very good yield. (254) For secondary sulfonamides two molar equivalents of an alkyl lithium are necessary to achieve nuclear metalation. The reactions are rapid and the lithiated species may be treated with a variety of substrates to give, quite generally, high yields of products such as the allylic alcohol **163**. (24) 1-Sulfamoylnaphthalenes are metalated in the 8 position predominantly, (255)

162 (79%)

163 (>80%)

whereas the 2 isomers give largely the 1-lithiated intermediates. (255) Because of the low yields of isolated products, the possibility of additional regioisomers, particularly in view of the facts stated about the 1-naphthyl

sulfones (p. 70), (253) cannot be excluded. A recent study on the competitive lithiation of N-*t*-butyl-N-methyl-*p*-benzenesulfonamide and 2-(*p*-chlorophenyl)-4,4-dimethyl-2-oxazoline reveals that the sulfonamide substrate is lithiated almost exclusively. (23)

One side reaction deserving elaboration pertains to an apparently quite general rearrangement observed with lithiated arylsulfonamides of N-substituted anilines (256-259) leading to N-substituted-*o*-(arylsulfonyl)anilines. The mechanism of this rearrangement is now rigorously established. (257) The initial step is the normal *ortho* lithiation, for example, of the sulfonamide **164** to give **165**, which is stable at –70°. Above –20° a rate-determining transmetalation occurs, giving **166** which then rearranges to the sulfone **167**. (256, 257) The intramolecular character of

the transmetalation is documented by the stability of the cyclic derivative **168**. Only upon addition of a second equivalent of *n*-butyllithium is **168** metalated to the dilithio species **169**. This then rearranges to produce, after workup, the tricyclic sulfone **170** in good yield. (257)

The preferential deprotonation of an *ortho*-methyl group rather than nuclear metalation is also observed with arylsulfonamides (p. 16). (66)

3.4.5. Halogens as Beta (Ortho)-Directing Atoms

3.4.5.1. Aryl Fluorides and Vinyl Fluorides

Fluorine is quite an effective *ortho* director largely because of its inductive capacity rather than any coordinating effect. Of all the halogens fluorine exerts the strongest acidifying effect on *ortho* positions. (31, 32) Pentafluorobenzene, for instance, exhibits a pK_a of 23 *vs.* 30.5 for pentachlorobenzene and 37 for benzene itself. (12) Although the products derived from metalation of such substrates, namely, 2-lithiofluorobenzenes, can undergo elimination to form benzynes, they may nevertheless be prepared efficiently and in a stable form at temperatures below –50°. Fluorobenzene itself can thus be lithiated in tetrahydrofuran solution, and upon carboxylation *o*-fluorobenzoic acid is obtained in 60% yield. (260) Lithiation of 1-fluoronaphthalene leads after carboxylation to 1-fluoro-2-naphthoic acid, (260) whereas the 2 isomer gives approximately equal amounts of 2-fluoro-1-naphthoic acid and 3-fluoro-2-naphthoic acid. (261) The ease of metalation, as well as the stability of the metalated species, is somewhat greater with polyfluorinated benzenes. (6) 1,2,3,4-Tetrafluorobenzene, for example, is lithiated readily even at –70°. Upon reaction with mercuric chloride the diarylmercury derivative **171** is isolated in high yield. (262) In terms of relative directing abilities toward coordinatively unsaturated metalating agents, fluorine ranks below the methoxyl group, since *p*-fluoroanisole is lithiated exclusively *ortho* to the ether function. (19) Fluorine also serves as a beta director for the metalation of cyclic olefins. The nonafluorocyclohexene **172**, for instance, is lithiated readily to produce after carboxylation the corresponding acid in very good yield. (263)

(60%)

171 (90%)

172   (77%)

3.4.5.2. Aryl Chlorides and Vinyl Chlorides

The metalation of chlorinated aromatics is complicated not only by their propensity for benzyne formation but also by the possibility of halogen–metal exchange. (6, 100) Although the *ortho* metalation of chlorobenzene is not practical because of the rapid formation of benzyne, in polychlorinated aromatics the inductive effect of neighboring halogen atoms is sufficient to provide some stability to the lithiated species. Metal–halogen exchange can often be suppressed and even eliminated by using appropriate metalating agents. A good example is the lithiation of 1,2,3,4-tetrachlorobenzene, where either the product of *ortho* lithiation (**173**) or chlorine–lithium exchange (**174**) can be obtained almost exclusively. (264)

	173	**174**
R = *t*-C₄H₉	(0%)	(100%)
R = CH₃	(93%)	(7%)

Metal–halogen exchange is apparently not a problem in the lithiation of 2,3,6-trichloropyridine, which metalates quite selectively to give the 4-picolyl derivative **175**. (265) In the lithiation of 3-chloro-4,5-dihydrofuran the beta-directing influence of the chlorine facilitates the alpha metalation of the dihydrofuran system. The methylated product **176** can be obtained in respectable yield. (266)

175 (45%)

176 (74%)

3.4.5.3. Aryl Bromides

Whereas metal–halogen exchange is only a minor side reaction with chlorinated aromatics, it becomes with relatively few exceptions almost the exclusive pathway in the attempted *ortho* lithiation of bromobenzenes with alkyllithiums. Nevertheless, bromine, like other halogen atoms, does have a pronounced *ortho*-directing capacity, as evinced by the rapid formation of *ortho*-lithiated intermediates when lithium dialkylamides are used. However, except for isolated instances in which special stabilizing effects are operative, these intermediates are of no preparative value for electrophilic reactions, because rapid aryne formation occurs. (32) The exchange and elimination problems are generally only minor in substrates bearing a powerful *ortho*- or alpha-directing group. In the metalation of 3-bromothiophene the inductive effect of bromine provides excellent regioselectivity, in that 3-bromo-2-thiophenecarboxylic acid is almost the exclusive product. (48) Another example of this type is the lithiation of 3-bromophenyl phenyl sulfone, which occurs regioselectively between both groups (p. 71). (69)

(72%)

3.4.5.4. Aryl Iodides

Lithiation at the position *ortho* to an iodo substituent in preference to metal–halogen exchange is only observed in readily metalated sulfur-containing heterocycles. By analogy with the bromo analog cited earlier, 3-iodothiophene can be metalated to produce after carboxylation 3-iodo-2-thiophenecarboxylic acid as the major product. (68) Likewise, 4-iodo-3-methylisothiazole is converted into the corresponding 5-carboxaldehyde **177** in respectable yield. (154)

177 (68%)

3.4.5.5. (Trifluoromethyl)benzenes

The trifluoromethyl group, generally considered a pseudo-halogen, exerts a moderate *ortho*-acidifying effect. It appears to be a considerably weaker director than the methoxyl group for coordinatively unsaturated metalating agents, since *p*-(trifluoromethyl)anisole is lithiated exclusively in the 2 position

by *n*-butyllithium. (19) Mono- or bis(trifluoromethyl)benzenes are lithiated quite readily, (49, 50) and the corresponding carboxylic acids are produced in good to excellent yield. However, it should be noted that the trifluoromethyl group is an exception in that, unlike most other *ortho*-directing groups, the bis-1,3-disubstituted derivatives, *e.g.*, *m*-bis(trifluoromethyl)benzene, do not metalate preferentially in the 2 position, as indicated by the isolation of the two acids **178** and **179**. (49, 267-269) The reasons for this unusual result are not clear.

3.4.6. Other Beta (Ortho)-Directing Groups
3.4.6.1. Arylphosphine Oxides and Imides
Although triphenylphosphine is reported to undergo an anomalous *meta* metalation, (1) arylphosphine oxides and imides can be lithiated in the expected *ortho* position. Thus, phenylbis(3-thienyl)phosphine oxide is dimetalated regioselectively with *n*-butyllithium in the 2 and 2 positions of the thiophene rings (270) to give, after reaction with ethyl benzoate, the tricyclic alcohol **180**. Metalation of the phosphine imide **181** occurs without halogen–metal exchange in the position *ortho* to phosphorus to give the silane **182**. (271) The ease of metalation can be ascribed to both the ligand effect of the phosphinimidyl group and its inductive effect on the *ortho* position. (271) The use of phenyllithium in such metalations appears rather critical, however. The scope of the phosphine oxide and imide metalations is limited to the triaryl derivatives, since the alkyl group is preferentially deprotonated in alkyl diarylphosphine imides. (271, 272)

180 (68%)

181   **182** (50%)

3.4.6.2. Selenides

As with its sulfur isostere, the *ortho*-directing potential of selenium is confined to diaryl selenides and the alkyl selenides of π-excessive five-membered heterocycles. In the heterocyclic examples the very modest directing ability of the selenide group provides minimal regioselectivity, as illustrated by the ratio of the acids **183** and **184**. (140) The only reported *ortho* metalation of a diarylselenide is that of dibenzoselenophene. After carboxylation an essentially quantitative yield (96%) of the 4-carboxylic acid was obtained. (273)

183   **184**

(6:4) (79% total)

3.5. Competitive Beta *vs.* Alpha Lithiation

The presence of both a beta- and an alpha-directing group within the same molecule provides for some interesting possibilities. Whereas it is accepted that alpha metalations generally proceed with greater facility than beta lithiations, specific cases have been studied in which both reactions can successfully compete. In fact, a judicious choice of conditions can allow either one of the two processes to become dominant. The following examples are illustrative of the general concept.

2-(2'-Thienyl)pyridine offers two potential sites for lithiation: the 3 position (invoking the beta-directing effect of the pyridine nitrogen) and the 5 position (alpha lithiation). By the appropriate combination of solvent, temperature, and metalating agent, either of these two positions can be lithiated predominantly, as documented by the formation of the silanes **187** and **188**. (138) It appears that the beta metalation is kinetically controlled because the species **185** slowly equilibrates to the thermodynamically more stable **186** under the reaction conditions. Evidently, under kinetic conditions *n*-butyllithium (tetrameric in ether (14)) preferentially coordinates with the pyridine nitrogen; abstraction of the nearest proton then leads to **185**. By contrast, in tetrahydrofuran, *n*-butyllithium, (a solvated dimeric species (15)) acts more as a base than as a Lewis acid (see p. 11), thus abstracting the most acidic proton in the alpha position of the thiophene nucleus. The fact that lithium diisopropylamide in ether produces essentially the same result is consistent with this rationale, as it displays, unlike tetrameric *n*-butyllithium, only negligible Lewis-acid character.

RLi	Solvent	Temperature (°C)	187	188
			Yields (%)	
n-BuLi	THF	0	4	93
LDA	ether	0	1	74
n-BuLi	ether	0	62	13

A similar observation is made in the lithiation of the oxazoline **189**. The major product in tetrahydrofuran is derived from alpha lithiation **(191)**, whereas the use of ether leads almost exclusively to beta lithiation and subsequently to the alcohol **190**. (139) This result is the basis for the generalization pointed out earlier (p. 36) that in the thiophene system oxazolines are the strongest beta-directing groups known.

Another example is 1-*t*-butyl-3-(*p*-chlorophenyl)pyrazole. Again, two different metalation sites are possible, but this time in two separate rings of the molecule. The first and evidently more reactive site is the 5 position of the pyrazole ring; the alternative site is the *ortho* position of the phenyl ring, for which the imine group of the pyrazole ring acts as the

Solvent	190	191
	Yields (%)	
THF	36	55
ether	91	4

ortho director. Here, the choice of appropriate conditions permits making either reaction dominant: in tetrahydrofuran the products are almost exclusively derived from the alpha-lithiated species **192**, whereas in ether the product arising from the *ortho*-lithio derivative **193** dominates. (23)

It is certainly no coincidence that in all these examples the azomethine linkage is the director that can successfully compete with the generally facile alpha lithiation process. As alluded to in the thiophene section (p. 36), this appears to be the only group capable of inducing beta lithiation in the presence of an alpha activator. The unique character of the azomethine linkage is apparently the combination of an appreciable electron-withdrawing effect with the pronounced coordinative capacity of the nonbonding orbital of the imine nitrogen.

One additional interesting facet of the competing alpha *vs.* beta lithiation is the relative reactivity of these carbon-lithium bonds toward electrophiles. Subtle differences can be turned into synthetic advantages, particularly in reactions with only moderately active electrophilic substrates. One such example is illustrated by the doubly protected arylpyrazole **194**, which is metalated both in its alpha and its *ortho* position. Because of the lesser reactivity of the lithiated pyrazole compared to the lithiated phenyl ring, a selective reaction with a tertiary amide is possible. The reactivity of the lithiated pyrazole in the dilithio species **195** is diminished, not only for electronic reasons, but additionally because of the combined chelating effect provided by the three ether oxygens. Accordingly, the product **196** of this reaction is the one derived from *ortho* lithiation. (23) It should be noted that more reactive substrates, such as deuterium oxide or dimethyl disulfide, do indeed lead to products arising from reaction at both sites. (23)

3.6. The Substrate

The number of substrates that react with alpha- or beta-lithiated species is legion. The highly nucleophilic character of such organometallics provides for a reactivity and versatility approaching that of normal alkyl- and aryllithium (6) or Grignard reagents. Thus, any electrophilic center in a given substrate apt to react with a Grignard reagent is very likely to react with an alpha- or beta-lithiated species. A rather detailed discussion of the behavior of a broad spectrum of electrophilic substrates toward organolithium compounds in general has been presented. (6) The following survey is organized according to the nature of the bonds formed.

3.6.1.1. C-D/T *Bonds*

Deuteration (or tritiation) with D_2O (T_2O) or ROD proceeds readily and can be used as a diagnostic tool for the extent and site of lithiation, (23, 24) except for metalations with lithium dialkylamides, where D incorporation may be lower.[*]

3.6.1.2. C- C *Bonds*

Formation of this particular bond is by far the most common, and a wide variety of substrates containing electrophilic functionalities of various oxidation states centered at carbon participate in this reaction. These include alkyl halides or sulfates, epoxides, aldehydes, ketones, carboxylate salts, carboxylic acid halides, anhydrides, esters, amides, nitriles, isocyanates, isothiocyanates, alicyclic and heterocyclic imines, as well as Michael acceptors, *e.g.*, the enol ethers of 1,3-diketones and β -amino nitroethylenes.

Alkylation of lithiated species proceeds best with *primary halides* or *sulfates*, in particular with methyl iodide (46, 95) or dimethyl sulfate. (274) Yields with secondary halides are often lower because of their decreased reactivity and/or tendency for elimination. Alkylations with *allylic* or *benzylic halides* are generally more successful with the somewhat less basic alpha-lithiated species, (20, 275) since deprotonation of these alkylating agents may occur, *e.g.*, benzyl bromide leading to stilbene. (23, 112) *Epoxides* generally are well suited for the introduction of -CH_2CHROH. (116) Ethylene oxide works especially well in this regard. *Aldehydes* never fail to react with metalated species, and in fact can be used as a label to follow the progress of a lithiation reaction (p. 95). (23, 112) *Ketones* react readily. However, with enolizable ketones the yields are often considerably lower than those of the corresponding reactions with aldehydes. (79) Lower temperatures or a change to a less polar solvent can be advantageous on occasion. (23, 24, 276) Reaction with *carbon dioxide* produces carboxylic acids. This substrate has often been used, particularly in the older literature, to determine the site and the extent of lithiations. (1, 277) In view of the possible further reactions of lithium carboxylates, (197) particularly at room temperature, the yields of acid do not always reflect the degree of lithiation. On the other hand, *lithium carboxylates* can be useful substrates for the preparation of ketones. (177, 197)

Anhydrides and *acid halides* are with few exceptions poor substrates for the preparation of ketones. However, the direct conversion of an organolithium species into an ester is feasible under certain conditions by utilizing alkyl chloroformates. (141) Similarly, the use of dialkylcarbamoyl halides leads to tertiary carboxamides. (24) Generally, the use of *esters* to prepare ketones has the disadvantage of overreaction. (6) Under certain conditions, however, the desired products may be obtained in good yield. (270) The reaction of lithioorganics with *dimethylformamide* (234) or N-methylformanilide (278) is exceedingly clean and useful for the preparation of aldehydes. Reactions with other *tertiary amides*, particularly those with no acidic alpha hydrogens, lead to the corresponding ketones. (113) The electrophilicity of tertiary amides is, however, not always high enough to make this a general reaction. *Isocyanates* are highly reactive substrates that produce carboxamides in high yield. (279) The addition to *isothiocyanates* proceeds equally well. (46) The reaction with *aldimines* gives access to secondary amines. (102) Alpha deprotonation of the substrate, however, does limit the generality of this reaction. (209, 210) The facile addition to the *azomethine* linkage of pyridines, (99) pyrimidines, (280) isoquinolines, (99) quinolines, (83, 281) and quinoxalines (282) gives access to the correspondingly substituted heterocycles. The initial products are oxidized readily to the heteroaromatic systems. *Nitriles*, particularly aromatic nitriles, react well to give the corresponding imines, (254) which in turn can be hydrolyzed to the respective ketones. (283) It should be noted, however, that aliphatic nitriles have a tendency to be deprotonated. (112) The *enol ethers* of 1,3-*diketones* may undergo addition/elimination to provide access to beta-substituted enones. (284) In analogous fashion 2-(*dialkylamino*)*nitroethylenes* react with lithiated species to yield beta-substituted nitroolefins. (285)

3.6.1.3. C-N *Bonds*

The types of substrates capable of forming this bond are currently very limited. The direct introduction of an amino group is best achieved with methoxylamine, (286) although yields are usually only poor to moderate. A similar conversion is feasible with phenyl azide. (287)

3.6.1.4. C- O *Bonds*

Direct oxygenation, although not a general reaction, can be accomplished. (288) The desired conversion, however, is more readily achieved via boronic acids or borate esters as intermediates. (150) The use of alkyl peroxybenzoates permits the direct introduction of alkoxyl groups. (289)

3.6.1.5. C-S *Bonds*

The reaction of an organolithium reagent with a diaryl or dialkyl disulfide is quite clean and gives high yields. In fact, dimethyl disulfide can be used successfully as a label for following the extent of metalations (p. 95). (65, 134, 196) Elemental sulfur can be used to produce lithium thiolates which may

either be alkylated *in situ* (143) or worked up directly to yield the corresponding mercaptans. (275, 290) Sulfinic acids, on the other hand, are accessible by reaction of the lithiated precursors with sulfur dioxide. (112, 163)

3.6.1.6. C - Se *Bonds*
The reaction of lithioorganics with diselenides corresponds to their reaction with disulfides, and the analogous products are obtained. (291) The same products are also accessible by treatment with elemental selenium, followed by *in situ* alkylation. (292)

3.6.1.7. C - *Halogen Bonds*
Synthetic procedures for the preparation of all carbon - halogen bonds are available. For example, the use of perchloryl fluoride with lithioorganic species leads directly to the corresponding fluorinated compounds. (149) N-Chlorosuccinimide may be used to produce chloro derivatives. (204) Similar results are obtained with hexachloroethane. (293) Reaction of these organometallics with bromine, (98, 249) 1,2-dibromoalkanes, (293) or *p*-toluenesulfonyl bromide (134) produces the brominated derivatives. Treatment of lithioorganics with iodine is frequently a remarkably good reaction, often producing the corresponding iodides in high yield. (46, 149, 294) The use of diiodomethane leads to the same iodinated compounds. (293)

3.6.1.8. C- B *Bonds*
Reaction with trialkyl borates produces boronic acids in high yields after acid hydrolysis. (114) These in turn may serve as precursors for phenols (treatment with CuOAc), chlorides (CuCl), bromides (CuBr), or iodides (CuI). (2) Boronic acid amides are accessible directly by treatment of lithioorganic species with bis(dialkylamino)boron halides. (295)

3.6.1.9. C-P *Bonds*
Reaction of lithioorganics with phosphorus trihalides leads directly to trisubstituted phosphines. (296) Use of phosphorus oxychloride, on the other hand, permits formation of the analogous phosphine oxides directly. (296)

3.6.1.10. C- Si *Bonds*
Chlorosilanes are excellent substrates for producing tetrasubstituted silanes. (93, 297, 298)

3.6.1.11. C-*Metal Bonds*
Since the carbon-lithium bond of organolithium reagents is considerably more reactive than the carbon-metal bond of most other metals, unidirectional lithium-metal exchange can be readily achieved. These new organometallic reagents are generally considerably more stable. Moreover, their reactivity is of a softer nature, and therefore they may be utilized for reaction with substrates generally not suited for direct treatment with lithiated species, *e.g.*, acid halides or anhydrides, and allylic or benzylic halides. In the preparation of

the new organometallics the source of the less electropositive metal is almost always the halide, although other ligands can be used as well. The following list encompasses some examples representative of the numerous possibilities for forming new carbon - metal bonds. A more comprehensive account of their formation and reactivity is available. (6)

C -Fe Organoiron derivatives are accessible via $Fe(CO)_5$. (299)

C - Co These derivatives are available through the use of $CoCl_2$. (300)

C - Ni Organonickel compounds can be generated from Ni^{2+}—phosphine complexes. (301)

C - Cu Organocopper derivatives or organolithio cuprates are readily available by treatment of lithiated species with cuprous halides. (105, 190) Their use in organic synthesis has been reviewed. (302) Reaction of organolithium reagents with cupric chloride produces coupled compounds. (144)

C - Pd $PdCl_2$ or its complexes with phosphines or sulfides are generally used to convert (C - Li) into (C - Pd) bonds. (303)

C - Ag The halides of Ag^+ or Ag^{2+}, when reacted with lithiated species, yield either organosilver derivatives (304) or lithioorganoargentates. (305)

C - Sn Organotin compounds are readily prepared from organotin halides of the general formula R_mSnCl_n, where $m + n = 4$, and R = organic residue. (306)

C - Pt Dialkyl sulfide complexes of $PtCl_2$ serve to form carbon–platinum complexes. (303)

C - Au The formation of carbon - gold bonds can be achieved by the use of Au^+ complexes such as $R_3P{\cdot}AuCl$. (307)

C - Hg The reaction between lithiated species and mercuric chloride is very general, leading either to R_2Hg or $RHgCl$, depending on the stoichiometry of the reaction. (262)

3.6.2. Ortho Interactions

The expected primary products from the reaction of an *ortho*-lithiated species with certain substrates are either not isolable or of only limited stability. The products actually obtained are either derived from a subsequent intramolecular nucleophilic attack of the newly introduced fragment on the electrophilic center of the *ortho*-directing group or, conversely, by a nucleophilic attack of the *ortho*-directing group on the electrophilic center of the new *ortho* substituent.

Thus, *ortho*-directing groups fall into one of two categories:

Electrophiles: CONHR, CSNHR, 2-oxazolines, 2-imidazolines, $CR(O^-)NR_1R_2$ (after hydrolysis to a carbonyl group).

Nucleophiles: CONHR, CSNHR, 2-imidazolines, SO_2NHR, CH_2NHR,

CH$_2$OLi.

Among newly introduced *ortho* groups, the following are apt to undergo intramolecular interactions:

  Electrophiles: CHO, CONR$_1$R$_2$, COR, CO$_2$H

  Nucleophiles: CR$_1$R$_2$OH, CH$_2$CR$_1$R$_2$OH, C(R) = NH, CR$_1$R$_2$NHR.

In addition to the examples illustrated on p. 46 (compound **70**) and p. 55 (compounds **104–107**), the following examples are representative of these types of intramolecular interactions:

(Ref. 65)

(Ref. 196)

(Ref. 201)

(Ref. 308)

4. Synthetic Utility

The multifaceted nature of heteroatom-facilitated lithiations, encompassing carbocyclic and heterocyclic aromatic as well as olefinic systems, is suggestive of broad synthetic applicability. Moreover, the high degree of regioselectivity and relative facility of this type of reaction, combined with the high reactivity of the new organolithium species toward a variety of electrophilic substrates, contribute to the attractiveness of heteroatom-facilitated lithiations as a synthetic tool. The purposes of the following discussion are, first, to underscore and pinpoint the distinct advantages of directed lithiations over other methods in the substitution of various aromatic systems; second, to put in perspective the role of lithiations in the development of modern synthetic methodology, in particular, of acyl anion equivalents; and third, to give a general idea of the synthetic potential of selected directing groups.

4.1. Carbocyclic Aromatic Systems

The most generally applicable reaction in synthetic benzenoid chemistry is electrophilic substitution. In monosubstituted benzenes this type of reaction produces either a *mixture* of *ortho* and *para* isomers or *meta* isomers, depending on the inductive and resonance effects of the original substituent. (309, 310) Whereas only certain *ortho* functionalizations can be achieved via Claisen-type rearrangements, (311) heteroatom-facilitated metalation is the only regioselective and direct, hence practical, synthetic procedure for making accessible *almost any ortho*-substituted benzene derivative. This method is capable of producing novel functionalities *ortho* to phenolic ethers, benzylamines, and more importantly, carboxylic acids and their derivatives, ketones, sulfones, and sulfonamides. The latter grouping is significant insofar as electrophilic substitution *ortho* to strongly electron-withdrawing groups is essentially impossible. The available alternatives, *i.e.*, nucleophilic substitution of either the appropriate diazonium salts or strongly activated leaving groups, (312) are limited by the availability of the respective starting materials as well as by the nature of the nucleophiles.

For 1,3-disubstituted benzenes electrophilic reactions generally lead to a variety of products depending on the character of the substituents. In contrast, with few exceptions (p. 15) heteroatom-facilitated lithiations permit the regioselective preparation of 1,2,3-trisubstituted compounds. For example, whereas 1,3-dimethoxybenzene undergoes electrophilic substitution in the 4 position, (313) lithiation occurs exclusively between the ether functions. (314) Alternatively, 1,2,3-trisubstituted benzenes are readily available by lithiating 1,2-disubstituted compounds, metalation occurring *ortho* to the more effective directing group (p. 15). In turn the trisubstituted derivatives can be utilized to prepare 1,2,3,4-tetrasubstituted compounds, *etc.*

For 1,4-disubstituted benzenes, electrophilic substitution may still occur in either of the two *ortho* positions unless the character of the respective substituents is sufficiently different. This is again a situation where *ortho* lithiation provides a viable alternative. For example, *p*-chlorotoluene is acylated under Friedel-Crafts conditions by benzoyl chloride in almost equal amounts at the 2 (56%) and 3 positions (44%), making this a preparatively impractical reaction. (23) In sharp constrast, *p*-chloro-N,N-dimethylbenzylamine is lithiated regiospecifically and almost quantitatively in the 2 position. (23, 24, 45) Electrophilic substitution of *p*-methylanisole occurs preferentially adjacent to the methoxyl group, (315) as does lithiation, (61) providing access to a 2-substituted-4-methylanisole. In contrast, lithiation and subsequent functionalization of *p*-methoxy-N,N-dimethylbenzylamine take place regioselectively *ortho* to the aminoalkyl group, (19) which in turn can be converted to a methyl group, thus leading to a 3-substituted 4-methylanisole.

Lithiation of naphthalene systems is also feasible, the most useful aspect probably being the accessibility of 1,8-disubstituted derivatives, whose availability by other routes requires more elaborate synthetic sequences. (316) Metalation in the *peri* (8) position of 1-substituted naphthalenes is particularly favored with 1-anilinonaphthalene, 181 1-[N,N-(dimethylamino)methyl]naphthalene, (191) and under special conditions, 1-methoxynaphthalene. (192)

It should be noted that certain lithiated species obtained by heteroatom-facilitated metalation can also be prepared either by metal–halogen exchange of the corresponding bromo derivatives (317-319) or by destannylation with *n*-butyllithium. (320-322) Although the direct lithiation is usually simpler, more economical, and far more versatile, there are substrates that are incompatible with alkyllithiums even at –78° (p. 16) or whose *ortho*-lithiated species self-condense at this temperature. In these instances metal–halogen exchange can occasionally be utilized to good advantage because of the extremely low temperatures at which the exchange can be effected, *e.g.*, –100°. (323, 324)

Ortho metalations with metals other than lithium have been studied extensively and used for synthetic purposes. (203, 325-328) However, the economy and high reactivity of lithioorganics as well as their lack of toxicity (compare thallium (326) or mercury (329)), clearly make heteroatom-facilitated lithiations a more generally acceptable and practical method.

4.2. Heterocyclic Aromatic Systems
The uses of alpha lithiation in heteroaromatic chemistry are legion. It would be redundant to reelaborate the metalation of every heterocyclic system, as much

of the utility of this methodology is covered implicitly in the appropriate sections (pp. 17–42). However, a few particularly noteworthy aspects should be emphasized.

For most five-membered heterocycles with one, two, or three heteroatoms, the two-step sequence of lithiation followed by reaction with an electrophile gives access to regioselectively substituted derivatives, many of which differ in the position of the newly introduced functionality from those obtained by direct electrophilic attack on the heterocycle. For example, both pyrazoles (330) and isothiazoles (331) undergo electrophilic substitution on carbon at their respective 4 positions, whereas they are lithiated at position 5 (pp. 23 and 39). In addition, imidazoles, (332) oxazoles, (333) and thiazoles (334) suffer electrophilic attack at either the 5 or a combination of both the 4 and 5 positions, whereas metalation occurs exclusively between the two heteroatoms (pp. 24, 31, and 39). Although few reports exist on the electrophilic substitution of 1,2,3-triazoles, there is evidence that the reaction takes place at the 4 position, (335) whereas lithiation is known to occur at position 5 (p. 26).

Benzimidazoles (332) and benzothiazoles (334) present a different picture in that they undergo electrophilic substitution in the benzenoid portion of the molecule, whereas metalation again occurs between the two heteroatoms (pp. 24 and 39). Another noteworthy example is that of indoles, whose behavior toward electrophiles parallels that of simple enamines. (336) By contrast, lithiation of N-substituted indoles occurs regioselectively at position 2 (p. 22).

4.3. Heterosubstituted Olefins–Acyl Anion Equivalents

The principle of reversing the polarity of synthons has received considerable attention during the past decade. (337, 338) In particular, it was the development of acyl anion equivalents which opened up numerous new possibilities in synthetic organic chemistry. Although metalated dithianes were first introduced to the armamentarium of acyl anion equivalents, (339) the discovery of the alpha lithiation of ethyl vinyl ether (103) considerably broadened the scope of this synthetic tool. Additionally, the facile metalation of other alkyl vinyl ethers, alkyl or aryl vinyl sulfides, and allenic ethers further extended the accessibility of acyl anion equivalents from commercially or readily available materials.

The highly nucleophilic character of these lithiated species permits reactions with a wide variety of electrophiles. Characteristically, like other organolithium reagents these acyl anion equivalents add 1,2 to most α , β -unsaturated systems. Conjugate addition, however, can be achieved via conversion into the corresponding organolithium cuprates, a topic covered in an earlier volume of this series. (302) Although this aspect has not been exploited to any great extent with the alpha- and beta-lithiated species discussed in this chapter, the

possibility nevertheless exists. (105) A representative list of these acyl anion equivalents follows:

Precursors	Lithiated Species	Products	Hydrolysis Products	Synthons	Ref.
OCH₃ (vinyl)	OCH₃ / Li	OCH₃ / R	O=C R	O=C⊖	104
SC₆H₅ (vinyl)	SC₆H₅ / Li	SC₆H₅ / R	O=C R	O=C⊖	121
=•—OCH₃	=•—OCH₃ / Li	=•—OCH₃ / R	allyl ketone R	acryloyl ⊖	108a
HCON(CH₃)₂	LiCON(CH₃)₂	RCO(CH₃)₂	RCO₂H	⊖CON(CH₃)₂ or ⊖CO₂H	78

4.4. Synthetic Potential of *Ortho*-Directing Groups

Of all the *ortho*-directing groups two types stand out as being particularly useful for subsequent elaborations, *i.e.*, dialkylaminoalkyls and carboxylic acid derivatives. The N,N-dialkylaminoalkyl functionality is an exceedingly useful synthetic handle, since it can readily be converted to either a reactive halide or quaternary salt suitable for further transformations. Alternatively, the basic functionality can be hydrogenolyzed to a simple alkyl substituent.

Reagent = H₂/catalyst   X = H
ClCO₂R   Cl
BrCN   Br
CH₃I   N(CH₃)₃⁺ I⁻

Of the carboxylic acid derivatives only the secondary amides, thioamides, and 2-oxazolines are noteworthy for their synthetic potential. Among the secondary amides the N-*t*-butylcarboxamides offer the most versatility for further transformations, as they can be cleaved either to primary amides with anhydrous acid or to nitriles with acidic dehydrating agents, (24) as well as completely hydrolyzed to carboxylic acids. The particular asset characteristic of thioamides is their potential for mild carbon - carbon bond formation via S-alkylation followed by sulfur extrusion. (340) The 2-oxazolines readily lend

themselves to transfunctionalization, as they are convertible not only to aldehydes or ketones (341-343) but also to acids and esters. (317)

X	Y	Reagent	Ref.
2-oxazoline	CHO	$CH_3I/NaBH_4$	342, 343
	COR	$CH_3I/RMgX$	341
	CO_2H, CO_2R	H_3O^+/ROH_2^+	317
$CONHC_4H_9$-t	$CONH_2$	CF_3CO_2H	24
	CN	$POCl_3$	24
CSNHR	RNH	1. $R'COCH_2Br$	340
		2. R_3P	

Other beta-directing groups with some synthetic potential are masked carbonyl functionalities, in particular α -alkoxidoaralkylamines and the acetals and ketals of aldehydes and ketones. Upon hydrolysis they collapse to the respective carbonyl groups that are well suited to further synthetic elaboration. The α -alkoxidoaralkylamines, generated by the addition of an organometallic to the carbonyl group of a tertiary amide, appear to have a reasonably general applicability, as they may serve to functionalize the *ortho* or beta positions of both carbocyclic and heterocyclic aromatic systems (p. 52). In contrast, the directing effect exerted by acetals and ketals is modest, restricting their synthetic utility to substrates in which lithiation is facilitated by the activating effect of an additional heteroatom (situated in a 1,3-relationship with respect to the acetal); the masked 3-acylated five-membered heterocycles (p. 66) are an example.

As alluded to earlier (p. 85), the intramolecular interaction of *ortho* directors or their transformation products with the newly introduced functionality can give access to numerous bicyclic systems. Such interactions are illustrated on p. 37 (compounds **54** and **55**) and pp. 85–86. Another particularly cogent example is the synthesis of 4-phenyl-1H-2,3-benzoxazine from N,N-dimethylbenzylamine in a four-step sequence. (344) This conversion not only demonstrates the elaboration of bicyclic systems, but also underscores the concept of transfunctionalization of the original directing group.

(51%)

5. Experimental Considerations

5.1. The Lithiating Agent
Numerous organolithium reagents are now available from commercial sources, generally as filtered solutions packed in bottles capped with serum stoppers or, for larger quantities, in metal cylinders.[*] If *n*-butyllithium is not available, it can be conveniently prepared from 1-chloro- or 1-bromobutane and lithium metal following detailed published directions. (1, 4, 6) The *n*-butyllithium/TMEDA complex in hexane (225) or ether (19) and lithium diisopropylamide (p. 98) are generally prepared *in situ*. The quality of fresh commercial solutions of *n*-butyllithium in hexane, the most commonly used lithiating agent, is generally good, and the indicated assay is accurate to within a ±5% range. Older preparations, particularly those with considerable sedimentation, or reagents prepared *in situ* should be assayed according to methods reviewed previously. (4, 8, 345, 346) We favor the direct titration with *s*-butyl alcohol employing the charge-transfer complex formed between the alkyllithium and 2,2′-biquinoline. (347) In hydrocarbon solvents most of the commonly used lithiating agents, in particular *n*-butyllithium, can be stored at room temperature under an inert atmosphere (nitrogen or argon) for several months. Storage at lower temperatures is not essential and may even prove to be disadvantageous, since the titers may vary because of crystallization or the possible condensation of moisture.

5.2. The Solvent
The most commonly used solvents for lithiation reactions are diethyl ether, tetrahydrofuran, and hexane. Other ethers, such as dimethoxyethane, (348) and hydrocarbons, such as cyclohexane (17) or benzene, (24) are used occasionally. As with other reactions involving organometallic reagents, all solvents should be dry.

One limitation in the use of ethereal solvents is their reaction with the lithiating agent itself. The rather rapid deprotonation of tetrahydrofuran by *n*-butyllithium leads to butane, ethylene, and the lithium enolate of acetaldehyde. (349-352) Even diethyl ether is slowly decomposed by *n*-butyllithium, (350, 353) the half-life in this solvent being 153 hours at 25°. (354) A compilation of the stability of various lithiating agents in ethereal solvents is available. (4, 6, 8)

5.3. Selection of Experimental Conditions
To determine the appropriate experimental conditions for an unfamiliar substrate, several factors must be considered. These include the number and types (alpha or beta) of potential sites of metalation, compatibility of additional functional groups with the lithiating agent, solubility of the substrate, and solvent dependence of any subsequent reactions.

If there is a single lithiatable site, the choice of conditions, *i.e.*, metalating agent, solvent, temperature, etc., is fairly straightforward. A suitable starting point may be a search for relevant examples such as those compiled in the tabular survey. However, it should be noted that many of the older procedures have to be viewed in the light of current experimental and theoretical knowledge. For example, the more reactive *n*-butyllithium/TMEDA in ether or hexane (p. 21) may be used to considerable advantage for rate enhancement of some of the more sluggish *ortho* lithiations, notably of those substrates activated by electron-withdrawing groups with moderate coordination potential (p. 44). With few exceptions, *e.g.*, pyrroles, indoles, and enamines, most other *ortho* and alpha lithiations are sufficiently rapid with *n*-butyllithium in ether to obviate the need for additives or accelerators. Still, if a lower temperature or a shorter duration is desirable, the *n*-butyllithium/TMEDA complex can potentially be advantageous. On occasion *n*-butyllithium in tetrahydrofuran can have a similar salutary effect on both alpha and *ortho* metalations. However, caution should be exercised when considering the use of this potential expedient because of the indicated instability of this combination of solvent and metalating agent.

Any solvent choice should also take into consideration the solubility characteristics of the substrate. It should be noted, however, that on occasion intractable starting materials dissolve on metalation. (23, 24) Alternatively, soluble substrates with acidic protons, *e.g.*, secondary arylcarboxamides, may precipitate on initial deprotonation and redissolve on lithiation. (23, 24) The nature of the solvent also affects the reactivity of the metalated species. For instance, it appears that alkylations are best performed in tetrahydrofuran. The use of ether or hexane may also be successful, however, if prior to the addition of the alkylating agent, an equimolecular amount of hexamethylphosphoramide is added to the lithiated species. On the other hand, tetrahydrofuran is often the least suitable solvent for reactions of metalated species with enolizable substrates such as ketones.

For those substrates that contain multiple lithiatable sites, the selection of experimental conditions becomes more exacting, since the success or failure of the desired metalation depends on competitive rates. If the competition is between a "coordination-only" group and either an alpha activator or an electron-withdrawing group (other than with pronounced coordination potential) (p. 44), the use of *n*-butyllithium/TMEDA in ether or hexane and in many instances *n*-butyllithium/tetrahydrofuran promotes lithiation adjacent to the inductively acidifying functionality, thus leading to the thermodynamic product. For this purpose lithium dialkylamides can also be used if the substrate site is sufficiently acidic ($pK_a < 30$). They are especially suitable for substrates containing functional groups susceptible to either nucleophilic attack or metal–halogen exchange. In contrast, utilization of a coordinatively

unsaturated, Lewis-acid-type metalating agent, such as *n*-butyllithium in ether or hexane, should favor lithiation *ortho* or beta to the more effective coordinating group, hence yielding the kinetic product. If there are *several* sites available *ortho* or beta to the dominant directing group, the position actually metalated is the one rendered most acidic by the inductive effect of additional substituents (for examples see compounds **101**, p. 53, and **148**, p. 66). It should be noted that low temperatures also favor kinetic products.

Analysis of the competition between other combinations of functionalities is no longer simple. Therefore the factors governing the facilitating ability of each functional group should be evaluated in the light of the discussion in preceding sections (pp. 7 and 77) before the choice of appropriate experimental conditions is made. Recent studies have been addressed to the problem of predicting metalation sites from ^{13}C—H bond couplings. (355)

5.4. Typical Procedure for an Exploratory Lithiation

The following general experimental procedure may serve as a guideline for the lithiation of a novel substrate. A three-necked, round-bottomed flask equipped with thermometer, serum stopper and dropping funnel, nitrogen inlet, and a magnetic stirring bar is purged with a stream of dry nitrogen. It is then charged with a solution of the substrate in the appropriate dry solvent, normally in a concentration of 3–10 mL/mmol. The solution of the lithiating agent is placed in the dropping funnel, usually 1.1 molar equivalents if a monolithio species is to be generated. The constant stream of nitrogen may then be replaced by a balloon filled with nitrogen, thus keeping the reaction system under a positive nitrogen pressure. In this manner the accumulation of traces of oxygen and moisture carried with the nitrogen can be avoided. Alternatively, a mercury bubbler system may be used. The solution is adjusted to the desired temperature. The metalating agent is then added from the dropping funnel. To monitor the progress of the metalation it is best to withdraw aliquots by means of a syringe and to quench these under an atmosphere of nitrogen at 0° with any of the following substrates: methyl alcohol-*d*, deuterium oxide, dimethyl disulfide, or acetaldehyde. If the proton to be removed is easily detectable in the nmr spectrum, both qualitatively and quantitatively, CH$_3$OD or D$_2$O are the reactants of choice, since the amount of deuterated product can be assayed (except with lithium amides as metalating agents; see p. 80). In other cases the use of acetaldehyde or dimethyl disulfide is advisable, particularly if the new methyl signals of the product are well defined and recognizable in the nmr spectrum. An additional advantage of all these "label reactants" is their relative volatility as well as the volatility of the addition products with the lithiating agent (*e.g.*, *n*-butyllithium) itself. Once the degree of lithiation reaches a satisfactory level, the actual reactant can be added. The procedure of the aqueous workup is generally determined by the nature of the expected products.

6. Experimental Procedures

Unless indicated otherwise, the following experiments were carried out in a three-necked flask equipped with a magnetic stirring bar, dropping funnel, thermometer, and nitrogen inlet.

6.1.1.1. 3-(p-Chlorophenyl)-1-(2-tetrahydropyranyl)pyrazole-5-methanol [Typical Alpha Lithiation of a 5-Membered Nitrogen Heterocycle (Pyrazole) with n-Butyllithium in Tetrahydrofuran] (23)
A solution of 5.25 g (20 mmol) of 3-(*p*-chlorophenyl)-1-(2-tetrahydropyranyl)pyrazole in 100 mL of tetrahydrofuran was cooled under an atmosphere of nitrogen in an ice bath, and 15 mL (24 mmol) of a 1.6 *M* solution of *n*-butyllithium in hexane was added dropwise. After the addition the mixture was stirred at 0–5° for 85 minutes. Then 1.6 g of powdered and dried (at 100°/0.1 mm for 1 hour) paraformaldehyde was added in one portion, and the reaction mixture was allowed to stir at room temperature for 16 hours. The reaction mixture was diluted with ether and washed with basic brine. The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The residue of 5.9 g was crystallized from ether–hexane to yield 4.2 g (72.5%) of product, mp 95–97°; ir (Nujol) 3150–3330 cm^{-1}; nmr (CDCl$_3$) δ 1.4–2.5 (m, 6*H*), 3.2–4.2 (m, 3*H*, 1 exch), 4.65 (s, 2*H*), 5.48 (dd, 1*H*), 6.48 (s, 1*H*), and 7.2–7.8 (AB quartet, 4*H*).

6.1.1.2. 3-O-Methyl-17α -(α -methoxyvinyl)estra-3,17β -diol (Preparation of α -Methoxyvinyllithium via Alpha Lithiation with t-Butyllithium in Tetrahydrofuran at Low Temperatures) (104, 356)
To a solution of 1.1 g (19.2 mmol) of methyl vinyl ether in dry tetrahydrofuran, cooled to –65°, was added under an atmosphere of nitrogen 7.5 mL (12 mmol) of a 1.6 *M* solution of *t*-butyllithium in pentane. After removal of the cooling bath, the yellow precipitate redissolved and the solution became colorless between –5 and 0°. This solution, now containing 12 mmol of α -methoxyvinyllithium, was cooled again to –60°. Then 1.15 g (4 mmol) of estrone methyl ether in 20 mL of dry tetrahydrofuran was added, and the mixture was allowed to warm to 0° over a period of 0.5 hour. The mixture was then quenched with aqueous ammonium chloride and extracted with ether. The organic layer was dried over anhydrous magnesium sulfate, and most of the ether was removed under reduced pressure. Addition of 50 mL of hexane induced crystallization of the product, which was collected in 74% yield (1.02 g), mp 144–146°; ir (CCl$_4$) 3650, 1665, and 1620 cm^{-1}; nmr (CCl$_4$) δ 0.90 (s, 3*H*), 1.0–2.4 and 2.6–3.0 (m, 16*H*), 3.54 (s, 3*H*), 3.70 (s, 3*H*), 4.02 and 4.15 (AB quartet, *J* = 2.5 Hz, 2*H*), 6.5–6.8 and 7.05–7.3 (m, 3*H*).

6.1.1.3. α , α -Diphenyl-2-furylmethanol (Alpha Lithiation of Furan with n-Butyllithium in Tetrahydrofuran or Ether) (23)

To an ice-cooled solution of 4.08 g (60 mmol) of furan in 60 mL of dry tetrahydrofuran was added dropwise 34.4 mL (55 mmol) of a 1:6 M solution of n-butyllithium in hexane under an atmosphere of nitrogen. After the addition the solution was allowed to stir at ice-bath temperature for 3 hours. Then a solution of 9.1 g of benzophenone (50 mmol) in 30 mL of dry tetrahydrofuran was added at a rapid rate, and the reaction mixture was stirred at room temperature for 2 hours. The mixture was poured onto brine, the aqueous layer was reextracted with ether, and the organic phases were dried over sodium sulfate. After evaporation of the solvents the residue of 12.8 g was crystallized from ether–hexane to give a total of 12.45 g of analytically pure product (98.8% based on benzophenone), mp 86–87°; ir (Nujol) 3380 cm^{-1}; nmr (CDCl$_3$) δ 3.5 (s, 1H), 5.9 (d, J = 3 Hz, 1H), 6.25 (dd, J = 3 and 2 Hz, 1H), and 7–7.7 (m, 11H).

Alternatively, the reaction can be carried out in ether (–20° during the addition of n-butyllithium, then reflux for 4 hours) to give the same product in 98% yield. (112)

6.1.1.4. 1-Hydroxycyclohexanecarboxylic Acid Dimethylamide (Alpha Lithiation of Dimethylformamide with Lithium Diisopropylamide and Reaction with an Enolizable Ketone) (23, 78)

A solution of 2.92 g (40 mmol) of dimethylformamide and 3.92 g (40 mmol) of cyclohexanone in 100 mL of dry ether–tetrahydrofuran (4:1) was cooled under an atmosphere of nitrogen to –78°. In a separate three-necked flask a solution of lithium diisopropylamide (44 mmol) [prepared from 6.16 mL (44 mmol) of diisopropylamine in 17 mL of ether and 27.5 mL of a 1.6 M solution of n-butyllithium in hexane (44 mmol)] was also precooled to –70° under nitrogen. The solution of lithium diisopropylamide was then withdrawn by means of a syringe via a serum stopper and transferred, again through a serum stopper, into the flask containing the substrates. The reaction mixture was then kept at –70° for 6 hours. Subsequently, the temperature was raised to 20°, the reaction was quenched with an aqueous solution of ammonium chloride, and the layers were separated. After reextraction of the aqueous layer with ether and washing of the organic layers with brine, the ethereal solution of the product was dried over sodium sulfate and evaporated. The oily residue, containing both product and unreacted (because of enolization) cyclohexanone, was kept under high vacuum at 70° to remove the unreacted ketone. The solidified colorless residue was recrystallized from cyclohexane to yield 3.1 g (45.5%) of 1-hydroxycyclohexanecarboxylic acid dimethylamide as colorless needles, mp 105°; ir (Nujol) 3340 and 1600 cm^{-1}; nmr (CDCl$_3$) δ1.2–2.1 (m, 10H), 3.14 (s, 6H), and 4.24 (s, 1H). A similar procedure gave a higher yield (62%). (78)

6.2. 3-Hydroxy-2-(phenylthio)-1-octene (Alpha Lithiation of Phenyl Vinyl Sulfide in Tetrahydrofuran) (124, 126)

6.2.1.1. A. With Lithium Diisopropylamide [*]

A solution of freshly distilled phenyl vinyl sulfide (1.36 g, 10 mmol) in 10 mL of dry tetrahydrofuran was added dropwise and under nitrogen to a cold (–60°) solution of lithium diisopropylamide (10 mL) [prepared from diisopropylamine(1.01 g) and *n*-butyllithium (7.69 mL of a 1.3 *M* solution in hexane)] and hexamethylphosphoramide (3 mL). After this solution was stirred at –60° for 30 minutes, 1.0 g (10 mmol) of *n*-hexanal in 5 mL of dry tetrahydrofuran was added dropwise. After an additional 30 minutes the cooling bath was removed, and the mixture was allowed to reach room temperature. The reaction mixture was then poured into water and extracted with two 10-mL portions of ether. The ethereal extracts were combined and dried over anhydrous sodium sulfate. After evaporation of the solvent the crude product was obtained as an oil, which was distilled to give 1.81 g (76%) of 3-hydroxy-2-(phenylthio)-1-octene, bp 120° (0.1 mm); nmr (CDCl$_3$) δ 1.4 (m, 12*H*), 4.2 (t, *J* = 6 Hz, 1*H*), 4.95 (s, 1*H*), 5.5 (m, 1*H*), and 7.4 (m, 5*H*).

6.2.1.2. B. With n-Butyllithium/TMEDA [*]

Procedure A was repeated by adding the phenyl vinyl sulfide to a cold solution (–70°) of TMEDA (1.16 g, 10 mmol) and *n*-butyllithium (7.69 mL of a 1.3 *M* solution in hexane, 10 mmol) in 30 mL of dry tetrahydrofuran. The yield of distilled product was 2.0 g (84%).

6.2.1.3. 2-Thiophenethiol

The preparation of this compound in 65–70% yield by alpha lithiation of thiophene and reaction with elemental sulfur is described in *Organic Syntheses*. (357)

6.2.1.4. Benzo[b]thiophen-2(3 H)-one (Alpha Lithiation of Benzothiophene with n-Butyllithium in Ether and Reaction with Trialkylborate–Hydrogen Peroxide) (150)

To a solution of 26.8 g (0.2 mol) of benzothiophene in 100 mL of anhydrous ether was added 130 mL of a 1.6 *M* solution of *n*-butyllithium in hexane (0.208 mol). The mixture was refluxed for 45 minutes, and the resulting solution of 2-lithiobenzothiophene was cooled in a dry ice–acetone bath and treated with 64.5 g (0.28 mol) of tri-*n*-butyl borate. The resulting gelatinous precipitate was hydrolyzed with 200 mL of 1 *N* hydrochloric acid, initially at 0°, then for 1 hour at room temperature. The two layers were separated, and the aqueous phase was reextracted with ether. The combined organic layers were then extracted with 200 mL of 1 *N* sodium hydroxide, and the basic aqueous layer was backwashed with ether. Acidification of the aqueous layer with ice-cold 3 *N* hydrochloric acid gave a pink-yellow, odorous precipitate of crude boronic acid, which was filtered and washed with water. The crude boronic acid was dissolved in a small volume of ether with stirring and treated with

96 mL of 10% hydrogen peroxide containing 2 mL of saturated aqueous sodium carbonate solution. The resulting mixture was refluxed for 1 hour and then stirred at room temperature. The layers were separated, and the aqueous phase was reextracted with ether. The combined organic phase was washed with water until the ferrous ion test no longer indicated the presence of hydrogen peroxide. Finally the ether was washed with brine, dried over magnesium sulfate, and evaporated under vacuum to give 21.7 g (72%) of crystalline product, mp 32–34°. Recrystallization from hot aqueous methanol and cooling to –20° gave pale-yellow needles, mp 34–35°; ir (CCl$_4$) 1723, 1595, and 1460 cm^{-1}; nmr (CDCl$_3$) δ 3.92 (s, 2*H*), and 7.24 (m, 4*H*).

6.2.1.5. 2-Chloro-3,3-diphenylacrylic acid (Alpha Lithiation of a Chloroalkene with n-Butyllithium in Tetrahydrofuran) (358)

To a solution of 6.45 g (30 mmol) of 1-chloro-2,2-diphenylethylene in 50 mL of tetrahydrofuran, cooled to –71°, was added over a 1-hour period 23 mL of a 1.32 *M* solution of *n*-butyllithium in ether (30 mmol). At the onset of the addition the color of the reaction mixture was pink, which then changed slowly to yellow and finally to a light brown. The mixture was poured onto solid powdered carbon dioxide which had been covered with dry ether. After the addition of water the ether–tetrahydrofuran mixture was removed on the rotary evaporator. The basic aqueous layer was then extracted successively with ether, acidified with an excess of dilute sulfuric acid, and extracted again with ether. The combined layer was dried over calcium chloride, filtered, and evaporated. The crude acid so obtained (6.43 g, 83%, mp 130–133°) was recrystallized from cyclohexane to give 6.20 g of 2-chloro-3,3-diphenylacrylic acid, mp 136°.

Evaporation of the neutral layer gave 0.8 g of crystals (mp 45–47°) consisting of a mixture of starting material (240 mg, 3.7%) and diphenylacetylene (560 mg, 10%).

An analogous lithiation in ether as solvent resulted in the recovery (99%) of starting material. (358)

6.2.1.6. [6-(Dimethylamino)-m-tolyl]diphenylmethanol

The preparation of this compound in 49–57% yield by *ortho* lithiation of N,N-dimethyl-*p*-toluidine with *n*-butyllithium–TMEDA is described in *Organic Syntheses*. (359)

6.2.1.7. 3-Chloro-6-[(dimethylamino)methyl]-2¢-fluorobenzophenone (Ortho Lithiation of a Tertiary Benzylamine with n-Butyllithium in Ether) (23)

A solution of 119 g (0.7 mol) of *p*-chloro-N,N-dimethylbenzylamine in 1.7 g/L of anhydrous ether was cooled to 2–4° in an ice bath. Then 480 mL (0.77 mol) of a 1.6 *M* solution of *n*-butyllithium in hexane was added at such a rate that the temperature did not exceed 4°. The reaction mixture was allowed to stir under a positive nitrogen pressure (balloon) at ice-bath temperature for 12 hours.

Subsequently a solution of 85 g (0.7 mol) of *o*-fluorobenzonitrile in 350 mL of ether was added, and the mixture was stirred at 25° for an additional 12 hours. After the flask was again cooled in an ice bath, 1.3 g/L of 5 *N* hydrochloric acid was added, carefully at the beginning, and the biphasic mixture was then refluxed for 40 minutes. The two layers were separated in a separatory funnel, the ethereal layer was reextracted with 200 mL of dilute hydrochloric acid, and the aqueous layers were combined. After the addition of ice, the acidic layer was brought to pH 11 with 30% aqueous sodium hydroxide solution. The oily product was then extracted into methylene chloride (two extractions), and the organic layer was separated and dried over sodium sulfate. The solvent was removed under vacuum, and the residue was crystallized from hexane (600 mL)/ether (50 mL) to give a total of 160.5 g (79%) (three crops) of analytically pure product, mp 89°; ir (Nujol) 1653 cm^{-1}; nmr (CDCl$_3$) δ 1.97 (s, 6H), 2.36 (s, 2H), and 7.0–7.8 (m, 7H).

6.2.1.8. 2-Acetyl-5-chlorobenzaldehyde (One-Pot Transformation of a Tertiary Benzamide into an Ortho-Functionalized Acetophenone by Addition of Methyllithium, Ortho Metalation with n-Butyllithium in Tetrahydrofuran, and Reaction with Dimethylformamide) (196)
A solution of 10 g (53.6 mmol) of *p*-chloro-N,N-dimethylbenzamide in 100 mL of dry tetrahydrofuran was cooled to –78°. Then 31.2 mL of a 2.0 *M* solution of methyllithium in ether (59 mmol) was added dropwise. After the mixture was stirred at that temperature for 1 hour, 368 mL (59 mmol) of a 1.6 *M* solution of *n*-butyllithium in hexane was added dropwise. The mixture was then stirred at 20–25° for 16 hours. The solution of the dilithio species thus formed was cooled in an ice bath and allowed to react with a solution of 4.4 g (59 mmol) of dimethylformamide in 20 mL of dry tetrahydrofuran. The reaction mixture was stirred at 0° for 0.5 hours, and then the temperature was raised to 25° and maintained for 1 hour. The mixture was quenched with 50 mL of 3 N hydrochloric acid and extracted with ether. The combined extracts were washed with water and dried over sodium sulfate. After evaporation of the solvents under vacuum the crude orange oil (6.5 g) was distilled [165–170° (0.7 mm)] to give 5.6 g (56%) of the product as a colorless oil; ir (film) 1688 cm^{-1}; nmr (CDCl$_3$) δ10.1 (s, 1H), 7.3–8.0 (m, 3H), and 2.68 (s, 3H).

6.2.1.9. 2-t-Butyl-3-hydroxyphthalimidine (Ortho Lithiation of a Secondary Benzamide in Tetrahydrofuran with 2 Equivalents of n-Butyllithium) (23, 24)
A solution of 5.32 g (30 mmol) of N-*t*-butylbenzamide in 100 mL of dry tetrahydrofuran was cooled in an ice bath under an atmosphere of nitrogen. To this solution was added 41.3 mL (66 mmol) of a 1.6 *M* solution of *n*-butyllithium in hexane at such a rate that the internal temperature did not exceed 10°. The generation of the monoanion is markedly exothermic. After the addition the mixture was allowed to stir at ice-bath temperature for 4 hours. The generation of the desired dianion is evident by the formation of a thick white precipitate. Subsequently, 2.9 g (3.1 mL, 40 mmol) of dry dimethylformamide was added

neat, and the mixture was allowed to stir for 2.5 hours at room temperature. The reaction was quenched with ice and excess 2 *N* hydrochloric acid, and the aqueous phase was reextracted with ether. The organic layers were washed with brine and dried over anhydrous sodium sulfate. The thick, viscous oil obtained after evaporation of the solvent was dissolved in hot hexane, whereupon the product crystallized to give 5.7 g, mp 105–125°. Recrystallization from hot toluene gave 5.05 g (82%) of pure 2-*t*-butyl-3-hydroxyphthalimidine, mp 132–135°; ir (Nujol) 3205 and 1655 cm^{-1}; nmr (DMSO-d$_6$) δ 1.58 (s, 9*H*), 6.0 (d, *J* = 10 Hz, 1*H*), 6.34 (d, *J* = 10 Hz, 1*H* exch), and 7.53 (s, 4*H*).

