# Lateral Lithiation Reactions Promoted by Heteroatomic Substituents

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1. Introduction

Heteroatom-facilitated lithiation reactions have assumed an increasingly important role in the elaboration of carbocýclic aromatic and heteroaromatic systems in the 40 years subsequent to the seminal review on metalation with organolithium reagents by Gilman and Morton. (1) Of particular note has been the development of methodology for the lateral lithiation of alkyl-substituted aromatic systems promoted by an extensive array of heteroatomic substituents. These lithiations, as defined by Eq. 1, involve deprotonation at a benzylic (side chain) position that is lateral to, or flanked by, a heteroatom-containing substituent

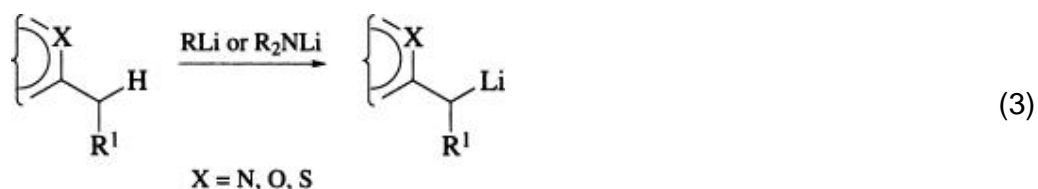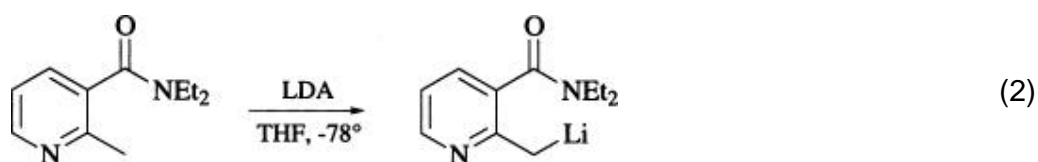G = heteroatomic substituent
R^1 = H, alkyl, or aryl

(1)
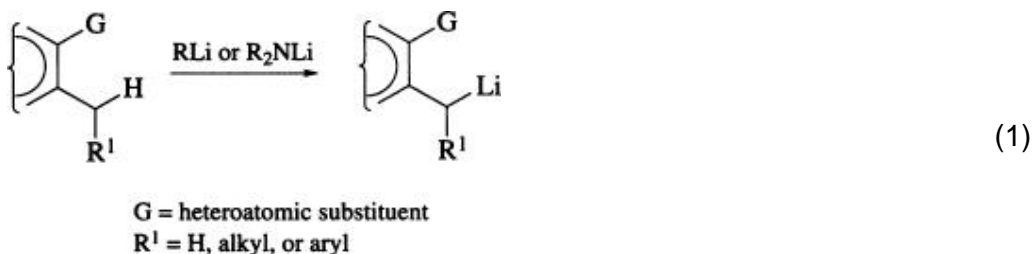
(G); this substituent facilitates lithiation relative to the parent system in which G is not present. The derived lithiated species have great synthetic utility for functionalization of benzylic sites, for chain extensions, and for the synthesis of fused carbocyclic and heterocyclic systems via annelation processes. This chapter summarizes the significant amount of work reported on heteroatom-facilitated lateral lithiations and the synthetic applications thereof. The survey covers the substituents that promote these reactions, and the methods of formation, stability, reactivity, and synthetic utility of the lithiated species.

Coverage is limited to examples of Eq. 1 in which the R^1 group is hydrogen (toluene derivatives), alkyl, or aryl. Examples that would be better classified as *alpha*-lithiations are not covered, for example, where R^1 is an anion-stabilizing group such as cyano, carboxy, and so on. Rare examples of lithiations of alkyl groups that are *meta* or *para* to the facilitating group G are included in the chapter, although these are not, strictly speaking, lateral lithiations as defined

by Eq. 1. Also included are a limited number of older lateral metalations that were originally effected with sodium or potassium bases but would now be more conveniently carried out with lithium dialkylamide bases.

The aromatic nucleus in Eq. 1 may be carbocyclic or heterocyclic, but lateral lithiations of heterocycles lacking the heteroatomic substituent are not covered. For example, lithiation of nicotinamides (Eq. 2) are included; however, lithiations of picolines, and other heterocyclic systems defined by Eq. 3, are considered beyond the scope of this chapter. The latter subject has been extensively reviewed in treatises on heterocyclic chemistry. (2-6)

$$\text{(2)}$$

$$\text{(3)}$$

$$X = N, O, S$$

The relationship of lateral lithiation reactions (Eq. 1) to heteroatom-facilitated *ortho* lithiations (Eq. 4) is obvious and the two fields have developed, for the most part, in concert. With several notable exceptions, the same heteroatomic substituents (G) promote both types of lithiations. A number of reviews cover

$$\text{(4)}$$

G = heteroatomic substituent
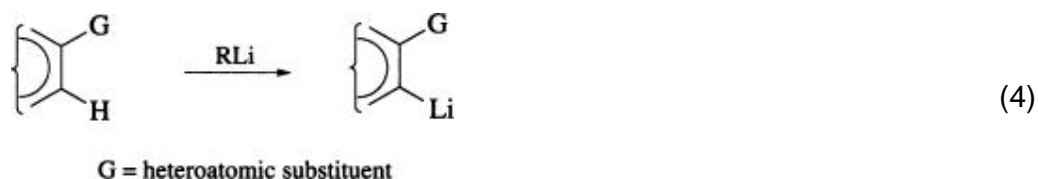
various aspects of *ortho* lithiation reactions, (7-11) including the comprehensive chapter in *Organic Reactions* by Gschwend and Rodriguez that surveyed the literature to 1979. (12) In the present chapter, the relationship of lateral lithiation and *ortho* lithiation reactions will be discussed within the contexts of mechanism, reactivity, and synthetic utility. In addition, the sequential use of these two lithiation processes for the synthesis of complex aromatic and heteroaromatic systems is covered.

2. Mechanism

Detailed studies on the mechanism of heteroatom-facilitated lateral lithiation reactions have not been reported. However, on the basis of extensive empirical observations of the reaction conditions and structural elements that promote these reactions, a mechanistic picture is emerging that can be used in a predictive manner for synthetic work and that may form a basis for future mechanistic investigations.

The mechanistic aspects of heteroatom-facilitated *ortho* lithiations of aromatic substrates (Eq. 4) have been thoroughly discussed in several reviews, (11, 12) and the principles described therein can be applied, with certain modifications, to a discussion of heteroatom-facilitated lateral lithiation reactions. Two major factors have been proposed for the facilitation of *ortho* lithiations by heteroatomic substituents. (12) One factor is described as a "coordination only" effect in which the predominant role of the substituent is to coordinate (or complex) with the organolithium reagent. This coordination increases the kinetic basicity of the organolithium reagent and concurrently directs deprotonation at the *ortho* position. The other factor is described as an "acid-base" effect wherein inductive and/or resonance effects of the heteroatomic substituent render the *ortho* position susceptible to proton loss. In many cases, the two effects act in concert as complexation of the organolithium reagent with the heteroatomic substituent may increase the acidifying inductive effect of that substituent.

Before applying the principles discussed above to lateral lithiations, it is instructive to briefly consider the lithiation chemistry of toluene, which of course contains no heteroatomic substituent to promote lithiation. Toluene is relatively difficult to lithiate, (13) requiring treatment with *n*-butyllithium in the presence of 1,4-diazabicyclo[2.2.2]octane (Dabco) (14) or *N*,*N*,*N*¢,*N*¢-tetramethylethylenediamine (TMEDA) (15) at or above room temperature. With *n*-butyllithium: TMEDA, lithiation occurs predominantly at the benzylic position with ca. 8–12%, predominantly *meta*, ring metalation also observed. This regiochemical outcome appears to result from direct deprotonation, as opposed to initial kinetic deprotonation on the ring followed by equilibration to the thermodynamically more stable benzylic anion. (15, 16) Complete regiochemical control in the benzylic metalation of toluene can be achieved with the "superbase" combination of 2-ethylhexyllithium and potassium *tert*-pentoxide. (17)

As compared to the lithiation of toluene, (13) benzylic lithiation of *N,N*-dimethyl-2-methylbenzylamine with *n*-butyllithium occurs under milder

conditions and is completely regioselective (Eq. 5). (18, 19) This facilitation can be attributed

(5)
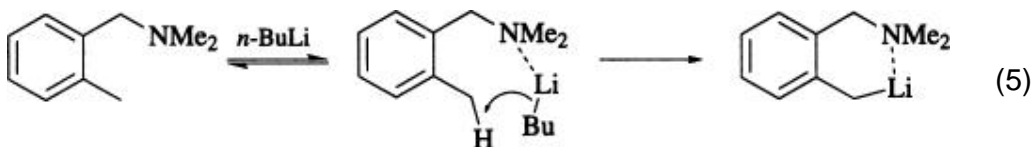
to coordination of *n*-butyllithium with the lone pair of the nitrogen which directs the organometallic reagent to the site of lateral metalation. The ability of amine ligands, such as TMEDA, to increase the kinetic basicity of alkyllithium reagents is well established, (10) and the activation provided by the dialkylamino group in the present example is a reflection of that effect. The process illustrated in Eq. 5 exemplifies the principle of the complex induced proximity effect (CIPE), (20) an effect that has widespread implications for interpreting the stereochemical and regiochemical results of a variety of reactions of organolithium reagents. Thus, as in the *ortho* lithiation field, (18, 21) the dimethylamino group provides a prototypic example of a heteroatomic substituent that facilitates lithiation predominantly, if not exclusively, through coordination.

The lithiation of *N,N*-diethyl-*o*-toluamide (Eq. 6) (22) is illustrative of a facilitated lateral lithiation in which the inductive and resonance effects of the heteroatomic

(6)
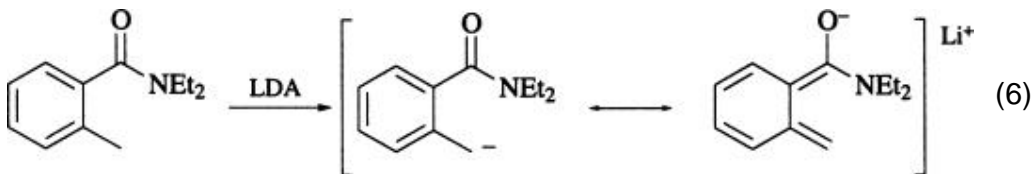
substituent predominate. Viewed simplistically, such lithiations involve extended enolate formation and the resultant lithio species can, in principle, be represented by *o*-quinodimethane resonance structures. However, it must be stressed that the structure of these lithio species has not been established; hence, whereas the intense color of the anions is indicative of electronic delocalization, the actual electronic structure is unknown. It is only as a matter of convenience, therefore, that the structures of laterally lithiated species are represented throughout the chapter as the benzyllithium (localized) form. Lithiations at benzylic positions of high intrinsic acidity are normally effected with lithium dialkylamide bases, such as lithium diisopropylamide (LDA) or lithium tetramethylpiperidide (LTMP). These bases are generally regarded to have negligible Lewis-acid character relative to organolithium reagents (12) and are therefore widely used in situations where coordination effects are not

required.

Support for the contention that coordination effects are not of major importance in the deprotonation in Eq. 6 derives from observations on the regiochemistry of lithiation of *N,N*-diisopropyl-*p*-toluamide (**1**). (23) As determined by deuteration studies, lithiation of **1** with LDA affords the benzylic anion,
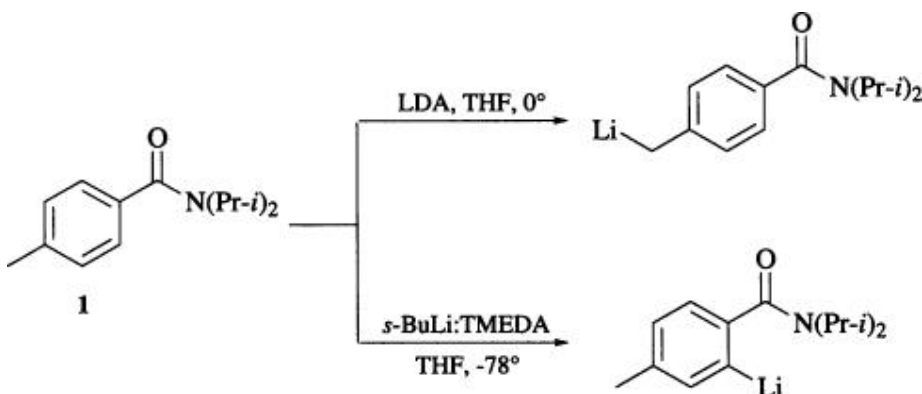
whereas lithiation with *sec*-butyllithium: TMEDA gives the *ortho* lithiated species. Lithiation with LDA appears to give the thermodynamically more stable lithio species, with the electronic effect of the amide group determining the regiochemistry of metalation. Formation of the *ortho* lithiated species with *sec*-butyllithium: TMEDA is presumably a kinetic result, and can be rationalized by complexation effects. While these results are illustrative of electronic versus coordination effects, in lateral lithiation reactions (Eqs. 1 and 6), the two effects will operate in concert and there is rarely ambiguity as to the position of lithiation; the benzylic anion is expected to be both the kinetic and thermodynamic product.

The discussion above provides a general overview of the features that promote lateral lithiation reactions and provides an empirical basis for selection of the experimental conditions under which a given lateral lithiation can be effected. However, the mechanistic details of these metalation processes remain to be elucidated. The task of defining the precise mechanism of these reactions is a daunting one, given the tendency of organolithium derivatives to associate into aggregates, a phenomenon that is highly dependent on reaction conditions (solvent, temperature, additives, etc). ^{6}Li and ^{15}N nuclear magnetic resonance spectroscopy, using isotopically enriched substrates, is providing insight into the solution structures of lithium dialkylamides and related *N*-lithiated species. (24) Similarly, X-ray structures of benzyllithium coordinated by various ligands have been determined. (25-28) Application of these techniques to the field of heteroatom-facilitated lithiation reactions will provide invaluable information on which a firmer mechanistic base can be established.

3. Scope and Limitations

3.1. Formation and Reactivity of the Lithiated Species
In this section, the alkyl-substituted carbocyclic aromatic and heteroaromatic derivatives that undergo lateral lithiation, and the conditions used to effect these metalations, are described on a class-by-class basis. A general indication of the stability and reactivity of the laterally lithiated species is also given. A more detailed description of the substrates that react with these lithio species and of the synthetic utility of these reactions is presented in subsequent sections.

3.1.1. Toluic Acid and Derivatives
3.1.1.1.1. Acids
The lateral lithiation of *o*-toluic acid is readily accomplished by treatment with two equivalents of lithium diisopropylamide (LDA) in tetrahydrofuran at 0° (Eq. 7). (29) Other bases that have been used to effect the dilithiation of *o*-toluic acid

$$\text{(7)}$$
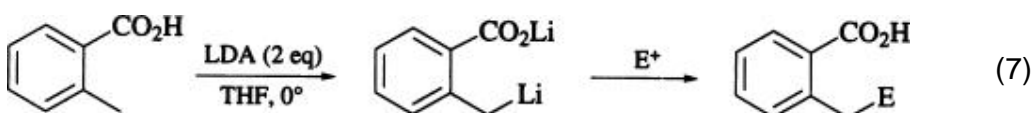
and ring-substituted derivatives thereof are lithium tetramethylpiperidide (LTMP), (30) *n*-butyllithium, (31) *sec*-butyllithium, (32) and *tert*-butyllithium. (33) Deprotonations with organolithium reagents are carried out at low temperature (–78°) to minimize addition to the carboxylate group. The toluic acid dilithio species are stable in tetrahydrofuran solution at room temperature and react with a variety of electrophiles to provide *ortho* substituted benzoic acids (Table I-A).

The *o*-toluic acid dianion generated with LDA (Eq. 7) does not incorporate deuterium upon treatment with deuterium oxide. (29, 34) This result is rationalized on the basis of a molecular complex between the dianion and diisopropylamine and the exclusive transfer of the amine NH to the benzylic position in a noncompetitive process. (29) Evidence for this complex was obtained from the ^{1}H NMR spectrum of the residue obtained after evaporation of the reaction mixture from deprotonation of *o*-toluic acid with LDA. This spectrum displayed signals for one molecule of diisopropylamine per molecule of *o*-toluic acid. Probably related to the failure to obtain deuterium incorporation are the observations that the presumed dianion–LDA complex affords *o*-ethylbenzoic acid in poor yield upon quenching with methyl iodide, whereas the dianion generated with *n*-BuLi at low temperature gives the methylated product in 84% yield. (31)

The facilitation in the lateral lithiation of *o*-toluic acid is presumably related to the electron-withdrawing properties of the carboxylate group. Thus it is not surprising that *p*-toluic acid is dilithiated with LDA under similar conditions. (29) Dilithiation of *m*-toluic acid can be accomplished with low efficiency relative to *o*- and *p*-toluic acids, an indication of the importance of the resonance effects of the carboxylate groups in the latter two isomers.

3.1.1.1.2. Esters

Although methyl *o*-toluate (**2**) undergoes lateral lithiation upon treatment with LDA at –78°, the resulting lithio species rapidly undergoes self-condensation to an isocoumarin. (35) The same dimerization occurs with the 3-methoxy derivative **3**.

2 R = H
3 R = OMe
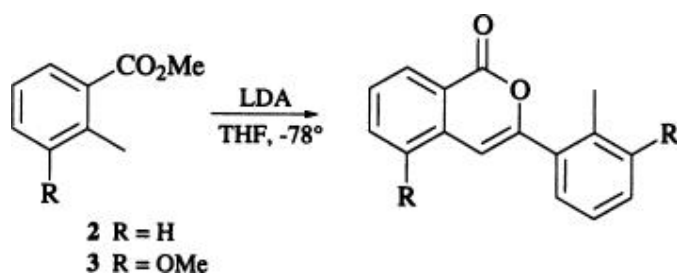
However, if the ester functionality is flanked by a methoxy group, the resulting lithio derivative is sufficiently stable at –78° to be trapped with electrophiles as in Eq. 8. (35) The increased stability of the lithio species conferred by the *ortho¢*

$$(8)$$

(87%)
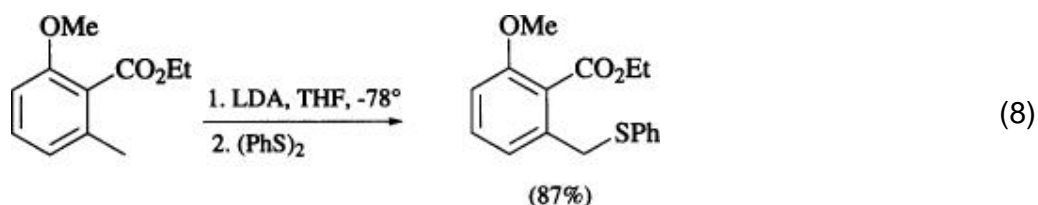
methoxy substituent is attributable to a decrease in the electrophilicity of the carboalkoxy group resulting from both electronic and steric factors. With the proviso that an *ortho¢* methoxy group is present, toluate ester lithio derivatives demonstrate good reactivity and have been condensed with a wide variety of electrophiles (Table I-B). An *ortho¢* hydroxy substituent, which as the lithium alkoxide is expected to decrease the electrophilicity of the carbomethoxy group to an even greater extent by an electronic effect, also confers stability to an alkyl toluate lithio derivative (Eq. 9). (36)

$$(9)$$

(69%)
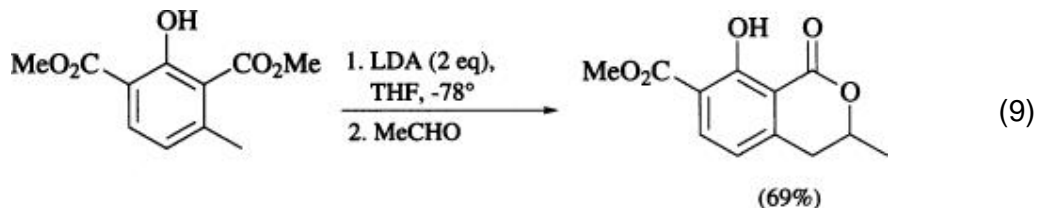
3.1.1.1.3. Phthalides and Thiophthalides

Phthalide can be viewed as a special case of a toluic acid ester. The weakly acidic nature of this heterocycle has long been recognized, and various base-catalyzed aldol and Dieckmann condensation reactions have been reported. (37, 38) Coverage in this chapter is limited to irreversible deprotonations of phthalides that are formally analogous to the lithiations of toluates discussed in the previous section. Phthalide is lithiated with LDA at temperatures ranging from –40 to –78°, and unlike the methyl toluate lithio derivative, the resulting lithio species is relatively stable toward dimerization and is effectively trapped with electrophiles (Eq. 10). (39) Although there is no direct evidence

$$(10)$$

(45%)
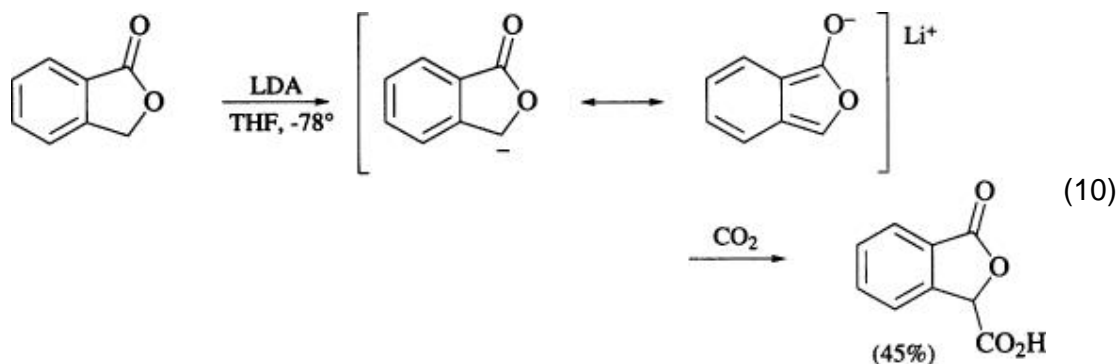
in this regard, the stability of the phthalide anion relative to lithiated methyl toluate may reflect an increase in resonance stabilization of the lithio species which can attain an essentially planar structure. A number of annelation processes based on addition of phthalide anions to α , β -unsaturated systems are described in subsequent sections.

Thiophthalide (**4**) can also be lithiated, although the resulting anion appears to be less stable than that derived from phthalide. (40, 41) Thus treatment of **4** with LDA at –60° followed by addition of ethyl acrylate affords an intractable mixture of products. Substitution of lithium *tert*-butoxide for LDA in the same reaction sequence results in formation of the adduct **5**, albeit in low yield. Low to moderate

4   **5 (26%)**
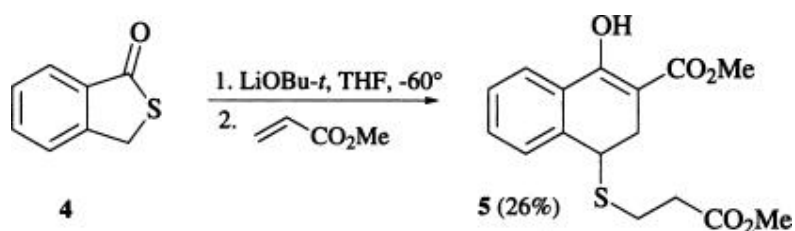
yields are also obtained in the addition of the lithio species of thiophthalide to other Michael acceptors. (40, 41)

3.1.1.1.4. Secondary Amides and Thioamides

The ease of generation, stability, and general reactivity of dilithiated secondary toluamides makes them one of the most useful laterally metalated derivatives. The lithiated alkylcarboxamido group, generated by addition of the first of two equivalents of base, is not only highly resistant to nucleophilic attack, but also facilitates the subsequent lateral lithiation of the methyl group by a combination of coordination and electronic effects. Thus the dilithiation of *N*-methyl-*o*-toluamide is accomplished by treatment with two equivalents of *n*-butyllithium in tetrahydrofuran at 0° (Eq. 11). (42)

(75%)   (11)
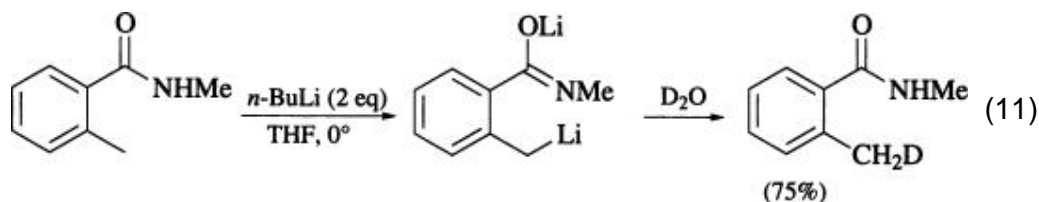
The dilithio species was originally prepared in tetrahydrofuran at reflux temperature, (43) and whereas these conditions give an indication of the stability of the dianion, they are much harsher than required to effect the lateral metalation.

The *N* substituent of the carboxamide can be almost any group that is otherwise compatible with the lithiation conditions; hence the nature of the substituent can in many cases be dictated by the structure of the desired final product as in Eq. 12. (44)

(70%)   (12)
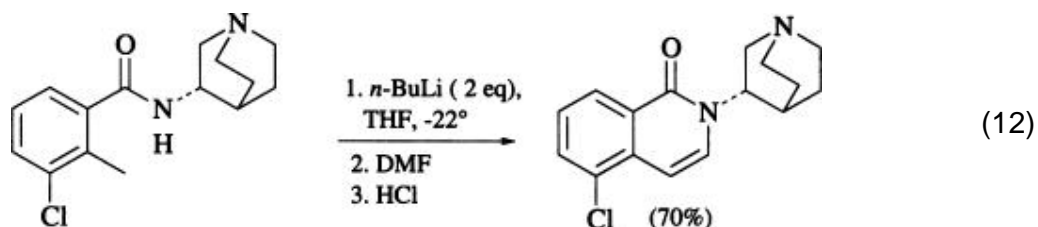
An interesting variant for the generation of a secondary toluamide dianion is shown in Eq. 13. (45) An ultrasound-promoted Barbier reaction is used to convert

$$M = Na, Li \qquad (13)$$

(63%)
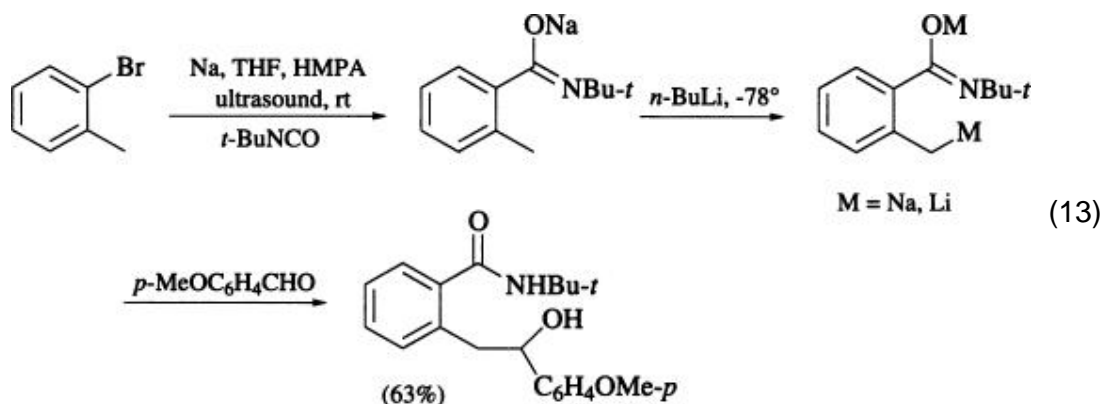
o-bromotoluene to the sodium salt of N-tert-butyl-o-toluamide. Subsequent addition of n-butyllithium effects lateral metalation to afford the dianionic species that can then be trapped with electrophiles in the usual way. As the only reported examples use tert-butyl isocyanate in the Barbier reaction, the scope of this procedure in terms of the amide nitrogen substituent has not been defined.

The inability to effect lateral lithiation of primary o-toluamides led to the development of methodology for dilithiation of secondary o-toluamides with N substituents that can subsequently be unmasked to the primary carboxamido group. Thus the acid-labile 1-propenyl (46) and 2-methyl-1-propenyl (47) moieties can be used as nitrogen "protecting groups." The symmetry inherent in the latter affords the practical advantage that cis/trans isomer mixtures are avoided. The utility of the N-(2-methyl-1-propenyl) substituent is illustrated by the synthesis of benzamide 6. (47, 48) A methoxy group can play a similar role as a removable nitrogen substituent. (49) Lateral lithiation of N-methoxy-o-toluamide (7) followed by condensation with N,N-dimethylformamide and acid treatment affords
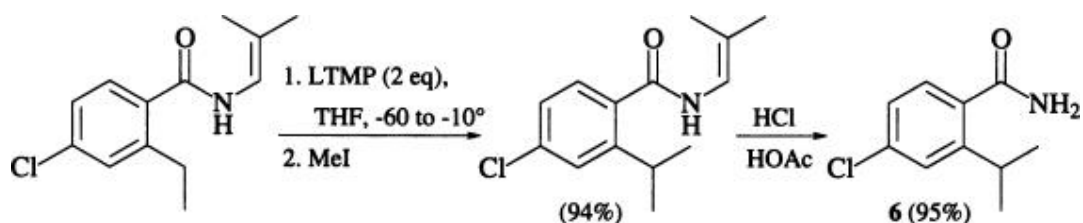
N-methoxyisoquinolone (**8**). The methoxy group is removed from the isoquinolone nitrogen by treatment with titanium trichloride.
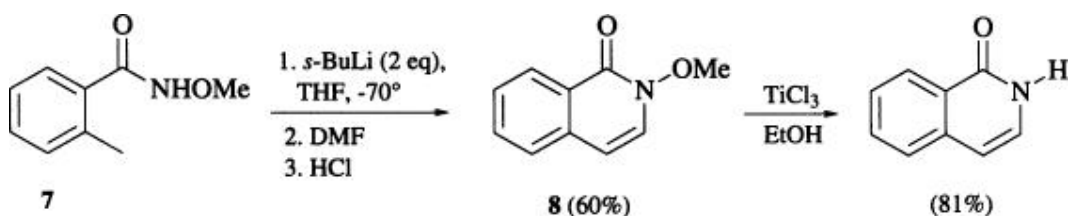
Secondary thioamides can be similarly dilithiated (Eq. 14), (50) and although this is the only reported example, the methodology would be expected to have general applicability.

(89%)　　　(14)
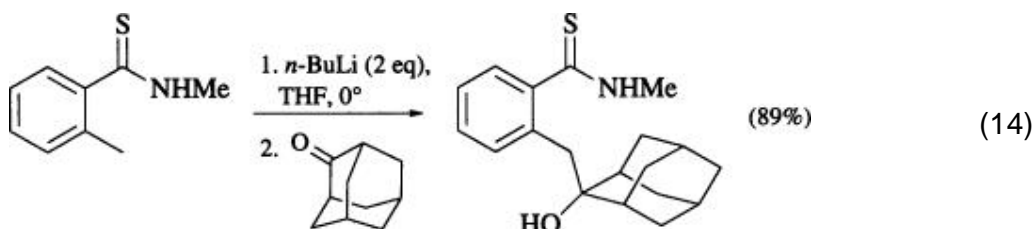
3.1.1.1.5. Tertiary Amides

The tertiary carboxamido group ranks as one of the most powerful directing groups for *ortho* lithiation reactions, (23) and numerous synthetic applications have been developed based on the resulting *ortho* lithiated species. (11) Similarly, the lateral lithiation of tertiary *o*-toluamides has been extensively investigated. Most widely used have been *N,N*-diethyltoluamides which are easily lithiated with LDA, generally at low temperature (Eq. 15). (51) The resulting lithio

(65%)　　　(15)
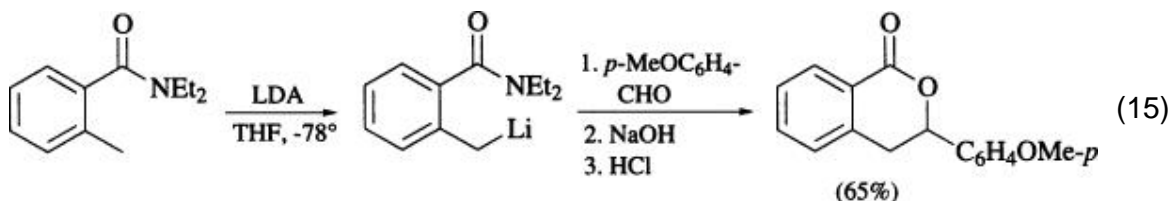
species are somewhat prone to self-condensation, hence the use of higher temperatures for the lithiation is generally to be avoided. Less commonly used have been *N,N*-dimethyl (51) and *N,N*-diisopropyl (22) amides which normally do not offer practical advantages relative to the corresponding diethyl

derivatives.

The *N,N*-diethylcarboxamido group is particularly useful in transformations involving subsequent ring closure reactions, either of the indirect type exemplified by the base-promoted cyclization to form the lactone in Eq. 15, or of the direct type as in cyclocondensation with imines to form dihydroisoquinolones. (52) However, the extremely unreactive nature of the tertiary amido group can be detrimental in other applications, for example, in hydrolysis to the corresponding carboxylic acid. Thus several protocols for the use of more labile tertiary amides have been developed. For example, lateral lithiation of the *N*-methylpiperazinyl-*o*-toluamide **9** followed by alkylation affords the *o*-butylbenzamide **10**. (53) Conversion

(72% overall from **9**)
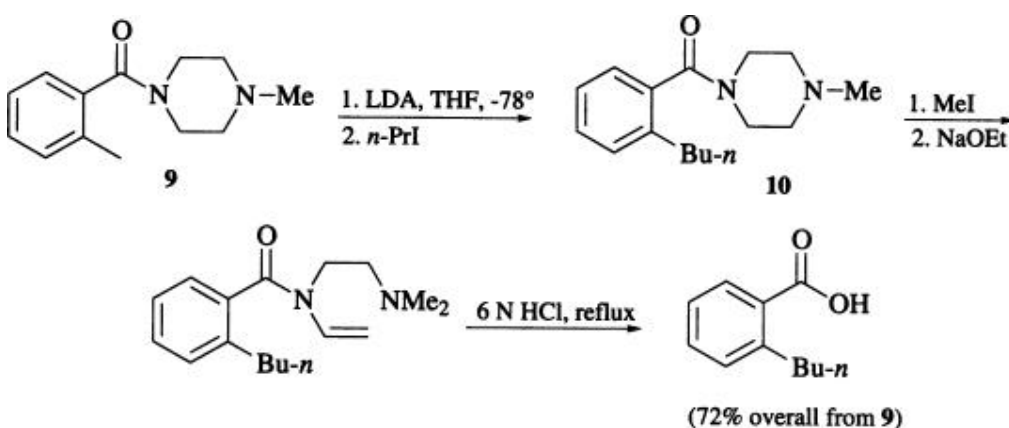
to the benzoic acid is accomplished by a one-pot reaction sequence involving quaternization. Hoffman-type elimination, and sequential hydrolysis, presumably first to the *N*-(2-dimethylaminoethyl)benzamide which then undergoes intramolecularly assisted hydrolysis to the final product. For comparison, *N,N*-diethyl-*o*-toluamide was completely resistant to hydrolysis with 6 N hydrochloric acid. (53) Alternative methodology involves lateral lithiation of *N*-(*tert*-butyl)-*N*-methyl-*o*-toluamides. (54) Cleavage of the *N*-(*tert*-butyl) group with trifluoroacetic acid provides the secondary amide, which can be converted to the acid by nitrosation and base treatment. These multistep sequences would appear to be useful only when the corresponding toluic acids or secondary toluamides are not readily available.

On the basis of its strong electron-withdrawing effect, the tertiary carboxamido group also facilitates lithiation of *meta* and *para* methyl groups. (22) Facilitation can also be extended to lithiation of a methyl group in an adjacent benzene ring, as in the transannular lithiation–cyclization of the biphenyl derivative **11**. (55)

11   (92%)
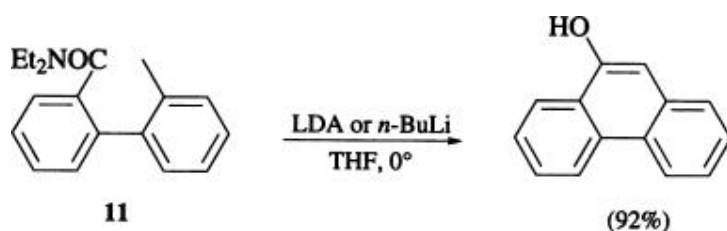
3.1.1.1.6. Nitriles

The metalation of *o*-tolunitrile was one of the earliest lateral metalation reactions to be studied. Potassium amide (56) or sodium amide (57, 58) in liquid ammonia was used to generate laterally metalated species which were quenched with electrophiles to provide substituted benzonitriles (e.g., Eq. 16). (57) Under

(16)
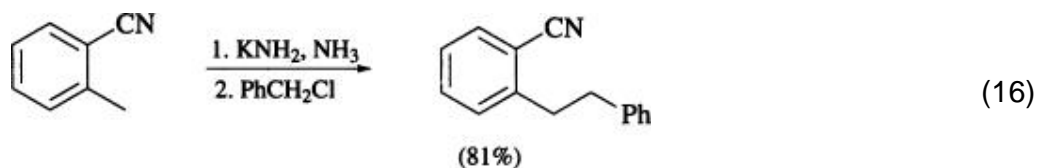
similar conditions, *p*-tolunitrile was metalated and alkylated in high yield whereas *m*-tolunitrile afforded only unidentified products. (58)

In the absence of added electrophile, laterally metalated *o*-tolunitriles dimerize to afford isoquinolines as exemplified by the formation of **12** from *o*-tolunitrile. (59)

12 (65%)
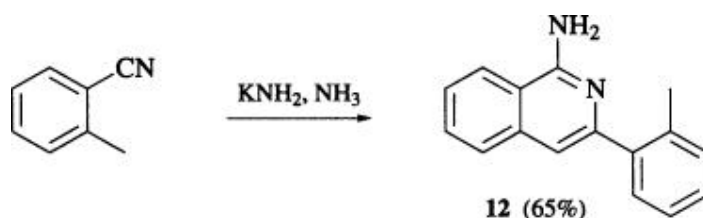
This transformation is accomplished in higher yield (80%) with lithium dimethylamide in tetrahydrofuran-hexamethylphosphoric triamide (HMPA) at –78°. (60) In general, use of the more common lithium dialkylamide bases LDA and LTMP in tetrahydrofuran (Eq. 17) (61) would appear to be more convenient for effecting lateral lithiation of 2-alkyl arylnitriles.

(17)

(85%)
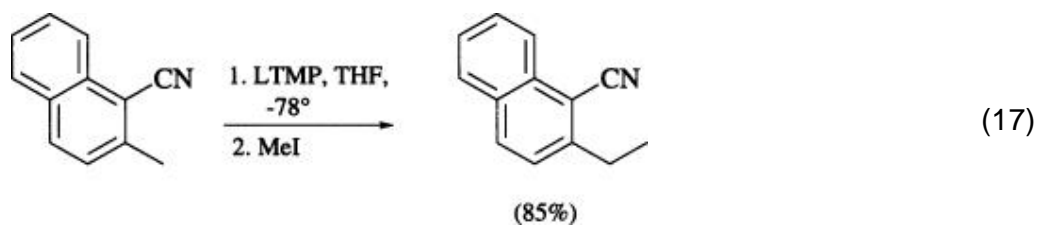
In situ generation of the lithio species from 2,6-dicyanotoluene is accomplished by treatment of the bis-*N,N*-dimethylhydrazone derivative **13** with three equivalents of LDA. (62) Conversion of the dimethylhydrazone group to the cyano group appears to involve base-promoted elimination of dimethylamine. Alkylation of the lithio species with iodomethane affords the same product (**14**) that can
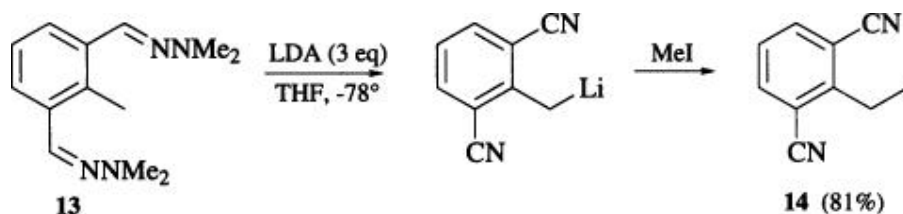
be obtained directly from lithiation and alkylation of 2,6-dicyanotoluene. In principle, these results indicate that derivatization of a tolualdehyde to the dimethylhydrazone followed by lateral metalation and electrophilic trapping could be a useful process for preparation of substituted *o*-tolunitriles.