6.2.1.10. 2-[p-Methoxyphenyl-2-(phenylthio)]-4,4-dimethyl-2-oxazoline (Ortho Lithiation of an Aryloxazoline Using n-Butyllithium in Ether and Reaction with a Diaryl Disulfide) ([46](#))

A solution of 3.07 g (15 mmol) of 2-(*p*-methoxyphenyl)-4,4-dimethyl-2-oxazoline in 65 mL of dry ether was cooled in an ice bath under an atmosphere of nitrogen. Then 10.3 mL (16.5 mmol) of a 1.6 *M* solution of *n*-butyllithium in hexane was added dropwise, and the mixture was stirred at this temperature for 4 hours. A solution of 3.65 g (16.5 mmol) of diphenyl disulfide in 30 mL of dry ether was added, and the reaction mixture was stirred for 16 hours at ambient temperature. The reaction was quenched with ice water, and the ethereal layer was washed with dilute sodium hydroxide solution to separate the thiophenol and finally with brine. The organic layer was dried over sodium sulfate and evaporated to produce a residue of 5.6 g. The thioether was crystallized from ether–hexane to give 4.2 g (89%), mp 51–53°; ir (Nujol) 1630 and 1590 cm^{-1}; nmr (CDCl$_3$) δ 1.4 (s, 6*H*), 3.55 (s, 3*H*), 4.02 (s, 2*H*), 6.35 (d, *J* = 3 Hz, 1*H*), 6.52 (dd, *J* = 8 and 2 Hz, 1*H*), 7.2–7.7 (m, 5*H*), and 7.75 (d, *J* = 8 Hz, 1*H*).

*6.2.1.11. 3-Chloro-2-(methoxymethoxy)benzaldehyde (Ortho Lithiation of a Protected Phenol with n-Butyllithium/*TMEDA *in Hexane and Reaction with Dimethylformamide)* ([234](#))

To a solution of 261 mL of 1.92 *M n*-butyllithium in hexane (0.5 mol) was added 86.3 g (0.5 mol) of TMEDA. After the mixture had cooled in an ice bath, 86.3 g (0.5 mol) of *o*-chlorophenyl methoxymethyl ether was added during 30 minutes, with the temperature maintained between 0–5°. The mixture was stirred for an additional 30 minutes at this temperature. The yellow slurry was transferred under an atmosphere of nitrogen through a polyethylene tube into an addition funnel, from which it was added over a 25-minute period to a solution of 43.8 g (0.6 mol) of dimethylformamide in 470 mL of xylene. During the addition the reaction mixture was stirred vigorously, and the temperature was maintained at 0–5° by external cooling. Stirring at this temperature was continued for an additional hour, after which the reaction mixture was transferred slowly through a polyethylene tube into a stirred mixture of 37% hydrochloric acid (190 mL) and crushed ice (900 g). The temperature was

watched carefully and not permitted to rise above 5°. Stirring at 0–5° was continued for 20 minutes after the transfer. The aqueous phase was then separated and discarded, and the organic layer was washed with cold dilute hydrochloric acid (1 *N*, 200 mL) and with brine (200 mL). The organic layer was stirred for 20 minutes with a solution of sodium bisulfite (52 g, 0.5 mol) in water (120 mL) mixed with ice (150 g). The aqueous solution was separated and kept cold. This extraction scheme was repeated twice, each time with half of the initial quantities. A solution of sodium hydroxide (45 g) was added slowly to the combined bisulfite extracts with stirring and cooling to maintain the temperature below 10° while the pH was adjusted to 11 toward the end. The crystals were collected by suction, washed with water, and air-dried overnight. The yield of product was 85.4 g (65%), mp 38–40°. Recrystallization of a sample from *n*-hexane afforded pure material, mp 40–41°; nmr ($CDCl_3$) δ 3.56 (s, 3*H*), 5.16 (s, 2*H*), 6.95–7.35 (m, 1*H*), 7.5–7.9 (m, 2*H*), and 10.25 (s, 1*H*).

6.2.1.12. N-*t*-Butyl-o-formyl-N-methylbenzenesulfonamide (Ortho Lithiation of a Tertiary Arylsulfonamide with n-butyllithium in Ether) (*24*)

A solution of 200 g (0.88 mol) of N-*t*-butyl-N-methylbenzenesulfonamide in 2.1 g/L of anhydrous ether was cooled to –70° under an atmosphere of nitrogen. At that temperature the sulfonamide precipitated partially. Then 570 mL of a 1.6 *M* solution of *n*-butyllithium in hexane (0.91 mol) was added dropwise. The mixture was warmed to 0° and kept at that temperature for 1 hour. Subsequently, a solution of dimethylformamide (76 g, 1 mol) in 200 mL of anhydrous ether was added dropwise. After an additional hour at ice-bath temperature, the reaction was quenched with water, and the ether was separated and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the residue was triturated with cold isopropyl alcohol to give 183 g (81%) of white crystalline product, mp 69–71°; ir (Nujol) 1690 cm^{-1}; nmr ($CDCl_3$) δ 1.20 (s, 9*H*), 2.72 (s, 3*H*), 7.2–7.8 (*m*, 4*H*), and 10.54 (s, 1*H*).

7. Tabular Survey

The information in the following tables is an extension of that reviewed previously, (1) covering the literature to the end of December 1977. Additional significant findings reported through August 1978 are included as well. Although the attempt has been made to present an exhaustive list of *successful* examples of this reaction, difficulties in searching the literature make it likely that some references were overlooked. The arrangement of the tabular survey parallels the text; *i.e.*, the main division is according to the *type* of lithiation. Alpha lithiations are presented first, followed by beta (*ortho*) lithiations. Within each type the next determinant is the heteroatom of the directing functionality, the tables being arranged in the order of the increasing atomic number of the heteroatom. The final arrangement is then determined by the specific directing functionality.

Within each table the compounds lithiated are listed according to the increasing number of carbon atoms. If a compound contains more than one director, it can be found in each table appropriate for the specific director. The conditions stated are those of the lithiation itself and not of subsequent reactions with electrophiles. To avoid ambiguity temperature ranges below 0° C are expressed, for example, as: –70° to –30°. If a reference contains more than one set of lithiation conditions for a particular compound, these data are fully presented only if it was deemed significant. When there is more than one reference for a given compound–substrate combination, the information tabulated is considered to describe the optimum lithiation conditions reported. This reference is listed first, and the remaining references are arranged in numerical order. In the substrate column, aside from the electrophile, other reagents are listed only if the initial intermediate is further transformed, *e.g.*, oxidized, hydrolyzed, *etc.* In naming products attempts have been made to conform to *Chemical Abstracts* nomenclature (Vols. **56–65**). Yields, which are indicated by a dash (–), are not specified in the reference(s) cited. Lithiation conditions or substrates, marked by an asterisk (*), are to be taken as an interpretation of the authors because the original report was not explicit.

Standard abbreviations used throughout the tables are the following:

BuLi	*n*-butyllithium
LDA	lithium diisopropylamide
LDCA	lithium dicyclohexylamide
LTMP	lithium tetramethylpiperidide
DMF	dimethylformamide
DMA	dimethylacetamide

THF	tetrahydrofuran
HMPA	hexamethylphosphoramide
ether	diethyl ether
pet. ether	petroleum ether
Ac	acetyl
Et	ethyl
THP	tetrahydropyranyl

Table I. Enamines (Alpha)

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Table II. Vinyl Isocyanides (Alpha)

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Table III. Formamides and Thioformamides (Alpha)

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Table IV. Pyrroles (Alpha)

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Table V. Indoles (Alpha)

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Table VI. Pyrazoles (Alpha)

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Table VII. Imidazoles (Alpha)

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Table VIII. Benzimidazoles (Alpha)

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Table IX. Imidazo[1,2-*a*]pyridines (Alpha)

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Table XI. Tetrazoles (Alpha)

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Table XIX. Vinyl Sulfides and Allenic Thioethers (Alpha)

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Table XX. Vinyl Sulfoxides (Alpha)

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Table XXI. Thiophenes (Alpha)

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Table XXII. Condensed Thiophenes (Alpha)

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Table XXIII. Isothiazoles (Alpha)

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Table XXIV. Thiazoles (Alpha)

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Table XXV. Benzothiazoles (Alpha)

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Table XXVI. Vinyl Selenides (Alpha)

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Table XXVII. Selenophenes (Alpha)

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Table XXXV.   a -Alkoxidoaralkylamines (*Ortho*, Beta)

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Table XLIV. Diaryl Ethers and Condensed Diaryl Ethers (*Ortho*)

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Table LIV. Aryl Bromides (*Ortho*, Beta)

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Table LV. Aryl Iodides (Beta)

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Table LVI. (Trifluoromethyl)benzenes (*Ortho*)

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Table LVII. Arylphosphine Oxides and Imides (*Ortho*, Beta)

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Table LVIII. Selenides (*Ortho*, Beta)

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TABLE I. Enamines (Alpha)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_7H_8N_2$	(1-methyl-1,4-dihydropyridine-3-carbonitrile)	LDA/THF/ −80°/20 hr	CH_3OD	X = D (65)	218
		''	FSO_2OCH_3	X = CH_3 (77)	218
	(1-methyl-1,6-dihydropyridine-3-carbonitrile)	LDA/THF/ −80°/1.5 hr	CH_3OD	X = D (54)	218
		''	FSO_2OCH_3	X = CH_3 (72)	218
$C_7H_{10}N_2$	(3-(pyrrolidin-1-yl)acrylonitrile)	LDA/THF, pentane/ −113°/40 min	CH_3OD	X = D (95)	57c
		''	CH_3I	X = CH_3 (74)	57c
		''	C_2H_5I	X = C_2H_5 (35)	57c
		''	C_6H_5CHO	X = $CH(OH)C_6H_5$ [a] (42)	57c
$C_9H_{15}NO_2$	(ethyl 3-(pyrrolidin-1-yl)acrylate) $C_2H_5CO_2CH=CHN$	t-BuLi/THF/ −113°/15 min	$C_2H_5CO_2CH=CHN$(pyrrolidine)	X = $CO_2C_2H_5$ Y = H Z = N(pyrrolidine) } (41)	57b
		''	$C_6H_5CH=CHCO_2C_4H_9\text{-}t$	X = $CO_2C_4H_9\text{-}t$ Y = H Z = C_6H_5 } (67)	57b
		''	$C_6H_5COCH=CHN$(piperidine)	X = COC_6H_5 Y = H Z = N(piperidine) } (49)	57b
		''	$C_6H_5CH=C(C_6H_5)CN$	X = Z = C_6H_5 Y = CN } (32)	57b
		''	$C_6H_5COCH=CHCOC_6H_5$	X = Z = COC_6H_5 Y = H } (25)	57b
		''	CH_3CHO	X = CH_3 Y = H } (49)	57b
		''	$HCO_2C_2H_5$	X = OC_2H_5 Y = H } (52)	57b
		''	$(CO_2CH_3)_2$	X = CO_2CH_3 Y = OCH_3 } (58)	57b
		''	C_6H_5CHO	X = C_6H_5 Y = H } (51)	57b
		''	$C_6H_5CO_2CH_3$	X = C_6H_5 Y = OCH_3 } (43)	57b
$C_{11}H_{11}N$	(1-phenyl-1,2-dihydropyridine)	BuLi/THF/0°/ 4.5 hr	D_2O	(2,6-dideuterio-1-phenyl-1,2-dihydropyridine) (82)	74

TABLE I. ENAMINES (ALPHA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
$C_{11}H_{20}N_2O$		*t*-BuLi/THF/ -115^a	CH_3OD		X = D (100)	57a
		"	CH_3I		X = CH_3 (95)	57a
		"	C_2H_5I		X = C_2H_5 (60)	57a
		"	$C_6H_5CO_2CH_3$		X = COC_6H_5 (95)	57a
		"	p-$CH_3C_6H_4CO_2CH_3$		X = $COC_6H_4CH_3$-p (60)	57a
		t-BuLi/THF/ $-120°/0.5$ hr	p-$O_2NC_6H_4CHO$		X = $CH(OH)C_6H_4NO_2$-p (60)	604
		"	C_6H_5CHO		X = $CH(OH)C_6H_5$ (61)	604
		"			X = O R_1R_2 = } (56)	604
		"	$(C_6H_5)_2CO$		X = O $R_1 = R_2 = C_6H_5$ } (45)	604
		"	$C_6H_5CH{=}NC_6H_5$		X = NC_6H_5 $R_1 = H$ $R_2 = C_6H_5$ } (26)	604
		"	p-$(CH_3)_2NC_6H_4CH{=}NC_6H_5$		X = NC_6H_5 $R_1 = H$ $R_2 = NC_6H_4N(CH_3)_2$-p } (21)	604

^{a}This compound was contaminated with the ring isomer.

Note: References 360–607 are on pp. 355–360.

TABLE II. Vɪɴʏʟ Isᴏᴄʏᴀɴɪᴅᴇꜱ (Aʟᴘʜᴀ)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
C_7H_9N		BuLi/THF, ether, pet. ether/−110°/ 0.5 hr	$(CH_3)_3SiCl$	α-(Trimethylsilyl)$\Delta^{1,\alpha}$-cyclopentane isocyanide (63)		76
C_9H_7N	$C_6H_5CH{=}CHNC$	BuLi/THF, ether, pet. ether/-110°/ 0.5 hr	CO_2	$C_6H_5CH{=}C(NC)X$	X = CO_2Li (95)	76
		,,	CH_3I		X = CH_3 (75)	76
		,,	$ClCO_2C_2H_5$		X = $CO_2C_2H_5$ (70)	76
		,,	$(CH_3)_3SiCl$		X = $Si(CH_3)_3$ (53)	76
		,,	C_6H_5COCl		X = COC_6H_5 (94)	76
		,,	CH_3COCH_3		R = R′ = CH_3 (77)	76
		,,	C_6H_5CHO		R = H, R′ = C_6H_5 } (36)	
		,,	$(C_6H_5)_2CO$		R = R′ = C_6H_5 (—)	76
$C_{10}H_9N$	$C_6H_5(CH_3)C{=}CHNC$	BuLi/THF, ether, pet. ether/−110°/ 0.5 hr	$(CH_3)_3SiCl$	β-Methyl-α-(trimethylsilyl)cinnamylisocyanide (78)		76

TABLE III. FORMAMIDES AND THIOFORMAMIDES (ALPHA)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
C_3H_7NO	$HCON(CH_3)_2$	LDA/THF/ether, $-78°$	$t\text{-}C_4H_9CHO$	$(CH_3)_2NCOX$	$X = CH(OH)C_4H_9\text{-}t$ (76)	78
		"	Cyclohexanone		$X = HO$ (62)	78
		"	C_6H_5CHO		$X = CH(OH)C_6H_5$ (45)	78
		"	$C_6H_5CH=CHCHO$		$X = CH(OH)CH=CHC_6H_5$ (48)	78
		"	$(C_6H_5)_2CO$		$X = C(C_6H_5)_2OH$ (85)	78
		"	Estra-1,3,5(10)–triene-17-one	17-Hydroxy-3-methoxy-N,N-dimethyl-1,3,5(10)–estratriene-17-carboxamide (72)		78
C_3H_7NS	$HCSN(CH_3)_2$	LDA/THF/-100°/ 3 min	CH_3I	$(CH_3)_2NCSX$	$X = CH_3$ (50)	77, 80
		LDA/THF, ether, HMPA/-100°/ 3 min	C_2H_5I		$X = C_2H_5$ (70)	77
		LDA/THF/-100° 3 min	C_2H_5CHO		$X = CH(OH)C_2H_5$ (80)	77
		"	CH_3COCH_3		$X = C(CH_3)_2OH$ (85)	77, 80
		"	Cyclohexenone		$X = HO$ (50)	77
		"	Cyclohexanone		$X = HO$ (65)	77, 80
		"	C_6H_5CHO		$X = CH(OH)C_6H_5$ (75)	77, 80
		"	$C_6H_5COCH_3$		$X = \underset{\underset{OH}{|}}{C(CH_3)C_6H_5}$ (65)	77, 80
		"	$C_6H_5CO_2CH_3$		$X = COC_6H_5$ (85)	77, 80
		"	$(C_6H_5)_2CO$		$X = C(C_6H_5)_2OH$ (85)	80
$C_4H_9NO_2$	$HCON(CH_3)CH_2OCH_3$	LDA/THF/-75°/ 3 hr	Cyclohexanone	$CH_3OCH_2(CH_3)NCOX$	$X = HO$ (39)	79
		"	C_6H_5CHO		$X = CH(OH)C_6H_5$ (76)	79
		"	$C_6H_5CH=CHCHO$		$X = CH(OH)CH=CHC_6H_5$ (40)	79
		"	$(C_6H_5)_2CO$		$X = C(C_6H_5)_2OH$ (85)	79
$C_5H_{11}NO_3$	$HCON(CH_2OCH_3)_2$	LDA/THF/$-75°$/ 3 hr	Cyclohexanone	$(CH_3OCH_2)_2NCOX$	$X = HO$ (44)	79
		"	C_6H_5CHO		$X = CH(OH)C_6H_5$ (74)	79
		"	$(C_6H_5)_2CO$		$X = C(C_6H_5)_2OH$ (88)	79
$C_5H_{11}NS$	$HCSN(C_2H_5)_2$	LDA/THF/$-100°$/ 3 min	C_6H_5CHO	N,N-Diethylthiomandelamide (86)		77
$C_7H_{15}NO$	$HCON(C_3H_7\text{-}i)_2$	t-BuLi/THF, ether, pentane/$-95°$	D_2O	$(i\text{-}C_3H_7)_2NCOX$	$X = D$ (70)	569, 578, 579
		LDA/THF/$-78°$/ 5 min	CH_3I		$X = CH_3$ (20)	579
		t-BuLi/THF, ether, pentane/$-95°$	C_2H_5CHO		$X = CH(OH)C_2H_5$ (62)	569, 578, 579
		"	CH_3COCH_3		$X = C(CH_3)_2OH$ (81)	569, 578, 579
		"	Cyclohexanone		$X = HO$ (83)	569
		"	C_6H_5CHO		$X = CH(OH)C_6H_5$ (80)	569, 578, 579
			$C_6H_5CH_2Br$		$X = CH(C_6H_5)CH_2C_6H_5$ (68)	569

TABLE III. FORMAMIDES AND THIOFORMAMIDES (ALPHA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
$C_7H_{15}NO$ (*Contd.*)	$HCON(C_3H_7\text{-}i)_2$	"	$C_6H_5CO_2C_2H_5$	$X = COC_6H_5$ (70)		569, 578, 579
		"	$C_6H_5CH{=}CHCHO$	$X = CH(OH)CH{=}CHC_6H_5$	(68)	569, 578
		LDA/THF/ $-78°/$ 5 min	$(C_6H_5)_2CO$	$X = C(C_6H_5)_2OH$ (92)		578, 579
		t-BuLi/THF, ether, pentane/$-95°/$ 45 min	"	$X = C(C_6H_5)_2OH$ (85)		569
$C_9H_{19}NS$	$HCSN(C_4H_9\text{-}n)_2$	LDA/THF/ $-100°/$ 3 min	C_6H_5CHO	N,N-Dibutylthiomandelamide (71)		77
		"		N,N-Dibutyl-2,2-dicyclohexyl-2-hydroxythioacetamide		77
$C_{13}H_{11}NS$	$HCSN(C_6H_5)_2$	LDA/THF/ $-100°/$ 3 min	C_6H_5CHO	N,N-Diphenylthiomandelamide (57)		77

Note: References 360–607 are on pp. 355–360.

TABLE IV. PYRROLES (ALPHA)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C_5H_7N	N-methylpyrrole	EtLi/ether, TMEDA/ reflux/1 hr	CuCl	X = (8)	68
		BuLi/ether, TMEDA/ reflux/1 hr	I_2	X = I (30)	68
		"	CO_2	X = CO_2H (70)	68, 81
		BuLi/ether/reflux/ "overnight"	$CH_2=CHCH_2Cl$	X = $CH_2CH=CH_2$ (20)	580
		BuLi/ether	$ClB(CH_3)N(CH_3)_2$	X = $B(CH_3)N(CH_3)_2$ (37)	295
		"	$ClB[N(CH_3)_2]_2$	X = $B[N(CH_3)_2]_2$ (45)	295
		"	Cl—B (cyclopentane)	X = B (20)	295
		"	$ClB(C_2H_5)_2$	X = $B(C_2H_5)_2$ (48)	295
		EtLi/ether, TMEDA/ 34°/1 hr	C_6H_5I/CuBr	X = C_6H_5 (41)	68
		2.5 BuLi/hexane, TMEDA/25°/0.5 hr	$CO_2(CH_2N_2)$	Dimethyl 1-methylpyrrole-2,4-dicarboxylate (I) (100)	40, 581
		2.5 BuLi/hexane, TMEDA/reflux/ 0.5 hr	"	I (41), Dimethyl 1-methylpyrrole-2,4-dicarboxylate (II) (7), dimethyl 1-methylpyrrole-2,5-dicarboxylate (III) (50)	40
		4.5 BuLi/hexane, TMEDA/reflux/ 120 hr	"	I (4), II (40), III (2)	40
		BuLi/hexane/ reflux/0.5 hr	DMF	1-Methylpyrrole-2,4-dicarboxaldehyde (—)	581

TABLE IV. PYRROLES (ALPHA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{10}H_9N$		BuLi/ether/ 25°/8 hr	CO_2	1-Phenylpyrrole-2-carboxylic acid (14)	81
		2 BuLi/ether/ reflux/14 hr	"	(5)	81
$C_{13}H_{11}NS$		BuLi/ether, pentane, heptane/25°/ 15 hr	$CO_2(CH_2N_2)$	(85)	582

Note: References 360–607 are on pp. 355–360.

TABLE V. INDOLES (ALPHA)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C_9H_9N		BuLi/ether/ reflux/8 hr	CO_2	$X = CO_2H$ (78)	83
		"	$(CO_2C_2H_5)_2$ (OH^-)	$X = COCO_2H$ (59)	583, 584
		"	C_6H_5NCO	$X = CONHC_6H_5$ (42)	83
		"	$p\text{-}ClC_6H_4CHO$	$X = CH(OH)C_6H_4Cl\text{-}p$ (50)	83
		"	$o\text{-}CH_3C_6H_4NCO$	$X = CONHC_6H_4CH_3\text{-}o$ (63)	83
		"	$p\text{-}CH_3OC_6H_4NCO$	$X = CONHC_6H_4OCH_3\text{-}p$ (40)	83
		"	$p\text{-}CH_3C_6H_4SO_2OCH_3$	$X = CH_3$ (45)	83
		"	$(C_6H_5NO_2)$	$X =$ (54)	83
		"	1-Naphthyliso-cyanate	$X = CONH$ (52)	83
		"	$(C_6H_5)_2CO$	$X = C(C_6H_5)_2OH$ (53)	83

TABLE V. INDOLES (ALPHA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{10}H_{11}NO$	(5-methoxy-1-methylindole)	BuLi/ether/ reflux/13 hr	(2-pyridinecarboxaldehyde)	(I), (II), (III) (I+II+III, 74) (I:II:III, 4:5:1)	84
		t-BuLi/THF/0°	"	I (39) X = CH(OH)(2-pyridyl)	84
	(1-(methoxymethyl)indole)	t-BuLi/ether/25°/ 1 hr	CO_2	X = CO_2H (80)	85
		"	(2-pyridinecarbonitrile) (H_3O^+)	X = CO(2-pyridyl) (56)	85
		"	(4-pyridinecarbonitrile) (H_3O^+)	X = CO(4-pyridyl) (56)	85
		"	C_6H_5CN (H_3O^+)	X = COC_6H_5 (84)	85
		"	C_6H_5CHO	X = $CH(OH)C_6H_5$ (40)	85
		"	$C_6H_5N(CH_3)CHO$	X = CHO (46)	85
		"	$p\text{-}CH_3OC_6H_4CN$ (H_3O^+)	X = $COC_6H_4OCH_3\text{-}p$ (70)	85
$C_{13}H_{18}N_2$	(3-[2-(dimethylamino)ethyl]-1-methylindole)	BuLi/THF/0°/ 75 min	D_2O	3-[2-(Dimethylamino)ethyl]-2-d-1-methylindole (74)[a]	153
$C_{14}H_{11}N$	(1-phenylindole)	BuLi/ether/reflux/ 12 hr	CO_2	1-(o-Carboxyphenyl)indole-2-carboxylic acid (15), (42)	83
$C_{14}H_{11}NO_2S$	(1-(phenylsulfonyl)indole)	t-BuLi/THF/−12°– 25°/20 min	CO_2	X = CO_2H (63)	85

TABLE V. INDOLES (ALPHA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{14}H_{11}NO_2S$ (*Contd.*)	[indole with N-$SO_2C_6H_5$]	*t*-BuLi/THF/ – 12°– 25°/20 min	$ClCO_2C_2H_5$	X = $CO_2C_2H_5$ (75)	85
		"	[pyridine-2-CHO]	X = CH(OH)—[2-pyridyl] (32)	85
		"	[pyridine-3-COCl]	X = CO—[3-pyridyl] (60)	85
		"	C_6H_5CHO	X = CH(OH)C_6H_5 (55)	85
		"	C_6H_5COCl	X = COC_6H_5 (65)	85
		"	[pyridine-4-COCH$_3$]	X = C(CH$_3$)—[4-pyridyl], OH (35)	85
			$C_6H_5COCH_3$	X = C(CH$_3$)C_6H_5, OH (64)	85
		"	p-CH$_3$OC$_6$H$_4$CHO	X = CH(OH)C$_6$H$_4$OCH$_3$-p (65)	85
		"	p-CH$_3$OC$_6$H$_4$COCH$_3$	X = C(CH$_3$)C$_6$H$_4$OCH$_3$-p, OH (35)	85
		"	[pyridine-2-CN] (H$_3$O$^+$) [indole 2-X, N–H]	X = CO—[2-pyridyl] (36)	85
		"	[pyridine-4-CN] (H$_3$O$^+$)	X = CO—[4-pyridyl] (26)	85
		"	C_6H_5CN(H$_3$O$^+$)	X = COC_6H_5 (30)	85
		"	[pyridine-3-CO$_2$C$_2$H$_5$]	X = CO—[3-pyridyl] (22)	85
		"	[pyridine-4-CO$_2$C$_2$H$_5$]	X = CO—[4-pyridyl] (31)	85
		"	$C_6H_5CO_2C_2H_5$	X = COC_6H_5 (26)	85
$C_{15}H_{13}NO_3S$	[5-CH$_3$O indole with N-$SO_2C_6H_5$]	*t*-BuLi/THF/0°– 25°/45 min	[pyridine-2-CHO]	X = CH(OH)—[2-pyridyl] (59)	84

TABLE V. INDOLES (ALPHA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C₁₅H₁₃NO₃S (*Contd.*)	CH₃O— indole —SO₂C₆H₅	,,	CHO-pyridine	X = CH(OH)-pyridine (84)	84
	CH₃O— indole —SO₂C₆H₅	*t*-BuLi/THF/0°– 25°/45 min	pyridine-CHO	CH₃O— indole —SO₂C₆H₅, X = CH(OH)-pyridine (62)	84
		,,	CHO-pyridine	X = CH(OH)-pyridine (70)	84
		,,	COCH₃-pyridine	X = C(CH₃)OH-pyridine (58)	84

ᵃ The isolated yield was 74%; the deuterium incorporation was 75%.

Note: References 360–607 are on pp. 355–360.

TABLE VI. PYRAZOLES (ALPHA)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
$C_3H_3BrN_2$	(4-bromopyrazole, N-H)	C_6H_5Li/ether/25°/ 2 hr	CO_2	4-Bromopyrazole-5-carboxylic acid (35)		87
$C_3H_4N_2$	(pyrazole, N-H)	BuLi/ether/−30°/ 2 hr	CO_2	Pyrazole-5-carboxylic acid (9)		87
$C_4H_6N_2$	(1-methylpyrazole)	BuLi/ether/−20°	CO_2	(I) $X = CO_2H$ (66)		87, 88
		BuLi/ether/−30°– 20°/2 hr	$(CH_3O)_2SO_2$		$X = CH_3$ (75)	87
		BuLi/ether/−30° – 20°/4 hr	$(C_6H_5)_2CO$		$X = C(C_6H_5)_2OH$ (87)	87
		BuLi/ether/25°/ 1.5 hr	C_6H_5CHO	I, (II) $X = CH(OH)C_6H_5$		86

(I + II, 88) (I : II, 66 : 34)

TABLE VI. PYRAZOLES (ALPHA) (Continued)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_5H_8N_2$		BuLi/ether/ reflux/0.5 hr	C_6H_5CHO	(III), (IV) X = CH(OH)C_6H_5 (III + IV, 90) (III : IV, 2 : 1)	86
$C_6H_{10}N_2$		BuLi/ether/25°/ 1 hr	C_6H_5CHO	α-Phenyl-1-propylpyrazole-5-methanol (81)	86
$C_7H_{12}N_2$		BuLi/ether/25°/ 0.5 hr	C_6H_5CHO	3-Methyl-α-phenyl-1-propylpyrazole-5-methanol (95)	86
$C_9H_8N_2$		BuLi/ether/0°– 25°/2 hr	CO_2	1-Phenylpyrazole-5-carboxylic acid (39), 1-(o-Carboxyphenyl)pyrazole (10)	88
		2 BuLi/ether/25° 7 hr	"	(8), (26)	88
$C_{10}H_{10}N_2$		C_6H_5Li/ether/ 25°/3 hr	CO_2	1-Benzylpyrazole-5-carboxylic acid (57)	87
		BuLi/ether/25°/ 2 hr	CO_2	3-Methyl-1-phenylpyrazole-5-carboxylic acid (—)	585
$C_{14}H_{15}ClN_2O$		BuLi/ether/0°/ 0.5 hr	CH_2O	X = CH_2OH (73)	23
		"	t-C_4H_9NCO	X = CONHC$_4$H$_9$-t (63)	23
		"	$(C_6H_5S)_2$	X = SC$_6$H$_5$ (80)	23
$C_{18}H_{14}N_4$		BuLi/THF/20°	CuI(O_2)	(11)	282

TABLE VII. IMIDAZOLES (ALPHA)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_4H_5BrN_2$	4-Bromo-1-methylimidazole (Br, N-CH₃)	BuLi/ether/$-80°$	CH_3CHO	4-Bromo-α,1-dimethylimidazole-2-methanol (50)	92
$C_4H_5ClN_2$	5-Chloro-1-methylimidazole (Cl, N-CH₃)	BuLi/ether/$-80°$	CH_3CHO	5-Chloro-α,1-dimethylimidazole-2-methanol (64)	92
$C_4H_6N_2$	1-methylimidazole	BuLi/ether/$-60°$/ 2 hr, 25°/3 hr	CO_2	(imidazole-2-X, N-CH₃) $X = CO_2H$ (32)	586
		BuLi/ether/$-78°$/ 1 hr	CH_3CHO	$X = CH(OH)CH_3\cdot$ (35)	92
		BuLi/ether/ reflux/1 hr	$(CH_3)_3SiCl$	$X = Si(CH_3)_3$ (56)	93
		BuLi/ether/25°/ 1 hr	2-pyridine-CHO	$X = CH(OH)$(2-pyridyl) (48)	587
		"	3-pyridine-CHO	$X = CH(OH)$(3-pyridyl) (33)	587
		—	$C_6H_5N_3$	$X = NH_2$ (—)	287
		BuLi/ether/25°/ 1 hr	Cyclohexanone	$X =$ (1-hydroxycyclohexyl) (56)	587
		"	$n\text{-}C_6H_{13}CHO$	$X = CH(OH)C_6H_{13}\text{-}n$ (41)	587
		"	$C_6H_5CH_2CHO$	$X = CH(OH)CH_2C_6H_5$ (44)	587
		"	$3,4\text{-}(CH_3O)_2C_6H_3CHO$	$X = CH(OH)C_6H_3(OCH_3)_2\text{-}3,4$ (23)	587
		"	$p\text{-}(CH_3)_2NC_6H_4CHO$	$X = CH(OH)C_6H_4N(CH_3)_2\text{-}p$ (48)	587
		"	1-naphthyl-NCO	$X = CONH$(1-naphthyl) (66)	586
		"	$(C_6H_5)_2CO$	$X = C(C_6H_5)_2OH$ (86)	586
		2 BuLi/ether/ $-70°$/2.5 hr	$(CH_3)_3SiCl$	1-Methyl-2,5-bis(trimethylsilyl)imidazole (32)	93
$C_5H_8N_2$	1,2-dimethylimidazole	BuLi/ether/$-10°$/ 15 min	DMF	(I) CH_3, N-CH₃, X; $X = CHO$ (20)	90
		"	$(C_2H_5)_2NBr$	$X = Br$ (26)	90
		BuLi/ether/0°/ 1 hr	C_6H_5CHO	(I), XCH_2-(1-methylimidazol-2-yl) (II) (I + II, 70) (I:II, 25:75) $X = CH(OH)C_6H_5$	588, 90

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TABLE VII. IMIDAZOLES (ALPHA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
$C_5H_8N_2$ (*Contd.*)		C_6H_5Li/ether, benzene/0°/ 0.5 hr	C_6H_5CHO	I, II (I+II, 60) (I:II, 1:1)		589
		BuLi/ether/−15°/ 5-20 min	[pyridine-CHO]	II (66)	$X = CH(OH)$[pyridine]	91
		BuLi/ether/−10°/ 15 min	$C_6H_5C\equiv CI$	I	$X = I$ (48)	90
		"	$(C_6H_5)_2CO$	I	$X = C(C_6H_5)_2OH$ (73)	90
	[imidazole]	BuLi/ether/−80°	CH_3CHO	α,1,5-Trimethylimidazole-2-methanol (30)		92
$C_5H_8N_2O$	[imidazole-CH₂OCH₃]	BuLi/ether	C_6H_5CHO	1-(Methoxymethyl)-α-phenylimidazole-2-methanol (45)		587
$C_6H_{10}N_2$	[imidazole]	BuLi/ether/−80°	CH_3CHO	α,1,4,5-Tetramethylimidazole-2-methanol (24)		92
$C_9H_8N_2$	[imidazole-C₆H₅]	BuLi/ether/25°/ 8 hr	CO_2	[imidazole-X]	$X = CO_2H$ (46)	586
		—	$C_6H_5N_3$		$X = NH_2$ (—)	287
		BuLi/ether/25°/ 8 hr	C_6H_5NCO		$X = CONHC_6H_5$ (39)	586
		"	$(C_6H_5)_2CO$		$X = C(C_6H_5)_2OH$ (76)	586
		3 BuLi/ether/ reflux/12 hr	CO_2	[tricyclic ketone] (5)		586
$C_9H_8N_2O_2S$	[imidazole-SO₂C₆H₅]	t-BuLi/THF/ −20°/10 min	D_2O	[imidazole-X SO₂C₆H₅]	$X = D$ (100)	573
		n-BuLi/THF/−10°/ 15 min	I_2		$X = I$ (7)	573
		t-BuLi/THF/ −20°/0.5 hr	CH_2O		$X = CH_2OH$ (10)	573
		n-BuLi/THF/0°/ 5 min	Cyclohexanone		$X = HO$[cyclohexyl] (15)	573
		t-BuLi/THF/0°/ 10 min	C_6H_5CHO		$X = CH(OH)C_6H_5$ (18)	573
$C_{10}H_{10}N_2$	[imidazole-CH₂C₆H₅]	BuLi/ether/−60°/ 2 hr, 25°/2 hr	CO_2	[imidazole-X CH₂C₆H₅] (III)	$X = CO_2H$ (67)	586

TABLE VII. Imidazoles (Alpha) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{10}H_{10}N_2$ (*Contd.*)		BuLi/ether/0°/ 2 hr	CH_3CHO	$X = CH(OH)CH_3$ (22)	587
		"	$HCO_2C_2H_5$	$X = CH(OH)$ (22)	587
		—	$C_6H_5N_3$	$X = NH_2$ (−)	287
		BuLi/ether/0°/ 2 hr	C_6H_5CHO	$X = CH(OH)C_6H_5$ (48)	587
		BuLi/ether/−60°/ 2 hr, 25°/2 hr	($C_6H_5NO_2$)	$X =$ (29)	586
		BuLi/ether/−70° −25°/2 hr	III (30), X (12)	$X =$	590

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TABLE VIII. BENZIMIDAZOLES (ALPHA)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_7H_6N_2$		BuLi/ether/$-70°$	$(CH_3)_3SiCl$	2-(Trimethylsilyl)benzimidazole (17)	93
$C_8H_8N_2$		BuLi/ether/$25°$	—	1,1'-Dimethyl-2,2'-bibenzimidazole (53)	591
		BuLi/ether/$-60°$/ 3 hr	CO_2	1-Methylbenzimidazole-2-carboxylic acid (45)	591
		BuLi/ether/$-70°$	$(CH_3)_3SiCl$	1-Methyl-2-(trimethylsilyl)benzimidazole (91)	93
$C_{12}H_{10}N_2$		BuLi/$-78°$	CO_2	(80)	607
		BuLi/$-78°$	CO_2	(72)	607
$C_{13}H_{10}N_2$		C_6H_5Li	CO_2	1-Phenylbenzimidazole-2-carboxylic acid (25)	592

TABLE VIII. BENZIMIDAZOLES (ALPHA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{14}H_{12}N_2$		BuLi/ether/−70°–25°/2 hr		(40)	590
		"		(25)	590

Note: References 360–607 are on pp. 355–360.

TABLE IX. Imidazo[1,2-a]pyridines (Alpha)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_7H_6N_2$		C_6H_5Li/ether/10 min	DMF	X = CHO (24)	94
		"	Cyclohexanone	X = (35)	94
		"	C_6H_5NCO	X = CONHC$_6$H$_5$ (15)	94
$C_8H_8N_2$		C_6H_5Li/ether/10 min	Cyclohexanone	1-(2-Methylimidazo[1,2-a]pyridin-3-yl) cyclohexanol (14)	94
		C_6H_5Li/ether/10 min	Cyclohexanone	1-(6-Methylimidazo[1,2-a]pyridin-3-yl) cyclohexanol (40)	94
		C_6H_5Li/ether/10 min	Cyclohexanone	1-(7-Methylimidazo[1,2-a]pyridin-3-yl) cyclohexanol (48)	94
		C_6H_5Li/ether/10 min	Cyclohexanone	1-(8-Methylimidazo[1,2-a]pyridin-3-yl) cyclohexanol (42)	94

TABLE X. Triazoles (Alpha)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_8H_7N_3$		BuLi/THF/−20° to −60°/0.5–1 hr	CH_3I	5-Methyl-1-phenyl-1H-1,2,3-triazole (94)	95
$C_9H_9N_3$		BuLi/THF/−20° to −60°/0.5–1 hr	CH_3I	4,5-Dimethyl-1-phenyl-1H-1,2,3-triazole (81)	95
$C_{14}H_{11}N_3$		BuLi/THF/−20° to −60°/0.5–1 hr	CO_2	1,4-Diphenyl-1H-1,2,3-triazole-5-carboxylic acid (62)	95
		"	CH_3I	5-Methyl-1,4-diphenyl-1H-1,2,3-triazole (78)	95
$C_{15}H_{13}N_3$		BuLi/THF/−78°	CH_2O	X = CH_2OH (78)	96
		"	$(C_6H_5)_2CO$	X = $C(C_6H_5)_2OH$ (92)	96
		"	$(p\text{-}CH_3OC_6H_4)_2CO$	X = $C(C_6H_4OCH_3\text{-}p)_2OH$ (94)	96
		"	$[p\text{-}(CH_3)_2NC_6H_4]_2CO$	X = $C[C_6H_4N(CH_3)_2\text{-}p]_2OH$ (91)	96

TABLE XI. Tetrazoles (Alpha)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
$C_2H_4N_4$		BuLi/THF/ $-50°/1$ hr	$[(C_2H_5)_3P]_2NiCl_2$	$\left(\begin{array}{c} N{-}N \\ N \end{array}\right)_2 Ni$ (80)		301
		BuLi/THF/ $-65°$	Br_2	X = Br (41)		98
		"	I_2	X = I (36)		98
		"	"S"	X = SH (67)		98
		"	C_6H_5CHO	X = $CH(OH)C_6H_5$ (63)		98
		"	$C_6H_5COCH_3$	X = $\underset{OH}{C(CH_3)C_6H_5}$ (67)		98
		"	$C_6H_5CO_2CH_3$	X = COC_6H_5 (41)		98
		"	$(C_6H_5)_2CO$	X = $C(C_6H_5)_2OH$ (75)		98
		.		X = CH_3 (35)		
		"	CH_3COCl	$\left(\begin{array}{c} N{-}N \\ N \end{array}\right)_2 C{-}OCOX$		98
		"	C_6H_5COCl	X = C_6H_5 (68)		98
$C_7H_6N_4$		BuLi/THF/ $-50°/$ 1 hr	—	[1-Phenyl-2(1H)tetrazolyl]lithium (—)		301
$C_7H_{12}N_4$		BuLi/THF/ $-50°/$ 1 hr	$[(C_2H_5)_3P]_2NiCl_2$	$\left(\begin{array}{c} N{-}N \\ N \end{array}\right)_2 Ni$ (—)		301

TABLE XII. PYRIDINES AND CONDENSED PYRIDINES (ALPHA)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C₅H₅N		LDA/ether, HMPA/ −70°/1 hr	—	2,2'-Bipyridine (50)	99
C₉H₇N		LDA/ether, HMPA/ −70°/1 hr	—	2,2'-Biquinoline (74)	99
		LDA/ether, HMPA/ −70°/1 hr	—	1,1'-Biisoquinoline (55)	99

TABLE XIII. Pyridine-N-Oxides (Alpha)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)			Refs.
C₅H₄ClNO		—	CO₂	4-Chloropicolinic acid 1-oxide (49)			593, 101
C₅H₅NO		BuLi/ether/ −65°/ 15 min	Cyclohexanone	(36),	(21)	X =	594
		BuLi/THF, ether/ −65°/1 hr	Br₂			X = Br (3),	595, 596
						X = (8)	
						X = (6)	
		"	Cl₂	2,6-Dichloropyridine 1-oxide (5)			595, 596
		BuLi/ether/ −65°– 25°	"S"	1-Hydroxy-2(1H)-pyridinethione (10)			102

TABLE XIII. Pʏʀɪᴅɪɴᴇ-N-Oxɪᴅᴇs (Aʟᴘʜᴀ) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)			Refs.
C₅H₅NO (*Contd.*)		BuLi/THF/−65°/ 15 min	CH₃CHO	(36)	(30)	X = CH(OH)CH₃	594
		···	CH₃COCH₃	(18)	(—)	X = C(CH₃)₂OH	594
		BuLi/ether/25°	Cyclohexanone	(13)	(36)	X = (1-hydroxycyclohexyl)	594
		—	···	(15)	(—)	X = (1-hydroxycyclohexyl)	593, 594
C₆H₆ClNO	4-Cl-3-CH₃-pyridine 1-oxide	BuLi/THF/−65°/ 1 hr	"S"	4-Chloro-1-hydroxy-5-methyl-2(1H)-pyridinethione (12)			102, 596
		BuLi/ether/−65°	CO₂	4-Chloro-5-methylpicolinic acid 1-oxide (24)			593, 101
		BuLi/ether/−65°/ 15 min	Cyclohexanone	(44)	(5)	X = (1-hydroxycyclohexyl)	594
		BuLi/ether/−65°	··	(38)	(—)		593
		BuLi/ether/−65°/ 15 min	C₆H₅CHO	(—)	(9)	X = CH(OH)C₆H₅	594
		BuLi/ether	C₆H₅CN	C₆H₅CO— (bipyridyl N-oxide structure) (12)			101
C₆H₇NO	2-methylpyridine 1-oxide	BuLi	CO₂	(14),	(10)	X = CO₂H	101
		BuLi/THF/−65°/ 15 min	Cyclohexanone	(4),	(20)	X = (1-hydroxycyclohexyl)	594
	3-methylpyridine 1-oxide	BuLi/THF, ether/ −65°/15 min	Cyclohexanone	(25),	(8)	X = (1-hydroxycyclohexyl)	594

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TABLE XIII. Pyridine-N-Oxides (Alpha) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C₆H₇NO (*Contd.*)		BuLi/THF/−65° 1 hr	Br₂	X = Br (5), X = (13), X = (18)	595, 596
		"	O₂	1-Hydroxy-4-methyl-2(1H)-pyridinone (13)	102, 596
		"	"S"	1-Hydroxy-4-methyl-2(1H)-pyridinethione (39)	102, 596
		BuLi/THF/−65°	CO₂	4-Methylpyridine-2,6-dicarboxylic acid 1-oxide (48)	101, 593
		BuLi/THF/−65°/ 15 min	Cyclohexanone	(21), (27) X =	594, 593
C₇H₉NO		BuLi	Br₂	X = Br (13–23), X = (2–4)	595, 596
		"	Cl₂	2,6-Dichloro-3,4-dimethylpyridine 1-oxide (9)	595, 596
		BuLi/THF/−65°/ 1 hr	O₂	1-Hydroxy-3,4-dimethyl-2(1H)-pyridinone (10), 1-hydroxy-4,5-dimethyl-2(1H)-pyridinone (14)	102, 596
		"	"S"	1-Hydroxy-3,4-dimethyl-2(1H)-pyridinethione (13), 1-hydroxy-4,5-dimethyl-2(1H)-pyridinethione (24) (37)	102, 596
		BuLi/THF/−65°	CO₂	4,5-Dimethylpicolinic acid 1-oxide (18)	101

TABLE XIII. Pyridine-N-Oxides (Alpha) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
C_7H_9NO (*Contd.*)		BuLi/THF	$CH_3CO_2C_2H_5$		X = H (65)	101
		BuLi/THF/−65°	DMA	"	X = (13)	101
		BuLi/THF/−65°/ 15 min	n-C_3H_7CHO	4,5-Dimethyl-α-propyl-2-pyridinemethanol 1-oxide (15)		594
		BuLi/ether/−65°/ 15 min	Cyclohexanone	(56) (16)	X =	594
			"	(84) (−)		593
		BuLi/THF/−65°/ 1 hr	$C_6H_5N=CHC_6H_5$	(12) (62)	X = $CH(C_6H_5)NHC_6H_5$	102
$C_7H_9NO_2$		BuLi/THF/−65°/ 15 min	n-$C_3H_7CO_2C_2H_5$	(19) (17)	X = COC_3H_7-n	101
		"	Cyclohexanone	(20) (21)	X =	594, 593

Note: References 360–607 are on pp. 355–360.

TABLE XIV. Pyrimidines (Alpha)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_5H_6N_2$		LDA/ether/ 0°–35°/1 hr	$(C_6H_5)_2CO$	(30)	99
$C_8H_6N_4$		LDA/THF/ −70°–0°	—	(38),	597
				(I) (12)	597
$C_{16}H_{10}N_2$		LDA/THF/ −70°–20°	—	1 (16)	597

Note: References 360–607 are on pp. 355–360.

TABLE XV. ALKYL VINYL ETHERS AND ALLENIC ETHERS (ALPHA)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
C_3H_6O	CH_2=CHOCH$_3$	t-BuLi*	CuI	[CH$_2$=C(OCH$_3$)]$_2$CuLi (—)		105
		t-BuLi/THF/ $-65°$–$0°$	CH$_3$CH=CHCHO	CH$_2$=C(OCH$_3$)X	X = CH(OH)CH=CHCH$_3$ (74)	104
		"	Cyclopentanone		X = (88)	104
		"	(CH$_3$)$_2$C=CHCOCH$_3$		X = C(CH$_3$)CH=C(CH$_3$)$_2$ (75)	104
		"	C$_6$H$_5$CHO		X = CH(OH)C$_6$H$_5$ (78)	104
		"	C$_6$H$_5$CN		X = COC$_6$H$_5$ (70)	104
		"	C$_6$H$_5$CO$_2$H		X = COC$_6$H$_5$ (62)	104
		"	C$_6$H$_5$CH$_2$COCH$_3$		X = C(CH$_3$)CH$_2$C$_6$H$_5$ (90)	104
		"	n-C$_3$H$_7$CHO (H$_3$O$^+$)	CH$_3$COX	X = CH(OH)C$_3$H$_7$-n (63)	104
		"	(CH$_3$)$_2$C=CHCH$_2$Br (H$_3$O$^+$)		X = CH$_2$CH=C(CH$_3$)$_2$ (74)	104
		"	Cyclohexanone (H$_3$O$^+$)		X = (90)	104
		"	n-C$_8$H$_{17}$I (H$_3$O$^+$)		X = C$_8$H$_{17}$-n (80)	104
		"	n-C$_4$H$_9$CO$_2$CH$_3$		R = n-C$_4$H$_9$ (82)	104, 563
		"	C$_2$H$_5$CH(CH$_3$)CO$_2$CH$_3$		R = CH(CH$_3$)C$_2$H$_5$ (93)	563
		"	t-C$_4$H$_9$CO$_2$CH$_3$		R = C$_4$H$_9$-t (95)	563
		"	C$_6$H$_5$CO$_2$CH$_3$		R = C$_6$H$_5$ (75)	563, 104

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TABLE XV. ALKYL VINYL ETHERS AND ALLENIC ETHERS (ALPHA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C_3H_6O (*Contd.*)	$CH_2=CHOCH_3$	t-BuLi/THF/ $-65°-0°$	$CH_3CH=CHCO_2CH_3$ (H_3O^+)	$(CH_3CO)_2C(OH)CH=CHCH_3$ (46)	104
		"	$C_6H_5COCH_2Br$ (H_3O^+)	3,4-Dihydroxy-3-phenyl-2-butanone (58)	104
		t-BuLi/THF/ $-80°$	$(i$-$C_4H_9)_3B$ (H_3O^+, H_2O_2, OH^-)	$CH_3C(OH)R_2$ $R = C_4H_9$-i (77)	598
		"	$(s$-$C_4H_9)_3B$ (H_3O^+, H_2O_2, OH^-)	$R = C_4H_9$-s (92)	598
		"	(cyclopentyl)$_3$B (H_3O^+, H_2O_2, OH^-)	$R =$ cyclopentyl (87)	598
		"	(cyclohexyl)$_3$B (H_3O^+, H_2O_2, OH^-)	$R =$ cyclohexyl (94)	598
		"	$(n$-$C_6H_{13})_3B$ (H_3O^+, H_2O_2, OH^-)	$R = C_6H_{13}$-n (100)	598
		t-BuLi/THF/ $-65°-0°$	Estrone methyl ether	3-O-Methyl-17α(α-methoxyvinyl)estra-3,17β-diol (83)	365, 104
C_4H_5ClO	3-chloro-2,3-dihydrofuran	BuLi/THF/ $-78°$	CH_3I	$X = CH_3$ (74)	266
		"	CH_3COCl	$X = C(CH_3)(OAc)$-chlorodihydrofuranyl (78)	266
		"	n-C_4H_9I	$X = C_4H_9$-n (62)	266
C_4H_6O	$CH_2=C=CHOCH_3$	BuLi/THF, ether/ $-40°/45$ min	CH_3COCH_2Cl	$CH_2=C=C(OCH_3)X$ $X = CH_3$-epoxide (50–75)	599
		BuLi/THF, ether/ $-20°/10$ min	n-C_3H_7Br	$X = C_3H_7$-n (47)	108a
		"	n-C_3H_7I	$X = C_3H_7$-n (51)	108a
		BuLi/THF, ether/ $-40°/45$ min	$CH_3COCH(CH_3)Cl$	$X = CH_3,CH_3$-epoxide (50–75)	599
		BuLi/THF, ether/ $-20°/10$ min	n-C_4H_9Br	$X = C_4H_9$-n (67)	108a
		BuLi/THF, ether/ $-40°/45$ min	$CH_3COC(CH_3)_2Cl$	$X = CH_3,(CH_3)_2$-epoxide (50–75)	599
		"	t-$C_4H_9COCH_2Cl$	$X = t$-C_4H_9-epoxide (50–75)	599
		BuLi/THF, ether/ $-20°/10$ min	$C_6H_5CH_2Br$	$X = CH_2C_6H_5$ (64)	108a
		BuLi/THF, ether/ $-40°/45$ min	$C_6H_5COCH_2Cl$	$X = C_6H_5$-epoxide (50–75)	599
	2,3-dihydrofuran	t-BuLi/ $-78°-5°/$ 0.5 hr	$(CH_3)_2C=CHCH_2Br$	$X = CH_2CH=C(CH_3)_2$ (67)	576
		"	n-$C_6H_{13}I$	$X = C_6H_{13}$-n (64)	576
$C_4H_7ClO_2$	CH_3O, OCH_3, Cl (chloro-dimethoxy ethylene)	s-BuLi/THF/ $-100°/0.5$ hr	$HgCl_2$	Bis[(Z)-2-chloro-1,2-dimethoxyvinyl]mercury (—)	600
		"	CO_2	(E)-3-Chloro-2,3-dimethoxyacrylic acid (45)	600

TABLE XV. ALKYL VINYL ETHERS AND ALLENIC ETHERS (ALPHA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
C_4H_6O	$CH_2=CHOC_2H_5$	t-BuLi/THF/ $-65°-0°*$	$(CH_3)_2SiHCl$	$CH_2=C(OC_2H_5)X$	$X = SiH(CH_3)_2$ (44)	601
		"	$(t-C_4H_9)_2SiF_2$		$X = SiF(C_4H_9-t)_2$ (50)	601
		t-BuLi/ TMEDA/ $-30°/40$ min	C_6H_5CHO		$X = CH(OH)C_6H_5$ (43)	103
		t-BuLi/THF/ $-65°-0°$	$(CH_3)_3SiCl$	Acetyltrimethylsilane (31)		601
	$CH_3CH=CHOCH_3$	t-BuLi/TMEDA	C_6H_5CHO	1-Hydroxy-1-phenyl-2-butanone (55)		104
C_5H_7ClO		BuLi/THF/25°/ 2 hr	CH_3I		$X = CH_3$ (>65)	562
		"	C_2H_5I		$X = C_2H_5$ (>65)	562
		"	$n-C_4H_9I$		$X = C_4H_9-n$ (>65)	562
C_5H_8O		BuLi/THF/50°/ 1 hr	CH_3I		$X = CH_3$ (35)	562
		"	$n-C_4H_9I$		$X = C_4H_9-n$ (35–75)	562
		t-BuLi/ pentane/ $-78°-5°/0.5$ hr			$X =$ (60)	576
		"	$CH_3CO(CH_2)_2CO_2CH_3$		$X = CH_3$ (68)	576
		BuLi/THF/50°/ 1 hr	$n-C_6H_{13}I$		$X = C_6H_{13}-n$ (75)	562, 576
C_5H_8O	$CH_2=CH-CH=CHOCH_3$	t-BuLi/THF/ $-65°-0°$	C_6H_5CHO	1-Hydroxy-1-phenyl-3-buten-2-one (30)		104
$C_6H_{10}O_2$		t-BuLi/ pentane/ 0°/1–2 hr		6-(2-Cyclohexen-1-yl)-3,4-dihydro-2-methoxypyran (52)		576
$C_7H_{10}O$	$(CH_3)_2C=C=C=CHOCH_3$	BuLi/ether/ $-30°/10$ min	CH_2O	$(CH_3)_2C=C=C=C(OCH_3)X$	$X = CH_2OH$ (55)	109
		"	CH_3CHO		$X = CH(OH)CH_3$ (74)	109
		"	CH_3COCH_3		$X = C(CH_3)_2OH$ (71)	109
		"	$C_2H_5COC_2H_5$		$X = C(C_2H_5)_2OH$ (68)	109
		"	Cyclohexanone		$X =$ (90)	109
	$CH_2=C(CH_3)CH=C=CH-OCH_3$	BuLi/ether/ $-30°/10$ min	CH_3COCH_3	$CH_2=C(CH_3)CH=C[C(CH_3)_2OH]OCH_3$ (75)		109
$C_7H_{12}O$	$CH_2=C=CHOC_4H_9-t$	LDCA/THF/ $-55°/15$ min	$n-C_4H_9I$ (H_3O^+)	2-Heptenal (80), 1-hepten-3-one (5)		108b
$C_7H_{12}O_2$		t-BuLi/ pentane/ 0°/1–2 hr	$(CH_3)_2C=CHCH_2Br$	3,4-Dihydro-2-methoxy-2-methyl-6-(3-methyl-2-butenyl)pyran (57)		576
$C_8H_{14}O_2$		s-BuLi,KOBu-t/ THF/$-78°$	CH_3I		(83)	107
$C_9H_{16}O$	$CH_2=C=CHOC_6H_{13}-n$	BuLi/ether/ $-35°$ to $-25°$	D_2O	$CH_2=C=CDOC_6H_{13}-n$ (—)		108a
$C_9H_{16}O_3$	$(C_2H_5O)_2$	t-BuLi/ pentane/ 0°/1–2 hr	CH_3COCH_3	2,2-Diethoxy-3,4-dihydro-α,α-dimethylpyran-6-methanol (53)		576

TABLE XV. ALKYL VINYL ETHERS AND ALLENIC ETHERS (ALPHA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
$C_{10}H_9LiO$	C_6H_5, Li, $C=C=C$, OCH₃, H	BuLi/ether/ −75°/15 min	CH₃I,(CH₃)₃SiCl	C_6H_5, X, $C=C=C$, OCH₃, Y		
				X	Y	
		BuLi/ether/ −75°	C₂H₅Br, —	$\overline{CH_3}$ C₂H₅	$\overline{Si(CH_3)_3}$ (78) H (87)	602 603
		BuLi/ether/ −75°/15 min	C₂H₅Br, CH₃I	C_6H_5, X, $C=C=C$, OCH₃, Y		
				X	Y	
				$\overline{C_2H_5}$	$\overline{CH_3}$ (76)	602, 603
		''	C₂H₅Br, (CH₃)₃SiCl	C₂H₅	Si(CH₃)₃ (82)	602, 603
		''	(CH₃O)₂SO₂, (CH₃O)₂SO₂	CH₃	CH₃ (70)	602, 603
		''	(CH₃)₃SiCl, CO₂	Si(CH₃)₃	CO₂H (90)	602
		''	(CH₃)₃SiCl, CH₃I	Si(CH₃)₃	CH₃ (70)	602, 603
		''	(CH₃)₃SiCl, CH₃COCH₃	Si(CH₃)₃	C(CH₃)₂OH (80)	602
		''	(CH₃)₃SiCl, (CH₃)₃SiCl	Si(CH₃)₃	Si(CH₃)₃ (80)	602, 603
		BuLi/ether/ −75°	n-C₄H₉Br,—	n-C₄H₉	H (86)	603
$C_{10}H_{18}O$	n-C₅H₁₁, CH₃, $C=C=C$, OCH₃, H	BuLi/ether	CH₃I	n-C₅H₁₁, CH₃, $C=C=C$, OCH₃, X; X = CH₃ (100)		360
		''	(CH₃)₃SiCl	X = Si(CH₃)₃ (100)		360
$C_{11}H_{11}LiO$	C_6H_5, Li, $C=C=C$, OC₂H₅, H	BuLi/ether/ −75°/15 min	(CH₃)₃SiCl, (CH₃)₃SiCl	C_6H_5, (CH₃)₃Si, $C=C=C$, OC₂H₅, Si(CH₃)₃ (70)		602
$C_{12}H_{24}O_4Si$	n-C₅H₁₁, (CH₃)₃Si, $C=C=C$, OCH₃, H	BuLi/ether	C₂H₅Br	n-C₅H₁₁, (CH₃)₃Si, $C=C=C$, OCH₃, X; X = C₂H₅ (61)		360
		''	C₂H₅I	X = C₂H₅ (70)		360
		''	(CH₃O)₂SO₂	X = CH₃ (100)		360
		''	(CH₃)₃SiCl	X = Si(CH₂)₃ (78)		360

Note: References 360–607 are on pp. 355–360.