3.1.1.1.7. Oxazolines
The 2-oxazolinyl moiety is a versatile substituent that functions as a director of *ortho* lithiation reactions and aromatic nucleophilic substitution processes. (63) In addition, procedures have been developed for unmasking oxazolines to the corresponding carboxylic acids, and for conversion to other functional groups including amides, nitriles, and aldehydes. (63) As regards lateral lithiation reactions, the chelating ability of the 2-oxazolinyl group facilitates lithiation of tolyl methyl groups. Thus lateral lithiation of *o*-tolyloxazoline **15** is achieved
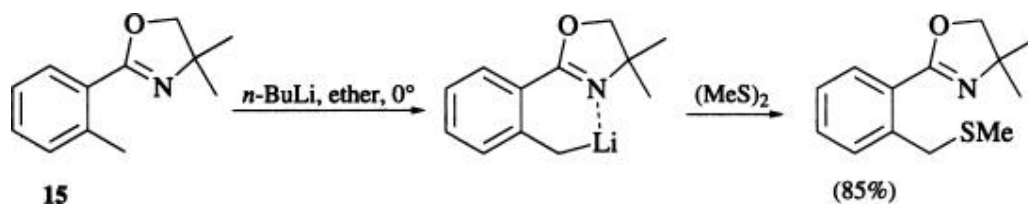
with *n*-butyllithium at 0°, and the resulting anion is trapped with electrophiles in high yield. (64) The 4,4-dimethyl-2-oxazolinyl group has been used most widely, whereas the unsubstituted parent 2-oxazoline and the corresponding 5-methyl derivative have found occasional use (Table I-I).

3.1.1.1.8. Imidazolines and Tetrazoles

The lithium salt of the 2-imidazolinyl group facilitates lateral lithiation although the conditions required to effect deprotonation are harsher than those required to effect metalation of the oxazolines discussed above. This difference probably reflects the decreased capability for chelation of the delocalized imidazolinyl lithio species. Condensation of the dilithio species with benzoate esters provides cyclic derivatives (Eq. 18). (65)

$$\text{(18)}$$
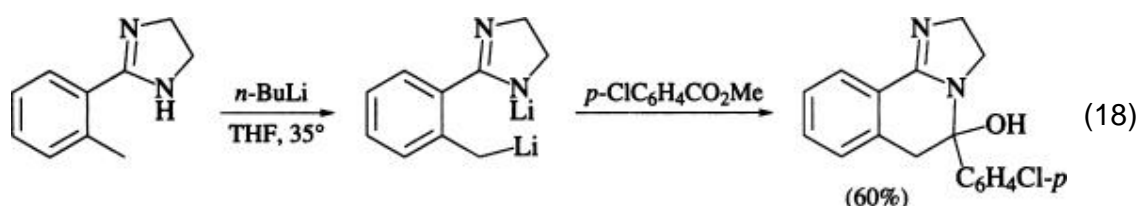
The related lateral lithiation of 5-(2-methylphenyl)tetrazole is effected with two equivalents of *sec*-butyllithium in the presence of TMEDA, and the resulting lithio species can be monoalkylated in good yield (Eq. 19). (66)

$$\text{(19)}$$
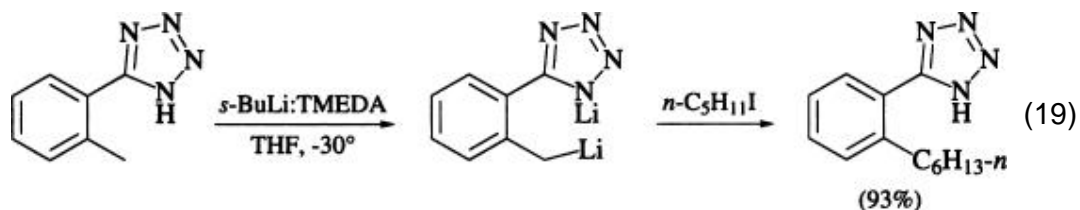
3.1.1.2. Tolyl Ketones

The only reported examples of lateral lithiations facilitated by a nonenolizable ketone function involve 2-alkylphenyl *tert*-butyl ketones (e.g., **16**). (67) Deprotonation of **16** with LDA followed by condensation with acetone affords an adduct that exists predominantly as the lactol.

16   (94%)
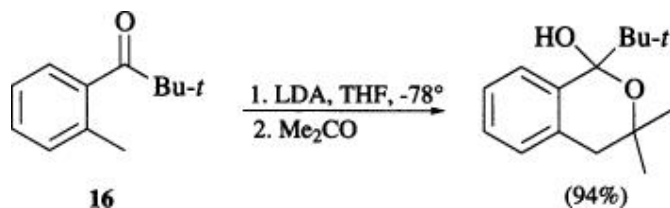
A ketone enolate can also facilitate lateral metalation. Treatment of 2,4,6-trimethylacetophenone with two equivalents of *n*-butyllithium: TMEDA affords predominantly the dianion **17** as determined by quenching with chlorotrimethylsilane. (68)

17   (85%)
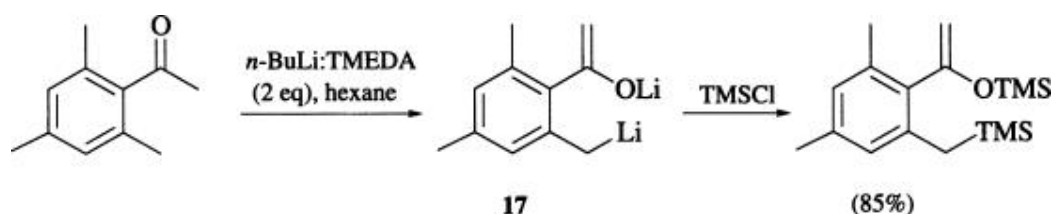
^{1}H NMR experiments establish that the ketone enolate is formed initially and that the lateral metalation occurs subsequently. A dilithio species can also be generated from 2-methylacetophenone by treatment of the silyl enol ether with excess *n*-butyllithium: TMEDA. Trapping with chlorotrimethylsilane gives the bis-silylated derivative **18** as the major product along with a number of minor

18   (80% of a mixture)
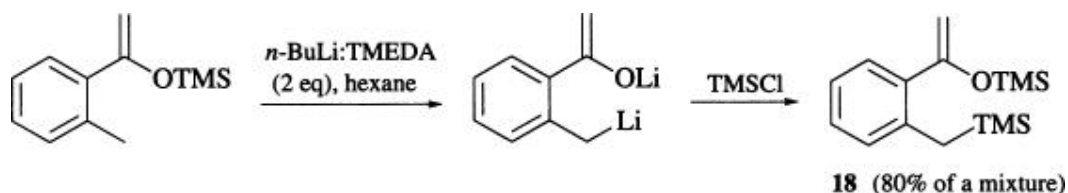
products resulting from disilylation of the 2-methyl group and from silylation of the acetophenone methyl group. (68) Reaction of these lithio species with other electrophiles has not been reported.

3.1.2. Tolualdehyde Derivatives
3.1.2.1.1. Amido Adducts
The electrophilicity of the aldehyde group clearly precludes direct lateral lithiation of *o*-tolualdehydes; hence, several protocols have been developed for lithiation of *o*-tolualdehyde derivatives in which the aldehyde group is protected. A particularly convenient procedure uses the amido adduct (e.g., **19**) formed by addition of the lithium salt of *N,N,N¢*-trimethylethylenediamine

(85%)
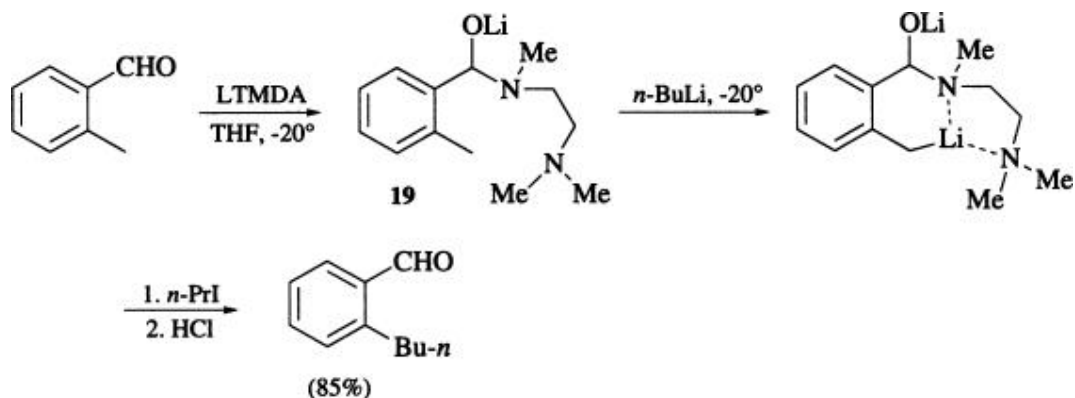
(LTMDA) to the aldehyde. (69) The amido adduct protects the aldehyde from nucleophilic attack while facilitating subsequent benzylic lithiation via coordination of the nitrogens of the ethylenediamine moiety with *n*-butyllithium. Treatment of the resultant lithio species with an electrophile, followed by acid hydrolysis of the aminal, provides the *ortho*-substituted benzaldehyde.

Use of the *N,N,N¢*-trimethylethylenediamine adduct is crucial to success of the lateral lithiation discussed above. The corresponding adduct **20** formed by addition
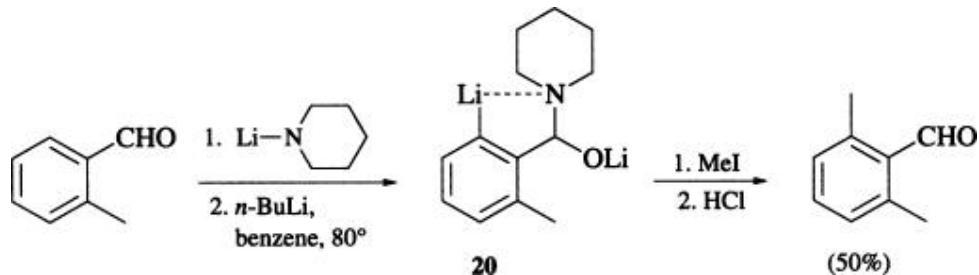
of lithium piperidide to *o*-tolualdehyde undergoes *ortho*, rather than lateral, lithiation as evidenced by the formation of 2,6-dimethylbenzaldehyde upon quenching with methyl iodide. (69) The underlying mechanisms responsible for the difference in regiochemistry observed in the lithiations of **19** and **20** remain to be elucidated.

3.1.2.1.2. Imines
The *N*-cyclohexylimine of *o*-tolualdehyde undergoes lateral lithiation with LTMP, and the resultant lithio species is trapped with electrophiles in good yield (Eq. 20). (70) Aqueous workup provides the imine product **21**, which is hydrolyzed

(20)

21 (89%)
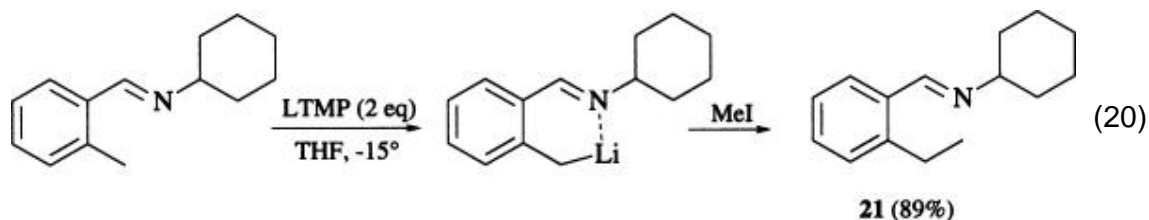
to the aldehyde with aqueous HCl. Two equivalents of LTMP are required to effect complete deprotonation of the tolualdehyde imine. Incomplete metalation was observed with LDA whereas alkyllithium reagents (*n*-butyllithium or *tert*-butyllithium) added to the carbon–nitrogen double bond of the imine.

3.1.2.1.3. Imidazolidines

The 1,3-dimethylimidazolidinyl group also serves as a protecting–facilitating group for the lateral lithiation of *o*-tolualdehyde (Eq. 21). (71)

(21)

(90%)
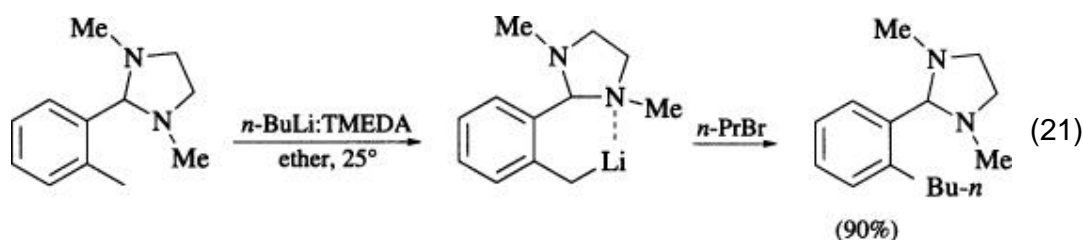
Alkylation at the benzylic position occurs in high yield, and the imidazolidine is subsequently hydrolyzed to the aldehyde upon brief treatment with aqueous HCl at room temperature.

3.1.2.2. 2-Methylbenzyl Alcohols

The benzylic alkoxide group affords relatively weak facilitation in the lateral lithiation of 2-methylbenzyl alcohol (**22**). This lateral lithiation requires treatment with *n*-butyllithium in ether for 24 hours at room temperature or 4 hours at reflux. The derived dilithio species is trapped with electrophiles at the benzylic position in fair to excellent yield. (72)

22

(92%)
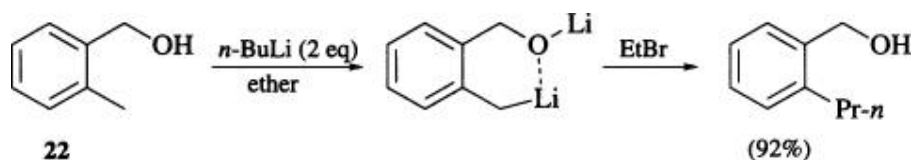
3.1.2.3. Cresol and Thiocresol Derivatives

o-Cresol can be laterally metalated with the "superbase" (73) *n*-butyllithium: potassium *tert*-butoxide in heptane at reflux although only ca. 85% conversion to the dianion **23** is achieved. (74) As the

23   M = Li or K
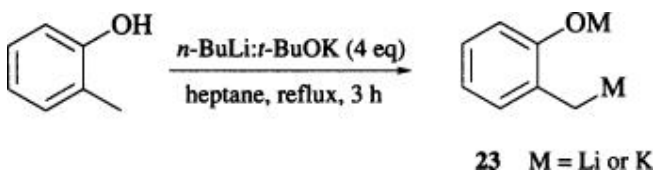
conditions required to effect this transformation are at least as vigorous as those required to metalate toluene itself, (17) classification of this dimetalation as "heteroatom facilitated" does not seem warranted. For this reason, the metalation chemistry of the cresols (74, 75) is not covered in this chapter although there are potentially useful synthetic aspects encompassed within that field.

3.1.2.3.1. Ethers

Lateral lithiation of *o*-methylanisole with organolithium reagents suffers from competing *ortho* lithiation. As determined by carbonation of the resulting lithio species, treatment with *n*-butyllithium in cyclohexane affords a 67:33 ratio of lateral to *ortho* metalation. With *n*-butyllithium:TMEDA, the ratio of lateral to *ortho* lithiation is reversed to 25:75. (76) Lateral metalation appears to be favored with *n*-butyllithium:potassium *tert*-butoxide, although an additional complication involving an apparent dealkylation–alkylation process enters into this lithiation reaction (Eq. 22). (77) Anions derived from *o*-alkylanisoles (as well

(22)
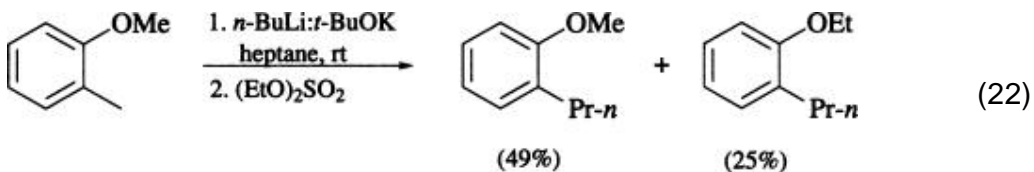
as from the *meta* and *para* isomers) can also undergo a rearrangement wherein migration of the methyl group from oxygen to carbon occurs, although this can largely be avoided by conducting the lithiation at or below room temperature. (77) Thus when these various complicating factors are taken into account, the lateral metalation of *o*-alkylanisoles appears to have limited synthetic utility.

Lateral metalation of 2,6-dimethylanisole (**24**) with *n*-butyllithium followed by quenching with cyclohexanecarboxaldehyde affords a moderate yield of mono-substitution product. (78) Treatment of **24** with excess

n-butyllithium:potassium *tert*-butoxide affords a laterally dimetalated intermediate as determined by quenching with diethyl sulfate. (77)

1. *n*-BuLi, THF, 0° to rt
2. C$_6$H$_{11}$CHO

(48%)

1. *n*-BuLi:*t*-BuOK, heptane, rt
2. (EtO)$_2$SO$_2$

(62%)
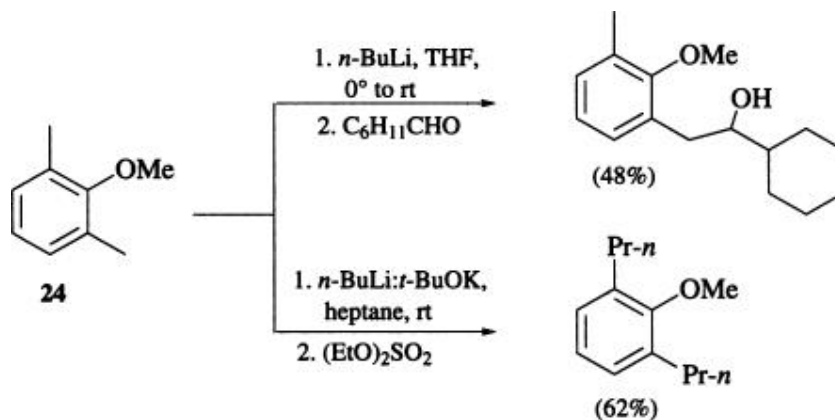
Lithiation of the methoxymethyl (MOM) ether of *o*-cresol (**25**) with *tert*-butyllithium affords the *ortho* lithio species with greater than 99% regio-specificity. (79-81) The corresponding methyl ether affords a 42:58 ratio of *ortho* to lateral lithiation under similar conditions. (76) There appears to be no experimental evidence on which to base an explanation for the different regiochemistries observed for these lithiations.

t-BuLi, hexane, 0°

ICH$_2$CH$_2$Cl

(87%)
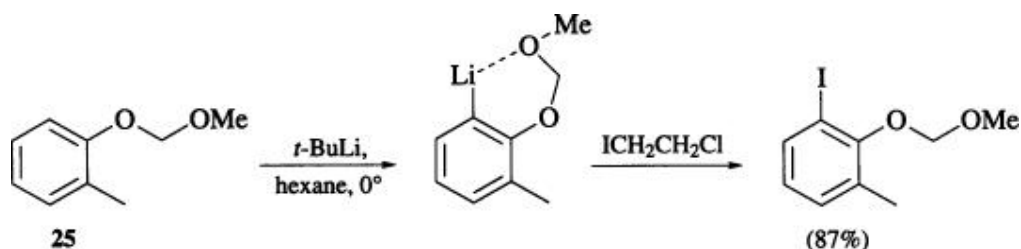
3.1.2.3.2. Thioethers

Treatment of 2-methylthioanisole with *n*-butyllithium results in lithiation predominantly at the thiomethyl group as determined by reaction with carbon dioxide (Eq. 23). (82) Products resulting from lateral and *ortho* lithiation are

$$26:27:28 = 68:29:3$$

(23)
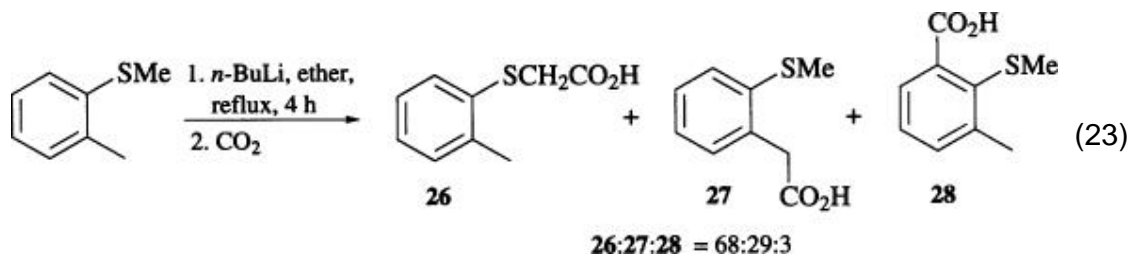
also observed. With *n*-butyllithium:TMEDA, lithiation of the thiomethyl group of 2-methylthioanisole is almost the exclusive pathway. Exclusive lateral lithiation is observed when both *ortho* positions are substituted with methyl groups and the alkyl group on sulfur is isopropyl, as in compound **29**. In the absence of one of the aryl methyl groups in **29**, *ortho* lithiation becomes a competing (with *n*-butyllithium), or almost exclusive (with *n*-butyllithium:TMEDA), reaction. (82)
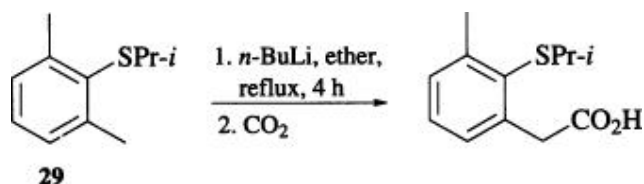
Treatment of 2-methylthioanisole with two equivalents of *n*-butyllithium: TMEDA gives dilithio species **30** as evidenced by formation of electrophilic trapping products such as **31**. (83) This dilithiation reaction is postulated to involve initial
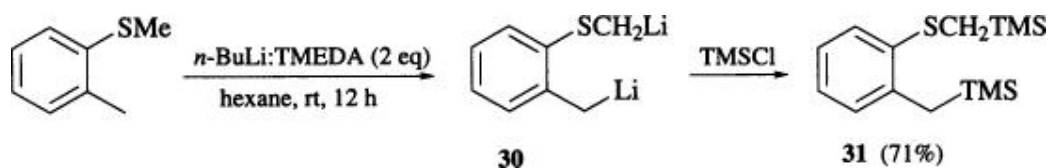
metalation of the thiomethyl group, an assumption in accord with the results given above on the monolithiation of the same substrate. The partially negative sulfur atom then directs the second equivalent of *n*-butyllithium to the site of benzylic deprotonation. Consistent with the proposed facilitation by the thioether group in the lateral lithiation is the lack of benzylic lithiation observed when the methyl group is *meta* or *para* to the thiomethyl group. (84) In those cases, *ortho* lithiation occurs in addition to lithiation of the thioether group.

3.1.2.3.3. Dialkyl Carbamates
The diethyl carbamate of *o*-cresol (**32**) undergoes lateral lithiation with LDA and affords the silylated derivative **33** upon quenching with trimethylsilyl

chloride along with a minor amount of the bis-silylated product **34**. (85) The latter product presumably derives from proton transfer during the
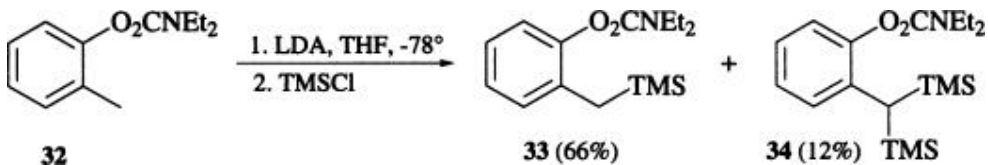
silylation reaction. As in the lithiation of 2-methylanisole described above, the regiochemistry of lithiation in carbamate **32** is base dependent. Thus, treatment of **32** with *sec*-butyllithium:TMEDA affords a 2:1 ratio of *ortho* to laterally lithiated species as determined by silylation. The benzylic anions derived from lateral lithiation of *o*-cresol carbamates undergo an oxygen-to-carbon carbamoyl migration upon warming to room temperature (Eq. 24). (86) This rearrangement is

(24)
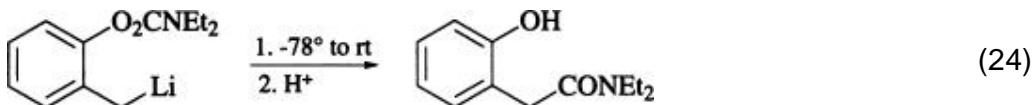
analogous to the oxygen-to-carbon 1;3-carbamoyl transfer observed with *ortho* lithiated *O*-aryl carbamates. (85)

3.1.2.3.4. Tetraalkylphosphorodiamidates
The bis(dimethylamino)phosphoryl group appears to be the most efficient facilitator of lateral lithiation of protected *o*-cresols. Lithiation of *o*-tolyl *N,N,N¢,N¢*-tetramethylphosphorodiamidate (**35**) with *sec*-butyllithium
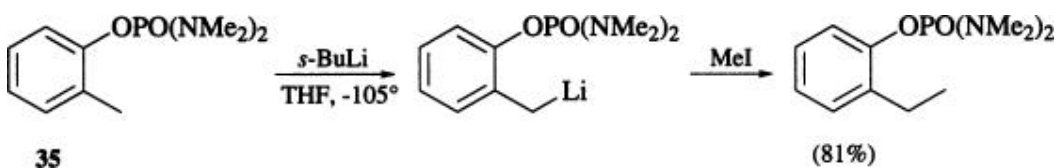
at –105° gives the extremely reactive benzylic anion which reacts with a number of electrophiles below –90° (Table V-D). (87) LDA can also be used to effect the lithiation, although *sec*-butyllithium appears to be more effective and has been used in almost all of the reported examples. With either base, lithiation of **35** occurs exclusively at the benzylic position. The corresponding *o*-thiocresol derivative **36** is lithiated and trapped with electrophiles under essentially the same conditions. (88)

SPO(NMe₂)₂ ... 1. *s*-BuLi, THF, -105° ... 2. CO₂ ... SPO(NMe₂)₂ CO₂H

36 ... (96%)
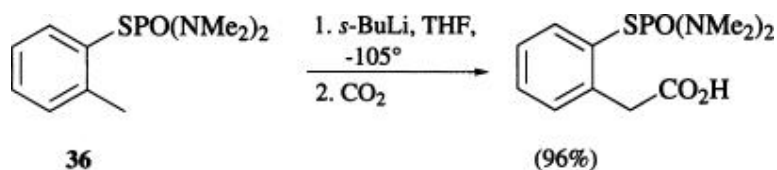
3.1.3. Toluidine Derivatives

3.1.3.1.1. *N,N*-Dialkyl

The metalation of *N,N*-dimethyl-*o*-toluidine (**37**) was studied in detail and use of *n*-butyllithium:TMEDA in hexane for ca. 3 hours at room temperature was found to maximize lateral, as opposed to ring, lithiation. (89) Deuteration studies indicate that under these conditions the ratio of benzylic to ring (presumed to be *ortho*) lithiation is 10:1. This is confirmed by the high yield of the adduct obtained by condensation of the lithio species with benzophenone (Eq. 25). (89) With *n*-butyllithium alone (no TMEDA), the lithiation is not

$$ (25) $$
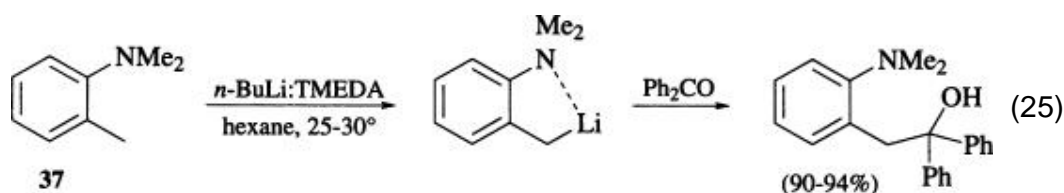
only considerably slower, but the amount of ring lithiation is increased. This is an unusual example of a less basic lithiating agent demonstrating greater selectivity for ring vs. lateral metalation. Evidence that the dimethylamino group facilitates lithiation of the methyl group of **37** through complexation with the *n*-butyllithium:TMEDA complex is provided by the regiochemistry of lithiation of *N,N*-dimethyl-*p*-toluidine. In this case, exclusive *ortho* lithiation is observed with either *n*-butyllithium or its TMEDA complex. (89)

3.1.3.1.2. Carboxamides

The synthetic utility of *N,N*-dialkyltoluidine derivatives is obviously somewhat limited; hence lateral lithiations of toluidines with more versatile nitrogen substituents have been developed. Acylated *o*-toluidines, as exemplified by the *N*-pivaloyl derivative **38**, readily undergo lateral lithiation upon
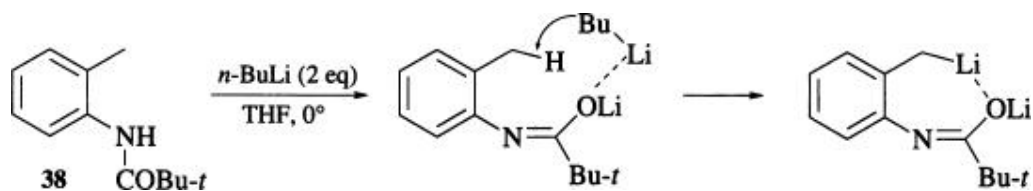
treatment with two equivalents of an organolithium reagent. (90) As in the corresponding *ortho* lithiation reaction, (90) the deprotonated carboxamido moiety presumably facilitates lateral lithiation through coordination with the organolithium reagent. Acyl residues that can be used are limited to secondary alkyl, (91) tertiary alkyl, (90, 92) or phenyl; (92) toluidine acetamides apparently do not undergo lateral lithiation with excess base. (92)

Dilithio species from *N*-acyl *o*-toluidines are quite stable and react well with electrophiles (Table VI-B). Upon prolonged storage at room temperature (in the absence of an added electrophile), these dianions undergo intramolecular condensation with elimination of lithium oxide to provide 2-substituted indoles in good yield (Eq. 26). (90-92) This synthetically useful transformation is discussed in greater detail in the Synthetic Utility section.

(26)
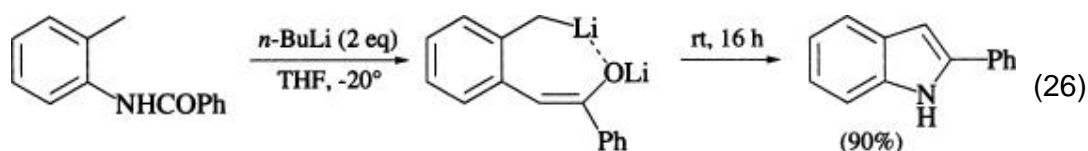
3.1.3.1.3. *tert*-Butyl Carbamates

The *N*-*tert*-butoxycarbonyl (Boc) group facilitates lateral lithiation in much the same manner as the *N*-pivaloyl group. The Boc derivative of *o*-toluidine (**39**) is rapidly converted to the dilithio species with
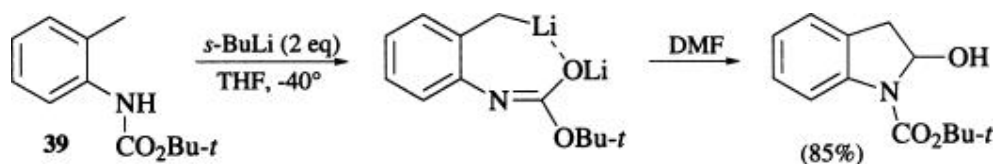
sec-butyllithium at –40°, and subsequent reactions with electrophiles proceed in good yield. (93) Formation of the dianion with *n*-butyllithium is less satisfactory, presumably because of competing addition to the Boc group. The dilithio species is less stable than the *N*-pivaloyl-*o*-toluidine dianion and undergoes decomposition upon warming to room temperature; the formation of oxindole, the potential intramolecular condensation product, is not observed under these conditions. Boc derivatives of secondary anilines also facilitate lateral metalation, as evidenced by the lithiation of Boc-indoline **40** and subsequent reaction with chlorotrimethylsilane. (94)

(74%)
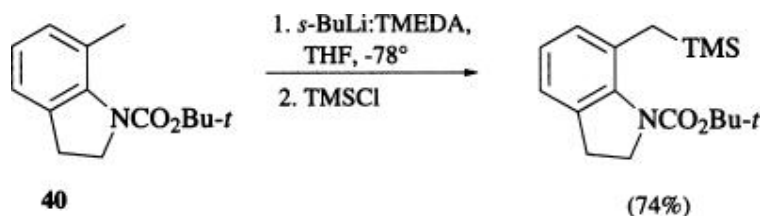
3.1.3.1.4. *tert*-Butoxycarbonyl Hydrazines

The lateral metalation of the Boc-hydrazine derivative **41** (95) is directly related to the lithiations of Boc-*o*-toluidines
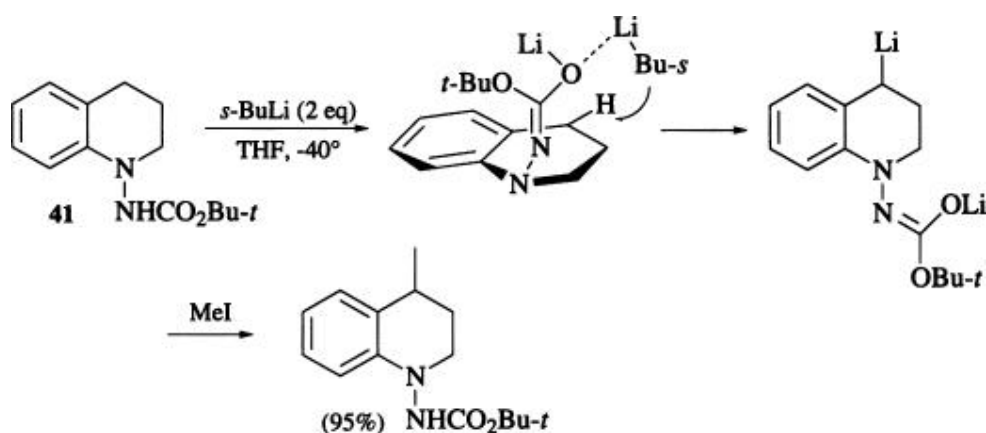
discussed in the previous section. The Boc group can be envisioned as "reaching over" the face of the tetrahydroquinoline ring, thereby directing the organolithium reagent to the site of benzylic lithiation. This is an interesting and somewhat unexpected result in light of the regiochemistry of lithiation of the analogous Boc-tetrahydroquinoline, (96) which undergoes *ortho* lithiation (i.e., at the 8 position), and the lithium carbamate (97) and formamidine derivatives (98) of tetrahydroquinoline, which undergo α lithiation (i.e., at the 2 position). The Boc-hydrazine directed lateral lithiation is also applicable to the indoline and benzazepine ring systems. (95)

3.1.3.1.5. Lithium Carbamates

A method for the in situ protection of the amino group of *o*-toluidine with simultaneous activation for lateral metalation is based on conversion to the lithium carbamate derivative. (99) Treatment of *o*-toluidine with *n*-butyllithium followed by quenching with carbon dioxide provides the lithium carbamate **42**. Removal of excess carbon dioxide by evaporation of solvent followed by addition of tetrahydrofuran and two equivalents of *tert*-butyllithium gives the trilithio species **43**. Treatment with an electrophile and subsequent decarboxylation
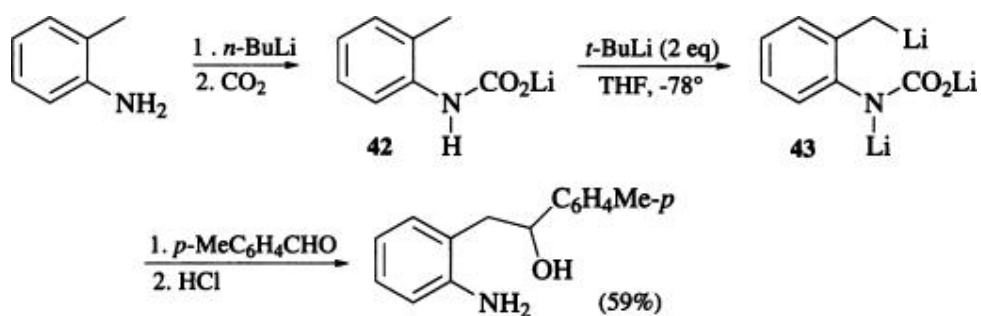
on workup with aqueous hydrochloric acid provide the 2-substituted aniline. The sequence is equally applicable to *N*-methyl-*o*-toluidine, in which case an intermediate dianion is involved. (100)

3.1.3.1.6. Trimethylsilyl Derivatives
Silylation can be used as an alternative to carboxylation in providing an easily removable *N*-protecting group for lateral metalation of *o*-toluidines. Lateral metalation of *N*-trimethylsilyl-*o*-toluidine (**44**), originally achieved with *n*-butyllithium in hexane at reflux, provides dianion **45**,
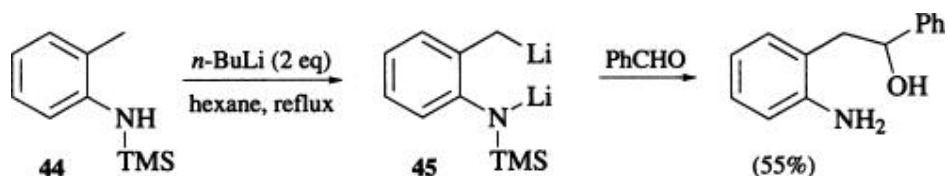
which furnishes 2-substituted anilines upon electrophilic quenching and aqueous workup. (101) The original procedure, which involves formation of **44** in a separate step, (101) has subsequently been modified to include in situ silylation and the use of *sec*-butyllithium in ether at room temperature to effect the second (lateral) lithiation. (102) With these improvements, this sequence would seem inherently simpler from an experimental point of view than the carboxylation sequence described above. As will be described later in the chapter, both procedures can be used to prepare 2-substituted indoles.

3.1.3.1.7. Isocyanides
The isocyanide group, readily available from the corresponding formamide, is a useful facilitator of lateral lithiations, as evidenced by the lithiation of *o*-tolyl isocyanide (**46**) and subsequent transformations of the derived lithio species **47**. (103, 104) Two equivalents of LDA in diglyme are required to achieve
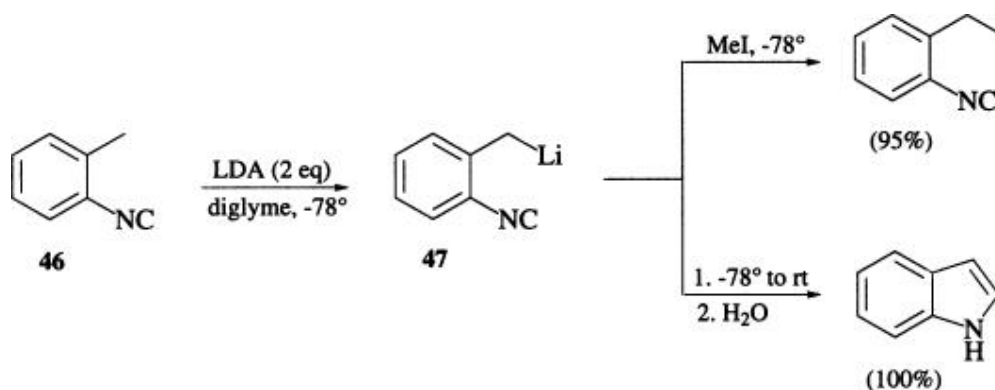
quantitative conversion to **47**, which may imply that the deprotonation is an equilibrium process. The use of organolithium bases is precluded by the electrophilicity of the isocyanide group. Solvent effects are also critical as lithiation of **46** in ether or tetrahydrofuran proceeds in low yield as a consequence of competing addition of LDA to the isocyanide carbon. Lithio species **47** is sufficiently reactive to be trapped with a wide range of electrophiles (Table VI-G). Whereas **47** is stable at –78° in diglyme for several days, cyclization occurs upon warming to room temperature to afford indole in quantitative yield. The isocyanide group also promotes lithiation of a *para* methyl group, (104) presumably through its electron-withdrawing inductive effect.

3.1.4. 2-(Alkylamino)toluene Derivatives
3.1.4.1.1. *N,N*-Dialkyl
As described in the Mechanism section, the lateral lithiation of *N,N*-dimethyl-2-methylbenzylamine (**48**) is prototypical of a lithiation facilitated by coordination effects. (18, 19) The degree of facilitation provided by the dimethylamino group of **48** is significantly greater than that provided in the lithiation of *N,N*-dimethylamino-*o*-toluidine (**37**) discussed previously. This is a reflection of the greater inductive effect of the aniline nitrogen, an effect that decreases the acidity of the *ortho* methyl group. The internally chelated lithio species **49**
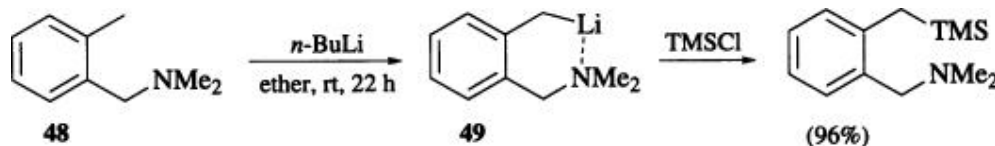
is stable at room temperature and reacts well with electrophiles (e.g., chlorotrimethylsilane (105, 106)). The facilitating dialkylamino group can also be contained in a ring, as in the lateral lithiation of 2-methyltetrahydroisoquinoline (Eq. 27). (105)

(27)
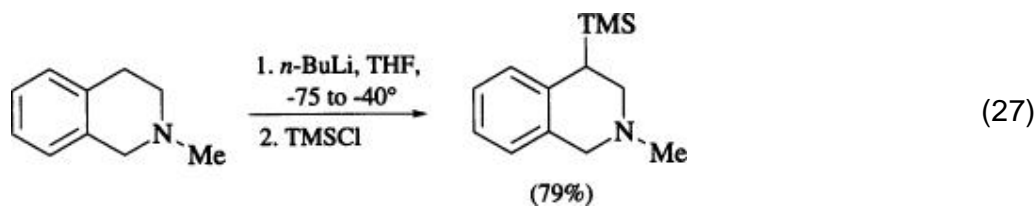
3.1.4.1.2. *tert*-Butyl Carbamates

The lateral lithiation of Boc-2-methylbenzylamine (**50**) also falls into the category of a coordination-facilitated metalation. Dilithiation of **50** is accomplished by treatment with *sec*-butyllithium at ca. –30° and,
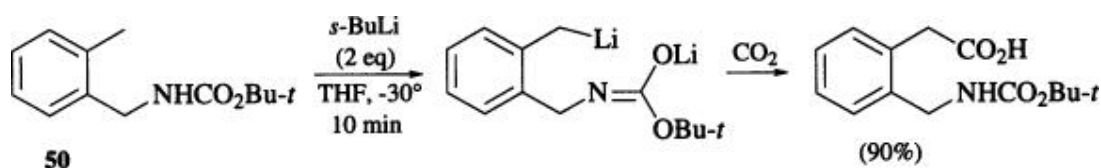
similar to the dilithio species from Boc-*o*-toluidine (**39**), the resulting dilithio species is stable up to ca. –15°. (47) It is noteworthy that lithiation of **50** occurs exclusively at the lateral position; in the absence of the *ortho* methyl group (Bocbenzylamine) lithiation α to the nitrogen is observed. (107)

The phenylethyl homolog **51** also undergoes lateral lithiation, although a stronger base and longer reaction time are required to effect complete metalation. (108)
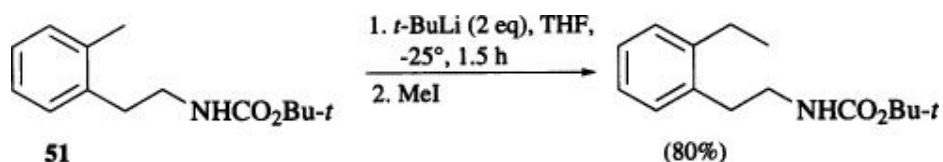
In the corresponding phenylpropyl homolog, lateral lithiation is still observed, but lithiation at the secondary benzylic position becomes a competing pathway. However, further homologation reduces the rate of lithiation (which is still predominantly at the lateral position) to a level that is not synthetically useful. (108) It is significant that lateral lithiation occurs in substrates such as **51** since delivery of the organolithium reagent to the site of deprotonation by coordination to the lithiated Boc group would involve at least a nine-atom ring in the transition state. Since these processes involve species of unknown aggregation states, invoking a simple intramolecular coordination model may not be justified.

3.1.5. Toluenesulfonic Acid Derivatives

3.1.5.1.1. Sulfonamides

Similar to their secondary carboxamido counterparts, *N*-substituted *o*-toluenesulfonamides readily undergo lateral lithiation (Eq. 28). (109, 110) The sulfonamido moiety appears to exert a strong coordination effect

(28)
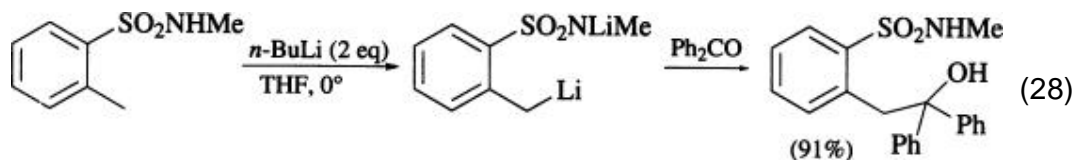
as *N*-methyl-*p*-toluenesulfonamide undergoes *ortho* lithiation, rather than benzylic lithiation, with *n*-butyllithium. (111)

3.1.5.1.2. Sulfonate Esters

The lateral metalation of *o*-toluenesulfonic acid has not been reported, although the observation that *p*-toluenesulfonic acid undergoes competitive *ortho* and benzylic lithiation implies that this may well be a viable process. (112, 113) On the other hand, lithiation of the corresponding ethyl sulfonate esters has been studied in detail. (114) Ethyl *o*-toluenesulfonate affords the lithio species **52** upon treatment with *n*-butyllithium at low temperature, and this benzylic anion can be trapped with a wide variety of electrophiles (Table VIII-B).
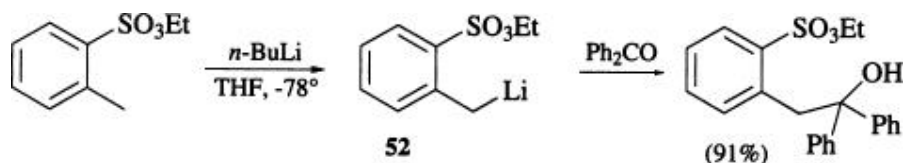
The ethyl ester is used rather than the methyl ester since displacement of the methyl group by organolithium reagents can be a competing reaction. Evidence that coordination with the organolithium base is an important feature in lithiations facilitated by the sulfonate ester moiety can be inferred by results on the metalation of ethyl *p*-toluenesulfonate, which undergoes kinetic lithiation at the *ortho* position followed by rearrangement to the thermodynamically more stable benzylic anion. (114)

3.1.6. Fluoro- and Trifluoromethyltoluenes

Lateral metalation of *o*-fluorotoluene (**53**) is observed upon treatment with LDA: *tert*-butyllithium at –75° in tetrahydrofuran, although the yield of carbon dioxide trapping product is moderate. (115) On the other hand, with the "superbase" (73) *n*-butyllithium: potassium *tert*-butoxide under the same conditions metalation occurs at the *ortho* position as evidenced by isolation of 2-fluoro-3-methylbenzoic acid (**54**) after carbon dioxide quench. These results have been rationalized on
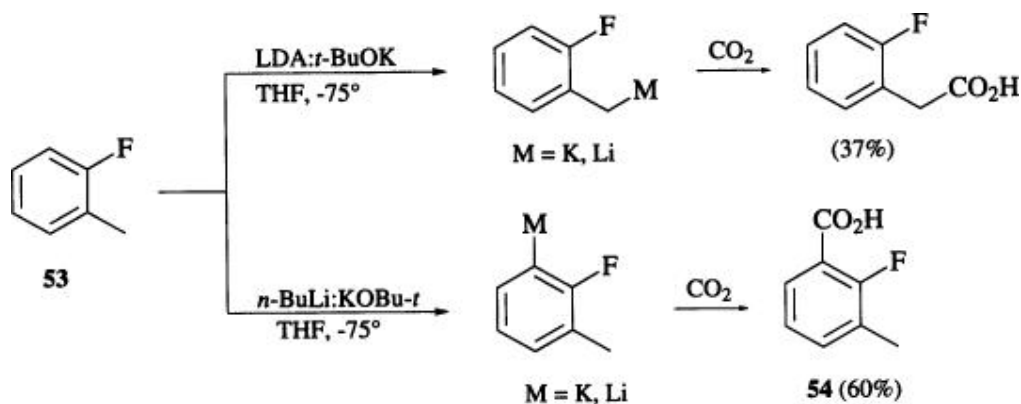
the basis of differential kinetic and thermodynamic acidities and the reactivity potentials of the respective bases. (115)

With LDA: *tert*-butyllithium, *o*-(trifluoromethyl)toluene also appears to give lateral metalation, but the lithio species decomposes, even at –100°. The mode of decomposition presumably involves elimination of fluoride to give the quinodimethane which undergoes polymerization (Eq. 29). (115)

(29)
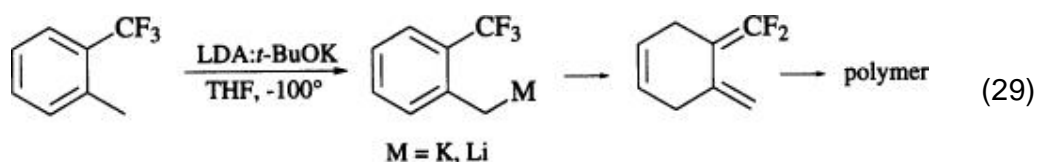
3.1.6.1. Alkyl-Substituted Heterocycles

Although lateral lithiation reactions promoted by heteroatomic substituents have been investigated for a number of heterocyclic ring systems, the volume of work that has been carried out in this field is considerably less than in the carbocyclic domains described in the previous sections. One reason for this discrepancy is the limited availability of contiguously disubstituted heterocycles relative to the corresponding carbocycles. Another contributing factor is the tendency of certain heterocycles to undergo nuclear lithiation, even in cases where lateral lithiation would otherwise be expected to occur (vide infra).

Metalation at the alkyl group of alkyl-substituted heterocycles is often an inherently facile process, most notably with π-deficient systems (e.g., pyridines), (2) hence the presence of a facilitating group other than the heteroatom of the ring system is not a prerequisite for these metalations. Nonetheless, although somewhat removed mechanistically from the carbocyclic counterparts, lateral lithiations of heterocycles that contain

heteroatomic substituents are of equal importance in synthesis and offer unique synthetic opportunities not afforded by the parent heterocycles or alkyl derivatives thereof. In the following sections, discussion is focused on lateral metalations of heterocycles substituted with the facilitating groups that have been previously described for carbocycles. The influence of these substituents on the regiochemistry of lithiation reactions is also discussed.

3.1.6.1.1. Pyridines

The facility with which pyridine derivatives undergo lateral metalation is illustrated by the conversion of alcohol **55** to the dimetalated species effected
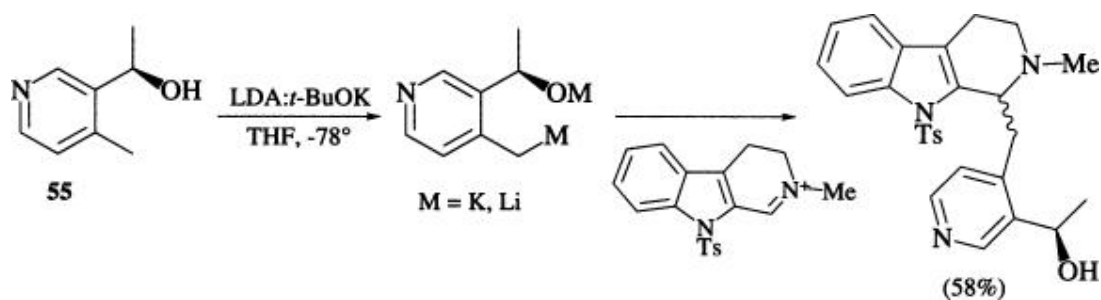
with LDA: KOBu-*t* at −78°. (116) This contrasts with the conditions required to dilithiate 2-methylbenzyl alcohol (*n*-butyllithium, reflux) (72) and underscores the increased acidity of 4-picoline relative to toluene. Other substituents that promote lateral lithiations of alkylpyridines include carboxy, (117) ester, (118) cyano, (119) pivalamide, (120) Boc-amino, (120) tertiary carboxamide, (52) and dimethylaminomethyl (105) groups as well as an aldehyde α -amido adduct. (121) In general, laterally metalated pyridines are generated and used at low temperatures to avoid nucleophilic attack on the pyridine ring.

The potential for regiochemical problems in the lateral lithiation of dimethylpyridine derivatives is apparent from the low yield of condensation product obtained from the lithio species derived from nitrile **56**. (122) In the absence of
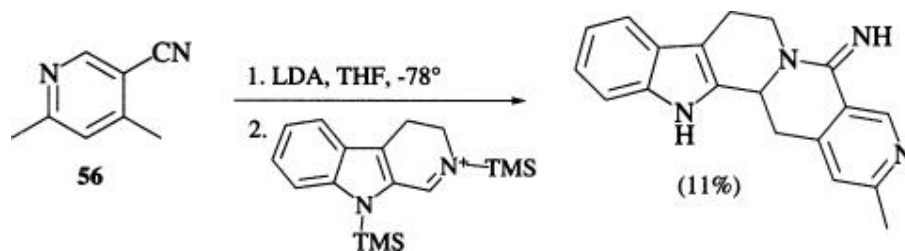
the 2-methyl group in **56**, yields of ca. 80% are obtained in this type of condensation reaction. (122) In the present example, there appears to be no

selectivity for lateral lithiation, for example, at the 4 position, vs. lithiation at the 2-methyl group. The latter lithiation is facilitated kinetically and thermodynamically by the inductive and resonance capabilities of the pyridine nitrogen.

3.1.6.1.2. Pyrroles and Indoles

The behavior of alkyl-substituted derivatives of pyrrole and indole in lateral metalation reactions is more closely aligned with carbocycles than with pyridines. This is primarily a reflection of the π -excessive nature of pyrrole and indole that does not afford the acidifying and anion-stabilizing effects available in π -deficient heterocyclic systems such as pyridine. Thus, lateral lithiation of the pyrrole amide **57** requires essentially the same conditions as those used in the lateral lithiation of the corresponding o-toluamide. (44)
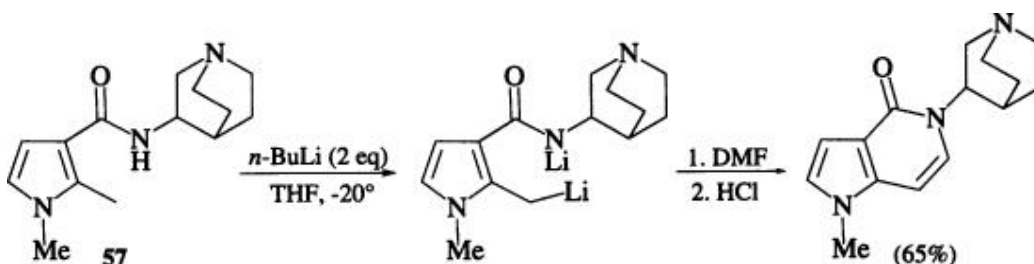
Lithiation of 2-alkylindoles can be achieved by the lithium carbamate protection-activation scheme previously described for the lateral lithiation of 2-alkylanilines. (123) Carboxylation of 1-lithio-2-methylindole followed by lateral lithiation with *tert*-butyllithium affords dianion **58**. Treatment with an electrophile followed by decarboxylation upon brief heating gives the 2-substituted indole **59**. Repetition of the sequence and quenching with a different electrophile provides further substitution of the 2-alkyl group as in the preparation of amide **60**. It has subsequently been
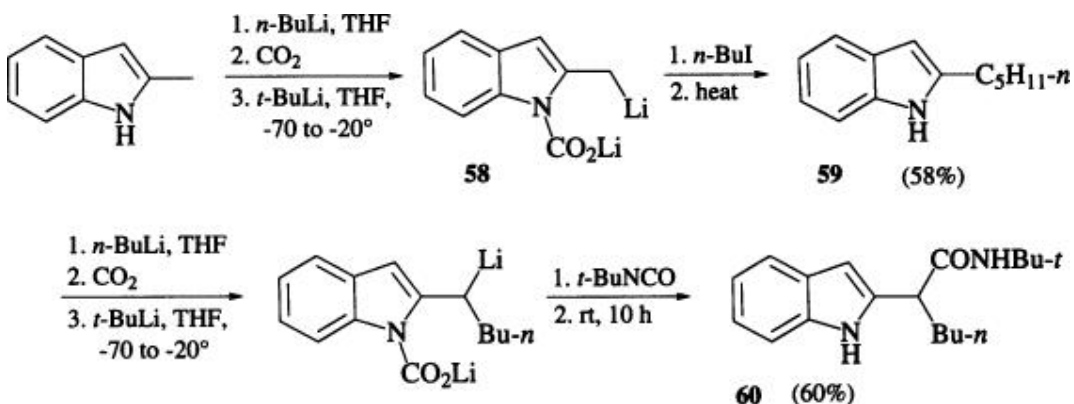
reported that 2-methylindole can be dimetalated directly with *n*-butyllithium: potassium *tert*-butoxide at room temperature and that the resulting *C,N*-dianion reacts selectively with electrophiles at the 2-lithiomethyl group. (124, 125) The overall scope of this procedure has not, however, been established.

One difference that can be noted between indole and carbocyclic systems is that esters of indole-3-carboxylic acid (e.g., **61**) can be used in lateral lithiations of 2-alkyl derivatives. (126) As previously discussed, *o*-toluic acid esters are too unstable for such applications unless substituted with an *ortho¢* alkoxy group. The
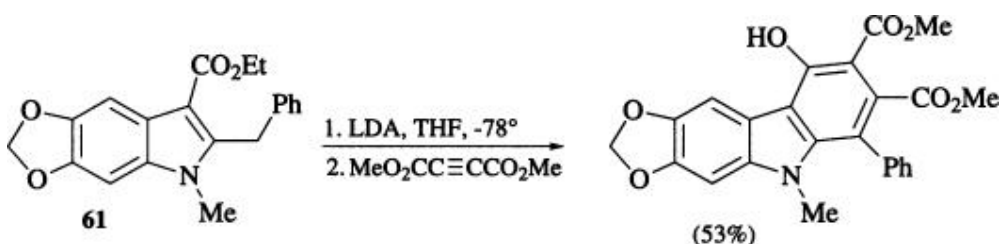
stability of the lithio species from **61** is a consequence of the reduced electrophilicity of the 3-indole ester, which can be viewed as a vinylogous carbamate.

A unique type of heteroatom-facilitated lateral lithiation reaction is observed with an α -amido adduct of *N*-methylpyrrole-2-carboxaldehyde (Eq. 30). (127) In this

(30)
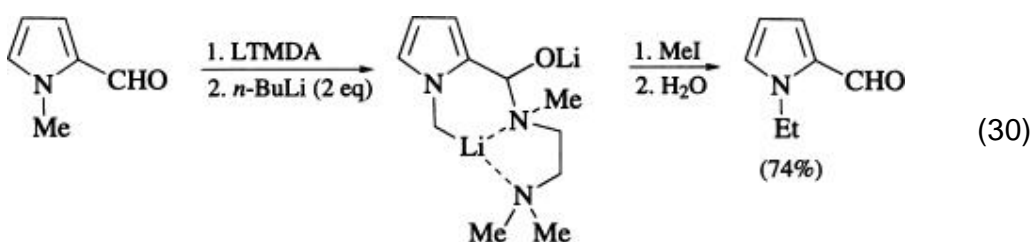
case, lithiation occurs regioselectively on the *N*-methyl group. This is a facilitated lithiation, as inferred from the absence of lithiation observed with other *N*-methylpyrroles. When applied to *N*-methylindole-2-carboxaldehyde, this protocol results in lithiation at the 3 position as well as at the *N*-methyl group. When the 3 position of the indole is blocked, as in chloro derivative **62**, lithiation of the
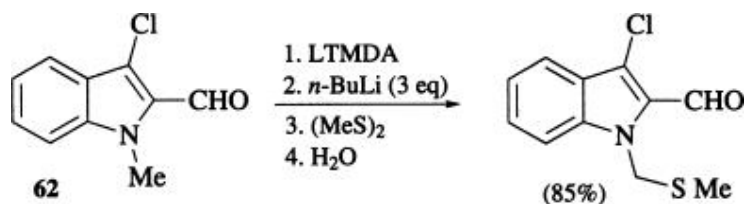
N-methyl group is an efficient process, and high yields of electrophilic trapping products are obtained. (128) Subsequent removal of the 3-chloro substituent can be effected by treatment with a mixture of palladium on carbon, triethylamine, and formic acid in ethanol.

3.1.6.1.3. Furans and Benzofurans

The propensity of furans to undergo lithiation α to the ring oxygen (12) introduces a serious complication when lateral metalations of this system are attempted. On the one hand, 2-methyl-3-furoic acid (**63**) readily undergoes lateral lithiation when treated with two equivalents of either LDA or *n*-butyllithium, and the resulting dilithio species can be trapped with electrophiles in generally good yields (Eq. 31). (129, 130) The dual activating effects of the carboxylate anion and the ring oxygen, both of which exert an electron-withdrawing effect, facilitate the lithiation of the methyl group. Similarly, 2,4-dimethyl-3-furoic acid
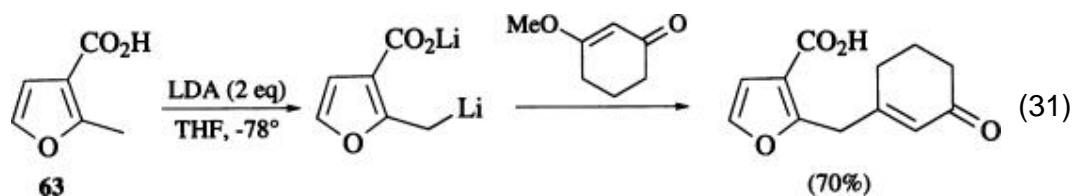
is lithiated at the 2-methyl group. (131) However, lithiation of 3-methyl-2-furoic acid with LDA occurs at the 5 position, as determined by deuteration studies (Eq. 32) and trapping with other electrophiles. (132) In this case, the activating effect of the furan oxygen wins out over that of the carboxylate anion.
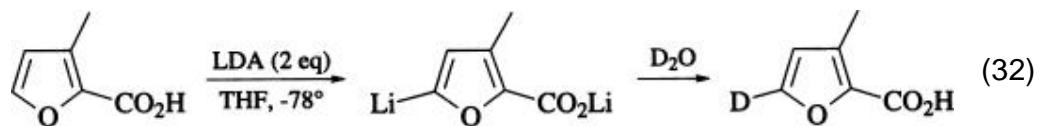
Selectivity for lithiation at C-5 is observed with the *N,N,N¢*-trimethylethylene-diamine adduct of 2-methylfuran-3-carboxaldehyde (Eq. 33). (127) However, an

$$(33)$$
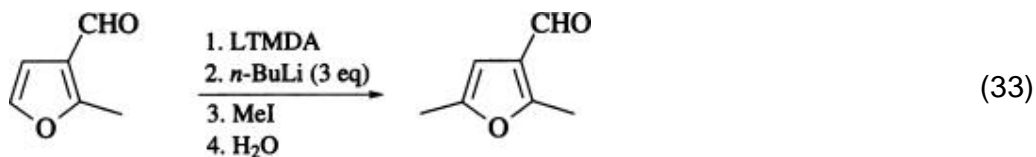
altogether different regiochemistry is observed in the lithiation of the dimethyl-aminomethylfuran derivative **64**, which affords the 4-substituted product upon
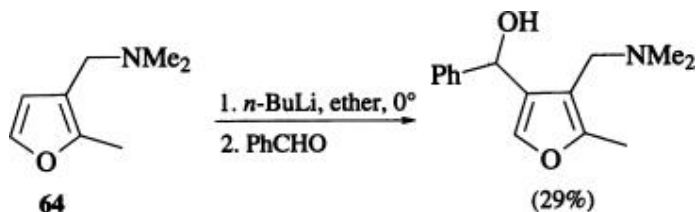
quenching with benzaldehyde, albeit in low yield. (133) This finding would have to be considered somewhat unexpected in light of the results given above and the facility with which the dialkylaminomethyl group normally facilitates lateral lithiation.

The lack of examples of lithiations of methylfurans substituted with other facilitating groups precludes generalizations regarding the factors that control lateral vs. α metalation in these systems. With 2,3-disubstituted benzo[*b*]furans, the possibility for competing αlithiation does not, of course, exist; dilithiation of 3-methylbenzo[*b*]furan-2-carboxylic acid (**65**) proceeds in the usual manner. (134)
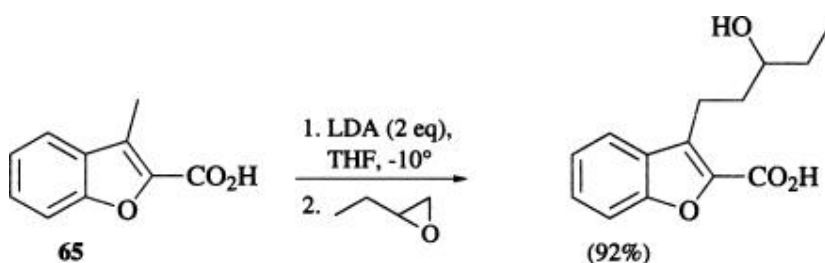
The lithio species derived from the methyl groups of **63** and **65** are more nucleophilic, that is, less basic, than the vinylic anions derived from 3-furoic acid (132) and benzo[*b*]furan-2-carboxylic acid, (134) respectively; hence they demonstrate significantly better reactivity toward a wider range of electrophiles than their desmethyl counterparts.

3.1.6.1.4. Thiophenes and Benzothiophenes

The ease with which thiophenes undergo α metalation (12) also limits the application of facilitated lateral lithiations to that ring system. Similar to the corresponding furan derivative (63), 2-methylthiophene-3-carboxylic acid (66) undergoes lateral lithiation upon treatment with LDA, and the
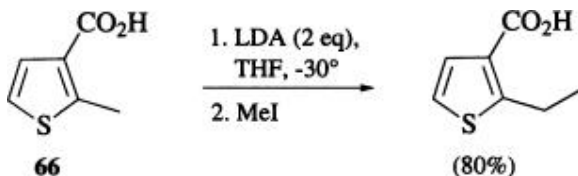
dilithio species reacts with electrophiles in high yield. (135) When *n*-butyllithium is used as base, a mixture of products derived from α lithiation (5 position) and lateral lithiation is obtained in a 1:1 ratio. Dilithiation of 3-methylthiophene-2-carboxylic acid (67) with LDA followed by quenching with deuterium oxide produces a mixture of deuterated products, with that derived from lateral lithiation predominating (Eq. 34). (136) Trapping with other reactive electrophiles (e.g.,

(34)
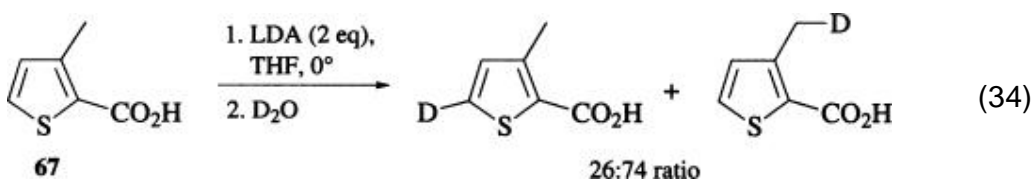
methyl iodide or acetone) affords similar regioisomeric mixtures, whereas the less reactive electrophile *n*-pentyl bromide affords only the product from the 3-lithiomethyl species (Eq. 35). A proposed rationale for these findings is that an

(35)
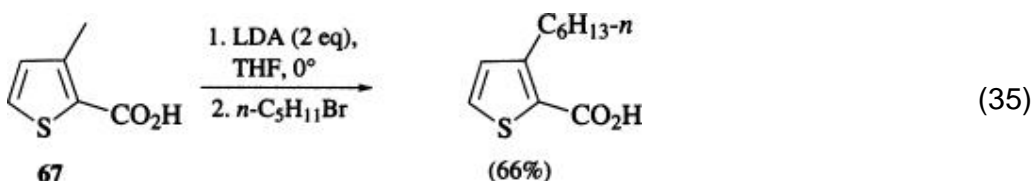
equilibrium mixture of dianions 68 and 69 is formed with the latter predominating. Quenching with reactive electrophiles gives a product mixture reflective of
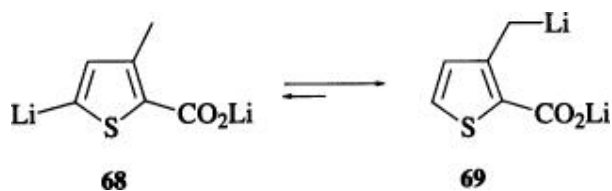
this equilibrium composition, whereas reaction with the less reactive electrophile occurs at the anionic site with greater *p* character. (136) Alternatively, the results in Eq. 34 could reflect trapping of a kinetic mixture of dilithio species **68** and **69**. The result in Eq. 35 would then be explained on the basis of equilibration to the thermodynamically more stable, resonance stabilized lithio species **69**.

Several other methylthiophenes that may, a priori, have been expected to undergo lateral metalation are lithiated at other positions. Dilithiation of 3,5-dimethylthiophene-2-carboxylic acid gives the dianion **70** as determined by
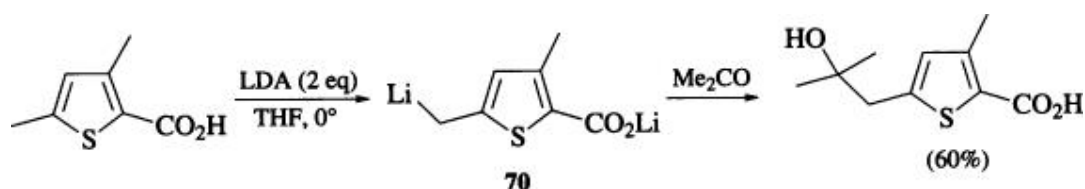
reaction with acetone or *n*-pentyl bromide. (136) The importance of charge separation has been proposed to explain the formation of **70** rather than the alternative lithio species from metalation of the 3-methyl group. (136) Lithiation of the dimethyl-aminomethyl derivative **71** appears to occur exclusively at C-5 as judged by the high yield of the benzaldehyde trapping product. (133) The regioisomer of **71**,
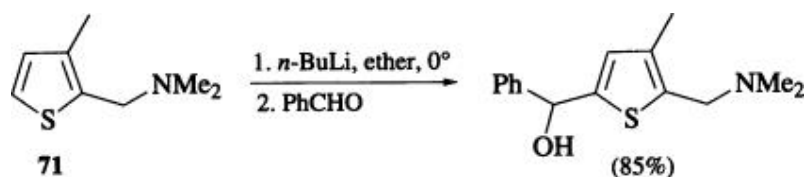
3-dimethylaminomethyl-2-methylthiophene, undergoes lithiation at the 4 and 5 positions (yields of benzaldehyde adducts of 24 and 59%, respectively). Other methylthiophenes that undergo metalation at C-5 rather than lateral metalation include the cyclohexylimine (70) and the lithium *N*-methylpiperazide adduct of 3-methylthiophene-2-carboxaldehyde, (127) and the *N*-methylpiperazide adduct of 2-methylthiophene-3-carboxaldehyde. (127)

Although only one example of a lateral lithiation of a benzo[b]thiophene derivative is reported, (44) this methodology should be generally applicable to this ring system with the proviso that the requisitely substituted alkyl derivatives are available.

3.1.6.1.5. Oxazoles and Thiazoles

The behavior of oxazoles and thiazoles in metalation reactions is similar and is therefore covered in the same section. The 2,4-dimethyloxazole- and 2,4-dimethylthiazole-5-carboxylic acids undergo selective lithiation at the 2-methyl group (Eq. 36). (137) The 2-methyl group is activated

$$X = O, S \qquad \xrightarrow[\text{2. MeI}]{\substack{\text{1. } n\text{-BuLi (2 eq),} \\ \text{THF, -78°}}} \qquad \begin{array}{l} X = O \ (87\%) \\ X = S \ (82\%) \end{array} \qquad (36)$$
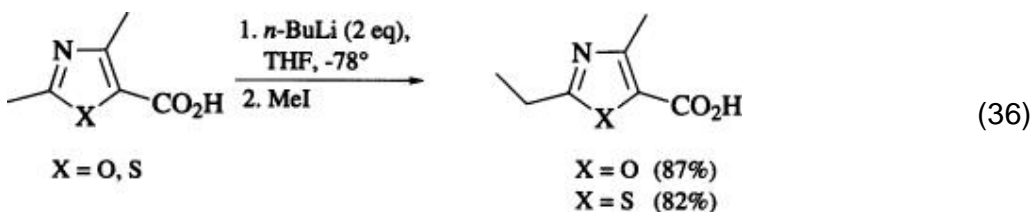
with respect to lithiation by the combined electron-withdrawing and chelation effects of the two ring heteroatoms; activation of the 4-methyl group by the adjacent carboxylate anion is not sufficient to overcome these effects. When the 2 position is blocked, as in the 2-phenyl derivatives **72**, carboxylate-facilitated

1. LDA (2 eq), THF, −30° (X = S) −78° (X = O)
2. MeI

72
X = O, S

X = O (84%)
X = S (89%)
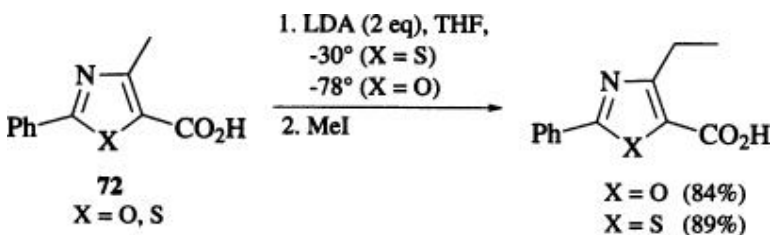
lateral lithiation occurs in the normal sense when LDA is used as the base. Lithiation of **72** (X = S) with *n*-butyllithium is slow at temperatures below −50°, whereas above that temperature nucleophilic addition of *n*-butyllithium to the thiazole ring becomes a competing process.

Because of its proximity to the more electronegative ring heteroatom, the 5-methyl group in 2,5-dimethyloxazole- and 2,5-dimethylthiazole-4-carboxylic acids is more activated toward lithiation than the 4-methyl group in the 2,4-dimethyl isomers (Eq. 36). Thus lithiation of the 5-methyl group in the 2,5-dimethyl derivatives is competitive with lithiation at the 2-methyl group, resulting in mixtures of electrophilic trapping products as in Eq. 37. (137) With a more

$$(37)$$

X = O, S

X = O ratio = 30:70 (71)
X = S ratio = 46:54 (—)
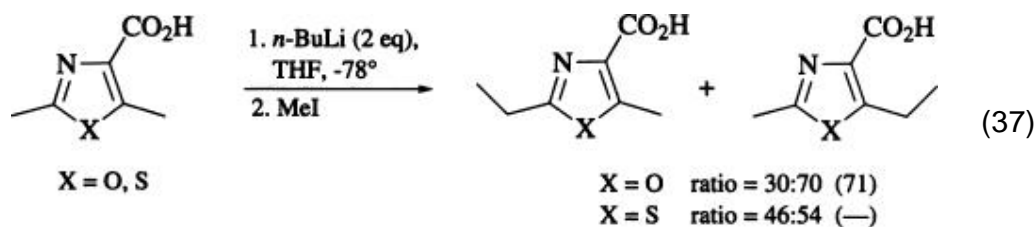
efficient facilitating group at the 4 position, lateral lithiation can become the exclusive pathway as with the corresponding *N,N*-diethylamides (Eq. 38). (137) Examples

$$(38)$$

X = O, S

X = O (98%)
X = S (97%)
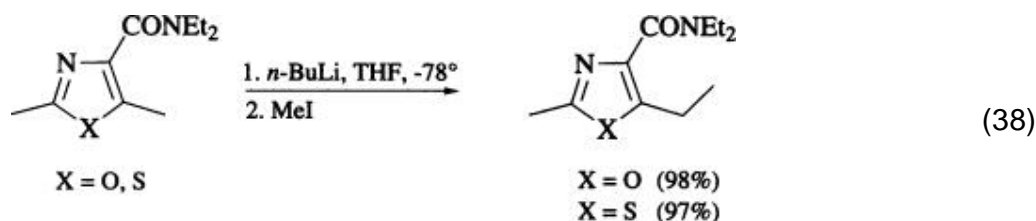
of lateral metalations of oxazoles and thiazoles that are unsubstituted at the 2 position are not reported. On the basis of the results described for furans and thiophenes, as well as those in this section, one can predict that lithiation at the 2 position in 2-unsubstituted oxazoles and thiazoles will compete effectively with lateral lithiation when relatively weak facilitating groups (e.g., carboxy) are present. With stronger facilitating groups, the outcome is more difficult to predict.

3.1.6.1.6. Imidazoles

The lithiation of 1-(*N,N*-dimethylaminomethyl)-2-methylimidazole (**73**) is the only reported example of a facilitated lateral metalation of an alkylimidazole.
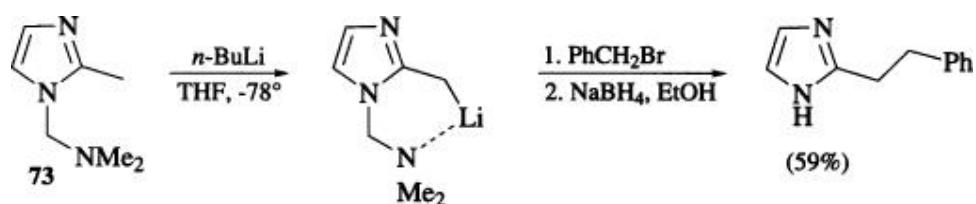
After electrophilic trapping of the 2-lithiomethyl species, the facilitating/protecting group is removed by treatment with sodium borohydride to give the parent imidazole. (138) The diethoxymethyl group affords similar facilitation of lateral lithiation of 2-methylbenzimidazole (Eq. 39). (139)

(39) (63%)
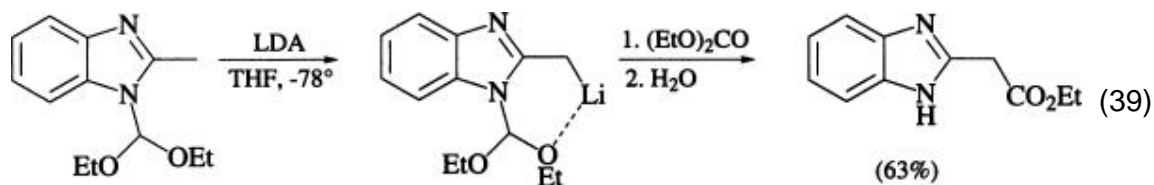
3.1.6.1.7. Isoxazoles

The lateral metalation of 3,5-dialkylisoxazoles substituted with a facilitating group at the 4 position has been extensively studied. The parent 3,5-dimethylisoxazole undergoes lithiation exclusively at the 5-methyl group upon treatment with *n*-butyllithium. (140) The ability of the ring oxygen atom to complex with the organolithium reagent is felt to be a major determinant of this regiochemical outcome. The 4-(*N*,*N*-dimethylamino)methyl derivative **74** is also lithiated exclusively at the 5-methyl group as determined by reaction of the lithio species with methyl iodide. (141) Thus the normal propensity for lithiation at the

74 (90%)
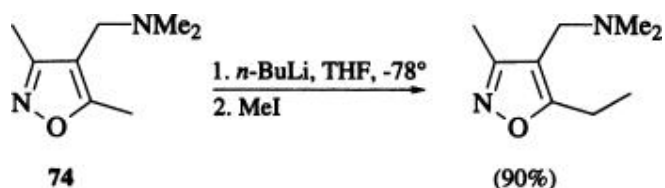
5-methyl group is reinforced by a facilitating group at the 4 position. Other facilitating moieties that afford the same regiochemical result include carboxy, (142) hydroxymethyl, (141) oxazolinyl, (142) tertiary carboxamide, (143) and Boc-aminomethyl groups. (141) The 5-lithiomethyl species derived from these metalations can be trapped in high yield with a large array of electrophiles (Table X-L).

An exception to the generalization made regarding selective lithiation at the 5-methyl group is noted with the proline-derived amide **75** wherein the regiochemistry of lithiation is dependent on the base and conditions used to effect the

Base: *n*-BuLi:TMEDA,
THF, -78°, 1 h ⟶ ratio **76:77** = 7:93
(amide added to base)

Base: *n*-BuLi, THF, -78°,
2 h (added to amide) ⟶ ratio **76:77** = >95:<5
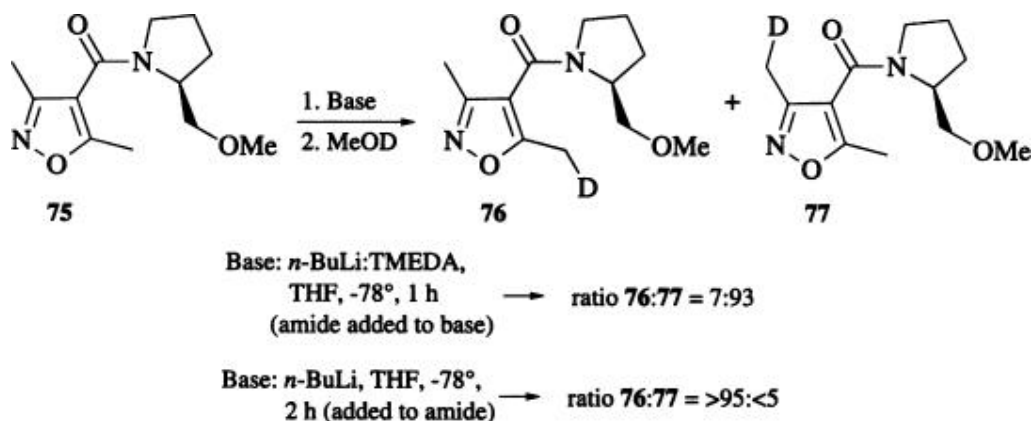
deprotonation. (144) Under "kinetically controlled" conditions (addition of the amide to *n*-butyllithium: TMEDA complex), regioselectivity for lithiation at the C-3 methyl group is observed. Under "thermodynamically controlled" conditions (addition of the base to the amide), the regiochemistry is reversed and almost exclusive lithiation at the C-5 methyl results. The latter result is rationalized on the basis of resonance stabilization afforded the C-5 lithiomethyl species by conjugation with the amide carbonyl. (144) The "kinetic" result is rationalized by invoking chelation of the organolithium reagent with the amide carbonyl which, for reasons not readily obvious, favors deprotonation at the C-3 methyl group.