TABLE XVI. Furans (Alpha)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_4H_2Br_2O$	(3,2-dibromofuran)	LDA/THF or ether/$-70°$	$(CH_3)_3SiCl$	(4,5-Dibromo-2-furyl)trimethylsilane ($—$)	246
C_4H_3BrO	(3-bromofuran)	LDA/THF/$-80°$/ 2.5 hr	CH_2O	X = CH_2OH (52) [furan with Br and X]	566
		"	CH_3OCH_2Cl	$X = CH_2OCH_3$ (49)	566
		LDA/THF or ether/$-70°$	$(CH_3)_3SiCl$	$X = Si(CH_3)_3$ ($—$)	246
		LDA/THF/$-80°$/ 2.5 hr	$(CH_3)_2C=CHCH_2Br$	$X = CH_2CH=C(CH_3)_2$ (66)	566
C_4H_3ClO	(3-chlorofuran)	LDA/THF/$-80°$/ 2.5 hr	$(CH_3)_2C=CHCH_2Br$	3-Chloro-2-(3-methyl-2-butenyl)furan (41)	566
C_4H_4O	(furan)	C_6H_5Li/ether	"S" + CH_3I	$X = SCH_3$ (35) [2-furyl-X]	292
		BuLi/ether/$-35°$– reflux/4 hr	"S" + C_2H_5I	$X = SC_2H_5$ (53)	361
		C_6H_5Li/ether	"S" + $CH_2=CHCH_2Br$	$X = SCH_2CH=CH_2$ (70)	292
		"	"S" + Ac_2O	$X = SAc$ (45)	292
		"	"S" + $C_6H_5CH_2Cl$	$X = SCH_2C_6H_5$ (60)	292
		"	"Se" + CH_3I	$X = SeCH_3$ (49)	292
		BuLi/ether/$-20°$*	"Se" + C_2H_5I	$X = SeC_2H_5$ (51)	362
		C_6H_5Li/ether	"Se" + $CH_2=CHCH_2Br$	$X = SeCH_2CH=CH_2$ (61)	292
		"	"Se" + Ac_2O	$X = SeAc$ (64)	292
		"	"Se" + $C_6H_5CH_2Cl$	$X = SeCH_2C_6H_5$ (58)	292
		BuLi/ether/$25°$– reflux/6 hr	SO_2	$X = SO_2Li$ (55)	363
		BuLi/ether/$-20°$– reflux/4 hr	CO_2	$X = CO_2H$ (77)	112
		BuLi/THF/$-15°$/ 4 hr	CH_3I	$X = CH_3$ (89)	566
		LDA/THF/$-15°$/ 4 hr	"	$X = CH_3$ (36)	566
		—	$CF_2=CCl_2$	$X = CF=CCl_2$ (53)	364
		EtLi/ether/$25°$	CCl_3CCl_3	$X = Cl$ (48)	365
		BuLi/ether/$20°$/ 3 hr	Ethylene oxide	$X = (CH_2)_2OH$ (57)	366
		BuLi/THF/$-15°$/ 6.5 hr	Propylene oxide	$X = CH_2CH(OH)CH_3$ (98)	367, 368 561
		BuLi/ether/ reflux/3 hr	$(CH_3)_3SiCl$	$X = Si(CH_3)_3$ (52)	369
		—	[pyrimidine] ($KMnO_4$)	$X =$ [methylpyrimidine] ($—$)	370
		BuLi/ether/ reflux/4 hr	Ac_2O	$X = COCH_3$ (26)	371
		BuLi/THF/$-15°$/ 6.5 hr	[epoxide]C_2H_5	$X = CH_2CH(OH)C_2H_5$ (85)	367
		BuLi	$ClB[N(CH_3)_2]_2$	$X = B[N(CH_3)_2]_2$ (15)	295
		BuLi/ether/$-20°$– reflux/4 hr	$(CH_3)_2CHCHO$	$X = CH(OH)CH(CH_3)_2$ (93)	112
		"	$CH_3COC_2H_5$	$X = \underset{OH}{C(CH_3)C_2H_5}$ (88)	112

TABLE XVI. Furans (Alpha) (Continued)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C₄H₄O (Contd.)		"	CH₃CO₂C₂H₅	$X = $ (94)	112
		BuLi/THF/−25° to −15°/4hr	n-C₄H₉Br	X = C₄H₉-n (77)	112
		BuLi/THF/−15°/ 4 hr	(CH₃)₂C=CHCHO	X = CH(OH)CH=C(CH₃)₂ (79)	566
		"	(CH₃)₂C=CHCH₂Br	X = CH₂CH=C(CH₃)₂ (76)	566
		BuLi/ether/−20°– reflux/4 hr	Cyclohexanone	$X = $ (95)	112
		BuLi/THF/−15°/ 6 hr	BrCH₂CH(OC₂H₅)₂	X = CH₂CH(OC₂H₅)₂ (70)	367
		BuLi/ether/−20°– reflux/4 hr	C₆H₅CN (H₃O⁺)	X = COC₆H₅ (89)	112
		BuLi/ether/−20°– reflux/4 hr	C₆H₅CHO	X = CH(OH)C₆H₅ (98)	112
		"	C₆H₅COCH₃	X = C(CH₃)C₆H₅ (96) OH	112
		"	C₆H₅CO₂C₂H₅	$X = $ (44)	112
		EtLi/ether/−40°– reflux/0.5 hr	(n-C₄H₉O)₃B (H₃O⁺)	X = B(OH)₂ (55)	115
		BuLi/ether/−20°– reflux/4 hr	(C₆H₅)₂CO	X = C(C₆H₅)₂OH (98)	112
		BuLi		$X = $ (30–36)	372
		3 BuLi/ether/ reflux/4 hr	D₂O	2,5-d₂-Furan (80)	373
		BuLi/ether		(35)	374
		C₆H₅Li/ether/1 hr	PBr₃	Tri-2-furylphosphine (33)	296
		"	POCl₃	Tri-2-furylphosphine oxide (68)	296
		BuLi/hexane, TMEDA/reflux/ 0.5 hr	CO₂ (CH₂N₂)	Methyl furan-2-carboxylate (I) (9), dimethyl furan-2,5-dicarboxylate (II) (91)	40
		BuLi/ether, TMEDA/reflux/ 0.5 hr	"	I (33), II (55)	40
C₅H₆O		BuLi/ether/ reflux/2.5 hr	"S"	X = SH (40)	497
		BuLi/ether/−35°– reflux/4 hr	"S" + C₂H₅I	X = SC₂H₅ (77)	361
		BuLi/ether/−20°– reflux	"S" + ClCH₂CO₂CH₃	X = SCH₂CO₂CH₃ (51)	362

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TABLE XVI. FURANS (ALPHA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
C_5H_6O (*Contd.*)	CH$_3$	BuLi/ether/−35°– reflux/4 hr	"S" + *n*-C$_4$H$_9$I	CH$_3$ — X	X = C$_4$H$_9$-*n* (66)	361
		"	"S" + *i*-C$_4$H$_9$I		X = C$_4$H$_9$-*i* (59)	361
		BuLi/ether/ reflux/4 hr	CuBr		X = CH$_3$ (25)	367
		BuLi/ether/−20°– reflux	"Se" + C$_2$H$_5$I		X = SeC$_2$H$_5$ (41)	362
		"	"Se" + ClCH$_2$CO$_2$CH$_3$		X = SeCH$_2$CO$_2$CH$_3$ (43)	362
		BuLi/hexane, TMEDA/reflux/ 0.5 hr	CO$_2$ (CH$_2$N$_2$)		X = CO$_2$CH$_3$ (62)	40
		BuLi/THF/−15°/ 6 hr	BrCH$_2$CH(OC$_2$H$_5$)$_2$		X = CH$_2$CH(OC$_2$H$_5$)$_2$ (45)	367
		—	(HClO$_4$)	X = ClO$_4^-$ (−)		375
		BuLi/ether/0°/ 1.5 hr	OC$_2$H$_5$	X = (58)		284
		BuLi/THF/−25°/ 1 hr, −15°/4 hr	CH$_2$=CHCH(CH$_3$)Br	X = CH$_2$CH=CHCH$_3$ (III), X = CH(CH$_3$)CH=CH$_2$ (IV) (III + IV, 59) (III : IV, 1 : 2)		367
		BuLi	BrCH(CH$_3$)CH(OC$_2$H$_5$)$_2$	X = CH(CH$_3$)CH(OC$_2$H$_5$)$_2$ (V), X = CH$_3$ OC$_2$H$_5$ (VI) (V + VI, 50) (V : VI, 2 : 1)		367
	CH$_3$	BuLi/hexane, TMEDA/reflux/ 0.5 hr	CO$_2$ (CH$_2$N$_2$)	Dimethyl 3-methylfuran-2,5-dicarboxylate (66), methyl 3-methylfuran-2-carboxylate (18), methyl 4-methylfuran-2-carboxylate (4)		40
C_6H_8O	C$_2$H$_5$	BuLi/ether/−35°– reflux/4 hr	"S" + C$_2$H$_5$I	2-Ethyl-5-(ethylthio)furan (76)		361
C_6H_8OS	SC$_2$H$_5$	BuLi/ether/−35°– reflux/4 hr	"S" + C$_2$H$_5$I	2,5-Di(ethylthio)furan (77)		361
$C_7H_7BrO_3$	Br	LDA/THF or ether/−70°	D$_2$O	2-(3-Bromo-2-furyl-5-*d*)-1,3-dioxolane (−)		246
$C_7H_8O_3$		BuLi/ether/−10°– reflux/15 min	CO$_2$ (H$_3$O$^+$)	CHO X	X = CO$_2$H (50)	376
		"	DMA (H$_3$O$^+$)		X = COC$_2$H$_5$ (40)	376
		BuLi/ether/0°/ 0.5 hr	CON(CH$_3$)$_2$ (H$_3$O$^+$)	X = CO (41)		113

TABLE XVI. FURANS (ALPHA) (Continued)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_7H_8O_3$ (Contd.)	[furan-1,3-dioxolane]	"	[thiophene]$CON(CH_3)_2$ (H_3O^+)	$X = CO$[thiophene] (30)	113
		" / BuLi/ether/ −30°–25°/0.5 hr	$C_6H_5CON(CH_3)_2$ (H_3O^+) / $(n-C_4H_9O)_3B$ (H_3O^+)	$X = COC_6H_5$ (61) / $X = B(OH)_2$ (36)	113 / 115, 114
$C_7H_{10}LiNO_2$	[furan]$CH(OLi)N(CH_3)_2$	EtLi/ether/ reflux/2 hr	$(n-C_4H_9O)_3B$ (H_3O^+)	[furan with CHO and $B(OH)_2$] (32)	114, 115
$C_7H_{10}O_2$	[furan]$CH_2CH(CH_3)OH$	BuLi/THF/−15°/ 6 hr	Ethylene oxide	5-[2-Hydroxyethyl]-α-methyl-2-furanethanol (80)	367
$C_7H_{12}OSi$	[furan]$Si(CH_3)_3$	BuLi/ether/ reflux/4 hr	CO_2	5-(Trimethylsilyl)-2-furoic acid (62)	369
$C_9H_{11}NO_2$	[furan-oxazoline]$N$$(CH_3)_2$	BuLi/THF/−70°/ 1 hr	C_6H_5CHO	[furan-oxazoline structures] (49), (36) $X = CH(OH)C_6H_5$	377
$C_9H_{14}O_3$	[furan]$CH(OC_2H_5)_2$	BuLi/ether/−10°– 25°/4 hr	D_2O	$(C_2H_5O)_2CH$[furan]X, $X = D$ (93)	297
		"	$(CH_3)_3SiCl$	$X = Si(CH_3)_3$ (80)	297
		"	$(CH_3)_2C_2H_5SiCl$	$X = SiC_2H_5(CH_3)_2$ (78)	297
		"	$(CH_3)_3SiCH_2Cl$	$X = CH_2Si(CH_3)_3$ (33)	297
		"	$(C_2H_5)_3SiCl$	$X = Si(C_2H_5)_3$ (69)	297
		"	$(CH_3)_2C_6H_5SiCl$	$X = SiC_6H_5(CH_3)_2$ (80)	297
		"	$(C_2H_5)_2C_6H_5SiCl$	$X = SiC_6H_5(C_2H_5)_2$ (80)	297
		—	[2,6-dimethyl-4-pyranone] ($HClO_4$)	$X = $ [2,4,6-trimethylpyrylium]$^+$ ClO_4^- (−)	375
		BuLi/ether/−10°– 25°/4 hr	CO_2 (H_3O^+)	5-Formyl-2-furoic acid (80)	297
		"	C_6H_5CN (H_3O^+)	5-Benzoyl-2-furaldehyde (48)	297
		EtLi/ether/−40°– 25°/2 hr	$(n-C_4H_9O)_3B$ (H_3O^+)	OHC[furan]$B(OH)_2$ (33)	115
$C_{10}H_{14}O_3$	[furan-1,3-dioxane]$(CH_3)_2$	BuLi	$(C_6H_5)_2CO$	$HO(C_6H_5)_2C$[furan-1,3-dioxane]$(CH_3)_2$ (67)	378
$C_{10}H_{16}O_3$	[furan]$CH_2CH(OC_2H_5)_2$	BuLi/THF/−15°/ 6 hr	Propylene oxide	C_2H_5O[furan]$CH_2CH(CH_3)OH$ (37)	367
$C_{11}H_{16}O_3$	[furan-1,3-dioxane]CH_3 $(CH_3)_2$	BuLi	DMF	OHC[furan-1,3-dioxane]CH_3 $(CH_3)_2$ (−)	379
$C_{12}H_{18}O_3$	[furan]$CH_2CH(CH_3)OTHP$	BuLi/THF/−15°/ 4 hr	$CH_2=CHCH_2Br$	$CH_2=CHCH_2$[furan]$CH_2CH(CH_3)OTHP$ (37)	367

Note: References 360–607 are on pp. 355–360.

TABLE XVII. Condensed Furans (Alpha)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C_8H_5ClO		BuLi/ether/ reflux/2 hr	D_2O	5-Chloro-2-d-benzofuran (—)	380
		BuLi	Ethylene oxide	5-Chloro-2-(2-hydroxyethyl)- benzofuran (45–62)	116
C_8H_6O		BuLi/ether/ 25°/40 min	D_2O	X = D (70)	381, 380
		BuLi/ether/ −10°/1 hr	CO_2	X = CO_2H (70)	479
		,,	CH_3I	X = CH_3 (63)	479
		BuLi/ether/ 22°/0.5 hr	Ethylene oxide	X = $(CH_2)_2OH$ (45)	382, 116
		BuLi/ether/ −10°/1 hr	DMF	X = CHO (70)	479
C_9H_8O		BuLi	Ethylene oxide	2-(2-Hydroxyethyl)-5-methyl- benzofuran (45–62)	116
$C_9H_8O_2$		BuLi	Ethylene oxide	2-(2-Hydroxyethyl)-5-methoxy- benzofuran (45–62)	116
$C_{12}H_8O$		BuLi/ether/ reflux/10 min	DMF	(45)	278

TABLE XVIII. Oxazoles and Oxazolines (Alpha)

Formula	Compound lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C_5H_9NO	$(CH_3)_2$ oxazoline	BuLi/THF	D_2O	2-d-4,4-Dimethyl-2-oxazoline (99)	119
		BuLi/THF/−60°	D_2O	2-d-5-Phenyloxazole (96)	118
C_9H_7NO	C_6H_5 oxazole	BuLi	C_6H_5CHO	α,5-Diphenyl-2-oxazolemethanol (—)	383
C_9H_9NO	C_6H_5 oxazoline	BuLi/THF/−70°/ 10 min	CH_3OD	2-d-5-Phenyl-2-oxazoline (—)	120
$C_{15}H_{11}NO$	C_6H_5 / C_6H_5 oxazole	BuLi/THF/−60°	D_2O	2-d-4,5-Diphenyloxazole (95)	118
		"	C_6H_5CHO	α,4,5-Triphenyl-2-oxazolemethanol (67)	118
$C_{15}H_{13}NO$	C_6H_5 / C_6H_5 oxazoline	BuLi/THF/−70°/ 10 min	C_6H_5CHO	α,4,5-Triphenyl-2-oxazoline-2-methanol (58)	120

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Note: References 360–607 are on pp. 355–360.

TABLE XIX. VINYL SULFIDES AND ALLENIC THIOETHERS (ALPHA)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
C_4H_6S	$CH_2{=}CHSC_2H_5$	s-BuLi/THF, HMPA/ −78°/0.5 hr	$Br(CH_2)_3Br$ (HgCl₂)	3-Methyl-2-cyclohexen-1-one (52)		121
		"	$Br(CH_2)_4Br$ (HgCl₂)	CH_3COX	X = $(CH_2)_4COCH_3$ (60)	121
		"	C_6H_5CHO (HgCl₂)		X = $CH(OH)C_6H_5$ (64)	121
		"	Styrene oxide (HgCl₂)		X = $CH{=}CHC_6H_5$ (68)	121
		"	$n\text{-}C_8H_{17}Br$ (HgCl₂)		X = $C_8H_{17}\text{-}n$ (90)	121
		"	$n\text{-}C_8H_{17}CHO$ (HgCl₂)		X = $CH(OH)C_8H_{17}\text{-}n$ (58)	121
$C_6H_4S_4$	[1,3-dithiole-1,3-dithiole (tetrathiafulvalene) structure]	BuLi	CO_2	(1,3-Dithiol-2-ylidene)-1,3-dithiole-4-carboxvlic acid (56)		162
$C_6H_{10}S$	$CH_3CH{=}C{=}CHSC_2H_5$	CH_3Li/ether	CH_2O	$CH_3CHC{\equiv}CSC_2H_5$ (I), $\overset{\mid}{CH_2OH}$; $CH_3CH{=}C{=}C(SC_2H_5)CH_2OH$ (II) (I+II, 75) (I:II, 3:2)		130
$C_6H_{10}S_2$	[butadiene—SCH₃ / SCH₃ structure]	BuLi/THF, TMEDA/−40°	CH_3I	1,4-Bis (methylthio)-1,3-pentadiene (96)		605
		BuLi/THF, TMEDA, HMPA/25°	H_2O	2-(Methylthio)thiophene (75–80)		605
		"	CH_3I	2-Methyl-5-(methylthio)thiophene (75–80)		605
$C_6H_{12}S_2$	[C_2H_5S ⟍⟋ SC_2H_5 cis structure]	LDA/THF/−80°/ 10 min	CH_3OD	[C_2H_5S, SC_2H_5, X product structure]	X = D (85)	128
		"	CH_3SO_3F		X = CH_3 (68)	128
		t-BuLi/THF/ −80°/10 min	$(CH_3S)_2$		X = SCH_3 (100)	128
		"	C_6H_5CHO		X = $CH(OH)C_6H_5$ (87)	128
C_8H_8S	$CH_2{=}CHSC_6H_5$	BuLi, pet. ether/ 25°/3.5 hr	CH_3I	Methyl phenyl sulfide (21), isopropenyl phenyl sulfide (53)		384
		LDA/THF/−78°	$(CH_3S)_2$	$CH_2{=}C(SC_6H_5)X$	X = SCH_3 (61)	125
		"	$(CH_3)_3SiCl$		X = $Si(CH_3)_3$ (97)	125
		"	C_6H_5SeBr		X = SeC_6H_5 (84)	125
		LDA/THF, HMPA/ −60°/0.5 hr	$n\text{-}C_5H_{11}CHO$		X = $CH(OH)C_5H_{11}\text{-}n$ (76)	124
		LDA/THF/−78°	$(C_6H_5S)_2$		X = SC_6H_5 (59)	125
		"	$(n\text{-}C_4H_9)_3SnCl$		X = $Sn(C_4H_9\text{-}n)_3$ (87)	125
$C_9H_{10}S$	$C_6H_5CH{=}CHSCH_3$	s-BuLi/THF, HMPA/ −78°/0.5 hr	Propylene oxide (HgCl₂)	$C_6H_5CH_2COX$	X = $CH{=}CHCH_3$ (57)	121
		"	C_6H_5CHO (HgCl₂)		X = $CH(OH)C_6H_5$ (54)	121
		"	$n\text{-}C_8H_{17}Br$ (HgCl₂)		X = $C_8H_{17}\text{-}n$ (65)	121
$C_9H_{18}OS$	[C_2H_5O / $SC_5H_{11}\text{-}n$ structure]	t-BuLi/THF/ −70°/1 hr	$n\text{-}C_4H_9Br$	[C_2H_5O, X, $SC_5H_{11}\text{-}n$ product]	X = $C_4H_9\text{-}n$ (42)	127
		"	$n\text{-}C_4H_9I$		X = $C_4H_9\text{-}n$ (60)	127
		"	$n\text{-}C_6H_{13}CHO$		X = $CH(OH)C_6H_{13}\text{-}n$ (82)	127
		"	C_6H_5CHO		X = $CH(OH)C_6H_5$ (80)	127
$C_{10}H_{12}OS$	[C_2H_5O / SC_6H_5 structure]	t-BuLi/THF/−70°/ 1 hr	D_2O	[C_2H_5O, X, SC_6H_5 product]	X = D (95)	127
		"	Ethylene oxide		X = $(CH_2)_2OH$ (60)	127
		"	Propylene oxide		X = $CH_2CH(OH)CH_3$ (55)	127
		"	$n\text{-}C_4H_9I$		X = $C_4H_9\text{-}n$ (55)	127
		"	$CH_3CH{=}CHCHO$		X = $CH(OH)CH{=}CHCH_3$ (78)	127
		"	Cyclopentanone		X = HO–[cyclopentane] (78)	127
		"	C_6H_5CHO		X = $CH(OH)C_6H_5$ (75)	127

TABLE XIX. VINYL SULFIDES AND ALLENIC THIOETHERS (ALPHA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
$C_{10}H_{12}OS$ (*Contd.*)	C₂H₅O / SC₆H₅ (structure)	"	$n\text{-}C_6H_{13}CHO$	X = CH(OH)C₆H₁₃-n (84)		127
$C_{11}H_{15}NS$	(CH₃)₂NCH₂ / SC₆H₅ (structure)	BuLi/ether/0°/ 1 hr	D_2O	(CH₃)₂NCH₂—X / SC₆H₅ (structure) X = D (>90%)		23
$C_{11}H_{22}S$	$n\text{-}C_8H_{17}CH{=}CHSCH_3$	"	$(CH_3S)_2$	X = SCH₃ (>90%)		23
		s-BuLi/THF, HMPA/−78°/ 0.5 hr	C_6H_5CHO (HgCl₂)	$n\text{-}C_9H_{19}COX$ X = CH(OH)C₆H₅ (51)		121
		"	$n\text{-}C_8H_{17}Br$ (HgCl₂)	X = C₈H₁₇-n (82)		121
$C_{11}H_{12}S_2$	SCH₃ / SC₆H₅ (structure)	BuLi/THF, TMEDA/−40°	CH_3I	1-(Methylthio)-4-(phenylthio)-1,3-butadiene (96)		605
		BuLi/THF, TMEDA, HMPA/25°	H_2O	2-(Methylthio)thiophene (75–80)		605
		"	CH_3I	2-Methyl-5-(methylthio)thiophene (75–80)		605
$C_{14}H_{12}S_2$	C₆H₅S—SC₆H₅ (structure)	BuLi/ether/−10°	$(CH_3O)_2SO_2$	C₆H₅C≡CX	X = H (26), X = CH₃ (45)	129
	C₆H₅S / SC₆H₅ (structure)	BuLi/ether/−10°	$(CH_3O)_2SO_2$	C₆H₅C≡CX	X = H (17), X = CH₃ (53)	129

Note: References 360–607 are on pp. 355–360.

TABLE XX. Vinyl Sulfoxides (Alpha)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C_8H_9NOS		LDA/THF/−100°/ 5 min	CH_3I	(E)-1-Methylpropenyl 2-pyridyl sulfoxide (96)	132
		"	C_6H_5CHO	(E)-1-Phenyl-2-(2-pyridylsulfinyl)-2-buten-1-ol (91)	132
$C_9H_{10}OS$	$C_6H_5SCH=CHCH_3$	LDA/THF/−100°/ 10 min	CH_3I	X = CH_3 (80)	132
		"	Propylene oxide	X = $CH_2CH(OH)CH_3$ (45)	132
		"	C_6H_5CHO	X = $CH(OH)C_6H_5$ (93)	132
		"	Styrene oxide	X = $CH(C_6H_5)CH_2OH$ (23)	132
$C_{10}H_{12}O_2S$	$C_6H_5SCH=CHCH_2OCH_3$	LDA/THF/−100°/ 5 min	D_2O	X = D (71)	132

TABLE XX. VINYL SULFOXIDES (ALPHA) (Continued)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
C$_{10}$H$_{12}$O$_2$S (Contd.)	C$_6$H$_5$SCH=CHCH$_2$OCH$_3$ (with O↑ on S)	"	CH$_3$I	(structure: C$_6$H$_5$S(O)−, X, CH$_2$OCH$_3$)	X = CH$_3$ (73)	132
		"	C$_6$H$_5$CHO		X = CH(OH)C$_6$H$_5$ (80)	132
		"	C$_6$H$_5$COCH$_3$		X = C(CH$_3$)C$_6$H$_5$ | OH (74)	132
C$_{15}$H$_{15}$NOS	(2-pyridyl)S(O)CH=CH(CH$_2$)$_2$C$_6$H$_5$	LDA/THF/−100°/ 5 min	CH$_3$I	(E)-1-Methyl-4-phenyl-1-butenyl 2-pyridyl sulfoxide (99)		132
C$_{16}$H$_{16}$OS	C$_6$H$_5$SCH=CH(CH$_2$)$_2$C$_6$H$_5$ (with O↑ on S)	LDA/THF/−100°/ 10 min	CH$_3$I	(E)-1-Methyl-4-phenyl-1-butenyl phenyl sulfoxide (89)		132

TABLE XXI. Thiophenes (Alpha)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C₄H₃BrS		LDA/THF or ether/−70°	(CH₃)₃SiCl	(5-Bromo-2-thienyl)trimethylsilane (—)	246
		C₆H₅Li/ether/ overnight	CO₂	3-Bromo-2-thiophenecarboxylic acid (72)	48
C₄H₃FS		BuLi/ether/ reflux/15 min	CO₂	3-Fluoro-2-thiophenecarboxylic acid (75)	385
C₄H₃IS		C₆H₅Li/ether, TMEDA	CO₂	5-Iodo-2-thiophenecarboxylic acid (30)	68
		Li/ether, CO₂ TMEDA/ −10°/0.5 hr		3-Iodo-2-thiophenecarboxylic acid (80), 4-iodo-2-thiophenecarboxylic acid (20)	68
C₄H₃NO₂S		LDA/THF or ether/−70°	(CH₃)₃SiCl	Trimethyl(3-nitro-2-thienyl)silane (—)	246
C₄H₃ST		BuLi/ether/ reflux/0.5 hr	CO₂	5-t-2-Thiophenecarboxylic acid (I), 2-thiophenecarboxylic acid (II) (I+II, 87) (I:II, 89:11)	386, 37

TABLE XXI. THIOPHENES (ALPHA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
C$_4$H$_4$S		BuLi/ether/0°/ 1 hr	FClO$_3$		X = F (49)	149
		BuLi/THF/−30° to −20°/1 hr	"S"		X = SH (65–70)	357
		BuLi/ether/ reflux/2 hr	"S" + ClCH$_2$CO$_2$H		X = SCH$_2$CO$_2$H (80)	387
		BuLi/ether	"S" + ClCH$_2$CO$_2$CH$_3$		X = SCH$_2$CO$_2$CH$_3$ (85)	388
		BuLi/ether/ reflux/6 hr	SO$_2$		X = SO$_2$Li (57)	363
		BuLi/ether/−20°	"Se" + C$_2$H$_5$I		X = SeC$_2$H$_5$ (73)	362
		BuLi/ether/ reflux/0.5 hr	CF$_2$=CCl$_2$		X = CF=CCl$_2$ (81)	364
		BuLi/ether	Ethylene oxide		X = (CH$_2$)$_2$OH (78)	389
		BuLi/ether/25°/ 1 hr	C$_2$H$_5$Br		X = C$_2$H$_5$ (61)	20
		BuLi/ether/−35°	ClCH$_2$OCH$_3$		X = CH$_2$OCH$_3$ (76)	390
		BuLi/ether/ reflux/3 hr	(CH$_3$)$_3$SiCl		X = Si(CH$_3$)$_3$ (75)	369
		BuLi/ether/25°/ 1 hr	(CH$_3$O)$_2$SO$_2$		X = CH$_3$ (65)	20
		BuLi/ether			X = (64)	391
		"			X = (90)	391
		—	(KMnO$_4$)		X = (−)	370
		BuLi/ether/ reflux/3 hr	ClB		X = B (35)	295
		BuLi/ether/25°/ 1 hr	n-C$_4$H$_9$Br		X = C$_4$H$_9$-n (47)	20
		BuLi/ether/ reflux/3 hr	ClB[N(CH$_3$)$_2$]$_2$		X = B[N(CH$_3$)$_2$]$_2$ (17)	295
		BuLi/ether/0°			X = (36)	137
		"			X = (48)	137
		BuLi/THF/−15°/ 2 hr	C$_6$H$_5$Br		X = C$_6$H$_5$ (31)	20
		BuLi/THF/25°/ 6 hr	BrCH$_2$CH(OC$_2$H$_5$)$_2$		X = CH$_2$CH(OC$_2$H$_5$)$_2$ (40)	392
		BuLi/ether	C$_6$H$_5$SCN		X = CN (19), X = SC$_6$H$_5$ (59)	393
		BuLi/ether/0°/ 2 hr	o-FC$_6$H$_4$CHO		X = CH(OH)C$_6$H$_4$F-o (90)	23
		BuLi/ether/25°/ 1 hr	C$_6$H$_5$CH$_2$Br		X = CH$_2$C$_6$H$_5$ (62)	20
		"	n-C$_8$H$_{17}$Br		X = C$_8$H$_{17}$-n (46)	20
		LDA/ether/0°/ 4.5 hr	(C$_6$H$_5$)$_2$CO		X = C(C$_6$H$_5$)$_2$OH (31)	23

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TABLE XXI. Thiophenes (Alpha) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
C_4H_4S (*Contd.*)		BuLi/hexane, TMEDA/ reflux/0.5 hr	$CO_2(CH_2N_2)$		$X = CO_2CH_3$ (III) (100)	40
		BuLi/ether/ reflux/3 hr	$ClB(CH_3)N(CH_3)_2$		$X = B(CH_3)N(CH_3)_2$ (22)	295
		BuLi/ether, TMEDA/ reflux/0.5 hr	$CO_2(CH_2N_2)$	III (46), methylthiophene-2-carboxylate (39)		40
		BuLi/ether			$X = I^+Cl^-$ (69)	394
		BuLi/ether/ reflux/3 hr	$Cl_2BN(CH_3)_2$		$X = BN(CH_3)_2$ (17)	295
		BuLi/ether/0°			$X =$ (18)	137
		BuLi/reflux/ 20 min	$(n\text{-}C_4H_9O)_3B$ (H_2O_2)	(28)		289
		C_6H_5Li/ether/ reflux/2 hr	$RCH_2CO_2C_2H_5$	$C(OH)CH_2R$		
		"	$R = CH(CH_3)NH_2$		$R = CH(CH_3)NH_2$ (34)	395
		"	$R = CH_2N(CH_3)_2$		$R = CH_2N(CH_3)_2$ (72)	395
		"	$R = CH(CH_3)N(CH_3)_2$		$R = CH(CH_3)N(CH_3)_2$ (71)	395
		"	$R = CH(CH_3)NHC_2H_5$		$R = CH(CH_3)NHC_2H_5$ (24)	395
		"	$R = CH(C_2H_5)N(CH_3)_2$		$R = CH(C_2H_5)N(CH_3)_2$ (73)	395
		"	$R = CH_2N$		$R = CH_2N$ (73)	395
		"	$R = CH(CH_3)N(C_2H_5)_2$		$R = CH(CH_3)N(C_2H_5)_2$ (79)	395
		"	$R = CH(CH_3)NHC_4H_9\text{-}n$		$R = CH(CH_3)NHC_4H_9\text{-}n$ (40)	395
		"	$R = CH_2N$		$R = CH_2N$ (66)	395
		"	$R = CH(CH_3)N$		$R = CH(CH_3)N$ (77)	395
		"	$R = CH(CH_3)N$ O		$R = CH(CH_3)N$ O (48)	395
		"	$R = CH(CH_3)N$		$R = CH(CH_3)N$ (55)	395
		"	$R = CH(CH_3)N(C_3H_7\text{-}n)_2$		$R = CH(CH_3)N(C_3H_7\text{-}n)_2$ (70)	395
		"	$R = CH(C_3H_7\text{-}n)N(CH_3)_2$		$R = CH(C_3H_7\text{-}n)N(CH_3)_2$ (43)	395
		"	$R = CH(C_3H_7\text{-}i)N(CH_3)_2$		$R = CH(C_3H_7\text{-}i)N(CH_3)_2$ (71)	395

TABLE XXI. Thiophenes (Alpha) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C_4H_4S (*Contd.*)			$RCH_2CO_2H_5$	$C(OH)CH_2R$	
		"	$R = CH(CH_3)N(CH_3)CH_2C_6H_5$	$R = CH(CH_3)N(CH_3)$-$CH_2C_6H_5$ (56)	395
C_5H_3NS		BuLi/ether/ −70°/1 hr	CO_2	3-Cyano-2-thiophenecarboxylic acid (68)	217, 396
$C_5H_4O_2S$		LDA/THF or ether, HMPA/−70°	$(CH_3)_3SiCl$	2-(Trimethylsilyl)-3-thiophenecarboxylic acid (—)	246
C_5H_5BrS		LDA/ether/25°	CO_2	3-Bromo-5-methyl-2-thiophenecarboxylic acid (56)	397
C_5H_6OS		EtLi/ether/ reflux/0.5 hr	$FClO_3$	$X = F$ (34)	385
		$C_6H_5Li/ether/$ 25°/1 hr	CO_2	$X = CO_2H$ (61)	231
		"	$(CH_3O)_2SO_2$	$X = CH_3$ (40)	231
		"	$CH_2=CHCH_2Cl$	$X = CH_2CH=CH_2$ (77)	231
		"	DMF	$X = CHO$ (67)	231
		$C_6H_5Li/ether/$ 25°/45 min	$p\text{-}CH_3OC_6H_4CH_2^-$ $COC_2H_5(H_3O^+)$	(46)	398
		BuLi/ether/ reflux/0.5 hr	$CH_3OSO_2C_6H_4CH_3\text{-}p$	$X = CH_3$ (78)	399
		BuLi/reflux/ 20 min	$t\text{-}C_4H_9OCO_2C_6H_5$	$X = OC_4H_9\text{-}t$ (72)	289
		$C_6H_5Li/ether/25°/$ 45 min	$C_6H_5CHO(H_3O^+)$	$X = H$ $Y = C_6H_5$ (17)	400
		"	$C_6H_5COCH_3(H_3O^+)$	$X = CH_3$ $Y = C_6H_5$ (11)	400
		"		(58)	400
		"	$(C_6H_5)_2CO$	$X = Y = C_6H_5$ (72)	400
		"	$p\text{-}CH_3OC_6H_4CH(C_2H_5)^-$ $COC_2H_5(H_3O^+)$	$X = CH(C_2H_5)C_6H_4\text{-}$ $OCH_3\text{-}p$ $Y = C_2H_5$ (30)	398
		BuLi/ether/ 25°−reflux/ 2 hr	I_2	$X = I$ (42)	567, 401
		BuLi/ether/ reflux/0.5 hr	CO_2	$X = CO_2H$ (86)	402

TABLE XXI. THIOPHENES (ALPHA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C_5H_6OS (*Contd.*)	3-methoxythiophene	BuLi	DMF	X = CHO (83)	165
		"	DMA	X = COCH₃ (32)	165
		BuLi/ether/ reflux/15 min	(CH₃O)₂SO₂	3-Methoxy-2-methylthiophene (IV), 4-methoxy-2-methylthiophene (V) (IV + V, 75) (IV:V, 93:7)	145
		BuLi/reflux/ 20 min	(n-C₄H₉O)₃B (H₂O₂)	3-methoxy thiophenone structure (24)	289
C_5H_6S	2-methylthiophene	EtLi/ether/ reflux/0.5 hr	FClO₃	CH₃-thiophene-X structure, X = F (53)	385, 149
		BuLi	"S"	X = SH (57)	290, 497
		BuLi/ether/ reflux/2 hr	"S" + CH₃I	X = SCH₃ (79)	403
		BuLi/ether/ reflux/1 hr	"S" + BrCH₂CO₂C₂H₅ (OH⁻)	X = SCH₂CO₂H (—)	404
		BuLi	CO₂	X = CO₂H (84)	405
		BuLi/hexane, TMEDA/reflux/ 0.5 hr	CO₂ (CH₂N₂)	X = CO₂CH₃ (95)	40
		BuLi/ether/ reflux/0.5 hr	(CH₃S)₂	X = SCH₃ (75)	399
		BuLi/ether/ reflux/4 hr	Ac₂O	X = COCH₃ (33)	371
		BuLi/ether/ reflux/3 hr	ClB(C₂H₅)₂	X = B(C₂H₅)₂ (28)	295
		BuLi/reflux/ 20 min	(n-C₄H₉O)₃B (H₂O₂)	thiophenone structure (47)	289
	3-methylthiophene	C₆H₅Li/ether/ reflux/2 hr	CO₂	(VI) (19), (VII) (68) structures, X = CO₂H	20, 48
		BuLi/ether, TMEDA/reflux/ 15 min	(CH₃O)₂SO₂	(VI + VII, 79) (VI:VII, 7:93) X = CH₃	145, 406
		BuLi/ether/ reflux/0.5 hr	DMF	(VI + VII, 59) (VI:VII, 17:83) X = CHO	399, 407
		BuLi/hexane, TMEDA/reflux/ 0.5 hr	CO₂ (CH₂N₂)	Dimethyl 3-methylthiophene-2,5-dicarboxylate (100)	40
		BuLi/reflux/ 20 min	(n-C₄H₉O)₃B (H₂O₂)	3-methyl thiophenone structure (50)	289
C_5H_6SSe	3-(methylseleno)thiophene (SeCH₃)	BuLi/2 hr	CO₂	3-(Methylselenyl)-2-thiophenecarboxylic acid (VIII), 4-(methylselenyl)-2-thiophenecarboxylic acid (IX) (VIII + IX, 75) (VIII:IX, 56:44)	140

TABLE XXI. THIOPHENES (ALPHA) (Continued)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C₅H₆S₂	(2-SCH₃ thiophene)	BuLi	"S"+CH₃I	2,5-Bis(methylthio)thiophene (57)	404
		BuLi/ether/0° 15 min	CO₂	5-(Methylthio)-2-thiophenecarboxylic acid (87)	404
	(3-SCH₃ thiophene)	BuLi/ether/ reflux/0.5 hr	CO₂	3-(Methylthio)-2-thiophenecarboxylic acid (70)	248
C₆H₇NOS	(3-CONHCH₃ thiophene)	BuLi/ether/25°– 35°/1 hr	D₂O	2-d-N-Methyl-3-thiophenecarboxamide (55)	134
		BuLi/ether/25°– 35°/3 hr	(C₆H₅)₂CO	2-(Hydroxymethyl)-N-methyl-α,α-diphenyl-3-thiophenecarboxamide (23)	134
C₆H₈OS	(3-CH₂OCH₃ thiophene)	BuLi/ether/25°/ 10 hr	CO₂	X = CO₂H (89)	142
		BuLi/ether/25°– 35°/1–1.5 hr	(CH₃S)₂	X = SCH₃ (61)	134, 43
		"	DMF	X = CHO (72)	43, 134
		"	(C₆H₅)₂CO	X = C(C₆H₅)₂OH (46)	134
C₅H₆S	(2-C₂H₅ thiophene)	EtLi/ether/ reflux/0.5 hr	FClO₃	X = F (55)	385
		BuLi/ether/ reflux/1 hr	"S"+C₂H₅I	X = SC₂H₅ (78)	408, 403
		—	"Se"+C₂H₅I	X = SeC₂H₅ (65)	362
		—	"Se"+ClCH₂CO₂CH₃	X = SeCH₂CO₂CH₃ (46)	362
	(3-C₂H₅ thiophene)	BuLi/ether/−35°	ClCH₂OCH₃	X = CH₂OCH₃ (65)	390
		BuLi/ether, TMEDA reflux/15 min	(CH₃O)₂SO₂	3-Ethyl-2-methylthiophene (X), 4-ethyl-2-methylthiophene (XI) (X+XI, 79) (X:XI, 3:97)	145
	(2,3-dimethyl thiophene)	BuLi/ether/ reflux/ 2 hr	CuCl₂	(68)	409
C₆H₈S₂	(2-SC₂H₅ thiophene)	—	CO₂	5-(Ethylthio)-2-thiophenecarboxylic acid (77)	404
C₆H₉NO₂S₂	(2-SO₂N(CH₃)₂ thiophene)	BuLi/THF/25°/ 20 min	(CH₃)₃SiCl	N,N-Dimethyl-5-(trimethylsilyl)-2-thiophenesulfonamide (41)	135
C₇H₆S		BuLi/ether/ −10°–0°/ 0.5 hr	CO₂ (CH₂N₂)	1 (10) 3 (21) 4 (39) 6 (29)	410
C₇H₈O₂S		BuLi/ether/ reflux/20 min	"S"+ClCH₂CO₂CH₃ (NaOEt)	X = S (94)	143
		BuLi/ether/ 25°–reflux/ 15 min	"Se"+ClCH₂CO₂CH₃ (NaOEt)	X = Se (48)	411
		BuLi/ether/ reflux/15 min	CO₂ (H₃O⁺)	3-Formyl-2-thiophenecarboxylic acid (78)	412
		BuLi/ether/−70°	C₆H₅CN (H₃O⁺)	2-Benzoyl-3-thiophenecarboxaldehyde (16)	413

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TABLE XXI. THIOPHENES (ALPHA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C_7H_9NOS	(thiophene with $CON(CH_3)_2$)	BuLi/ether/25°/ 20 min	—	(fused dithienoquinone structure) (41)	134, 43
$C_7H_{10}LiNOS$	(thiophene with $CH(OLi)N(CH_3)_2$)	BuLi/reflux/ 135 min	CO_2	3-Formyl-2-thiophenecarboxylic acid (44)	414
$C_7H_{10}S$	(thiophene with C_3H_7-*n*)	EtLi/ether/ reflux/0.5 hr	$FClO_3$	2-Fluoro-5-propylthiophene (55)	385
	(thiophene with C_3H_7-*i*)	BuLi/ether, TMEDA/ reflux/15 min	$(CH_3O)_2SO_2$	3-Isopropyl-2-methylthiophene (XII), 4-isopropyl-2-methylthiophene (XIII) (XII + XIII, 66) (XII:XIII, 1:99)	145
$C_7H_{10}S_2$	(thiophene with $CH_2SC_2H_5$)	BuLi/ether	CO_2	5-[(Ethylthio)methyl]-2-thiophene-carboxylic acid (53)	415
$C_7H_{11}NS$	(thiophene with $CH_2N(CH_3)_2$)	BuLi/THF	D_2O	(CH$_3$)$_2$NCH$_2$—thiophene—X, X = D (88)	134
		"	DMF	X = CHO (40)	134
		"	$(CH_3)_3SiCl$	X = Si(CH$_3$)$_3$ (71)	134
		"	C_6H_5CHO	X = CH(OH)C$_6$H$_5$ (50)	416
		"	$(C_6H_5)_2CO$	X = C(C$_6$H$_5$)$_2$OH (47)	416
	(thiophene with $CH_2N(CH_3)_2$)	BuLi/ether/25°– 35°/4 hr	D_2O	(thiophene with $CH_2N(CH_3)_2$ and X), X = D (80)	43, 134
		BuLi/ether/25°– 35°/1 hr	DMF	X = CHO (75)	134, 43
		BuLi/ether/25°– 35°/1 hr	C_6H_5CN (H_3O^+)	X = COC$_6$H$_5$ (54)	134, 43
		"	$(C_6H_5)_2CO$	X = C(C$_6$H$_5$)$_2$OH (67)	134, 43
		"	p-CH$_3$C$_6$H$_4$SO$_2$Br	X = Br (32)	134
		"	p-CH$_3$C$_6$H$_4$SO$_2$Cl	X = Cl (25)	134
$C_7H_{12}SSi$	(thiophene with $Si(CH_3)_3$)	BuLi/ether/ reflux/4 hr	CO_2	5-(Trimethylsilyl)-2-thiophenecarboxylic acid (62)	369
$C_8H_4Br_2S_2$	(dibromobithiophene)	EtLi/THF/−70°/ 2 min	CO_2	4,4'-Dibromo-[3,3'-bithiophene]-5-carboxylic acid (51)	417
$C_8H_6S_2$	(2,2'-bithiophene)	C_6H_5Li/ether/ reflux/15 min	CO_2	[2,2'-Bithiophene]-5-carboxylic acid (74)	418
		BuLi/reflux/ 45 min	"	[2,2'-Bithiophene]-5,5'-dicarboxylic acid (72)	419
$C_8H_6S_2$	(2,3'-bithiophene)	C_6H_5Li/reflux/ 15 min	CO_2	[2,3'-Bithiophene]-2'-carboxylic acid (XIV), [2,3'-bithiophene]-5'-carboxylic acid (XV) (XIV + XV, 75) (XIV:XV, 38:52)	418

TABLE XXI. Thiophenes (Alpha) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_8H_4S_3$		BuLi/ether/ reflux/1 hr	$CuCl_2$	(52)	144
$C_8H_8S_2$	C_2H_5—	—	"S"$+C_2H_5I$	5-Ethyl-2-(ethylthio)thieno[2,3-*b*]-thiophene (79)	420
	C_2H_5—	BuLi/ether	"S"$+C_2H_5I$	5-Ethyl-2-(ethylthio)thieno[3,2-*b*]-thiophene (69)	420
$C_8H_{10}O_2S$		BuLi/ether/25°/ 1 hr	$(CH_3)_3SiCl$	$X=Si(CH_3)_3$ (96)	421, 298
		BuLi/ether/25°/ 1.5 hr	$(C_2H_5)_3SiCl$	$X=Si(C_2H_5)_3$ (74)	298
		BuLi/ether/25°/ 1 hr	CO_2 (H_3O^+)	$X=CO_2H$ (70)	421
		BuLi/ether/25°/ 1.5 hr	$(CH_3)_3SiCl$ (H_3O^+)	$X=Si(CH_3)_3$ (93)	298
		"	$C_2H_5(CH_3)_2SiCl$ (H_3O^+)	$X=Si(CH_3)_2C_2H_5$ (85)	298
		BuLi/ether/25°/ 1 hr	C_6H_5CN (H_3O^+)	$X=COC_6H_5$ (66)	421
		BuLi/ether/25°/ 1.5 hr	$CH_3(C_6H_5)_2SiCl$ (H_3O^+)	$X=Si(C_6H_5)_2CH_3$ (67)	298
		"	$(C_6H_5)_3SiCl$ (H_3O^+)	$X=Si(C_6H_5)_3$ (73)	298
		BuLi/ether/25°/ 1 hr	C_6H_5CHO	$X=CH(OH)C_6H_5$ (60)	421
		"	C_6H_5NCO	$X=CONHC_6H_5$ (65)	421
		BuLi/ether/25°/ 45 min, reflux/ 15 min	C_6H_5CN (H_3O^+)	3-Acetyl-2-benzoylthiophene (27)	413
$C_8H_{12}LiNOS$	$\underset{}{\overset{OLi}{|}}C(CH_3)N(CH_3)_2$	BuLi	"S"$+BrCH_2CO_2CH_3$	Methyl [(3-acetyl-2-thienyl)thio]acetate (—)	422
$C_8H_{12}OS$	—OC_4H_9-*t*	BuLi/ether/ reflux/2 hr	"S"	*t*-C_4H_9O—X $X=SH$ (73)	275
		"	CO_2	$X=CO_2H$ (75)	275
		"	$(CH_3S)_2$	$X=SCH_3$ (87)	275
		"	$(CH_3O)_2SO_2$	$X=CH_3$ (87)	275
		"	$ClCO_2C_2H_5$	$X=CO_2C_2H_5$ (46)	275
		"	$CH_2\!=\!CHCH_2Br$	$X=CH_2CH\!=\!CH_2$ (86)	275
		"	$C_6H_5CH_2Cl$	$X=CH_2C_6H_5$ (73)	275
		"	*t*-$C_4H_9OCO_2C_6H_5$ ($MgBr_2$)	$X=OC_4H_9$-*t* (78)	275
		"	Cyclopentanone (H_3O^+)	(80)	275

TABLE XXI. Thiophenes (Alpha) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_8H_{12}OS$	(3-OC_4H_9-t thiophene)	BuLi/ether/ reflux/0.5 hr	CO_2	(3-OC_4H_9-t, 2-X thiophene) X = CO_2H (62)	423
		BuLi/ether/ reflux/2 hr	$(CH_3O)_2SO_2$	X = CH_3 (87)	141
		"	$ClCO_2C_2H_5$	X = $CO_2C_2H_5$ (75)	141
		BuLi/ether/−30°– reflux/1 hr	DMF	X = $CH(OLi)N(CH_3)_2$ (—)	148
		BuLi/ether/ reflux/2 hr	Ac_2O ($MgBr_2$)	X = $COCH_3$ (75)	141
		"	t-$C_4H_9OCO_2C_6H_5$ ($MgBr_2$)	X = OC_4H_9-t (70)	141
$C_8H_{12}O_2S_2$	(2-$SO_2C_4H_9$-t thiophene)	BuLi/THF/−20°/ 9.5 hr	CO_2	5-(t-Butylsulfonyl)-2,4-thiophene-dicarboxylic acid (68)	136
		"	DMF	5-(t-Butylsulfonyl)-2,4-thiophene-dicarboxaldehyde (59)	136
	(3-$SO_2C_4H_9$-t thiophene)	BuLi	CO_2	3-(t-Butylsulfonyl)-2,4-thiophenedicarboxylic acid (42), 3-(t-butylsulfonyl)-2-thiophenecarboxylic acid (4), 3-(t-butylsulfonyl)-2,5-thiophenedicarboxylic acid (8)	565
$C_8H_{12}S$	(2-C_4H_9-n thiophene)	EtLi/ether/ reflux/0.5 hr	$FClO_3$	2-Butyl-5-fluorothiophene (55)	385
	(2-C_4H_9-t thiophene)	EtLi/ether/ reflux/0.5 hr	$FClO_3$	2-t-Butyl-5-fluorothiophene (49)	385
		BuLi/ether/ reflux/45 min	CO_2	5-t-Butyl-2-thiophenecarboxylic acid (55)	399
	(3-C_4H_9-t thiophene)	BuLi/ether, TMEDA/ reflux/15 min	$(CH_3O)_2SO_2$	3-t-Butyl-5-methylthiophene (72)	145
$C_8H_{12}SSe$	(3-SeC_4H_9-n thiophene)	BuLi/ether/−30°	"S" + CH_3I	(XVI) (3-SeC_4H_9-n, 2-X) (XVII) (4-SeC_4H_9-n, X-)	
				(XVI:XVII, 70:30) X = SCH_3	140
		"	"Se" + CH_3I	(XVI + XVII, 67) X = $SeCH_3$	140
		BuLi/2 hr	CO_2	(XVI + XVII, 79) (XVI:XVII, 60:40) X = CO_2H	140
$C_8H_{12}S_2$	(3-SC_4H_9-t thiophene)	BuLi	CO_2	3-(t-Butylthio)-2-thiophenecarboxylic acid (—), 4-(t-butylthio)-2-thiophenecarboxylic acid (—), 3-(t-butylthio)-2,5-thiophenecarboxylic acid (—)	424
		"	—	(3-SC_4H_9-t, 2,5-diLi thiophene) (—)	565
$C_8H_{13}NO_2S_2$	(2-$SO_2N(C_2H_5)_2$ thiophene)	BuLi/ether/25°/ 1 hr	CO_2	5-(Diethylsulfamoyl)-2-thiophenecarboxylic acid (82)	135
		BuLi/ether/25°/ 0.5 hr	$(CH_3)_3SiCl$	N,N-Diethyl-5-(trimethylsilyl)-2-thiophenesulfonamide (79)	135

TABLE XXI.   THIOPHENES (ALPHA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)			Refs.
C₉H₆ClNS		BuLi/THF/0°/ 0.5 hr	(CH₃)₃SiCl				
				(0.4)	(91)	X = Si(CH₃)₃	138
		BuLi/ether/0°/ 0.5 hr	(CH₃)₃SiCl	(36)	(43)	X = Si(CH₃)₃	138
		t-BuLi/THF/−60°	(C₆H₅)₂CO	(—)	(83)	X = C(C₆H₅)₂OH	137
C₉H₇NS		*t*-BuLi/THF/−60°	CuCl₂(O₂)				
				(—)	(63)	X =	137
		BuLi/ether/0°/ 0.5 hr	(CH₃)₃SiCl	(62)	(13)	X = Si(CH₃)₃	138
		BuLi/THF/0°/ 0.5 hr	″	(4)	(93)	X = Si(CH₃)₃	138
		t-BuLi/THF/−60°	(C₆H₅)₂CO	(—)	(87)	X = C(C₆H₅)₂OH	137
		BuLi/ether/0°/ 15 min	CuCl₂		X = (45)		280
		″	(ox.)		X = (55)		280
C₉H₈OS		BuLi/ether/0°/ 2 hr	Ac₂O	5-Furfuryl-2-thienyl methyl ketone (16)			371
C₉H₈S₂		—	CO₂	5-(2-Thienyl)-2-thiophenecarboxylic acid (—)			389
		BuLi/ether/ 10 min	Ethylene oxide				
				(13)	(74)		389
		2 BuLi	″	(77)	(13)		389
C₉H₉OPS₂		BuLi	CO₂		X = CO₂H (33)		270

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TABLE XXI. Thiophenes (Alpha) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_9H_9OPS_2$ (*Contd.*)		''	CH_3COCH_3	$X = C(CH_3)_2OH$ (40)	270
$C_9H_{11}NOS$		BuLi/THF/−70°/ 1 hr	C_6H_5CHO	(36) (55) $X = CH(OH)C_6H_5$ 139	139
		BuLi/ether/−70°– 25°	''	(91) (4) $X = CH(OH)C_6H_5$ 139	
$C_9H_{14}OS$		BuLi/ether/ reflux/2 hr	$ClCO_2C_2H_5$	Ethyl 4-*t*-butoxy-5-methyl-2-thiophenecarboxylate (66)	141
		BuLi/ether/ reflux/0.5 hr	t-$C_4H_9OCO_2C_6H_5$	2,3-Di-*t*-butoxy-4-methylthiophene (79)	147
$C_9H_{14}O_2S$		BuLi/2.5 hr	$ClCH_2OCH_3$	$X = CH_2OCH_3$ (56)	390
		BuLi/ether/ −30°–25°/ 2.5 hr	DMF	$X = CHO$ (—)	425
		BuLi/ether/25°/ 1 hr	$(CH_3)_3SiCl (H_3O^+)$	$X = Si(CH_3)_3$ (94)	298
		''	$(C_2H_5)_3SiCl (H_3O^+)$	$X = Si(C_2H_5)_3$ (87)	298
		BuLi/ether/ −10°–25°/ 2.5 hr	$CO_2 (H_3O^+)$	$X = CO_2H$ (60)	426
		BuLi/ether/25°/ 1 hr	$C_2H_5(CH_3)_2SiCl (H_3O^+)$	$X = Si(CH_3)_2C_2H_5$ (83)	298
		''	$CH_3(C_6H_5)_2SiCl (H_3O^+)$	$X = Si(C_6H_5)_2CH_3$ (49)	298
		''	$(C_6H_5)_3SiCl (H_3O^+)$	$X = Si(C_6H_5)_3$ (72)	298
		BuLi/ether/−30°– reflux/20 min	"S" + $ClCH_2CO_2CH_3$ (H_3O^+)	Methyl [3-formyl-2-thienyl)thio]acetate (77)	327
		BuLi	$DMF (H_3O^+)$	2,3-Thiophenedicarboxaldehyde (85)	428
$C_{10}H_7BrS$		BuLi/−35°– 25°	$CO_2 (CH_2N_2)$	(XVIII), (XIX), (XX) (XVIII+XIX+XX, 44) (XVIII:XIX:XX, 1:2:3)	429

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TABLE XXI. Thiophenes (Alpha) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{10}H_7BrS$		BuLi/ether/ reflux	$CO_2(CH_2N_2)$	(XXI + XXII, 49) (XXI:XXII, 2:3)	429
$C_{10}H_8Br_2S_2$		BuLi/ether/−70°	CO_2	X = H (XXIII) X = CO_2H (XXIV) (XXIII + XXIV, 56) (XXIII:XXIV, 1:1)	417
$C_{10}H_8O_2S_2$		BuLi/ether/0°	CO_2	5-(Phenylsulfonyl)-2-thiophenecarboxylic acid (42)	69
$C_{10}H_8S$		EtLi/ether/ reflux/0.5 hr	$FClO_3$	2-Fluoro-5-phenylthiophene (55)	385
		BuLi/ether/25°/ 0.5 hr	CO_2	(XXV) (XXVI) X = CO_2H (XXV + XXVI, 72) (XXV:XXVI, 45:55) (XXV + XXVI, 59) (XXV:XXVI, 55:45)	146 429
		BuLi/ether/0°	CO_2 (CH_2N_2)	X = CO_2CH_3	
$C_{10}H_{10}S_2$		BuLi/ether/ reflux/2 hr	CO_2	5,5′-Dimethyl-[3,3′-bithiophene]-2,2′-dicarboxylic acid (45)	430, 431
		BuLi/ether/ reflux/1.5 hr	CO_2 ($SOCl_2$, MeOH)	Methyl 4,4′-dimethyl-[3,3′-bithiophene]-2,2′-dicarboxylate XXVIII, methyl 4,4′-dimethyl-[3,3′-bithiophene]-5,5′-dicarboxylate XXIX (XXVIII + XXIX, 82) (XXVIII:XXIX, 2:3)	432
		BuLi/ether/−5°	CO_2	X = CO_2H (31)	433
		"	Ethylene oxide	X = $(CH_2)_2OH$ (59)	433
		"	DMF	X = CHO (37)	433

TABLE XXI. THIOPHENES (ALPHA) (Continued)

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Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{10}H_{14}S$	(2-cyclohexylthiophene)	BuLi	$ClCH_2OCH_3$	2-Cyclohexyl-5-(methoxymethyl)thiophene (78)	390
$C_{10}H_{15}NS$	(2-(piperidinomethyl)thiophene)	BuLi	$ClCH_2OCH_3$	1-[5-(Methoxymethyl)-2-thienyl]piperidine (50)	390
$C_{10}H_{16}O_2S$	(2-thienyl-$CH_2CH(OC_2H_5)_2$)	BuLi/ether/25°/5 min	$(CH_3)_3SiCl$	C_2H_5O —CH=...—thiophene—X. X = Si(CH_3)_3 (87)	392
		BuLi/ether/25°/10 min	C_6H_5CHO	X = CH(OH)C_6H_5 (66)	392
	(2-thienyl-$C(OC_2H_5)_2CH_3$)	BuLi/2.5 hr	$ClCH_2OCH_3$	5-(Methoxymethyl)-2-thienyl methyl ketone, diethyl acetal (50)	390
		BuLi	DMF	5-(1,1-Diethoxyethyl)thiophene-2-carboxaldehyde (48)	434
		BuLi/−10°/0.5 hr	(2-chloromethylfuran)	5-Furfuryl-2-thienyl methyl ketone, diethyl acetal (22)	371
$C_{11}H_8LiNS$	(3-thienyl-C(=NLi)C_6H_5)	BuLi/ether/reflux/2 hr	CO_2 (H_3O^+)	3-Benzoylthiophene-2-carboxylic acid (70)	570
		"	C_6H_5CN (H_3O^+)	2,3-Dibenzoylthiophene (47)	570
$C_{11}H_8S$	(indeno-thiophene tricyclic)	BuLi/ether/reflux	CO_2	(XXX) CO_2H, (XXXI) CO_2H, (XXXII) CO_2H (XXX + XXXI + XXXXII, 45) (XXX : XXXI : XXXII, 7 : 19 : 24)	435
$C_{11}H_{10}O_2S_2$	(2,2'-dithienyl-1,3-dioxolane)	BuLi/ether/−35° to −20°/20 min	"S" (H_3O^+)	(thieno-thiopyranthione) (35), (thieno-thiopyranone) (9), (dioxolane-fused) (6)	436
		BuLi/ether/−35°	I_2	(2-iodo-thienyl dioxolane)$_2$ (56)	294
		BuLi/ether/reflux/15 min	CO_2 (H_3O^+)	3,3'-Carbonyldi-2-thiophenecarboxylic acid (93)	437

TABLE XXI. THIOPHENES (ALPHA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{11}H_{10}S$	(2-benzylthiophene, $CH_2C_6H_5$)	BuLi/ether/ reflux/0.5 hr	CO_2	5-Benzyl-2-thiophenecarboxylic acid (77)	438
	(3-benzylthiophene, $CH_2C_6H_5$)	BuLi/ether/ reflux	CO_2	3-Benzyl-2-thiophenecarboxylic acid (XXXII), 4-benzyl-2-thiophenecarboxylic acid (XXXIV) (XXXIII+XXXIV, 80) (XXXIII:XXXIV, 3:22)	439
$C_{11}H_{18}LiNO_2S$	(thiophene, OC_4H_9-t, $CH(OLi)N(CH_3)_2$)	BuLi/ether/−30°– reflux	DMF	3-t-Butoxy-2,5-thiophenedicarboxaldehyde (60)	148
	($(CH_3)_2N(LiO)HC$, OC_4H_9-t)	BuLi/ether/25°/ 3 hr	DMF	4-t-Butoxy-2,3-thiophenedicarboxaldehyde (60)	148
$C_{12}H_8N_2S$	(2-(3-thienyl)quinoxaline)	LDA/ether	CuI_2	(9)	440
$C_{12}H_{14}S_2$	(3,3'-bithiophene, CH_3, CH_3, CH_3, CH_3)	BuLi/ether/ reflux/2 hr	CO_2	4,4',5,5'-Tetramethyl-[3,3'-bithiophene]-2,2'-dicarboxylic acid (84)	409
	(3,3'-bithiophene, CH_3, CH_3, CH_3, CH_3)	EtLi/ether/ reflux/3 hr	CO_2	2,2',4,4'-Tetramethyl-[3,3'-bithiophene]-5,5'-dicarboxylic acid (77)	406
		EtLi/ether/ reflux/2 hr	$(CH_3O)_2SO_2$	2,2',4,4',5,5'-Hexamethyl-3,3'-bithiophene (84)	406
$C_{13}H_{20}O_2S$	(thiophene, OC_4H_9-t, OC_4H_9-t)	BuLi/ether/20°/ 0.5 hr	$(CH_3O)_2SO_2$	2,3-Di-t-butoxy-5-methylthiophene (69)	147
		BuLi/ether/ reflux/1.5 hr	$ClCO_2C_2H_5$	Ethyl 4,5-di-t-butoxy-2-thiophenecarboxylate (51)	141
	(t-C_4H_9O, OC_4H_9-t)	BuLi/ether/20°/ 0.5 hr	$(CH_3O)_2SO_2$	3,4-Di-t-butoxy-2-methylthiophene (91)	147
		BuLi/ether/ −20°– reflux/1 hr	DMF	3,4-Di-t-butoxy-2-thiophenecarboxaldehyde (50)	148
$C_{13}H_9NS$	(2-(2-thienyl)quinoline)	BuLi/ether/0°/ 0.5 hr	$(CH_3)_3SiCl$	(8) (45)	138
		BuLi/THF/0°/ 0.5 hr	"	(85) (0)	138

TABLE XXI. THIOPHENES (ALPHA) (*Continued*)

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Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{13}H_{11}FO_2S$	*o*-FC$_6$H$_4$ (dioxolane-thiophene)	BuLi/ether/0°/ 2 hr	CH$_3$CHO	(thiophene)–CH(OH)CH$_3$; C$_6$H$_4$F-*o* (60)	23
$C_{13}H_{12}O_2S$	C$_6$H$_5$ (dioxolane-thiophene)	BuLi/ether/ reflux/2 hr	CO$_2$ (H$_3$O$^+$)	3-Benzoyl-2-thiophenecarboxylic acid (43)	413
$C_{13}H_{22}O_2S$	*t*-C$_4$H$_9$O, OC$_4$H$_9$-*t*, CH$_3$ (thiophene)	BuLi/ether/20°/ 0.5 hr	(CH$_3$O)$_2$SO$_2$	3,4-Di-*t*-butoxy-2,5-dimethylthiophene (81)	147
$C_{14}H_{11}OPS_2$	O=P–C$_6$H$_5$ di(3-thienyl)	BuLi/THF/25°/ 1 hr	Br$_2$	X = Br (65)	270
		"	CO$_2$	X = CO$_2$H (75)	270
		BuLi/THF/25°/ 1 hr	CH$_3$COCH$_3$	X = C(CH$_3$)$_2$OH (45)	270
		"	(CH$_3$)$_3$SiCl	X = Si(CH$_3$)$_3$ (30)	270
		"	C$_6$H$_5$CHO	X = CH(OH)C$_6$H$_5$ (70)	270
		"	C$_6$H$_5$COCH$_3$	X = C(CH$_3$)C$_6$H$_5$ OH (50)	270
		"	(C$_6$H$_5$)$_2$CO	X = C(C$_6$H$_5$)$_2$OH (80)	270
		BuLi	CH$_3$CO$_2$C$_2$H$_5$	X = CH$_3$ (35)	270
		"	(pyridine)CO$_2$C$_2$H$_5$	X = (3-pyridyl) (35)	270
		"	C$_6$H$_5$CO$_2$C$_2$H$_5$	X = C$_6$H$_5$ (68)	270
		"	HCO$_2$C$_2$H$_5$	3-(Phenyl-3-thienylphosphinyl)-2-thiophenecarboxaldehyde (48)	270
$C_{14}H_{11}PS_2$	di(2-thienyl)–P–C$_6$H$_5$	BuLi	CO$_2$	X = Z = CO$_2$H (40) ; Y = —	270
		"	(C$_6$H$_5$)$_2$CO (H$_2$O$_2$)	X = C(C$_6$H$_5$)$_2$OH ; Y = O ; Z = H (35)	270
		"	CH$_3$CO$_2$C$_2$H$_5$ (H$_2$O$_2$)	[di(2-thienyl)P(O)C$_6$H$_5$]$_2$ C(CH$_3$)OH (30)	270
$C_{14}H_{18}N_2O_2S$	CH$_3$–N–N (pyrazole), CH$_2$OTHP (thiophene)	BuLi/ether/ 25°/16 hr	*o*-FC$_6$H$_4$CHO	(thiophene)–CH(OH)C$_6$H$_4$F-*o* ; CH$_3$; N–N ; THPOCH$_2$ (60)	23

TABLE XXI. Thiophenes (Alpha) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{14}H_{24}O_4S$	(C$_2$H$_5$O)$_2$CH— —CH(OC$_2$H$_5$)$_2$ (thiophene)	BuLi/ether/ −40°/1 hr	DMF	2,3,4-Thiophenetricarboxaldehyde, 3,4-bis(diethyl acetal) (30)	283
$C_{15}H_{26}LiNO_3S$	t-C$_4$H$_9$O— —OC$_4$H$_9$-t (thiophene) —CH(OLi)N(CH$_3$)$_2$	BuLi/reflux	DMF	3,4-Di-t-butoxy-2,5-thiophenedi-carboxaldehyde (30)	148
$C_{16}H_{13}OPS$	P(C$_6$H$_5$)$_2$ with O (thiophene)	BuLi/THF/25°/ 1 hr	CO$_2$	thiophene with P(C$_6$H$_5$)$_2$, O and X X = CO$_2$H (30)	270
		"	(C$_6$H$_5$)$_2$CO	X = C(C$_6$H$_5$)$_2$OH (50)	270
$C_{19}H_{34}O_6S$	(C$_2$H$_5$O)$_2$CH— —CH(OC$_2$H$_5$)$_2$ (thiophene) —CH(OC$_2$H$_5$)$_2$	BuLi/"long time"	DMF	2,3,4,5-Thiophenetetracarboxaldehyde, 2,3,4-tris(diethyl acetal) ("good")	441
$C_{22}H_{14}S$	(polycyclic thiophene structure)	BuLi/ether/ reflux/0.5 hr	CO$_2$	HO$_2$C-(polycyclic thiophene structure) (63)	442

Note: References 360–607 are on pp. 355–360.

TABLE XXII. CONDENSED THIOPHENES (ALPHA)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C_7H_5NS		CH_3Li/ether/ $-25°$/4 hr	D_2O	$X = CH_3$ $Y = H$ } (11),	443
				$X = H$ $Y = D$ } (40)	443
		BuLi/hexane, TMEDA/$-70°$	DMF	$X = H$ $Y = CHO$ }(66)	444
C_8H_5ClS		BuLi/ether/0°/* 1 hr	CO_2	$X = CO_2H$ (83)	445
		"	$(CH_3S)_2$	$X = SCH_3$ (82)	445
		"	$(CH_3O)_2SO_2$	$X = CH_3$ (96)	445
C_8H_6S		BuLi	Br_2	$X = Br$ (39)	279
		BuLi/ether/0°	$FClO_3$	$X = F$ (70)	149
		BuLi/ether	"S"+C_2H_5I	$X = SC_2H_5$ (69)	420
		BuLi/ether/25°/ "overnight"	CO_2	$X = CO_2H$ (82)	48, 279, 446, 281
		BuLi/hexane, TMEDA/reflux/ 0.5 hr	CO_2 (CH_2N_2)	$X = CO_2CH_3$ (55), Dimethyl benzo[b]thiophene- 2,7-dicarboxylate (12)	40
		BuLi	C_2H_5I	$X = C_2H_5$ (30)	446
		BuLi	CH_3CHO	$X = CH(OH)CH_3$ (72)	279
		EtLi/ether/ reflux/45 min	CCl_3CHO	$X = CH(OH)CCl_3$ (86)	447
		BuLi/ether/0°/* 1 hr	$(CH_3S)_2$	$X = SCH_3$ (87)	445

TABLE XXII. CONDENSED THIOPHENES (ALPHA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C₈H₆S (*Contd.*)		BuLi	(CH₃O)₂SO₂	X = CH₃ (91)	274, 448
		BuLi/THF/−10°–25°/2 hr	(CH₃)₃SiCl	X = Si(CH₃)₃ (25)	251
		BuLi	DMA	X = COCH₃ (79)	446
		—	(CH₃)₂N—CH=CH—NO₂	X = CH=CHNO₂ (26)	285
		BuLi	(C₂H₅O)₂SO₂	X = C₂H₅ (81)	274, 448
		"		X = CONH— (71)	279
		"		X = CONH— (54)	279
		"		X = CONH— (74)	279
		BuLi/ether/25°/24 hr	C₆H₅F	X = C₆H₅ (55)	449
		BuLi	o-BrC₆H₄Cl	X = C₆H₅ (7)	450
		"		X = HO— (41)	450
		"	C₆H₅CHO	X = CH(OH)C₆H₅ (70)	279
		"	p-ClC₆H₄CHO	X = CH(OH)C₆H₄Cl-p (68)	279
		"	p-CH₃C₆H₄CHO	X = CH(OH)C₆H₄CH₃-p (—)	279
		"	p-(CH₃)₂NC₆H₄CHO	X = CH(OH)C₆H₄N(CH₃)₂-p (47)	279
		"	C₆H₅NCO	X = CONHC₆H₅ (81)	279
		"	o-CH₃C₆H₄NCO	X = CONHC₆H₄CH₃-o (41)	279
		BuLi/ether/−10°	C₆H₅COCH₃	X = C(CH₃)C₆H₅ / OH (77)	451
		BuLi/ether/−20°/1.5 hr	(C₆H₅)₃SiCl	X = Si(C₆H₅)₃ (71)	452
		BuLi		X = CONH— (23)	279
		"	C₆H₅N(CH₃)CHO	X = CHO (42)	278
		"	CH₃OSO₂C₆H₅CH₃-p	X = CH₃ (43)	279
		"	(C₆H₅NO₂)	X = (49)	281
		BuLi/ether/25°/1 hr	(n-C₄H₉O)₃B (H₃O⁺, H₂O₂)	(76)	151, 150
		BuLi		(17)	279
C₉H₈S		BuLi/ether/reflux	CO₂	3-Methylbenzo[b]thiophene-2-carboxylic acid (65)	18

TABLE XXII. CONDENSED THIOPHENES (ALPHA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C_9H_8S (*Contd.*)	(5-methylbenzo[b]thiophene)	BuLi/ether/*ᵃ 0°/1 hr	$(CH_3S)_2$	5-Methyl-2-(methylthio)benzo[b]thiophene (91)	445
		"	$(CH_3O)_2SO_2$	2,5-Dimethylbenzo[b]thiophene (85)	445
$C_{10}H_6S_2$	(thieno-benzothiophene)	BuLi/ether/−40°– 25°/2 hr	DMF	(2-CHO product) (70)	453
	(thieno-benzothiophene)	BuLi/ether/−40°– 25°/2 hr	CO_2	(CO₂H product) (63)	453
	(dithieno-naphthalene)	BuLi/ether/25° 15 min	$C_6H_5N(CH_3)CHO$	(mono-CHO product) (54)	278
		4 BuLi/ether/ reflux/0.5 hr	"	(di-CHO product) (99)	278
$C_{10}H_8O_2S$	CH_2COOH (benzo[b]thiophene-3-acetic acid)	BuLi/THF/−78°/ 0.5 hr	D_2O	2-d-Benzo[b]thiophene-3-acetic acid (81)ᵃ	153
$C_{10}H_{11}NS$	$(CH_2)_2NH_2$ (benzo[b]thiophene)	BuLi/THF/−78°/ 0.5 hr	D_2O	2-d-Benzo[b]thiophene-3-ethylamine (83)ᵇ	153
$C_{11}H_{12}LiNOS$	$CH(OLi)N(CH_3)_2$ (benzo[b]thiophene)	BuLi/−70° to −30°	"S"	2-Mercaptobenzo[b]thiophene-3-carboxaldehyde (—)	454
$C_{12}H_8S$	(naphthothiophene)	BuLi/ether/25°/ 2 hr, reflux/ 2 hr	CO_2	$X = CO_2H$ (75)	455
			$C_6H_5N(CH_3)CHO$	$X = CHO$ (68)	455, 278
$C_{12}H_{15}NS$	$(CH_2)_2N(CH_3)_2$ (benzo[b]thiophene)	BuLi/THF/−78°/ 0.5 hr	D_2O	N,N-Dimethyl-2-d-benzo[b]thiophene-3-ethylamine (83)	153
$C_{14}H_{10}S$	C_6H_5 (3-phenylbenzo[b]thiophene)	BuLi/ether/0°– 25°/1 hr	CO_2	3-Phenylbenzo[b]thiophene-2-carboxylic acid (53)	456
$C_{16}H_{10}N_2S$	(quinoxaline-benzothiophene)	LDA/ether	CuI_2	(macrocyclic product) (61)	440

TABLE XXII. CONDENSED THIOPHENES (ALPHA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{24}H_{12}S_3$		BuLi/ether/0°–25°/10 min	$C_6H_5N(CH_3)CHO$	(65)	278
$C_{24}H_{14}N_2S_2$		LDA/THF/−50°/1 hr		(69), (18)	282

[a] The isolated yield was 81%; the deuterium incorporation was 70%.

[b] The isolated yield was 83%; the deuterium incorporation was 80%.

Note: References 360–607 are on pp. 355–360.

TABLE XXIII. Isothiazoles (Alpha)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
C_3H_2BrNS	(structure: 4-bromoisothiazole)	BuLi/THF/ −65°/15 min*	CO_2	4-Bromo-5-isothiazolecarboxylic acid	(70)	154
		"	DMF	4-Bromo-5-isothiazolecarboxaldehyde	(73)	154
C_3H_2ClNS	(structure: 4-chloroisothiazole)	BuLi/THF/ −65°/15 min*	CO_2	4-Chloro-5-isothiazolecarboxylic acid	(68)	154
		"	DMF	4-Chloro-5-isothiazolecarboxaldehyde	(65)	154
C_3H_2INS	(structure: 4-iodoisothiazole)	BuLi/THF/ −65°/15 min*	DMF	4-Iodo-5-isothiazolecarboxaldehyde	(33)	154
C_3H_3NS	(structure: isothiazole)	BuLi/THF/ −65°/15 min	Br_2	(structure) X = Br	(34)	154
		"	CO_2	X = CO_2H	(48)	154
		"	CH_3I	X = CH_3	(40)	154
		"	DMF	X = CHO	(75)	154
$C_4H_3NO_2S$	(structure: 4-carboxyisothiazole)	BuLi/THF/ −65°/15 min*	CO_2	4,5-Isothiazoledicarboxylic acid	(15)	154
C_4H_4BrNS	(structure: 3-methyl-4-bromoisothiazole)	BuLi/THF/ −65°/15 min*	CO_2	(structure) X = CO_2H	(56)	154

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TABLE XXIII. ISOTHIAZOLES (ALPHA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C_4H_4BrNS (*Contd.*)	(3-methyl-4-bromoisothiazole)	"	CH_3I	X = CH₃ (40)	154
		"	DMF	X = CHO (51)	154
		"	$C_2H_5I^*$	X = C₂H₅ (34)	154
		"	n-$C_3H_7I^*$	X = C₃H₇-n (28)	154
		"	$C_6H_5CH_2Br$	X = CH₂C₆H₅ (13)	154
C_4H_4ClNS	(3-methyl-4-chloroisothiazole)	BuLi/THF/ −65°/15 min*	CO_2	4-Chloro-3-methyl-5-isothiazole-carboxylic acid (75)	154
		"	DMF	4-Chloro-3-methyl-5-isothiazole-carboxaldehyde (47)	154
C_4H_4INS	(3-methyl-4-iodoisothiazole)	BuLi/THF/ −65°/15 min*	CO_2	4-Iodo-3-methyl-5-isothiazolecarboxylic acid (58)	154
		"	DMF	4-Iodo-3-methyl-5-isothiazolecarboxaldehyde (68)	154
C_4H_5NS	(3-methylisothiazole)	BuLi/THF/−70°	"S"+BrCH₂CO₂C₂H₅ (OH⁻)	X = SCH₂CO₂H (36)	457
		BuLi/THF/ −65°/15 min	CO_2	X = CO₂H (50)	154
		"	DMF	X = CHO (50)	154
	(4-methylisothiazole)	BuLi/THF/−70°	"S"+BrCH₂CO₂C₂H₅ (OH⁻)	X = SCH₂CO₂H (51)	457
		BuLi/THF/ −65°/15 min	CO_2	X = CO₂H (40)	154
		"	DMF	X = CHO (55)	154
$C_5H_5NO_2S$	(3-methylisothiazole-4-carboxylic acid)	BuLi/THF/ −70°/15 min	Br_2	X = Br (52)	154
		BuLi/THF/ −65°/15 min*	CO_2	X = CO₂H (29)	154
		"	DMF	X = CHO (25)	154

Note: References 360–607 are on pp. 355–360.

TABLE XXIV. Thiazoles (Alpha)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
C_3H_2ClNS	2-chlorothiazole	BuLi/ether/$-80°$	CH_3CHO	2-Chloro-α-methyl-5-thiazolemethanol (88)		157
C_3H_3NS	thiazole	$C_6H_5Li/-60°$	CO_2	X = CO_2H (40)		156
		BuLi/ether/ $-60°$/0.5 hr	Ethylene oxide	X = $(CH_2)_2OH$ (30)		564
		"	CH_3CHO	X = $CH(OH)CH_3$ (30)		564
		"	C_2H_5CHO	X = $CH(OH)C_2H_5$ (50)		564
		"	n-C_3H_7CHO	X = $CH(OH)C_3H_7$-n (90)		564
		"	$(CH_3)_2CHCHO$	X = $CH(OH)CH(CH_3)_2$ (85)		564
		"	n-$C_6H_{13}CHO$	X = $CH(OH)C_6H_{13}$-n (90)		564
		"	$(C_6H_5)_2CO$	X = $C(C_6H_5)_2OH$ (22)		564
C_4H_5NS	4-methylthiazole	BuLi/ether/ $-60°$/0.5 hr	CH_3I	X = CH_3 (26)		564
		"	Ethylene oxide	X = $(CH_2)_2OH$ (42)		564
		BuLi/ether/ $-75°$/10 min	CH_3CHO	X = $CH(OH)CH_3$ (48)		564
		BuLi/ether/ $-60°$/0.5 hr	Propylene oxide	X = $CH_2CH(OH)CH_3$ (51)		564
		"	n-C_3H_7CHO	X = $CH(OH)C_3H_7$-n (93)		564
	2-methylthiazole	BuLi/ether/$-70°$	CO_2	X = CO_2H (42)		158
		BuLi/ether/$-25°$	CH_3I	X = CH_3 (70)		158
		BuLi/ether/$-70°$	C_6H_5CN (H_3O^+)	X = COC_6H_5 (50)		158
		"	n-C_3H_7CHO	X = $CH(OH)C_3H_7$-n (74), 2-Methyl-α-propyl-5-thiazolemethanol (26)		158
C_5H_7NS	4-methyl-2-methylthiazole	BuLi/THF/ $-78°$/0.5–1 hr	CH_3I	(12) X = CH_3	(88)	159, 460
		BuLi/ether/ $-60°$/0.5 hr	CH_3CHO	(—) X = $CH(OH)CH_3$	(57)	564
		"	n-C_3H_7CHO	(—) X = $CH(OH)C_3H_7$-n	(72)	564
		BuLi/THF/ $-78°$/0.5–1 hr	$C_6H_5CH_2Cl$	(10) X = $CH_2C_6H_5$	(90)	159
	4,5-dimethylthiazole	C_6H_5Li/ether/ $25°$/1 hr	CH_2O	X = CH_2OH (58)		459
		"	$ClCH_2OCH_3$	X = CH_2OCH_3 (42)		459
		"	C_6H_5CHO	X = $CH(OH)C_6H_5$ (55)		459
C_6H_9NS	4-methyl-5-ethylthiazole	BuLi/ether/ $-60°$/0.5 hr	Propylene oxide	5-Ethyl-α,4-dimethylthiazole-2-ethanol (76)		564
$C_{10}H_8ClNS$	4-(p-chlorophenyl)-2-methylthiazole	BuLi/THF/$-78°$/ 0.5–1 hr	CH_3I	4-(p-Chlorophenyl)-2,5-dimethylthiazole (93), 4-(p-chlorophenyl)-2-ethylthiazole(3)		159

TABLE XXIV. THIAZOLES (ALPHA) (*Continued*)

Formula	Compounded Lithiated	Conditions	Substrate	Product and Yield (%)			Refs.
$C_{10}H_9NS$		BuLi/THF/−78°/ 0.5–1 hr	CH_3I				
				(5)	$X = CH_3$ (95)		460, 159
		"	C_2H_5I	(7)	$X = C_2H_5$ (86)		159
		"	$(CH_3)_3SiCl$	(4)	$X = Si(CH_3)_3$ (96)		159
		"	C_6H_5CHO	(—)	$X = CH(OH)C_6H_5$ (97)		159
$C_{11}H_{11}NOS$		BuLi/THF/−78°/ 0.5–1 hr	CH_3I	4-(*p*-Methoxyphenyl)-2,5-dimethylthiazole (86), 2-ethyl-4-(*p*-methoxyphenyl)thiazole (6)			159

Note: References 360–670 are on pp. 355–360.

TABLE XXV. BENZOTHIAZOLES (ALPHA)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
C_7H_5NS		BuLi/ether/−70°	$CF_2{=}CCl_2$		$X = CF{=}CCl_2$ (59)	364
		BuLi/ether/−75°/ 15 min	$(CH_3)_3SiCl$		$X = Si(CH_3)_3$ (77)	160, 461
		BuLi/THF/−78°	$C_2H_5(CH_3)_2SiCl$		$X = Si(CH_3)_2C_2H_5$ (27)	462
		"	$(C_2H_5)_3SiCl$		$X = Si(C_2H_5)_3$ (30)	462
		—	(KMnO$_4$)	$X =$ (−)		370
		—	$C_6H_5N_3$	$X = NH_2$ (—)		287
		BuLi/ether/−70°– 25°/2 hr		$X =$ (56)		590
		"		$X =$ (23)		590

TABLE XXV. BENZOTHIAZOLES (ALPHA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
C_7H_5NS (*Contd.*)		BuLi/ether/−65°/ 5 min	$(C_6H_5)_3SiBr$	$X = Si(C_6H_5)_3$	(19)	452
		BuLi			(30–36)	372
		BuLi/THF/−78°/ 5 hr	$SiCl_4$	$X = Y = Cl$	(33)	461
		"	CH_3SiCl_3	$X = CH_3$ } $Y = Cl$	(39)	461
		"	$(CH_3)_2SiCl_2$	$X = Y = CH_3$	(51)	461

Note: References 360–607 are on pp. 355–360.

TABLE XXVI. Vɪɴʏʟ Sᴇʟᴇɴɪᴅᴇs (Aʟᴘʜᴀ)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C_8H_8Se	CH_2=$CHSeC_6H_5$	LDA/THF/$-78°$/1 hr	D_2O	CH_2=$C(SeC_6H_5)X$ X = D (80)	161
		"	n-$C_5H_{11}CHO$	X = $CH(OH)C_5H_{11}$-n (40)	161
		LDA/THF, HMPA	n-$C_{10}H_{21}Br$	X = $C_{10}H_{21}$-n (40)	161

TABLE XXVII. SELENOPHENES (ALPHA)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
C_4H_4Se		BuLi/ether/1 hr	SO_2		$X = SO_2Li$ (57)	163
		BuLi/ether/reflux/0.5 hr	$CuCl_2$		$X =$ (47)	575
		BuLi/ether/reflux/15 min	"Se" +		$X =$ (48)	575
		"	CO_2		$X = CO_2H$ (56)	163
		BuLi/ether/25°	CCl_3CCl_3		$X = Cl$ (45)	365
		BuLi/ether/reflux/15 min	$(C_2H_5Se)_2$		$X = SeC_2H_5$ (66)	575
		BuLi/ether		(71)		374
C_5H_3NSe		BuLi/ether/0.5 hr	CO_2	5-Cyano-2-selenophenecarboxylic acid (—)		396
		"	DMF	5-Formyl-2-selenophenecarboxamide (—)		396
		BuLi/ether/0.5 hr	CO_2	3-Cyano-2-selenophenecarboxylic acid (—)		396
		"	DMF	2-Formyl-3-selenophenecarboxamide (—)		396
C_5H_6Se		BuLi/ether/reflux/2.5 hr	"S"		$X = SH$ (35)	497
		BuLi/ether/1 hr	SO_2		$X = SO_2Li$ (62)	163
		"	CO_2		$X = CO_2H$ (43)	163
C_5H_6OSe		BuLi	DMF	3-Methoxy-2-selenophenecarboxaldehyde (50)		165
		"	DMA	3-Methoxyselenophen-2-yl methyl ketone (40)		165
C_6H_8Se		BuLi/ether/reflux	DMF	5-Ethyl-2-selenophenecarboxaldehyde (64)		463
$C_7H_8O_2Se$		BuLi/ether/reflux/0.5 hr	"Se" + $ClCH_2CO_2CH_3$ (H_3O^+, $NaOC_2H_5$)	Selenolo[2,3-b]selenophene-2-carboxylic acid (45)		575
$C_8H_{12}OSe$		BuLi	$(CH_3O)_2SO_2$		$X = CH_3$ (—)	464
		"	CH_3CHO		$X = CH(OH)CH_3$ (—)	465
		"	$(CH_3S)_2$		$X = SCH_3$ (—)	464
		"	DMF		$X = CHO$ (—)	464
		"	DMA		$X = COCH_3$ (—)	464
		"			$X =$ (—)	465
		"	C_6H_5CHO		$X = CH(OH)C_6H_5$ (—)	465
		"	$C_6H_5CH_2Cl$		$X = CH_2C_6H_5$ (—)	465
		"	$C_6H_5CO_2OC_4H_9-t$		$X = OC_4H_9-t$ (—)	464
		BuLi/ether/−30°–reflux/1 hr	DMF			148
		"	"	3-t-Butoxy-2-selenophenecarboxaldehyde (32)		466
		"	DMA	3-t-Butoxyselenophen-2-yl methyl ketone (55)		466

TABLE XXVII. SELENOPHENES (ALPHA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_9H_{14}O_2Se$		BuLi/ether/reflux BuLi/ether/ $-30°$ to $-10°$	I_2 DMF	2-(Diethoxymethyl)-5-iodoselenophene (—) 2,5-Selenophenedicarboxaldehyde, 5-(diethyl acetal) (40)	396 467
		BuLi/ether/reflux BuLi/ether/$-40°$/ 1 hr	I_2 DMF	3-(Diethoxymethyl)-2-iodoselenophene (—) 2,3-Selenophenedicarboxaldehyde, 3-(diethyl acetal) (80)	396 283
$C_{11}H_{16}LiNO_2Se$		BuLi/ether/$-30°$ – reflux/1 hr	DMF	3-*t*-Butoxy-2-selenophenecarboxaldehyde (90), 3-*t*-butoxy-2,5-selenophenedicarboxaldehyde (10)	148
		BuLi/ether/reflux 1 hr	DMF	4-*t*-Butoxy-2,3-selenophenedicarboxaldehyde (50)	148
$C_{12}H_{20}O_2Se$		BuLi/ether/$-20°$– reflux/1 hr	DMF	3,4-Di-*t*-butoxy-2-selenophenecarboxaldehyde (5)	148
$C_{14}H_{24}O_4Se$		BuLi/ether/ $-50°$/5 hr	DMF	2,3,5-Selenophenetricarboxaldehyde, 3,5-bis(diethyl acetal) (40)	283
		BuLi/ether/$-40°$/ 1 hr	DMF	2,3,4-Selenophenetricarboxaldehyde, 3,4-bis(diethyl acetal) (40)	283
$C_{19}H_{34}O_6Se$		BuLi/"long time"	DMF	2,3,4,5-Selenophenetetracarboxaldehyde, 2,3,4-tris(diethyl acetal) ("good")	441

Note: References 360–607 are on pp. 355–360.

TABLE XXVIII. TELLUROPHENES (ALPHA)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
C_4H_4Te	[Te ring]	BuLi/ether/25°/ 45 min	CO_2	[Te ring]-X X = CO_2H	(37)	164
		BuLi/ether/25°/ 0.5 hr	Cl_3CCCl_3	X = Cl	(53)	568
		"	Br_3CCBr_3	X = Br	(44)	568
		BuLi/ether/25°/ 45 min	$(CH_3O)_2SO_2$	X = CH_3	(75)	164
		"	CH_3CHO	X = $CH(OH)CH_3$	(60)	164
		"	$C_6H_5N(CH_3)CHO$	X = CHO	(24)	164
		BuLi/ether/25°/ 0.5 hr	"Te"	$(Te ring)_2 X$ X = Te	(—)	568
		"	ICl_2 / Cl	X = I^+Cl^-	(—)	568
C_5H_6Te	[Te-CH₃ ring]	BuLi/ether/25°/ 45 min	CO_2	5-Methyl-2-tellurophenecarboxylic acid (35)		164

Note: References 360–607 are on pp. 355–360.

TABLE XXIX. FLUORO-, CHLORO-, AND BROMOALKENES (ALPHA)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
C_2HClF_2	$CF_2=CClH$	BuLi/ether/$-100°$ to $-78°$/0.5–1 hr	CH_3COCH_3	2-Chloro-3-methylcrotonic acid (15)		172
		"	CF_3COCF_3	$CF_2=CClX$	$X = C(CF_3)_2OH$ (56)	172
		"	CH_3COCF_3		$X = C(CF_3)CH_3$ (61) $\quad$ OH	172
		"	$(C_2H_5)_3SiCl$		$X = Si(C_2H_5)_3$ (10)	173
C_2HCl_2F	$CFCl=CClH$	BuLi/ether/$-100°$ to $-78°$/0.5–1 hr	C_6H_5CHO	(Z)-2-Chlorocinnamic acid (I) (44)		172
		"	CF_3COCF_3	$CFCl=CClX$	$X = C(CF_3)_2OH$ (66)	172
		"	CH_3COCH_3		$X = C(CH_3)_2OH$ (60)	172
		"	$(C_2H_5)_3SiCl$		$X = Si(C_2H_5)_3$ (55)	173
C_2HCl_3	$CCl_2=CClH$	BuLi/THF, ether, pet. ether/$-110°$/50 min	CO_2	Trichloroacrylic acid (81)		167, 168
C_2HF_3	$CF_2=CFH$	BuLi/ether/$-100°$ to $-78°$/0.5–1 hr	CH_3COCH_3	2-Fluoro-3-methylcrotonic acid (30)		172
		"	CO_2	$CF_2=CFX$	$X = CO_2H$ (57)	172
		"	CF_3COCF_3		$X = C(CF_3)_2OH$ (63)	172
		"	$(C_2H_5)_3SiCl$		$X = Si(C_2H_5)_3$ (79)	173
$C_2H_2Cl_2$		BuLi/THF, ether, pet. ether/$-100°$/20 min	CO_2	Chloropropiolic acid (100)		167, 168
		BuLi/THF, ether, pet. ether/$-110°$/40 min	Br_2	(Z)-1-Bromo-1,2-dichloroethylene (26)		167
		"	CO_2	(E)-2,3-Dichloroacrylic acid (99)		167, 168

TABLE XXIX. Fluoro-, Chloro-, and Bromoalkenes (Alpha) (*Continued*)

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Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C_2H_3Cl	$CHCl{=}CH_2$	BuLi/THF, ether, pet. ether/−110°/ 70 min	CO_2	2-Chloroacrylic acid (100)	167, 168
C_4H_7BrO	Br, OC_2H_5 (cis)	BuLi/THF, hexane/ −100°	CO_2	(Z)-2-Bromo-3-ethoxyacrylic acid (22), (Z)-3-ethoxyacrylic acid (10)	174a
	Br, OC_2H_5	BuLi/ether/ −78°–50°/5 hr	Cyclopentanone (H_3O^+)	α-Bromo-$\Delta^{1,\alpha}$-cyclopentaneacetaldehyde (30)	174b
	"	"	$t\text{-}C_4H_9CHO$	(E)-2-Bromo-1-ethoxy-4,4-dimethyl-1-penten-3-ol (58)	174b
C_4H_7ClO	Cl, OC_2H_5 (cis)	BuLi/THF, hexane/ −100°	CO_2	(Z)-2-Chloro-3-ethoxyacrylic acid (40)	174a
		"	Cyclohexanone	α-Chloro-$\Delta^{1,\alpha}$-cyclohexeneacetaldehyde (40)	174a
		2 BuLi/THF, hexane/ −100°	"	Ethyl $\Delta^{1,\alpha}$-cyclohexeneacetate (20)	174a
	Cl, OC_2H_5	BuLi/THF, hexane/ −100°	CO_2	(E)-2-Chloro-3-ethoxyacrylic acid (100)	174a
C_8H_7Cl	C_6H_5, Cl (cis)	BuLi/−115°/2 min	CO_2	Phenylacetylene (8), 1 (13)	169
	C_6H_5, Cl	BuLi/THF, ether, hexane/−80°/ 15 min	CO_2	(E)-2-Chlorocinnamic acid (90)	169
		"	C_2H_5OD	(E)-β-d-β-Chlorostyrene (80)	169
$C_{14}H_9Cl_3$	o-ClC_6H_4, Cl / o-ClC_6H_4	BuLi/THF, ether, pet. ether/−108°/ 45 min	CO_2	2-Chloro-3,3-bis(o-chlorophenyl)acrylic acid (76)	171
	p-ClC_6H_4, Cl / p-ClC_6H_4	BuLi/THF, ether, pet. ether/ −41°/20 min	CO_2	2-Chloro-3,3-bis(p-chlorophenyl)acrylic acid (86)	171, 170
$C_{14}H_{10}Cl$	p-ClC_6H_4, Cl / C_6H_5	BuLi/THF/−108°/ 40 min	CO_2	(Z)-2-Chloro-3-(p-chlorophenyl)-3-phenylacrylic acid (84)	170
	C_6H_5, Cl / p-ClC_6H_4	BuLi/THF/−108°/ 40 min	CO_2	(E)-2-Chloro-3-(p-chlorophenyl)-3-phenylacrylic acid (87)	170
$C_{14}H_{11}Cl$	C_6H_5, Cl / C_6H_5	BuLi/THF, ether, pet. ether/ −93°/17 min	Br_2	C_6H_5, Cl / C_6H_5, X X = Br (94)	358
		BuLi/THF, ether, pet. ether/ −93°/10 min	I_2	X = I (98)	358

TABLE XXIX. Fluoro-, Chloro-, and Bromoalkenes (Alpha) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{14}H_{11}Cl$ (*Contd.*)	(structure: C_6H_5, Cl, C_6H_5)	$^tBuLi/THF$, ether/ $-93°/2$ hr	$HgCl_2$	(structure: C_6H_5, Cl, C_6H_5, X) X = (structure: Cl, C_6H_5, Hg, C_6H_5) (69)	358
		BuLi/THF/$-71°$/ 1 hr	CO_2	X = CO_2H (83)	171, 358, 170
		BuLi/THF, ether/ $-93°/2$ hr	CH_3I	X = CH_3 (86)	358
		BuLi/THF/$-100°$/ 30 min	CH_3OCH_2I	X = CH_2OCH_3 (30)	468
		"	CH_2=$CHCH_2I$	X = CH_2CH=CH_2 (66)	468
		BuLi/THF/$-100°$/ 30 min	C_6H_5COI	X = COC_6H_5 (62)	468
		"	$C_6H_5CH_2I$	X = $CH_2C_6H_5$ (68)	468
$C_{14}H_{21}Cl$	(structure: $(CH_3)_2$, CH_3, H, Cl, CH_3)	BuLi/THF, ether, pet. ether/ $-105°/15$ hr	CO_2	(structure: $(CH_3)_2$, CH_3, X, Cl, CH_3) X = CO_2H (82)	469
		"	(structure: $(CH_3)_2N$, CH_3, CHO) ($HClO_4$)	X = (structure: CH_3, $N(CH_3)_2$)$^+$ ClO_4^- (68)	469
$C_{16}H_{15}Cl$	(structure: o-$CH_3C_6H_4$, Cl, o-$CH_3C_6H_4$)	BuLi/THF, ether, pet. ether/ $-108°/50$ min	CO_2	2-Chloro-3,3-di-o-tolylacrylic acid (45)	171
	(structure: p-$CH_3C_6H_4$, Cl, p-$CH_3C_6H_4$)	BuLi/THF/$-108°$/ 45 min	CO_2	2-Chloro-3,3-di-p-tolylacrylic acid (78)	170
	(structure: $C_6H_5CH_2$, Cl, $C_6H_5CH_2$)	BuLi/$-100°$	I_2	2-Benzyl-1-chloro-1-iodo-3-phenylpropene (97)	470
		BuLi/THF, ether, pet. ether/ $-100°$	CO_2	3-Benzyl-2-chloro-4-phenylcrotonic acid (93)	471, 470
$C_{16}H_{15}ClO_2$	(structure: o-$CH_3OC_6H_4$, Cl, o-$CH_3OC_6H_4$)	BuLi/THF/$-120°$/ 35 min	CO_2	2-Chloro-3,3-bis(o-methoxyphenyl)acrylic acid (61)	171, 170
	(structure: p-$CH_3OC_6H_4$, Cl, p-$CH_3OC_6H_4$)	BuLi/THF, ether, pet. ether/ $-108°/45$ min	CO_2	2-Chloro-3,3-bis(p-methoxyphenyl)acrylic acid (67)	171, 170

Note: References 360–607 are on pp. 355–360.

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TABLE XXX. Miscellaneous Mesoionic Compounds

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
$C_5H_4N_4$		C_6H_5Li/ether/ 25°/3 hr*	CO_2	(28)		472
$C_6H_6N_4$		C_6H_5Li/ether/ 25°/3 hr*	CO_2	(11)		472
		C_6H_5Li/ether/ 25°/3 hr*	CO_2	(5)*		472
		C_6H_5Li/ether/ 25°/3 hr*	CO_2	(18)		472
$C_7H_5N_3O_2$		BuLi/ether, benzene/−20°/ 1 hr	CH_3COCH_3	(64)		473
$C_8H_6N_2O_2$		BuLi/ether, benzene/−20°/ 1 hr	CH_3CHO		$X=CH(OH)CH_3$ (43)	473
		,,	$CH_3COC_3H_7$-i		$X=\underset{OH}{C(CH_3)C_3H_7}$-$i$ (39)	473
		BuLi/THF/−20°/ 1 hr	$(C_6H_5)_2CO$		$X=C(C_6H_5)_2OH$ (84)	474
$C_8H_{12}N_2O_2$		BuLi/ether, benzene/−20°/ 1 hr	CH_3COCH_3	(57)		473

Note: References 360–607 are on pp. 355–360.

TABLE XXXI. Mono-, Di-, and Triarylamines (Ortho)

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Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_8H_{11}N$	$C_6H_5N(CH_3)_2$	BuLi/hexane/ reflux/16 hr	CF_3COCF_3	$X = C(CF_3)_2OH$ (49)	179
		"	$CH_3COC_2H_5$	$X = C(CH_3)C_2H_5$ (20) OH	179
		"	Cyclohexanone	$X =$ (31)	179
		"		$X =$ (14), (7)	179
		"	$C_6H_5COCH_3$	$X = C(CH_3)C_6H_5$ (34) OH	179
		BuLi/hexane, TMEDA/25°/4 hr	$(C_6H_5)_2CO$	$X = C(C_6H_5)_2OH$ (71)	63, 179, 180
$C_9H_{13}N$	o-$CH_3C_6H_4N(CH_3)_2$	BuLi/ether/25°/ 40 hr	D_2O	(I), (II) (I + II, 94) (I:II, 1.5:1)	63
	p-$CH_3C_6H_4N(CH_3)_2$	BuLi/hexane, TMEDA/25°/ 3 hr	D_2O	2-d-N,N-Dimethyl-p-toluidine (>90)	63
		BuLi/hexane, TMEDA/25°/4 hr	$(C_6H_5)_2CO$	[6-(Dimethylamino)-m-tolyl]diphenyl-methanol (80)	63, 359
$C_9H_{13}NO$	m-$CH_3OC_6H_4N(CH_3)_2$	BuLi/ether/35°/ 12 hr	$(C_6H_5)_2CO$	[2-(Dimethylamino)-6-methoxyphenyl]-diphenylmethanol (71)	19
$C_{10}H_9N$	[structure: 1-phenylpyrrole]	BuLi/ether/25°/ 8 hr	CO_2	1-Phenylpyrrole-2-carboxylic acid (14)	81
		2 BuLi/ether/ reflux/14 hr	"	(5)	81
	[structure: 1-naphthylamine, NH_2]	BuLi/ether/ reflux/50 hr	CO_2	(10)	486
$C_{11}H_{14}ClNO$	p-$ClC_6H_4NHCOC_4H_9$-t	BuLi/THF/0°/ 2 hr	CH_3I	4'-Chloro-o-pivalotoluidide (71)	181a
		"	$(CH_3S)_2$	4'-Chloro-2'-(methylthio)pivalanilide (79)	181a

TABLE XXXI. MONO-, DI-, AND TRIARYLAMINES (ORTHO) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{11}H_{14}ClNO$ (*Contd.*)	p-$ClC_6H_4NHCOC_4H_9$-t	''	o-FC_6H_4CN	2-t-Butyl-6-chloro-4-(o-fluorophenyl)-quinazoline (57)	181a
$C_{11}H_{13}NO$	$C_6H_5NHCOC_4H_9$-t	BuLi/ether, THF/ 25°/18 hr	$(CH_3S)_2$	2'-(Methylthio)pivalanilide (78)	181a
		''	DMF	2'-Formylpivalanilide (53)	181a
$C_{12}H_9NS$	(phenothiazine, N–H)	BuLi/ether/25°/ 30 hr	CO_2	(phenothiazine with X substituent) X = CO_2H (53)	177
		''	CH_3CO_2Li	X = $COCH_3$ (40)	177
		''	$C_2H_5CO_2Li$	X = COC_2H_5 (33)	177
		''	$C_6H_5CO_2Li$	X = COC_6H_5 (41)	177
		BuLi	$(C_6H_5)_2CO$	X = $C(C_6H_5)_2OH$ (70)	178
$C_{12}H_{17}NO_2$	m-$CH_3OC_6H_4NHCOC_4H_9$-t	BuLi/THF/0°/ 2 hr	$(CH_3S)_2$	3'-Methoxy-2'-(methylthio)pivalanilide (82)	181a
		''	C_6H_5CHO	3'-Methoxy-2'-[(α-phenyl)hydroxymethyl]-pivalanilide (79)	181a
	p-$CH_3OC_6H_4NHCOC_4H_9$-t	BuLi/ether, THF/25°/18 hr	$(CH_3S)_2$	4'-Methoxy-2'-(methylthio)pivalanilide (53), 2',5'-bis(methylthio)-4'-methoxypivalanilide (28), 4'-methoxy-3'-(methylthio)-pivalanilide (15)	181a
$C_{13}H_{11}NS$	(N-methylphenothiazine)	BuLi/ether/30 hr	CO_2	(phenothiazine, N-CH_3, CO_2H) (14), (phenothiazine, N-CH_3, CO_2H) (16)	177, 183a
$C_{14}H_{11}N$	(N-phenylindole)	BuLi/ether/ reflux/12 hr	CO_2	1-(o-Carboxyphenyl)indole-2-carboxylic acid (15), (indoloquinolinone) (42)	83
$C_{14}H_{13}N$	(N-ethylcarbazole)	BuLi/THF, ether/ 25°/5 hr	CO_2	(carbazole, N-C_2H_5, X) X = CO_2H (21)	560
		BuLi/ether/ reflux/44 hr	$(C_6H_5)_3SiBr$	X = $Si(C_6H_5)_3$ (12)	452
$C_{14}H_{13}NS$	(N-ethylphenothiazine)	BuLi/ether/ 30 hr	CO_2	(phenothiazine, N-C_2H_5, CO_2H) (13), (phenothiazine, N-C_2H_5, CO_2H) (14)	177, 183a
$C_{16}H_{11}NS$	(benzophenothiazine, N–H)	BuLi/ether/ reflux/24 hr	CO_2	(benzophenothiazine, N–H, CO_2H) (41)	183b

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TABLE XXXI. Mono-, Di-, and Triarylamines (Ortho) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{16}H_{11}NS$ (*Contd.*)		BuLi/ether/ 25°	CO_2	(94)	176
$C_{16}H_{13}N$	NHC₆H₅	BuLi/ether/25°/ 20 hr	CO_2	(25), (56)	181b
	NHC₆H₅	BuLi/ether/25°/ 20 hr	CO_2	2-Anilino-3-naphthoic acid (53)	181b
$C_{20}H_{13}NS$		-BuLi/ether/ reflux/4.5 hr	CO_2	(77)	182
		BuLi/ether/ reflux/5 hr	CO_2	(80)	182
		BuLi/ether/ 25°/23 hr	CO_2	(85)	182

Note: References 360–607 are on pp. 355–360.