3.1.6.1.8. Pyrimidines
In analogy with the lithiation of *o*-toluates, the dimethoxy-pyrimidine **78** can be laterally metalated and condensed with electrophiles in good yield. (145)
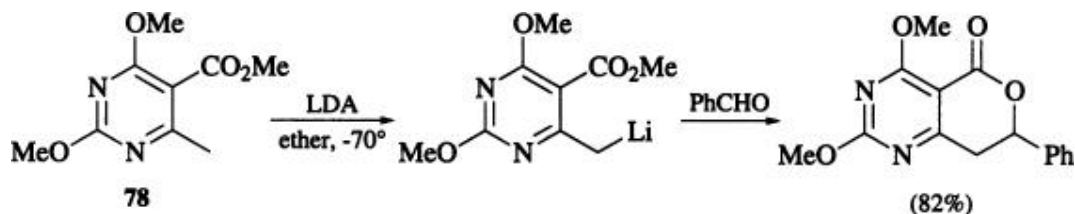
3.1.6.1.9. Benzotriazoles
The *N*-Boc-1-aminobenzotriazole **79** undergoes dilithiation with *n*-butyllithium: TMEDA. The resulting dilithio species decomposes at temperatures above 0° but is efficiently trapped at the benzylic position with electrophiles at low temperature (–78°). At higher temperatures, competitive *N*-alkylation is observed. (146)
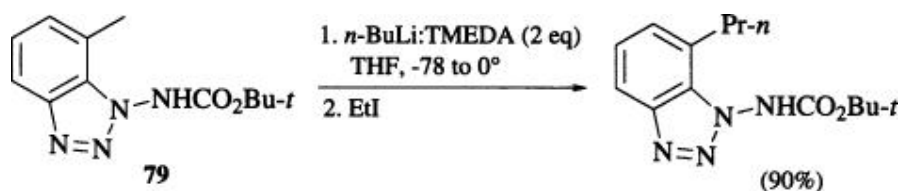
3.2. The Substrate

Laterally metalated species react with a diverse and extensive array of substrates. In general, electrophiles that react with normal organolithium or Grignard reagents can be used efficiently with these benzylic anions. Substrates have been catalogued for reactions with organolithium reagents in general (10) and for aryllithium reagents derived from heteroatom-facilitated *ortho* lithiations. (12) The present discussion is general, therefore, and covers aspects of substrate reactivity that are particularly relevant, or unique, to tolyl lithio species. Differences in reactivity of lithio species from heteroatom-facilitated *ortho* and lateral lithiation reactions are also covered. Reactivity differences exist among laterally metalated species, and the reader is referred to Tables I–X for a complete listing of substrates used for each particular class. The following survey is patterned after the earlier review according to the bond formed. (12)

3.2.1.1. C - D Bonds

Deuteration with D_2O or MeOD is generally a reliable reaction that can be used to determine the position of metalation. However, as noted earlier, deuteration of the LDA-derived *o*-toluic acid dianion is not successful. (29, 34) This does not appear to be a general phenomenon as treatment of the LDA generated dianion from 3-methylthiophene-2-carboxylic acid with deuterium oxide results in deuterium incorporation. (136) It is also reported that the dianion from 5-(2-methylphenyl)tetrazole (generated with *sec*-butyllithium: TMEDA) fails to incorporate deuterium at the benzylic position. (66)

3.2.1.2. C -C Bonds

Primary, allylic, and benzylic halides usually give good yields of alkylated products. Secondary and acetylenic (147) halides have been used in several instances. Successful reaction with these substrates is not eworthy since many aryllithiums from *ortho* lithiation reactions do not alkylate with halides other than methyl iodide. (12) For example, the dilithio species from 5-phenyltetrazole does not alkylate on the aryl ring with 1-iodopentane or benzyl bromide. (66) On the other hand, the dilithio species from lateral lithiation of 5-(2-methylphenyl)tetrazole undergoes alkylation at the benzylic position in excellent yield with either halide. (66) Delocalized tolyl anions, for example, those from *o*-toluic acid esters, phthalides, and tertiary *o*-toluamides, undergo cyclocondensation reactions with unsaturated systems. These

reactions are postulated to involve 1,4-addition to the substrate followed by intramolecular acylation. (148) Substrates that undergo such reactions include α ,β -unsaturated esters, (148, 149) lactones, (150, 151) nitriles, (148) trialkylsilanes, (152) sulfones, (152) and cyclic and acyclic enol ethers, (153) as well as α -pyrones (154) and γ -pyrones. (155) Addition to these substrates in a 1,4 sense is generally not observed with *ortho* lithiated species. Benzynes have also been used as substrates for cyclocondensation with phthalide anions. (156)

In most other respects, carbon–carbon bond-forming reactions of laterally metalated species with other substrates are analogous to those of normal organolithium reagents and *ortho* lithiated aromatics. Thus carboxylation with carbon dioxide or dimethyl carbonate is an efficient process. Addition to aliphatic and aromatic aldehydes is a dependable reaction while the efficiency of addition to enolizable ketones varies with the basicity of the lithium reagent. Similarly, benzaldimines and aryl nitriles are generally good substrates, whereas addition to aliphatic aldimines, ketimines, (157) and nitriles (158) is often less efficient because of deprotonation of the substrate. Esters and tertiary dialkylamides can used as acylating agents, although *N*-methoxy-*N*-methylcarboxamides (93, 159) are more reliable. Addition to *N,N*-dimethylformamide is a useful reaction only when subsequent intramolecular capture (93, 106, 160) of the initial adduct occurs.

3.2.1.3. C - N Bonds
Diethyl azodicarboxylate is the only substrate that has been used to effect this type of bond formation. (161, 162)

3.2.1.4. C -O Bonds
Direct oxygenation with molecular oxygen followed by reduction of the intermediate hydroperoxide with sodium sulfite affords a high yield of benzylic hydroxylation of dilithiated secondary toluamides. (163) Treatment of a lithiated tertiary toluamide (generated with *sec*-butyllithium: TMEDA) with oxygen affords the hydroxymethyl derivative in moderate yield. (164) Moderate to good yields of hydroxylation have been obtained in other systems with the molybdenumoxodiperoxy pyridine hexamethylphosphoramide complex (MoOPH) (142) and with *N*-(phenylsulfonyl)-3-phenyloxaziridine (NPSPO). (142, 162)

3.2.1.5. C - S and C -Se Bonds
Benzylic lithio reagents react with dialkyl or diaryl disulfides and diselenides to afford good yields of monosubstitution products. In some reactions with diphenyl disulfide, minor amounts of disubstituted product are obtained since the thiophenyl group exerts an additional acidifying effect on the benzylic position resulting in proton transfer. (165) Dithiophenylated products can be obtained exclusively when excess base and diphenyl disulfide are used. (35)

3.2.1.6. C - Si and C - Sn Bonds
Treatment of tolyl lithio species with chlorotrialkylsilanes affords good yields of benzyltrialkylsilanes. In situ deprotonation and silylation of these products affords bis-silylated derivatives. (166) Chlorotrialkylstannanes can be used to prepare benzyltrialkylstannanes. (167) Reaction of the dianion of 2-methylthioanisole with dichlorodimethyl or dichlorodiphenylsilanes and stannanes gives benzo-fused heterocycles containing two heteroatoms. (83)

3.2.1.7. C–Halogen Bonds
The reactive nature of benzyl halides precludes their synthesis by halogenation of benzylic anions. For example, treatment of dilithiated *p*-toluic acid with iodine results in dimerization to 1,2-diphenylethane. (31)

3.3. Influence of Alkyl Substitution at the Benzylic Position
Studies on the metalation of alkylbenzenes show that increasing the number of methyl groups at the benzylic position results in increased ring metalation at the expense of benzylic lithiation. Whereas a 90:10 ratio of benzylic to ring deprotonation is observed for toluene upon treatment with *n*-butyllithium: TMEDA, ratios of ca. 40:60 and 3:97 are observed for ethylbenzene and isopropylbenzene (cumene), respectively, under the same conditions. (15) These rate retardation effects have been ascribed to the inductive, rather than the steric, effects of the methyl groups. (15) Thus, it is not suprising that alkyl substitution at the benzylic position can have significant effects on lateral lithiation reactions. A decrease in the rate of lithiation at secondary positions is generally observed. For example, lateral lithiation of *N*-trimethylsilyl-2-ethylaniline is significantly slower than lithiation of *N*-trimethylsilyl-*o*-toluidine and requires use of *n*-butyllithium: TMEDA rather than *n*-butyllithium. (101) Despite the decrease in rate, the site of lithiation, that is, at the benzylic position, is maintained in the 2-ethyl derivative. In other examples, the regiochemistry of lithiation is reversed upon alkyl substitution at the benzylic position; the 2-ethylphenol phosphorodiamidate **80** undergoes *ortho* lithiation as determined by reaction of the lithio species with methyl iodide. (87)
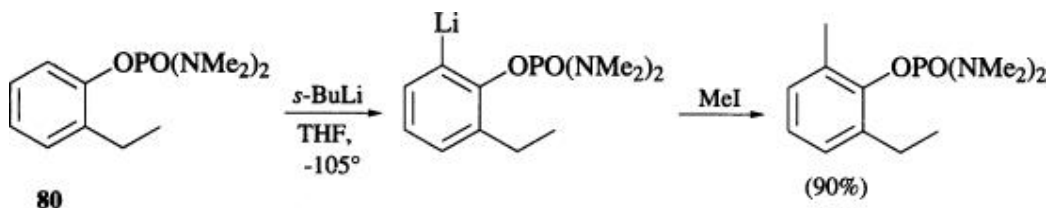
In certain cases the site of lithiation is base dependent. Lithiation of the 2-ethyl

secondary benzamide **81** occurs exclusively at the benzylic position with LTMP as determined by reaction with methyl iodide. (47) With organolithium bases, *ortho* lithiation is also observed and is the major reaction pathway with *tert*-butyllithium. These results are qualitatively similar to those previously described

Base	82:83
LTMP	100:0
n-BuLi	70:30
s-BuLi	70:30
t-BuLi	40:60
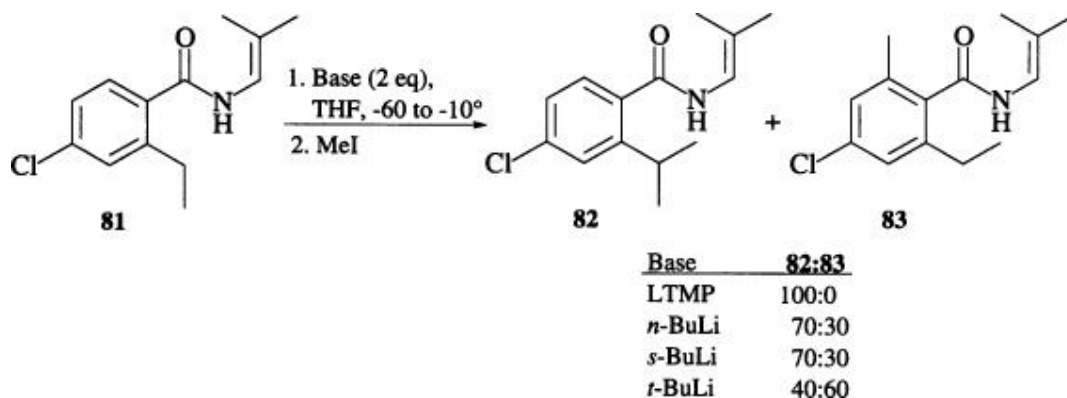
for the lithiation of *N,N*-diisopropyl-*p*-toluamide (**1**). In that example, it is suggested that the benzylic lithio species is the thermodynamic product and the *ortho* lithiated species is the kinetic product. (23) Whether a similar interpretation can be applied to explain the results for **80** and **81** is not clear because additional variables, for example, steric factors, are involved.

The decreased rate of lithiation at secondary positions can allow deprotonation at alternative sites in the molecule to become competitive with lateral lithiation. For example, lateral lithiation of the Boc-benzylamine **84** is not a synthetically useful process because of competing lithiation *ortho* to the methoxy group. (47)
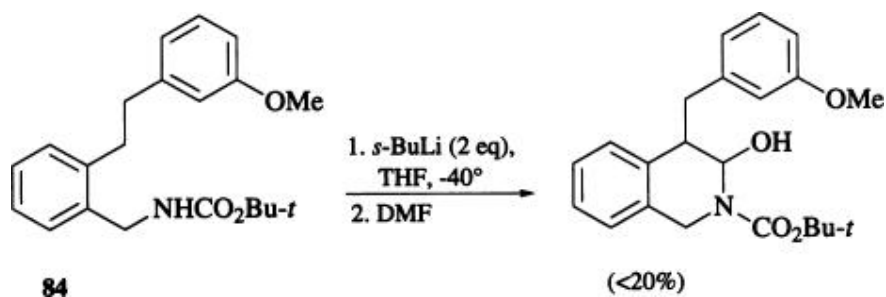
Heteroatom facilitated lateral lithiations of isopropylbenzenes have not been achieved. Whereas *N*-ethyl-2-ethylbenzamide and *N,N*-diethyl-2-ethylbenzamide are lithiated at the benzylic position with

sec-butyllithium: TMEDA (Eq. 40), the corresponding isopropyl derivatives undergo *ortho* lithiation (Eq. 41). (168) The

$$(40)$$

R = H (87%)
R = Et (52%)

$$(41)$$

R = H (63%)
R = Et (95%)
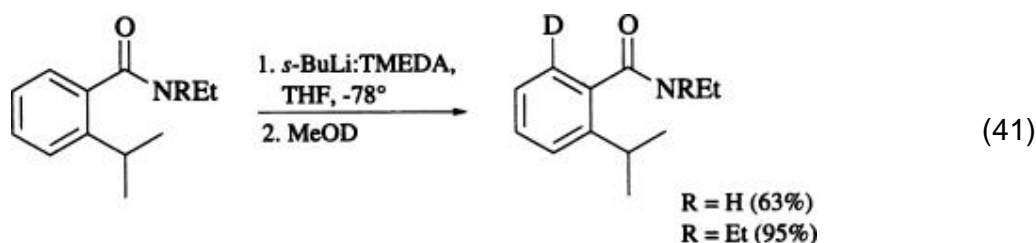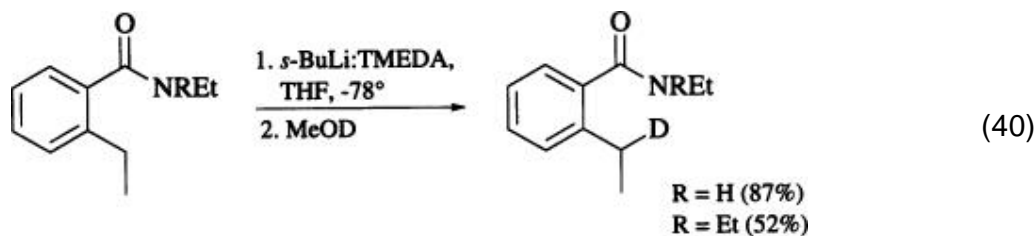
failure of these isopropyl derivatives to undergo benzylic lithiation has been attributed to a destabilizing steric interaction between the isopropyl group and the carboxamide group. This interaction may cause the amide group to twist out of the plane of the aromatic ring and thereby assume an orientation that favors *ortho*, rather than lateral, lithiation. (168) However, additional data are required to confirm this hypothesis as the results of a recent study indicate that coplanarity of the amide carbonyl and the *ortho* hydrogen increases the efficiency of *ortho* lithiation. (169)

3.4. Influence of Ring Substituents

3.4.1.1. Effect on Rate of Lateral Lithiation

Ring substituents, that is, substituents other than the facilitating group G in Eq. 1, have been reported to affect the rate of lateral lithiation reactions only in isolated cases. These reports are of a general nature and detailed rate studies have not been performed. A noticeable decrease in rate of benzylic lithiation can occur when a methoxy group is situated *para* to a methyl group, as in the methoxy substituted Boc-*o*-toluidine **85**. (93) Whereas
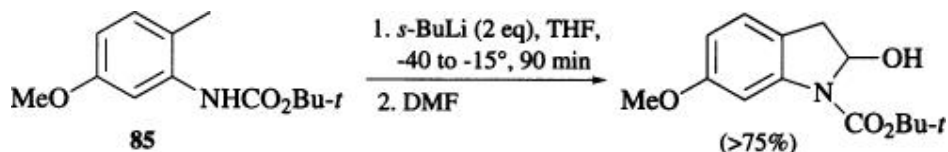
dilithiation of Boc-*o*-toluidine with *sec*-butyllithium is complete within five minutes at –40°, dilithiation of **85** requires a longer reaction time and a higher temperature. The electron-donating effect of the methoxy group, which

decreases the acidity of the *para*-disposed methyl group, appears to be the major determinant of this rate decrease. This rationale is supported by the observation that the 4-methoxy analog, in which the resonance effect of the methoxy does not affect the acidity of the methyl group, is lithiated at approximately the same rate as Boc-*o*-toluidine. (93) The deacidifying effect of a *para* methoxy group on a benzylic position has also been observed in the lithiation of *p*-methoxy-*N,N*-dimethylphenethylamine. (170) The 3,4-dimethoxy derivative **86** undergoes lithiation at a rate comparable to that of **85**; (93) however, because *ortho* methoxy groups
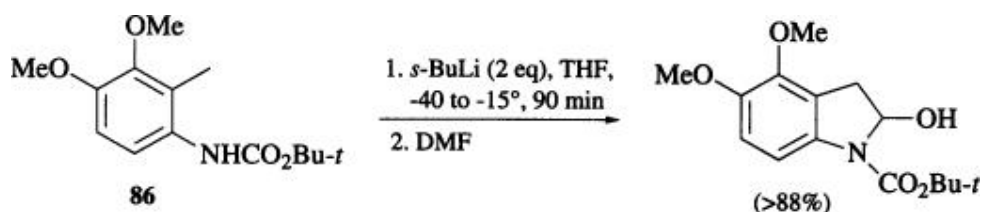
normally facilitate lateral lithiation, (76) this rate retardation relative to Boc-*o*-toluidine is not easy to rationalize. The reported inefficiency of lateral lithiation of 4,5-methylenedioxy-2-methylbenzoic acid (30) may be related to a similar rate decrease induced by *para* alkoxy substitution.

3.4.1.2. Competitive ortho vs. Lateral Lithiation

Ring substituents rarely induce *ortho* lithiation in substrates that can undergo heteroatom facilitated lateral lithiation. The lithiation of the Boc-*o*-toluidine **85** described above is illustrative of this point. A priori, lithiation might have been expected at the 6 position of **85** since that position would appear to be doubly activated for *ortho* lithiation by the combined effects of the methoxy group and the Boc group. (93, 171) However, products of substitution at the 6 position are not observed, despite the relatively low rate of lateral lithiation. Information on kinetic and thermodynamic acidities is not available for this system; therefore the possibility cannot be excluded that kinetic deprotonation occurs at the 6 position followed by proton transfer to form the benzylic lithio species. However, in a somewhat related example (Eq. 42), an

(42)
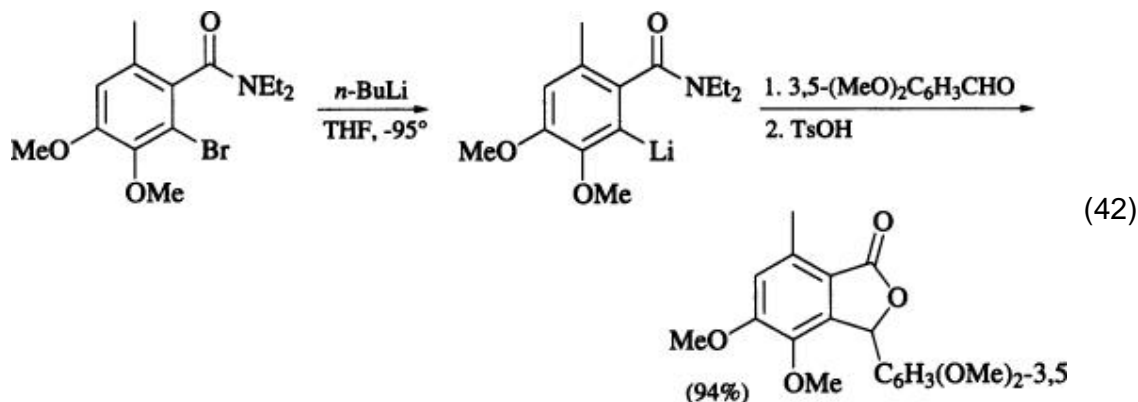
ortho lithio species (generated by halogen-metal exchange) does not interconvert with the benzylic lithio species, albeit at lower temperature than in lithiation of **85**. (172) Another noteworthy feature of the lithiation in Eq. 42 is that the halogen-metal exchange is significantly faster than deprotonation of the methyl group.

The lithiation of the phosphorodiamidate **87** is one example in which the co-operative effects of directing groups induce *ortho*, rather than lateral, metalation. (173) On the other hand, the related *tert*-butyldimethylsilyloxy derivative **88**
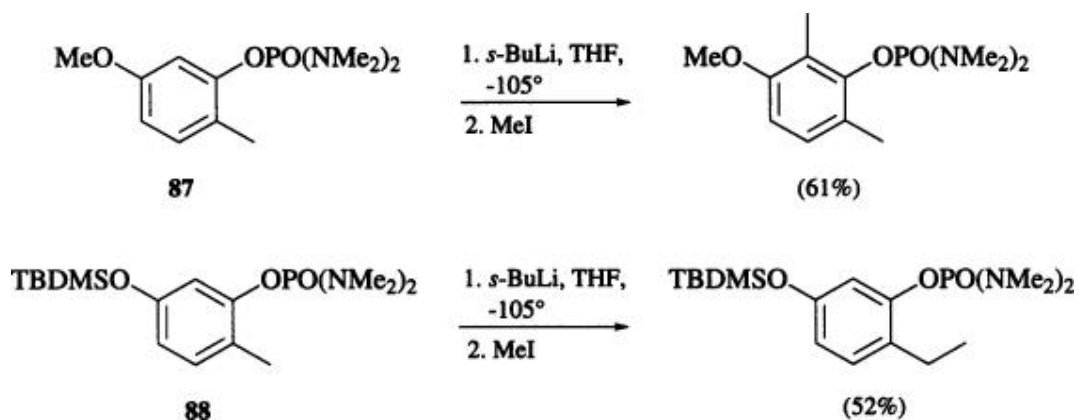
undergoes lateral lithiation. The steric effect of the bulky trialkylsilyl group is implicated as the major factor that changes the regiochemical outcome of these lithiations. Information on mechanism is available in neither case, however, and as is discussed above for the lithiation of **85**, the assumption cannot be made that the observed lithio species are formed directly.

3.4.1.3. Compatibility
The compatibility of aromatic substituents in lateral lithiation reactions is dependent on the conditions used to effect the lithiation (base, temperature,

etc.) and, to a certain extent, on the reactivity of the lithio species thus generated. Given the wide variations in the conditions used in these reactions, and the disparate nature of the laterally metalated derivatives, it is difficult to make general statements regarding the compatibility of substituents. Nonetheless, for certain types of substituents, generalizations regarding compatibility are valid; however, for other substituents compatibility must be determined experimentally. Examples of both types are given in the following discussion.

Substituents that are susceptible to electrophilic attack by organolithium reagents should generally be considered to be incompatible with lateral metalation processes. This group includes aldehydes, ketones, esters, nitriles, nitro groups, and unhindered tertiary amides. Lateral lithiations in which certain secondary amides (174) and hindered tertiary amides (55) are present as substituents are known. An example of a lateral lithiation in which an ester substituent is present was shown earlier in Eq. 9. In that case, however, the ester is deactivated toward electrophilic attack by the electronic (and possibly steric) effect of an adjacent alkoxide group. In certain instances, a carboxy group is a compatible substituent (Eq. 43). (175) The inductive effect of the *meta*-carboxy group also facilitates, albeit weakly, lithiation of the methyl group.

$$\text{(43)}$$
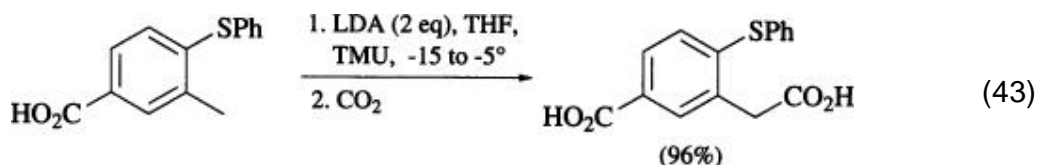
Alkyl, alkenyl, (87) and allyl (87) substituents can generally be considered as compatible in lateral lithiation reactions. As has already been alluded to, certain groups (i.e., carboxy, (29) tertiary amide, (22) cyano, (58) isocyano, (104) sulfonamide, (176) sulfonate (114)) facilitate lithiation of *para*-methyl groups. However, in heteroatom facilitated lithiations of 2,4- or 2,5-dimethyl derivatives, lateral lithiation of the 2-methyl group is the exclusive pathway. (29, 104) In the lithiation of 2,4-dimethylphenyl iso-cyanide, use of a large excess of lithium diisopropylamide results in lithiation of both methyl groups. (104)

Chlorine and fluorine are widely used as substituents in lateral lithiations. Halogen-metal exchange or aryne formation is not observed with these substituents in lateral metalation reactions. On the other hand, bromine undergoes halogen-metal exchange with organolithium reagents at such a rate as to preclude its use as a substituent in lateral lithiations involving organolithium bases. As shown previously in Eq. 42, a ring-brominated

diethyl-*o*-toluamide undergoes halogen-metal exchange, rather than lateral lithiation, upon treatment with *n*-butyllithium. (172) Similarly, treatment of Boc-4-bromo-2-methylaniline with *sec*-butyllithium results in halogen-metal exchange at the expense of lateral lithiation. (48) Lateral lithiation of bromotoluic acid **89** with lithium diisopropylamide proceeds normally; (177) however, the generality of lithium diisopropylamide promoted lateral lithiations of other brominated substrates remains to be established.
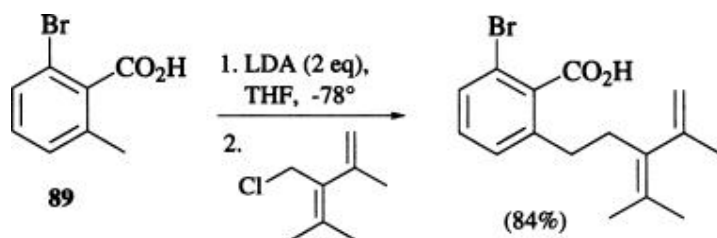
On the basis of the observations on lithiations of trifluoromethyl-substituted toluenes, trifluoromethyl would appear to be a viable substituent only when situated *meta* to the position of lateral lithiation. (115)

4. Synthetic Utility

Lithio species derived from heteroatom facilitated lateral lithiation reactions have numerous synthetic applications. The utility of these metalated derivatives for effecting chain extension and simple functionalization of alkyl groups adjacent to facilitating groups on aromatic and heteroaromatic rings has been amply demonstrated earlier in the chapter, and additional examples can be found throughout the tables. These synthetic transformations do not require further elaboration in this section. Another extremely useful application of these lithio species is in annelation of carbocyclic and heterocyclic rings onto aromatic (and heteroaromatic) systems. In these transformations, functionalization of the lateral position by treatment with an electrophile is followed by an intramolecular reaction with the facilitating group to effect ring closure. Depending on the structures of the facilitating group and the electrophile, the annelated product is obtained either from nucleophilic attack of the functionalized lateral position on an electrophilic facilitating group, or by nucleophilic attack of the facilitating group on an electrophilic lateral moiety. Examples of these annelations, which may be single or multistep processes, are presented in the following sections.

4.1. Carbocyclic Systems
1-Tetralones can be prepared in 40–50% yield by condensation of toluate anions and acrylates followed by hydrolysis and decarboxylation of the intermediate β -ketoesters (Eq. 44). (149) As previously noted, the synthetic utility of

$$(44)$$
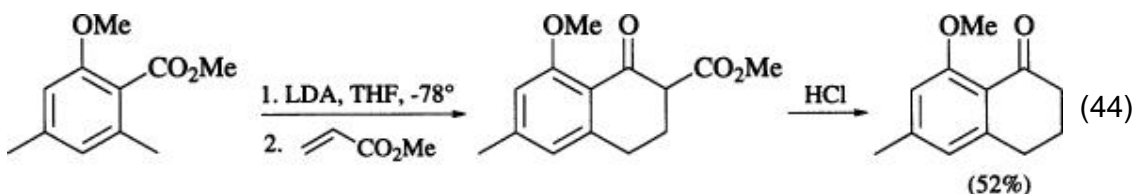
toluate lithio species is dependent on *ortho*-alkoxy substitution; hence, only 8-alkoxy-1-tetralones are accessible by this route. Nonetheless, the preparation of these derivatives is noteworthy since classical syntheses of 1-tetralones, for example, by intramolecular Friedel–Crafts acylation, generally do not provide 8-substituted products. 1-Tetralones are also obtained by addition of *N,N*-diethyl-*o*-toluamide anions to vinylsilanes (Eq. 45). (152) Yields in this condensation

(45)
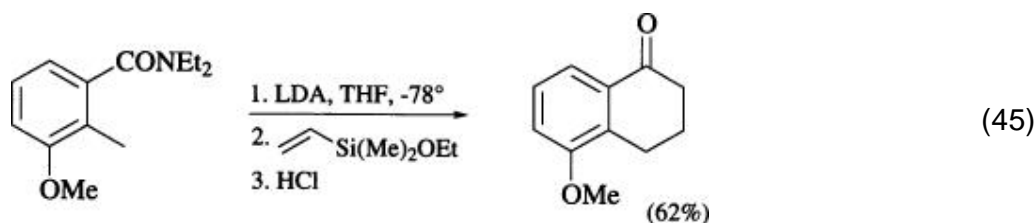
reaction are significantly higher with ethoxydimethylvinylsilane than with trimethylvinylsilane. In contrast to the synthesis of 8-methoxy-1-tetralones from toluic acid esters as in Eq. 44, the preparation of these derivatives from reaction of 6-methoxytoluamide anions with vinylsilanes proceeds in less than 10% yield, a result ascribed to steric hindrance in the cyclization step. (152) 2-Phenylsulfonyl-8-methoxy-1-tetralones can be prepared in high yield from toluate anions and 1-(trimethylsilyl)vinylsulfones (Eq. 46). (152) The corresponding reaction of the

(46)

(65-98%)
R = H, Aryl
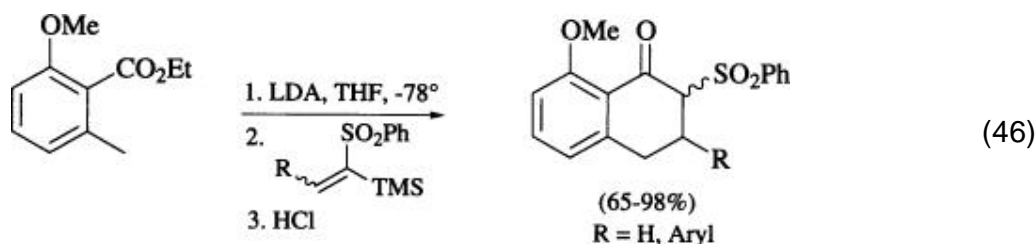
lithio species from *N,N*-diethyl-*o*-toluamide affords Michael adduct **90**. Subsequent treatment with LDA at reflux in tetrahydrofuran is required to effect cyclization to the tetralone.
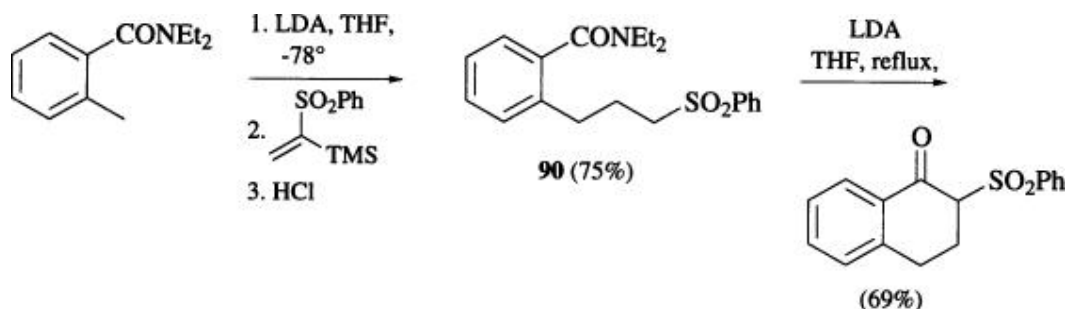
1-Naphthols are prepared in high yield by cyclization of anions derived from lateral lithiation of *o*-allyl tertiary benzamides. (178) Thus base induced cyclization of allylbenzamide **91** affords 5-methoxy-1-naphthol (**92**) in high yield. Methyllithium was found to be the base of choice for effecting these anionic cyclizations
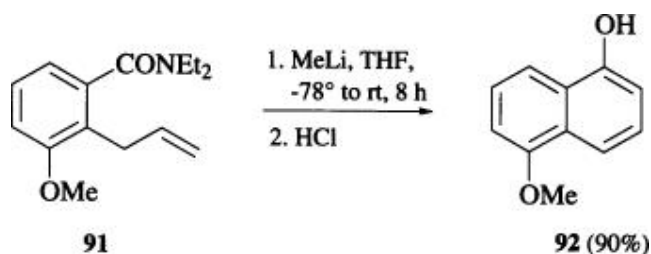
as, for example, the yield in the LDA-promoted cyclization of **91** was only 58%. A mechanistic hypothesis for these benzoannelation reactions invokes initial formation of the sickle-shaped allyl anion shown in Eq. 47. This anion may
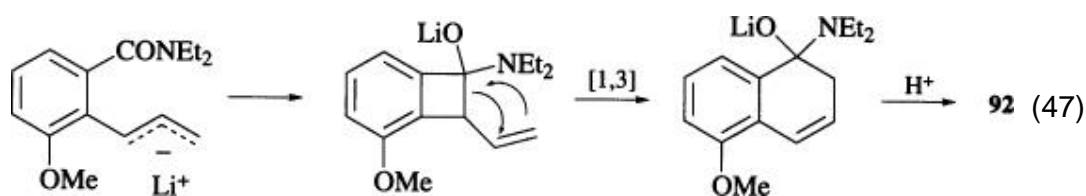
cyclize to the vinylbenzocyclobutane alkoxide adduct, which can undergo a [1,3]-sigmatropic rearrangement leading to the observed product. An alternative mechanistic pathway involving direct cyclization of the U-shaped allyl anion is felt to be less likely on the basis that the rotational barrier between the sickleshaped anion and the U-shaped anion is expected to be very high. (178)

More highly substituted 1-naphthols are obtained by a two-step sequence commencing with addition of lithiated phthalides to Michael acceptors. For example, reaction of phthalide anions with α , β -unsaturated esters affords 4-hydroxy-1-tetralone adducts in moderate yield as in the formation of the methyl crotonate adduct **93**. (148) Dehydration to the naphthol is easily effected upon treatment
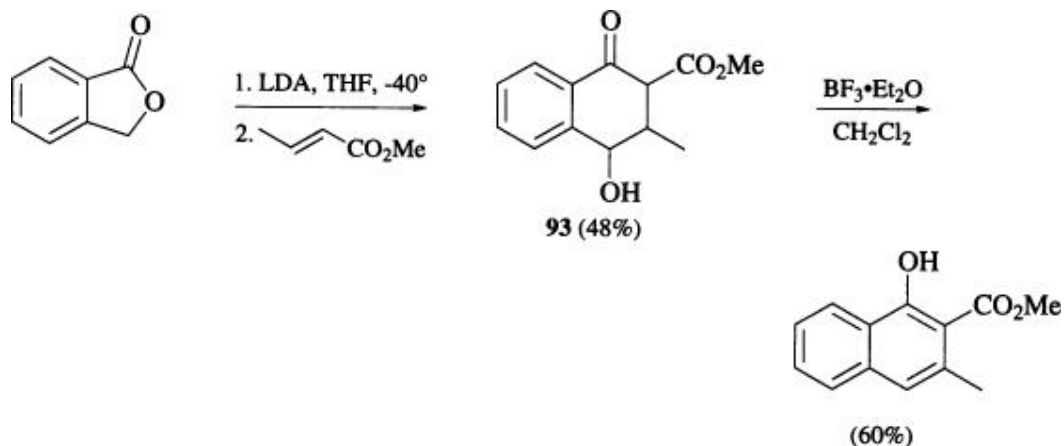
of the 4-hydroxy-1-tetralone with an acid catalyst. Other Michael acceptors that can be used in this protocol include acrylonitrile, dimethyl fumarate, dimethyl maleate, and 1-(trimethylsilyl)vinylsulfones. The overall yields of naphthols obtained from vinylsulfones, as in Eq. 48, (152) are generally higher than those obtained from the ester and nitrile Michael acceptors.