TABLE XXXII. α-Lithio-(N-alkylidene)arylamines (Aryl Isocyanides) (Ortho)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Ref.
$C_{11}H_{14}LiN$	$C_6H_5N{=}C(Li)C_4H_9\text{-}t^a$	t-BuLi/ether, TMEDA/25°/4 hr	O_2	(structure: $N{=}C(X)C_4H_9\text{-}t$ with ortho X on benzene)	$X = OH$ (29)	184
		,,	CH_3I		$X = CH_3$ (92)	184
		,,	CO_2 (H_3O^+)	Anthranilic acid (54)		184
		,,	SCl_2	(benzoxazole-type structure: $C_4H_9\text{-}t$)	$X = S$ (65)	184
		,,	$(CH_3)_2SiCl_2$		$X = Si(CH_3)_2$ (53)	184
		,,	$(CH_3)_2GeCl_2$		$X = Ge(CH_3)_2$ (68)	184
		,,	$(CH_3)_2SnCl_2$		$X = Sn(CH_3)_2$ (41)	184
		,,	$C_6H_5PCl_2$		$X = PC_6H_5$ (52)	184
		,,	$(C_6H_5)_2SiCl_2$		$X = Si(C_6H_5)_2$ (63)	184

[a] This compound was formed by the reaction of phenyl isocyanide and t-BuLi.[184]

TABLE XXXIII. ARALKYLAMINES AND ALLYLAMINES (ORTHO, BETA)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
C₇H₁₁NS	(3-thienyl-CH₂N(CH₃)₂)	BuLi/ether/ 25°–35°/4 hr	D₂O	(thiophene CH₂N(CH₃)₂, X)	X = D (80)	134, 43
		BuLi/ether/ 25°–35°/1 hr	DMF		X = CHO (75)	134, 43
		"	C₆H₅CN (H₃O⁺)		X = COC₆H₅ (54)	134, 43
		"	(C₆H₅)₂CO		X = C(C₆H₅)₂OH (67)	134, 43
		"	p-CH₃C₆H₅SO₂Br		X = Br (32)	134
		"	p-CH₃C₆H₄SO₂Cl		X = Cl (25)	134
C₇H₁₂N₂O	(5-methyl-isoxazole-CH₂N(CH₃)₂)	BuLi/THF	CH₃I	(I), (II) (I+II,–) (I:II, 1:1)		186
C₈H₁₁N	C₆H₅CH₂NHCH₃	BuLi/ether, TMEDA/ 5 hr	D₂O	(benzyl CH₂NHCH₃, X)	X = D (100)	188
		"	Cyclohexanone		X = (1-hydroxycyclohexyl) (51)	188
		"	C₆H₅CHO		X = CH(OH)C₆H₅ (63)	188
		"	C₆H₅COCH₃		X = C(CH₃)C₆H₅ OH (40)	188
		"	C₆H₅COC₂H₅		X = C(C₂H₅)C₆H₅ OH (43)	188

TABLE XXXIII. ARALKYLAMINES AND ALLYLAMINES (ORTHO, BETA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_8H_{11}N$ (*Contd.*)	$C_6H_5CH_2NHCH_3$	"	$(C_6H_5)_2CO$	X = C(C$_6$H$_5$)$_2$OH (48–52)	188
		BuLi/hexane, TMEDA/ 0.5 hr	C_6H_5CHO	2-[(Methylamino)methyl]-α,α'-diphenyl-*m*-xylene-α,α'-diol (65–75)	188
$C_8H_{13}NS$	CH$_3$—(thiophene)—CH$_2$N(CH$_3$)$_2$	BuLi/ether/ 25°–35°/4 hr	$(C_6H_5)_2CO$	2-[(Dimethylamino)methyl]-α,α-diphenyl-5-methyl-3-thiophenemethanol (65)	43, 134
$C_9H_{11}Cl_2N$	$2,4\text{-}Cl_2C_6H_3CH_2N(CH_3)_2$	BuLi/ether/ 25°/10 min	$o\text{-}ClC_6H_4CN$	2'-Chloro-3,5-dichloro-2-[(dimethylamino)methyl]benzophenone (70)	23
$C_9H_{12}ClN$	$o\text{-}ClC_6H_4CH_2N(CH_3)_2$	BuLi/ether/ 25°	Cu Br	X = Cu (25)	190
		BuLi/ether/ 25°/24 hr	$(C_6H_5)_2CO$	X = C(C$_6$H$_5$)$_2$OH (81)	45
	$p\text{-}ClC_6H_4CH_2N(CH_3)_2$	BuLi/ether/ 25°	CuBr	X = Cu (41)	190
		BuLi/ether/ 0°/12 hr	$(CH_3S)_2$	X = SCH$_3$ (77)	23
		BuLi/ether/ 25°/3 hr	$ClCON(CH_3)_2$	X = CON(CH$_3$)$_2$ (85)	24
		"	$t\text{-}C_4H_9NCO$	X = CONHC$_4$H$_9$-*t* (29)	24
		BuLi/ether/ 0°/12 hr	$o\text{-}ClC_6H_4CN$ (H$_3$O$^+$)	X = COC$_6$H$_4$Cl-*o* (73)	23
		"	$o\text{-}FC_6H_4CN$ (H$_3$O$^+$)	X = COC$_6$H$_4$F-*o* (78)	23
		BuLi/ether/ 25°/3 hr	2-phenylcyclopentanone	X = 1-hydroxy-2-phenylcyclopentyl (38)	24
		BuLi/ether/ 0°/12 hr	$(C_6H_5S)_2$	X = SC$_6$H$_5$ (90)	23
		BuLi/ether/ 25°/24 hr	$(C_6H_5)_2CO$	X = C(C$_6$H$_5$)$_2$OH (82)	45
$C_9H_{12}FN$	$o\text{-}FC_6H_4CH_2N(CH_3)_2$	BuLi/ether/ 25°/1 hr	$(C_6H_5)_2CO$	[α-(Dimethylamino)-3-fluoro-*o*-tolyl]diphenylmethanol (33)	45
$C_9H_{13}N$	$C_6H_5CH_2N(CH_3)_2$	BuLi/ether/ 25°	—	X = Li (100)	9
		BuLi/ether/ 25°/24 hr	D_2O	X = D (94)	30
		BuLi/ether/ 25°	CuBr	X = Cu (44)	190, 475
		BuLi/ether/ 25°/65 hr	AgBr	X = Ag (61)	304
		BuLi/ether/ 25°	CO$_2$ (CH$_2$N$_2$)	X = CO$_2$CH$_3$ (35)	185
		BuLi/ether/ 25°/18 hr	CH_2I_2	X = I (64)	293
		BuLi/ether/ 25°/20 hr	CH_3CN	X = COCH$_3$ (25)	476
		BuLi/ether/ 25°/18 hr	CCl_3CCl_3	X = Cl (63)	293
		BuLi/ether/ 25°/27–29 hr	DMF	X = CHO (80)	23
		BuLi/ether/ 25°/18 hr	CH_3COCH_3	X = C(CH$_3$)$_2$OH (46)	33
		BuLi/THF/ 25°–45°/6 hr	$(CH_3O)_3B$ (H$_3$O$^+$)	X = B(OH)$_2$ (10)	416

TABLE XXXIII. ARALKYLAMINES AND ALLYLAMINES (ORTHO, BETA) (Continued)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_9H_{13}N$ (Contd.)	$C_6H_5CH_2N(CH_3)_2$	BuLi/ether/ 25°/18 hr	$(CH_3)_2CBrCBr(CH_3)_2$	X = Br (69)	293
		—	CH_3 CH_2CHO	X = CH(OH)CH$_2$ CH_3 (−)	477
		BuLi/ether/ 25°/18 hr		X = (36)	33
		″	o-ClC$_6$H$_4$CHO	X = CH(OH)C$_6$H$_4$Cl-o (80)	33
		BuLi/ether/ 25°/27–29 hr	m-ClC$_6$H$_4$CN (H$_3$O$^+$)	X = COC$_6$H$_4$Cl-m (50)	23
		″	o-ClC$_6$H$_4$CN (H$_3$O$^+$)	X = COC$_6$H$_4$Cl-o (90)	23
		″	p-ClC$_6$H$_4$CN (H$_3$O$^+$)	X = COC$_6$H$_4$Cl-p (85)	23
		BuLi/ether/ 25°/30 hr	C_6H_5CHO	X = CH(OH)C$_6$H$_5$ (78)	33
		BuLi/ether/ 25°/18 hr	C_6H_5CN (H$_3$O$^+$)	X = COC$_6$H$_5$ (63)	33, 344
		BuLi/ether/ 25°/30 hr	C_6H_5NCO	X = CONHC$_6$H$_5$ (65)	33
		BuLi/ether/ 25°/18 hr	p-CH$_3$OC$_6$H$_4$CHO	X = CH(OH)C$_6$H$_4$OCH$_3$-p (78)	33
		BuLi/ether/ 25°/ "overnight"	C_6H_5	X = (28)	24
		BuLi/ether/ 25°/30 hr	$C_6H_4COC_4H_9$-n	X = C(C$_6$H$_5$)C$_4$H$_9$-n ("good") OH	33
		BuLi/ether/ 25°/18 hr	3,4,5-(CH$_3$O)$_3$C$_6$H$_2$CHO	X = CH(OH)C$_6$H$_2$(OCH$_3$)$_3$- 3,4,5 (56)	33
		BuLi/ether/ 25°/27 hr	3,4,5-(CH$_3$O)$_3$C$_6$H$_2$CN (H$_3$O$^+$)	X = COC$_6$H$_2$(OCH$_3$)$_3$- 3,4,5 (90)	23
		BuLi/ether/ 25°/30 hr	$(C_6H_5)_2CO$	X = CO(C$_6$H$_5$)$_2$OH (77)	33, 45, 180
		BuLi/ether/ 25°/30 hr	$C_6H_5CO_2C_2H_5$	Bis[(α-dimethylamino)-o-tolyl]phenylmethanol (59)	33
		BuLi/hexane/ reflux/6 hr	CoCl$_2$	(45)	300
		BuLi/ether/ 25°/90 hr	$\frac{1}{2}$AgBr$_2$	(10)	305
		BuLi/hexane/ reflux/16 hr	Fe(CO)$_5$	(−)	299
		″	Ni(CO)$_4$	(−)	299
		BuLi	[(C$_2$H$_5$)$_3$P]$_2$NiCl$_2$	(60) (trans)	303

TABLE XXXIII. ARALKYLAMINES AND ALLYLAMINES (ORTHO, BETA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_9H_{13}N$ (*Contd.*)	$C_6H_5CH_2N(CH_3)_2$	BuLi/ether/ 25°	$(CH_3)_2SnBr_2$	$R = CH_3$ (50)	480
		"	$(CH_3)C_6H_5SnBr_2$	$R = C_6H_5$ (90)	481
		BuLi/ether/ 25°	$(CH_3)_2SnBr_2$	(—)	480
		BuLi	$[(C_2H_5)_2S]_2PdCl_2$	Me = Pd (—) *cis*	303
		"	$[(C_2H_5)_2S]_2PtCl_2$	Me = Pt (—)	303
		—	$(C_6H_5)_3PAuBr$	$\cdot$ $P(C_6H_5)_3$ (65)	307
$C_{10}H_{12}F_3N$	m-$CF_3C_6H_4CH_2N(CH_3)_2$	BuLi/ether/ 25°/1 hr	$(C_6H_5)_2CO$	[α^6-(Dimethylamino)-$\alpha^2,\alpha^2,\alpha^2$-trifluoro-2,6-xylyl]diphenylmethanol (72)	45
$C_{10}H_{13}NO_2$		BuLi/ether/ 25°/1 hr	$(C_6H_5)_2CO$	[α-(Dimethylamino)-5,6-(methylenedioxy)-*o*-tolyl]diphenylmethanol (60)	483
$C_{10}H_{14}ClNS$		BuLi/ether/ 0°/2 hr	$(C_6H_5)_2CO$	[5-Chloro-α-(dimethylamino)-3-(methylthio)-*o*-tolyl]diphenylmethanol (35)	23
$C_{10}H_{15}N$	p-$CH_3C_6H_4CH_2N(CH_3)_2$	BuLi/ether/ 25°	CuBr	X = Cu (66)	190, 39
		BuLi/ether/ 25°/30 hr	C_6H_5CN	X = COC_6H_5 (80)	23
		BuLi/ether/ 25°/"overnight"		X = (21)	24
		BuLi/ether/ 25°/24 hr	$(C_6H_5)_2CO$	X = $C(C_6H_5)_2OH$ (82)	45
$C_{10}H_{15}NO$	m-$CH_3OC_6H_4CH_2N(CH_3)_2$	BuLi/ether	Ethylene oxide	[2-(Dimethylamino)methyl]-6-methoxyphenethyl alcohol (—)	189
		BuLi/ether/ 27°/2 hr	$(C_6H_5)_2CO$	[α-(Dimethylamino)-6-methoxy-*o*-tolyl]diphenylmethanol (79)	19, 45, 189
	o-$CH_3OC_6H_4CH_2N(CH_3)_2$	BuLi/ether/ 27°/2 hr	$(C_6H_5)_2CO$	[α-(Dimethylamino)-2-methoxy-*m*-tolyl]diphenylmethanol (58), [α-(dimethylamino)-3-methoxy-*o*-tolyl]diphenylmethanol (<5)	19
	p-$CH_3OC_6H_4CH_2N(CH_3)_2$	BuLi/ether/ 27°/24 hr	D_2O	(III) X = D (70)	19
		BuLi/ether/ 25°	CuBr	X = Cu (38)	190
		BuLi/ether	Ethylene oxide	X = $(CH_2)_2OH$ (—)	189

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TABLE XXXIII. Aralkylamines and Allylamines (Ortho, Beta) (*Continued*)

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Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C₁₀H₁₅NO (*Contd.*)	p-CH₃OC₆H₄CH₂N(CH₃)₂	BuLi/ether/ 25°/20 hr	Cyclopentanone	X = [1-hydroxycyclopentyl] (32)	24
		"	[norcamphor structure]	X = [2-hydroxy-bicyclic] (39)	24
		"	C₆H₅CH₂CHO	X = CH(OH)CH₂C₆H₅ (10)	24
		"	[2-phenoxycyclopentanone]	X = [2-OC₆H₅-1-hydroxycyclopentyl] (12)	24
		"	[2-(phenylthio)cyclopentanone]	X = [2-SC₆H₅-1-hydroxycyclopentyl] (12)	24
		"	[2-phenylcyclopentanone]	X = [2-C₆H₅-1-hydroxycyclopentyl] (20)	24
		"	[2-benzylcyclopentanone]	X = [2-CH₂C₆H₅-1-hydroxycyclopentyl] (31)	24
		"	[2-phenoxycyclohexanone]	X = [2-OC₆H₅-1-hydroxycyclohexyl] (21)	24
		BuLi/ether/ 27°/24 hr	(C₆H₅)₂CO	X = C(C₆H₅)₂OH (80)	19, 45, 180, 189
		BuLi/ether, TMEDA/ 27°/15 hr	D₂O	(III), [3-methoxy-4-X-benzyl-N(CH₃)₂] (18) (48) X = D	19
		BuLi/ether, TMEDA/ 27°/2 hr	(C₆H₅)₂CO	(7) (55) X = C(C₆H₅)₂OH	19, 180
C₁₁H₁₄ClNO	[2-(4-chlorophenyl)-2,3-dimethyloxazolidine]	BuLi/ether/ 0°/4 hr	(CH₃S)₂	2-[4-Chloro-2-(methylthio)phenyl]-2,3-dimethyloxazolidine (80)	23
C₁₁H₁₅NS	[C₆H₅S–CH=CH–CH₂N(CH₃)₂]	BuLi/ether/ 0°/1 hr	D₂O	[C₆H₅S, X, CH₂N(CH₃)₂ vinyl] X = D (>90)	23
		"	(CH₃S)₂	X = SCH₃ (>90)	23
C₁₁H₁₅NO	C₆H₅CH₂N(morpholine)	BuLi/ether/ 25°/20 hr	[4-chloropyrrole-2-carbaldehyde]	[2-CH₂-morpholino-benzyl CH(OH)X] X = [4-chloro-5-methylpyrrol-2-yl] (—)	187
		"	[thiophene-2-carbaldehyde]	X = [5-methylthiophen-2-yl] (—)	187
		"	3,4-Cl₂C₆H₃CHO	X = C₆H₃Cl₂-3,4 (—)	187
C₁₁H₁₇N	2,4-(CH₃)₂C₆H₃CH₂N(CH₃)₂	BuLi/ether/ 25°/24 hr	(C₆H₅)₂CO	[2-[(Dimethylamino)methyl]-3,5-dimethylphenyl]diphenylmethanol (52)	45
	C₆H₅C(CH₃)₂N(CH₃)₂	BuLi/ether/ 18 hr	(C₆H₅)₂CO	[(α-(Dimethylamino)-o-cumenyl]-diphenylmethanol (57)	33

TABLE XXXIII. Aralkylamines and Allylamines (Ortho, Beta) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{11}H_{17}NO_2$	$3,4\text{-}(CH_3O)_2C_6H_3CH_2N(CH_3)_2$	BuLi/ether/ 0°/3 hr	I_2	X = I (77)	23
		"	Ethylene oxide	X = $(CH_2)_2OH$ (60)	23
		"	CH_3CHO	X = $CH(OH)CH_3$ (65)	23
		"	CH_3OCH_2Cl	X = CH_2OCH_3 (66)	23
$C_{12}H_{17}N$		BuLi/ether/ 25°/20 hr	CH_3I	1-Methyl-2-(*o*-tolyl)piperidine (93)	24
$C_{12}H_{17}NO$	$p\text{-}CH_3C_6H_4CH_2N{\bigcirc}O$	BuLi/ether/ 25°/20 hr	C_6H_5CHO	[5-Methyl-2-(4-morpholinomethyl)] benzhydrol (27)	187
$C_{12}H_{21}NSi$	$o\text{-}(CH_3)_3SiC_6H_4CH_2N(CH_3)_2$	BuLi/ether/ 25°	$(CH_3)_3SiCl$	N,N-Dimethyl-bis-2,6- (trimethylsilyl)benzylamine (—)	9
$C_{13}H_{13}N$	$C_6H_5CH_2NHC_6H_5$	BuLi/hexane, TMEDA/ 1.5–4 hr	CO_2	2-Phenylphthalimidine (8),	188
				X = CO_2H (61)	
		"	C_6H_5CHO	X = $CH(OH)C_6H_5$ (72–75)	188
		"	$C_6H_5COCH_3$	X = $\underset{OH}{\overset{\displaystyle C(CH_3)C_6H_5}{\mid}}$ (10)	188
		"		X = (93–98)	188
		"	$(C_6H_5)_2CO$	X = $C(C_6H_5)_2OH$ (86)	188
$C_{13}H_{15}N$		BuLi/ether/ 25°/24 hr	D_2O	(IV), (V)	
				(IV:V, 12:88) X = D	484
		"	$(C_6H_5)_2CO$	(IV+V, 79) (IV:V, 8:92) X = $C(C_6H_5)_2OH$	191
		BuLi/ether/ 25°	$CO_2(O_2)$	N-Methyl-1,8-naphthalenedicarboximide (57)	185
		BuLi/ether/ 25°	D_2O	(VI), (VII)	
				(VI:VII, 2:1) X = D	484
		"	$CO_2(CH_2N_2)$	VI (29) VII (23) X = CO_2CH_3	185
		BuLi/ether/ 25°/48 hr	$(C_6H_5)_2CO$	(VI+VII, 79) (VI:VII, 43:58) X = $C(C_6H_5)_2OH$	191
$C_{13}H_{21}N$	$p\text{-}t\text{-}C_4H_9C_6H_4CH_2N(CH_3)_2$	BuLi/hexane/ reflux/6 hr	$CoCl_2$	(33)	300

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TABLE XXXIII. ARALKYLAMINES AND ALLYLAMINES (ORTHO, BETA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{14}H_{17}NO$	[naphthalene with $CH_2N(CH_3)_2$ and OCH_3]	BuLi/ether/ 25°	$CO_2(CH_2N_2)$	Methyl [1-(dimethylamino)methyl]-3-methoxy-2-naphthoate (39)	185
	[naphthalene with $CH_2N(CH_3)_2$ and OCH_3]	BuLi/25°/ 24 hr	CuBr	[Cu–naphthalene complex with $N(CH_3)_2$, CH_2, OCH_3] (50)	190
	[naphthalene with $CH_2N(CH_3)_2$ and OCH_3]	BuLi/ether/ 25°	$CO_2(CH_2N_2)$	Methyl [3-(dimethylamino)methyl]-1-methoxy-2-naphthoate (56)	185
	[naphthalene with OCH_3 and $CH_2N(CH_3)_2$]	BuLi/ether/ 25°	$CO_2(CH_2N_2)$	Methyl [3-(dimethylamino)methyl]-5-methoxy-2-naphthoate (38)	185
$C_{15}H_{17}N$	$(C_6H_5CH_2)_2NCH_3$	BuLi/ether/ 25°/48 hr	D_2O	N-Methyl(dibenzyl)-2-*d*-amine (100)	30
		"	C_6H_5CHO	2-[(Benzylmethylamino)methyl]benzhydrol (56)	33
$C_{15}H_{19}NO_2$	[naphthalene with OCH_3, $CH_2N(CH_3)_2$, OCH_3]	BuLi/ether/ 25°	$CO_2(CH_2N_2)$	Methyl [3-(dimethylamino)methyl]-1,5-dimethoxy-2-naphthoate (52)	185
$C_{18}H_{24}N_2$	$[C_6H_5CH_2N(CH_3)CH_2]_2$	BuLi/25°/ 48 hr	D_2O	$C_6H_5CHDN(CH_2)_2N(CH_3)CH_2C_6H_5$ (30), [and ortho-D product with $CH_2N(CH_3)(CH_2)_2N(CH_3)CH_2C_6H_5$] (65)	485
$C_{23}H_{23}N$	[benzene with $CH_2N(CH_3)_2$ and $C(=C_6H_5)_2$ vinyl]	BuLi/ether/ 25°/24 hr	$(C_6H_5)_2CO$	[product with $C(C_6H_5)_2OH$, $CH_2N(CH_3)_2$, and $C(=C_6H_5)_2$ vinyl substituents] (32)	45

Note: References 360–607 are on pp. 355–360.

TABLE XXXIV. 2-ARYLETHYLAMINES (ORTHO, BETA)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_9H_{13}NO$	$C_6H_5CH(OH)CH_2NHCH_3$	BuLi/ether/25°/ 24 hr	$(CH_3)_3SiCl$	α-[(Methylamino)methyl]-o-(trimethylsilyl)benzyl alcohol (21)	175
$C_{10}H_{11}NS$	[Benzo[b]thiophene with $(CH_2)_2NH_2$ at 3-position]	BuLi/THF/−78°/ 0.5 hr	D_2O	2-d-Benzo[b]thiophene-3-ethylamine (83)[a]	153
$C_{10}H_{15}N$	$C_6H_5(CH_2)_2N(CH_3)_2$	BuLi BuLi/ether/25°/ 11 hr	C_6H_5CHO $(C_6H_5)_2CO$	2-[2-(Dimethylamino)ethyl]benzhydrol (—) [o-2-(Dimethylamino)ethyl]phenyl]-diphenylmethanol (7)	193 194, 195, 193
$C_{10}H_{15}NO$	$C_6H_5CH(OH)CH_2N(CH_3)_2$	BuLi/ether/25°/ 24 hr	CH_3I	[structure: $CH(OH)CH_2N(CH_3)_2$ on benzene ring with X ortho] $X = CH_3$ (47)	175
		"	CH_2O	$X = CH_2OH$ (33)	175
		"	$(CH_3)_3SiCl$	$X = Si(CH_3)_3$ (61)	175
		"	$(C_6H_5)_2CO$	$X = C(C_6H_5)_2OH$ (48)	175
$C_{11}H_{17}NO_2$	$p\text{-}CH_3OC_6H_4CH(OH)CH_2N(CH_3)_2$	BuLi/ether/25°/ 24 hr	$(C_6H_5)_2CO$	α^1-[(Dimethylamino)methyl]-4-methoxy-α^2, α^2-diphenyl-o-xylene-α^1, α^2-diol (48)	175
$C_{12}H_{15}NS$	[Benzo[b]thiophene with $(CH_2)_2N(CH_3)_2$ at 3-position]	BuLi/THF/−78°/ 0.5 hr	D_2O	N,N-Dimethyl-2-d-benzo[b]thiophene-3-ethylamine (83)	153
$C_{12}H_{19}N$	$C_6H_5C(CH_3)_2CH_2N(CH_3)_2$	BuLi/ether/25°/ 120 hr	$(C_6H_5)_2CO$	[o-[2-(Dimethylamino)-1,1-dimethylethyl]phenyl]-diphenylmethanol (17)	195
$C_{13}H_{18}N_2$	[Indole with $(CH_2)_2N(CH_3)_2$ at 3-position, CH_3 on N]	BuLi/THF/0°/ 75 min	D_2O	3-[2-Dimethylamino)ethyl]-2-d-1-methylindole (74)[b]	153

[a] The isolated yield was 83%; the deuterium incorporation was 80%.
[b] The isolated yield was 74%; the deuterium incorporation was 74%.

TABLE XXXV. α-ALKOXIDOARALKYLAMINES (ORTHO, BETA)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_7H_{10}LiNO_2$	CH(OLi)N(CH₃)₂ (furan)	Et/Li/ether/ reflux/2 hr	$(n-C_4H_9O)_3B$ (H_3O^+)	CHO / B(OH)₂ (32)	114, 115
$C_7H_{10}LiNOS$	CH(OLi)N(CH₃)₂ (thiophene)	BuLi/reflux/ 135 min	CO_2	3-Formyl-2-thiophenecarboxylic acid (44)	414
$C_8H_{12}LiNOS$	OLi | C(CH₃)N(CH₃)₂ (thiophene)	BuLi	"S"+BrCH₂CO₂H₃	Methyl [(3-acetyl-2-thienyl)thio]acetate (—)	422
$C_{10}H_{13}ClLiNO$	$p\text{-}ClC_6H_4C(CH_3)N(CH_3)_2$ OLi	BuLi/THF/0°– 25°/16 hr	CH_3I	COCH₃ / Cl—X X = CH₃ (81)	196
		"	$(CH_3S)_2$	X = SCH₃ (45)	196
		"	DMF	X = CHO (56)	196
		"	$t\text{-}C_4H_9NCO$	X = CONHC₄H₉-t (41)	196
		BuLi/THF/0°/ 8 hr	$o\text{-}ClC_6H_4CN$	X = CC₆H₄Cl-o ‖ NH (53)	196
		BuLi/THF/0°– 25°/16 hr	$(C_6H_5)_2CO$	X = C(C₆H₅)₂OH (47)	196
$C_{10}H_{14}LiNO$	$C_6H_5C(CH_3)N(CH_3)_2$ OLi	BuLi/THF/0°– 25°/16 hr	$(CH_3S)_2$	2'-(Methylthio)acetophenone (60)	196
$C_{11}H_{12}LiNOS$	CH(OLi)N(CH₃)₂ (benzo[b]thiophene)	BuLi/THF/−30° to -20°	"S"	2-Mercaptobenzo[b]thiophene-3- carboxaldehyde (—)	454
$C_{11}H_{15}ClLiNO$	$p\text{-}ClC_6H_4C(C_2H_5)N(CH_3)_2$ OLi	BuLi/THF/0°/ 20 hr	$(CH_3S)_2$	4'-Chloro-2'-(methylthio)propiophenone (47)	196
$C_{11}H_{18}LiNO_2S$	t-C₄H₉O—CH(OLi)N(CH₃)₂ (thiophene)	BuLi/ether/ reflux/1 hr	DMF	4-t-Butoxy-2,3-thiophenedicarboxaldehyde (60)	148
$C_{11}H_{18}LiNO_2Se$	t-C₄H₉O—CH(OLi)N(CH₃)₂ (selenophene)	BuLi/ether/ reflux/1 hr	DMF	4-t-Butoxy-2,3-selenophenedicarboxaldehyde (50)	148
$C_{13}H_{19}ClLiNO$	$p\text{-}ClC_6H_4C(C_4H_9\text{-}n)N(CH_3)_2$ OLi	BuLi/THF/0°/ 16 hr	$(CH_3S)_2$	4'-Chloro-2'-(methylthio)valerophenone (56)	196
$C_{15}H_{15}ClLiNO$	$p\text{-}ClC_6H_4C(C_6H_5)N(CH_3)_2$ OLi	BuLi/THF/0°– 25°/16 hr	$(CH_3S)_2$	4-Chloro-2-(methylthio)benzophenone (53)	196
		"	DMF	4-Chloro-2-formylbenzophenone (55)	196

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Note: References 360–607 are on pp. 355–360.

TABLE XXXVI. ARYLCARBOXAMIDES (ORTHO, BETA)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C₆H₇NOS		BuLi/ether/ 25°–35°/ 1 hr	D₂O	2-d-N-Methyl-3-thiophenecarboxamide (55)	134
C₇H₉NOS		BuLi/ether/ 25°/20 min	—	(41)	134, 43
C₈H₈ClNO	p-ClC₆H₄CONHCH₃	BuLi/THF/ −30°–25°/ 2 hr	I₂(CH₃I)	X=I (30)	23
		"	o-ClC₆H₄CHO (CH₃I)	X=CH(OCH₃)C₆H₄Cl-o (90)	23
		"	o-FC₆H₄CHO (CH₃I)	X=CH(OCH₃)C₆H₄F-o (90)	23
		"	(C₆H₅S)₂ (CH₃I)	X=SC₆H₅ (62)	23
		"	Ethylene oxide	2-(2-Hydroxyethyl)-4-chloro-N-methylbenzamide (58)	23
		"	o-FC₆H₄CN	3-Amino-5-chloro-3-(o-fluorophenyl)-2-methylphthalimidine (26)	23
C₈H₉NO	C₆H₅CONHCH₃	BuLi/THF/0°/ 1 hr	Cyclohexanone	X= (40)	198
		BuLi/THF/ reflux/15 min	C₆H₅CN	X=CC₆H₅ (53) ‖ NH	54
		BuLi/THF/5°/ 1 hr	2,4-Cl₂C₆H₃CHO	X=CH(OH)C₆H₃Cl₂-2,4 (—)	199
		"	p-ClC₆H₄CHO	X=CH(OH)C₆H₄Cl-p (—)	199
		BuLi/THF/0°/ 1 hr	C₆H₅CHO	X=CH(OH)C₆H₅ (28)ᵃ (—)	198, 199
		BuLi/THF/5°/ 1 hr	m-CF₃C₆H₄CHO	X=CH(OH)C₆H₄CF₃-m (—)	199
		"	o-CH₃C₆H₄CHO	X=CH(OH)C₆H₄CH₃-o (—)	199
		"	p-CH₃C₆H₄CHO	X=CH(OH)C₆H₄CH₃-p (—)	199
		"	p-CH₃OC₆H₄CHO	X=CH(OH)C₆H₄OCH₃-p (—)	199
		BuLi/THF/ reflux/15 min	C₆H₅COCH₃	X=C(CH₃)C₆H₅ (43) │ OH	54, 198, 487
		BuLi/THF/0°/ 1 hr	C₆H₅COC₂H₅	X=C(C₂H₅)C₆H₅ (70) │ OH	198
		BuLi/THF/5°/ 1 hr		X= (—)	488

TABLE XXXVI. Arylcarboxamides (Ortho, Beta) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C₈H₉NO (*Contd.*)	C₆H₅CONHCH₃	BuLi/THF/0°/ 1 hr		X = (47)	198
		BuLi/THF/ reflux/ 15 min	p-ClC₆H₄COC₆H₅	X = C(C₆H₅)C₆H₄Cl-p ‖ OH (51)	54
		"	(C₆H₅)₂CO	X = C(C₆H₅)₂OH (81)	54, 198, 487, 489
		BuLi/THF/5°/ 1 hr	p-ClC₆H₄COC₆H₄CH₂N(CH₃)₂-o	X = C(C₆H₄Cl-p)C₆H₄- CH₂N(CH₃)₂-o OH (—)	490
		BuLi/THF/ reflux/ 15 min	Cyclohexanone (H₃O⁺)	R₁R₂ = (27)	54
		"	C₆H₅CHO (H₃O⁺)	R₁ = H, R₂ = C₆H₅ (42)	54
		"	(H₃O⁺)	R₁,R₂ = (58)	54 54
		"	Cyclohexene oxide (H₃O⁺)	(11)	54
		BuLi/THF/0°/ 0.5 hr	C₆H₅CN	3-Amino-2-methyl-3-phenylphthalimidine (62)	201, 54
		BuLi/THF/ reflux/ 45 min	C₆H₅N(CH₃)CHO	3-Hydroxy-2-methylphthalimidine (53)	491
		BuLi/THF/5°/ 1 hr		(—), (—)	492
		BuLi/THF/0°/ 0.5 hr	(C₆H₅)₂SiCl₂	(10)	571
C₉H₁₁NO₂	m-CH₃OC₆H₄CONHCH₃	BuLi/THF, ether/ reflux/1 hr	Ethylene oxide	3,4-Dihydro-5-methoxyisocoumarin (67)	493, 189
		BuLi/THF, ether/1 hr	(C₆H₅)₂CO	4-Methoxy-3,3-diphenylphthalide (91)	493, 189, 19
	o-CH₃OC₆H₄CONHCH₃	BuLi/THF, ether/ reflux/1 hr	Ethylene oxide	2-(2-Hydroxyethyl)-6-methoxy-N-methylbenzamide (50)	493, 494
		"	Propylene oxide	2-(2-Hydroxypropyl)-6-methoxy-N-methylbenzamide (60)	493, 494

TABLE XXXVI. ARYLCARBOXAMIDES (ORTHO, BETA) (Continued)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_9H_{11}NO_2$ (Contd.)	o-$CH_3OC_6H_4CONHCH_3$	BuLi/−70°–0°/ 1 hr		(24)	200
		BuLi/THF, ether/ reflux/1 hr	$(C_6H_5)_2CO$	7-Methoxy-3,3-diphenylphthalide (60)	493, 189, 19
	p-$CH_3OC_6H_4CONHCH_3$	BuLi/ether, TMEDA/ 35°/5 hr	D_2O	2-d-N-Methyl-p-anisamide (50)	19
		BuLi/THF, ether/ reflux/1 hr	Ethylene oxide	3,4-Dihydro-6-methoxyisocoumarin (50)	493, 189
		BuLi/THF/ 65°/15 min	$(C_6H_5)_2CO$	α-Hydroxy-4-methoxy-N-methyl-α,α-diphenyl-o-toluamide (47)	19
$C_{11}H_{14}ClNO$	m-$ClC_6H_4CONHC_4H_9$-t	BuLi/THF/ −70°/3 hr	$(CH_3S)_2$	N-t-Butyl-3-chloro-2-(methylthio)benzamide (31)	24
$C_{11}H_{15}NO$	$C_6H_5CONHC_4H_9$-t	BuLi/THF/0°/ 1 hr	CO_2	X = CO_2H (80)	24
		"	CH_3I	X = CH_3 (50)	24
		"	t-C_4H_9NCO	X = $CONHC_4H_9$-t (75)	24
		"	$C_6H_5CH_2Cl$	X = $CH_2C_6H_5$ (28)	24
		"	$(C_6H_5S)_2$	X = SC_6H_5 (62)	24
		"	DMF	2-t-Butyl-3-hydroxyphthalimidine (86)	24
	$C_6H_5CON(C_2H_5)_2$	LTMP/THF/ 45 min	—	2-Benzoyl-N,N-diethylbenzamide (57)	55
$C_{11}H_{15}NO_4$		BuLi/THF, ether/ reflux/1 hr	Propylene oxide	3,4-Dihydro-6,7,8-trimethoxy-3-methylisocoumarin (35)	202
$C_{11}H_{20}N_2O$		t-BuLi/THF/ −115°	CH_3OD	X = D (100)	57a
		"	CH_3I	X = CH_3 (95)	57a
		"	C_2H_5I	X = C_2H_5 (60)	57a
		"	$C_6H_5CO_2CH_3$	X = COC_6H_5 (95)	57a
		"	p-$CH_3C_6H_4CO_2CH_3$	X = $COC_6H_4CH_3$-p (60)	57a
$C_{12}H_{11}NO$		BuLi/THF, ether/25°	Ethylene oxide (OH−)	R = H (28)	495
		BuLi/THF, ether/ reflux/40 min	Propylene oxide	R = CH_3 (48)	482
		BuLi/THF, ether/25°	Ethylene oxide (OH−)	R = H (25)	495
		BuLi/THF, ether/ reflux/40 min	Propylene oxide	R = CH_3 (28)	482

TABLE XXXVI. ARYLCARBOXAMIDES (ORTHO, BETA) (Continued)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
$C_{13}H_{10}ClNO$	$p\text{-}ClC_6H_4CONHC_6H_5$	BuLi/THF/ $-10°$– $0°/0.5$ hr			$R = CH_3$ (25)	200
	"	"		"	$R = CH_2C_6H_5$ (17)	200
$C_{13}H_{10}FNO$	$p\text{-}FC_6H_4CONHC_6H_5$	BuLi/THF/ $-70°$– $0°/1$ hr			(45)	200
$C_{13}H_{11}NO$	$C_6H_5CONHC_6H_5$	BuLi/THF/0°/ 1 hr	Cyclohexanone		$X=$ (56)	198
		"	$C_6H_5COC_2H_5$		$X = C(C_2H_5)C_6H_5$ (80) OH	198
		"			$X=$ (55)	198
		"	$(C_6H_5)_2CO$		$X = C(C_6H_5)_2OH$ (75)	198
		BuLi/THF/ 0°/0.5 hr	$(CH_3)_2SiCl_2$		$R = CH_3, m = n = 2$ (67)	571
		"	$(CH_3)_3SiCl$		$R = CH_3, m = 1, n = 3$ (60)	571
		"	$(C_6H_5)_2SiCl_2$		$R = C_6H_5, m = n = 2$ (70)	571
		BuLi/THF/ $-70°$– $0°/1$ hr			$R_1, R_2 =$ (50)	200
		"	$C_2H_5CO(CH_2)_2N(CH_3)_2$		$R_1 = C_2H_5$ $R_2 = (CH_2)_2N(CH_3)_2$ (55)	24
		"			$R_1, R_2 =$ (25)	24

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TABLE XXXVI. ARYLCARBOXAMIDES (ORTHO, BETA) (Continued)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{13}H_{11}NO$ (Contd.)	$C_6H_5CONHC_6H_5$	''		$R_1, R_2 =$ (42)	200
$C_{14}H_{13}NO$	$C_6H_5CONHCH_2C_6H_5$	BuLi/THF/0°/ 0.5 hr	C_6H_5CN	3-Amino-2,3-diphenylphthalimidine (65)	201
		BuLi/THF/0°/ 0.5 hr	C_6H_5NCO	N-Benzyl-N'-phenylphthalamide (20)	496
$C_{14}H_{13}NO_2$	m-$CH_3OC_6H_4CONHC_6H_5$	BuLi/THF/ −10°− 0°/0.5 hr		(19)	200
	p-$CH_3OC_6H_4CONHC_6H_5$	BuLi/THF/ −10°− 0°/0.5 hr		(34)	200
$C_{14}H_{21}ClN_2O$		BuLi/THF/ −78°/1 hr	$(CH_3S)_2$	N-t-Butyl-3-chloro-6-[(dimethylamino)methyl]-2-(methylthio)benzamide (56)	24
$C_{16}H_{24}N_2O_2$		BuLi/THF, ether	Ethylene oxide	(−)	51
		BuLi/THF/0°/ 6 hr	$(CH_3S)_2$	N,N'-Di-t-butyl-4-(methylthio)isophthalamide (51)	24

^a The product was contaminated with the corresponding phthalide.

Note: References 360–607 are on pp. 355–360.

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TABLE XXXVII. ARYLTHIOCARBOXAMIDES (ORTHO)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C_8H_8ClNS	p-$ClC_6H_4CSNHCH_3$	BuLi/THF/ $-45°-10°$	CH_3CHO (H_3O^+)	5-Chloro-3-methylphthalide (68)	65
		"	DMF	(77)	65
		"	t-C_4H_9NCO	$X = CONHC_4H_9$-t (61)	65
		"	$(C_6H_5S)_2$	$X = SC_6H_5$ (91)	65
C_8H_9NS	$C_6H_5CSNHCH_3$	BuLi/THF/0°/ 4 hr	$(CH_3)_3SiCl$	N-Methyl-o-(trimethylsilyl)thiobenzamide (49)	65
$C_9H_{11}NOS$	p-$CH_3OC_6H_4CS$-$NHCH_3$	BuLi/THF/0°/ 25°/8.5 hr	$(CH_3S)_2$	4-Methoxy-N-methyl-2-(methylthio)thiobenzamide (78)	65

TABLE XXXVIII. 2-ARYLOXAZOLINES AND 2-ARYLOXAZINES (ORTHO, BETA)

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Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
$C_9H_{11}NOS$		BuLi/THF/ −70°/1 hr	C_6H_5CHO	(36)	(55) X = CH(OH)C₆H₅	139
		BuLi/ether/ −70°–0°	ʼʼ	(91)	(4) X = CH(OH)C₆H₅	139
$C_9H_{11}NO_2$		BuLi/THF/ −70°/1 hr	C_6H_5CHO	(49),	(36) X = CH(OH)C₆H₅	377
$C_{10}H_{12}N_2O$		CH₃Li/THF/ −78°–0°/ 1 hr	D₂O		X = D (80)	207
		ʼʼ	CH₃I		X = CH₃ (63)	207
		ʼʼ	C₂H₅I		X = C₂H₅ (56)	207
		ʼʼ	CH₂=CHCH₂Br		X = CH₂CH=CH₂ (55)	207
		ʼʼ	DMF		X = CHO (52)	207
		ʼʼ	C₂H₅COC₂H₅		X = C(C₂H₅)₂OH (76)	207
		ʼʼ	C₆H₅CHO		X = CH(OH)C₆H₅ (83)	207
$C_{11}H_{11}D_2NO$		BuLi/THF/ −45°/6 hr	D₂O	4,4-Dimethyl-2-(phenyl-2,4-6-d_3)-2-oxazoline (92)		204

TABLE XXXVIII. 2-ARYLOXAZOLINES AND 2-ARYLOXAZINES (ORTHO, BETA) (Continued)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
$C_{11}H_{12}ClNO$		BuLi/ether/ 0°/1 hr	I_2	2-(4-Chloro-2-iodophenyl)-4,4-dimethyl-2-oxazoline (66)		46
		"	CH_3I	2-(4-Chloro-o-tolyl)-4,4-dimethyl-2-oxazoline (71)		46
$C_{11}H_{12}DNO$		BuLi/THF/ −45°/6 hr	D_2O	4,4-Dimethyl-2-(phenyl-2,6-d_2)-2-oxazoline (90)		204
		BuLi/THF/ −45°/7.5 hr,	D_2O	4,4-Dimethyl-2-(phenyl-2,3,6-d_3)-2-oxazoline (88)		204
		BuLi/THF/ −45°/1.5 hr	D_2O	4,4-Dimethyl-2-(phenyl-2,4-d_2)-2-oxazoline (90)		204
$C_{11}H_{13}NO$		s-BuLi/ ether −70°–0°	D_2O	4,4-Dimethyl-2-(phenyl-2-d)-2-oxazoline (92)		46
		"	t-C_4H_9NCO	2-(2-t-Butylcarbamoylphenyl)-4,4-dimethyl-2-oxazoline (81)		46
$C_{12}H_{15}NO_2$	p-$CH_3OC_6H_4$	BuLi/ether/ 0°/4 hr	CH_3NCS		X = CSNHCH₃ (77)	46
		"	DMF		X = CHO (70)	46
		"	$(C_6H_5S)_2$		X = SC₆H₅ (89)	46
$C_{13}H_{16}ClNO$	p-ClC_6H_4	BuLi/ether/ 0°/1 hr	o-FC_6H_4CHO		(80) (2 isomers)	23
$C_{13}H_{17}NO_3$		BuLi/THF/ −45°/1.5 hr	D_2O		X = D (95)	204
		"	$(CH_3S)_2$		X = SCH₃ (92)	204
		"	N-Chloro-succinimide		X = Cl (90)	204
$C_{16}H_{20}N_2O_2$		LDA/ benzene, TMEDA/ 25°/7 hr	CH_3I		R = CH₃ (98)	208d
		"	$CH_2=CHCH_2Br$		R = CH₂CH=CH₂ (41)	208d

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TABLE XXXIX.   ARYLCARBIMINES (ORTHO, BETA)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.

TABLE XXXIX. ARYLCARBIMINES (ORTHO, BETA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C_9H_7NS (*Contd.*)		BuLi/ ether/ 0°/15 min	(ox.)	$X =$ (55)	280
$C_9H_9ClN_2$		BuLi/ THF/ 50°/3 hr	$p\text{-}ClC_6H_4CO_2CH_3$	$R = C_6H_4Cl\text{-}p$ (—)	308
		"	$p\text{-}FC_6H_4CO_2C_2H_5$	$R = C_6H_4F\text{-}p$ (—)	308
$C_9H_{10}N_2$		BuLi/ THF/ reflux/ 1 hr	$p\text{-}ClC_6H_4CHO$	$X = CH(OH)C_6H_4Cl\text{-}p$ (—)	216
		"	$p\text{-}ClC_6H_4COC_6H_5$	$X = \overset{OH}{CC_6H_5(C_6H_4Cl\text{-}p)}$ (—)	216
		"	$(C_6H_5)_2CO$	$X = C(C_6H_5)_2OH$ (—)	216
$C_{10}H_{12}N_2$		BuLi/ THF/ 25°/24 hr	$p\text{-}ClC_6H_4CN$	(—)	308
$C_{10}H_{13}ClN_2$	$p\text{-}ClC_6H_4\overset{CH_3}{\underset{}{C}}=NN(CH_3)_2$	BuLi/ THF/ −70°–0°/ 3 hr	$(CH_3S)_2$	(60)	23
$C_{11}H_8LiNS$		BuLi/ ether/ reflux/ 2 hr	$CO_2 (H_3O^+)$	3-Benzoylthiophene-2-carboxylic acid (70)	570
		"	$C_6H_5CN (H_3O^+)$	2,3-Dibenzoylthiophene (47)	570
$C_{12}H_8N_2S$		LDA/ether	CuI_2	(9)	440
$C_{13}H_9NS$		BuLi/ ether/ 0°/0.5 hr	$(CH_3)_3SiCl$	(45) (8) $X = Si(CH_3)_3$	138
		BuLi/THF/ 0°/0.5 hr	"	(—) (85) $X = Si(CH_3)_3$	138
$C_{13}H_{10}N_2$		BuLi/ether	CO_2	2-(o-Carboxyphenyl)benzimidazole (41)	606

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TABLE XXXIX. Arylcarbimines (Ortho Beta) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{13}H_{15}ClN_2$	*p*-ClC$_6$H$_4$ pyrazole N—C$_4$H$_9$-*t*	BuLi/ether/ 0°	*o*-ClC$_6$H$_4$CN (H$_3$O$^+$)	(50)	23
$C_{13}H_{15}ClN_2O$	*p*-ClC$_6$H$_4$ pyrazole N—C(CH$_3$)$_2$OCH$_3$	*s*-BuLi/ ether/ −70°/5 min	*o*-ClC$_6$H$_4$CON(CH$_3$)$_2$ (H$_3$O$^+$)	(40)	23
$C_{14}H_{17}NO_2$	methylenedioxy-benzaldehyde N-cyclohexyl imine	BuLi/THF/ −78°/ 15 min	D$_2$O	(100)	212
		"	I$_2$	X=I (60)	212
		"	CO$_2$ (H$_3$O$^+$)	X=CO$_2$H (54)	212
		"	CH$_3$I (H$_3$O$^+$)	X=CH$_3$ (61)	212
		"	ClCO$_2$CH$_3$ (H$_3$O$^+$)	X=CO$_2$CH$_3$ (68)	212
		"	CH$_2$=CHCH$_2$Br (CuI) (H$_3$O$^+$)	X=CH$_2$CH=CH$_2$ (72)	212
$C_{14}H_{19}N$	C$_6$H$_5$C(CH$_3$)=N-cyclohexyl	BuLi/ether	(C$_6$H$_5$)$_2$CO	CH$_2$C(C$_6$H$_5$)$_2$OH / C(C$_6$H$_5$)$_2$OH (16)	211
$C_{16}H_{10}N_2S$	quinoxaline-benzothiophene	LDA/ether	CuI$_2$	(61)	440
$C_{16}H_{17}N$	C$_6$H$_5$-azepinopyridine	C$_6$H$_5$Li/ ether/ reflux/ 1 hr	D$_2$O	(I), (II) (I:II, 1:0.4)	213
		C$_6$H$_5$Li/ ether/ reflux/ 5 hr	"	(I:II, 1:4.2)	213
$C_{17}H_{19}N$	C$_6$H$_5$-azocinopyridine	C$_6$H$_5$Li/ ether/ reflux/ 1 hr	D$_2$O	(III), (IV) (III:IV, 1:0.5)	213

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TABLE XXXIX. ARYLCARBIMINES (ORTHO, BETA) (Continued)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{17}H_{19}N$ (Contd.)	C_6H_5 (bicyclic structure)	C_6H_5Li/ether/ reflux 5 hr	"	(III : IV, 1 : 2.2)	213
$C_{18}H_{25}ClN_2O_3$	$CH_3O(CH_3)_2COCH_2$ ... $N—C(CH_3)_2OCH_3$ p-ClC_6H_4 (pyrazole structure)	s-BuLi/ ether/ $-50°$-$0°$/ 1 hr	o-$ClC_6H_4CON(CH_3)_2$ (H_3O^+)	(structure) (64)	23

Note: References 360–607 are on pp. 355–360.

TABLE XL. N-ARYLPYRAZOLES (ORTHO)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_9H_8N_2$		BuLi/ether/0°–25°/2 hr	CO_2	1-Phenylpyrazole-5-carboxylic acid (39), 1-(o-carboxyphenyl)pyrazole (10)	88
		2 BuLi/ether/25°/7 hr	''	(8), (26)	88
$C_{11}H_{12}N_2$		BuLi/THF/−70°	CO_2	(44)	155
$C_{11}H_{12}N_2O$		BuLi/THF/−70°	CO_2	(53)	155

TABLE XLI. ARYLNITRILES AND α, β-UNSATURATED NITRILES (ORTHO, BETA)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
C_5H_3NS	(3-cyanothiophene)	BuLi/ether/ −70°/1 hr	CO_2	3-Cyano-2-thiophenecarboxylic acid (68)		271, 396
		BuLi/ether/ 0.5 hr	DMF	2-Formyl-3-thiophenecarboxamide (—)		396
C_5H_3NSe	(3-cyanoselenophene)	BuLi/ether/ 0.5 hr	CO_2	3-Cyano-2-selenophenecarboxylic acid (—)		396
		''	DMF	2-Formyl-3-selenophenecarboxamide (—)		396
C_7H_5ClN	$m\text{-}ClC_6H_4CN$	LTMP/THF/ −70°/1 hr	$(CH_3S)_2$	3-Chloro-2-(methylthio)benzonitrile (30)		24
$C_7H_8N_2$	(1-methyl-3-cyano-dihydropyridine)	LDA/THF/ −80°/0.5 hr	CH_3OD	(structure) (37)		218
	(1-methyl-3-cyano-dihydropyridine)	LDA/THF/ −80°/20 hr	CH_3OD		X = D (65)	218
		''	FSO_2OCH_3		X = CH₃ (77)	218
	(1-methyl-3-cyano-dihydropyridine)	LDA/THF/ −80°/1.5 hr	CH_3OD		X = D (54)	218
		''	FSO_2OCH_3		X = CH₃ (72)	218

Note: References 360–607 are on pp. 355–360.

TABLE XLII. ALKYL VINYL ETHERS AND ALKYL ARYL ETHERS (ORTHO, BETA)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C₄H₇BrO	(Br, OC₂H₅ vinyl ether)	BuLi/ether/ −78° to −50°/5 hr	Cyclopentanone (H₃O⁺)	α-Bromo-Δ¹·ᵅ-cyclopentaneacetaldehyde (30)	174b
		"	t-C₄H₉CHO	(E)-2-Bromo-1-ethoxy-4,4-dimethyl-1-penten-3-ol (58)	174b
C₄H₇ClO	(Cl, OC₂H₅ vinyl ether)	BuLi/THF, hexane/ −100°	CO₂	(E)-2-Chloro-3-ethoxyacrylic acid (100)	174a
C₅H₆OS	(OCH₃ thiophene)	BuLi/ether/ 25°–reflux/ 2 hr	I₂	(thiophene OCH₃, X) X = I (42)	567, 401
		BuLi/ether/ reflux/ 0.5 hr	CO₂	X = CO₂H (86)	402
		BuLi	DMF	X = CHO (83)	165
		"	DMA	X = COCH₃ (32)	165
		BuLi/ether/ reflux/ 15 min	(CH₃O)₂SO₂	3-Methoxy-2-methylthiophene (I), 4-methoxy-2-methylthiophene (II) (I+II, 74) (I:II, 93:7)	145
		BuLi/reflux/ 20 min	(n-C₄H₉O)₃B (H₂O₂)	(OCH₃ dihydrothiophenone) (24)	289
C₅H₆OSe	(OCH₃ selenophene)	BuLi	DMF	3-Methoxy-2-selenophenecarboxaldehyde (50)	165
		"	DMA	3-Methoxyselenophen-2-yl methyl ketone (40)	165
C₅H₇NO₂	(OCH₃, CH₃ isoxazole)	BuLi/THF/ −75°/1 hr	CO₂	(HO₂C, OCH₃, CH₃ isoxazole) (10), (CH₃O, CH₂CO₂H isoxazole) (47)	498
C₆H₈OS	(CH₃, S, OCH₃ thiophene)	BuLi/ether/ 25°/24 hr	CO₂	2-Methoxy-5-methylthiophene-3-carboxylic acid (50)	231
C₇H₇FO	p-FC₆H₄OCH₃	BuLi/THF/ 27°/5 hr	CO₂	5-Fluoro-o-anisic acid (32)	19
C₇H₈O	C₆H₅OCH₃	BuLi/ether/ 2 hr	D₂O	(OCH₃, X benzene) X = D (30)	27
		BuLi/THF/ 24 hr	CO₂	X = CO₂H (51)	35
		BuLi/ether/ reflux	CO₂(CH₂N₂)	X = CO₂CH₃ (65)	50
		BuLi/ether/ reflux/ 12 hr	CF₂=CCl₂	X = CF=CCl₂ (41)	364
		BuLi/THF, ether/ 25°/6 hr	n-C₁₂H₂₅Br	X = C₁₂H₂₅-n (54)	499
C₇H₈O₂	m-CH₃OC₆H₄OH	BuLi/ether/ 25°/22 hr	CO₂	6-Hydroxy-o-anisic acid (7), 4-hydroxy-o-anisic acid (2)	233
C₈H₇F₃O	p-CH₃OC₆H₄CF₃	BuLi/ether/ 35°/21 hr	D₂O	3-d-α,α,α-Trifluoro-4-methoxytoluene (92)	19
		"	(C₆H₅)₂CO	(6-Methoxy-α,α,α-trifluoro-m-tolyl)diphenylmethanol (90)	19

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Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C_8H_8O	$C_6H_5O-CH=CH_2$	s-BuLi/THF/ 0°/2 hr	CH_3I	[2-methylphenyl vinyl ether] (20)	384
$C_8H_8O_2$	[5-methyl-1,3-benzodioxole]	BuLi/ether/ 25°/1 hr	CO_2	[benzodioxole structure] $X = CO_2H$ (20)	483
		"	$(C_6H_5)_2CO$	$X = C(C_6H_5)_2OH$ (50)	483
C_8H_9BrO	[2-bromo-6-methyl-anisole, Br, CH$_3$, OCH$_3$]	$C_6H_5Li/$ ether/25°/ 18 hr, reflux/ 8 hr	Cyclopentanone	1-(3-Bromo-6-methoxy-p-tolyl)cyclopentanol (33)	221, 220
$C_8H_{10}O$	$C_6H_5OC_2H_5$	BuLi/THF/ 24 hr	CO_2	o-Ethoxybenzoic acid (42)	35
		BuLi/ether/ reflux/ 27 hr	$CO_2(CH_2N_2)$	Methyl o-ethoxybenzoate (63)	50
	$m\text{-}CH_3OC_6H_4CH_3$	BuLi/cyclo-hexane	CO_2	(III), (IV) (III:IV, 9:1) $X = CO_2H$	17
		BuLi/cyclo-hexane, TMEDA	"	(III:IV, 13:12) $X = CO_2H$	17
		BuLi/ether/ reflux	$CO_2(CH_2N_2)$	(III+IV, 53) (III:IV, 3:2) $X = CO_2CH_3$	50
	$o\text{-}CH_3OC_6H_4CH_3$	BuLi/cyclo-hexane/ reflux/10 hr	CO_2	2-Methoxy-m-toluic acid (V), 2-methoxyphenylacetic acid (VI) (V+VI, 57) (V:VI, 1:2)	62, 61
		BuLi/cyclo-hexane, TMEDA/ 25°/10 hr	"	(V+VI, 72) (V:VI, 3:1)	62
	$p\text{-}CH_3OC_6H_4CH_3$	BuLi/ether/ reflux/ 40 hr	CO_2	6-Methoxy-m-toluic acid (31)	61, 348
$C_8H_{10}OS$	$m\text{-}CH_3OC_6H_4SCH_3$	BuLi/ether/ reflux/ 4 hr	CO_2	6-(Methylthio)-o-anisic acid (46)	574
	$p\text{-}CH_3OC_6H_4SCH_3$	BuLi/ether/ reflux/ 4 hr	CO_2	5-(Methylthio)-o-anisic acid (50)	574
$C_8H_{10}O_2$	$C_6H_4(OCH_3)_2\text{-}m$	$C_6H_5Li/$ ether/ 2–3 days	Cl_2	[2,6-dimethoxyphenyl structure] $X = OCl$ (39)	314
		$C_6H_5Li/$ ether/ 60 hr	Cu	$X =$ [2,6-dimethoxyphenyl] (48)	219
		BuLi/ether/ 25°/70 hr	CuBr	$X = Cu$ (93)	501

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TABLE XLII. ALKYL VINYL ETHERS AND ALKYL ARYL ETHERS (ORTHO, BETA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C$_8$H$_{10}$O$_2$ (*Contd.*)	C$_6$H$_4$(OCH$_3$)$_2$-*m*	C$_6$H$_5$Li/ ether/ 2–3 days	Br$_2$	X = Br (18)	314
		BuLi/ether	AgBr	X = Ag (21)	304
		C$_6$H$_5$Li/ether/ 2–3 days	I$_2$	X = I (80)	314
		BuLi/ether/ 25°/70 hr	(CH$_3$)$_2$SnBr$_2$	X = Sn(CH$_3$)$_2$Br (87)	480
		C$_6$H$_5$Li	B(OCH$_3$)$_3$	X = B(OH)$_2$ (48)	502
		BuLi	(CH$_3$)$_3$SnCl	X = Sn(CH$_3$)$_3$ (80)	306
		—	BrAuP(C$_6$H$_5$)$_3$	X = AuP(C$_6$H$_5$)$_3$ (90)	307
		BuLi/ether/ reflux/2 hr	CO$_2$	X = CO$_2$H (70)	503
		C$_6$H$_5$Li/ether/ 2–3 days	BrCN	X = Br (46)	314
		"	ICN	X = I (46)	314
		C$_6$H$_5$Li/ether/ 25°/60 hr	CH$_3$I	X = CH$_3$ (95)	504
		C$_6$H$_5$Li/ether/ 2–3 days	(SCN)$_2$	X = CN (6), X = SCN (21)	314
		"	AcCl	X = Ac (14)	314
		"	Ethylene oxide	X = (CH$_2$)$_2$OH (57)	314
		"	Br(CH$_2$)$_2$Br	X = Br (71)	314, 219
		"	ClCH$_2$OCH$_3$	X = CH$_2$OCH$_3$ (62)	314
		"	C$_2$H$_5$I	X = C$_2$H$_5$ (6)	314
		C$_6$H$_5$Li/25°/ 3 days	(CH$_3$O)$_2$SO$_2$	X = CH$_3$ (74–76)	505
		C$_6$H$_5$Li/ether 2–3 days	BrCH$_2$CH=CH$_2$	X = CH$_2$CH=CH$_2$ (88)	314
		"		X = CH$_2$ (42), X = CH$_2$CH(OH)CH$_2$Cl (18)	314
		BuLi/THF/ reflux/ 1 hr		X = CH$_2$CH(OH)CH$_3$ (28)	506
		C$_6$H$_5$Li/ether/ 2–3 days	CH$_3$COCH$_3$	X = C(CH$_3$)$_2$OH (61)	314
		C$_6$H$_5$Li/ether/ 60 hr	½Br(CH$_2$)$_3$Br	X = (42)	219
		C$_6$H$_5$Li/ether/ 25°/2 days	ClCH$_2$N(CH$_3$)$_2$	X = CH$_2$N(CH$_3$)$_2$ (33)	507
		C$_6$H$_5$Li/ether/ 2–3 days	BrCH$_2$CH=CHCH$_3$	X = CH$_2$CH=CHCH$_3$ (75)	314
		"	(CH$_3$)$_2$CHCHO	X = CH(OH)CH(CH$_3$)$_2$ (76)	314
		C$_6$H$_5$Li/ether/ 60 hr	½Cl(CH$_2$)$_4$Cl	X = (33)	219
		"	½Br(CH$_2$)$_4$Br	X = (63)	219
		"	Cl(CH$_2$)$_4$Cl	X = (CH$_2$)$_4$Cl (45)	219
		"	Br(CH$_2$)$_4$Br	X = (CH$_2$)$_4$Br (50)	219

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
$C_8H_{10}O_2$ (Contd.)	$C_6H_4(OCH_3)_2$-m	C_6H_5Li/ether/ 2–3 days	$(C_2H_5O)_2SO_2$		$X = C_2H_5$ (18)	314
		"	CH_2=$C(CH_3)$-COCH_3		$X = C(CH_3)C(CH_3)$=CH_2 (35) $\overset{|}{OH}$	314
		"	$BrCH_2CH$=$C(CH_3)_2$		$X = CH_2CH$=$C(CH_3)_2$ (98)	314
		C_6H_5Li/ether/ 25°/2 days	$ClCH_2N\langle pyrrolidine\rangle$		$X = CH_2N\langle pyrrolidine\rangle$ (55)	507
		"	$ClCH_2N\langle morpholine\rangle$		$X = CH_2N\langle morpholine\rangle$ (55)	507
		C_6H_5Li/ether/ 60 hr	$\frac{1}{2}Br(CH_2)_5Br$		$X =$ (58)	219
		C_6H_5Li/ether/ 25°/2 days	$ClCH_2N(C_2H_5)_2$		$X = CH_2N(C_2H_5)_2$ (68)	507
		C_6H_5Li/ether/ 2–3 days	$(CH_3)_2C$=$CHCOCH_3$		$X = C(CH_3)CH$=$C(CH_3)_2$ (59) $\overset{|}{OH}$	314
		"	$CH_3COC_4H_9$-t		$X = C(CH_3)C_4H_9$-t (28) $\overset{|}{OH}$	314
		C_6H_5Li/ether/ 25°/2 days	$ClCH_2N\langle piperidine\rangle$		$X = CH_2N\langle piperidine\rangle$ (49)	507
		C_6H_5Li/ether/ 60 hr	$\frac{1}{2}Br(CH_2)_6Br$		$X =$ (64)	219
		$BuLi$/ether/$-5°$			$X =$ ("high")	508
		C_6H_5Li/ether/ 2–3 days	C_6H_5CH=$CHCHO$		$X = CH(OH)CH$=CHC_6H_5 (75)	314
		$BuLi$/THF/ $-20°/2$ hr	n-$C_{12}H_{25}Br$		$X = (C_{12}H_{25}$-n (70)	499
		t-$BuLi$	CO_2	(VII), (VIII)	(VII + VIII, 60) (VII: VIII, 19:1) $X = CO_2H$	36
		$BuLi$/ether/ reflux	$CO_2(CH_2N_2)$		(VII + VIII, 60–75) (VII: VIII, 24:1) $X = CO_2CH_3$	50
		C_6H_5Li/ether/ 2–3 days	$(CN)_2$	(54)		314

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
$C_8H_{10}O_2$ (Contd.)	$C_6H_4(OCH_3)_2$-o	C_6H_5Li	$B(OCH_3)_3$		$X = B(OH)_2$ (20)	502
		BuLi/ether/ 25°/24 hr	Cyclohexanone		$X = $ (60)	509
		"			$X = $ (70)	509
		BuLi/heptane, TMEDA/ 25°/20 hr	I_2	1,4-Diiodo-2,3-dimethoxybenzene (2)		510
	m-$CH_3OC_6H_4CH_2OH$	BuLi/hexane, TMEDA/ 60°/5 hr	$CO_2(CH_2N_2)$	(53),	(6)	245
$C_8H_{12}OS$		BuLi/ether/ reflux/ 0.5 hr	CO_2		$X = CO_2H$ (62)	423
		BuLi/ether/ reflux/ 2 hr	$(CH_3O)_2SO_2$		$X = CH_3$ (87)	141
		"	$ClCO_2C_2H_5$		$X = CO_2C_2H_5$ (75)	141
		BuLi/ether/ −30°–reflux/ 1 hr	DMF		$X = CH(OLi)N(CH_3)_2$ (—)	148
		BuLi/ether/ reflux/2 hr	Ac_2O $(MgBr_2)$		$X = COCH_3$ (75)	141
		"	t-$C_4H_9OCO_2C_6H_5$ $(MgBr_2)$		$X = OC_4H_9$-t (70)	141
$C_8H_{12}OSe$		BuLi/ether/ −30°–reflux/ 1 hr	DMF	(—)		148
		"	"	3-t-Butoxy-2-selenophenecarboxaldehyde (32)		466
		"	DMA	3-t-Butoxyselenophen-2-yl methyl ketone (55)		466
$C_9H_{10}O_2$		BuLi/THF, ether/3°/ 45 min, 25°/3 hr	D_2O	3-d-1,2-(Propylidenedioxy)benzene (54)[a]		500
$C_9H_{11}ClO_3$		BuLi/THF/ −70°/3 min	CO_2	2-Chloro-3,5,6-trimethoxybenzoic acid (79), 3-chloro-2,5,6-trimethoxybenzoic acid (16)		222
		BuLi/THF/ 25°/10 min	Ac_2O	2-Chloro-3,5,6-trimethoxyacetophenone (68)		223
$C_9H_{11}NO_2$	m-$CH_3OC_6H_4CONHCH_3$	BuLi/THF, ether/reflux 1 hr	Ethylene oxide	3,4-Dihydro-5-methoxyisocoumarin (67)		493, 189
		BuLi/THF, ether/1 hr	$(C_6H_5)_2CO$	4-Methoxy-3,3-diphenylphthalide (91)		493, 189, 19

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Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_9H_{12}O$	$C_6H_5OCH(CH_3)_2$	BuLi/THF/ 24 hr	CO_2	o-Isopropoxybenzoic acid (25)	35
	o-$C_2H_5C_6H_4OCH_3$	BuLi/ether/ reflux/ 60 hr	CO_2	3-Ethyl-o-anisic acid (32)	61
	3,5-$(CH_3)_2C_6H_3OCH_3$	BuLi/cyclo- hexane/ reflux/ 10 hr	CO_2	(IX+X+XI, 40) (IX:X:XI, 24:51:30)	17
		BuLi/ether	$(C_6H_5)_2CO$	2-Methoxy-4,6-dimethyl-α,α- diphenylbenzyl alcohol (80)	511
$C_9H_{12}O_2$	$C_6H_5OCH_2CH_2OCH_3$	BuLi/ether/ 2 hr	D_2O	o-d-2-Methoxyethoxybenzene (52), phenol (12), phenyl vinyl ether (8)	27
	m-$CH_3OC_6H_4CH(OH)CH_3$	BuLi/hexane, TMEDA/ 60°/5 hr*	CO_2 (CH_2N_2)	(62), (14)	245
	3,4-$(CH_3O)_2C_6H_3CH_3$	BuLi/ether/ 0°/5 hr, 25° 5 hr	$Br(CH_2)_{10}Br$	$m = 10$ (46)	512
		"	$I(CH_2)_{12}I$	$m = 12$ (46)	512
	3,5-$(CH_3O)_2C_6H_3CH_3$	BuLi/ether/ 0°/48 hr	I_2	4-Iodo-3,5-dimethoxytoluene (65)	513
		BuLi	CO_2	2,6-Dimethoxy-p-toluic acid (56)	514
$C_9H_{12}O_3$	1,2,3-$C_6H_3(OCH_3)_3$	BuLi/THF/ 25°/2 hr	D_2O	X=D (94)	224
		BuLi	CO_2	X=CO_2H (40)	514
		BuLi/THF/ 25°/2 hr	C_2H_5Br	X=C_2H_5 (56)	224
		"	n-$C_{12}H_{25}Br$	X=$C_{12}H_{25}$-n (55)	224
	1,3,5-$C_6H_3(OCH_3)_3$	BuLi/ether/ 25°/70 hr	CuBr	X=Cu (65)	501
		BuLi/ether	AgBr	X=Ag (21)	304
		BuLi/ether/ 25°/70 hr	$(CH_3)_2SnBr_2$	X=$Sn(CH_3)_2Br$ (95)	480
		BuLi/THF	$(CH_3)_3SnCl$	X=$Sn(CH_3)_3$ (—)	306
		—	$BrAuP(C_6H_5)_3$	X=$AuP(C_6H_5)_3$ (60)	307

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Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_9H_{12}O_3$ (Contd.)	$3,5-(CH_3O)_2C_6H_3CH_2OH$	BuLi/hexane, TMEDA/ 60°/5 hr*	$CO_2(CH_2N_2)$	(22), (8), (13)	245
$C_9H_{13}NO$	$m-CH_3OC_6H_4N(CH_3)_2$	BuLi/ether/ 35°/12 hr	$(C_6H_5)_2CO$	[2-(Dimethylamino)-6-methoxyphenyl]diphenylmethanol (71)	19
	$o-CH_3OC_6H_4N(CH_3)_2$	BuLi/ether/ 35°/12 hr	$(C_6H_5)_2CO$	[2-Methoxy-3-(dimethylamino)phenyl]diphenylmethanol (56)	19
	$p-CH_3OC_6H_4N(CH_3)_2$	BuLi/ether/ 35°/12 hr	D_2O	3-d-N,N-Dimethyl-p-anisidine (85)	19
		"	$(C_6H_5)_2CO$	[2-Methoxy-5-(dimethylamino)phenyl]diphenylmethanol (71)	19
$C_9H_{14}OS$		BuLi/ether/ reflux/ 0.5 hr	$t-C_4H_9OCO_2C_6H_5$	2,3-Di-t-butoxy-4-methylthiophene (79)	147
$C_9H_{18}OS$	$n-C_5H_{11}S$	t-BuLi/THF −70°/1 hr	$n-C_4H_9Br$	$X = n-C_4H_9$ (42)	127
		"	$n-C_4H_9I$	$X = n-C_4H_9$ (60)	127
		"	$n-C_6H_{13}CHO$	$X = CH(OH)C_6H_{13}-n$ (82)	127
		"	C_6H_5CHO	$X = CH(OH)C_6H_5$ (80)	127
$C_{10}H_7Cl_2NO_2$		BuLi/THF/ −70°/0.5 hr	CO_2	5-(2,6-Dichlorophenyl)-3-methoxy-4-isoxazolecarboxylic acid (75)	232
$C_{10}H_8ClNO_2$		BuLi/THF/ −70°/0.5 hr	CO_2	5-(o-Chlorophenyl)-3-methoxy-4-isoxazolecarboxylic acid (62)	232
$C_{10}H_9NO_2$		BuLi/THF/ −70°/0.5 hr	I_2	4-Iodo-3-methoxy-5-phenylisoxazole (88)	232
		"	CO_2	3-Methoxy-5-phenyl-4-isoxazolecarboxylic acid (99)	232
$C_{10}H_{11}NO$		BuLi/ether/ reflux/ 13 hr		(XII), (XIII), (XIV) X = CH(OH) (XII + XIII + XIV, 74) (XII : XIII : XIV, 4 : 5 : 1)	84
$C_{10}H_{12}O$		BuLi/hexane, CO₂ TMEDA/ 25°/6 hr		2,3,4,5-Tetrahydro-1-benzoxepin-9-carboxylic acid (73)	225

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TABLE XLII. ALKYL VINYL ETHERS AND ALKYL ARYL ETHERS (ORTHO, BETA) (Continued)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
$C_{10}H_{12}OS$	C_6H_5S–CH=CH–OC_2H_5	t-BuLi/THF/ −70°/1 hr	D_2O	C_6H_5S–C(X)=CH–OC_2H_5	X = D (95)	127
		"	Ethylene oxide		X = $(CH_2)_2OH$ (60)	127
		"	Propylene oxide		X = $CH_2CH(OH)CH_3$ (55)	127
		"	$n\text{-}C_4H_9I$		X = $n\text{-}C_4H_9$ (55)	127
		"	$CH_3CH{=}CHCHO$		X = $CH(OH)CH{=}CHCH_3$ (78)	127
		"	Cyclopentanone		X = 1-hydroxycyclopentyl (78)	127
		"	C_6H_5CHO		X = $CH(OH)C_6H_5$ (75)	127
		"	$n\text{-}C_6H_{13}CHO$		X = $CH(OH)C_6H_{13}\text{-}n$ (84)	127
$C_{10}H_{13}NO$	methylenedioxy–C_6H_3–$CH_2N(CH_3)_2$	BuLi/ether/ 25°/1 hr	$(C_6H_5)_2CO$	[α-(Dimethylamino)-5,6-methylenedioxy)-o-tolyl]diphenylmethanol (60)		483
$C_{10}H_{14}O$	$C_6H_5OC_4H_9\text{-}t$	t-BuLi/cyclohexane/ reflux/ 17 hr	CO_2	o-t-Butoxybenzoic acid (82)		36
		BuLi/THF/ 24 hr	"	Salicylic acid (27)		35
$C_{10}H_{14}OS$	$m\text{-}CH_3OC_6H_4SC_3H_7\text{-}i$	BuLi/ether/ reflux/ 4 hr	CO_2	6-(Isopropylthio)-o-anisic acid (43)		574
	$o\text{-}CH_3OC_6H_4SC_3H_7\text{-}i$	BuLi/ether/ reflux/ 4 hr	CO_2	3-(Isopropylthio)-o-anisic acid (45)		574
	$p\text{-}i\text{-}C_3H_7OC_6H_4SCH_3$	BuLi/ether/ reflux/ 4 hr	CO_2	2-Isopropoxy-5-(methylthio)benzoic acid (38)		574
$C_{10}H_{14}O_2$	$C_6H_4(OC_2H_5)_2\text{-}m$	BuLi/THF	$(CH_3)_3SnCl$	(2,6-Diethoxyphenyl)trimethylstannane (73)		306
	$m\text{-}CH_3OC_6H_4C(CH_3)_2OH$	BuLi/hexane, TMEDA/ −60°/5 hr	$CO_2(CH_2N_2)$	7-Methoxy-3,3-dimethylphthalide (46)		245
$C_{10}H_{14}O_3$	$3,5\text{-}(CH_3O)_2C_6H_3CH(OH)CH_3$	BuLi/hexane TMEDA/ 60°/5 hr	$CO_2(CH_2N_2)$	4,6-dimethoxy-3-methylphthalide (8), and methyl 2,4-dimethoxy-6-(1-hydroxyethyl)benzoate (24)		245
$C_{10}H_{14}O_4$	2,3,4-trimethoxy (1,2,3,4-tetramethoxybenzene structure, CH_3O, CH_3O, OCH_3, OCH_3)	BuLi/THF/ 25°	CO_2	1,2,3,6-Tetramethoxybenzoic acid (61)		514
	1,2,4,5-tetramethoxy (CH_3O, OCH_3, CH_3O, OCH_3) structure	BuLi/THF/25°/ 10 min	CO_2	(XV) X=CO_2H (78)		223, 222, 514
		BuLi/THF, ether/ 25°/0.5 hr	CH_3I	X=CH_3 (75)		513
		BuLi/THF/ 25°/10 min	DMF	X=CHO (62)		223

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{10}H_{14}O_4$ (*Contd.*)		BuLi/THF/ 25°/40 min	$ClCH_2N(CH_3)_2$	$X = CH_2N(CH_3)_2$ (55)	507
		BuLi/THF/ 25°/10 min	Ac_2O	$X = Ac$ (64)	223
		BuLi/THF/ 25°/40 min	$ClCH_2N\overset{}{\underset{}{O}}$	$X = CH_2N\overset{}{\underset{}{O}}$ (64)	507
		BuLi/THF/ 25°/10 min	C_6H_5COCl	$X = COC_6H_5$ (88)	223
		BuLi/THF, ether/ 25°/0.5 hr	I_2	XV, (70) X = I (9) X = Y = I	513
		4 BuLi/THF, ether/25°/ 15 min	I_2, CH_3I	(—) (39) X = I Y = CH_3	513
		5 BuLi/ether/ reflux/ 38 hr	CO_2	(—) (35) X = Y = CO_2H	222, 514
		2 BuLi/THF/ 25°	$(CH_3O)_2SO_2$	(—) (86) X = Y = CH_3	514
$C_{10}H_{14}O_5$		BuLi/THF/ 25°/10 min	Ac_2O	2-Hydroxy-3,4,5,6-tetramethoxyacetophenone (85)	223
$C_{10}H_{15}NO$	m-CH$_3$OC$_6$H$_4$CH$_2$N(CH$_3$)$_2$	BuLi/ether	Ethylene oxide	[2-(Dimethylamino)methyl]-6-methoxyphenethyl alcohol (—)	189
		BuLi/ether/ 27°/2 hr	$(C_6H_5)_2CO$	[α-(Dimethylamino)-6-methoxy-*o*-tolyl]diphenylmethanol (79)	19, 45, 189
	o-CH$_3$OC$_6$H$_4$CH$_2$N(CH$_3$)$_2$	BuLi/ether/ 27°/2 hr	$(C_6H_5)_2CO$	[α-(Dimethylamino)-2-methoxy-*m*-tolyl]diphenylmethanol (58),	19
				[α-(Dimethylamino)-3-methoxy-*o*-tolyl]diphenylmethanol (<5)	
	p-CH$_3$OC$_6$H$_4$CH$_2$N(CH$_3$)$_2$	BuLi/ether, TMEDA 15 hr	D_2O	(18) (48) X = D	19
		BuLi/ether, TMEDA/ 2 hr	$(C_6H_5)_2CO$	(7) (55) X = C(C_6H_5)_2OH	19, 180
$C_{11}H_{10}O$		BuLi/ether/ reflux/ 20 hr	CO_2	(XVI+XVII, 29) (XVI:XVII, 65:35) X = CO_2H	226, 227

TABLE XLII. ALKYL VINYL ETHERS AND ALKYL ARYL ETHERS (ORTHO, BETA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{11}H_{10}O$ (*Contd.*)	1-methoxynaphthalene (OCH_3)	BuLi/hexane, TMEDA/ 25°/2 hr	CO_2 (CH_2N_2)	(XVI + XVII, 60) (XVI:XVII, 99:0.3) $X = CO_2CH_3$	192
		t-BuLi/cyclohexane	"	(XVI + XVII, 35) (XVI:XVII, 1:99)	192
		BuLi/ether/ reflux/ 18 hr	$C_6H_5N(CH_3)CHO$	(37) (9) $X = CHO$	229, 515
		BuLi/THF/25°/ 2.5 hr	C_6H_5CN	(35) $X = H$	516
		"	p-ClC_6H_4CN	(31) $X = Cl$	516
	2-methoxynaphthalene (OCH_3)	BuLi/ether	CO_2	(XVIII), (XIX) (XVIII + XIX, 70) (XVIII:XIX, 7:43) $X = CO_2H$	17
		BuLi/ether/ reflux/18 hr	$C_6H_5N(CH_3)CHO$	(7) (65) $X = CHO$	229, 515
		BuLi/ether	Ethylene oxide	(—) (55) $X = (CH_2)_2OH$	230
		"	$BrCH_2CH{=}CH_2$	(—) (57) $X = CH_2CH{=}CH_2$	230
		BuLi/THF/ 25°/2.5 hr	C_6H_5CN	(—) (90) $X = CC_6H_5$ (‖ NH)	516
$C_{11}H_{11}NO$	quinoline OC_2H_5	BuLi/ether/ 0°/1 hr	Ethylene oxide, HBr	(4)	559
$C_{11}H_{11}NO_2$	2,4-dimethoxyquinoline (OCH_3, OCH_3)	BuLi	C_6H_5CN (H_3O^+)	C_6H_5, C_6H_5, OCH_3 pyrimido-quinoline (—)	478
		BuLi/ether/ 0°/45 min	$C_6H_5N(CH_3)CHO$	2,4-Dimethoxy-3-quinolinecarboxaldehyde (68)	517, 515
	3-phenyl-5-ethoxyisoxazole (C_6H_5, OC_2H_5)	BuLi/THF/ −70°/0.5 hr	CO_2	5-Ethoxy-3-phenyl-4-isoxazolecarboxylic acid (81)	232
$C_{11}H_{14}O$	2,2-dimethylchroman (O, $(CH_3)_2$)	BuLi/ether/ reflux/30 hr	O_2	2,2-Dimethyl-9-chromanol (18)	518
		"	CO_2	2,2-Dimethyl-9-chromancarboxylic acid (30)	518
	7-methyl-benzoxepine (CH_3)	BuLi/hexane, TMEDA/ 25°/6 hr	CO_2	2,3,4,5-Tetrahydro-7-methyl-1-benzoxepin-9-carboxylic acid (59)	225

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{11}H_{14}O_2$		BuLi/hexane, TMEDA/ 60°/5 hr	$CO_2(CH_2N_3)$	(80)	245
$C_{11}H_{16}O$	$C_6H_5OCH(C_2H_5)_2$	BuLi/THF/ 24 hr	CO_2	o-(1-Ethylpropoxy)benzoic acid (17)	35
		t-BuLi/ cyclo-hexane	CO_2	4-t-Butyl-o-anisic acid (XX), 6-t-butyl-o-anisic acid (XXI) (XX+XXI, 73) (XX:XXI, 91:9)	17
$C_{11}H_{16}O$	o-t-$C_4H_9C_6H_4OCH_3$	BuLi/ether, TMEDA/ reflux/1 hr	$(CH_3)_3SiCl$	(3-t-Butyl-2-methoxyphenyl) trimethylsilane (29)	519
		"	$(C_6H_5)_2CO$	3-t-Butyl-2-methoxy-α,α-diphenylbenzyl alcohol (25)	519
$C_{11}H_{16}O_2$	3,5-$(CH_3O)_2C_6H_3C_3H_7$-n	C_6H_5Li/ether/ reflux/ 20 hr	CO_2	2,6-Dimethoxy-4-propylbenzoic acid (48)	520
$C_{11}H_{16}O_3$		BuLi/THF/ 25°/2 hr	C_2H_5Br	1,5-Diethyl-2,3,4-trimethoxybenzene (13)	224
$C_{11}H_{17}NO$	p-$CH_3OC_6H_4(CH_2)_2$ $N(CH_3)_2$	BuLi/ether/ 27°/28 hr	D_2O	3-d-4-Methoxy-N,N-dimethylphenethylamine (72)	19
		BuLi/ether/ 27°/32 hr	$(C_6H_5)_2CO$	[2-Methoxy-5-(dimethylamino)ethylphenyl]-α,α-diphenylbenzyl alcohol (60)	19
$C_{11}H_{17}NO_2$	3,4-$(CH_3O)_2C_6H_3CH_2$-$N(CH_3)_2$	BuLi/ether/ 0°/3 hr	I_2	X=I (77)	23
		"	Ethylene oxide	X=$(CH_2)_2OH$ (60)	23
		"	CH_3CHO	X=$CH(OH)CH_3$ (65)	23
		"	CH_3OCH_2Cl	X=CH_2OCH_3 (66)	23
$C_{12}H_{12}O_2$		BuLi/ether/ reflux/ 9 hr	CO_2	X=CO_2H (72)	521
		"	$(CH_3O)_2SO_2$	X=CH_3 (75)	521
		"	$C_6H_5N(CH_3)CHO$	X=CHO (84)	521
$C_{12}H_{13}NO_2$		BuLi/THF/ −70°/0.5 hr	CO_2	5-Isopropoxy-3-phenyl-4-isoxazolecarboxylic acid (77)	232
$C_{12}H_{13}NO_3$		BuLi/ether/ 0°/3 hr, 25°/ "overnight"	Ethylene oxide	2,4,6-Trimethoxy-3-quinolinethanol (26)	559
		BuLi/ether/ 0°/1.5 hr	$C_6H_5N(CH_3)CHO$	2,4,6-Trimethoxy-3-quinoline-carboxaldehyde (58)	517

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{12}H_{13}NO_3$ (Contd.)		BuLi/ether/ 0°/1.5 hr	$C_6H_5N(CH_3)CHO$	2,4,7-Trimethoxy-3-quinolinecarboxaldehyde (53)	517
		BuLi/ether/ 0°/3 hr, 25°/ "overnight"	Ethylene oxide	2,4,8-Trimethoxy-3-quinolinethanol (14)	517
		BuLi/ether/ 0°/20 min	$C_6H_5N(CH_3)CHO$	2,4,8-Trimethoxy-3-quinolinecarboxaldehyde (40)	559
$C_{12}H_{14}O_2$		BuLi/THF, ether/3°/ 45 min, 25°/3 hr	D_2O	$X = D$ (92)[b]	500
		BuLi/THF, ether/0°/ 5 hr, 25°/ 5 hr	$\frac{1}{2}Br(CH_2)_{10}Br$	$X = (CH_2)_{10}$ (76)	512
		BuLi/THF, ether/0°/ 1 hr, 25°/ 2.5 hr	$n\text{-}C_{12}H_{25}Br$	$X = C_{12}H_{25}\text{-}n$ (71)	499
		BuLi/THF, ether/ 0°–25°/7 hr	$Br(CH_2)_{11}OTHP$	$X = (CH_2)_{11}OTHP$ (84)	500
$C_{12}H_{16}O_2$		BuLi/hexane, TMEDA/ 60°/5 hr	$CO_2(CH_2N_2)$	(42), (23)	245
		BuLi/hexane, TMEDA/25°/ 6 hr	CO_2	2,3,4,5-Tetrahydro-5-methoxy-7-methyl-1-benzoxepin-9-carboxylic acid (65)	225
$C_{12}H_{16}O_3$		BuLi/ether/ 25°/22 hr	CO_2 (H_3O^+)	6-Hydroxy-o-anisic acid (26)	233
$C_{12}H_{18}O$		BuLi/cyclo-hexane/ reflux/ 10 hr	CO_2	(XXII) (12), (XXIII) (24), (XXIV) (63)	17

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TABLE XLII. ALKYL VINYL ETHERS AND ALKYL ARYL ETHERS (ORTHO, BETA) (Continued)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{12}H_{18}O$ (Contd.)	(3,5-CH₃, OCH₃, C₄H₉-t benzene)	BuLi/cyclo-hexane, TMEDA/25°	CO_2	XXII (3), XXIII (97), XXIV (0)	17
$C_{12}H_{19}NO$	p-CH₃OC₆H₄(CH₂)₃N(CH₃)₂	BuLi/ether/ 27°/24 hr	D_2O	3-(3-d-4-Methoxyphenyl)-N,N-dimethylpropylamine (70)	19
		"	$(C_6H_5)_2CO$	[5-[(3-Dimethylamino)propyl]-2-methoxyphenyl]-α,α-diphenylbenzyl alcohol (71)	19
$C_{12}H_{20}O_2S$	t-C₄H₉O, OC₄H₉-t thiophene	BuLi/ether/ 20°/0.5 hr	$(CH_3O)_2SO_2$	3,4-Di-t-butoxy-2-methylthiophene (91)	147
		BuLi/ether/ −20°–reflux 1 hr	DMF	3,4-Di-t-butoxy-2-thiophenecarboxaldehyde (50)	148
$C_{12}H_{20}O_2Se$	t-C₄H₉O, OC₄H₉-t selenophene	BuLi/ether/ −20°–reflux/ 1 hr	DMF	3,4-Di-t-butoxy-2-selenophenecarboxaldehyde (5)	148
$C_{13}H_{10}O$	(biphenylene-OCH₃)	BuLi	$B(OC_4H_9-n)_3$, (H_2O_2)	2-Methoxy-1-biphenylenol (61)	522
$C_{13}H_{13}NO_2$	(3-C₆H₅-5-OC₄H₉-t isoxazole)	BuLi/THF/ −70°/0.5 hr	CO_2	5-t-Butoxy-3-phenyl-4-isoxazolecarboxylic acid (75)	232
$C_{13}H_{17}NO_3$	(2-(3,4-dimethoxyphenyl)-4,4-dimethyloxazoline)	BuLi/THF/ −45°/1.5 hr	D_2O	X=D (95)	204
		"	$(CH_3S)_2$	X=SCH₃ (92)	204
		"	N-Chloro-succinimide	X=Cl (90)	204
$C_{13}H_{20}O_2$	3,5-(CH₃O)₂C₆H₃C₅H₁₁-n	BuLi/ether, hydrocarbon/ 25°/16 hr	$C_6H_5N(CH_3)CHO$	X=CHO (83)	523
		—	(citral with CH₃...CHO, Pyridine/TosOH)	X= (cyclohexenyl) (−)	524
$C_{13}H_{22}O_2S$	t-C₄H₉O, OC₄H₉-t, CH₃ thiophene	BuLi/ether/ 20°/0.5 hr	$(CH_3O)_2SO_2$	3,4-Di-t-butoxy-2,5-dimethylthiophene (81)	147
$C_{14}H_{17}NO$	(1-OCH₃-naphthalene-CH₂N(CH₃)₂)	BuLi/ether/ 25°	CO_2 (CH_2N_2)	Methyl [3-(dimethylamino)methyl]-1-methoxy-2-naphthoate (56)	185

TABLE XLII. ALKYL VINYL ETHERS AND ALKYL ARYL ETHERS (ORTHO, BETA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{14}H_{17}NO$ (*Contd.*)		BuLi/ether/ 25°	CO_2 (CH_2N_2)	Methyl [1-(dimethylamino)methyl]-3-methoxy-2-naphthoate (39)	185
$C_{14}H_{17}NO_2$		BuLi/THF/ −78°/15 min	D_2O	(100)	212
		''	I_2	X = I (60)	212
		''	CO_2 (H_3O^+)	X = CO_2H (54)	212
		''	CH_3I (H_3O^+)	X = CH_3 (61)	212
		''	$ClCO_2CH_3$ (H_3O^+)	X = CO_2CH_3 (68)	212
		''	CH_2=$CHCH_2Br$ (CuI) (H_3O^+)	X = CH_2CH=CH_2 (72)	212
$C_{14}H_{18}O_2$		BuLi, NaOC₄H₉-*t*/ hexane/ 25°/1 hr	CO_2	(88)	525
$C_{15}H_{19}NO_2$		BuLi/ether/25°	CO_2 (CH_2N_2)	Methyl [3-(dimethylamino)methyl]-1,5-dimethoxy-2-naphthoate (52)	185
$C_{15}H_{20}O_2$		BuLi/hexane, TMEDA/ reflux/ 45 min	CO_2 (CH_2N_2)	(−), (−)	525
$C_{16}H_{22}O_2$		BuLi/hexane, TMEDA/60°/ 5 hr	CO_2 (CH_2N_2)	(80)	245
$C_{17}H_{18}O$		BuLi/hexane, TMEDA/25°/ 6 hr	CO_2	2,3,4,5-Tetrahydro-7-methyl-5-phenyl-1-benzoxepin-9-carboxylic acid (48)	225
$C_{18}H_{26}O_6$		BuLi/THF/25°/ 45 min	CO_2 (H_3O^+)	2,5-Dihydroxy-3,6-dimethoxybenzoic acid (86)	223, 222

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{16}H_{26}O_6$ (*Contd.*)	THPO, OCH$_3$, CH$_3$O, OTHP	BuLi/THF/25°	DMF	X = CHO (74)	223
		BuLi/THF/25°/ 45 min	Ac$_2$O	X = Ac (82)	223
$C_{20}H_{34}O_2$	2,4-(CH$_3$O)$_2$C$_6$H$_3$-C$_{12}$H$_{25}$-n	BuLi/THF/ −20°/2 hr, 0°/0.5 hr	n-C$_{12}$H$_{25}$Br	1,3-Didodecyl-2,4-dimethoxybenzene (45)	499
$C_{20}H_{34}O_3$	3,4-(CH$_3$O)$_2$C$_6$H$_3$-(CH$_2$)$_{11}$OCH$_3$	BuLi/THF, ether/0°/ 5 hr, 25°/5 hr	½Br(CH$_2$)$_{10}$Br	[CH$_3$O, OCH$_3$, (CH$_2$)$_5$, (CH$_2$)$_{11}$, OCH$_3$]$_2$ (38)	512
$C_{21}H_{36}O_3$	CH$_3$O, OCH$_3$, OCH$_3$, n-C$_{12}$H$_{25}$	BuLi/THF, TMEDA/ 25°/3 hr	D$_2$O	1-d-5-Decyl-2,3,4-trimethoxybenzene (100)	224
		BuLi/THF/25°/ 2 hr	n-C$_{12}$H$_{25}$Br	1,5-Didodecyl-2,3,4-trimethoxybenzene (25)	224
$C_{26}H_{30}O_4$	(benzodioxole-spiro-cyclohexane CH$_2$)$_2$	2 BuLi/THF, ether/0°/ 5 hr, 25°/5 hr	Br(CH$_2$)$_{11}$OTHP (H$_3$O$^+$)	X=Y=(CH$_2$)$_{11}$OH (19), X=H, Y=(CH$_2$)$_{11}$OH (47)	512
$C_{27}H_{46}O_2$	benzodioxole-(C$_{10}$H$_{21}$-n)$_2$	BuLi/THF, ether/−15°–25°/2 hr	D$_2$O	D-benzodioxole-(C$_{10}$H$_{21}$-n)$_2$ (70)	500
$C_{28}H_{44}O_4$	benzodioxole-spiro-cyclohexane (CH$_2$)$_{11}$OTHP	BuLi/THF, ether/0°–25°/8 hr	Br(CH$_2$)$_{11}$OTHP	(CH$_2$)$_{11}$OTHP, (CH$_2$)$_{11}$OTHP (61)	500

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Note: References 360–607 are on pp. 355–360.

TABLE XLIII. ALKOXYALKYL ARYL ETHERS (ORTHO)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_8H_9ClO_2$	o-$ClC_6H_4OCH_2OCH_3$	BuLi/hexane, TMEDA/0°/ 0.5 hr	DMF	3-Chloro-2-(methoxymethoxy)-benzaldehyde (85)	234
$C_9H_{11}BrO_2$		C_6H_5Li/ether, pet. ether/ 25°/24 hr	CO_2 (CH_2N_2)	Methyl 5-bromo-2-(methoxymethoxy)-p-toluate (I), methyl 3-bromo-6-(methoxymethoxy)-o-toluate (II) (I+II, 93) (I:II, 92:8)	526
$C_9H_{12}O_2$	m-$CH_3C_6H_4OCH_2OCH_3$	t-BuLi/pet. ether/0°/ 2 hr	CO_2 (CH_2N_2)	Methyl 2-(methoxymethoxy)-p-toluate (90)	526
	o-$CH_3C_6H_4OCH_2OCH_3$	BuLi/hexane, TMEDA/0°/ 0.5 hr	DMF	2-(Methoxymethoxy)-m-tolualdehyde (80)	234
	p-$CH_3C_6H_4OCH_2OCH_3$	BuLi/hexane, TMEDA/0°/ 0.5 hr	DMF	6-(Methoxymethoxy)-m-tolualdehyde (81)	234
	$C_6H_5O(CH_2)_2OCH_3$	BuLi/ether/ 2 hr	D_2O	2-d-(2-Methoxyethoxy)benzene (52) phenol (12), phenoxyethylene (8)	27
$C_{10}H_{14}O_4$		BuLi/ether/ 25°/24 hr	Ethylene oxide	2,3-Bis(methoxymethoxy)phenethyl alcohol (72)	527
		BuLi/ether/ 25°/24 hr	Ethylene oxide	2,5-Bis(methoxymethoxy)phenethyl alcohol (92)	527
$C_{11}H_{14}O_2$		BuLi	CO_2 (H_3O^+)	Salicylic acid (52)	528
			Ethylene oxide (H_3O^+)	o-Hydroxyphenethyl alcohol (70)	235
$C_{12}H_{16}O_3$		BuLi/ether/ 25°/22 hr	CO_2 (H_3O^+)	6-Hydroxy-o-anisic acid (26)	233
$C_{16}H_{18}O_4$		BuLi/ether/ 25°/5 min	Ethylene oxide	X = $(CH_2)_2OH$ (28)	527
	"		CH_3CHO	X = $CH(OH)CH_3$ (11)	527

TABLE XLIII. ALKOXYALKYL ARYL ETHERS (ORTHO) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{16}H_{22}O_4$	(benzene with 1,3-OTHP)	BuLi	CO_2 (H_3O^+)	2,6-Dihydroxybenzoic acid (60)	528
	(benzene with 1,2-OTHP)	BuLi/ether/ reflux/20 hr	CO_2 (H_3O^+)	2,3-Dihydroxybenzoic acid (48)	528
	(benzene with 1,4-OTHP)	BuLi	CO_2 (H_3O^+)	2,5-Dihydroxybenzoic acid (65)	528, 235
$C_{18}H_{26}O_6$	(benzene with CH$_3$O, OTHP, THPO, OCH$_3$)	BuLi/THF/ 25°/45 min	CO_2 (H_3O^+)	2,5-Dihydroxy-3,6-dimethoxybenzoic acid (86)	223, 222
		BuLi/THF/ 25°	DMF	(substituted benzene with CH$_3$O, OTHP, THPO, OCH$_3$, X) X = CHO (74)	223
		BuLi/THF/ 25°/45 min	Ac$_2$O	X = COCH$_3$ (82)	223

Note: References 360–607 are on pp. 355–360.

TABLE XLIV. Diaryl Ethers and Condensed Diaryl Ethers (Ortho)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
$C_{12}H_8O$		BuLi/ether	Br_2		X = Br (17)	249
		"	O_2		X = OH (45)	288
		BuLi/THF, ether/ −55°–0°/1 hr	CO_2		X = CO_2H (86)	529, 560
		BuLi/ether/25°/ 38 hr	CH_3ONH_2		X = NH_2 (79)	286
		—			X = CH=CHNO_2 (56)	285
		BuLi/ether/ reflux/17 hr	$(C_6H_5)_3SiCl$		X = $Si(C_6H_5)_3$ (63)	452
$C_{12}H_8OS$		BuLi/ether/ reflux/24 hr	O_2		(16) X = OH	288
		BuLi	CO_2		(37) X = CO_2H	237
		BuLi/ether/reflux	"	(35), (1–9)		236, 237

TABLE XLIV. Diaryl Ethers and Condensed Diaryl Ethers (Ortho) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
$C_{12}H_9ClO$	p-$ClC_6H_4OC_6H_5$	C_6H_5Li/ether/ 20°/26 hr*	$(C_6H_5)_2SiCl_2$		$m = n = 2$ (7)	243
		"	$(C_6H_5)_3SiCl$		$\begin{matrix} m=1 \\ n=3 \end{matrix}$ (38)	243
$C_{12}H_9NO$		BuLi/ether/25°/ 110 hr	CO_2		(5)	238
$C_{12}H_{10}O$	$(C_6H_5)_2O$	BuLi/THF/25°/ 2 hr	Ethylene oxide		$X = (CH_2)_2OH$ (93)	23
		BuLi/ether/reflux/ 24 hr	$(C_6H_5)_3SiCl$		$X = Si(C_6H_5)_3$ (67)	243
		BuLi/ether/reflux/ 72 hr	CO_2		$X = CO_2H$ (23)	239
		"	$(CH_3)_3SiCl$		$X = Si(CH_3)_3$ (60)	242
		BuLi/THF, ether/ reflux/5 hr	$(CH_3)_2SiCl_2$		$R = R' = CH_3$ (32)	240, 239
		"	$C_6H_5SiH_3$		$\begin{matrix} R = H \\ R' = C_6H_5 \end{matrix}$ (26)	241
		"	$(C_6H_5)_2SiH_2$		$R = R' = C_6H_5$ (20)	241
		BuLi/ether/reflux/ 72 hr	$(C_6H_5)_2SiCl_2$		$R = R' = C_6H_5$ (34)	239
		"	$(C_6H_5CH_2)_2SiCl_2$		$R = R' = CH_2C_6H_5$ (52)	242
		"	$(n-C_{12}H_{25})_2SiCl_2$		$R = R' = n-C_{12}H_{25}$ (17)	242
		"	$SiCl_4$		(25)	239
		BuLi/ether/reflux/ 24 hr	$C_6H_5SiCl_3$		$\begin{matrix} m=3 \\ n=1 \\ R = C_6H_5 \end{matrix}$ (14)	243
		"	$(C_6H_5)_2SiCl_2$		$\begin{matrix} m=n=2 \\ R = C_6H_5 \end{matrix}$ (40)	243
		"	$(n-C_{12}H_{25})_2SiCl_2$		$\begin{matrix} m = n = 2 \\ R = n-C_{12}H_{25} \end{matrix}$ (53)	242

TABLE XLIV. DIARYL ETHERS AND CONDENSED DIARYL ETHERS (ORTHO) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
$C_{14}H_{12}O$		BuLi/THF/25°/ 7 hr	CH_2O		$X = CH_2OH$ (56)	23
		"	Ethylene oxide		$X = (CH_2)_2OH$ (52)	23
		BuLi/ether/reflux/ 68 hr	CO_2 (CH_2N_2)		$X = CO_2CH_3$ (30)	530
		"	CH_2O		$X = CH_2OH$ (55)	530
$C_{14}H_{13}NO$		BuLi/reflux/42 hr	CO_2		(35)	238
$C_{14}H_{14}O_2$	$C_6H_5O(CH_2)_2OC_6H_5$	BuLi/ether/25°/ 1.5 hr	CO_2		$X = CO_2H$ (14)	243
		"	$(C_6H_5)_3SiCl$		$X = Si(C_6H_5)_3$ (7)	243
$C_{15}H_{18}OSi$	p-$(CH_3)_3SiC_6H_4OC_6H_5$	BuLi/THF, ether/ 15 hr	$(C_6H_5)_2SiCl_2$		(17)	241
$C_{18}H_{13}NO$		BuLi/ether/reflux/ 23 hr	CO_2		(4)	238
$C_{20}H_{14}O$		C_6H_5Li/ether/ 25°/6 days	CO_2		$X = CO_2H$ (46)	531
		"	CH_3I		$X = CH_3$ (15)	531
		"	$(C_6H_5)_2CO$		$X = C(C_6H_5)_2OH$ (59)	531

Note: References 360–607 are on pp. 355–360.

TABLE XLV. ALKYL ARALKYL ETHERS AND ARALKYL ALCOHOLS (ORTHO, BETA)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C_6H_8OS		BuLi/ether/25°/ 10 hr	CO_2	X=CO$_2$H (89)	142
		BuLi/ether/25°– 35°/1–1.5 hr	(CH$_3$S)$_2$	X=SCH$_3$ (61)	134, 43
		BuLi	DMF	X=CHO (72)	43, 134
		BuLi/ether/25°– 35°/1–1.5 hr	(C$_6$H$_5$)$_2$CO	X=C(C$_6$H$_5$)$_2$OH (46)	134
$C_6H_9NO_2$		BuLi/THF/−60°/ 1 hr	CH$_3$I	(I), (II) (I+II, 90) (I:II, 1:4)	186
C_7H_8O	$C_6H_5CH_2OH$	BuLi/pet. ether, TMEDA/ reflux/11 hr	I$_2$	X=I (58)	244b
		"	CH$_2$O	X=CH$_2$OH (70)	244b
		"	CH$_3$I	X=CH$_3$ (30)	244b
		"	n-C$_4$H$_9$Br	X=C$_4$H$_9$-n (21)	244b
		"	n-C$_4$H$_9$Cl	X=C$_4$H$_9$-n (55)	244b
		"	Cyclohexanone	X= (71)	244b
		"	C$_6$H$_5$CHO	X=CH(OH)C$_6$H$_5$ (95)	244b
		"		X= (68)	244b
		"	CO$_2$	Phthalide (50)	244b
$C_7H_8O_2S$		BuLi/ether/ reflux/20 min	"S"+ClCH$_2$CO$_2$CH$_3$ (NaOEt)	X=S (94)	143
		BuLi/ether/25°– reflux/15 min	"Se"+ClCH$_2$CO$_2$CH$_3$ (NaOEt)	X=Se (48)	245
		BuLi/ether/ reflux/15 min	CO$_2$ (H$_3$O$^+$)	3-Formyl-2-thiophenecarboxylic acid (78)	412
		BuLi/ether/−70°	C$_6$H$_5$CN (H$_3$O$^+$)	2-Benzoyl-3-thiophenecarboxaldehyde (16)	413
$C_7H_8O_2Se$		BuLi/ether/ reflux/0.5 hr	"Se"+ClCH$_2$CO$_2$CH$_3$ (H$_3$O$^+$, NaOC$_2$H$_5$)	Selenolo[2,3-b]selenophene-2-carboxylic acid (45)	575
$C_7H_8O_3$		BuLi/ether/−10°– reflux/15 min	CO$_2$ (H$_3$O$^+$)	X=CO$_2$H (50)	376
		"	C$_2$H$_5$CON(CH$_3$)$_2$ (H$_3$O$^+$)	X=COC$_2$H$_5$ (40)	376
		BuLi/ether/0°/ 0.5 hr	CON(CH$_3$)$_2$ (H$_3$O$^+$)	X= (41)	113

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_7H_8O_3$ (Contd.)		"	$CON(CH_3)_2$ (H_3O^+)	$X = CO$ —thienyl (30)	113
		BuLi/ether/0°/ 0.5 hr	$C_6H_5CON(CH_3)_2$ (H_3O^+)	$X = COC_6H_5$ (61)	113
		BuLi/ether/−30°– 25°/0.5 hr	$(n\text{-}C_4H_9O)_3B$ (H_3O^+)	$X = B(OH)_2$ (36)	115, 114
$C_8H_{10}O$	$C_6H_5CH(CH_3)OH$	BuLi/pet. ether, TMEDA/reflux/ 11 hr	C_6H_5CHO	α^1-Methyl-α^2-phenyl-o-xylene-α^1,α^2-diol (88)	244b
$C_8H_{10}O_2$	$m\text{-}CH_3OC_6H_4CH_2OH$	BuLi/hexane, TMEDA/60°/ 5 hr	CO_2 (CH_2N_2)	(53), (6)	245
$C_8H_{10}O_2S$		BuLi/ether/25°/ 45 min, reflux/15 min	C_6H_5CN (H_3O^+)	3-Acetyl-2-benzoylthiophene (27)	413
$C_9H_{12}O$	$C_6H_5CH(C_2H_5)OH$	BuLi/pet. ether, TMEDA/reflux/ 11 hr	C_6H_5CHO	α^1-Ethyl-α^2-phenyl-o-xylene-α^1,α^2-diol (82)	244b
	$C_6H_5C(CH_3)_2OH$	BuLi/pet. ether, TMEDA/reflux/ 11 hr	C_6H_5CHO	α^1,α^1-Dimethyl-α^2-phenyl-o-xylene-α^1,α^2-diol (86)	244b
$C_9H_{12}O_2$	$m\text{-}CH_3OC_6H_4CH(OH)CH_3$	BuLi/hexane, TMEDA/60°/* 5 hr	CO_2 (CH_2N_2)	(62), (14)	245
$C_9H_{12}O_3$	$3,5\text{-}(CH_3O)_2C_6H_3CH_2OH$	BuLi/hexane, TMEDA/60°/* 5 hr	CO_2 (CH_2N_2)	(22), (8), (13)	245
$C_9H_{13}NO$	$C_6H_5CH(OH)CH_2NHCH_3$	BuLi/ether/25°/ 24 hr	$(CH_3)_3SiCl$	$\alpha\text{-}[(Methylamino)methyl]\text{-}o\text{-}(trimethylsilyl)benzyl alcohol (21)$	175

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_9H_{14}O_2S$		BuLi/ether/−30°– reflux/20 min	"S"+ClCH$_2$CO$_2$CH$_3$ (H$_3$O$^+$)	Methyl[(3-formyl-2-thienyl)thio]acetate (77)	427
		BuLi	DMF (H$_3$O$^+$)	2,3-Thiophenedicarboxaldehyde (85)	428
$C_9H_{14}O_2Se$		BuLi/ether/ reflux	I$_2$	3-(Diethoxymethyl)-2-iodoselenophene (—)	396
		BuLi/ether/−40°/ 1 hr	DMF	2,3-Selenophenedicarboxaldehyde, 3-(diethyl acetal) (80)	283
$C_{10}H_{11}NO$		t-BuLi/ether/ 25°/1 hr	CO$_2$	X=CO$_2$H (80)	85
		,,	CN (H$_3$O$^+$)	X= (56)	85
		,,	(H$_3$O$^+$)	X= (56)	85
		,,	C$_6$H$_5$CN (H$_3$O$^+$)	X=COC$_6$H$_5$ (84)	85
		,,	C$_6$H$_5$CHO	X=CH(OH)C$_6$H$_5$ (40)	85
		,,	C$_6$H$_5$N(CH$_3$)CHO	X=CHO (46)	85
		,,	p-CH$_3$OC$_6$H$_4$CN (H$_3$O$^+$)	X=COC$_6$H$_4$OCH$_3$-p (70)	85
$C_{10}H_{14}O_2$	m-CH$_3$OC$_6$H$_4$C(CH$_3$)$_2$OH	BuLi/hexane, TMEDA/60°/ 5 hr	CO$_2$ (CH$_2$N$_2$)	7-Methoxy-3,3-dimethylphthalide (46)	245
$C_{10}H_{14}O_3$	3,5-(CH$_3$O)$_2$C$_6$H$_3$CH(OH)CH$_3$	BuLi/hexane, TMEDA/60°/ 5 hr	CO$_2$ (CH$_2$N$_2$)	(8), (24)	245
$C_{10}H_{15}NO$	C$_6$H$_5$CH(OH)CH$_2$N(CH$_3$)$_2$	BuLi/ether/25°/ 24 hr	CH$_3$I	X=CH$_3$ (47)	175
		,,	CH$_2$O	X=CH$_2$OH (33)	175
		,,	(CH$_3$)$_3$SiCl	X=Si(CH$_3$)$_3$ (61)	175
		,,	(C$_6$H$_5$)$_2$CO	X=C(C$_6$H$_5$)$_2$OH (48)	175
$C_{11}H_{10}O_2S_2$		BuLi/ether/−35° to −20°/20 min	"S" (H$_3$O$^+$)	(35), (9), (6)	436

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Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{11}H_{10}O_2S_2$ (*Contd.*)		BuLi/ether/−35°	I_2	(56)	294
		BuLi/ether/reflux/15 min	CO_2 (H_3O^-)	3,3′-Carbonyldi-2-thiophenecarboxylic acid (93)	437
$C_{11}H_{14}ClNO$		BuLi/ether/0°/4 hr	$(CH_3S)_2$	2-[4-Chloro-2-(methylthio)phenyl]-2,3-dimethyloxazolidine (80)	23
$C_{11}H_{14}O_2$		BuLi/hexane, TMEDA/60°/5 hr	CO_2 (CH_2N_2)	(80)	245
$C_{11}H_{16}O$	$C_6H_5CH(C_4H_9-n)OH$	BuLi/pet. ether, TMEDA/reflux/11 hr	C_6H_5CHO	α^1-Butyl-α^2-phenyl-o-xylene-α^1,α^2-diol (92)	244b
$C_{11}H_{17}NO_2$	p-$CH_3OC_6H_4CH(OH)CH_2N(CH_3)_2$	BuLi/ether/25°/24 hr	$(C_6H_5)_2CO$	α^1-[(Dimethylamino)methyl]-4-methoxy-α^2,α^2-diphenyl-o-xylene-α^1,α^2-diol (48)	175
$C_{12}H_{16}O_2$		BuLi/hexane, TMEDA/60°/5 hr	CO_2 (CH_2N_2)	(42), (23)	245
$C_{13}H_{11}FO_2S$		BuLi/ether/0°/2 hr	CH_3CHO	(60)	23
$C_{13}H_{12}O_2S$		BuLi/ether/reflux/2 hr	CO_2 (H_3O^+)	3-Benzoyl-2-thiophenecarboxylic acid (43)	413
$C_{14}H_{15}ClN_2O$		BuLi/ether/0°/0.5 hr	CH_2O	X = CH_2OH (73)	23
		''	t-C_4H_9NCO	X = $CONHC_4H_9$-t (63)	23
		''	$(C_6H_5S)_2$	X = SC_6H_5 (80)	23
$C_{14}H_{18}O_2$		BuLi, NaOC_4H_9-t/hexane/25°/1 hr	CO_2	(88)	525
$C_{14}H_{24}O_4S$		BuLi/ether/−40°/1 hr	DMF	2,3,4-Thiophenetricarboxaldehyde, 3,4-bis(diethyl acetal) (30)	283

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TABLE XLV. ALKYL ARALKYL ETHERS AND ARALKYL ALCOHOLS (ORTHO, BETA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{14}H_{24}O_4Se$		BuLi/ether/~50°/ 5 hr	DMF	2,3,5-Selenophenetricarboxaldehyde, 3,5-bis(diethyl acetal) (40)	283
		BuLi/ether/~40°/ 1 hr	DMF	2,3,4-Selenophenetricarboxaldehyde, 3,4-bis(diethyl acetal) (40)	283
$C_{15}H_{20}O_2$		BuLi/hexane, TMEDA/ reflux/45 min	$CO_2(CH_2N_2)$	(–), (–)	525
$C_{16}H_{22}O_2$		BuLi/hexane, TMEDA/60°/ 5 hr	$CO_2(CH_2N_2)$	(80)	245
$C_{19}H_{34}O_6S$		BuLi/"long time"	DMF	2,3,4,5-Thiophenetetracarboxaldehyde, 2,3,4-tris(diethyl acetal) (—)	441
$C_{19}H_{34}O_6Se$		BuLi/"long time"	DMF	2,3,4,5-Selenophenetetracarboxaldehyde, 2,3,4-tris(diethyl acetal) ("good")	441
$C_{20}H_{18}O$	$(C_6H_5)_2C(OCH_3)$	C_6H_5Li/ether, toluene/ reflux/24 hr	H_2O	X = H (17)	532
		BuLi/ether, toluene/ reflux/24 hr	CO_2	X = CO_2H (13)	532
		BuLi/ether/ reflux/24 hr	CO_2	3,3-Diphenylphthalide (—)	532
$C_{26}H_{22}O$	$[(C_6H_5)_2CH]_2O$	BuLi/ether, benzene/25°/ 50 hr	CO_2	(3)	533

Note: References 360–607 are on pp. 355–360.

TABLE XLVI. α-SILYLOXYSTYRENES (ORTHO)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{11}H_{16}OSi$		BuLi/hexane, TMEDA/−30° −25°/24 hr	CH_3Br (H_3O^+)	Acetophenone (8), 2′-methylacetophenone (34), 2′-methylpropiophenone (26), 2′-methylisobutyrophenone (26)	228
		"	$(CH_3)_3SiCl$	(90)	228
$C_{12}H_{18}OSi$		BuLi/hexane, TMEDA/−30° −25°/24 hr	$(CH_3)_3SiCl$	(71), (10), (10) $X = Si(CH_3)_3$	228

TABLE XLVII. ARYLCARBOXYLIC ACIDS, ESTERS, AND DIARYLKETONES (ORTHO, BETA)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
$C_4H_3NO_2S$	(isothiazole-CO_2H structure)	BuLi/THF/−65°/ 15 min*	CO_2	4,5-Isothiazoledicarboxylic acid (15)		154
$C_5H_4O_2S$	(thiophene-CO_2H structure)	LDA/THF or ether, HMPA/ −70°	$(CH_3)_3SiCl$	2-(Trimethylsilyl)-3-thiophenecarboxylic acid (—)		246
$C_5H_5NO_2S$	(CH_3, CO_2H isothiazole structure)	BuLi/THF/−70° 15 min	Br_2	(product structure with X)	X = Br (52)	154
		BuLi/THF/−65°/ 15 min*	CO_2		X = CO_2H (29)	154
		,,	DMF		X = CHO (25)	154
$C_9H_{10}O_2$	$C_6H_5CO_2C_2H_5$	LTMP/THF/ −78°*	(—)	(benzene with CO_2R and COC_6H_5) (I) (44)	R = C_2H_5	53
$C_{10}H_{12}O_2$	$C_6H_5CO_2C_3H_7$-n	LTMP/THF/−78°	(—)	I (46)	R = C_3H_7-n	53
	$C_6H_5CO_2C_3H_7$-i	LTMP/THF/−78°	(—)	I (10)	R = C_3H_7-i	53
$C_{11}H_{14}O_2$	$C_6H_5CO_2C_4H_9$-n	LTMP/THF/−78°	(—)	I (38)	R = C_4H_9-n	53
$C_{13}H_{10}O$	$(C_6H_5)_2CO$	LTMP/THF/−78°	(—)	3-Hydroxy-1,1,3-triphenylphthalan (80)		53

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TABLE XLVIII. ALKYL ARYL SULFIDES (ORTHO, BETA)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_5H_6S_2$	3-(methylthio)thiophene (SCH₃ at 3-position)	BuLi/ether/ reflux/0.5 hr	CO_2	3-(Methylthio)-2-thiophenecarboxylic acid (70)	248
$C_6H_8S_2$	CH_3–thiophene–SCH_3 (2,5-disubstituted)	BuLi	CO_2	5-Methyl-2-(methylthio)-3-thiophene-carboxylic acid (27)	404
C_7H_8S	$C_6H_5SCH_3$	BuLi/5 min	CO_2 (CH_2N_2)	Benzene with SCH₃ and CO₂CH₃ — $o+m$ (I), Benzene with SCH₂CO₂CH₃ (II); (I+II, 30) (I:II, 37:63)	58
$C_8H_{10}OS$	m-$CH_3OC_6H_4SCH_3$	BuLi/ether/ reflux/4 hr	CO_2	6-(Methylthio)-o-anisic acid (46)	574
$C_8H_{10}S$	$C_6H_5SC_2H_5$	BuLi/15 hr	$CO_2(CH_2N_2)$	Benzene with SC₂H₅ and CO₂CH₃ — o (III), m (IV), p (V); (III+IV+V, 27) (III:IV:V, 55:19:5)	58
$C_8H_{12}S_2$	3-(t-butylthio)thiophene (SC₄H₉-i at 3-position)	BuLi	CO_2	3-(t-Butylthio)-2-thiophenecarboxylic acid (—), 4-(t-butylthio)-2-thiophenecarboxylic acid (—), 3-(t-butylthio)-2,5-thiophenedicarboxylic acid (—)	424,
	C_2H_5–thiophene–SC_2H_5 (2,5-disubstituted)	—	CO_2	5-Ethyl-2-(ethylthio)-3-thiophene-carboxylic acid (7)	404
$C_{10}H_{14}OS$	m-$CH_3OC_6H_4SC_3H_7$-i	BuLi/ether/ reflux/4 hr	CO_2	6-(Isopropylthio)-o-anisic acid (43)	574
$C_{11}H_{11}NOS$	3-phenyl-5-(ethylthio)isoxazole (C_6H_5, SC_2H_5)	BuLi/THF/−30°/ 0.5 hr	CO_2	5-(Ethylthio)-3-phenyl-4-isoxazole-carboxylic acid (73)	232
$C_{12}H_{13}NOS$	3-phenyl-5-(isopropylthio)isoxazole (C_6H_5, SC_3H_7-i)	BuLi/THF/−30°/ 0.5 hr	CO_2	5-(Isopropylthio)-3-phenyl-4-isoxazole-carboxylic acid (85)	232

Note: References 360–607 are on pp. 355–360.

TABLE XLIX. DIARYL SULFIDES AND CONDENSED DIARYL SULFIDES (ORTHO, BETA)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_8H_6S_3$		BuLi/ether/ reflux/1 hr	$CuCl_2$	(52)	144
$C_{12}H_8OS$		BuLi/ether/ reflux/24 hr	O_2	$X = OH$ (16)	288
		BuLi	CO_2	$X = CO_2H$ (37)	237
		BuLi/ether/ reflux	"	(35), (1–9)	236, 237
$C_{12}H_8S$		BuLi/ether	Br_2	$X = Br$ (77)	152, 249
		BuLi/THF, ether/ 25°/5 hr	CO_2	$X = CO_2H$ (60)	560
		BuLi/ether/ reflux/3 hr	$(C_6H_5)_3SiCl$	$X = Si(C_6H_5)_3$ (42)	452
$C_{12}H_8S_2$		BuLi/ether/ reflux/22 hr	O_2	$X = OH$ (3)	288
		BuLi/ether/ 25°/40 hr	CO_2	$X = CO_2H$ (28)	250
		"	CH_3ONH_2	$X = NH_2$ (26)	250
		"	$(n\text{-}C_4H_9O)_3B$ (H_3O^+)	$X = B(OH)_2$ (22)	250
		"	$(C_6H_5)_3SiCl$	$X = Si(C_6H_5)_3$ (10)	250
$C_{12}H_{10}S$	$(C_6H_5)_2S$	BuLi/ether	$(CH_3)_3SiCl$	Trimethyl[o-(phenylthio)phenyl]silane (I), trimethyl[m-(phenylthio)phenyl]silane (II) (I:II, 9:1)	252
		"	"	I (23)	251
$C_{13}H_{11}NS$		BuLi/ether/ 30 hr	CO_2	, (III) (16) (IV) (14) $X = CO_2H$	177, 183a
		"	CH_2O	III $X = CH_2OH$ (10)	177
		"	Ethylene oxide	" $X = (CH_2)_2OH$ (10)	177
		"	$(CH_3O)_2SO_2$	" $X = CH_3$ (25)	177
		"	CH_3CO_2Li	" $X = COCH_3$ (23)	177
		"	$C_2H_5CO_2Li$	" $X = COC_2H_5$ (17)	177
		"	$C_6H_5CO_2Li$	" $X = COC_6H_5$ (20)	177
		"	$C_6H_5N(CH_3)CHO$	" $X = CHO$ (10)	177
$C_{14}H_{13}NS$		BuLi/ether/30 hr	CO_2	, (V) (14) (VI) (13) $X = CO_2H$	177, 183a
		"	CH_3CO_2Li	V $X = COCH_3$ (13)	177

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
$C_{14}H_{13}NS$ (*Contd.*)		"	$C_6H_5CO_2Li$	"	$X = COC_6H_5$ (18)	183a, 177
		"	$(C_6H_5)_2CO$	"	$X = C(C_6H_5)_2OH$ (55)	178
$C_{16}H_{10}S$		BuLi	CO_2		$X = CO_2H$ (51)	534
		"	$(CH_3O)_2SO_2$		$X = CH_3$ (70)	534
$C_{19}H_{24}N_2S$		BuLi	$(C_6H_5)_2CO$	10-[(3-Diethylamino)propyl]-α,α-diphenyl-4-phenothiazinemethanol (8)		178

Note: References 360–607 are on pp. 355–360.