(48)
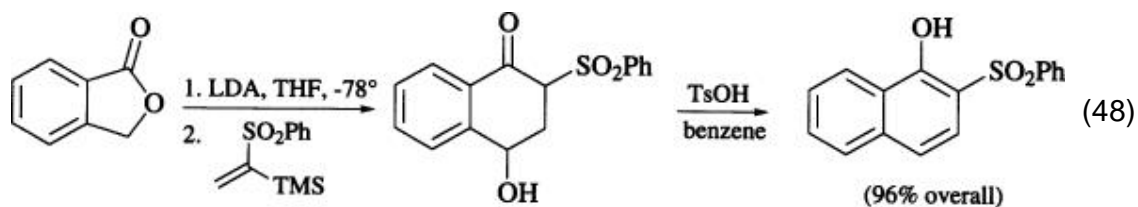
Highly substituted 1-naphthols can also be prepared by condensation of toluate anions with β -alkoxy enones as exemplified by the synthesis of the pentasubstituted naphthalene **94**. (153) When applied to cyclic β -alkoxy enones, this reaction provides linear polycyclic systems (e.g., **95**). (153) As in the tetralone syntheses described
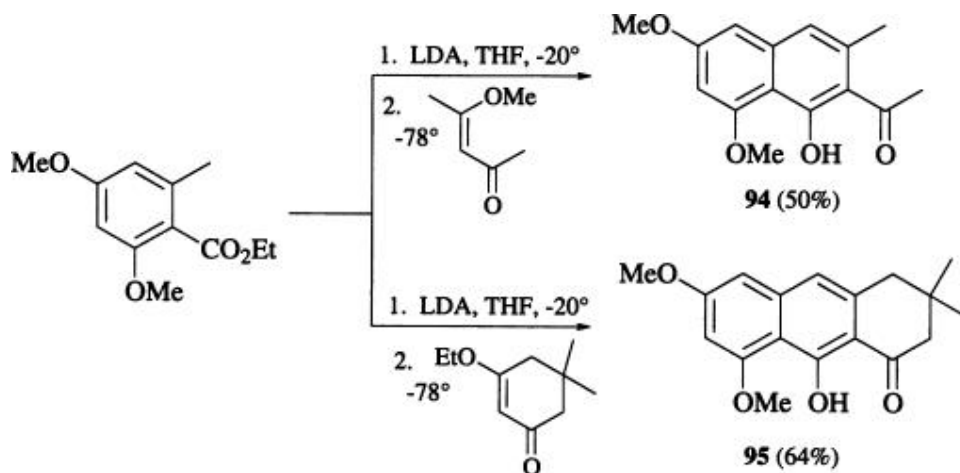
above, an alkoxy group *ortho* to the toluate ester carbonyl is essential to the success of these reactions; however, as discussed later in the chapter, this apparent liability is used to advantage in the synthesis of oxygenated polycyclic natural products. The analogous condensation of 6-alkoxytoluate anions with 4-methoxy-5,6-dihydro-2-pyranones affords dihydro-1*H*-naphtho[2,3-*c*]pyrans such as **96**. (179) The corresponding tetrahydro derivatives (e.g., **97**) can be prepared by condensation of the toluate anion with the 5,6-dihydro-2-pyranone. (151)

3-Substituted-2-naphthols **98** are prepared by acylation of *o*-tolualdehyde cyclohexylimine followed by treatment with aqueous sodium hydroxide. (180) Condensation of lithiated tertiary *o*-toluamides with homophthalic anhydrides provides a route to 3-aryl-1,3-naphthalenediols as in Eq. 49. (181) Effectively, the lithio species derived from homophthalic anhydride is the substrate in this condensation; this accounts for the observed regiochemistry of addition and for the necessity for using two equivalents of lithiated *o*-toluamide.
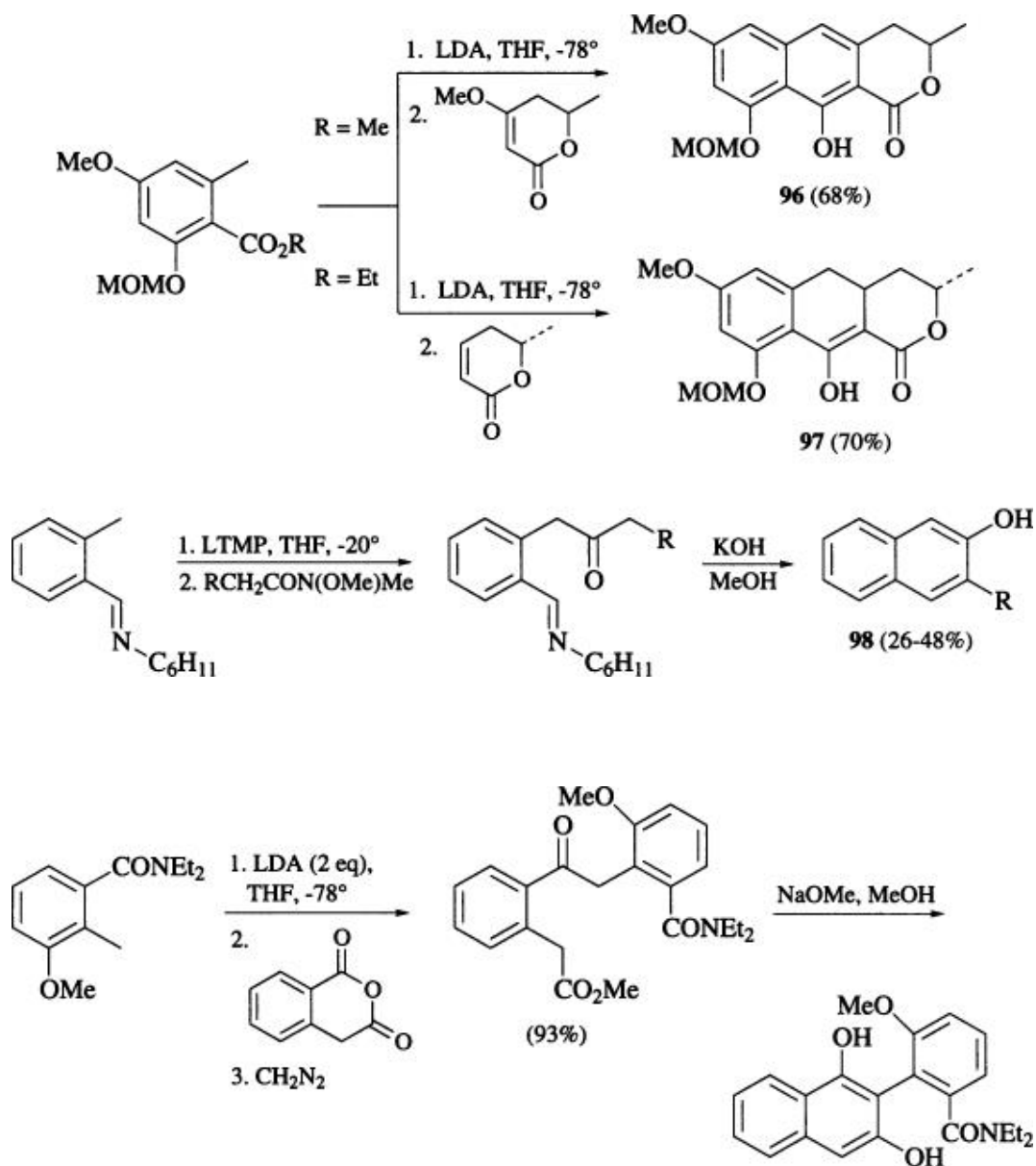
(49)

Phenanthrols are obtained in excellent yield by remote lateral lithiation of 1¢-methylbiphenyl-l-dialkylamides, (55) a process that is formally related to the cyclization of allylbenzamides discussed above. The preparation of 9-phenanthrol by this reaction is shown earlier in the chapter (page 15). More highly condensed polycyclic aromatics can also be prepared by this method, as exemplified by the synthesis of 5-hydroxybenz[a]anthracene (**100**) from the naphthylphenylbenzamide **99**. However, the related benzamide **101** fails to undergo cyclization,
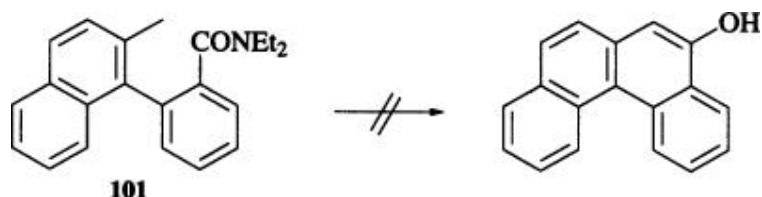
presumably as a consequence of developing *peri* hydrogen–phenyl interaction. (55) This methodology also provides heterocyclic ring-annelated naphthoquinones (Eq. 50). (182) In these cases, the naphthols formed in the initial condensation reaction

$$X = O \quad (50\%)$$
$$X = S \quad (55\%)$$

(50)
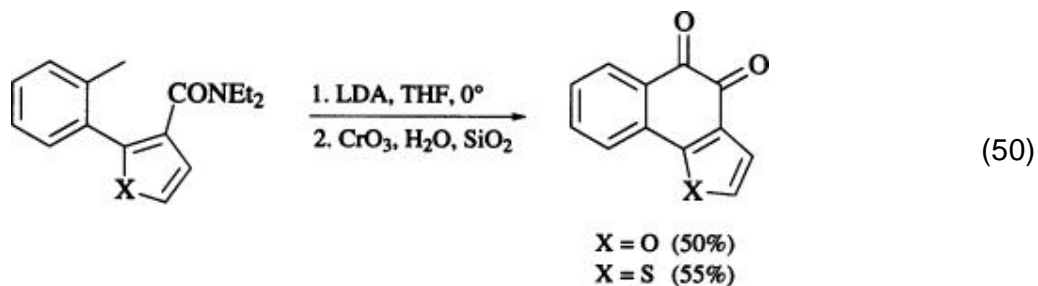
are unstable and therefore are oxidized to the naphthoquinones without purification. The corresponding pyrido-fused naphthoquinones are prepared in a similar manner.

Anthraquinones can be prepared in moderate to good yield by reaction of phthalide anions with arynes. (156) This transformation is effected by preparation of the phthalide lithio species in the presence of two equivalents of base followed by addition of a bromobenzene and in situ generation of the aryne. The reaction mixture is allowed to warm to room temperature with eventual exposure to air to oxidize the intermediate hydroxyanthrone lithio salt. In the example shown in Eq. 51, the yield of anthraquinone obtained by this procedure is increased from

(51)
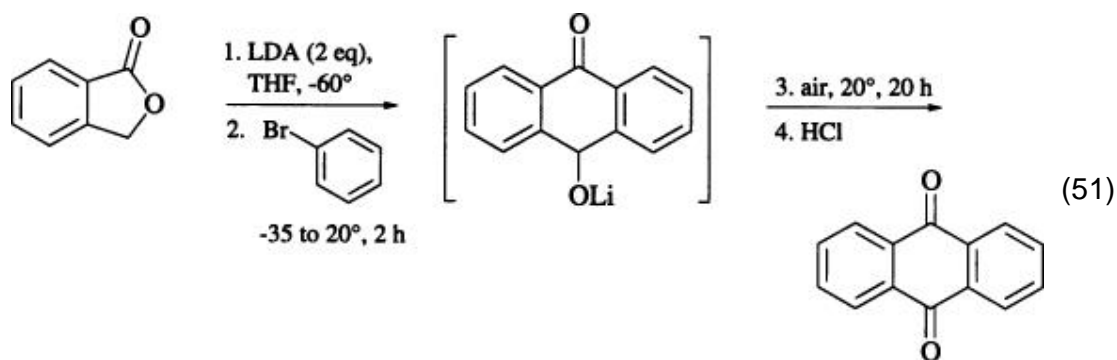
29 to 75% when the amount of aryne precursor is increased from one to two equivalents. Phthalide anions undergo regioselective addition to certain arynes as in the formation of 1,7-dimethoxyanthraquinone (**102**) via the benzyne generated from 2-bromoanisole. (156)

102 (41%)
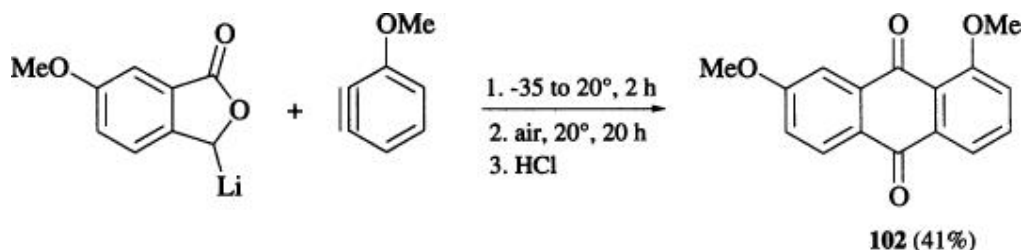
Lateral lithiation reactions have been used to prepare precursors of *o*-quinodimethanes, and these reactive intermediates have in turn been used for the synthesis of di- and tetrahydronaphthalenes via Diels–Alder cycloadditions. The generation of these *o*-quinodimethanes is generally accomplished by fluoride-induced 1,4-elimination of *o*-[(trimethylsilyl)methyl]benzyl derivatives (166, 183-185) such as the trimethylammonium salt **103**. (105) Intramolecular variations

(95%)   103

(88% from 103)
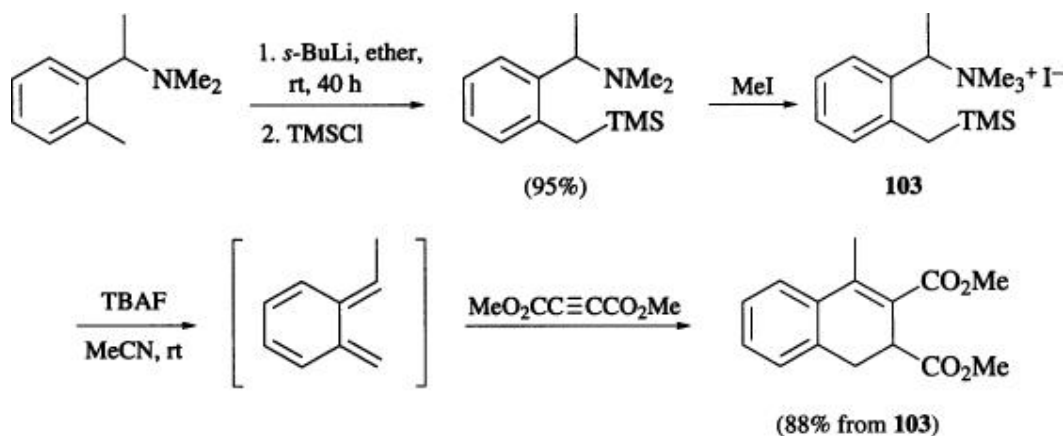
of this reaction have been used in the synthesis of estrone (186) and 11-hydroxyestrone methyl ether. (187) A related protocol for the generation of *o*-quinodimethanes involves proton-induced 1,4-elimination of *O*-(1-hydroxy-alkyl)benzyltributylstannanes (e.g., **104**). (167, 188) This procedure appears to give

22   104   (85%)
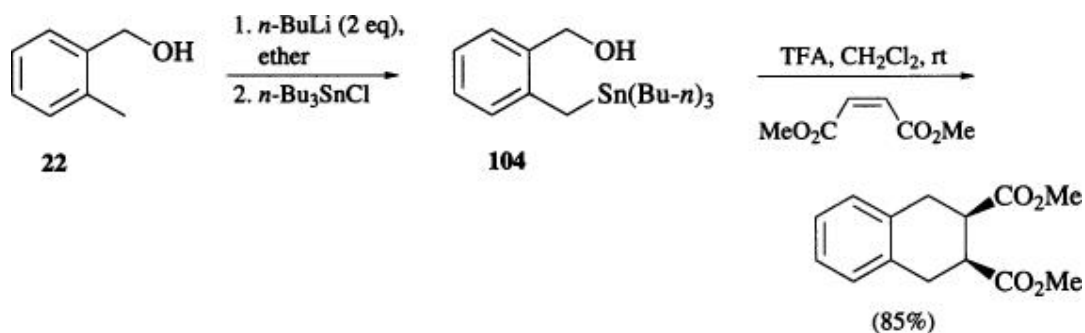
higher yields of cycloadducts with electron-deficient alkenes than does the fluoride-induced elimination process. Diels–Alder reaction of 1-trialkylsilyloxy-3-arylisobenzofurans, which are prepared by lateral lithiation of 3-arylphthalides followed by *O*-silylation, represents yet another aspect of *o*-quinodimethane cycloaddition chemistry. (189)

4.2. Heterocyclic Systems

4.2.1.1. Oxygen and Sulfur Containing

Homophthalic anhydrides (e.g., **105**) are readily available from *o*-toluic acids by carboxylation of the dilithio species followed by dehydration of the homophthalic acid thus produced. (190) Acetylation of the homophthalic anhydride followed by thermal decarboxylation of the 4-carboxy intermediate provides the corresponding 3-methylisocoumarins (1*H*-2-benzopyran-1-ones)(e.g., **106**). (190) Homophthalic anhydrides can also be prepared by sequences commencing with carboxylation of diethyl-*o*-toluamides (191) and (2-methylphenyl)-2-oxazolines. (192, 193)
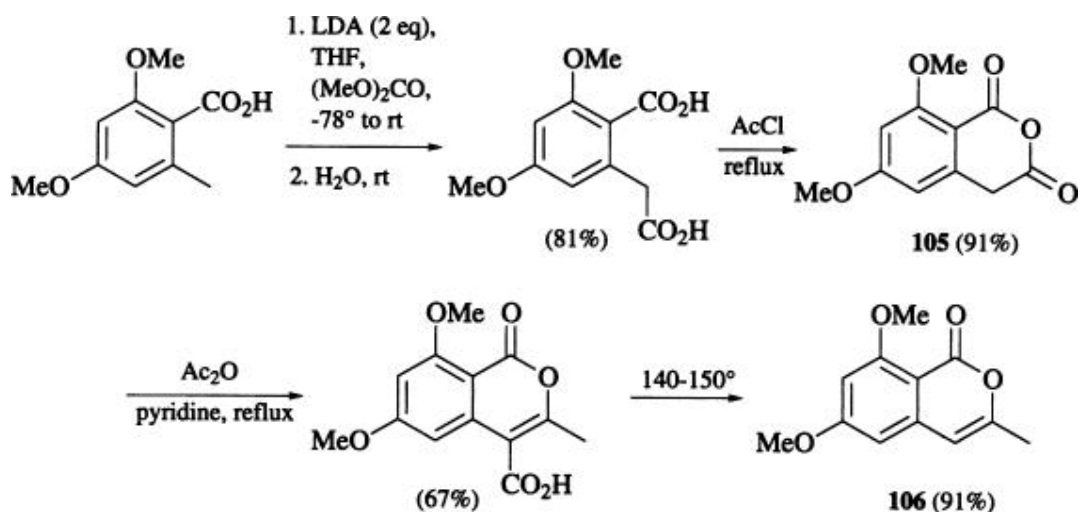
Acylation of 6-methoxytoluate esters with *N*-methoxy-*N*-methylcarboxamides followed by base-promoted cyclization of the resulting ketoesters provides 3-substituted 8-methoxyisocoumarins **107**. (159) A more general route to 3-substituted
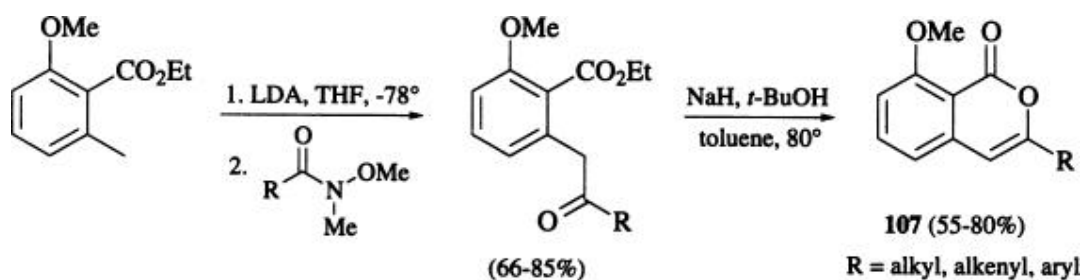
isocoumarins, involving a similar acylation of toluic acid dianions followed by dehydrative cyclization, has apparently not been investigated. Condensation of lithiated *N,N*-diethyl-*o*-toluamide with thioesters gives 3-substituted thioisocoumarins (1*H*-2-benzothiopyran-1-ones) **108** in a one-pot procedure. (194) The
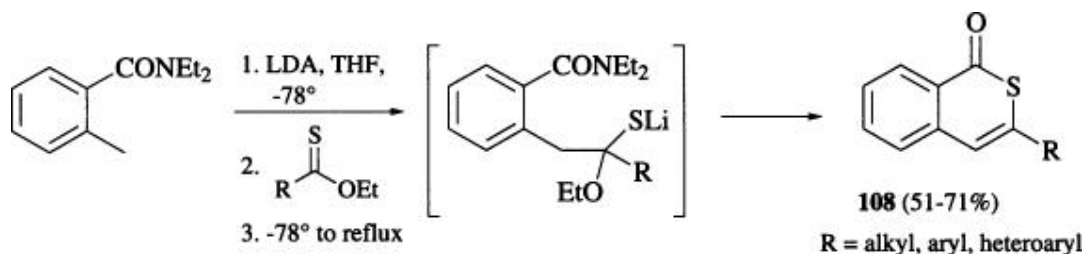
thioalkoxide adduct is presumed to be an intermediate in this cyclocondensation reaction.

A variety of methods are available for synthesis of 3,4-dihydroisocoumarins (3,4-dihydro-1*H*-2-benzopyran-1-ones). Condensation of the dilithio species from *N*-methyl-*o*-toluamide with alkyl or aryl aldehydes followed by thermolysis affords 3-substituted dihydroisocoumarins, and application of this reaction sequence to ketones affords 3,3-disubstituted derivatives (Eq. 52). (43) Analogous

(52)
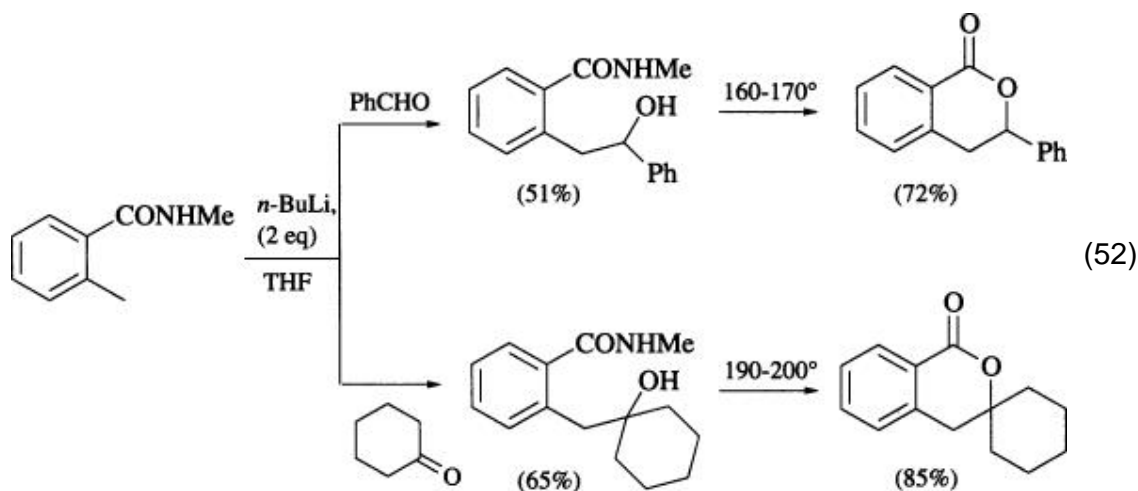
3-aryl products are obtained by reaction of *o*-toluic acid dianion with benzaldehydes, although the reported yields (24–28%) are lower than in the toluamide procedure. (29) Overall yields of 3-aryl-3,4-dihydroisocoumarins in the 30–65% range are obtained from condensation of *N,N*-diethyl-*o*-toluamides with benzaldehydes followed by treatment with 50% sodium hydroxide in ethanol at reflux. (51) As an alternative, *N*-[2-(dimethylamino)ethyl]-*N*-methyl-*o*-toluamide can be used, in which case the cyclization step is accomplished by treatment with 6 N HCl. (53) Reaction of the lithio species from *o*-tolyloxazoline **109** with aryl aldehydes followed by acid hydrolysis provides an efficient synthesis of 3-aryl-3,4-dihydroisocoumarins that proceeds in higher yield and under milder conditions than the preparations from tolyl amides described above. (195) One example of the application of this procedure to the preparation of a 3,3-disubstituted analog via reaction with a ketone has been reported. (195)

109　(80%)
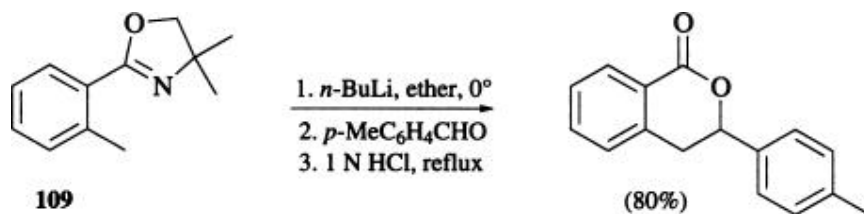
The reaction of lithiated 6-methoxytoluate esters with aldehydes gives 3-substituted 8-methoxy-3,4-dihydroisocoumarins in a single step. (36, 196-198) The example shown in Eq. 53 is noteworthy in that use of a chiral dialkylamide base

(53)

55% ee (41%)
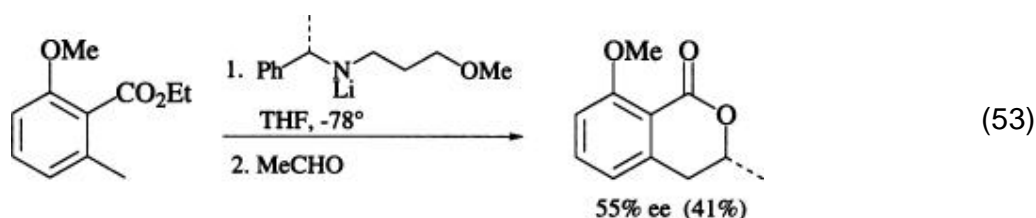
affords the product, (3R)-mellein methyl ether, with an enantiomeric excess of 55%. (196) The ability of the amine produced by protonation of the amide base to function as a chiral complexing agent has been proposed as a rationale for the observed asymmetric induction. (199) Asymmetric induction has also been observed in reactions of the benzylic lithio species derived from treatment of ethylbenzene with n-butyllithium in the presence of the chiral diamine (–)-sparteine. (200)

Condensation of the dilithio species from 2-methylbenzyl alcohol with carbon dioxide affords a simple route to 3-isochromanone (Eq. 54). (72) 3-Substituted

(54)

(56%)
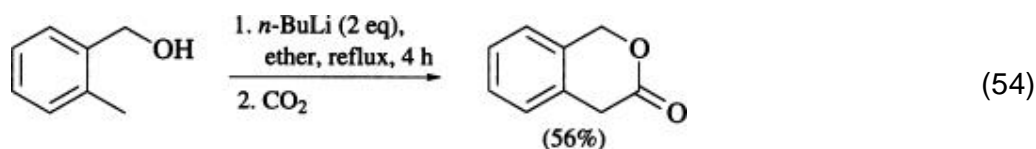
isochromans are available by reaction of 2-dimethylaminomethylbenzyllithium with carbonyl compounds followed by quaternization and thermolysis as illustrated by the synthesis of 3-phenylisochroman (Eq. 55). (19)

(55)
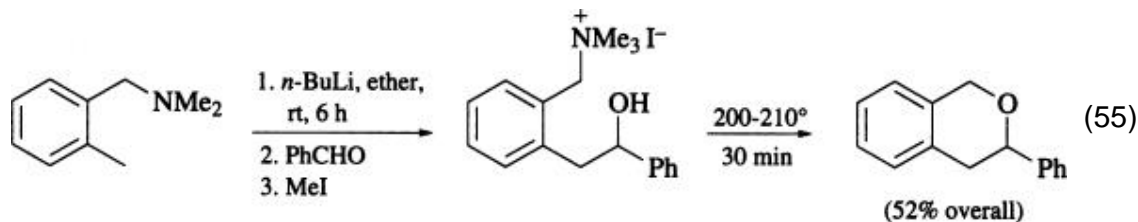
Preparation of 2-arylbenzo[b]furans (87) and 2-aryl-2,3-dihydrobenzo[b]furans (201) via lateral lithiation of o-tolyl tetramethylphosphorodiamidates is shown in Eq. 56. Synthesis of 2-methylbenzo[b]furan can be accomplished in analogous

(56)
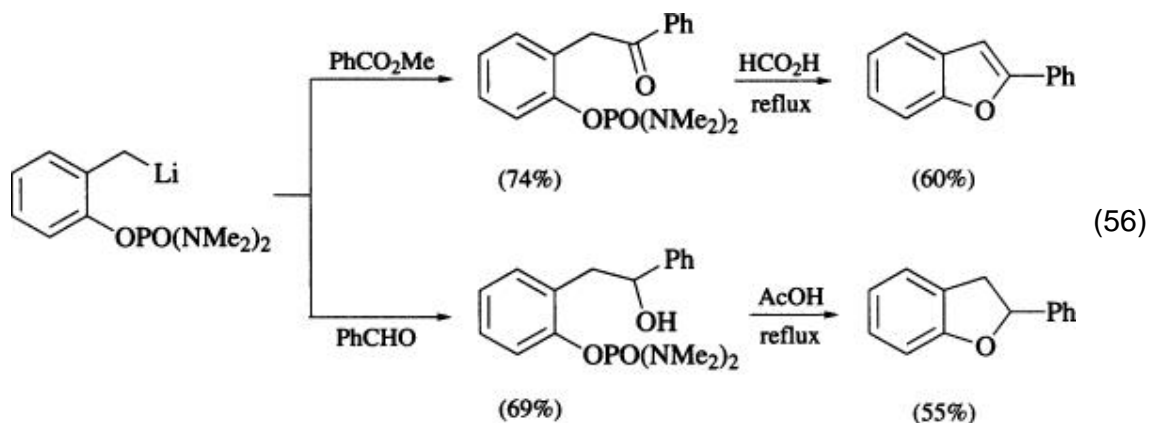
fashion by acylation of the phosphorodiamidate lithio species with N-methoxy-N-methylacetamide followed by formic acid treatment. (87) The preparation of 2,3-dihydrobenzo[b]furans by the route shown in Eq. 56 is limited to 2-aryl substituted examples. Reaction of the tolyl lithio species with carbon dioxide followed by formic acid treatment affords benzo[b]furan-2(3H)-one. (87) Similar methodology can be used for the synthesis of 2-aryl- and 2-alkylbenzo[b]thiophenes and benzo[b]thiophen-2(3H)-one (110) from the corresponding ortho-thiocresol tetramethylphosphoryl derivative. (88)
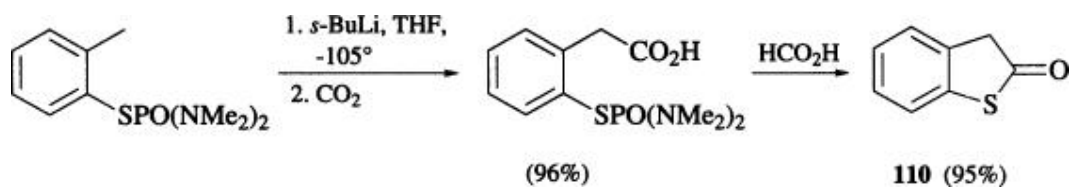
The dilithio species **111** from lateral metalation of 2-methylthioanisole is a versatile intermediate for preparation of benzannelated sulfur-containing heterocycles. For example, condensation with benzoyl chloride affords the 3,4-dihydro-2*H*-1-benzothiopyran derivative **112**. (83) Reaction of **111** with dichlorosilanes, dichlorostannanes, and sulfur chloride affords derivatives of 1,3-benzothiasilane, 1,3-benzothiastannane, and 1,3-benzodithiane, respectively (Table V-B). (83)
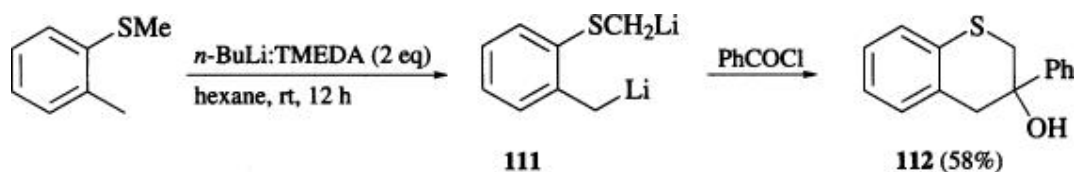
4.2.2. Nitrogen Containing

4.2.2.1.1. Indoles and Oxindoles

A number of indole syntheses based on lateral lithiation reactions of *o*-toluidine derivatives are available. The simplest of these procedures involves the preparation of 2-substituted indoles via cyclization of the dilithio species from acylated *o*-toluidines, an example of which has already been presented in Eq. 26. (90, 92) A reasonable mechanistic pathway for this transformation, which is essentially a modification of the Madelung indole synthesis, (202) is represented by the sequence of steps in Eq. 57. This reaction proceeds in low yield

(57)
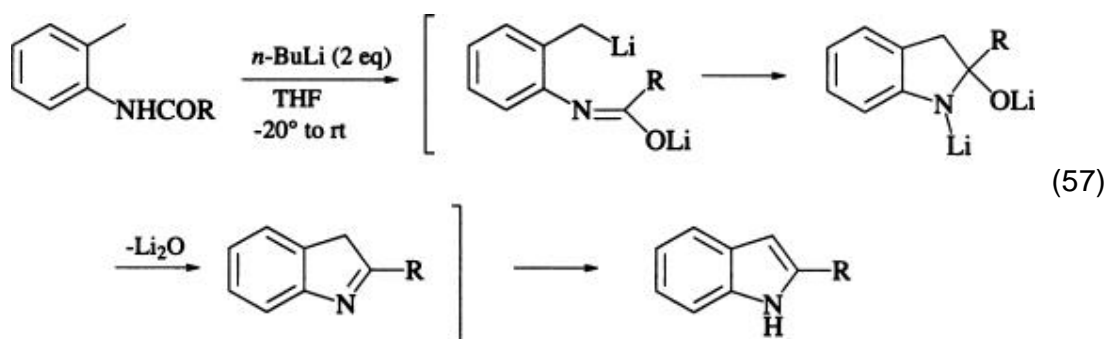
(<50%) if the R group contains enolizable protons; (91) hence the process is most applicable to the synthesis of 2-arylindoles or 2-(tertiary alkyl)indoles. It is noteworthy, however, that 5-chloro- and 5-methoxy-2-phenylindoles can be prepared in high yield by this reaction. (92) Indoles substituted with halogen or alkoxy groups in the benzene ring are not accessible by the original Madelung

procedure. (202)

A more versatile synthesis of 2-substituted indoles is based on condensation of the dilithio species from *N*-trimethylsilyl-*o*-toluidine with carboxylic acid esters (Eq. 58). (101, 102) This reaction can be envisioned as proceeding by initial acylation

(58)

R = aryl, alkyl
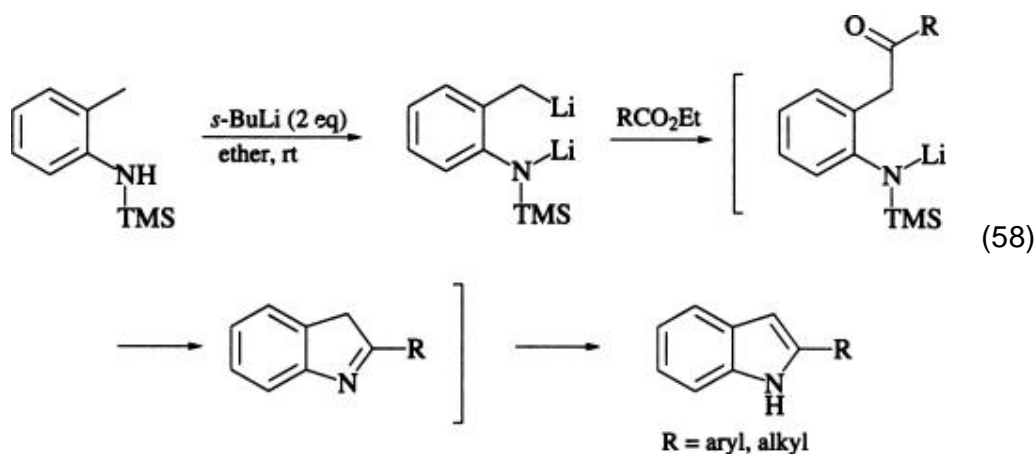
of the benzylic anion followed by intramolecular heteroatom Peterson olefination to form the indolinine. Tautomerization of the indolinine then leads to the observed indole product. The yields of 2-substituted indoles obtained by this procedure are generally in the 60% range. Application to the preparation of 2,3-disubstituted indoles (e.g., **113**) is also possible, although with somewhat reduced

113 (45%)
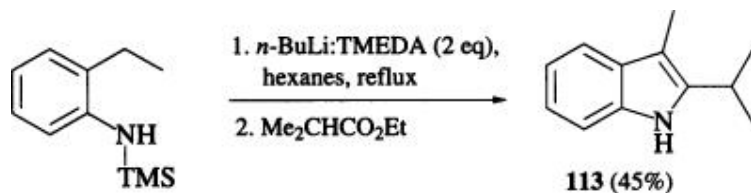
efficiency relative to the 2-substituted examples. (101) A related route that affords 2-substituted *N*-methylindoles involves condensation of the benzylic anion of the lithium carbamate of *o*-toluidine with carboxylic acid esters as in Eq. 59. (100) Upon workup with aqueous hydrochloric acid, the intermediate

(59)

(58-65%)

R = aryl, alkyl
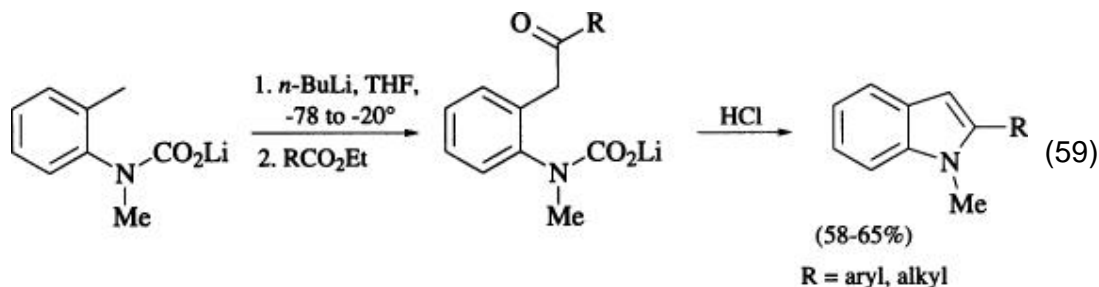
N-carboxyaniline undergoes decarboxylation, and subsequent cyclization of the resulting aminoketone gives the indole.

N-Boc protected indoles are readily available from Boc-*o*-toluidines by dilithiation followed by reaction of the dilithio species with *N,N*-dimethylformamide and dehydration of the resulting amidal. (93) A variety of Boc-indoles containing substituents in the benzene ring can be prepared in this way (e.g., **114**). The

114 (73%)
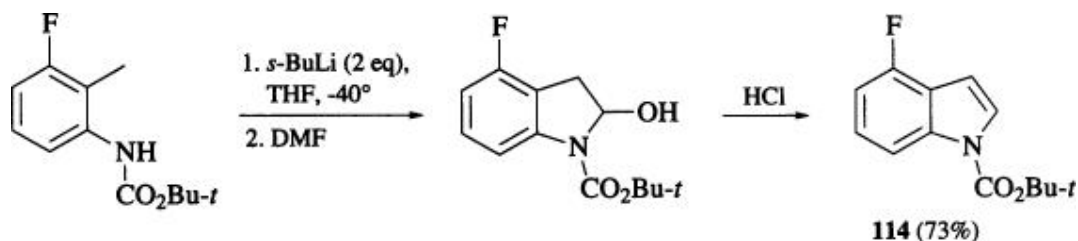
preparation of Boc-protected 2-substituted indoles from Boc-*o*-toluidines is illustrated in Eq. 60. Acylation of Boc-*o*-toluidine dilithio species is most readily accomplished by treatment with *N*-methoxy-*N*-methylamides; yields of ketones are significantly higher than in condensations with the corresponding esters. Cyclization of these acyl derivatives is accomplished upon brief exposure to a catalytic amount of trifluoroacetic acid in dichloromethane to afford the

(60)

(60-70% overall)

R = aryl, alkyl
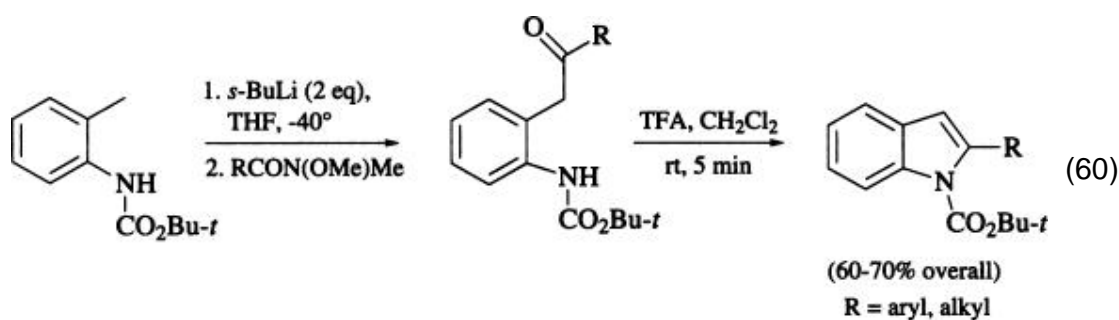
1-Boc-indoles. Alternatively, cyclization and subsequent removal of the Boc group to give 2-substituted indoles is effected upon treatment of the ketone

intermediates with trifluoroacetic acid as cosolvent for longer reaction times. Lateral lithiation of Boc-*o*-toluidines also affords a simple route to oxindoles [indol-2(3*H*)-ones] as illustrated by the preparation of 5-chlorooxindole (**115**). (**93**) Certain indol-2(3*H*)-thiones can be prepared using extensions of this methodology. (**203**)

115 (75%)
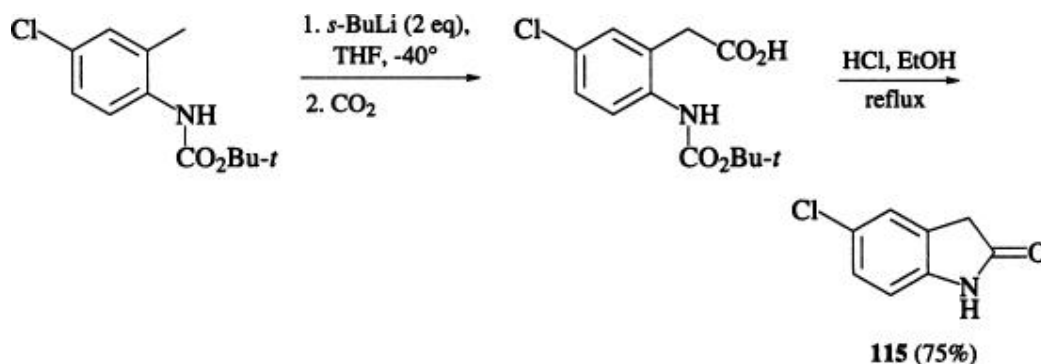
As described earlier, *o*-(lithiomethyl)phenyl isocyanides undergo cyclization to indoles in high yield upon warming from –78° to room temperature. Elaboration of these lithio species prior to the cyclization reaction allows the preparation of a diverse array of substituted indoles. (**103**, **104**) For example, functionalization of the benzylic position of *o*-tolyl isocyanide is accomplished via lateral lithiation followed by treatment with an electrophile. The lithio species produced in a second lateral lithiation is then allowed to cyclize to produce the 3-substituted indole as in Eq. **61**. In addition to alkyl (and allylic) halides, other electrophiles that can be used in this sequence include epoxides, (**104**) trimethylsilyl chloride, (**104**) dimethyl disulfide, (**104**)

(61)
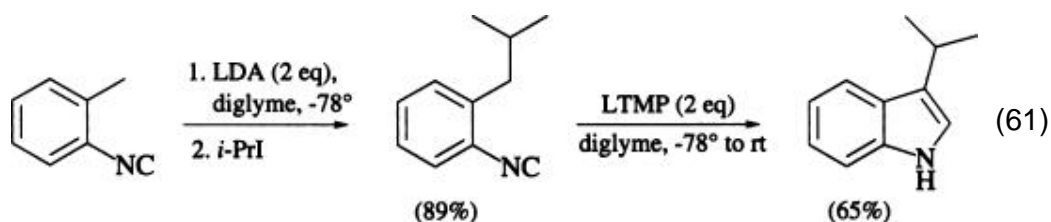
isocyanates, (**204**) and isothiocyanates. (**204**) Ketones produced by acylation of *o*-(lithiomethyl)phenyl isocyanides do not undergo the base-promoted ring closure. For these substrates, cyclization to the 3-acylindole can be effected by heating in benzene in the presence of a catalytic amount of copper(I) oxide (Eq. **62**). (**205**) Upon treatment with aqueous acid, an alternative cyclization mode, leading to the formation of 2-substituted indoles, is observed. (**205**)