TABLE L. Sulfones (Ortho, Beta)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_8H_{12}O_3S_2$		BuLi/THF/ −20°/9.5 hr	CO_2	5-(t-Butylsulfonyl)-2,4-thiophenedicarboxylic acid (68)	136
		"	DMF	5-(t-Butylsulfonyl)-2,4-thiophenedicarboxaldehyde (59)	136
		BuLi	CO_2	3-(t-Butylsulfonyl)-2,4-thiophenedicarboxylic acid (42), 3-(t-butylsulfonyl)-2,5-thiophenecarboxylic acid (8), 3-(t-butylsulfonyl)-2-thiophenecarboxylic acid (4)	565
$C_9H_8N_2O_2S$		t-BuLi/THF/ −20°/10 min	D_2O	X = D (100)	573
		BuLi/THF/ −10°/15 min	I_2	X = I (71)	573
		t-BuLi/THF/ −20°/0.5 hr	CH_2O	X = CH_2OH (10)	573
		BuLi/THF/ 0°/5 min	Cyclohexanone	X = (15)	573
		t-BuLi/THF/ 0°/10 min	C_6H_5CHO	X = $CH(OH)C_6H_5$ (18)	573
$C_{10}H_{14}O_2S$	$C_6H_5SO_2C_4H_9$-t	BuLi	—	X = Li (—)	572
		BuLi/THF/ −10°/3 hr	CO_2	X = CO_2H (45)	535

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TABLE L. Sulfones (Ortho, Beta) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{10}H_{14}O_2S$ (*Contd.*)	$C_6H_5SO_2C_4H_9$-t	RLi/20°/20 hr	CO_2	R=C_2H_5 (42) R=C_4H_9-n (44)	535
		"Excess" BuLi	"	(40)	572
$C_{11}H_{16}O_2S$	p-$CH_3C_6H_4SO_2C_4H_9$-t	BuLi	—	(–)	572
		"Excess" BuLi	CO_2	(5)	572
$C_{12}H_8O_2S$		BuLi/ether/ −30°	CO_2	(18)	536
		$\S$ BuLi	"	(20)	536
$C_{12}H_8O_2S_2$		BuLi/ether/ −70°/16 hr	CO_2	(41)	250
		C_6H_5Li/ether/ 0°/1 hr, 25°/ 3 hr	"	(54)	250
$C_{12}H_8O_3S$		BuLi/ether/ 0°–25°	CO_2	(46)	537
		BuLi/ether/ −45° to −10°	"	(52)	236
$C_{12}H_9BrO_2S$	$C_6H_5SO_2C_6H_4Br$-m $C_6H_5SO_2C_6H_4Br$-p	BuLi/ether/0° BuLi/ether/0°	CO_2 CO_2	2-Bromo-6-(phenylsulfonyl)benzoic acid (54) 5-Bromo-2-(phenylsulfonyl)benzoic acid (52)	69 69

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TABLE L. SULFONES (ORTHO, BETA) (*Continued*)

Formula	Compond Lithiated	Conditions	Substrate	Product and Yield (%)		Ref.
$C_{12}H_{10}O_2S$	$(C_6H_5)_2SO_2$	BuLi/ether/−40° to −30°/1 hr	CO_2		X = CO_2H (90)	538, 69, 536
		BuLi/ether/−40° to −30°/1 hr	$C_6H_5SO_2F$		X = $SO_2C_6H_5$ (73)	538
		"	$C_6H_5SO_2Cl$		X = Cl (90)	538
		"	$(C_6H_5)_2CO$		X = $C(C_6H_5)_2OH$ (63)	538
		4 BuLi/ether/ −30°	CO_2	(22)		536
		BuLi/ether	$SiCl_4$	(−)		539
		"	$(CH_3)_2SiCl_2$		R = CH_3 (24)	539
		"	$(C_6H_5)_2SiCl_2$		R = C_6H_5 (8)	539
$C_{12}H_{20}O_4S_3$	t-$C_4H_9SO_2$ — thiophene — $SO_2C_4H_9$-t	BuLi/−40° to −20°	CO_2	2,5-Bis(t-butylsulfonyl)thiophene-3-carboxylic acid (I) (41)		540
		"Excess" BuLi	"	I, 2,5-Bis(t-butylsulfonyl)thiophene-3,4-dicarboxylic acid (II)		540
				(I + II, —) (I : II, —)		
$C_{13}H_{12}O_2S$	$C_6H_5SO_2C_6H_4CH_3$-p	BuLi/ether/0°/ 1.5 hr, 25°/1 hr	CO_2	6-(Phenylsulfonyl)-m-toluic acid (III), o-(p-toluenesulfonyl)benzoic acid (IV)		
				(III + IV, 60) (III : IV, 3 : 2)		541
$C_{14}H_{11}NO_2S$		t-BuLi/THF/ −12°–25°/ 20 min			X = CO_2H (63)	85
		"	$ClCO_2C_2H_5$		X = $CO_2C_2H_5$ (75)	85
		"			X = CH(OH)— 2-pyridyl (32)	85
		"			X = CO— 3-pyridyl (60)	85
		"	C_6H_5CHO		X = $CH(OH)C_6H_5$ (55)	85
		"	C_6H_5COCl		X = COC_6H_5 (65)	85
		"			X = $C(CH_3)(OH)$— 4-pyridyl (35)	85

TABLE L. Sulfones (Ortho, Beta) (Continued)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C$_{14}$H$_{11}$NO$_2$S (Contd.)	[indole-N-SO$_2$C$_6$H$_5$ structure]	t-BuLi/THF/−12°–25°/20 min	C$_6$H$_5$COCH$_3$	[indol-2-yl-X with SO$_2$C$_6$H$_5$] X = C(CH$_3$)C$_6$H$_5$ (64), OH	85
		''	p-CH$_3$OC$_6$H$_4$CHO	X = CH(OH)C$_6$H$_4$OCH$_3$-p (65)	85
		''	p-CH$_3$OC$_6$H$_4$COCH$_3$	X = C(CH$_3$)C$_6$H$_4$OCH$_3$-p, OH (35)	85
		''	[2-cyanopyridine] (H$_3$O$^+$)	[indol-2-yl-X, N–H] X = CO(2-pyridyl) (36)	85
		''	[4-cyanopyridine] (H$_3$O$^+$)	X = CO(4-pyridyl) (26)	85
		''	C$_6$H$_5$CN (H$_3$O$^+$)	X = COC$_6$H$_5$ (30)	85
		''	[ethyl nicotinate, 3-CO$_2$C$_2$H$_5$ pyridine]	X = CO(3-pyridyl) (22)	85
		''	[ethyl isonicotinate, 4-CO$_2$C$_2$H$_5$ pyridine]	X = CO(4-pyridyl) (31)	85
		''	C$_6$H$_5$CO$_2$C$_2$H$_5$	X = COC$_6$H$_5$ (26)	85
C$_{14}$H$_{14}$ClNO$_2$S	[2-Cl, 3-N(CH$_3$)$_2$, 1-SO$_2$C$_6$H$_5$ benzene]	BuLi/ether/−80°/24 hr	CO$_2$	2-Chloro-3-(dimethylamino)-6-(phenylsulfonyl)-benzoic acid (82)	542
C$_{14}$H$_{16}$O$_2$S	[1-(SO$_2$C$_4$H$_9$-t)naphthalene]	BuLi/ether/−70°/7 hr	CO$_2$	1-(t-Butylsulfonyl)-2-naphthoic acid (47)	253
	[2-(SO$_2$C$_4$H$_9$-t)naphthalene]	BuLi	CO$_2$	1-Butyl-2-naphthoic acid (14), 2-(t-butylsulfonyl)-1-naphthoic acid (13)	543
C$_{15}$H$_{13}$NO$_3$S	[5-CH$_3$O indole-N-SO$_2$C$_6$H$_5$]	t-BuLi/THF/0°–25°/45 min	[2-pyridinecarboxaldehyde]	[5-CH$_3$O indol-2-yl-X, N-SO$_2$C$_6$H$_5$] X = CH(OH)(2-pyridyl) (59)	84
		''	[3-pyridinecarboxaldehyde]	X = CH(OH)(3-pyridyl) (84)	84

TABLE L. SULFONES (ORTHO, BETA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C₁₅H₁₃NO₃S (*Contd.*)		*t*-BuLi/THF/0°–25°/45 min		X = CH(OH) (62)	84
		··		X = CH(OH) (70)	84
		··		X = C(CH₃)OH (58)	84
C₁₆H₁₂O₂S		BuLi/ether/−70°	Cl₂POC₂H₅	(25)	577
C₁₆H₁₈O₂S	C₆H₅SO₂C₆H₄C₄H₉-*t-p*	BuLi/ether/0°	CO₂	*o*-(*p-t*-Butylphenylsulfonyl)benzoic acid (69), 3-*t*-butyl-6-(phenylsulfonyl)benzoic acid (31)	544
C₂₀H₁₄O₂S		BuLi/ether/−70°	Cl₂POC₂H₅	(25)	577

Note: References 360–607 are on pp. 355–360.

TABLE LI. Arylsulfonamides (Ortho, Beta)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
$C_7H_8ClNO_2S$	$p\text{-}ClC_6H_4SO_2NHCH_3$	BuLi/THF/ $-10°/1$ hr	$CH_2{=}CHCHO$		(>90)	24
$C_7H_9NO_2S$	$C_6H_5SO_2NHCH_3$	BuLi/THF/0°/ 15–20 min	CO_2		$X = CO_2H$ (49)	545
		BuLi/THF/ $-10°/3$ hr	$CH_2{=}CHCHO$		$X = CH(OH)CH{=}CH_2$ (>80)	24
		BuLi/THF/0°/ 15–20 min	Cyclohexanone		$X =$ (72)	545
		BuLi/THF/0°	C_6H_5NCO		$X = CONHC_6H_5$ (67)	496
		BuLi/THF/0°/ 15–20 min	$C_6H_5COCH_3$		$X = \underset{\overset{|}{OH}}{C(CH_3)C_6H_5}$ (58)	545
		"	$(C_6H_5)_2CO$		$X = C(C_6H_5)_2OH$ (82)	545
		BuLi/THF/0°/ 0.5 hr	C_6H_5CN	(64)		201
$C_8H_{11}NO_2S$	$C_6H_5SO_2N(CH_3)_2$	BuLi/THF/0°/ 0.5 hr	CO_2		$X = CO_2H$ (75)	254

TABLE LI. ARYLSULFONAMIDES (ORTHO, BETA) (Continued)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)		Refs.
C$_9$H$_{11}$NO$_2$S (Contd.)	C$_6$H$_5$SO$_2$N(CH$_3$)$_2$	''	C$_6$H$_5$CN	X = CC$_6$H$_5$ (79) (‖ NH)		254
		''	C$_6$H$_5$NCO	X = CONHC$_6$H$_5$ (57)		254
		''	(C$_6$H$_5$)$_2$CO	X = C(C$_6$H$_5$)$_2$OH (82)		254
C$_9$H$_{17}$NO$_2$S$_2$Si	(CH$_3$)$_3$Si—S—SO$_2$N(CH$_3$)$_2$	BuLi/ether/0°/ 6 hr	CO$_2$	2-(Dimethylsulfamoyl)-5-(trimethylsilyl)- 3-thiophenecarboxylic acid (10)		135
C$_{10}$H$_{14}$ClNO$_2$S	p-ClC$_6$H$_4$SO$_2$NHC$_4$H$_9$-t	BuLi/THF/25°/ 1–2 hr	CO$_2$	(SO$_2$NHC$_4$H$_9$-t, Cl, X) X = CO$_2$H (25)		255
		BuLi/THF/ −30°/1 hr	(pyridyl-S)$_2$	X = (2-pyridylthio) (32)		24
		''	(4-pyridyl-S)$_2$	X = S—(4-pyridyl) (30)		24
		''	(C$_6$H$_5$S)$_2$	X = SC$_6$H$_5$ (50)		24
C$_{10}$H$_{14}$FNO$_2$S	p-FC$_6$H$_4$SO$_2$NHC$_4$H$_9$-t	BuLi/THF/25°/ 1–2 hr	CO$_2$	2-(t-Butylsulfamoyl)-5-fluorobenzoic acid (35)		255
C$_{10}$H$_{15}$NO$_2$S	C$_6$H$_5$SO$_2$NHC$_4$H$_9$-t	BuLi/THF/25°/ 1–2 hr	CO$_2$	(CO$_2$NHC$_4$H$_9$-t, X) X = CO$_2$H (48)		255
		BuLi/THF/0°/	CH$_2$=CHCHO	X = CH(OH)CH=CH$_2$ (>80)		24
		''	t-C$_4$H$_9$NCO	X = CONHC$_4$H$_9$-t (>80)		24
C$_{11}$H$_{17}$NO$_2$S	C$_6$H$_5$SO$_2$N(CH$_3$)C$_4$H$_9$-t	BuLi/ether/0°/ 1 hr	DMF	N-t-Butyl-o-formyl-N-methylbenzenesulfonamide (72)		24
	p-CH$_3$C$_6$H$_4$SO$_2$NHC$_4$H$_9$-t	BuLi/THF/25°/ 1–2 hr	CO$_2$	6-(t-Butylsulfamoyl)-m-toluic acid (28)		255
C$_{11}$H$_{17}$NO$_3$S	p-CH$_3$OC$_6$H$_4$SO$_2$NHC$_4$H$_9$-t	BuLi/THF/25°/ 1–2 hr	CO$_2$	6-(t-Butylsulfamoyl)-m-anisic acid (27)		255
C$_{11}$H$_{21}$NO$_2$S$_2$Si	(CH$_3$)$_3$Si—S—SO$_2$N(C$_2$H$_5$)$_2$	BuLi/ether, hexane, TMEDA/ −30°/6 hr	CO$_2$	2-(Diethylsulfamoyl)-5-(trimethylsilyl)- 3-thiophenecarboxylic acid (44)		135
C$_{12}$H$_{11}$NO$_2$S	C$_6$H$_5$SO$_2$NHC$_6$H$_5$	BuLi/THF/0°/ 15–20 min	CO$_2$	(SO$_2$NHC$_6$H$_5$, X) X = CO$_2$H (22)		545
		BuLi/THF/0°/ 0.5 hr	C$_6$H$_5$CN	X = CC$_6$H$_5$ (64)^a (‖ NH)		201
		BuLi/THF/0°	C$_6$H$_5$NCO	X = CONHC$_6$H$_5$ (53)		496
		BuLi/THF/0°/ 15–20 min	C$_6$H$_5$COCH$_3$	X = C(CH$_3$)C$_6$H$_5$ (48) (OH)		545
		''	(C$_6$H$_5$)$_2$CO	X = C(C$_6$H$_5$)$_2$OH (50)		545
C$_{13}$H$_{11}$NO$_3$S	C$_6$H$_5$SO$_2$NHCOC$_6$H$_5$	BuLi/THF/ −78°/4 hr	—	(3-phenyl-benzisothiazole-SO$_2$) (9)		546
C$_{13}$H$_{13}$NO$_2$S	C$_6$H$_5$SO$_2$N(CH$_3$)C$_6$H$_5$	CH$_3$Li/THF/ 25°/1–2 hr	H$_2$O	N-Methyl-o-(phenylsulfonyl)aniline (89)		256
		''	C$_6$H$_5$CHO	(SO$_2$C$_6$H$_4$NHCH$_3$-o, CH(OH)C$_6$H$_5$) (85)		256
	p-CH$_3$C$_6$H$_4$SO$_2$NHC$_6$H$_5$	BuLi/THF	(C$_6$H$_5$)$_2$CO	α^2-Hydroxy-α^2,α^2-diphenyl-2,4-xylenesulfonanilide (80)		545

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TABLE LI. Arylsulfonamides (Ortho, Beta) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{14}H_{15}NO_2S$	$C_6H_5SO_2N(C_2H_5)C_6H_5$	$CH_3Li/THF/$ $25°/1-2\,hr$	H_2O	N-Ethyl-o-(phenylsulfonyl)aniline (40)	256
	$o\text{-}CH_3C_6H_4SO_2N(CH_3)C_6H_5$	"	H_2O	N-Methyl-o-(o-tolylsulfonyl)aniline (50)	256
	$p\text{-}CH_3C_6H_4SO_2N(CH_3)C_6H_5$	"	H_2O	N-Methyl-o-(p-tolylsulfonyl)aniline (52)	256,257
$C_{14}H_{15}NO_3S$	$p\text{-}CH_3OC_6H_4SO_2N(CH_3)C_6H_5$	$BuLi/THF/25°/$ $1-2\,hr$	H_2O	o-(p-Methoxyphenylsulfonyl)-N-methylaniline (45)	256
$C_{14}H_{17}NO_2S$	(naphthalene-1-$SO_2NHC_4H_9$-t)	$BuLi/THF/25°/$ $1-2\,hr$	CO_2	8-(t-Butylsulfamoyl)-1-naphthoic acid (14)	255
	(naphthalene-2-$SO_2NHC_4H_9$-t)	$BuLi/THF/25°/$ $1-2\,hr$	CO_2	2-(t-Butylsulfamoyl)-1-naphthoic acid (30)	255
$C_{15}H_{15}NO_2S$	(benzisothiazoline SO_2, $N\!-\!C_6H_5$, $(CH_3)_2$)	$BuLi/THF/25°$	H_2O	(dibenzothiazepine ring product) ("good")	257
$C_{15}H_{17}NO_2S$	$p\text{-}CH_3C_6H_4SO_2N(C_2H_5)C_6H_5$	$CH_3Li/THF/$ $25°/1-2\,hr$	H_2O	N-Ethyl-o-(p-tolylsulfonyl)aniline (81)	256
$C_{15}H_{17}NO_3S$	$p\text{-}CH_3C_6H_4SO_2N(CH_3)C_6H_4OCH_3$-$p$	"		N-Methyl-2-(p-tolylsulfonyl)-p-anisidine (61)	256
	$p\text{-}CH_3OC_6H_4SO_2N(C_2H_5)C_6H_5$	$CH_3Li/THF/$ $25°/1-2\,hr$	H_2O	N-Ethyl-o-(p-methoxyphenylsulfonyl)aniline (57)	256
$C_{15}H_{17}NO_4S$	$p\text{-}CH_3OC_6H_4SO_2N(CH_3)C_6H_4\text{-}$ OCH_3-p	$BuLi/THF/$ $25°/1-2\,hr$	H_2O	2-(p-Methoxyphenylsulfonyl)-N-methyl-p-anisidine (53)	256
$C_{15}H_{18}N_2O_2S$	$p\text{-}(CH_3)_2NC_6H_4SO_2N(CH_3)C_6H_5$	$BuLi/THF/25°/$ $1-2\,hr$	H_2O	o-(p-Dimethylaminophenylsulfonyl)-N-methylaniline (54)	256
$C_{16}H_{17}NO_2S$	(CH_3-substituted benzisothiazoline SO_2, $N\!-\!C_6H_5$, $(CH_3)_2$)	$BuLi/THF/25°$	H_2O	(CH_3-substituted dibenzothiazepine ring product) ("good")	257
$C_{18}H_{15}NO_2S$	$C_6H_5SO_2N(C_6H_5)_2$	$BuLi/THF/25°/$ $1-2\,hr$	H_2O	N-Phenyl-o-(phenylsulfonyl)aniline (86)	256
$C_{19}H_{17}NO_2S$	$p\text{-}CH_3C_6H_4SO_2N(C_6H_5)_2$	$C_6H_5Li/ether/$ $34°$	H_2O	N-Phenyl-p-(tolylsulfonyl)aniline (48)	258
$C_{26}H_{21}NO_2S$	(CH_3-substituted benzisothiazoline SO_2, $N\!-\!C_6H_5$, $(C_6H_5)_2$)	$BuLi/THF/25°$	H_2O	(ring product with $(C_6H_5)_2$) ("good")	257

a The product is a mixture of open-chain and ring isomers.

Note: References 360–607 are on pp. 355–360.

TABLE LII. Aryl Fluorides and Vinyl Fluorides (Ortho, Beta)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C_2HClF_2	$CF_2{=}CClH$	BuLi/ether/−100° to −78°/0.5–1 hr	CH_3COCH_3	2-Chloro-3-methylcrotonic acid (15)	172
		"	CF_3COCF_3	$CF_2{=}CClX$ $\quad$ X = C(CF_3)_2OH (56)	172
		"	CH_3COCF_3	X = C(CF_3)CH_3 (61) $\;$ $\underset{\text{OH}}{|}$	172
		"	$(C_2H_5)_3SiCl$	X = Si(C_2H_5)_3 (10)	173
C_2HF_3	$CF_2{=}CFH$	BuLi/ether/−100° to −78°/0.5–1 hr	CH_3COCH_3	2-Fluoro-3-methylcrotonic acid (30)	172
		"	CO_2	$CF_2{=}CFX$ $\quad$ X = CO_2H (57)	172
		"	CF_3COCF_3	X = C(CF_3)_2OH (63)	172
		"	$(C_2H_5)_3SiCl$	X = Si(C_2H_5)_3 (79)	173
C_4HF_5	[fluorocyclobutene structure, F_2, F_2, F]	CH_3Li/ether/−70°	CH_3CHO	2,3,3,4,4-Pentafluoro-α-methyl-1-cyclobutene-1-methanol (23)	263
C_4H_3FS	[3-fluorothiophene structure]	BuLi/ether/reflux/15 min	CO_2	3-Fluoro-2-thiophenecarboxylic acid (75)	385
C_5HF_7	[fluorocyclopentene structure, F_2, F_2, F_2, F]	CH_3Li/ether/−70°	CH_3CHO	2,3,3,4,4,5,5-Heptafluoro-α-methyl-1-cyclopentene-1-methanol (42)	263
C_6HF_5	Pentafluorobenzene	BuLi/THF/−70°/5 min	CO_2	[pentafluorophenyl-X structure] $\quad$ X = CO_2H (82)	547
		BuLi/ether/−55°/2 hr	CF_3COCF_3	X = C(CF_3)_2OH (79)	548
C_6HF_9	[nonafluorocyclohexene structure, F_2, F_2, F_2, F_2, F]	CH_3Li/ether/−70°	Br_2	[substituted cyclohexene structure, X] $\quad$ X = Br (46)	263
		"	I_2	X = I (59)	263
		"	CO_2	X = CO_2H (77)	263
		"	CH_3CHO	X = CH(OH)CH_3 (63)	263
$C_6H_2F_4$	1,2,3,4-Tetrafluoro-benzene	BuLi/THF/−70°/0.5 hr	$HgCl_2$	[tetrafluorophenyl-X structure] $\quad$ X = Hg[bis(tetrafluorophenyl)] (90)	262
		"	CuI	X = [tetrafluorophenyl] (69)	262
		"	CO_2	X = CO_2H (—)	262
		"	$(CH_3)_2SiHCl$	X = SiH(CH_3)_2 (64)	262
		"	$(CH_3)_3SiCl$	X = Si(CH_3)_3 (82)	262
	1,2,4,5-Tetrafluoro-benzene	BuLi/ether/−65°/2 hr	CO_2	[tetrafluorophenyl-X structure] (I) $\quad$ X = CO_2H (85)	277

TABLE LII. ARYL FLUORIDES AND VINYL FLUORIDES (ORTHO, BETA) (Continued)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_6H_2F_4$ (Contd.)	1,2,4,5-Tetrafluoro-benzene	BuLi/THF/−65°/ 2 hr	CF_3COCF_3	(tetrafluorobenzene disubstituted with X) (I) (11), (61) X = C(CF3)2OH	548
$C_6H_2F_4S$	2,3,5,6-Tetrafluoro-benzenethiol	BuLi/THF/−70°/ 1 hr	CO_2	2,3,5,6-Tetrafluoro-4-mercaptobenzoic acid (77)	549
$C_6H_3F_3$	1,3,5-Trifluoro-benzene	BuLi	$(CH_3)_3SiCl$	(trifluorobenzene tris(trimethylsilyl) derivative) (—)	550
$C_6H_3F_4N$	2,3,5,6-Tetrafluoro-aniline	BuLi/THF/−70°/ 3 hr	CO_2	4-Amino-2,3,5,6-tetrafluorobenzoic acid (37)	549
C_6H_4ClF	$p\text{-}FC_6H_4Cl$	BuLi/THF/−70°/ 4 hr	$(CH_3S)_2$	5-Chloro-2-fluorophenyl methyl sulfide (>90)	23
$C_6H_4F_2$	m-Difluorobenzene	BuLi/THF/−65°	CO_2	2,6-Difluorobenzoic acid (88)	549, 551
		BuLi/THF	$(CH_3)_3SnCl$	(2,6-Difluorophenyl)trimethylstannane (60)	306
	o-Difluorobenzene	BuLi/THF, hexane/−50°	$FClO_3$	1,2,3-Trifluorobenzene (—)	551
		"	CO_2	2,3-Difluorobenzoic acid (74)	551
C_6H_5F	C_6H_5F	BuLi/THF/−50°/ 7 hr	CO_2	2-Fluorobenzoic acid (60)	260
C_7HF_7	(2,3,4,5-tetrafluoro-6-CF3 benzene)	BuLi/THF/−70°/ 1 hr	CO_2	X = CO2H (77)	549
		BuLi/THF/−60°/ 0.5 hr	CF_3COCF_3	X = C(CF3)2OH (61)	548
$C_7H_2F_4O_2$	(2,3,5,6-tetrafluoro CO2H benzene)	BuLi/THF/−65°/ 45 min	Cl_2	X = Cl (—)	277
		"	"S"	X = SH (69)	277
		"	CO_2	X = CO2H (94)	277
$C_7H_4F_4$	2,3,5,6-Tetrafluoro-toluene	BuLi/THF/−70°/ 1 hr	CO_2	X = CO2H (88)	549
		BuLi/THF/−60°/ 0.5 hr	CF_3COCF_3	X = C(CF3)2OH (91)	548
C_7H_7F	$o\text{-}FC_6H_4CH_3$	BuLi/THF/−50°/ 7 hr	CO_2	2-Fluoro-m-toluic acid (3)	260
	$p\text{-}FC_6H_4CH_3$	BuLi/THF/−50°/ 7 hr	CO_2	6-Fluoro-m-toluic acid (58)	260
$C_{10}H_7F$	1-Fluoronaphthalene	BuLi/THF/−50°/ 7 hr	CO_2	1-Fluoro-2-naphthoic acid (30)	260
	2-Fluoronaphthalene	BuLi/THF/−60°/ 6.5 hr	CO_2	2-Fluoro-1-naphthoic acid (II), 3-fluoro-2-naphthoic acid (III) (II+III, 70) (II:III, 54:46)	261

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TABLE LII. ARYL FLUORIDES AND VINYL FLUORIDES (ORTHO, BETA) (*Continued*)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_{12}H_2F_8$		BuLi/THF/−70°/ 1 hr	CO_2	$X = CO_2H$ (97)	549
		BuLi/THF/−60°/ 1 hr	CF_3COCF_3	$X = C(CF_3)_2OH$ (74)	548
$C_{12}H_7F_4N$	C_6H_5NH	BuLi	CO_2	4-Anilino-2,3,5,6-tetrafluorobenzoic acid (56)	552
$C_{14}H_9F$		BuLi/THF/−50°/ 7 hr	Br_2	9-Bromo-10-fluorophenanthrene (42)	531
		"	CO_2	10-Fluoro-9-phenanthrenecarboxylic acid (65)	531

Note: References 360–607 are on pp. 355–360.

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TABLE LIII. ARYL CHLORIDES AND VINYL CHLORIDES (ORTHO, BETA)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C_2HCl_3	CCl_2=CClH	BuLi/THF, ether, pet. ether/−100°/50 min	CO_2	Trichloroacrylic acid (81)	167, 168
$C_2H_2Cl_2$	CCl_2=CH_2	BuLi/THF/−110°/ 68 min	CO_2	Chloropropiolic acid (86)	167
		BuLi/THF/−110°/ 40 min	Br_2	(Z)-1-Bromo-1,2-dichloroethylene (26)	167, 168
		''	CO_2	(E)-2,3-Dichloroacrylic acid (99)	167
C_3H_2ClNS		BuLi/THF/−65°/ 15 min*	CO_2	4-Chloro-5-isothiazolecarboxylic acid (68)	154
		''	DMF	4-Chloro-5-isothiazolecarboxaldehyde (65)	154
$C_4H_2Cl_2Se$		LDA/ether/−70°/2 hr	CO_2	2,5-Dichloro-3-selenophenecarboxylic acid (78)	291
		LDA/ether/−70°/4 hr	$(CH_3Se)_2$	2,5-Dichloro-3-(methylselenyl)selenophene (51)	291
C_4H_3ClO		LDA/THF/−80°/2.5 hr	$(CH_3)_2C$=$CHCH_2Br$	3-Chloro-2-(3-methyl-2-butenyl)furan (41)	566
C_4H_4ClNS		BuLi/THF/−65°/ 15 min*	CO_2	4-Chloro-3-methyl-5-isothiazolecarboxylic acid (75)	154
		''	DMF	4-Chloro-3-methyl-5-isothiazolecarboxaldehyde (47)	154

TABLE LIII. ARYL CHLORIDES AND VINYL CHLORIDES (ORTHO, BETA) (Continued)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C_4H_5ClO		BuLi/THF/−78°	CH_3I	$X = CH_3$ (74)	266
		"	CH_3COCl	(78)	266
		"	n-C_4H_9I	$X = C_4H_9$-n (62)	266
		"	C_6H_5CHO	$X = CH(OH)C_6H_5$ (77)	266
$C_4H_7ClO_2$		s-BuLi/THF/−100°/ 0.5 hr	$HgCl_2$	Bis[(Z)-2-chloro-(1,2-dimethoxyvinyl)]mercury (−)	600
		"	CO_2	(E)-3-Chloro-2,3-dimethoxyacrylic acid (45)	600
$C_5H_2Cl_3N$		BuLi/ether/−70°/ 45 min, −20°/2 hr	$(CH_3O)_2SO_2$	2,3,6-Trichloro-4-methylpyridine (45)	265
C_5H_7ClO		BuLi/THF/25°/2 hr	CH_3I	$X = CH_3$ (>65)	562
		"	C_2H_5I	$X = C_2H_5$ (>65)	562
		"	n-C_4H_9I	$X = C_4H_9$-n (>65)	562
C_6HCl_5	Pentachlorobenzene	BuLi/THF/−65°	CO_2	$X = CO_2H$ (91)	553
$C_6H_2Cl_4$	1,2,3,4-Tetrachlorobenzene	BuLi/THF/−70° BuLi/THF/−78°/3 hr CH₃Li/THF/−70°	$(CH_3)_3SiCl$ $(CH_3)_3SnCl$ $(CH_3)_3SiCl$	$X = Si(CH_3)_3$ (95) $X = Sn(CH_3)_3$ (73) Trimethyl(2,3,6-trichlorophenyl)silane (7), trimethyl(2,3,4,5-tetrachlorophenyl)silane (93)	264, 554 554 264
	1,2,4,5-Tetrachlorobenzene	BuLi/ether/−65°	CO_2	$X = CO_2H$ (48) (27)	553
		2 BuLi/THF BuLi/THF/−78° BuLi/THF, ether/ −78°/5 hr BuLi/THF/−78° " "	" $(CH_3)_2SiHCl$ $(CH_3)_3SiCl$ $C_6H_5(CH_3)_2SiCl$ $CH_3(C_6H_5)_2SiCl$ $(CH_3)_3SnCl$	(30) (43) $X = CO_2H$ (58) $X = SiH(CH_3)_2$ (24) (56) $X = Si(CH_3)_3$ (−) (67) $X = Si(CH_3)_2C_6H_5$ (−) (62) $X = Si(C_6H_5)_2CH_3$ (−) (32) $X = Sn(CH_3)_3$	553 554 554 554 554 554
$C_6H_3Cl_3$	1,3,5-Trichlorobenzene	3 BuLi/THF/−65° 2 BuLi/THF/−65°/ 0.5 hr	$(CH_3)_3SiCl$ "	(2,4,6-Trichloro-s-phenenyl)tris[trimethylsilane] (38) (2,4,6-Trichloro-m-phenylene)bis[trimethylsilane] (44)	555 555
$C_7H_3Cl_2F_3$		BuLi/THF/−50°/ 1 hr	CO_2	2,6-Dichloro-α,α,α-trifluoro-m-toluic acid (−)	556
C_7H_5ClN	m-ClC_6H_4CN	LTMP/THF/−70°/ 1 hr	$(CH_3S)_2$	3-Chloro-2-(methylthio)benzonitrile (30)	24

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TABLE LIII. ARYL CHLORIDES AND VINYL CHLORIDES (ORTHO, BETA) (Continued)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_7H_6Cl_2$		BuLi/THF/−50°	$C_6H_5SO_2F$	(2,6-Dichloro-m-tolyl)phenyisulfone (—)	557
		''	C_6H_5COCl	2,6-Dichloro-3-methylbenzophenone (—)	557
C_9H_6ClNO		BuLi/THF/−70°/ 0.5 hr	I_2	X=I (73)	232
		''	CO_2	X=CO_2H (80)	232
		''	CH_3I	X=CH_3 (74)	232
$C_9H_8Cl_2O_2$		BuLi/THF/−50°	$C_6H_5COCl\,(H_3O^+)$	2,4-Dichloro-3-benzoylbenzaldehyde (—)	557
$C_9H_{11}ClO_3$		BuLi/THF/−70°/ 3 min	CO_2	2-Chloro-3,5,6-trimethoxybenzoic acid (79), 3-chloro-2,5,6-trimethoxybenzoic acid (16)	222
		BuLi/THF/25°/ 10 min	Ac_2O	2-Chloro-3,5,6-trimethoxyacetophenone (68)	223
$C_{11}H_{14}ClNO$	m-ClC$_6$H$_4$CONHC$_4$H$_9$-t	BuLi/THF/−70°	$(CH_3S)_2$	N-t-Butyl-3-chloro-2-(methylthio)benzamide (31)	24
$C_{14}H_{14}ClNO_2S$		BuLi/ether/−80°/ 24 hr	CO_2	2-Chloro-3-(dimethylamino)-6-(phenylsulfonyl)-benzoic acid (82)	542
$C_{18}H_{18}Cl_2O_2$		BuLi/THF/−50°	$CO_2\,(H_3O^+)$	2,6-Dichloro-3-benzoylbenzoic acid (—)	557

Note: References 360–607 are on pp. 355–360.

TABLE LIV. ARYL BROMIDES (ORTHO, BETA)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C_3H_2BrNS		BuLi/THF/−65°/ 15 min*	CO_2	4-Bromo-5-isothiazolecarboxylic acid (70)	154
		"	DMF	4-Bromo-5-isothiazolecarboxaldehyde (73)	154
$C_3H_3BrN_2$		C_6H_5Li/ether/25°/ 2 hr	CO_2	4-Bromopyrazole-5-carboxylic acid (35)	87
$C_4H_2Br_2S$		LDA/THF or ether/−70°	$(CH_3)_3SiCl$	(2,5-Dibromo-3-thienyl)trimethylsilane (—)	246
C_4H_3BrO		LDA/THF/−80°/ 2.5 hr	CH_2O	$X = CH_2OH$ (52)	566
		"	CH_3OCH_2Cl	$X = CH_2OCH_3$ (49)	566
		LDA/THF or ether/−70°	$(CH_3)_3SiCl$	$X = Si(CH_3)_3$ (—)	246
		LDA/THF/ −80°/2.5 hr	$(CH_3)_2C=CHCH_2Br$	$X = CH_2CH=C(CH_3)_2$ (66)	566
C_4H_3BrS		C_6H_5Li/ether/ "overnight"	CO_2	3-Bromo-2-thiophenecarboxylic acid (72)	48
C_4H_4BrNS		BuLi/THF/−65°/ 15 min*	CO_2	$X = CO_2H$ (56)	154
		"	CH_3I	$X = CH_3$ (40)	154
		"	DMF	$X = CHO$ (51)	154
		"	C_2H_5I*	$X = C_2H_5$ (34)	154
		"	n-C_3H_7I*	$X = C_3H_7$-n (28)	154
		"	$C_6H_5CH_2Br$	$X = CH_2C_6H_5$ (13)	154
C_5H_5BrS		LDA/ether/25°	CO_2	3-Bromo-5-methyl-2-thiophenecarboxylic acid (56)	397
$C_8H_4Br_2S_2$		EtLi/THF/−70°/ 2 min	CO_2	4,4'-Dibromo-[3,3'-bithiophene]-5-carboxylic acid (51)	417
$C_{12}H_9BrO_2S$	$C_6H_5SO_2C_6H_4Br$-m	BuLi/ether/0°	CO_2	2-Bromo-6-(phenylsulfonyl)benzoic acid (54)	69

Note: References 360–607 are on pp. 355–360.

TABLE LV. ARYL IODIDES (BETA)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C₃H₂INS		BuLi/THF/ −65°/15 min*	DMF	4-Iodo-5-isothiazolecarboxaldehyde (33)	154
C₄H₃IS		Li/ether, TMEDA/ −10°/0.5 hr	CO₂	3-Iodo-2-thiophenecarboxylic acid (80), 4-iodo-2-thiophenecarboxylic acid (20)	68
C₄H₄INS		BuLi/THF/ −65°/15 min*	CO₂	4-Iodo-3-methyl-5-isothiazolecarboxylic acid (58)	154
		,,	DMF	4-Iodo-3-methyl-5-isothiazolecarboxaldehyde (68)	154

TABLE LVI. (Trifluoromethyl)benzenes (Ortho)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_7H_5F_3$	$C_6H_5CF_3$	BuLi	$CO_2(CH_2N_2)$	Methyl α,α,α-trifluoro-o-toluate (73), methyl α,α,α-trifluoro-m-toluate (26)	50
$C_8H_4F_6$	m-$CF_3C_6H_4CF_3$	BuLi/ether/ 20°/1 hr	CO_2	2,4-Bis(trifluoromethyl)benzoic acid (I), 2,6-bis(trifluoromethyl)benzoic acid (II) (I+II, 85) (I:II, 3:2)	49, 267, 268, 269
		BuLi/ether, TMEDA/25°	,,	(II) (30)	558
		BuLi/THF	$(CH_3)_3SnCl$	[2,6-Bis(trifluoromethyl)phenyl] tri-methylstannane (30), [2,4-bis(tri-fluoromethyl)phenyl] trimethyl stannane (—)	306
	p-$CF_3C_6H_4CF_3$	BuLi/ether/25° 1.5 hr	CO_2	2,5-Bis(trifluoromethyl)benzoic acid (87)	49, 268, 269
$C_{10}H_9F_6N$		BuLi/ether, hexane/reflux	CO_2	4-(Dimethylamino)-2,6-bis-(trifluoromethyl)benzoic acid (76)	558
$C_{10}H_{12}F_3N$	m-$CF_3C_6H_4CH_2$-$N(CH_3)_2$	BuLi/ether/ 25°/1 hr	$(C_6H_5)_2CO$	[α^6-(Dimethylamino)-$\alpha^2,\alpha^2,\alpha^2$-trifluoro-2,6-xylyl]diphenylmethanol (72)	45

Note: References 360–607 are on pp. 355–360.

TABLE LVII. ARYLPHOSPHINE OXIDES AND IMIDES (ORTHO, BETA)

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Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
$C_9H_9OPS_2$		BuLi/THF/25°/ 1 hr	CO_2	X = CO_2H (33)	270
		″	CH_3COCH_3	X = $C(CH_3)_2OH$ (40)	270
$C_{14}H_{11}OPS_2$		BuLi/THF/25°/ 1 hr	Br_2	X = Br (65)	270
		″	CO_2	X = CO_2H (75)	270
		″	$(CH_3)_3SiCl$	X = $Si(CH_3)_3$ (30)	270
		″	CH_3COCH_3	X = $C(CH_3)_2OH$ (45)	270
		″	C_6H_5CHO	X = $CH(OH)C_6H_5$ (70)	270
		″	$C_6H_5COCH_3$	X = $C(OH)C_6H_5$, CH_3 (50)	270
		″	$(C_6H_5)_2CO$	X = $C(C_6H_5)_2OH$ (80)	270
		″	CH_3CO_2Et	X = CH_3 (35)	270
				X = (pyridyl) (35)	270
		″	$C_6H_5CO_2C_2H_5$	X = C_6H_5 (68)	270
		″	$HCO_2C_2H_5$	3-(Phenyl-3-thienylphosphinyl)-2-thiophenecarboxaldehyde (48)	270
$C_{16}H_{13}OPS$		BuLi/THF/25°/ 1 hr	CO_2	3-(Diphenylphosphinyl)-2-thiophene-carboxylic acid (30)	270
		″	$(C_6H_5)_2CO$	3-(Diphenylphosphinyl)-α,α-diphenyl-2-thiophenemethanol (50)	270
$C_{24}H_{10}BrNP$		$C_6H_5Li/ether/$ 25°/3 hr	$CO_2 (H_3O^+)$	2-(Diphenylphosphinyl)benzoic acid (I) (67)	27
		″	$(CH_3)_3SiCl$	Diphenyl-2-[(trimethylsilyl)phenyl]phosphine-N-(p-bromophenyl)imide (50)	27
$C_{24}H_{20}NP$		$C_6H_5Li/ether/$ 25°/3 hr	$CO_2 (H_3O^+)$	(I) (62)	271

TABLE LVIII. Selenides (Ortho, Beta)

Formula	Compound Lithiated	Conditions	Substrate	Product and Yield (%)	Refs.
C_5H_6SSe	SeCH$_3$ (3-substituted thiophene)	BuLi/2 hr	CO_2	3-(Methylselenyl)-2-thiophenecarboxylic acid (I), 4-(methylselenyl)-2-thiophene-carboxylic acid (II) (I+II, 75) (I:II, 56:44)	140
$C_8H_{12}SSe$	SeC$_4$H$_9$-n (3-substituted thiophene)	BuLi/2 hr	CO_2	(III), (IV) (III+IV, 79) (III:IV, 6:4) X=CO_2H	140
		BuLi/ether/$-30°$	"S"+CH$_3$I	(III:IV, 7:3) X=SCH_3	140
		,,	"Se"+CH$_3$I	(III+IV, 67) X=$SeCH_3$	140
$C_{12}H_8Se$	(dibenzoselenophene)	BuLi/ether/reflux	CO_2	(96) CO_2H	273

8. Acknowledgment

End Throughout the text TMEDA is taken to stand for tetramethylethylenediamine.

Notes

*

* The inductive effect of the halogens decreases from fluorine to iodine. (22) Although chlorine is not included in Huisgen's studies, (32) it is arbitrarily put on the same level with the trifluoromethyl group.

* The use of lithium diisopropylamide gives better results (personal communication from R. A. Lyle, North Texas State University).

* See Note on page 105.

* Personal communication from B. M. Trost, University of Wisconsin, Madison, Wisconsin.

* U.S. suppliers: Aldrich Chemical Co., Alpha Inorganics, Inc., Columbia Organics, Foote Mineral, Lithium Corporation of America, Tridom Chemical, Inc.

  In Europe: Fluka Ltd.

* Lithiation of phenyl vinyl sulfide with lithium diisopropylamide proceeds efficiently under these conditions, but the yields of adducts obtained are variable. The use of *n*-butyllithium/TMEDA appears to give more consistent results.

* See footnote on p. 98.

* Under thermodynamic conditions, tertiary amides are more powerful *ortho* directors than sulfonamides and oxazolines (personal communication from P. Beak, University of Illinois, Urbana, Illinois).

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Intramolecular Reactions of Diazocarbonyl Compounds

Steven D. Burke, University of Pittsburgh, Pittsburgh, Pennsylvania
Paul A. Grieco, University of Pittsburgh, Pittsburgh, Pennsylvania

1. Introduction

Since the demonstration by Stork and Ficini in 1961 that unsaturated diazoketones undergo intramolecular cyclization to form cyclopropanes (Eq. 1), (1) the intramolecular reactions of α -diazocarbonyl compounds have been extensively studied under thermal, catalytic, and photochemical conditions. Intramolecular cyclization ofα-carbonyl carbenes and carbenoids has found widespread application to the synthesis of theoretically interesting compounds such as bullvalene, (2) twistane, (3) bridged annulenes, (4, 5) and barbaralone, (2) as well as syntheses of natural products such as sabinene, (6) sirenin, (7-12) α-chamigrene, (13) and phyllocladene. (14) The reaction has also allowed the construction of several intriguing polycyclic systems that were unattainable by alternative methods. (15)

$$(1)$$

A recent review has covered the reactions of diazoacetic esters with alkenes, alkynes, heterocyclics, and aromatic compounds. (16) Unsaturated alkoxycarbonyl carbenes (:CHCO$_2$R) and unsaturated carbonyl carbenes (:CHCOR) (where R contains either aromatic or olefinic groups), which are considered to be intermediates in the absence of catalyst, have been the subject of several other reviews. (17-20) A review concerning photo-chemically, thermally, and catalytically induced Wolff rearrangements ofα-diazocarbonyl compounds has recently appeared. (21) However, to date no comprehensive review has appeared which demonstrates the synthetic potential ofα-diazocarbonyl insertion and addition reactions.

In reviewing the reactions ofα-diazocarbonyl compounds we have chosen not to include certain peripheral topics such as intermolecular reactions, intramolecular dimerization of bis(α-carbonyl carbenoids) to give diacyl cycloolefins (Eq. 2), (22) and intramolecular trimerizations of tris(α-keto carbenoids), affording triacylcyclopropanes (Eq. 3). (23) Also excluded are base-catalyzed reactions ofα-diazocarbonyl compounds (24) and certain

ring-contraction reactions involving C—C bond insertion of intermediate α-ketocarbenes (Eq. 4). (25)

$$\text{(2)}$$

$$\text{(3)}$$

$$\text{(4)}$$

The topics included in this report are the intramolecular reactions of α-carbonyl carbenes and carbenoids with olefinic and aromatic unsaturation, with C—H bonds, and with C — C and N — H single bonds. Also included are acid-catalyzed cyclization reactions of α-diazoketones.

2. Mechanism

The intramolecular reactions of α -carbonyl carbenes and carbenoids elaborated in this review are referred to as additions if the divalent center is reacting with olefinic or aromatic unsaturation, and as insertions if the carbenic center is reacting with a C-C, C-H, or N- H single bond. Although mechanistic studies based on intramolecular reactions of α -diazocarbonyl compounds are relatively few, analogous intermolecular reactions have been rather extensively studied, and it is from these reports that much of the contemporary thought on the mechanism of the intramolecular reactions has been inferred. (16-20)

Photochemical, catalytic, or thermal conditions have been employed in the decomposition of α -diazocarbonyl compounds. Catalytic conditions are most commonly used. They generate a carbene complex (as opposed to a free carbene generated by photochemical decomposition). The carbene complex is referred to in this report as a carbenoid species. The catalytic decompositions are carried out under homogeneous or heterogeneous conditions with a wide variety of catalysts, usually copper or a copper salt. However, soluble complexes of copper and palladium have also been used.

Several investigations have strongly implicated a carbene-metal-olefin complex in the homogeneous copper-catalyzed decomposition of α -diazocarbonyl compounds. (26-29) The effects of varying the steric and electronic requirements of (trialkyl and triarylphosphite)copper(I) chloride catalysts have been studied in terms of the intermolecular addition of ethyl diazoacetate to olefins. (26, 27) Early work considered both intermolecular and intramolecular additions of α -carbonyl carbenoids to olefins using soluble copper(II) chelates. (28, 29) Strong evidence has been provided for a carbene-copper-olefin complex as an intermediate by utilizing an optically active copper(II) complex to induce asymmetry in reaction products (Eqs. 5 and 6). (29) Although interpretations differ slightly

(5)

(6)

on the exact nature of the intermediate complexes, it is proposed that intermediates are formed where the carbene acts as a ligand coordinated to the copper by donation of its electron pair. Concomitant $d_\pi - p_\pi$ back donation from the metal to the empty p orbital of the carbene carbon results in a stabilization of the complex. Analogous carbenoid complexes have been proposed as intermediates in the catalytic decomposition of α -diazocarbonyls with di- μ-chlorodi- π -allylpalladium (1) (30) and bis-(acetylacetonato)copper(II) (2). (28, 29, 31-34)

The carbenoid intermediates generated by the decomposition of α -diazocarbonyl compounds in the presence of copper or its salts generally show reduced reactivity (hence greater selectivity), as evidenced by a lack of intermolecular C-H insertion reactions which are prevalent in thermally or photochemically generated free carbenes. One example of this type of behavior is the photolysis of allyl diazoacetate, which gave only the intermolecular insertion product. (35) In order to obtain the olefin addition product copper catalysis was required. The enhanced selectivity of the modified carbenes obtained through catalysis explicitly allows the intramolecular reactions to be of synthetic importance.

It has been suggested that the intramolecular insertion reactions of photolytically generated alkoxycarbonyl carbenes are realized only to a slight extent because of dominant conformational effects. (36, 37) For example, the low yields observed in the intramolecular C-H insertion reactions of the carbenes generated from *t*-butyl- and *t*-pentyldiazoacetates (38) can be attributed to the inability of the O-alkyl moieties to attain sufficient proximity to the carbenic center. In support of this premise, it has been demonstrated that N,N-dialkyldiazoamides (Eq. 7) undergo principally lactam formation via intramolecular C-H insertion of the photolytically generated carbene. (36, 37) In this reaction one of the alkyl groups must be held in close proximity to the divalent center by the planar amide bond.

(7)

It has also been observed that the intramolecular C-H insertion reaction proceeds with retention of configuration. (39)

As elaborated in the following section, the intramolecular addition reactions of unsaturated alkoxycarbonyl carbenoids and unsaturated ketocarbenoids are stereospecific. (40) Thus the intramolecular addition of an α -diazocarbonyl compound to a suitably substituted olefinic site allows for the simultaneous construction of three asymmetric centers. The observed stereospecificity of the process has been applied to several syntheses of the sesquiterpene hormone sirenin (3) (7-12) as well as to other bicyclo[*x*.1.0] systems.

3

3. Scope and Limitations

Reactions involving intramolecular additions (1) and insertions 41a of α-carbonyl carbenes and carbenoids have found widespread use in the relatively short time since their initial application. The early applications are exemplified in syntheses of compounds of theoretical interest. Highly strained compounds containing the tricyclo[2.1.0.0^{2,5}]pentane carbon skeleton were obtained via olefin addition of photolytically and catalytically decomposed diazoketones. (42-44) A large number of more recent applications were directed toward total syntheses of the following natural products containing cyclopropane rings: 3-carone, (45) aristolone, (46) thujopsene, (47) sabinene, (6) sirenin, (7-12, 48) and several others. Studies have also been directed at intramolecular C- H insertion of carbenes derived from α-diazoamides to afford a new synthetic approach to β -lactam antibiotics. (49-55)

The following discussion elaborates some of these areas of interest, including consideration of the factors involved in the relative success or failure of the intramolecular insertion and addition reactions. Examples are chosen which illustrate a general principle or have some especially interesting characteristic features. The applications are organized into sections corresponding to the table headings.

3.1. Diazoketone Additions to Olefins

The ketocarbene or ketocarbenoid addition reaction with a suitably situated olefinic moiety within the same molecule is by far the most widely encountered application. Since the prototype (Eq. 1), (1) reactions of this type have come into utilization for a wide range of synthetic goals.

For the synthesis of bicyclo [x.1.0] compounds it was found that the controlling factor in determining the usefulness of this method was the proximity of the olefin to the divalent center, whereas the nature of the substitution on the double bond had little effect. (56)

This method proved useful for the construction (albeit in low yield) of strained polycyclic compounds, notably the tricyclo[2.1.0.0^{2,5}] pentane system. Interestingly, one synthesis is based on a photochemical decomposition of the diazoketone (Eq. 8), (42, 43) whereas the other is based on catalytic carbenoid generation (Eq. 9). (44)

$$R = C_6H_5,\ n\text{-}C_3H_7 \tag{8}$$

$$(9)$$

The low yields associated with the conversions indicated in Eqs. 8 and 9 are undoubtedly attributable to fragmentation of the initially formed tricyclic systems. It has recently been observed 57–60a that catalytic decomposition of β , γ -unsaturated diazoketones of this type can lead to rearranged γ , δ -unsaturated carboxylic acid derivatives in a process termed the vinylogous Wolff rearrangement. (59) Mechanistic pathways for this process have been proposed. 60a This method provides a synthetic alternative to the Claisen rearrangement.

Other theoretically intriguing compounds prepared by intramolecular carbenoid addition are barbaralone (Eq. 10), (2) twistane (4), (3) a [4.4.4]propellane (5), (61) and a bridged [14] annulene (Eq. 11). (4) Hydrocarbons 4 and 5 are of course not directly attainable by this method, but their syntheses do proceed through cyclopropyl ketones obtained via intramolecular diazoketone-olefin addition.

(10)

4

5

(11)

Many natural products have been obtained through synthetic application of this type of reaction. The stereospecific nature of the addition is put to good use in achieving the proper stereochemistry about the three-membered ring in natural products that contain a cyclopropyl ring. Examples of compounds synthesized in this manner are sirenin (3) (p. 370), (7-12)

aristolone (**7**), (45) thujopsene (**8**), (47), 62a longicyclene (**9**), (63, 64) and sesquicarene (**10**). (65-69)

In several applications the cyclopropyl ketone resulting from intramolecular cyclization of an olefinic ketocarbenoid is subsequently cleaved by hydrogenolysis, (70-75) protonolysis, (70, 72, 74, 76-78) lithium/ammonia reduction, (70, 74, 79) or Lewis-acid treatment. (80-83) The spiro sesquiterpenoids, α-chamigrene (11) (13) and epihinesol (12), (77, 84) as well as the tetracyclic diterpenes kaurene (13) (14) and phyllocladene (14), (14) have been synthesized in this manner.

This strategy involving intramolecular olefinic ketocarbenoid addition followed by regio- and stereospecific cleavage of one of the conjugated cyclopropane bonds has been applied to the synthesis of many compounds containing the bicyclo[3.2.1]octane (71, 72, 75, 76, 78, 79) and bicyclo[2.2.2]octane (76, 78) ring systems in addition to phyllocladene and kaurene. The two-step, intramolecular, angular-alkylation sequence takes on particular importance in that it has allowed the construction of skeletal analogs of the plant-growth-regulatory gibberellin diterpenes [*e.g.*, gibberellic acid (15)] and of the sesquiterpenoid helminthosporins [*e.g.*,

helminthosporic acid (**16**)] which possess gibberellin-like activity. Exemplary of this application are the tricyclic compounds **17** and **18**. (79)

An interesting application to the synthesis of bicylo[3.2.1]octane and bicylo[2.2.2]octane systems uses a retrograde Michael reaction to effect regiocontrolled cleavage of the cyclopropane. (78) The cyclopropane bond

15 **16**

17 **18**

cleaved in Eqs. 12 and 13 is the one that is activated by both carbonyl groups. Conceptually the sequence allows for intramolecular γ alkylation of an incipient α , β -unsaturated ketone.

(12)

(13)

The intramolecular olefinic ketocarbenoid addition reaction provided ready

access to a series of compounds which were used to demonstrate a Lewis-acid-catalyzed cleavage of an acylcyclopropane with simultaneous participation of a suitably situated olefinic or aromatic center, leading to ring formation. 80–83a Illustrative of this study, which also nicely demonstrates the stereospecificity of the internal diazoketone addition, (40) is the sequence shown in Eqs. 14 and 15. 83a

(14)

(15)

In another intramolecular addition of ketocarbenoids to unsaturated centers, bicyclo[5.3.0]decatrienones have been synthesized (85-87) and subsequently converted to azulenes. (87) The sequence outlined in Eq. 16 is representative. (87)

The unstable norcaradiene resulting from addition of the ketocarbenoid to the

1,2 position of the aromatic ring isomerizes by ring opening and subsequent 1,5-hydrogen shift to the trienone (**19**).

(16)

Finally, an interesting example has been reported involving the intramolecular addition of a ketocarbenoid to a furan ring. (88) The intermediate heterocyclic ring system thus formed undergoes ring opening to give the ketoaldehyde **20**.

3.2. Diazoester Additions to Olefins

The addition of alkoxycarbonyl carbenoids to internally situated olefinic sites has not been used as extensively as olefinic ketocarbenoid additions. However, the synthetic potential of this type of reaction is clear.

The decomposition of allyl diazoacetate is catalyzed by various copper reagents, and the bicyclic lactone (**21**) is formed in an optimium yield of 52%. (35) Similar applications provided syntheses of three bicyclic lactone esters in yields of 50–55%. (89, 90)

In an extension of this method to the construction of tetracyclic lactones such as **22** and **23** it was found that the intramolecular addition reaction is complicated by the formation of maleate and fumarate esters, formally carbene dimer products. (91) This type of behavior was also observed elsewhere, (35) implying that alkoxycarbonyl carbenoids are not as selective in their reactions as the analogous ketocarbenoids.

More recently it was found that the intramolecular addition reactions of carbenoids derived from mixed diazomalonates yielded lactones of 1-hydroxymethyl-7-carboxycycloheptatrienes. 92,93a

The copper-catalyzed decomposition of *trans, trans*-farnesyl diazoacetate **(24)** provided a stereoselective route to racemic presqualene alcohol through bicyclic lactone **25**. (94)

An interesting application has been made to the synthesis of a promising intermediate **26** for prostanoid synthesis. (95) The demonstration that cleavage of the cyclopropane can be achieved via homoconjugate addition of an organocopper (Gilman) reagent to compound **26** suggests a stereocontrolled route to prostaglandins.

Interest in certain cytotoxic natural products containing α-methylene-γ-butyrolactones prompted the sequence shown in Eq. 17. (96) A similar study led to the synthesis of spiro lactone **27** and spiro ketone **28**. (97)

(17)

The stereocontrolled generation of acyclic side chains of natural products (*e.g.*, steroids and prostaglandins) has recently been reported, (98-100) utilizing the nucleophilic ring opening of appropriately substituted acylcyclopropanes.

3.3. Diazocarbonyl Insertions into C-H Bonds

Although the majority of the synthetic intramolecular reactions of α -diazocarbonyl compounds have relied on conditions that supress insertion into C-H bonds in favor of intramolecular cycloaddition of the carbene or carbenoid to an olefinic moiety, many important and otherwise difficult synthetic transformations have been based on intramolecular C-H insertion of α -diazocarbonyl compounds.

Initial observation of intramolecular cyclization via such a C-H insertion reaction was made when 21-diazo-5 α -pregnan-20-one **(29)** was decomposed in refluxing toluene in the presence of copper(I) oxide. (41)

Several examples demonstrate that in geometrically rigid systems intramolecular C- H insertion is a highly favored process. Indicative of this is the study in which diazocamphor was catalytically decomposed to give cyclocamphanone **(30)** in high yield with no evidence of intermolecular addition or insertion products. (101) Contrast this with the behavior of 3-diazobicyclo[2.2.2]octan-2-one **(31)** which, upon copper-catalyzed decomposition in benzene, gives mainly the Wolff rearrangement product with only 5% formation of compound **32**. (102) Another illustration of geometrically favored intramolecular attack at an unactivated C- H bond is furnished by the 1-substituted adamantane derivative, which gives the tetracyclic ketone **33** in 70–80% yield. (103)

In some instances intramolecular C- H insertion has been observed when diazoketones are decomposed under Wolff rearrangement conditions. (104-107) For example, anomalous Wolff rearrangement products **34** and **35** are formed, *inter alia*, from the corresponding diazoketone. (104) Similarly, one of the products of the attempted Wolff rearrangement of diazoketone **36** is the C-H insertion product **37**, which was obtained in 22% yield. (105)

A general study of intramolecular C- H insertion reactions of diazoketones catalyzed by copper(II) sulfate in cyclohexane is summarized in Eq. 18. (105)

n	% yield A	% yield B
1	(−)	(−)
2	19	3
3	62	(−)
4	72	9

(18)

Several transannular C- H insertions have been reported in which monocyclic α-diazoketones are converted to cis-fused bicyclic ketones. (108)

Applications have also been made to functionalization of diterpenoids. The isopropyl group of dehydroabietic acid was functionalized by intramolecular C-H insertion of the C–12 diazomethyl ketone 38. (109) A partial synthesis of

the tetracyclic diterpene isohibaene **39** (p. 382) uses as the key step a regiospecific C- H ketocarbenoid insertion. (110) The observed insertion is toward the tertiary C_8- H bond, whereas insertion into the secondary C_{11}- H (axial) bond is not observed. The key step in the total

synthesis of atisine, veatchine, and gibberellin-A_{15} involves an intramolecular angular alkylation based on the regioselective and stereospecific intramolecular α -ketocarbenoid insertion reaction illustrated in Eq. 19. (111-113)

$$(19)$$

The intramolecular C- H insertion reactions of α -diazoamides have been shown to give fused and monocyclic β -lactams. (36, 37, 49-55) The initial demonstration of this type of reaction was made in the synthesis of methyl-6-phenylpenicillinate **(41)**. (49) The ease with which carbenes derived from α-diazo amides undergo intramolecular C-H insertion, in contrast to the

behavior of nonrigid alkoxycarbonyl carbenes, (38) has been attributed to a conformational effect of the planar amide bond forcing the C- H bond close to the divalent center. (36, 37) The photochemical decomposition of N,N-diethyldiazoacetamide gives the two possible intramolecular C-H insertion products unaccompanied by any intermolecular insertion products (Eq. 7). (36, 37) Further applications have been made to the synthesis of nuclear analogs of the penicillin-cephalosporin antibiotics leading to compounds **42**, (52, 53) **43**, (54) **44**, (54) and **45**. (55)

The copper-catalyzed decomposition of mixed diazomalonates has been used to prepare γ -butyrolactones. (39, 114) It was found that chlorobenzene is a superior solvent for intramolecular C-H insertions of this type.