(62)
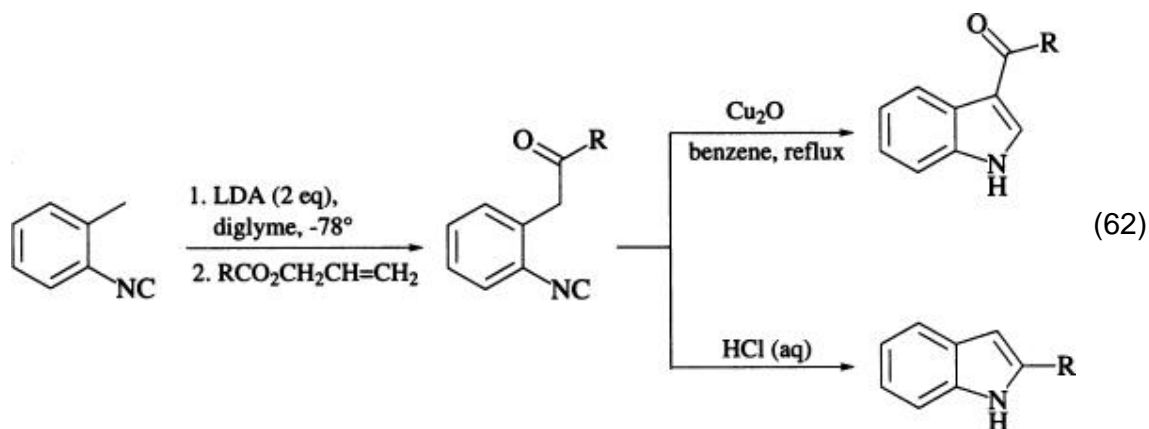
7-Substituted indoles can be prepared by iterative lateral lithiations of 2,6-dimethylphenyl isocyanide as illustrated by the "one-pot" synthesis of **116**.
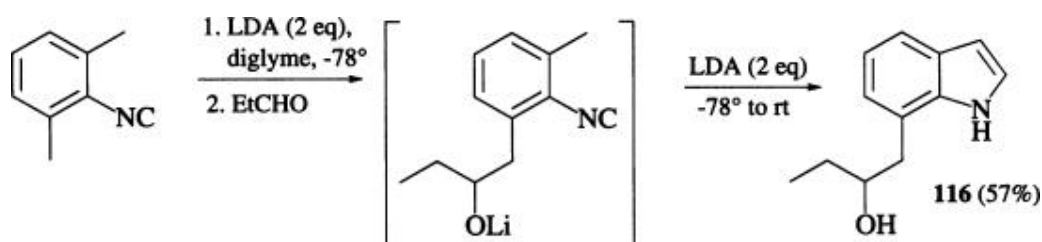
Sequential lithiations of 2,4-dimethylphenyl isocyanide can also be carried out to produce 3,5-dialkylindoles. (104)

Lewis acid catalyzed cyclization of adducts obtained by addition of lithiated *o*-tolyl isocyanide to carbonyl compounds affords *N*-formylindolines. (206) Addition to ketones, as in Eq. 63, gives 2,2-disubstituted indolines after cyclization, and

(63)
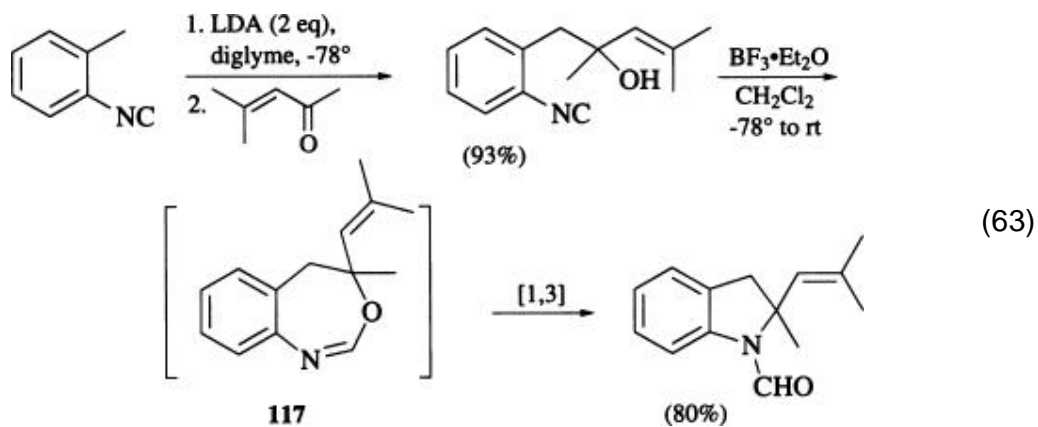
addition to aldehydes gives 2-substituted derivatives. The cyclization step works best with adducts from α , β -unsaturated or aryl aldehydes and ketones. Formation of the indolines appears to involve a 1,3-rearrangement of dihydro-3,1-benzoxazepine intermediates (e.g., **117**). (206) Another preparation of indolines based on a lateral lithiation reaction is represented by the synthesis of **118** from
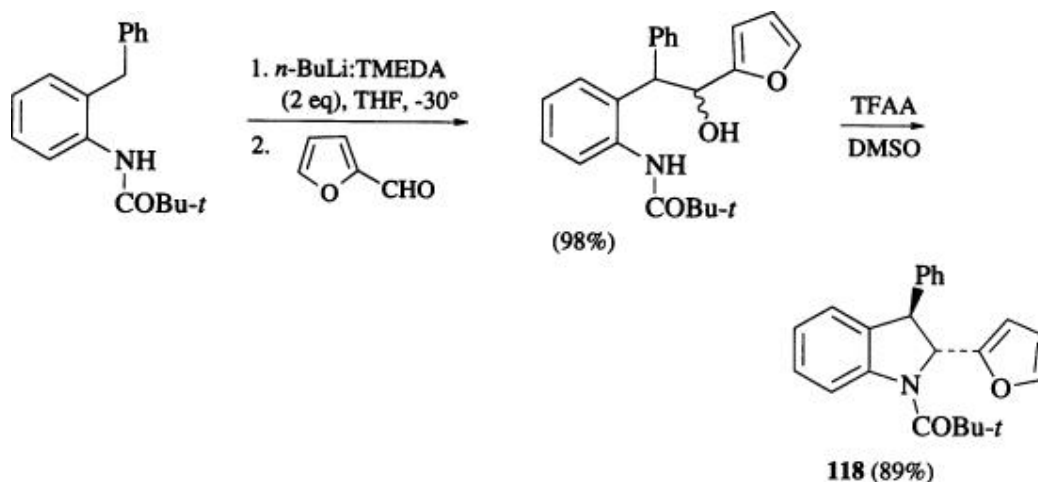
o-pivaloylamidodiphenylmethane. (207) The cyclization to form indoline **118** probably occurs via a stabilized carbonium ion; hence this type of synthesis would be expected to be limited to the preparation of 2-aryl (or heteroaryl) indolines. (47)

4.2.2.1.2. Isoquinoline Derivatives
Concise syntheses of 3-substituted and 3,4-disubstituted isoquinolines based on lateral lithiation of *o*-tolualdehyde cyclohexylimine are shown in Eq. 64. (208) Acylation of the derived lithio species with

$$(64)$$
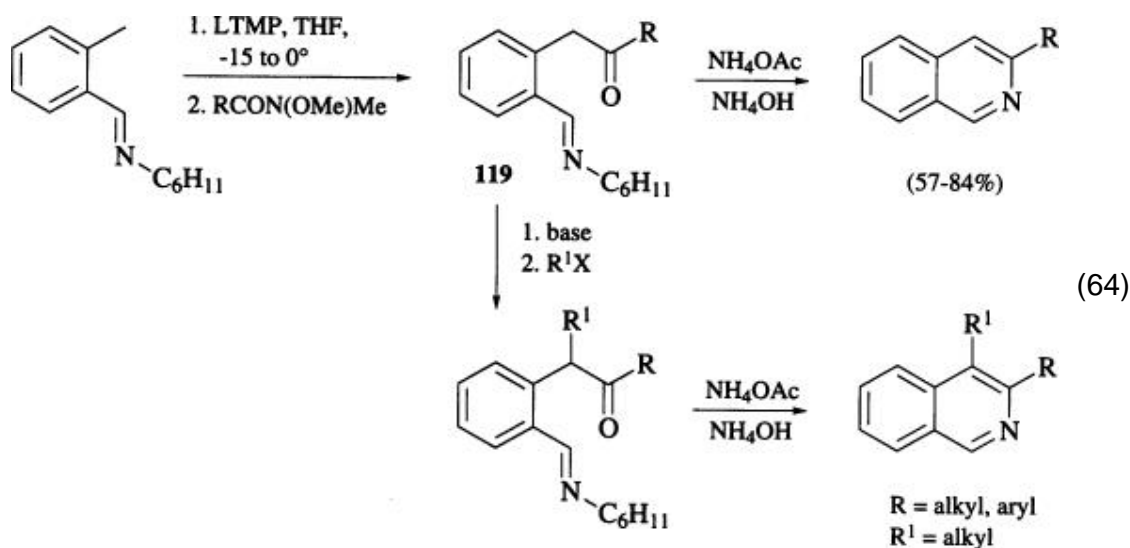
N-methoxy-N-methylamides provides ketone intermediates **119** which, without purification, can be converted to 3-substituted isoquinolines by treatment with ammonium acetate and ammonium hydroxide. Alternatively, ketones **119** can be alkylated at the benzylic position and similarly cyclized to afford 3,4-disubstituted derivatives. (209) Use of N,N-dimethylformamide in the acylation step provides the corresponding isoquinolines in which the R substituent is hydrogen. Application of these protocols to o-tolualdehyde imines containing substituents in the aromatic ring allows the preparation of substituted isoquinolines with more diverse substitution patterns. 3-Substituted isoquinolines can also be prepared via a route based on acylation of o-tolunitrile anions; however, the multistep nature of this procedure makes it less attractive than the more direct routes outlined in Eq. 64. (210)

A variety of isoquinoline derivatives can be prepared from the dilithio species obtained from lateral lithiation of Boc-2-methylbenzylamine (Eq. 65). (47) Condensation

(65)
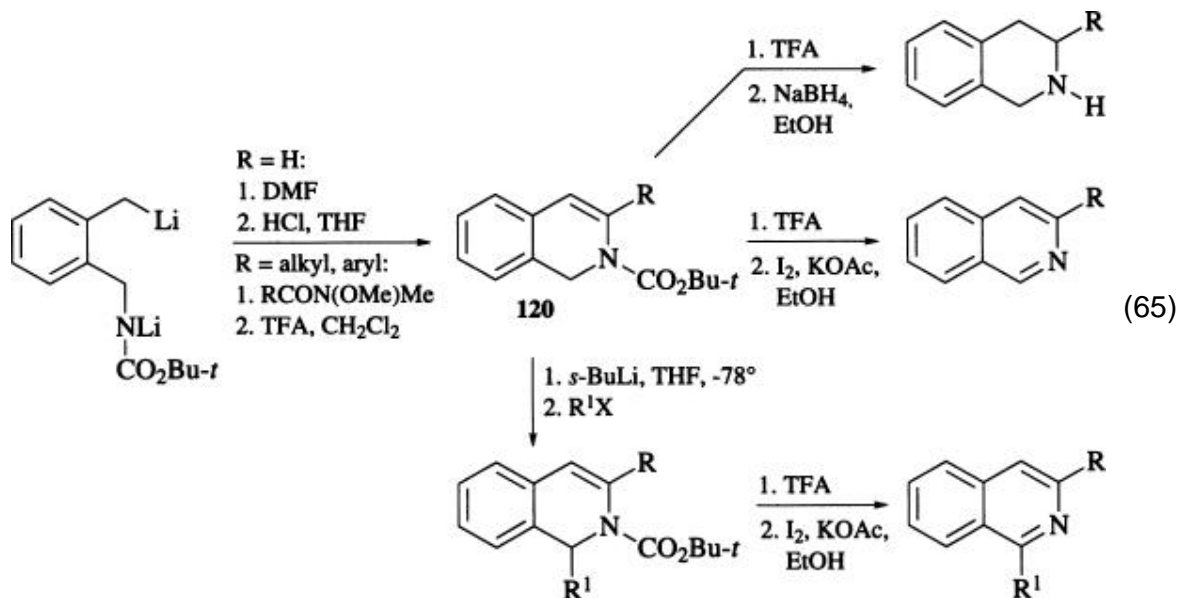
of the dilithio species with *N,N*-dimethylformamide or *N*-methoxy-*N*-methylamides affords *N*-Boc protected 1,2-dihydroisoquinolines **120** after acid treatment. Deprotection of **120** followed by reduction affords 1,2,3,4-tetrahydroisoquinolines, or, conversely, deprotection followed by oxidation affords isoquinolines. The Boc derivative **120** can also be alkylated at the benzylic position and similarly deprotected and oxidized to provide 1,3-disubstituted isoquinolines. (48) The alkylation of **120** proceeds in high yield when the 3-substituent R is alkyl or aryl, but fails when this substituent is hydrogen. As in the syntheses described above (Eq. 64), a noteworthy feature of the syntheses described in Eq. 65 is the ability to prepare isoquinoline derivatives with additional substitution at positions 5–8 from ring-substituted precursors.

Several protocols are available for preparation of isoquinolones from secondary *o*-toluamides (Eq. 66). Condensation of dilithiated *N*-methyl-*o*-toluamide

(66)
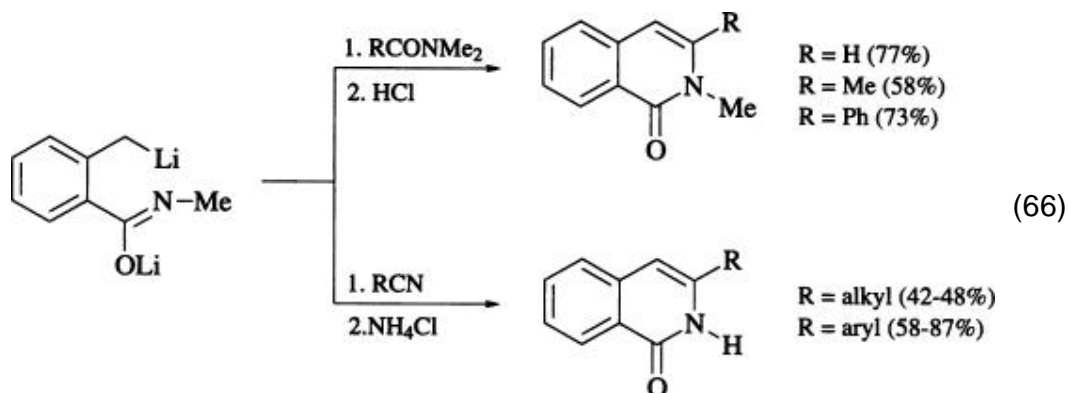
with amides followed by acid treatment affords
N-methyl-3-substituted-1(2H)-isoquinolones in fair to good yield. (160) Addition
of the N-methyl-o-toluamide dilithio species to nitriles affords the
corresponding (N-unsubstituted)-3-substituted-1(2H)-isoquinolones. (158) This
reaction is most efficiently applied to the synthesis of 3-aryl and 3-heteroaryl
isoquinolones. Moderate yields are obtained with secondary or tertiary alkyl
nitriles, and the reaction fails with primary alkyl nitriles, presumably because of
competing deprotonation of the nitrile substrate. An alternative procedure for
the preparation of 3-alkyl derivatives (e.g., **121**) involves condensation of
dilithiated N-methoxy-o-toluamide (methyl 2-methylbenzohydroxamate)
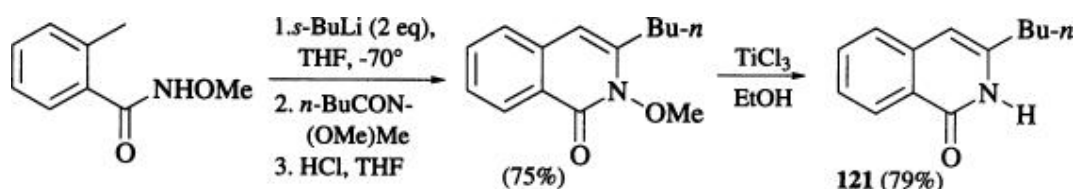
with N-methoxy N-methylamides. (49) The derived
N-methoxy-1(2H)-isoquinolones are deprotected to the parent isoquinolones
upon treatment with titanium trichloride. In a similar sequence, the
N-(1-propenyl) group is used in place of the N-methoxy group as a removable
protecting group for the synthesis of N-unsubstituted isoquinolones. (46)

Lithiated phthalides undergo cyclocondensation reactions with benzaldimines
to give mixtures of cis- and
trans-4-hydroxy-3-phenyl-3,4-dihydro-1(2H)-isoquinolinones with the cis
isomer predominating (Eq. 67). (211) The cis:trans
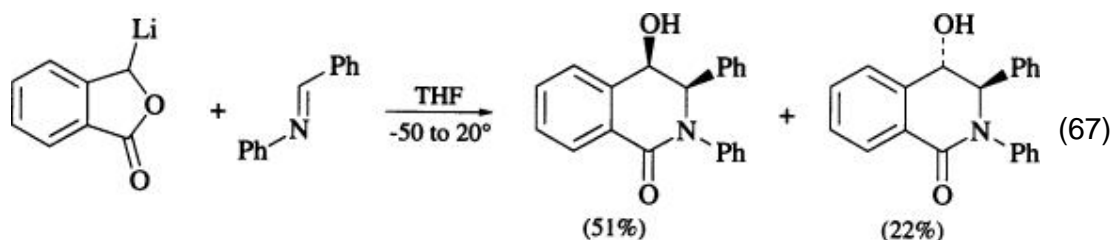
isomer ratios observed in this reaction are typically ~ 2:1. In condensations of
phthalide anions with 3,4-dihydroisoquinolines, trans cycloadducts such as
122

122 (68%)
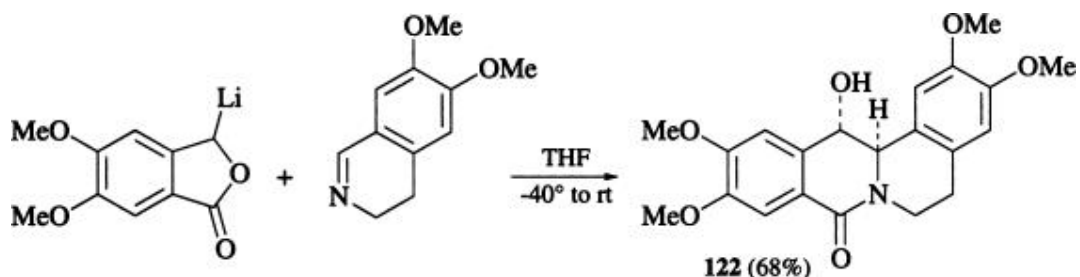
are formed exclusively. (212) These stereochemical results are rationalized by transition states involving coordination of the lithium cation with the lone pair of the imine nitrogen and with the two oxygens of the phthalide anion. (212)

There are two reports in the literature on the synthesis of 3,4-dihydro-1(2*H*)-isoquinolones by acid-catalyzed cyclization of adducts obtained by addition of dilithiated *N*-substituted-*o*-toluamides to aldehydes and ketones. (213, 214) However, on the basis of a detailed study of these cyclization reactions, it has been established that the major products are the cyclic imino ethers **123** rather than the dihydroisoquinolones **124**. (215)
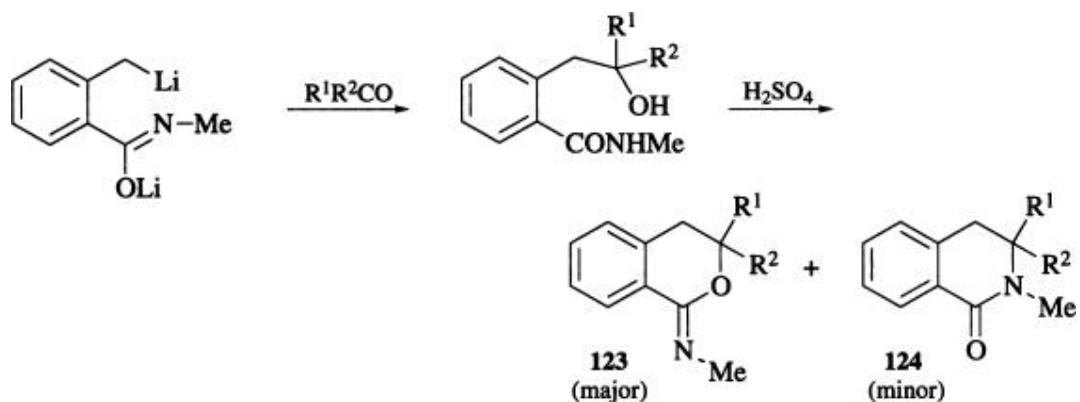
An alternative route to 3,4-dihydro-1(2*H*)-isoquinolones is shown in Eq. 68. (52) In this procedure, which is clearly related to the phthalide–imine condensation in

(68)

Eq. 67, lithiated *N,N*-diethyl-*o*-toluamide is condensed with imines to provide, in situ, the 4-lithio dihydroisoquinolone derivative **125**. Subsequent treatment of intermediate **125** with electrophiles (E$^+$) provides *trans*-3,4-disubstituted-3,4-dihydro-1(2*H*)-isoquinolones in moderate yield. The formation of lithio species **125** can be rationalized on the basis of initial formation of the 3,4-dihydroisoquinoline via addition of the toluamide anion to the imine followed by attack of the resulting nitrogen anion on the amide carbonyl with subsequent expulsion of the diethylamide anion. The dialkylamide base thus generated can then deprotonate the cycloadduct at the benzylic position leading to formation of anion **125**. The overall sequence affords highest yields with benzaldimines (R^1 = aryl) including 3,4-dihydroisoquinolines. Addition of the toluamide anion to cyclohexanone imines, which affords 3,3-disubstituted (spiro) dihydroisoquinolones, proceeds in moderate (40–45%) yield. (52, 157) Cyclopentanone imines apparently undergo enolization upon treatment with the toluamide lithio species. (157) Addition of the toluamide anion to (*S*)-glyceraldehyde acetonide *p*-methoxybenzyl (PMB) imine occurs with complete diastereoselectivity, albeit in moderate yield (Eq. 69). (216) A

(69)
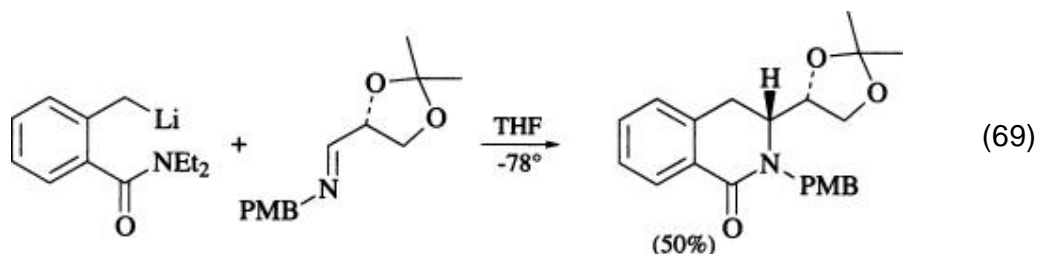
complete survey of 3,4-dihydro-1(2*H*)-isoquinolones prepared by Eq. 68 is provided in Table I-G.

An unusual transformation in which the *N,N*-diethyltoluamide anion serves in a temporary role in the activation of isoquinoline to electrophilic attack is shown in Eq. 70. (217) The toluamide lithio species adds to isoquinoline to afford adduct **126** in quantitative yield as determined by aqueous quench and subsequent isolation

(70)
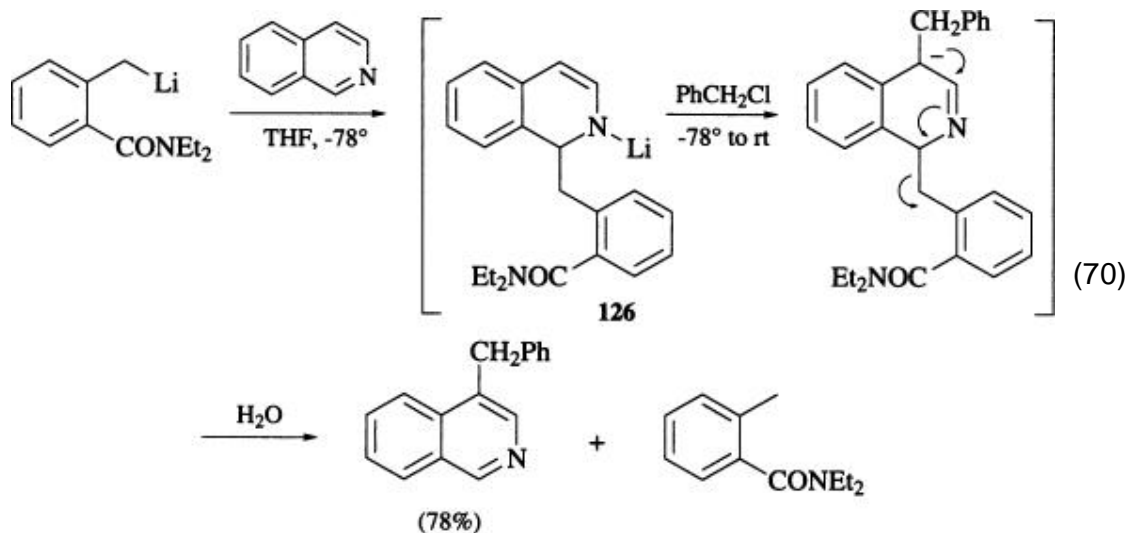
of the 1,2-dihydroisoquinoline. Treatment of the adduct with benzyl chloride followed by warming to room temperature affords 4-benzylisoquinoline along with recovered toluamide. The formation of these products is rationalized by the base-catalyzed fragmentation process shown in Eq. 70. Ring-substituted benzyl halides work equally well in this reaction; however, the procedure fails with other alkylating agents.

4.2.2.1.3. Tetrahydrobenzazepines
The lithio derivative of o-tolyl isocyanide undergoes 1,4-addition to α , β -unsaturated esters to afford γ -(o-isocyanophenyl)butyrate esters **127**. (218) The yield of 1,4-addition product is significantly higher with crotonate esters than with acrylates. Hydrolysis of isocyanides **127** to the corresponding anilines followed by thermolysis gives 1,3,4,5-tetrahydro-2H-benzazepin-2-ones **128**. The Boc derivative of 2,3,4,5-tetrahydro-1H-1-benzazepine (**130**) is prepared
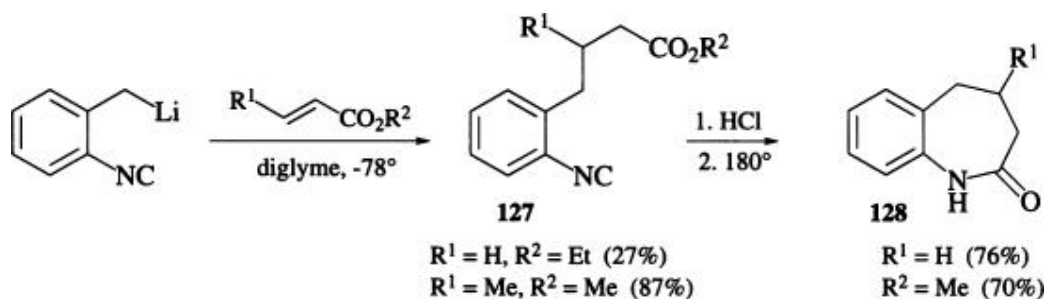
in two steps from lithiated Boc-o-toluidine. (219) Alkylation of this lithio species with 3-chloro-1-iodopropane gives chloride **129**, which is cyclized in a subsequent step upon treatment with potassium $tert$-butoxide. A one-pot

procedure for synthesis of **130** was not realized because of the failure of the lithio derivative of **129**

129 (98%) **130** (95%)
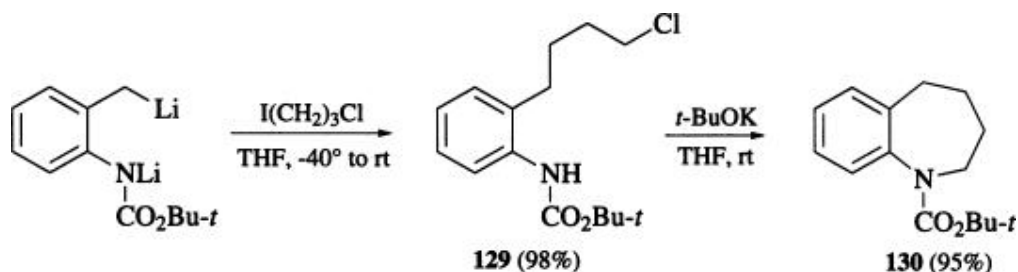
to undergo cyclization, even upon addition of potassium *tert*-butoxide to the original reaction mixture. The 1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-one system **132** is available via conversion of dilithio species **131** to the phenylacetic ester followed by removal of the Boc group and thermolysis. (108)

131 (67%) **132** (57%)
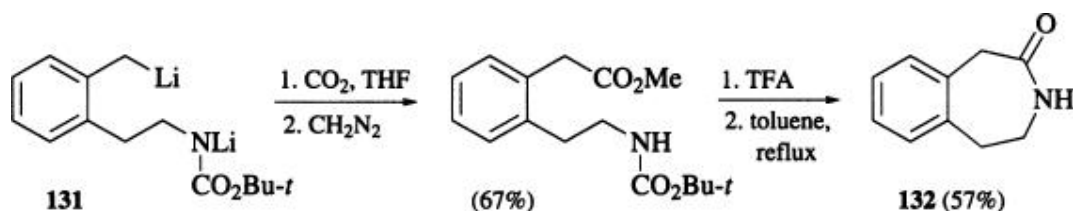
4.2.2.1.4. Miscellaneous Nitrogen Heterocycles

As described earlier in Eq. 18, 5-aryl-2,3,5,6-tetrahydroimidazo[2,1-*a*]isoquinolin-5-ols are prepared by condensation of dilithio-2-(*o*-methylphenyl)imidazoline with aryl esters. (65) The intermediacy of 4,5-dihydro-3,1-benzoxazepine derivatives in the formation of certain indolines was also mentioned (Eq. 63). This ring system can be prepared, without rearrangement to the indoline, by copper(I) oxide-catalyzed cyclization of *o*-tolyl isocyanide adducts **133**. (220) *N*-Substituted 3-aryl-2*H*-1,2-benzothiazine-1,1-dioxides

133 (ca. 90% overall)
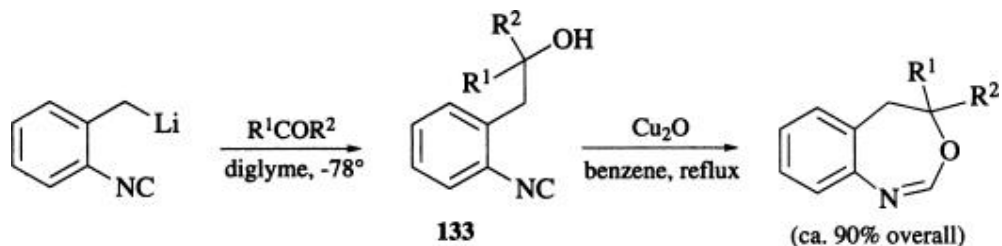
134 are available by condensation of dilithio-*o*-toluenesulfonamide with aryl nitriles followed by acid-catalyzed cyclodehydration. (110)

R = Me (71%)
R = Ph (76%)

R = Me (94%)
R = Ph (94%)
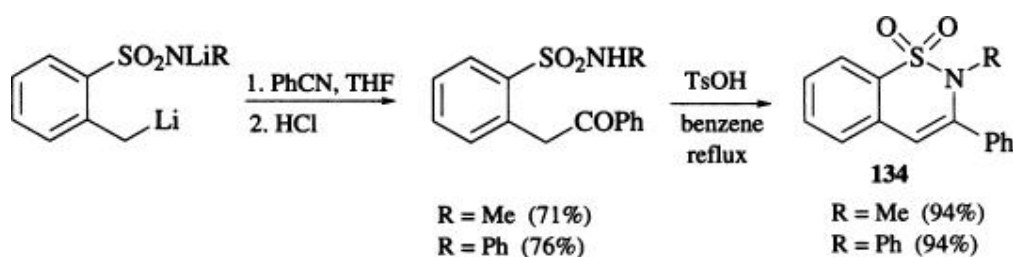
It will be appreciated that the annelation processes described above can be applied to the synthesis of a wide variety of heterocyclic systems via lateral lithiation of heterocycles. For example, commencing from methylpyridine derivatives the following ring systems have been prepared: azaindole, (120, 93) azaindolone, (221) dihydro-8(5*H*)-isoquinolinone, (222) dihydroazaisocoumarin, (117) 1,7-naphthyridine, (223) and dihydro-1,6-naphthyridin-5(6*H*)-one. (52, 224, 225) Annelation reactions have also been applied to methylindole, methylpyrrole, methylbenzofuran, and methylbenzothiophene carboxamides to afford heteroaryl-fused pyridones. (44) The range of other systems available by this methodology would appear to be limited only by the availability of appropriately substituted heterocycles for further elaboration.

4.3. Sequential *Ortho* and Lateral Lithiations
The introduction of a methyl group by heteroatom-facilitated *ortho* lithiation followed by elaboration via lateral lithiation technology is an important protocol for the synthesis of aromatic systems with substitution patterns that are not readily accessible by other synthetic routes. One of the more useful applications of this tactic involves the preparation of contiguously trisubstituted (and occasionally tetrasubstituted) toluene derivatives through *ortho* lithiation and the subsequent use thereof in lateral lithiation reactions. The following two examples illustrate different aspects of this protocol. In Eq. 71, the complementary *ortho*

(71)
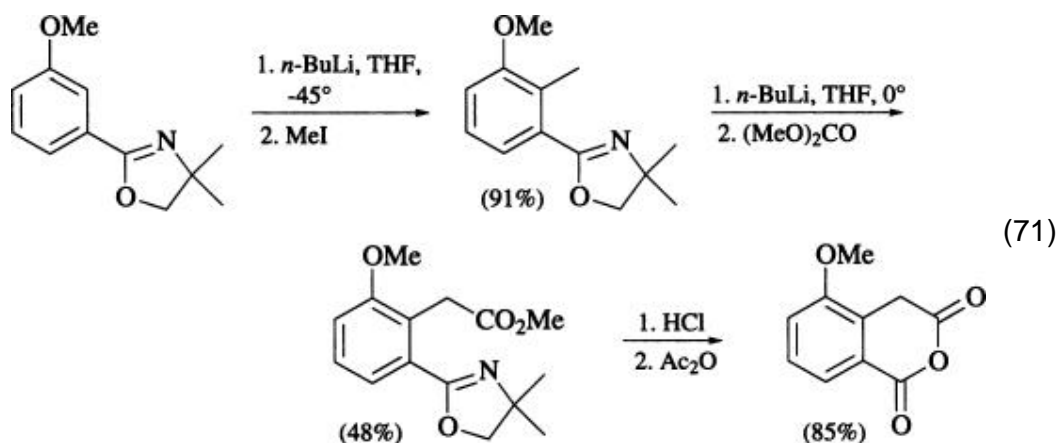
directing effects of the methoxy and oxazoline groups allow introduction of a methyl substituent between the two groups. (187, 192, 193) Lateral lithiation then allows functionalization of the newly introduced methyl group as in the preparation of 5-methoxyhomophthalic anhydride. (192) The second example illustrates the use of *ortho* lithiation in the preparation of contiguously trisubstituted toluene derivatives such as the Boc-toluidine **135**. (93) The success of this protocol is obviously dependent on regioselective *ortho* lithiation. In this example, the overriding *ortho*-directing effect of the Boc group relative to fluorine is taken advantage of. The utility of intermediates such as **135** for the synthesis of ring-substituted heterocycles via lateral lithiation based sequences is illustrated by the preparation of Boc-7-fluoroindole (**136**). (93)
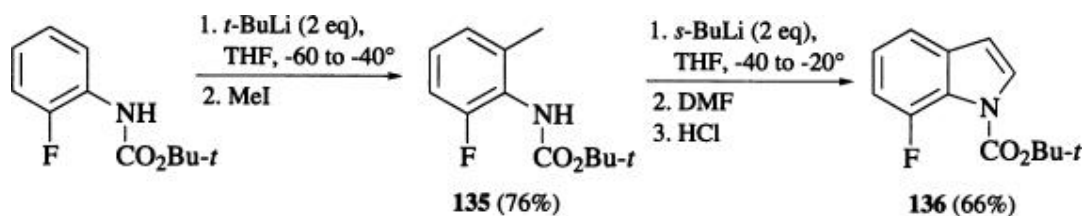
Sequential *ortho* and lateral lithiations can also be employed to accomplish, in two steps, transformations that otherwise cannot be directly accomplished in a single step. For example, laterally metalated species generally do not undergo alkylation with 2-phenethyl halides because of base-induced elimination of the alkylating agent. (138) However, methylation of the *ortho* lithiated species followed by lateral lithiation and alkylation with a benzyl halide accomplishes the desired transformation in good overall yield (138) as in Eq. 72. (54) This example also illustrates selective *ortho* lithiation proximal to the tertiary carboxamide group as

(72)
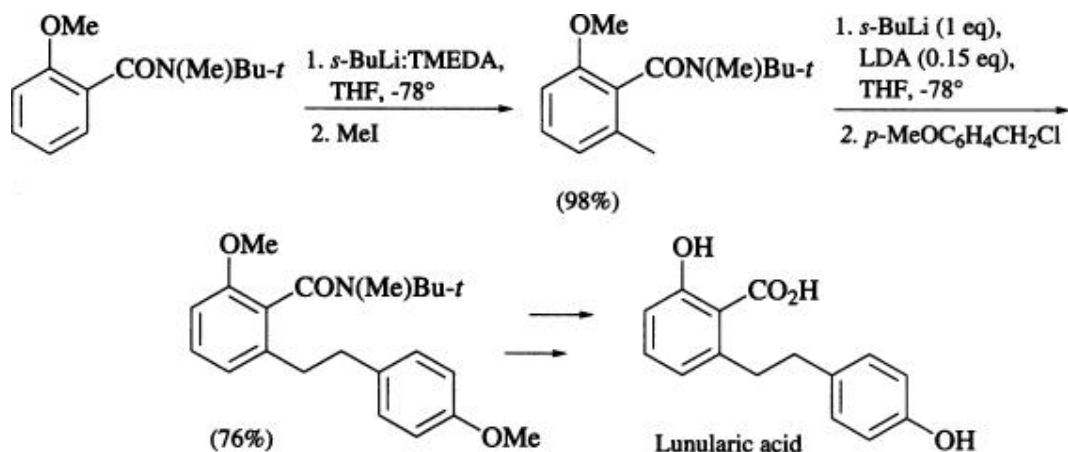
opposed to an alkoxy group, a tactic that has been used in other sequential *ortho*/lateral lithiation applications. (51, 191, 226) Sequential lithiation protocols of this type can often be carried out as a one-pot procedure, (100) however, product yield and purity are often improved if the intermediate *ortho* alkylated product is isolated and purified prior to the lateral lithiation reaction. (93, 191)

Lateral lithiation followed by *ortho* lithiation can be effected only when the lateral position is blocked to further lithiation as in the isopropyl-substituted benzamides shown previously in Eq. 41. Consideration of this phenomenon led to the development of a protocol for the protection of benzylic sites from lithiation. (166) Thus disilylation of *N,N*-diethyl-*o*-toluamide is accomplished in a one-pot procedure by sequential lateral lithiations and silylations to provide derivative **137**. Ortho lithiation of **137** and electrophilic trapping provides 1,2,3-trisubstituted benzamides such as **138**. The trimethylsilyl protecting groups can then be removed by treatment with fluoride to provide the corresponding toluene derivative.
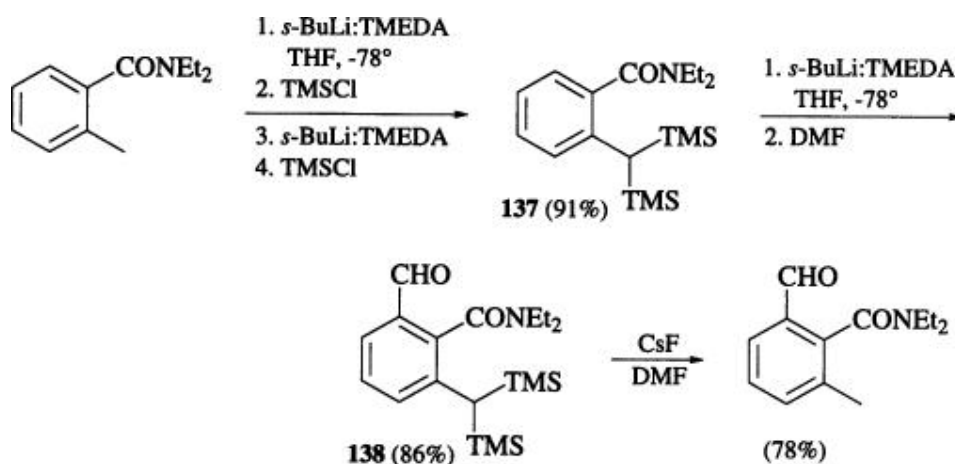
4.4. Applications to Natural Product Synthesis

The synthetic utility of heteroatom-facilitated lateral lithiation reactions is underscored by the extensive use of this methodology in the synthesis of natural products. Lateral lithiations have been used to effect key transformations in the total synthesis of over 30 natural products, encompassing a diverse array of carbocyclic and heterocyclic structures. One example is shown in Eq. 72 in the previous section, and additional examples that are illustrative of these synthetic applications are described in this section. A comprehensive list of the lateral lithiation reactions used in total synthesis endeavors, organized by structural class, is presented in Table XI.

Within the realm of carbocyclic aromatic natural product synthesis, lateral lithiation reactions have been imaginatively employed in synthetic approaches to olivin, the aglycone of the antibiotic olivomycin A. (150, 227, 228) In a synthesis of optically active olivin trimethyl ether, successive lateral lithiation reactions are used to assemble the carbocyclic framework of the antibiotic. (150) A phthalide–acrylate condensation provides the functionalized naphthalene ester **139** which undergoes subsequent cyclocondensation with unsaturated lactone **140** to afford key intermediate **141**. Related protocols involving ester–enol ether and phthalide–acrylate
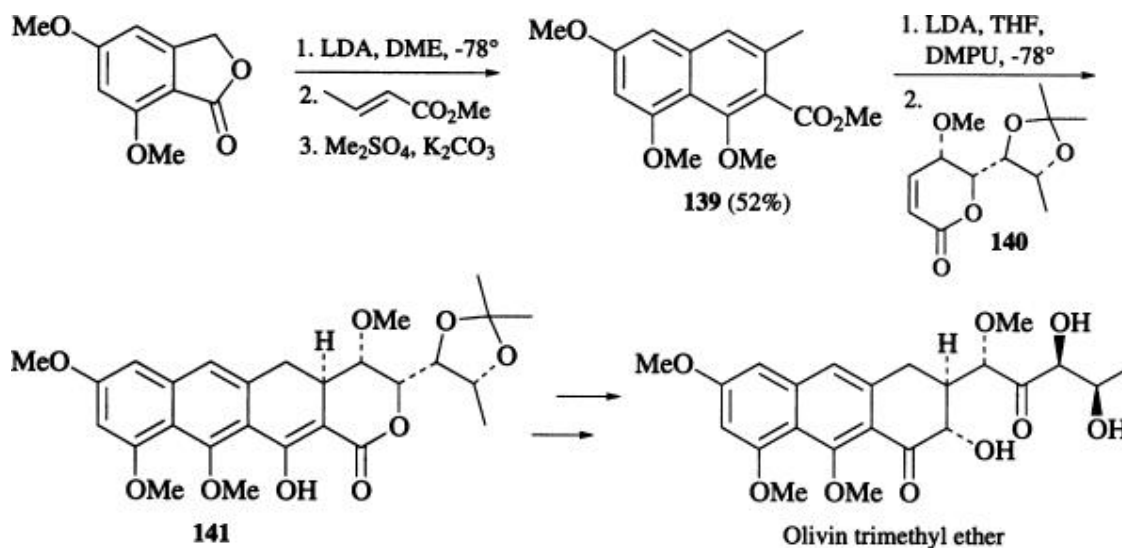
cyclocondensations have been used to prepare racemic olivin trimethyl ether (227) and (+)-olivin, (228) respectively.

In the total synthesis of the macrocyclic lactone antibiotic milbemycin β₃, 1,2 addition of dilithiated 2-ethylbenzoic acid **143** to the highly elaborated α , β -unsaturated aldehyde **142** provides a key carbon–carbon bond formation. (33)

This example illustrates the preparation of a complex 3,4-dihydroisocoumarin (**144**) via lateral lithiation, although in this particular application the lactone moiety is cleaved in a subsequent step.

Synthesis of the naturally occurring neolignan eupomatenoid-1 exemplifies the application of sequential *ortho* and lateral lithiations to the preparation of highly substituted benzo[*b*]furan derivatives. (**87**) Sequential methylation of phosphorodiamidate **145**, accomplished in a one-pot procedure, gives the ethyl derivative **146** (the possibility of direct conversion of **145** to **146** via ethylation of the

Milbemycin β₃
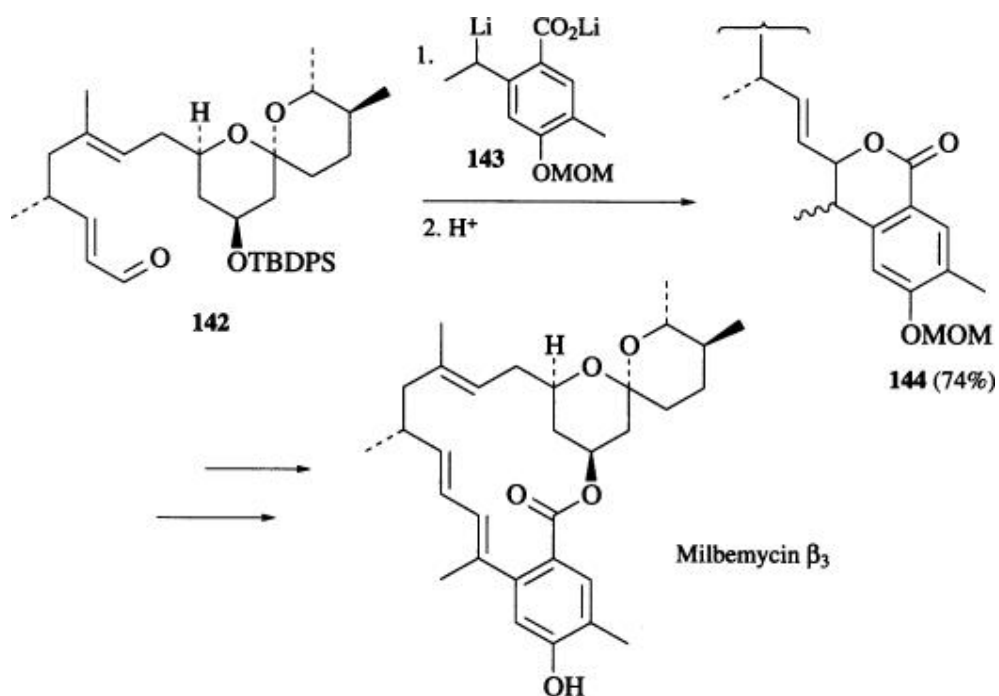
ortho lithio species was not discussed by the authors). Lateral lithiation of **146** followed by acylation with methyl piperonylate affords ketone **147** which is
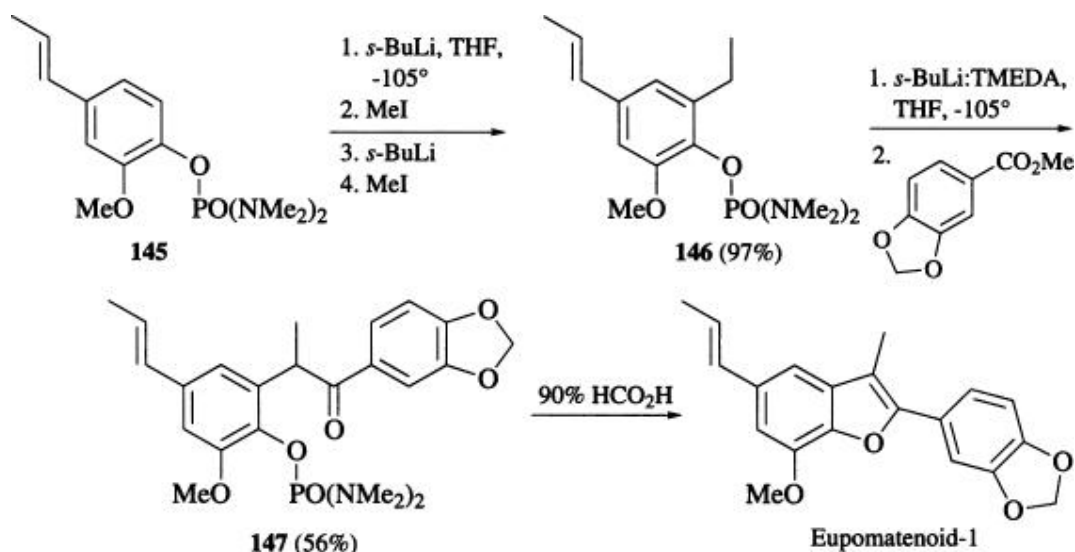
converted to eupomatenoid-1 upon treatment with aqueous formic acid. Several 2,3-dihydrobenzo[*b*]furanoid neolignans have been synthesized using related methodology. (87, 173, 201)

Lateral lithiation reactions of *ortho*-toluidine derivatives afford important methodology for the synthesis of natural products containing the indole nucleus. The concise synthesis of the indoloquinuclidine alkaloid (+)-cinchonamine (**150**) is representative of such an application. (101) The key step in this synthesis is condensation of the dilithio species from *N*-trimethylsilyl-*o*-toluidine with optically active ester **148** to give 2-substituted indole **149** without epimerization α to the
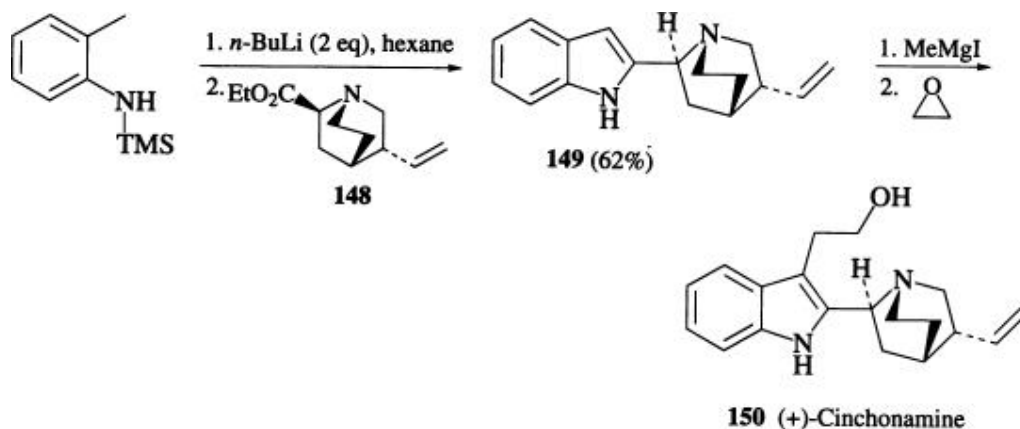
quinuclidine nitrogen. In a model study for the synthesis of the tremorgenic mycotoxin penitrem D, preparation of indole **152** via the *N*-trimethylsilyl-*o*-toluidine protocol (condensation with 2,2-dimethylbutyrolactone) proceeded in only 20–30% yield. (102) In this case,

the yield in the key indole-forming step was significantly improved by lateral lithiation-induced cyclization of the derived amide **151**.

151 → *n*-BuLi (4 eq), THF, 0° to rt → **152** (83%)
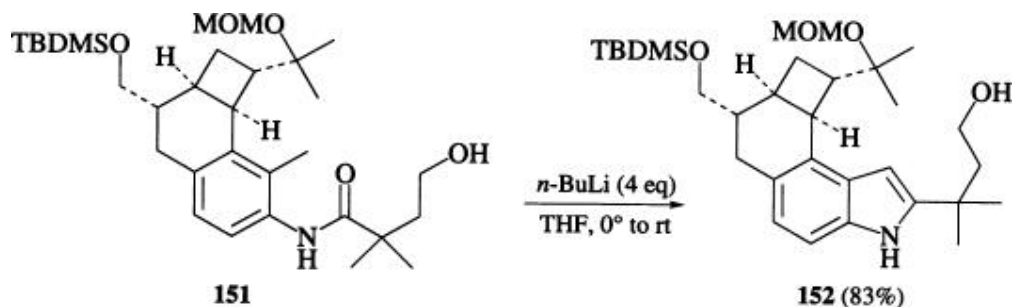
The preparation of natural products containing the isoquinoline ring system is particularly well-suited to applications of heteroatom facilitated lithiation technology. (229) Three successive lithiations, two *ortho* and one lateral, are employed for the assembly of isoquinolone **155**, a key intermediate in the synthesis of the antineoplastic agent fredericamycin A. (230) *Ortho* lithiation of methoxymethyl (MOM) ether **153** followed by treatment with diethylcarbamoyl chloride furnishes the diethylcarboxamide derivative that is, in turn, *ortho* lithiated and methylated to afford amide **154**. Lateral lithiation of **154** and condensation with diethoxyacetonitrile gives **155**, which is ultimately converted to racemic fredericamycin A. Two other syntheses of this natural product, in which different lateral lithiation strategies are used, have been reported. (231, 232)

153 → 1. *s*-BuLi, THF, -78°; 2. Et₂NCOCl; 3. *t*-BuLi, THF, -78°; 4. MeI → **154** (60% overall)

154 → 1. LTMP, THF, -78°; 2. EtO–CH(OEt)–CN → **155** (>90%) → (±)-Fredericamycin A
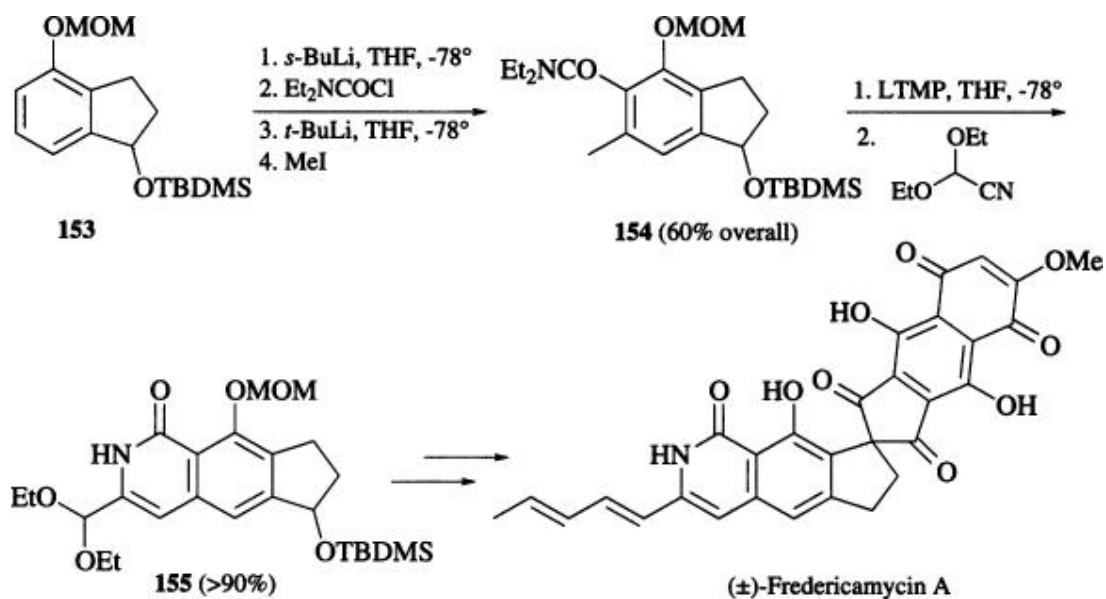
The cyclocondensation–electrophilic trapping route to 3,4-disubstituted dihydroisoquinolones (52) provides a convergent route to the benzo[c]phenanthridine alkaloid oxynitidine (158). (233) The toluamide lithio species 156 is condensed with N-methylpiperonalimine to afford, in situ, a 4-lithio-3,4-dihydroisoquinoline intermediate which is quenched with ethylene oxide to afford adduct 157. The
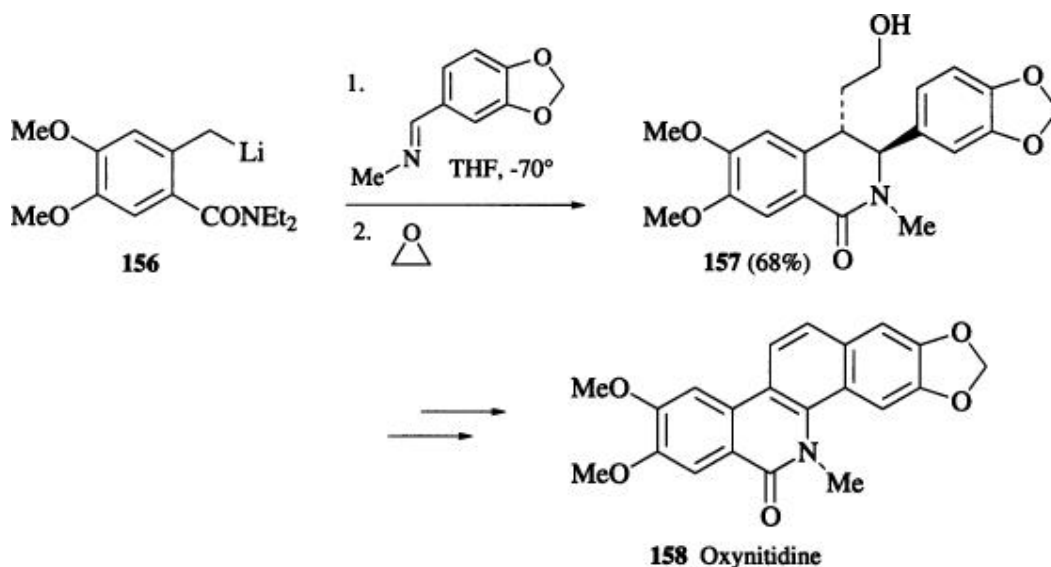
trans stereochemistry of 157 is of no consequence in the subsequent conversion to the achiral oxynitidine; however, a trans-3,4-disubstituted tetrahydroisoquinoline alkaloid, (±)-corydalic acid methyl ester, is synthesized using related methodology. (226) Condensations of lithiated picolyl nitriles with cyclic iminium salts represents another facet of the utility of lateral lithiations in alkaloid synthesis. Preparation of the indolo [2¢:3¢,3:4]pyrido[1,2-b][2,7]napht hyridine alkaloid angustine via reaction of the lithio derivative of picolyl nitrile 159 with the iminium salt 160 is typical of these syntheses. (122) Five other members of this alkaloid family

1. LDA, THF, -78°

2.

159

160 TMS $CF_3SO_3^-$

(93%)

Angustine
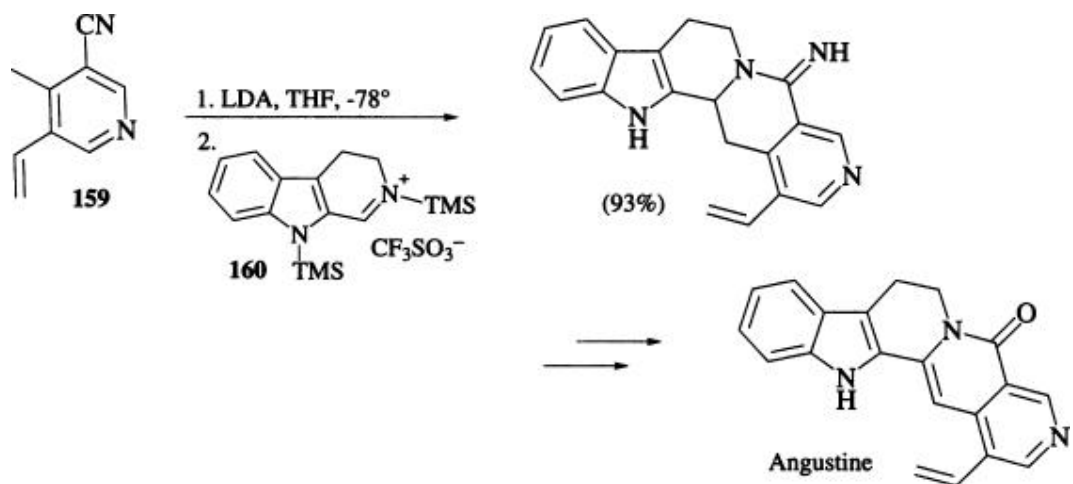
have been synthesized using this methodology. (122, 234) In addition, the related 8*H*-isoquino[2,1-*b*][2,7]naphthyridine alkaloids are also accessible by this general route. (235)

5. Comparison with Other Methods

In general, syntheses of contiguously substituted aromatic systems by classical electrophilic substitution chemistry are hampered by the inability to control regiochemistry in the introduction of substituents. (236, 237) With the proviso that the requisite starting material is available, heteroatom facilitated lateral lithiation reactions offer the clear advantage of regiochemical certainty over classical methodology for the preparation of aromatics contiguously disubstituted with functionalized substituents. In principle, a number of products derived from lateral lithiation reactions could also be obtained from *ortho* lithiation based routes. As noted earlier in the chapter (pages 40 and 69), reactivity differences can dictate the use of lateral, rather than *ortho*, lithiated species for the preparation of certain types of products. However, as also noted in previous sections, the availability of aromatic systems suitably configured for lateral lithiations is considerably enhanced by use of *ortho* lithiation technology; hence, the two methodologies should in general be viewed as complementary, rather than alternative. A recent review covers numerous other protocols that have been developed for the preparation of 1,2-disubstituted aromatics. (11)

In addition to the lateral lithiation reactions discussed in this chapter, other useful methods for the elaboration of benzylic derivatives of aromatic systems have been developed. In this section, a brief discussion of the potential advantages or disadvantages of these methods relative to lateral lithiation procedures is presented.

The formation of alkylbenzene–tricarbonylchromium complexes is an alternative method for the activation of benzylic positions toward deprotonation. (238, 239) Thus the chromium tricarbonyl complex of *N,N*-dimethylamphetamine is lithiated with *n*-butyllithium at –78°, and the resulting anion is trapped in a stereospecific manner with methyl iodide (Eq. 73). (240) Decomplexation of the

$$\text{(73)}$$
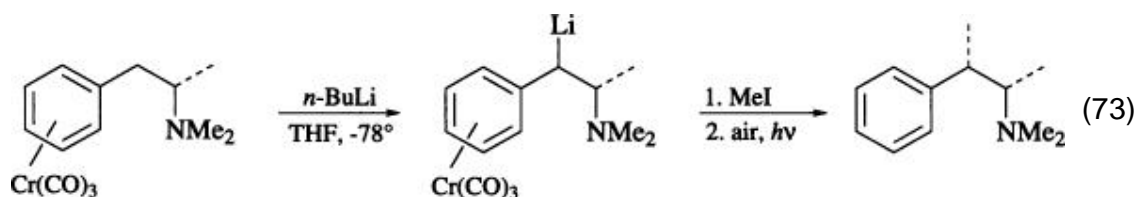
product is effected by exposure to air and sunlight. A number of other stereoselective and enantioselective processes have been developed on the basis of this methodology. (239) A noteworthy facet of benzylic lithiations of arenetricarbonylchromium complexes is the tolerance of alkyl substitution at

the benzylic position, a tolerance that is often not exhibited in heteroatom-facilitated lateral lithiations. An obvious disadvantage, at least in large-scale work, is the waste disposal problem inherent in the use of stoichiometric amounts of chromium reagents.

Zinc-promoted coupling of benzyl bromides and iminium salts is an efficient method for the synthesis of 1-benzyl-1,2,3,4-tetrahydroisoquinolines (Eq. 74) and

(74)

(74%)
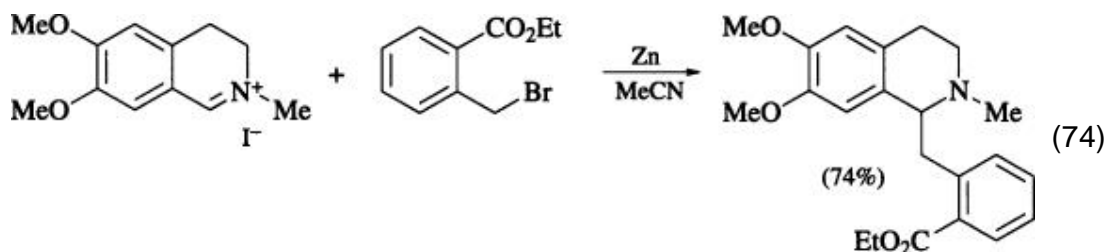
related structures. (241) Whereas certain laterally lithiated species (phthalides, (211) azaphthalides, (224) secondary and tertiary *o*-toluamides, (52) picolyl nitriles, (242) picolyl ethanols (116)) will add to imines and iminium salts, an advantage of the zinc-promoted process is that substituents that are incompatible with organolithium reagents, such as ethoxycarbonyl or bromine, can be present in the introduced benzyl group.

A related method for functionalization of benzylic positions involves the reaction of mixed copper–zinc benzylic organometallics with electrophiles. (243) This general method would appear to have great utility for the synthesis of a wide variety of benzylated systems. The preparation of 2-substituted indoles using this methodology (244) is clearly related to the indole synthesis based on the addition of dilithiated *N*-trimethylsilyl-*o*-toluidines to esters (Eq. 58). Thus bromination of *N,N*-bis(trimethylsilyl)-*o*-toluidine (161) affords the corresponding benzyl bromide which is converted to the organozinc derivative. Transmetallation to the mixed copper–zinc organometallic followed by addition of an acyl chloride affords indoles (e.g., 163) in high yield. This method is notable for the reactive functionality, such as the chloromethyl group in substrate 162, that is tolerated in the acyl
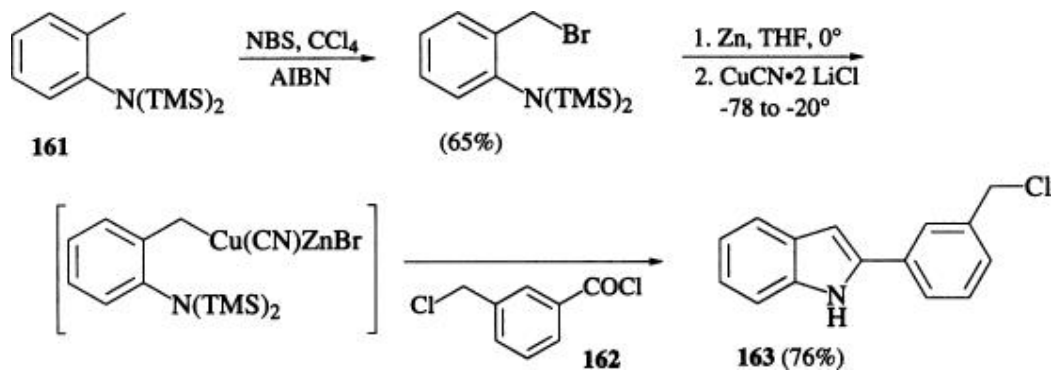
halide moiety. In other cases, the overall length of this procedure may constitute a disadvantage relative to the essentially one-step lateral lithiation procedure.

Carbodesilylation of benzylsilanes is an alternative to lateral lithiation methodology for certain carbon–carbon bond-forming reactions. (166) Fluoride-induced coupling of o-[(trimethylsilyl)methyl]benzamides and aldehydes produces carbinols as in Eq. 75. Treatment of disilylated derivatives (e.g., **137**) with fluoride

(75)
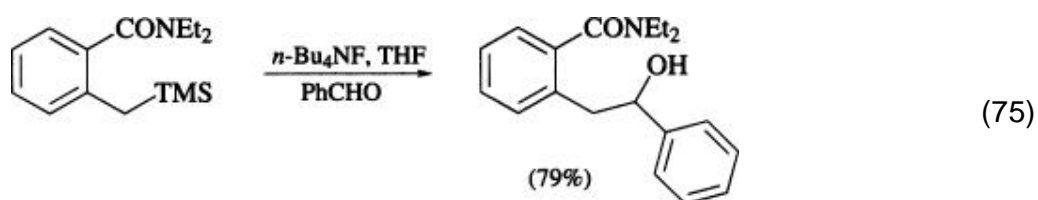
in the presence of an aryl aldehyde gives stilbenes in a Peterson olefination process (Eq. 76). The potential utility of these procedures derives from the essentially

(76)
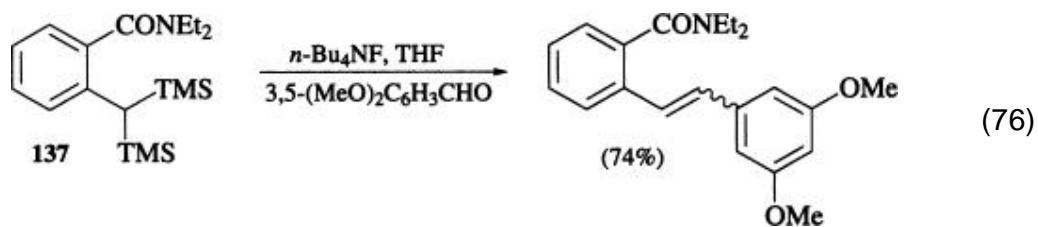
neutral conditions under which they proceed; hence, carbodesilylations may be useful when applied to substrates containing functional groups that are not compatible with organolithium reagents. These processes are, of course, used in conjunction with lateral lithiation reactions since the starting benzylsilanes are obtained by silylation of the o-toluamide lithio species. (166)

Peterson olefinations of benzyltrimethylsilanes can be used for the preparation of 2-substituted indoles, either by intramolecular cyclization of N-methyl-o-trimethylsilylmethyl anilides (245) or by intermolecular condensations of o-trimethylsilylmethyl anilides with esters as in Eq. 77. (246) These processes can

$$(77)$$

(54%)
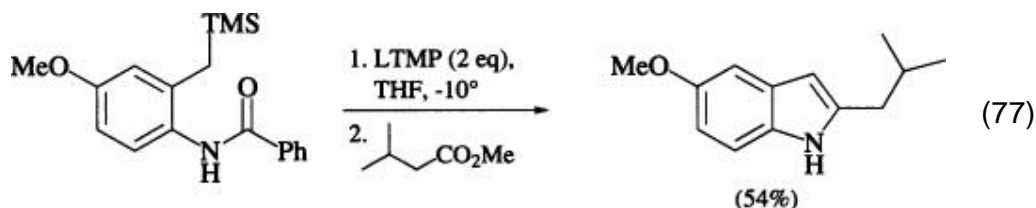
be viewed as lateral lithiations in which the lateral position is further activated toward lithiation by the trimethylsilyl group. The route shown in Eq. 77 is clearly more efficient for the preparation of 2-substituted indoles than the modified Madelung route described earlier (Eq. 57). Like the Peterson olefination, Wittig olefination can be used to induce carbon–carbon bond formation at benzylic positions. The synthesis of N-methyl-3-substituted isoquinolones via an intramolecular Wittig reaction (Eq. 78) is an example of such an application. (247) The

$$(78)$$

R = aryl, i-Pr
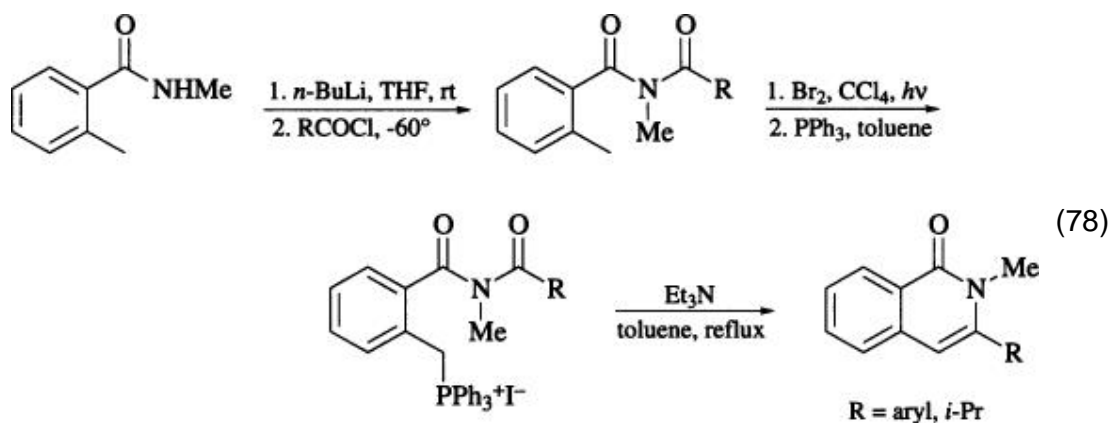
multistep nature of this route underscores the synthetic utility of lateral lithiation approaches, which accomplish the same overall transformation in essentially a single step (Eq. 66). Nonetheless, the methodology in Eq. 78 would appear to be applicable to systems containing aryl ring substitutents, such as bromine, that could not be used in the lateral lithiation sequence.

As applied to the synthesis of heterocycles in general, lateral lithiation based protocols afford significant advantages relative to classical methods in ensuring the regiochemical placement of substituents. For example, classical

syntheses of isoquinoline-related systems (e.g., Pictet–Spengler, (248) Bischler–Napieralski, (249) and Pomeranz–Fritsch methods (250, 251)) generally rely on electrophilic cyclization reactions to form the nitrogen-containing ring; hence, the application of these processes is often limited to electron-rich aromatic substrates. This limitation does not apply to the various protocols available for the synthesis of isoquinoline derivatives by heteroatom-facilitated lateral lithiation reactions. Similar advantages pertain to the synthesis of indoles by lateral lithiation methods. As compared to other indole syntheses that commence with toluene derivatives (e.g., Reissert, (252) Madelung, (202) and Leimgruber–Batcho methods (253)), approaches based on lateral lithiations proceed under milder conditions and allow greater flexibility in the introduction of substituents, particularly at the 2 and 3 positions. The Leimgruber–Batcho protocol, (253) however, is compatible with substituents (e.g., cyano, carboxy, and bromine) that do not tolerate lateral lithiation conditions.

Cycloaddition of 1-alkoxyisobenzofurans (254) and 1-(dialkylamino)isobenzofurans (255) (e.g., **164**) with dienophiles affords aromatic ring annelation products
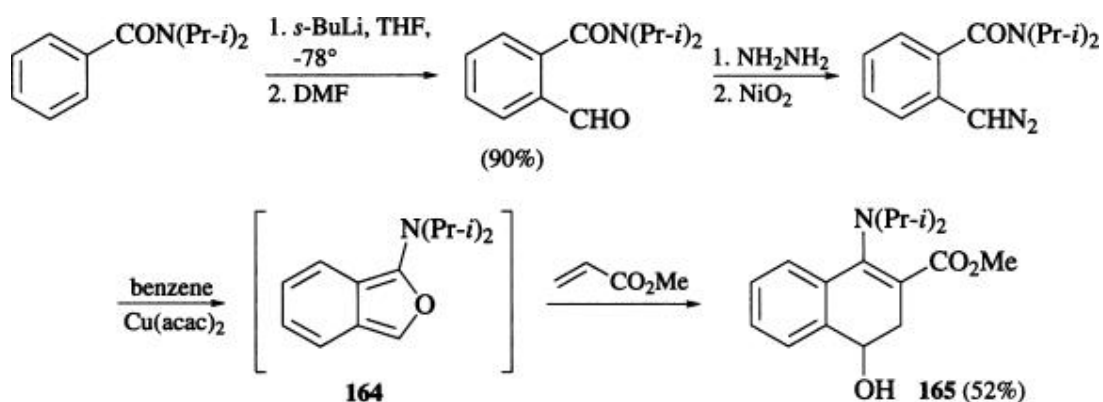
such as the substituted dihydronaphthalene **165**. These annelation reactions are formally, if not mechanistically, related to the phthalide anion–acrylate condensations (148) which also afford dihydronaphthalene products. The two methods would appear to be complementary in that they provide naphthalene derivatives with different substitution patterns: for example, 1-dialkylamino and 1-alkoxynaphthalenes by the isobenzofuran route and 1-hydroxy derivatives by the phthalide route.

6. Experimental Considerations

The experimental conditions under which heteroatom-facilitated lithiation reactions are carried out are typical of those involving organolithium reagents. Detailed discussion of the lithiating agents and solvents commonly used, and of other practical considerations pertaining to the use of organolithium reagents, are presented elsewhere; (10) therefore, these subjects are not covered in detail in this chapter.

The color of certain laterally lithiated species can be used to practical advantage in determining the presence of an adventitious proton source in the reaction mixture. For example, solutions of lithio species derived from lateral metalation of *o*-toluic acid and its derivatives range in color from red (toluic acids) to deep purple (tertiary amides), and those from *o*-toluidine derivatives (e.g., Boc-*o*-toluidine) are generally yellow-orange. In lateral lithiations involving facilitating groups that contain an acidic proton (*o*-toluic acids, secondary-*o*-toluamides, acylated *o*-toluidines, etc.), the color of the dilithio species is observed only after addition of one equivalent of the lithiating reagent; in effect, this color can be used as an indicator to determine the strength of the solution of organolithium reagent. When the facilitating group does not contain an acidic proton, the failure to obtain the color of the laterally metalated species upon initial addition of base can be indicative of an unwanted proton source in the reaction mixture. However, these types of empirical observations do not apply in all cases since not all laterally metalated species have characteristic colors; nor do all lateral metalations occur instantaneously upon addition of base.

7. Experimental Procedures

The following experiments are typically carried out in a three-necked flask equipped with a thermometer, magnetic stirring bar (or a mechanical stirrer for larger scale reactions), and either a dropping funnel or rubber septum. All reactions are performed under an inert atmosphere (nitrogen or argon). Transfers of organolithium reagents are made by syringe or cannula.

7.1.1.1. Homophthalic Acid (Lateral Lithiation of o-Toluic Acid with Lithium Diisopropylamide) (256)

To a solution of diisopropylamine (12.5 g, 124 mmol) in 40 mL of tetrahydrofuran under nitrogen at 0° was added *n*-butyllithium in hexane (124 mmol). The solution was stirred for 10 minutes and then cooled to –78°. A solution of *o*-toluic acid (4.22 g, 31 mmol) and dimethyl carbonate (6.65 mL, 62 mmol) in 40 mL of tetrahydrofuran was added dropwise over 10 minutes. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature. The mixture was stirred for 4 hours, 50 mL of water was added, and stirring was continued overnight. The solution was concentrated under reduced pressure until water began to distill. The solution was acidified (pH 1) and extracted with ethyl acetate (4 × 75 mL). The extract was dried with magnesium sulfate and evaporated under reduced pressure. Trituration of the residue with boiling chloroform afforded 4.75 g (85%) of pure homophthalic acid, mp 140–141°.

7.1.1.2. 2-Ethylbenzoic acid (Lateral Lithiation of o-Toluic Acid with sec-Butyllithium) (32)

To a solution of *o*-toluic acid (1.0 g, 7.4 mmol) in 100 mL of tetrahydrofuran at –78° was added *sec*-butyllithium (13.5 mL of 1.2 M in cyclo-hexane, 16.2 mmol) over a 2-minute period. The resulting orange-red solution was stirred at –78° for 1 hour, and iodomethane (3.3 mL, 53 mmol) was added. After the mixture was stirred at room temperature for 4 hours, it was quenched by slow addition of concentrated hydrochloric acid. The organic solvents were removed under reduced pressure and the residue was diluted with water and extracted with ether (3×). The extract was washed with water and brine, dried over magnesium sulfate, and evaporated under reduced pressure to provide a colorless solid. Recrystallization from ether/hexanes gave 1.05 g (95%) of product, mp 61°; IR (CHCl$_3$) 3350–2400 (br), 1710 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.26 (t, 3H, J = 7.4 Hz), 3.06 (q, 2H, J = 7.4 Hz), 7.24–7.32 (m, 2H), 7.50 (dt, 1H, J = 1.5, 7.8 Hz), 8.03 (d, 1H, J = 7.8 Hz). Anal. Calcd for C$_9$H$_{10}$O$_2$: C, 71.98: H, 6.71. Found: C, 71.94: H, 6.62.

95 (64%)
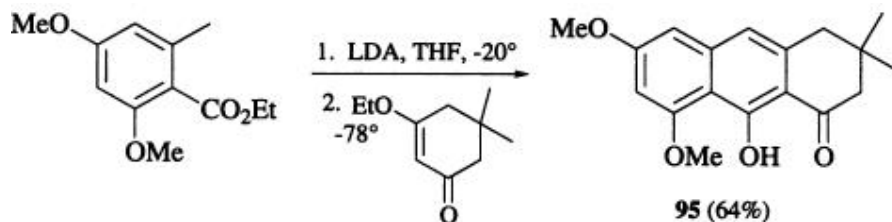
7.1.1.3. 3,3-Dimethyl-3,4-dihydro-9-hydroxy-6,8-dimethoxy-1-(2H)-anthraceno ne (95) (Lateral Lithiation of an o-Toluate Ester and Subsequent Condensation with an Enol Ether) (153)

A solution of diisopropylamine (0.60 mL, 4.4 mmol) and *n*-butyllithium (2.6 mL of 1.6 M in hexane, 4.2 mmol) in 5 mL of tetrahydrofuran was cooled to –78°. A solution of ethyl 2,4-dimethoxy-6-methylbenzoate (252 mg, 1.2 mmol) in 3 mL of tetrahydrofuran was added and the mixture was stirred for 10 minutes. A solution of 3-ethoxy-5,5-dimethyl-2-cyclohexen-1-one (201 mg, 1.2 mmol) in 5 mL of tetrahydrofuran was added over 5 minutes. The resulting mixture was allowed to slowly warm to room temperature. The reaction mixture was diluted with 5% hydrochloric acid and extracted with ether. The ether extract was washed twice with water and dried over sodium sulfate. The solvent was removed in vacuo, and the residue was purified by silica gel chromatography (chloroform) to afford 232 mg (64%) of 95, mp 157–159°; IR (CHCl$_3$) 3025, 2965, 1620 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.05 (s, 6H), 2.52 (s, 2H), 2.76 (s, 2H), 3.88 (s, 3H), 3.96 (s, 3H), 6.42 (d, 1H, *J* = 2.0 Hz), 6.54 (d, 1H, *J* = 2.0 Hz), 6.79 (s, 1H), 15.45 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 27.9 (q), 32.7 (s), 43.7 (t), 51.8 (t), 55.3 (q), 56.0 (q), 97.7 (d), 98.8 (d), 109.7 (s), 110.3 (s), 116.5 (d), 138.5 (s), 141.9 (s), 161.2 (s), 162.0 (s), 165.6 (s), 203.5 (s); mass spectrum, m/z: 300 (M$^+$), 285, 244. Anal. Calcd for C$_{18}$H$_{20}$O$_4$: C, 71.98: H, 6.71. Found: C, 71.95: H, 6.77.