3.4. Acid-Catalyzed Diazoketone Cyclizations

A facet of diazocarbonyl chemistry that was observed some 30 years ago (115, 116) and is continuing to generate a great deal of interest is the acid-catalyzed cyclization of diazomethyl ketones through π participation of suitably situated olefinic bonds or aromatic groups. (117-121) The reaction probably proceeds via initial protonation (Brönsted-acid catalysis) or complexing (Lewis-acid catalysis) of the diazocarbonyl functionality, followed by displacement of nitrogen from the resultant diazonium species by π -bond participation. (122) This method promises to be of great synthetic utility for carbocyclic ring annulation, as a single product is frequently obtained in essentially quantitative yield.

This method was applied to construct the skeleton of the sesquiterpene α -patchoulane. 118a The one-step, acid-catalyzed cyclization of diazomethyl ketone **46** proceeded under mild conditions to give two cyclization products, **47** and **48**. Other applications generate compounds containing the bicyclo[3.2.1]octane system by means of olefinic π -bond participation. (72, 119, 123-125) In this way intermediates are readily accessible for prospective total synthesis of a large class of tetracyclic diterpenoids. This use is illustrated by the preparation of compounds **49**, (119) **50**, (124) and **51**. (125)

Aromatic π -bond participation has also been applied to the generation of compounds containing the bicyclo [3.2.1] system. (119, 126, 127) Examples of this are the two diketones shown in the following reactions (126, 127):

A further application was made to the synthesis of norhelminthosporin analogs via **52** and **53**. (123)

Compound **54**, containing the bicyclo[2.2.2]octane ring system, has also been prepared in fair yield by this acid-catalyzed cyclization procedure. (120, 126)

It has been shown that angularly fused cyclobutanones are available through acid-catalyzed intramolecular C alkylation of ββ , γ-unsaturated α-diazomethyl ketones. (128)

Spirodienones and products derived from a dienonephenol rearrangement have also been prepared by acid-catalyzed cyclization of aromatic diazoketones. (122)

A synthesis of semibullvalene has been reported in which the key step is the acetolysis of 4-*endo*-diazoacetylbicyclo[3.1.0]hexene **(55)** to give the tricyclic ketoacetate. (129)

This acid-catalyzed cyclization method has been developed into a cyclopentenone annulation sequence. An example is the conversion of diazoketone **56** to the α , β -unsaturated cyclopentenone. (130)

Similarly, the cyclization of acyclic β , α-unsaturated diazoketones provided a synthesis of cyclopentenones, *e.g., cis*-jasmone. (131)

It has been proposed that the transformation of the type **56** **57** involves initial complexation of the Lewis acid to the carbonyl oxygen, producing an intermediate which can, in either a stepwise or concerted process, lose nitrogen and undergo a π cyclization. (121, 122, 130, 131) Appropriately functionalized diazoketones of this type have been demonstrated to undergo Lewis-acid-catalyzed polyene cyclization via internal trapping of the initially formed carbonium ion (Eq. 20). (121)

(20)

3.5. Miscellaneous

Among the reactions that do not fall into the preceding categories is the insertion of an α -carbonyl carbene or carbenoid into a C-C single bond to give an olefin (Eq. 21) 132a or a new ring (Eq. 22). (101)

(21)

(22)

The catalytic decomposition of bisdiazoketones has been shown to yield the 3,3′-spirobis(bicyclo[3.1.0]hexane) system. (133, 134)

(6:1)

There has been one report in which a vinylogous α-diazo ester was used for an intramolecular cyclopropanation reaction. (48) This reaction was applied to the following synthesis of sirenin:

Recently an example of a diazoester insertion reaction into an N-H bond employing rhodium catalysis has been reported. (135)

Copper(II)-catalyzed decomposition of penicillin-derived diazoketones in aprotic solvents has been shown to result in the formation of tricyclic ketones. (136)

Finally, the acid-catalyzed decomposition of *o*-substituted diazoacetophenones possessing an oxygen functionality at the *ortho* position leads to coumaranones in high yield. (137-139)

4. Experimental Procedures

4.1.1.1. Tricyclo[2.2.1.0^{2,6}]heptan-3-one (Nortricyclanone) (140)
A solution of crude 3-cyclopenten-1-yl diazomethylketone (from 23.9 g of the corresponding acid chloride) in 100 mL of tetrahydrofuran was added through a high-dilution head over a 4.5-hour period to a stirred slurry of 25 g of Cu powder in 700 mL of boiling tetrahydrofuran. The mixture was stirred at reflux for another 2 hours, filtered, dried over magnesium sulfate, and concentrated on a steam bath. Distillation of the residue under reduced pressure gave 12.9 g (65%) of nortricyclanone (bp 72–79°/29 mm), which was 95% pure by glpc analysis on a Carbowax 20 M column. Redistillation in a vacuum-jacketed

Vigreux column (3:1 reflux ratio) gave material with bp 75–77°/15 mm, n_D^{25}

1.4864, and a 2,4-dinitrophenylhydrazine derivative, mp 185–187° with decomposition.

4.1.1.2. Tricyclo[2.2.2.0^{2,6}]octan-3-one (104)
To a cold (5°) suspension of the anhydrous sodium salt from 3.77 g (30 mmol) of $\triangle$ ^{3}-cyclohexene-1-carboxylic acid in 30 mL of benzene containing 0.8 mL of pyridine was added, with stirring, 15 g (0.12 mol) of oxalyl chloride. The resulting mixture was stirred for 2 hours at 5°, filtered, and concentrated. The residue was dissolved in 30 mL of benzene. This solution of the crude acid chloride was added to a cold (0–5°) ethereal solution of 60 mmol of diazomethane. The solution was stirred for 2 hours at 0–5° and 12 hours at room temperature, then filtered, dried, and concentrated, leaving 4.88 g of the crude diazoketone as a yellow liquid.

To a suspension of 400 mg of copper bronze in 250 mL of refluxing cyclohexane was added dropwise over a 1-hour period 3.79 g (25 mmol) of the diazoketone in 50 mL of cyclohexane. After stirring at reflux for 24 hours the mixture was filtered and concentrated, leaving 2.95 g of yellow liquid, which upon short-path distillation gave 2.34 g of a yellow liquid (bp 120–130°/20–25 mm). Chromatography of this material on 60 g of Florisil (elution with ether-petroleum ether mixtures) followed by distillation gave 1.85 g of tricyclo[2.2.2.0^{2,6}]octan-3-one as a colorless liquid, bp

100–108°/17 mm, n_D^{25} 1.5086, which solidified on standing, mp 41–43°.

Short-path distillation (150°/25 mm) of the residue from the above distillation gave another 300 mg of product for a total yield of 2.15 g (57%).

4.1.1.3. Tetracyclo[3.3.1.0^{2,8}.0^{4,6}]nonan-3-one (Triasteranone) (141)
To a solution of *endo*-7-diazoacetyl- $\triangle$ ^{3}-norcarene (from 2.76 g of the corresponding acid) in 1.2 L of *n*-hexane was added 19.2 g of activated copper powder. The suspension was refluxed for 12 hours, filtered, concentrated to a

volume of 100 mL, and shaken with 150 mL of water. The water phase was washed with 100 mL of *n*-hexane and then with four portions (100 mL each) of chloroform. The combined organic layers were dried over sodium sulfate, and the solvent was removed under reduced pressure, yielding 1.73 g of crude triasteranone. Recrystallization from *n*-hexane and sublimation at 60°/1 mm gave 1.21 g (45%) of pure product, mp 74.5°; infrared (carbon tetrachloride) cm^{-1}: 1672 (C=O).

4.1.1.4. 8-Tetracyclo[4.3.0.0^{2,4}.0^{3,7}]nonen-5-one (*142*)
A solution of 7-diazoacetylnorbornadiene (870 mg) in 10 mL of dry tetrahydrofuran was added slowly to a stirred suspension of copper powder in 20 mL of refluxing tetrahydrofuran. The mixture was heated at reflux for 1.8 hours, then set aside at room temperature overnight. The catalyst was filtered, and approximately 1 mL of water was added to the filtrate. After a few minutes the solution was diluted with ether, extracted with water and saturated aqueous sodium bicarbonate solution, and then dried and evaporated. This procedure removed two impurities observed in the glpc analysis of the crude product. Further purification was effected by passage through a column of 15 g of silica gel (elution with 25% ether–pentane), giving 577 mg (54%) of pure cyclopropyl ketone as a colorless, clear liquid; infrared (film) cm^{-1}: 1764, 1750 (C=O).

4.1.1.5. 1,5,6-Triphenyltricyclo[3.1.0.0^{2,6}]hexan-3-one (*143*)
In a dry, three-necked flask equipped with a reflux condenser, dropping funnel, and a nitrogen inlet tube were placed 30 mL of benzene and 0.9 g of copper powder. The mixture was heated to reflux. A solution of 1-(1,2,3-triphenylcycloprop-2-enyl)-3-diazopropan-2-one (0.992 g) in 30 mL of benzene was added dropwise over a 10-minute period, and the mixture was refluxed for 1 hour, cooled, filtered, and concentrated. Chromatography with benzene on Fisher alumina (80–120 mesh) gave two fractions: 0.51 g (57%) with mp 155.5–156° and 0.068 g (7%) with mp 148–156°. Recrystallization from ethyl acetate provided an analytical sample, mp 155–157°; infrared (KBr) cm^{-1}: 1750 (C=O).

4.1.1.6. Tricyclo[3.3.1.0^{2,8}]nona-3,6-dien-9-one (Barbaralone) (*2*)
Cycloheptatrien-7-yl diazomethyl ketone (from 14 g of the acid chloride) was dissolved in 80 mL of anhydrous benzene and 80 mL of dry hexane. This solution was divided into two equal parts, and each was added dropwise over a 45-minute period to a vigorously stirred, boiling suspension of 16 g of anhydrous cupric sulfate in 160 mL of *n*-hexane under nitrogen. The mixture was refluxed for an additional hour. The supernatant liquid was decanted, and the residue was washed with acetone. The solutions were combined, concentrated to about 80 mL by distillation through a Vigreux column, and steam distilled. The distillate was extracted with three 100-mL portions of ether, and the ethereal extracts were dried over magnesium sulfate, concentrated to

50 mL, and cooled to –70°. The crystals were collected by filtration at –70°. Recrystallization from 30 mL of pentane at –70° and again at –10 to –20° followed by vacuum sublimation gave 1.6–3.5 g of barbaralone, mp 40–48°. Recrystallization from water gave colorless needles, mp 53.5°; oxime, mp 130–131°; thiosemicarbazone, mp 165°; semicarbazone, mp 205–207° (dec).

4.1.1.7. 7-endo-Methyl-7-(4-methyl-3-pentenyl)bicyclo[4.1.0]heptan-2-one (11)
trans-6,10-Dimethyl-5,9-decadienyl diazomethyl ketone obtained from 2.1 g of the corresponding acid was dissolved in 1.1 mL of dry cyclohexane containing 3.0 g of anhydrous copper sulfate and refluxed for 2 hours with stirring. The mixture was then filtered and the cyclohexane removed under reduced pressure. The residue was dissolved in ether, washed with aqueous sodium bicarbonate and aqueous sodium chloride solutions, dried, and the ether was evaporated. Chromatography on 250 g of silica gel (elution with benzene, benzene–ethyl acetate mixtures) gave 1.35 g (66%) of 7-*endo*-methyl-7-(4-methyl-3-pentenyl)bicyclo[4.1.0]heptan-2-one; infrared (film) cm^{-1}: 1685 (C=O). A gas chromatogram (5% Carbowax 20 M, 10 ft × 0.25 in., 165°) of the oil gave one major peak with a retention time of 14 min (60 mL/min, He).

4.1.1.8. 1-Carbethoxy-3-oxa-6,6-dimethylbicyclo[3.1.0]hexan-2-one (89)
To a cold (0–5°) solution of 10 g (0.05 mol) of ethyl 3-methyl-2-butenyl malonate in ether (approximately 60 mL) containing 9.8 g of tosyl azide was added dropwise 5 mL of diethylamine. After the addition was complete, the mixture was stirred for 15 minutes at 0° and 2 hours at ambient temperature. Addition of approximately 200 mL of pentane, followed by filtration, removed the tosyl azide. The filtrate was dried over sodium sulfate and concentrated to give 11 g of the diazomalonate.

The crude diazomalonate (11 g) was dissolved in 700 mL of octane and added dropwise to a suspension of 20 g of copper powder in 300 mL of octane at reflux. After 3 hours at reflux the suspension was filtered, and the solvent was removed by distillation, leaving 5 g (50%) of 1-carbethoxy-3-oxa-6,6-dimethyltricyclo[3.1.0]hexan-2-one, bp 100–105° (0.5 mm); $n_D^{22} = 1.4670$; infrared (film) cm^{-1}: 1785, 1735 (C=O).

4.1.1.9. 3-Hydroxytricyclo[4.4.1.0]undecylcarboxylic Acid Lactone (91)
A cold (0°) solution of 1.01 g (3.89 mmol) of the acid chloride of the *p*-toluene sulfonylhydrazone of glyoxylic acid in 10 mL of methylene chloride was treated successively with 577 mg (3.79 mmol) of $\triangle$ $^{9(10)}$ -2-octalol and with a solution of 397 mg (3.95 mmol) of triethylamine in 2 mL of methylene chloride, and was then stirred for 30 minutes at room temperature. After a second 404-mg (3.98-mmol) portion of triethylamine was added, the mixture was stirred for 1 hour at room temperature and then concentrated under reduced pressure. A

solution of the residue in benzene was filtered through a 12-g column of Florisil to give 783 mg (89%) of the crude diazo ester. A solution of this material in hexane, when cooled to dry-ice temperatures, deposited the diazoester as yellow prisms, mp 29–32°; infrared (carbon tetrachloride) cm^{-1}: 2100 (C=N=N), 1700 (C=O); ultraviolet (*n*-hexane), nm max(ε): 217 (8100), 245 (12, 700).

A solution of 2.2 g (10 mmol) of the diazo ester in 125 mL of cyclohexane was added to a suspension of 3.1 g of cuprous oxide in 125 mL of cyclohexane over a 12.5-hour period. Filtration and concentration of the filtrate gave 2.58 g of crude product, which was chromatographed on Florisil. The early fractions (eluted with 5% ether in hexane) were followed by fractions eluted with 50% ether in hexane, affording 434 mg of material containing the lactone. Repetition of the chromatography and crystallization from an ether–hexane mixture gave the pure lactone as white needles, mp 54–55.5°; infrared (carbon tetrachloride): 1735 (C =O), 1715 (shoulder).

4.1.1.10. Adamantocyclopentan-2-one (*103*)
A solution of 1-(adamantan-1-yl)-3-diazopropan-2-one (3.8 g) in 100 mL of dry toluene was added dropwise during 5–6 hours to 400 mL of refluxing dry toluene containing 0.8 g of cupric sulfate. The mixture was refluxed for an additional 2 hours, filtered, and washed with water, 5 *N* sodium hydroxide solution, and again with water. The organic layer was dried over sodium sulfate and evaporated under reduced pressure, yielding approximately 2.8 g of a thick, light-brown oil. Glpc analysis of this oil showed a main peak consisting of 70–80% of the desired material. This peak was collected by preparative glc (6 ft × 0.25 in. glass column, 3% JRX, temperature programmed from 60 to 200°,6°/min) and concentrated to give crystalline adamantocyclopentan-2-one; mp 74–76°; semicarbazone, mp 234–236°.

4.1.1.11. 1,4,5,6,7,7,a-Hexahydro-(2 H)-inden-2-one (*144*)
A rapidly stirred solution containing 390 mg (2.38 mmol) of the α -diazoketone derived from 1-cyclohexeneacetic acid and 50 mL of dry nitromethane (distilled and stored over 4-Å molecular sieves) was treated dropwise with 355 μL (1.2 eq) of boron trifluoride etherate. After the evolution of nitrogen had ceased (» 10 min), 20 mL of 10% (v/v) aqueous hydrochloric acid was then added, and the resulting mixture was heated at reflux under nitrogen for 1 hour, cooled, and added to a 1 : 1 mixture of brine and ethyl acetate. The organic phase was then separated, washed with 5% (w/v) aqueous sodium bicarbonate solution, water, brine, and dried over anhydrous magnesium sulfate. Removal of the solvent under vacuum yielded 340 mg of an oil which contained 162 mg (50%) of the title enone. An analytical sample obtained by glpc (10 ft × 0.375 in. 25% Carbowax 20 M, column temperature 205°C) gave the following spectral data: infrared (carbon tetrachloride) cm^{-1}: 1715(C=O),1630(C=C).

5. Tabular Survey

The five tables that follow contain reported examples of reactions discussed in this chapter. Tables I and II list examples of the intramolecular addition of diazoketones and diazoesters to olefins, respectively, and Table III lists examples of the intramolecular insertion of diazocarbonyl compounds into C-H bonds. Table IV deals with the acid-catalyzed cyclization of diazoketones. Table V lists miscellaneous reactions of diazocarbonyl compounds.

The examples are arranged in the tables according to increasing carbon number. Products appearing in brackets represent initial cyclopropane adducts that were not isolated. Throughout all the tables the reaction conditions, when available, have been summarized. Product ratios and/or percentage yields are recorded; a dash indicates that no yield was given in the reference.

The literature has been reviewed through December 1977.

Table I. Intramolecular Addition of Diazoketones to Olefins

View PDF

Table II. Intramolecular Addition of Diazoesters to Olefins

View PDF

Table III. Intramolecular Insertion of Diazocarbonyl Compounds into C -H Bonds

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Table IV. Acid-Catalyzed Cyclizations of Diazoketones

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Table V. Miscellaneous Reactions

[View PDF](#)

TABLE I. Intramolecular Addition of Diazoketones to Olefins

Reactant	Conditions	Product(s)	Yield (%)	Refs.
C₆	CuSO₄, cyclohexane, reflux		59	56
C₇	Cu powder, tetrahydrofuran, reflux		65	140
	Cu powder, hexane, reflux		(ca. 1)	44
	Cu bronze, cyclohexane, reflux		(ca. 50)	1
	CuSO₄, cyclohexane, reflux	,,	37	56
	Cu powder, cyclohexane, reflux		—	158
	CuSO₄, cyclohexane, reflux	,,	30	159
	CuSO₄, cyclohexane, reflux		30	159
	Cu catalyst		—	160
C₈	Tetrahydrofuran, hν		Major	161
	Cu powder, benzene	,,	30	162
	CuSO₄, cyclohexane, reflux	CHO	60	88
	CuSO₄, benzene, reflux	COCH₃	37	145
	Cu powder, hexane, reflux		31	140
	Cu bronze, cyclohexane, reflux	,,	57	104
	CuCl, cyclohexane, reflux	,,	53	163
	CuSO₄, cyclohexane, reflux		53	164

TABLE I. INTRAMOLECULAR ADDITION OF DIAZOKETONES TO OLEFINS (*Continued*)

Reactant	Conditions	Product(s)	Yield (%)	Refs.
C₈ (*Contd.*)				
	''	''	67	159
	''		31	164
	CuSO₄, cyclohexane, reflux		41	164
	Cu(acetylacetonate)₂		—	57
	Cu(acetylacetonate)₂		—	57
	CuSO₄, cyclohexane, reflux		*ca.* 3	56
	Cu powder, cyclohexane, reflux		—	158, 165
	CuSO₄, cyclohexane, reflux	''	—	159
	Cu powder, cyclohexane, reflux		—	158
	CuSO₄, cyclohexane, reflux	''	—	158
	Cu powder, cyclohexane, reflux		35–42	167, 168
C₉				
	CuSO₄		—	166
	CuSO₄, benzene–hexane (1:3), reflux		—	2

TABLE I.   INTRAMOLECULAR ADDITION OF DIAZOKETONES TO OLEFINS (*Continued*)

Reactant	Conditions	Product(s)	Yield (%)	Refs.
C₉ (*Contd.*)	Cu powder, tetrahydrofuran, reflux		54	142, 169
	Cu powder, tetrahydrofuran, reflux		—	170
	Cu powder, hexane, reflux		45	171, 141
	CuSO₄, cyclohexane, reflux		38	172
	CuSO₄, dioxane, reflux	"	38	73
	CuSO₄, cyclohexane, reflux		37	159
	CuSO₄, hexane, reflux	"	39	140
	Di-μ-dichloro-π-allylpalladium, benzene	(53) + (3)		146a
	Pd(OAc)₂, benzene	" + " (<1)		146a
	Bis(benzoylacetonato)palladium benzene, 80°	" + " (<1)		146a
	Bis(benzoylacetonato)copper, benzene, 80°	" (50) + " (13)		146a
	(C₂H₅O)₃P·CuCl, benzene	" (3) + " (32)		146a
	(CH₃O)₃P·CuI, benzene	" (3) + " (35)		146a
	Rh₂(OAc)₄, benzene	" (1) + " (58)		146a
	Benzene, 80°	" (15) + " (54)		146a
	Cu₂I₂, tetrahydrofuran		—	146b

TABLE I. INTRAMOLECULAR ADDITION OF DIAZOKETONES TO OLEFINS (*Continued*)

Reactant	Conditions	Product(s)	Yield (%)	Refs.
C₉ (*Contd.*)				
	CuCl, cyclohexane, reflux		50	163
	CuSO₄, hexane, reflux	"	55	140
	Cu powder, hexane, reflux	"	47	140
	CuI, hexane or acetontrile–hexane (1:1), reflux	"	—	140
	CuSO₄, cyclohexane, reflux		—	173
	CuSO₄, cyclohexane, methanol, reflux		—	59
	Cu powder, hexane, reflux		47	174
	Cu powder, hexane, reflux		—	175
	Cu powder, CuSO₄, cyclohexane, reflux		44	176
	Cu, CuSO₄, cyclohexane, reflux		38	177
	CuSO₄, cyclohexane, reflux	"	—	6
	Cu bronze, cyclohexane, reflux	"	—	160
	Cu powder, cyclohexane, reflux	(2:3)	70	167, 168

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TABLE I.   INTRAMOLECULAR ADDITION OF DIAZOKETONES TO OLEFINS (*Continued*)

Reactant	Conditions	Product(s)	Yield (%)	Refs.
	CuSO₄, benzene, reflux		41.5	56
	Cu powder, decalin, reflux		15, 20	85, 178
	CuCl, benzene, reflux		40–50	87
	Cu bronze, cyclohexane or heptane, reflux		5	179
	Cu powder, tetrahydrofuran, reflux		38	2
	CuSO₄, tetrahydrofuran, reflux		27	180, 181
	Cu bronze, cyclohexane, reflux		78	3, 182
	CuSO₄, dioxane, reflux		61	73
	CuSO₄, tetrahydrofuran, reflux		—	183
	Cu powder, cyclohexane, reflux		76	85, 178
	CuSO₄, hexane, reflux		47	140

TABLE I. INTRAMOLECULAR ADDITION OF DIAZOKETONES TO OLEFINS (*Continued*)

Reactant	Conditions	Product(s)	Yield (%)	Refs.
C₁₀ (*Contd.*)	CuSO₄, hexane, reflux		36	140, 159
	CuSO₄, cyclohexane, methanol, reflux		—	59
	Cu powder, CuSO₄, cyclohexane, reflux		28	176
	Cu dust, cyclohexane, reflux	''	58	45
	Cu powder, cyclohexane, reflux		70	167, 184
	Cu bronze, cyclohexane, reflux		—	147
	CuSO₄ or Cu(acetylacetonate)₂, cyclohexane, reflux	(24) + (35)		60a
	CuCl, tetrahydrofuran (0.3 *M*), 4.5 hr		61	60b
	CuCl, tetrahydrofuran (0.16 *M*), 4.5 hr	''	79	60b
	CuCl, benzene (0.16 *M*), 5.5 hr	''	80	60b
	CuI, benzene (0.16 *M*), 5.5 hr	''	55	60b
	CuCl, benzene, 20 min	(34) + (8)		60b
C₁₁	Cu bronze, benzene, 80°		43	185

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TABLE I. Intramolecular Addition of Diazoketones to Olefins (*Continued*)

Reactant	Conditions	Product(s)	Yield (%)	Refs.
C₁₁ (*Contd.*)	CuCl, benzene, reflux		—	87
	CuCl, tetrahydrofuran (0.16 *M*), 2 hr		60	60b
	CuCl, benzene (0.16 *M*), 2 hr		90	60b
	Cu bronze, cyclohexane, reflux		41	104
	Cu bronze, cyclohexane, reflux		43	186
	CuSO₄, dioxane, reflux		50	73
	CuSO₄, tetrahydrofuran, reflux		51	188
	Cu powder, cyclohexane, reflux		55	189
	CH₃OH, *hv*,		10–15	42, 43
	CuSO₄, cyclohexane, CH₃OH, reflux		—	59
	CuSO₄, benzene, reflux		15	149

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TABLE I. INTRAMOLECULAR ADDITION OF DIAZOKETONES TO OLEFINS (*Continued*)

Reactant	Conditions	Product(s)	Yield (%)	Refs.
C₁₁ (*Contd.*)				
	CuSO₄ or Cu(acetylacetonate)₂, cyclohexane, 1% CH₃OH, reflux		60	60
	Cu bronze, cyclohexane, reflux		—	147
	CuSO₄, hexane, reflux		57	187
	Cu powder, cyclohexane, reflux		29	56
	Cu bronze, cyclohexane, reflux	"	47	190
	CuSO₄, cyclohexane, reflux	"	35	190
	Cu powder, tetrahydrofuran, reflux		—	191
	Cu catalysis		65	118a
	Cu, tetrahydrofuran, reflux		73	118b
C₁₂				
	Di-μ-dichloro-π-allylpalladium, (C₂H₅)₂O, low temperature		*ca.* 15	134
	CuSO₄, cyclohexane, reflux		59	56

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TABLE I. INTRAMOLECULAR ADDITION OF DIAZOKETONES TO OLEFINS (*Continued*)

Reactant	Conditions	Product(s)	Yield (%)	Refs.
C_{12} (*Contd*)				
	n-Decane, 174°, 10 min		34	151a
	Cu, reflux		—	118b
			64	29
	Cu powder, cyclohexane, reflux		42	86, 178
	PdCl/2, ether		—	192
	Cu bronze, cyclohexane, reflux		—	80
	"		80	81, 160
	Cu bronze, cyclohexane, reflux		—	82
	Cu, cyclohexane, reflux	(9:1)	44	84
	Cu powder, cyclohexane, reflux		97	123

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TABLE I. INTRAMOLECULAR ADDITION OF DIAZOKETONES TO OLEFINS (*Continued*)

Reactant	Conditions	Product(s)	Yield (%)	Refs.
C₁₂ (*Contd.*)	Cu powder, cyclohexane, reflux		85	86, 178
	Cu powder, cyclohexane, reflux		48	193
C₁₃	CuSO₄, cyclohexane, reflux		30	56
	PdCl/2, ether		—	192
	CuSO₄ or Cu(acetylacetonate)₂, cyclohexane, 1% CH₃OH, reflux		60a
C₁₄	Cu		—	194
	Activated Cu₂O, cyclohexane, reflux		80	152
	Activated Cu₂O, cyclohexane, reflux	"	70	152
	CuSO₄, cyclohexane, reflux	"	57	152
	Cu		—	194
	Cu powder, cyclohexane, reflux		22	56

TABLE I. Intramolecular Addition of Diazoketones to Olefins (*Continued*)

Reactant	Conditions	Product(s)	Yield (%)	Refs.
C₁₄				
(*Contd.*)				
	Cu bronze, cyclohexane, reflux		23	70
	Cu bronze, cyclohexane, reflux	"	40	74
	CuSO₄, toluene, reflux	23 + 21		149
	n-Decane, 174°, 10 min		44	151a
	n-Decane, 174°, 10 min		10	151
	Cu catalysis		—	62a
	Cu powder, CuSO₄, cyclohexane, reflux		47	62b
	Activated CuO, cyclohexane or cyclohexane/tetra-hydrofuran (7:3), *hv*		80	75
	CuSO₄, cyclohexane, reflux		(Very low)	56
	Cu bronze, benzene		80	195
	CuSO₄	+		196

TABLE I. INTRAMOLECULAR ADDITION OF DIAZOKETONES TO OLEFINS (*Continued*)

Reactant	Conditions	Product(s)	Yield (%)	Refs.
C₁₄ *(Contd.)*	Cu bronze, cyclohexane, reflux		50	179
	Cu powder, cyclohexane, reflux		78	78
	Cu₂O, cyclohexane, reflux	"	(Trace)	78
	CuSO₄, cyclohexane, reflux	"	(45–50)	78
	Cu powder, cyclohexane, reflux		62	78
	Cu powder, cyclohexane, reflux		74	78
	Cu₂O, cyclohexane, reflux	"	(Traces)	78
	CuSO₄, cyclohexane, reflux	"	(45–50)	76, 78
	Cu powder, cyclohexane, reflux		42	78
	CuSO₄, cyclohexane, reflux	"	—	76
	CuSO₄, cyclohexane, reflux		60	61
	CuSO₄, cyclohexane, reflux	(2:1)	—	197
	1. CuSO₄, cyclohexane, reflux 2. NaOH, CH₃OH, heat	" + "	15	198

TABLE I. INTRAMOLECULAR ADDITION OF DIAZOKETONES TO OLEFINS (*Continued*)

Reactant	Conditions	Product(s)	Yield (%)	Refs.
C$_{14}$ (*Contd.*)	Cu, benzene	(1:9)	40	77
	Cu, cyclohexane, reflux	" + "	31	84
	Cu		16	118
	PdCl/2, ether		25	192
	CuSO$_4$, cyclohexane, reflux		66	7, 11, 65
	Cu bronze, cyclohexane, reflux	"	55	8
	CuSO$_4$, cyclohexane, reflux		65	11
	Cu powder, CuSO$_4$, cyclohexane, reflux	(2:1)	84	10, 12
	CuSO$_4$, cyclohexane, reflux	(3:5)	78	199
	Cu powder, cyclohexane, reflux	" (1:1)	24	200
	CuSO$_4$, cyclohexane, reflux		High	201
	CuSO$_4$, n-hexane, reflux		—	202

TABLE I. INTRAMOLECULAR ADDITION OF DIAZOKETONES TO OLEFINS (*Continued*)

Reactant	Conditions	Product(s)	Yield (%)	Refs.
C$_{14}$ (*Contd.*)	CuSO$_4$, Cu powder, cyclohexane, reflux		42.5	47
C$_{15}$	Activated CuO, cyclohexane or cyclohexane–tetrahydrofuran, (7:3), hν	C$_6$H$_5$	88	75
	Cu bronze, cyclohexane, reflux		40	70, 74
	CuSO$_4$, cyclohexane, reflux	(30) + (15)		46
	CuSO$_4$, cyclohexane, reflux	C$_3$H$_7$-*i*	8	203
	Cu powder, tetrahydrofuran, reflux		33	63, 64
	Cu powder, tetrahydrofuran	(1:1)	54	67, 68
	CuSO$_4$, cyclohexane, reflux	''	10	69
C$_6$H$_5$	Activated Cu$_2$O, cyclohexane, hν, reflux	C$_6$H$_5$	88	152
p-CH$_3$OC$_6$H$_4$	Activated Cu$_2$O, cyclohexane/ tetrahydrofuran (3:1), hν, reflux	*p*-CH$_3$OC$_6$H$_4$	80	152
SO$_2$C$_6$H$_5$	Cu, 80°, 10 hr, *n*-heptane	SO$_2$C$_6$H$_5$	14	151a
	Cu, 174°, 10 min, *n*-decane	''	19	151a
	Cu, 174°, 10 min, *n*-decane	''	21	151a
	Cu(acetylacetonate)$_2$, 174°	''	22	151a

TABLE I. INTRAMOLECULAR ADDITION OF DIAZOKETONES TO OLEFINS (*Continued*)

Reactant	Conditions	Product(s)	Yield (%)	Refs.
C₁₅ (*Contd.*) OSO₂C₆H₄CH₃-*p* COCHN₂	Cu(acetylacetonate)₂	OSO₂C₆H₄CH₃-*p*	54	151b
i-C₃H₇ COCHN₂	Cu powder, cyclohexane, reflux	*i*-C₃H₇	38	153
CHN₂	Cu powder, CuSO₄, cyclohexane, reflux	+ (2.4:1)	59	12, 66
i-C₃H₇(CH₂)₃ CHN₂	Cu powder, CuSO₄, cyclohexane, reflux	(CH₃)₂CH(CH₂)₃ + (CH₂)₃C₃H₇-*i* (1:1)	—	176
C₁₆ C₆H₅ CHN₂	CuCl, cyclohexane	C₆H₅	>70	204
O O (diazo N₂)	Bis(N-*n*-propylsalicylidene-aminate) Cu(II), cyclohexane, 75–80°	O O	45	13
p-CH₃OC₆H₄ COCHN₂	Activated Cu₂O, cyclohexane tetrahydrofuran (3:1), *hν*, reflux	*p*-CH₃OC₆H₄	87	152
CH₃O CHN₂	CuSO₄, tetrahydrofuran, reflux	CH₃O	27	72
	Cu bronze, cyclohexane, reflux	"	24	72
	Activated CuO, cyclohexane or cyclohexane : tetrahydrofuran (7:3), *hν*	"	50	75
	Cu bronze	"	—	71

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TABLE I. INTRAMOLECULAR ADDITION OF DIAZOKETONES TO OLEFINS (*Continued*)

Reactant	Conditions	Product(s)	Yield (%)	Refs.
C₁₆ (*Contd.*)				
	Activated Cu₂O, *hν*, cyclohexane : tetrahydrofuran		—	154
	Cu bronze, cyclohexane, reflux		51	71, 72
	Activated CuO, cyclohexane or cyclohexane–tetrahydrofuran (7:3), *hν*		59	75
	CuSO₄, *n*-hexane, reflux		65	205
	Cu bronze, cyclohexane, reflux		—	83a
	Cu bronze, cyclohexane, reflux		—	83a
	Cu, benzene, reflux		61	83b
	Cu, benzene, reflux		40	83b
C₁₇				
	Tetrahydrofuran, *hν*		10–15	42, 43

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TABLE I. INTRAMOLECULAR ADDITION OF DIAZOKETONES TO OLEFINS (*Continued*)

Reactant	Conditions	Product(s)	Yield (%)	Refs.
C₁₇ (*Contd.*)				
	CuCl, cyclohexane, reflux or Cu powder, benzene, reflux		30	206
	CuSO₄, benzene, reflux		44	149
	Cu		—	4
	Cu bronze, cyclohexane, reflux		—	58
	Cu, cyclohexane, reflux		*ca.* 50	5
	Activated CuO, cyclohexane or cyclohexane : tetrahydrofuran (7:3), *hv*		63	75
	Activated CuO, cyclohexane or cyclohexane : tetrahydrofuran (7:3), *hv*		76	75
	Activated CuO, cyclohexane or cyclohexane : tetrahydrofuran (7:3), *hv*		72	75
	Cu bronze, cyclohexane, reflux	''	41	72
	Cu bronze, cyclohexane, reflux		35	74
C₁₈				
	Cu		—	207

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TABLE I. INTRAMOLECULAR ADDITION OF DIAZOKETONES TO OLEFINS (*Continued*)

Reactant	Conditions	Product(s)	Yield (%)	Refs.
C$_{18}$ (*Contd.*)				
			15	208
	Activated Cu$_2$O, cyclohexane: tetrahydrofuran, *hv*		50	155
	Activated CuO, cyclohexane or cyclohexane: tetrahydrofuran (7:3), *hv*		87	75
	Cu bronze, cyclohexane, reflux	"	55	72
	Cu powder, benzene, reflux		—	209
	CuSO$_4$, cyclohexane, reflux		—	14
C$_{21}$				
	Cu powder, cyclohexane, reflux		46	156
C$_{24}$				
	Cu powder, benzene, reflux		57	143, 210
	CuSO$_4$, cyclohexane, reflux		58	a

TABLE I. INTRAMOLECULAR ADDITION OF DIAZOKETONES TO OLEFINS (*Continued*)

Reactant	Conditions	Product(s)	Yield (%)	Refs.
C$_{25}$				
	Cu powder, reflux		42	157
C$_{27}$				
	Cu powder, cyclohexane, reflux		37	156

Note: References 145–230 are on pp. 474–475.

TABLE II. INTRAMOLECULAR ADDITION OF DIAZOESTERS TO OLEFINS

Reactant	Conditions	Product(s)	Yield (%)	Refs.
C₅	CuSO₄, cyclohexane, reflux		37	35
	CuCl₂, cyclohexane, reflux	"	34	35
	CuCl, cyclohexane, reflux	"	28	35
	Cu powder, cyclohexane, reflux	"	38	35
			42	29
	Cu powder, n-octane, reflux		50	89, 90
	Cu dust, benzene, reflux	"	40–70	211
C₆	Cu dust, benzene, reflux		30	211
	Cu₂O, cyclohexane, reflux		39	91

TABLE II.   Intramolecular Addition of Diazoesters to Olefins (*Continued*)

Reactant	Conditions	Product(s)	Yield (%)	Refs.
C₇				
	Cu powder, *n*-octane, reflux		30	89, 90
	Cu or CuBr		50	89, 90
	Cu powder, *n*-octane, reflux		50	89, 90
C₈				
	Cu powder, *n*-octane, reflux		55	89
	CuSO₄, benzene, reflux		69	145
C₉				
	Cu powder, *n*-octane, reflux		30	89, 90
	Cu powder, *n*-octane, reflux		—	89
	CuSO₄, benzene, reflux		58	150
	CuSO₄, benzene, reflux		60	150
C₁₀				
	(CH₃O)₃P·CuI, benzene, reflux		65	95, 96

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TABLE II. INTRAMOLECULAR ADDITION OF DIAZOESTERS TO OLEFINS (*Continued*)

Reactant	Conditions	Product(s)	Yield (%)	Refs.
C₁₀ (*Contd.*)				
	Cu powder, *n*-octane, reflux		50	89
	Cu powder, *n*-octane, reflux		50	89
C₁₁				
	Cu powder, *n*-octane, reflux, or benzene, 130°		20	92, 93
	Cu, *n*-octane, reflux		67	212
	Cu, *n*-octane, reflux		52	212
	CuSO₄, benzene, reflux		64	150
	Cu₂O, cyclohexane, reflux		21	91
C₁₂				
	Cu powder, *n*-octane, reflux		19	92, 93a
	Cu(>10 eq), cyclohexane, reflux		27	148
	Cu₂O(>10 eq),	"	33	148
	Cu(acac)₂ (>10 eq), toluene, reflux	"	22	148
	Cu(acac)₂ (<0.1 eq), toluene, reflux	"	76	148

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TABLE II. INTRAMOLECULAR ADDITION OF DIAZOESTERS TO OLEFINS (*Continued*)

Reactant	Conditions	Product(s)	Yield (%)	Refs.
C$_{12}$ (*Contd.*)				
	Cu powder, *n*-octane, reflux		60	92, 93a
	Cu$_2$O, cyclohexane, reflux		<23	91, 211
	(CH$_3$O)$_3$P·CuI, toluene, reflux		72	97
	(CH$_3$O)$_3$P·CuI, toluene, reflux		70	97
C$_{13}$				
	Cu, Cu$_2$O, CuSO$_4$, toluene, reflux		—	213
	Cu powder, octane, reflux		45	92, 93a
	Cu(acetylacetonate)$_2$, toluene, reflux		71	93b
C$_{14}$				
	Cu powder, xylene, reflux		50	95

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TABLE II. INTRAMOLECULAR ADDITION OF DIAZOESTERS TO OLEFINS (*Continued*)

Reactant	Conditions	Product(s)	Yield (%)	Refs.
C₁₄	Cu bronze, toluene, reflux		73–80	98
C₁₅	Cu(acetylacetonate)₂, benzene, reflux		63	100
C₁₆	Cu bronze, toluene, reflux		50	99
C₁₇	Cu (>10 eq) or Cu(acac)₂(>10 eq), toluene, reflux		20	94, 148
	Cu(acac)₂(<0.1 eq), toluene, reflux	"	71	148
C₁₈	Cu bronze, toluene, reflux		65	214a
	Cu bronze, toluene, reflux		81	214a
C₂₆	Cu bronze, toluene, reflux			214b

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Note: References 145–230 are on pp. 474–475.

Reactant	Conditions	Product(s)	Yield (%)	Refs.
C₆				
(C₂H₅)₂NCOCHN₂	Dioxane, *hν*	(43) + (57)		35, 36
	Methanol, *hν*	„ (5) + „ (43)		35, 36
	Cyclopentane, *hν*	„ (47) + „ (53)		36
	Ethyl acetate, *hν*	„ (37) + „ (63)		36
	Methylene chloride, *hν*	„ (38) + „ (62)		36
	Acetone, *hν*	„ (40) + „ (60)		36
	Acetonitrile, *hν*	„ (31) + „ (69)		36
	Cyclopentane–methanol (9:1), *hν*	„ (19) + „ (81)		36
	Dioxane, LiBr (1%), *hν*	„ (34) + „ (66)		36
	Acetone, LiBr (3.5%), *hν*	„ (13) + „ (87)		36
	Cyclohexane, *hν*		(ca. 4)	37
C₇				
	Cu powder, benzene, reflux	(60)		85
	CuSO₄, cyclohexane, reflux		—	105
	C_6H_5 C_6H_5, cyclohexane, *hν*		—	215
	CH₂Cl₂, *hν*		—	50
	Cyclohexane, *hν*	(<2) + (<2)		38
C₈				
	Cu powder, benzene, reflux		5	102
	Dioxane, *hν*		23	37
	Petroleum ether (60–90°), CuO, heat		31	108

Reactant	Conditions	Product(s)	Yield (%)	Refs.
C₈ (*Contd.*)				
	CuSO₄, cyclohexane, reflux	(19) + (3)		105
	Cu powder or Cu salts, benzene, reflux		14–30	39
	Cu powder or Cu salts, chlorobenzene, reflux	"	62	39
	Freon, tetrahydrofuran, *hν*	"	Trace	114
	CCl₄, *hν*	"	Trace	114
	Benzene, 140°	"	4	114
	Cu, *n*-octane, 120°	"	Trace	114
	CuCN, benzene, 140°	"	14	114
	Cu, benzene, 140°	"	30	114
	Cu, chlorobenzene, 131°	"	62	114
	CuSO₄, chlorobenzene, reflux		11	39
	Cu powder, chlorobenzene, reflux	"	11	114
	CCl₄, *hν*	"	10	114
	Cyclopentane, *hν*		35	132a
C₉				
	CCl₄, *hν*		—	51
	Silver benzoate, (C₂H₅)₃N; CH₃OH, heat		8	216
	CuSO₄, cyclohexane	"	48	216
	CuSO₄, cyclohexane, reflux	(2) + (26)		216
	CuO, petroleum ether (60–90°), heat		52	108
	CuSO₄, chlorobenzene, reflux		47.5ᵃ	39
	Cu or CuSO₄, chlorobenzene, reflux	"	32	114

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Reactant	Conditions	Product(s)	Yield (%)	Refs.
C₉ (*Contd.*)				
	Ag₂O, methanol		6	105
	CuSO₄, cyclohexane, reflux	"	62	105
C₁₀				
	Cu, ethanol		91	101
	Cu, cyclohexene	"	94	101
	CuSO₄, chlorobenzene, reflux	(5) + (*ca.* 30)		39
	CCl₄, *hν*	(*ca.* 55)		55
	CCl₄, *hν*	+ 80 (1:2)		51
	CuSO₄, cyclohexane, reflux	(72) + (9)		105
	Silver benzoate, (C₂H₅)₃N, methanol	+ (2:1)	—	107
	CuO, petroleum ether (60–90°), heat		13	108
	CuSO₄, cyclohexane, reflux	(58) + (22)		216
	Silver benzoate, (C₂H₅)₃N, methanol, heat		40	216
	CuSO₄, cyclohexane, heat	"	67	216

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Reactant	Conditions	Product(s)	Yield (%)	Refs.
C₁₁				
	Cu, toluene, reflux		51	217a
	CuSO₄, toluene, reflux		74	217b
	Cu, toluene, reflux		59	217a
	Silver benzoate, (C₂H₅)₃N, methanol			104
	CCl₄, hv		—	51
C₁₂				
	Methylene chloride, hv		—	50
	Cu powder, benzene		12	218
	CCl₄, hv		14	51
	CuSO₄, cyclohexane, heat		16	216

Reactant	Conditions	Product(s)	Yield (%)	Refs.

C₁₂
(*Contd.*)

| | CuSO₄, cyclohexane, heat | (51) + (7) | | 216 |

C₁₃

	Dioxane, reflux		32	50
	CuSO₄, chlorobenzene, reflux		8.5	114
	Dioxane, reflux		39.5	50
	Methylene chloride, *hν* or heat	''	50	49
	CuSO₄ or CuO, toluene, reflux		70–80	103

C₁₄

| | *n*-Decane, 174°, 10 min | | 12 | 151a |

C₁₅

	Cu, 80°, 10 hr, *n*-heptane		26	151a
	Cu, 174°, 10 min, *n*-decane	''	12	151a
	n-Decane, 174°, 10 min	''	13	151a
	Cu(acetylacetonate)₂, 174°, 10 min, *n*-decane	''	23	151a
	Methylene chloride, 10°, *hν* (also thermal)		—	49

TABLE III. INTRAMOLECULAR INSERTION OF DIAZOCARBONYL COMPOUNDS INTO C–H BONDS (*Continued*)

Reactant	Conditions	Product(s)	Yield (%)	Refs.
C₁₅ (*Contd.*)				
	Cu₂O, cyclohexane, *hν*, reflux	(9:2)	55–60	113
	CuSO₄, cyclohexane, reflux	"	65–70	113
C₁₆	Cu₂O, cyclohexane, *hν*, reflux	(9:2)	58–60	113
	CuSO₄, cyclohexane, reflux	"	75	113
C₁₇	Cu₂O, cyclohexane–tetrahydrofuran (1:1), *hν*, reflux		55	113, 219
	CuSO₄, cyclohexane, tetrahydrofuran, reflux	"	54	111, 219
	CuSO₄, tetrahydrofuran, heat		53	111
	CuSO₄, tetrahydrofuran, reflux	"	52.5	220
	Cu₂O, cyclohexane, *hν*, reflux	"	58	220
	Cu₂O, cyclohexane, *hν*, reflux		23	220
C₁₈	CCl₄, *hν*	(50) + (–)		51

Reactant	Conditions	Product(s)	Yield (%)	Refs.
C_{21} (*Contd.*)				
	CuSO$_4$, cyclohexane, tetrahydrofuran, reflux		38	111, 219
	Cu$_2$O, cyclohexane–tetrahydrofuran (1:1), *hv*, reflux	"	55	113, 219
C_{20}	CCl$_4$, *hv*	(8) (11)	52, 53
	Cu$_2$O, cyclohexane, *hv*, reflux		95	110
C_{21}	Benzene, *hv*	(7:3)		54

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Reactant	Conditions	Product(s)	Yield (%)	Refs.
C$_{21}$ (*Contd.*)	Ag$_2$O, methanol		22	105
	Methanol, *hν*	···	—	105
	CuSO$_4$, cyclohexane, reflux	+		105
	Ag$_2$O, benzene, heat		—	106
	CuO, toluene, heat		—	41a
C$_{21}$	CuSO$_4$, benzene, *hν*		40	41b
C$_{23}$	Cu$_2$O, cyclohexane, heat		—	109

* Insertion occurs with retention of configuration.

Note: References 145–230 are on pp. 474–475.

TABLE IV. ACID-CATALYZED CYCLIZATIONS OF DIAZOKETONES

Reactant	Conditions	Product(s)	Yield (%)	Refs.

C₅

1. BF₃ · (C₂H₅)₂O, CH₃NO₂
2. 10% aq HCl, reflux

13 | 131

C₆

1. BF₃ · (C₂H₅)₂O, CH₃NO₂
2. 10% aq HCl, reflux

40–65 | 131

C₇

HClO₄, dioxane–H₂O (3:2)

60 | 117

1. BF₃ · (C₂H₅)₂O, CH₃NO₂
2. 10% aq HCl, reflux

40–65 | 131

C₈

AcOH, 40°

70–80 | 129

HClO₄, dioxane–H₂O (3:2)

90 | 117

Glacial acetic acid

49 | 221

C₉

BF₃ · (C₂H₅)₂O, CH₃NO₂

56 | 122

HClO₄, dioxane–H₂O (3:2)

100 | 117

1.1 N Hydrochloric acid, 3 hr, 25°

86.5 | 222

Glacial acetic acid, ether   " | 75 | 137
Ag₂O   " | (—) | 223

HClO₄, dioxane–H₂O (3:2)

15 | 117

TABLE IV. Acid-Catalyzed Cyclizations of Diazoketones (*Continued*)

Reactant	Conditions	Product(s)	Yield (%)	Refs.
C₉ *(Contd.)*				
	HClO₄, dioxane–H₂O (3:2)		100	117
	1. BF₃ · (C₂H₅)₂O, CH₃NO₂ 2. 10% aq HCl, reflux		50–68	130
	Glacial acetic acid, 50°, 10% H₂SO₄		(—)	137
	Formic acid, 0–5°		(—)	223
C₁₀				
	BF₃ · (C₂H₅)₂O, CH₃NO₂		67	122
	Sulfuric acid, ether		4	224
	Sulfuric acid, dioxane	''	15	224
	BF₃, ether	''	35	224
	1. BF₃ · (C₂H₅)₂O, CH₃NO₂ 2. 10% aq HCl, reflux		40–65	131
C₁₁				
	CF₃CO₂H		20	127
	50% Formic acid or dilute alcoholic H₂SO₄		35	225
	BF₃ · (C₂H₅)₂O, CH₃NO₂		11	122
	BF₃ · (C₂H₅)₂O, ClCH₂CH₂Cl	(56) + (6)		118a
	1. BF₃ · (C₂H₅)₂O, CH₃NO₂ 2. 10% aq HCl, reflux		50–68	130

TABLE IV. Acid-Catalyzed Cyclizations of Diazoketones (*Continued*)

Reactant	Conditions	Product(s)	Yield (%)	Refs.
C$_{11}$ (*Contd.*)				
n-C$_5$H$_{11}$ ... CHN$_2$	1. BF$_3$ · (C$_2$H$_5$)$_2$O, CH$_3$NO$_2$ 2. 10% aq HCl, reflux	n-C$_5$H$_{11}$ ...	40–65	131
C$_{12}$				
	HBF$_4$, CH$_3$NO$_2$		70–74	119, 126
	CF$_3$CO$_2$H, −20°	''	100	119, 126
	HCl, ethanol, heat		64	226
C$_6$H$_5$ CH$_3$ ... COCHN$_2$	Glacial acetic acid	C$_6$H$_5$ CH$_3$ ...	(—)	227
	HCl, methanol	''	(—)	227
	BF$_3$ · (C$_2$H$_5$)$_2$O, CH$_3$NO$_2$, room temperature		32	120
	CF$_3$CO$_2$H	''	48	126
	CF$_3$CO$_2$H, CH$_2$Cl$_2$, 0°		96	127
	CF$_3$CO$_2$H, CH$_2$Cl$_2$, 0°		74	127
	BF$_3$ · (C$_2$H$_5$)$_2$O, CH$_3$NO$_2$, 0°	(80) + (20)		123
	1. BF$_3$ · (C$_2$H$_5$)$_2$O, CH$_3$NO$_2$ 2. 10%, aq HCl, reflux		50–68	130

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TABLE IV. ACID-CATALYZED CYCLIZATIONS OF DIAZOKETONES (*Continued*)

Reactant	Conditions	Product(s)	Yield (%)	Refs.

C₁₃

	CF₃CO₂H		86	119, 126
	CF₃CO₂H, CH₂Cl₂, −20°	(33) +		126
	CF₃CO₂H, CH₂Cl₂, −20°		58	126

C₁₄

	BF₃·(C₂H₅)₂O, ClCH₂CH₂Cl	(30) + (3)		118
	BF₃·(C₂H₅)₂O, CH₂Cl₂		74	152
	50% aq HBF₄, CH₃NO₂	(30) + (21)		152
	10% H₂SO₄ solution in acetic acid		80	115
	BF₃·(C₂H₅)₂O, CH₃NO₂		21	121
	Aq HCl, 0–5°		61.5	228

TABLE IV. Acid-Catalyzed Cyclizations of Diazoketones (*Continued*)

Reactant	Conditions	Product(s)	Yield (%)	Refs.
C15				
	CF₃CO₂H, CH₂Cl₂, −20°		70	119, 126
	—		16	119
	BF₃·(C₂H₅)₂O, CH₂Cl₂		82	152
	BF₃·(C₂H₅)₂O, CH₃NO₂	(46) + (10)		121
		+ (2)		
	BF₃·(C₂H₅)₂O, CH₂Cl₂		80	152
	50% Aq HBF₄	(26) + (18)		152
C16				
	BF₃·(C₂H₅)₂O, CH₂Cl₂, −10–5°		45	72
	HBF₄, CH₃NO₂	"	97	119
	CF₃CO₂H, CH₂Cl₂, 0°	"	100	125

TABLE IV. ACID-CATALYZED CYCLIZATIONS OF DIAZOKETONES (*Continued*)

Reactant	Conditions	Product(s)	Yield (%)	Refs.
	$BF_3 \cdot (C_2H_5)_2O$, CH_2Cl_2		85	152
	$BF_3 \cdot (C_2H_5)_2O$, CH_3NO_2	(31) + (12) + (10)		121
	$HClO_4$ or HI		50–55	128
	HBF_4, CH_3NO_2		78	119
	70% Aq $HClO_4$ or 48% aq HBF_4 or conc H_2SO_4, $CHCl_3$		80–99	128
	57% HI, $CHCl_3$	'''	60	128
	$BF_3 \cdot (C_2H_5)_2O$, $ClCH_2CH_2Cl$, 0°		43	72
	HBF_4, CH_3NO_2	''	97	119, 124
	CF_3CO_2H, 0°	''	100	124
C_{18}				
	1. CF_3CO_2H, CH_2Cl_2, 0° 2. Hydrolysis		62	125

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TABLE IV. Acid-Catalyzed Cyclizations of Diazoketones (*Continued*)

Reactant	Conditions	Product(s)	Yield (%)	Refs.
	$BF_3 \cdot (C_2H_5)_2O$, CH_2Cl_2, 0°		41	72
	CF_3CO_2H, 0°	"	100	124
	10% Soln H_2SO_4 in acetic acid, room temp		(—)	116
	$BF_3 \cdot (C_2H_5)_2O$, CH_2Cl_2		50	155
	70% Aq $HClO_4$ or 57% HI, $CHCl_3$		50–70	128
C_{19}	1. CF_3CO_2H, 0° 2. Hydrolysis		60	124
C_{21}	Phosphoric acid, dioxane		(—)	229
C_{22}	Glacial acetic acid, 25°		78	230
C_{24}	Glacial acetic acid, heat		82	230

Note: References 145–230 are on pp. 474–475.

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TABLE V. Miscellaneous Reactions

Reactant	Conditions	Product(s)			Yield (%)	Refs.

C₈

Dioxane, $h\nu$ — 77 — 37

Cyclopentane, $h\nu$ — 65 — 132a

C₉

Acetone, 1 N H₂SO₄ (4:1 v/v) — (47) + (28) — 132b

+ (25)

| | | .. | ." | .. | | |

Acetone, 1 N H₂SO₄ (4:1 v/v) — (3) (23) (1) — 132b

C₁₀

Cu bronze, benzene, reflux — 53 — 101

Cyclohexene, 130° — " — 43ª — 101

C₁₁

CuSO₄, dioxane, 100° — (2:1) — 15 — 133

Di-μ-dichloro-π-allyl-palladium, (C₂H₅)₂O, 5–15° — " (6:1) " — 22 — 133

Di-μ-dichloro-π-allyl-palladium, tetrahydrofuran, 5–15° — " (6:1) " — 24 — 133

Di-μ-dichloro-π-allyl-palladium, dioxane, 5–15° — " (6:1) " — 35 — 133

Di-μ-dichloro-π-allyl-palladium, benzene, 5–15° — " (3:1) " — 23 — 133

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TABLE V. MISCELLANEOUS REACTIONS (*Continued*)

Reactant	Conditions	Product(s)	Yield (%)	Refs.
C₁₂				
	Di-μ-dichloro-π-allyl-palladium, (C₂H₅)₂O, low temp		20	134
	Cu powder, DMSO, room temp		1	218
C₁₃				
	Di-μ-dichloro-π-allyl-palladium, (C₂H₅)₂O, low temp		15	134
C₁₆				
	CuI, tetrahydrofuran, 35°		50	48
C₁₇				
	Cu(acac)₂, tetrahydrofuran, reflux		90	136
	Cu(acac)₂, tetrahydrofuran, reflux		80	136
	Cu(acac)₂, tetrahydrofuran, reflux		43	136
C₂₁				
	Rhodium acetate, benzene, 3 hr		20	135

ᵃ No norcarane derivative was formed.

Note: References 145–230 are on pp. 474–475.

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6. Acknowledgment

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