166
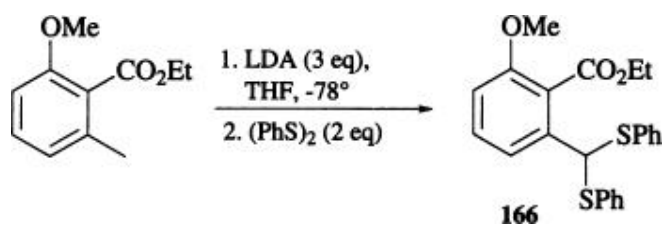
7.1.1.4. Ethyl 2-Methoxy-6-[bis(thiophenyl)methyl]benzoate (166) (Difunctionalization of a Laterally Lithiated o-Toluate Ester) (35)

A solution of ethyl 2-methoxy-6-methylbenzoate (1.0 g, 5.15 mmol) in 15 mL of tetrahydrofuran was added to a –78° solution of lithium diisopropylamide

(15.5 mmol) in 15 mL of tetrahydrofuran. To the orange-red solution was added diphenyl disulfide (2.47 g, 11.3 mmol) in 15 mL of tetrahydrofuran and the resulting solution was allowed to warm to room temperature. Acetic acid (10 mL) and water (30 mL) were added and the organic layer was evaporated in vacuo. The precipitated oil was dissolved in ethyl acetate (75 mL) and successively washed with water (50 mL), 5% sodium hydroxide (25 mL), water, and brine. The extract was dried over magnesium sulfate and evaporated in vacuo. Chromatography of the residue on silica gel (dichloromethane) afforded 2.11 g (83%) of the dithiophenylated product **166**, mp 75–76°; ^{1}H NMR (CDCl$_3$) δ 1.17 (t, 3H, J = 7 Hz), 3.72 (s, 3H), 4.15 (q, 2H, J = 7 Hz), 5.63 (s, 1H), 6.68 (dd, 1H, J = 7, 2 Hz), 7.00–7.35 (m, 12H).
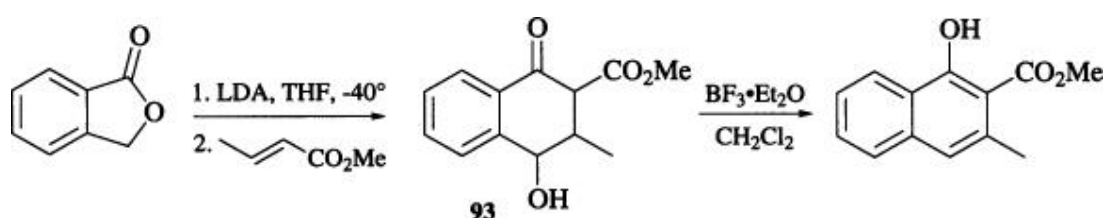
7.1.1.5. Methyl 1-Hydroxy-3-methyl-2-naphthoate (Synthesis of a Naphthalene by Condensation of a Lithiated Phthalide with an α , β -Unsaturated Ester) (148)

To a stirred solution of diisopropylamine (0.31 mL, 2.25 mmol) in 12 mL of tetrahydrofuran at –40° was slowly added a solution of *n*-butyllithium (1.07 mL of 2.5 M in hexane, 2.25 mmol). After 15 minutes a solution of phthalide (288 mg, 2.15 mmol) in 6 mL of tetrahydrofuran was added to produce an orange solution. The solution was stirred for 15 minutes at –40° and a solution of methyl crotonate (215 mg, 2.15 mmol) in 1 mL of tetrahydrofuran was added. After an additional 30 minutes, the mixture was allowed to warm to room temperture. The mixture was poured into 2 N hydrochloric acid and extracted with ether (4 × 40 mL). The ether extract was dried and evaporated to afford 253 mg (48%) of 4-hydroxy-2-methoxycarbonyl-3-methyl-1-tetralone (93) as a mixture of diastereomers. A solution of 180 mg (0.77 mmol) of this material was dissolved in 10 mL of dichloromethane and boron trifluoride etherate (2 drops) was added. The resulting solution was stirred for 15 minutes at room temperature. Water (10 mL) was added and the mixture was extracted with dichloromethane (3 × 7 mL). The extract was dried over sodium sulfate and evaporated to afford 113 mg (68%) of product, mp 84–86° (ethanol); IR (Nujol) 1650 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.53 (s, 3H), 3.90 (s, 3H), 6.96 (s, 1H), 7.22–7.52 (m, 3H), 8.20–8.32 (m, 1H), 12.52 (s, 1H, exchanges with D$_2$O). Anal. Calcd for C$_{13}$H$_{12}$O$_3$: C, 72.2; H, 5.6. Found: C, 72.2; H, 5.5.
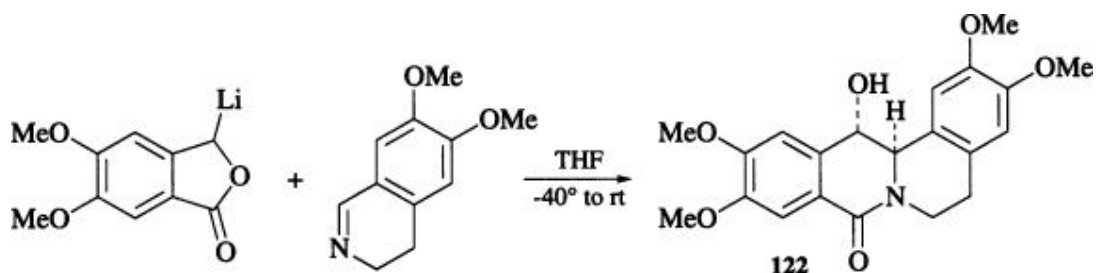
7.1.1.6. trans-13-Hydroxy-2,3,10,11-tetramethoxy-8-oxotetrahydroprotoberberine (122) (Cyclocondensation of a Lithiated Phthalide and a 3,4-Dihydroisoquinoline) (212)

A solution of 5,6-dimethoxyphthalide (582 mg, 3 mmol) in 6 mL of tetrahydrofuran was added dropwise to a solution of lithium diisopropylamide (3.3 mmol) in tetrahydrofuran at –70°. The yellow-orange solution was stirred for 15 minutes, the temperature was raised to –40°, and a solution of 6,7-dimethoxy-3,4-dihydroisoquinoline (570 mg, 3 mmol) in 6 mL of tetrahydrofuran was added. After stirring at –40° for 1 hour, the mixture was allowed to warm to room temperature and stirred overnight. The tetrahydrofuran was evaporated under reduced pressure, water was added, and the mixture was extracted with chloroform. The extract was dried over sodium sulfate and evaporated. Purification of the residue by medium pressure chromatography on silica gel (applying the oil to the column in ethyl acetate-dichloromethane, 1:1, then eluting with ethyl acetate) afforded 790 mg (68%) of **122** as a white powder, mp 208–210° (ethanol-petroleum ether); IR (CHCl$_3$) 1640 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.7–3.0 (m, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 3.94 (s, 3H), 3.97 (s, 3H), 4.5–4.7 (m, 2H), 4.85–4.95 (m, 1H), 6.73 (s, 1H), 6.98 (s, 1H), 7.17 (s, 1H), 7.58 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 30.2, 39.4, 56.0, 56.2, 62.0, 71.6, 106.7, 110.8, 111.9, 112.0, 120.2, 124.7, 129.1, 135.1, 147.4, 148.4, 148.8, 152.7, 164.3; mass spectrum: m/z 385 (M$^+$, 3), 194 (8), 192 (100).
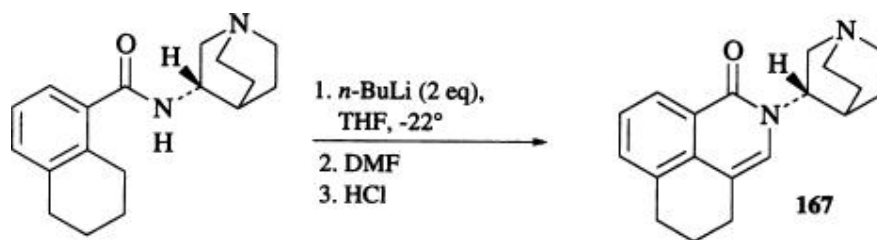
*7.1.1.7. 2-[(S)-1-Azabicyclo[2.2.2]oct-3-yl]-2,4,5,6-tetrahydro-1H-benz[de]
isoquinolin-1-one Hydrochloride (167) (Lateral Lithiation of a Secondary
o-Toluamide and Condensation with N,N-Dimethylformamide) (44)*

A solution of
N-[(*S*)-1-azabicyclo[2.2.2]oct-3-yl]-5,6,7,8-tetrahydronaphthalene-1-carboxamide (118.8 g, 0.42 mol) in 1.3 L of tetrahydrofuran was cooled to –22° and a solution of *n*-butyllithium in hexanes (530 mL of 1.6 M, 0.85 mol) was added at such a rate as to maintain the internal temperature between –22 and –14°. The resulting deep red solution was stirred at –22° for 30 minutes and DMF (37 mL, 0.48 mol) was added at a temperature below –14°. After the addition was complete, the solution was stirred at –22° for 30 minutes. Hydrochloric acid (332 mL of 6 N, 2.0 mol) was slowly added, keeping the temperature below 5°. The mixture was concentrated in vacuo to remove most of the organic solvents. The mixture was made basic with aqueous sodium hydroxide (ice bath) and extracted with ethyl acetate (4×). The extract was dried over magnesium sulfate and evaporated to afford the crude base as a thick oil. This was dissolved in 290 mL of 2-propanol, and a solution of 2-propanol containing 17 g (0.47 mol) of HCl was added. After having been stirred overnight, the mixture was filtered to afford the crude HCl salt. Recrystallization from 1 L of 2-propanol and 32 mL of water (concentrated to 850 mL) afforded 106 g (77%)

of **167** as a white solid, mp >270°; $[\alpha]_D^{25}$ −8.4° (*c* 0.5, H_2O); ^{1}H NMR (Me_2SO-d_6)

δ 1.74–2.10 (m, 6H), 2.32 (m, 1H), 2.80 (br t, 2H), 2.94 (br t, 2H), 3.20–3.40 (m, 3H), 3.60–3.72 (m, 2H), 3.84 (m, 1H), 5.20 m, 1H), 7.42 (dd, 1H, *J* = 6.4, 7.0 Hz), 7.52 (dd, 1H, *J* = 0.9, 6.4 Hz), 7.54 (s, 1H), 8.06 (dd, 1H, *J* = 0.9, 7.0 Hz), 11.0 (br s, 1H, exchanges with D_2O); mass spectrum, m/z 294 (M$^+$-HCl), 236, 211, 185, 110, 109. Anal. Calcd for $C_{19}H_{22}N_2O \cdot HCl$: C, 68.98: H, 7.01; N, 8.47. Found: C, 68.86; H, 7.00; N, 8.28.
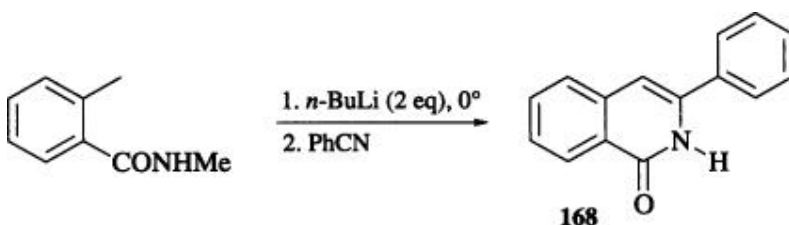
*7.1.1.8. 3-Phenylisoquinolin-1(2H)-one (168) (Condensation of a Dilithiated
Secondary o-Toluamide with a Nitrile) (158)*

A solution of *N*-methyl-*o*-toluamide (14.9 g, 0.100 mol) in 200 mL of tetrahydrofuran was cooled in an ice-salt bath and *n*-butyllithium in hexane (96 mL of 2.4 M, 0.23 mol) was slowly added. The addition rate was maintained so that the reaction temperature never exceeded 20°. After the

addition was complete (ca. 30 minutes), the orange-red solution was stirred at 0° for 1 hour and then cooled to –50°. A solution of benzonitrile (12.9 g, 0.125 mol) in 50 mL of tetrahydrofuran was added, the cooling bath was removed, and the resulting mixture was allowed to warm to room temperature. Saturated aqueous ammonium chloride solution (50 mL) was then carefully added and the resulting phases were separated. The organic portion was washed with water (50 mL) and dried over magnesium sulfate. The solvent was removed in vacuo to afford the crude isoquinolinone **168**. Recrystallization from ethanol afforded the product in 87% yield, mp 198–199°.

169
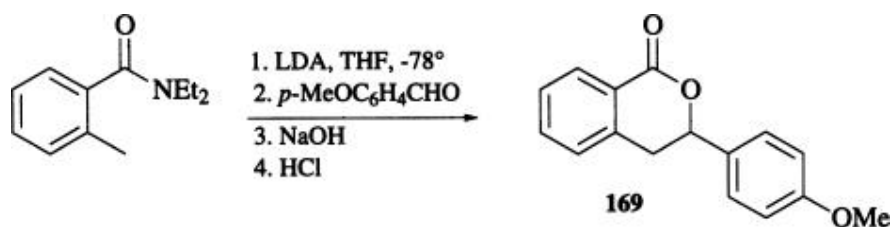
7.1.1.9. 3-(4-Methoxyphenyl)-3,4-dihydroisocoumarin (*169*) (Lateral Lithiation of a Tertiary o-Toluamide) (*51*)

To a solution of lithium diisopropylamide (7.5 mmol, prepared from 5.4 mL of 1.4 M *n*-butyllithium in hexane and 1.05 mL of diisopropylamine) in 60 mL of tetrahydrofuran at –78° was added a solution of *N,N*-diethyl-*o*-toluamide (0.96 g, 5 mmol) in 5 mL of tetrahydrofuran. After being stirred for 1 hour at –78°, the burgundy red solution was treated with *p*-anisaldehyde (1.02 g, 7.5 mmol), the cooling bath was removed, and stirring was continued for 8 hours. Saturated ammonium chloride solution was added and the mixture was extracted with ethyl acetate. The extract was dried over sodium sulfate and evaporated under reduced pressure to afford 1.06 g (65%) of the amide alcohol product. Recrystallization from ethanol gave an analytical sample, mp 111°; IR (KBr) 1610 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.96 (t, 3H, $J = 7$ Hz), 1.21 (t, 3H, $J = 7$ Hz), 2.90 (q, 2H, $J = 7$ Hz), 3.08 (q, 2H, $J = 7$ Hz), 3.48 (br s, 2H), 3.70 (s, 3H), 4.79 (br s, 1H), 5.52 (br s, 1H), 6.76–7.32 (m, 8H): mass spectrum, m/z 327 (M^{+}). The crude product from above was treated with a mixture of 50% aqueous sodium hydroxide (20 mL) and ethanol (20 mL) and the whole was heated under reflux for 8 hours. The reaction mixture was evaporated to dryness, acidified with hydrochloric acid at 0°, and extracted with ethyl acetate. The extract was dried over sodium sulfate and concentrated to give 0.82 g (65% overall) of the dihydroisocoumarin **169**, mp 109° (methanol).
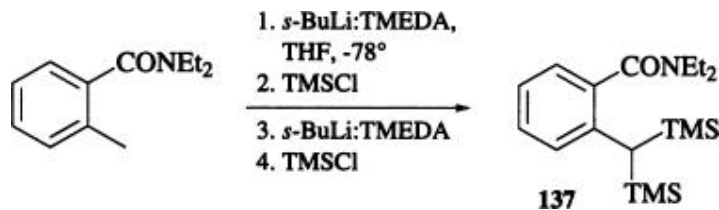
7.1.1.10. N,N-Diethyl-2-[bis(trimethylsilyl)methyl]benzamide (137) (One-Pot Bis-Silylation of a Tertiary o-Toluamide) (166)

A solution of *N,N*-diethyl-*o*-toluamide (4.39 g, 22.9 mmol) in 20 mL of tetrahydrofuran was added dropwise to a stirred solution of *sec*-butyllithium (18.7 mL of 1.3 M in cyclohexane, 23 mmol) and TMEDA (3.8 mL, 23 mmol) in 150 mL of tetrahydrofuran at –78°. The resulting burgundy solution was stirred at –78° for 1 hour and treated with chlorotrimethylsilane (3.0 mL, 23 mmol). To this solution were added consecutively TMEDA (3.8 mL, 23 mmol) and *sec*-butyllithium (18.7 mL, 23 mmol), regenerating the burgundy color. The mixture was stirred for 45 minutes at –78°, chlorotrimethylsilane (4.4 mL, 34 mmol) was added, and the resulting clear solution was allowed to warm to room temperature overnight. Saturated ammonium chloride was added and the mixture was extracted with ethyl acetate. The extract was washed with dilute hydrochloric acid, water, and brine, dried over sodium sulfate, and evaporated. Short-path distillation of the residue afforded 7.03 g (91%) of the bis-silylated product **137**, bp 110–112° (0.02 mm); IR (neat) 1629 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.05 (s, 18H), 1.11 (t, 3H, *J* = 7 Hz), 1.32 (t, 3H, *J* = 7 Hz), 1.82 (s, 1H), 2.80–4.00 (br, 4H), 6.91–7.20 (m, 4H); ^{13}C NMR (CDCl$_3$) δ 0.5, 12.7, 13.9, 24.6, 38.2, 43.0, 122.6, 126.0, 128.0, 128.8, 135.5, 141.2, 170.6; mass spectrum, m/z 335 (M$^+$, 25), 334 (55), 320 (43), 249 (21), 248 (100), 73 (90). Anal. Calcd for C$_{18}$H$_{33}$NOSi$_2$: C, 64.41; H, 9.91; N, 4.17. Found: C, 64.21; H, 9.96; N, 4.19.
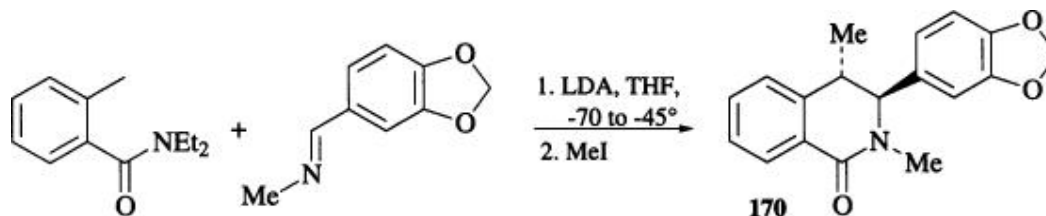
7.1.1.11. trans-3-(1,3-Benzodioxol-5-yl)-2,4-dimethyl-3,4-dihydroisoquinolin-1-(2H)-one (170) (Condensation of a Lithiated Tertiary o-Toluamide with an Imine Followed by Electrophilic Trapping) (52)

A solution of *N,N*-diethyl-*o*-toluamide (0.95 g, 5 mmol) and piperonal *N*-methylimine (0.90 g, 5.5 mmol) in 6 mL of tetrahydrofuran was added dropwise to a –70° solution of lithium diisopropylamide [from 0.84 mL (6 mmol) of diisopropylamine and 3.75 mL (6 mmol) of *n*-butyllithium in hexane] in 10 mL of tetrahydrofuran. The reaction mixture was allowed to stir with gradual warming to –45° over 2 hours and was then cooled back to –70°. Iodomethane (1.24 mL, 20 mmol) was added, and the mixture was allowed to warm to room temperature. After dilution with ether, the mixture was washed with dilute hydrochloric acid, and the ether layer was separated and dried over sodium sulfate. The ether was evaporated under reduced pressure and the residue was purified by medium pressure chromatography on silica gel (50% ethyl acetate–hexane) to afford 0.92 g (62%) of **170** as a white solid, mp 98–99°; ^{1}H NMR (CDCl$_3$) δ 1.45 (d, 3H, J = 7.1 Hz), 3.10 (dq, 1H, J = 1.5, 7.1 Hz), 3.12 (s, 3H), 4.38 (d, 1H, J = 1.5 Hz), 5.87 (AB, 2H J = 1.4 Hz), 6.50 (m, 2H), 6.65 (d, 1H, J = 7.9 Hz), 7.01 (m, 1H), 7.35 (m, 2H), 8.14 (m, 1H). Anal. Calcd for C$_{18}$H$_{17}$NO$_3$: C, 73.22; H, 5.76; N, 4.75. Found: C, 73.08, H, 5.83, N, 4.69.

1. *n*-BuLi, ether, 0°
2. *p*-MeC$_6$H$_4$CHO
3. 1 N HCl, reflux

171
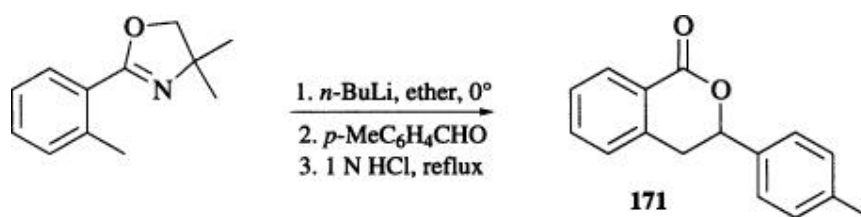
7.1.1.12. 3-(4-Methylphenyl)-3,4-dihydroisocoumarin (**171**) [Lateral Lithiation of a 2-(o-Tolyl)-2-oxazoline] (**195**)

A solution of 2-(2-methylphenyl)-4,4-dimethyl-2-oxazoline (1.89 g, 10 mmol) in 30 mL of ether was cooled to <0° with an icesalt bath, and *n*-butyllithium (10 mmol) in ether (20 mL) was added slowly to maintain the temperature below 0°. The resulting deep red solution was stirred for 1 hour, and *p*-tolualdehyde (1.20 g, 10 mmol) was then added. After stirring overnight at room temperature, the reaction mixture was hydrolyzed by heating to reflux with 1 N hydrochloric acid (70 mL) for 1 hour. The cooled mixture was partitioned between ether and water. The organic layer was separated, dried over magnesium sulfate, and evaporated. Purification of the crude product by chromatography over Florisil (benzene) afforded dihydroisocoumarin **171** in 80% yield, mp 95–96°; IR (Nujol) 1715 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 2.37 (s, 3H), 3.10 (dd, 1H, J = 12.0, 16.3 Hz), 3.34 (dd, 1H, J = 3.0, 16.3 Hz), 5.50 (dd, 1H, 3.0, 12.0 Hz), 7.24 (d, 2H, J = 7.9 Hz), 7.31 (d, 1H, J = 7.4 Hz), 7.36 (d, 2H, J = 7.9 Hz), 7.43 (t, 1H), 7.58 (t, 1H, J = 8.9 Hz), 8.09 (d, 1H, J = 7.9 Hz). Anal. Calcd for C$_{16}$H$_{14}$O$_2$: C, 80.65; H, 5.92. Found: C, 80.88; H, 6.07.
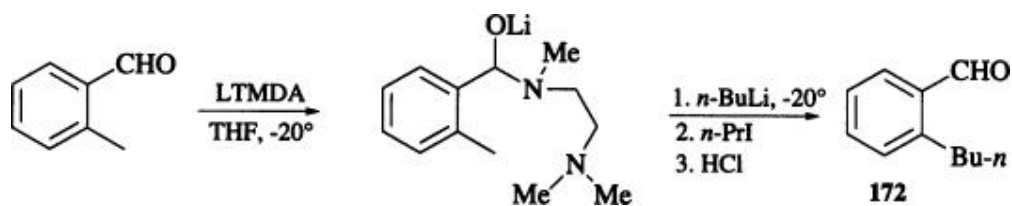
7.1.1.13. o-Butylbenzaldehyde (172) (Lateral Lithiation of an o-Tolualdehyde Amido Adduct) (69)

To a solution of N,N,N¢-trimethylethylenediamine (0.41 mL, 3.2 mmol) in 8 mL of tetrahydrofuran at –20° was added a hexane solution of n-butyllithium (3.1 mmol). After 15 minutes, o-tolualdehyde (360 mg, 3 mmol) was added and the resulting solution was stirred for 15 minutes. A hexane solution of n-butyllithium (9 mmol) was added at –20°, and the mixture was stirred at –20° for 1.5 hours. After cooling to –78°, n-propyl iodide (1.7 mL, 18 mmol) was added, the cooling bath was removed, and the mixture was stirred at room temperature for 30 minutes. The mixture was poured into cold stirred 10% hydrochloric acid, extracted with ether, washed with brine, dried over magnesium sulfate, and concentrated to give the crude product. Purification by silica gel chromatography (acetone-hexanes) afforded aldehyde 172 in 85% yield.
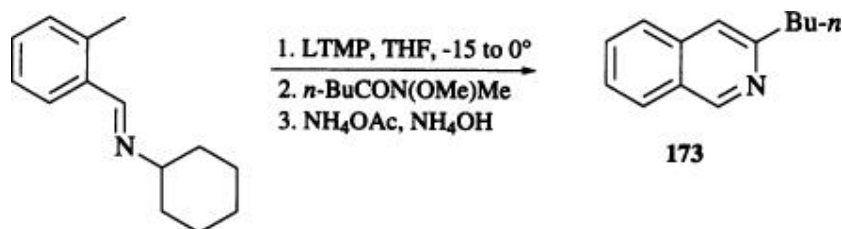
7.1.1.14. 3-Butylisoquinoline (173) (Lateral Lithiation of an o-Tolualdehyde Cyclohexylimine and Condensation with an N-Methoxy-N-methylamide) (208)

To a solution of 2,2,6,6-tetramethylpiperidine (3.00 g, 21 mmol) in 50 mL of tetrahydrofuran at –15° was added a solution of sec-butyllithium in cyclohexane (16.0 mL of 1.3 M, 21 mmol). After 15 minutes, o-tolualdehyde cyclohexylimine (2.00 g, 10 mmol) was added dropwise over 5 minutes to give a deep purple solution. The solution was allowed to warm to 0° over 20 minutes and N-methoxy-N-methylvaleramide (1.90 g, 13 mmol) was added. The mixture was allowed to stand at room temperature for 30 minutes and was then poured into saturated ammonium chloride solution and extracted with ether. The ether extract was washed with water, dried over magnesium sulfate, and concentrated in vacuo to give 2.76 g of a yellow oil. Concentrated

aqueous ammonium hydroxide (50 mL) and acetic acid (3 mL) were added and the resulting mixture was heated under reflux for 4 hours. The reaction mixture was allowed to cool to room temperature, diluted with 100 mL of water, and extracted with ether. The ether extract was washed with water, dried over magnesium sulfate, and concentrated in vacuo. Kugelrohr distillation of the residue afforded 1.52 g (82%) of a colorless oil, bp 90–100° (0.6 mm); ^{1}H NMR (CDCl$_3$) δ 0.96 (t, 3H, J = 7.5 Hz), 1.42 (sextet, 2H), 1.80 (m, 2H), 2.94 (t, 2H, J = 7.7 Hz), 7.46 (s, 1H), 7.51 (td, 1H, J = 1.0, 8.0 Hz), 7.63 (td, 1H, J = 1.0, 6.5 Hz), 7.74 (d, 1H, J = 8.0 Hz), 7.92 (d, 1H, J = 8.0 Hz), 9.20 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 13.9, 22.4, 32.0, 37.7, 117.8, 125.9, 126.1, 126.9, 127.3, 130.0, 136.4, 151.9, 155.7. The picrate salt had mp 172–173° (ethanol). Anal. Calcd for C$_{19}$H$_{18}$N$_4$O$_7$: C, 55.07; H, 4.38; N, 13.52. Found: C, 55.18; H, 4.36; N, 13.59.

174
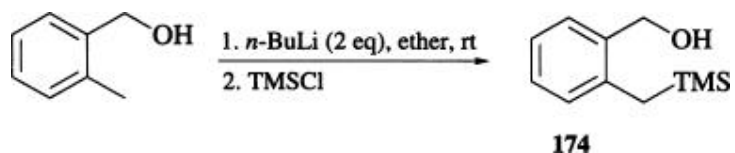
7.1.1.15. o-[(Trimethylsilyl)methyl]benzyl alcohol (174) (Lateral Lithiation of an o-Methylbenzyl Alcohol) (257)

To a stirred solution of *o*-methylbenzyl alcohol (**22**) (1.16 g, 9.50 mmol) in 10 mL of ether was added *n*-butyllithium (2.7 mL of 10.5 M, 28.34 mmol) at –78°. After being stirred for 24 hours at 25°, the reaction mixture was cooled to –78° and chlorotrimethylsilane (4.2 mL, 33.25 mmol) was rapidly added. The solution was stirred at 25° for an additional 1.5 hours before being poured into water and extracted with ether. The extract was dried and concentrated in vacuo. The residue was purified by medium pressure chromatography on silica gel (30% ether-hexane) to give 1.45 g (79%) of alcohol **174**; IR (CHCl$_3$) 3420 (br), 2955, 1600, 1480, 1240, 1000, 850 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.01 (s, 9H), 2.18 (s, 2H), 4.61 (s, 2H), 7.00–7.34 (m, 4H); ^{13}C NMR (CDCl$_3$) δ –1.5, 22.8, 63.4, 124.4, 127.5, 128.1, 129.3, 137.1, 138.6.

175
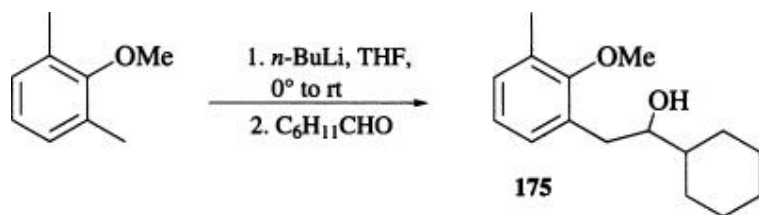
7.1.1.16. 1-Cyclohexyl-2-(2¢methoxy-3¢-methylphenyl)-1-ethanol (175)
(Lateral Lithiation of 2,6-Dimethylanisole) (78)

n-Butyllithium (14.0 mL of a 2.5 M solution in hexane, 35 mmol) was added dropwise to a solution of 2,6-dimethylanisole (4.95 mL, 35 mmol) in 60 mL of tetrahydrofuran at 0°, and the resulting solution was stirred at 0° for 1 hour and then at ambient temperature for 4 hours. The reaction mixture was cooled to 0°, treated with cyclohexanecarboxaldehyde (4.2 mL, 35 mmol), allowed to warm to ambient temperature again, and poured into saturated aqueous ammonium chloride solution. The mixture was extracted with ether and the ether extract was washed with water and brine and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane-ether, 5:1 v/v) to give 4.2 g (48%) of **175** as a colorless oil; ^{1}H NMR (CDCl$_3$) δ 1.05–1.50 (m, 6H), 1.64–1.82 (m, 4H), 1.92 (m, 1H), 2.28 (d, 1H, *J* = 3 Hz), 2.31 (s, 3H), 2.68 (dd, 1H, *J* = 10, 13 Hz), 2.85 (dd, 1H, *J* = 3, 13 Hz), 3.57 (m, 1H), 3.75 (s, 3H), 6.95–7.10 (m, 3H).

31
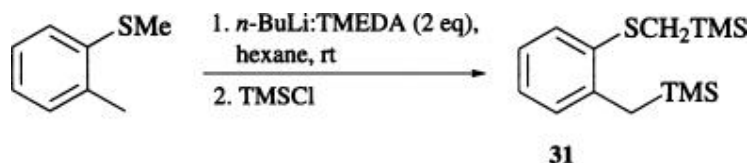
7.1.1.17. Trimethyl([[2-[(trimethylsilyl)methyl]thio)phenyl]methyl)silane (31)
(Alpha, Lateral Dilithiation of o-Methylthioanisole) (83)

To a vigorously stirred solution of *o*-methylthioanisole (5 g, 36 mmol) and TMEDA (9.2 g, 79 mmol) in 100 mL of hexane at 0° was added *n*-butyllithium in hexane (65.8 mL of 1.2 M, 79 mmol) and stirring was continued at room temperature for 12 hours. The resulting solution was cooled to 0° and treated dropwise with chlorotrimethylsilane (7.8 g, 72 mmol). The mixture was then stirred at room temperature for 12 hours, and the pH was adjusted to 5–6 by addition of 10% aqueous hydrochloric acid. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic extract was dried over sodium sulfate and concentrated in vacuo. The crude product was purified by medium-pressure chromatography (hexane) to give **31** in 71% yield, bp 60–61° (12 mm); ^{1}H NMR (CDCl$_3$) δ 0.3 (s, 18H), 2.10 (s, 2H), 2.20 (s, 2H), 6.90 (m, 4H); mass spectrum, m/z 282(M$^+$). Anal. Calcd for C$_{14}$H$_{26}$SSi$_2$: C, 59.51; H, 9.28; S, 11.35. Found: C, 59.38; H, 9.34; S, 11.17.

176
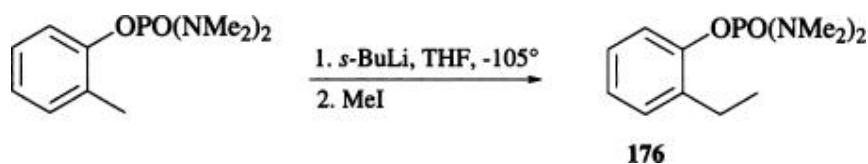
7.1.1.18. 2-Ethylphenyl N,N,N¢,N¢-Tetramethylphosphorodiamidate (176)
(Lateral Lithiation of a Protected o-Cresol) (87)
A solution of *sec*-butyllithium (6.0 mL of 1.0 M in cyclohexane, 6.0 mmol) was added to a stirred solution of *o*-tolyl tetramethylphosphorodiamidate (1.2 g, 5.0 mmol) in 50 mL of tetrahydrofuran at –105° (liquid nitrogen–ethanol bath). The mixture was stirred at –105° for 1 hour, and iodomethane (1.0 g, 7.0 mmol) in 20 mL of tetrahydrofuran was then added to the yellow solution. The yellow color gradually disappeared during the addition of the electrophiles. Stirring was continued at –105° for 1 hour. The reaction mixture was quenched with saturated ammonium chloride solution at –90° and the solution was allowed to warm to room temperature. The mixture was concentrated in vacuo and the residue was extracted with dichloromethane. The dichloromethane was washed with 5% aqueous sodium thiosulfate solution, dried over sodium sulfate, and evaporated to an oil. Distillation provided 1.04 g (81%) of **176**, bp 130° (0.5 mm); IR (KBr) 3470, 2940, 1590, 1490, 1460, 1310, 1240, 1180, 990, 920 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.19 (t, 3H, J = 7.2 Hz), 2.15–2.50 (m, 2H), 2.70 (d, 12H, J = 10.2 Hz), 6.92–7.28 (m, 4H); mass spectrum, m/z 256 (M$^+$). Anal. Calcd for C$_{12}$H$_{21}$N$_2$O$_2$P : C, 56.23; H, 8.26; N, 10.93. Found: C, 55.85; H, 8.19; N, 10.65.
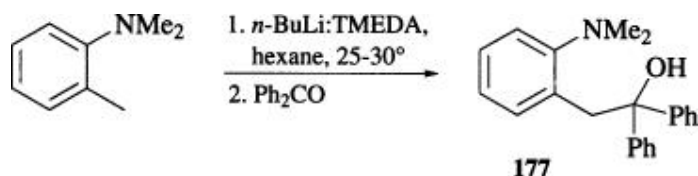
7.1.1.19. 2-[2-(Dimethylamino)phenyl]-1,1-diphenyl-1-ethanol (177) (Lateral Lithiation of N,N-Dimethyl-o-toluidine) (89)
To a solution of TMEDA (2.2 g, 19 mmol) in 100 mL of hexane was added *n*-butyllithium (33 mL of 2.25 M in hexane, 75 mmol). The resulting mixture was stirred for 10–15 minutes, during which time the TMEDA–butyllithium complex usually precipitated. A hexane solution of *N,N*-dimethyl-*o*-toluidine (5.0 g, 38 mmol) was added dropwise over 2–10 minutes. Stirring was continued for 3 hours. The lithio species precipitated during this time affording a yellow-white suspension. An ethereal solution of benzophenone (13.4 g, 75 mmol) was added dropwise over 15 minutes and the resulting green solution was stirred for 5–30 minutes. The mixture was poured into a solution of 5.0 g (83 mmol) of acetic acid in 30 mL of ether. After the solution had been stirred for several minutes, 50 mL of water was added. The resulting suspension was filtered, affording the product **177** as a white crystalline solid.

The filtrate was extracted with 10% aqueous hydrochloric, acid (solid HCl salt of the product precipitated). The aqueous suspension was made basic with sodium hydroxide and the mixture was filtered to afford additional product. Recrystallization of the combined solids from benzene-hexane gave white needles (total yield 60–94%), mp 153–155°; IR (KBr) 1060, 935, 767, 756 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.71 (s, 6H), 3.62 (s, 2H), 6.64 (br s, 1H, -OH), 7.00–7.50 (m, 14H). Anal. Calcd for C$_{22}$H$_{23}$NO : C, 83.24; H, 7.30; N, 4.41. Found: C, 83.03: H, 7.40: N, 4.48.
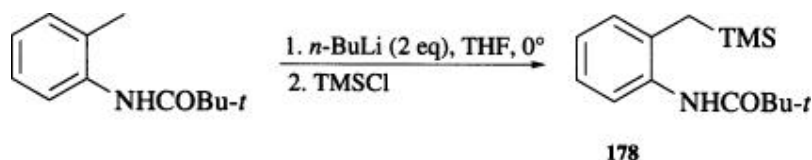
7.1.1.20. 2,2-Dimethyl-2¢-(trimethylsilymethyl)propionanilide (*178*) (Lateral Lithiation of N-Pivaloyl-o-toluidine) (*90*)

A solution of *N*-pivaloyl-*o*-toluidine (1.91 g, 10 mmol) in 30 mL of tetrahydrofuran was cooled in an ice bath and a hexane solution of *n*-butyllithium (10 mL of 2.5 M, 25 mmol) was added dropwise. The mixture was stirred in the ice bath for 1.5 hours, and chlorotrimethylsilane (2.5 mL, 20 mmol) was then slowly added. The mixture was stirred for 1 hour at room temperature, diluted with ether, quenched with ice and water, washed with brine, and dried over magnesium sulfate. The crude product obtained after concentration in vacuo was purified by silica gel chromatography (chloroform–ethyl acetate 9:1) followed by crystallization from pentane to give 1.9 g (73%) of **178**, mp 79–81°; IR (Nujol) 3255, 1639, 1605, 1587 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.00 (s, 9H), 1.30 (s, 9H), 2.02 (s, 2H), 6.98–7.91 (m, 5H). Anal. Calcd for C$_{15}$H$_{25}$NOSi : C, 68.38; H, 9.56; N, 5.31. Found: C, 68.17; H, 9.65; N, 5.21.
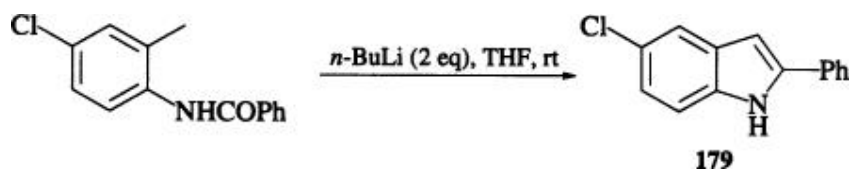
7.1.1.21. 5-Chloro-2-phenylindole (*179*) [Preparation of an Indole by Dilithiation of an N-(2-Alkylphenyl)carboxamide] (*92*)

A stirred solution of *N*-(4-chloro-2-methylphenyl)benzamide (50 mmol) in 100 mL of tetrahydrofuran was cooled to –20° and treated dropwise with a solution of *n*-butyllithium in hexane (100 mmol). The stirred mixture was kept at

ambient temperature for 15 hours, cooled in an ice bath, and treated dropwise with 60 mL of 2 N hydrochloric acid. The organic layer was separated and the aqueous layer was extracted with benzene. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo. Recrystallization of the residue from ether–benzene afforded indole **179** in 94% yield, mp 195–196°.
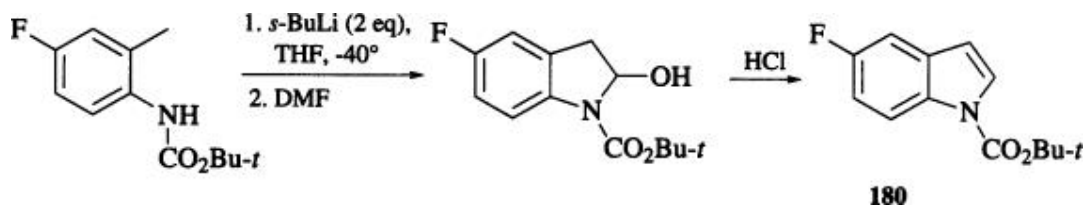
7.1.1.22. 1-(tert-Butoxycarbonyl)-5-fluoroindole (180) (Preparation of a Boc-Protected Indole by Lateral Lithiation of a Boc-o-Toluidine) (93)

A solution of *N*-(*tert*-butoxycarbonyl)-4-fluoro-2-methylaniline (2.25 g, 10 mmol) in 35 mL of tetrahydrofuran was cooled to –40° and *sec*-butyllithium (17 mL of 1.3 M in cyclohexane, 22 mmol) was added at such a rate as to maintain the internal temperature below –20°. The yellow-orange color of the dilithio species persisted after slightly more than 1 equivalent of the *sec*-butyllithium had been added. The mixture was cooled to –40° over a 5-minute period and DMF (1.5 mL, 20 mmol) was added. The now colorless solution was poured into 100 mL of water and extracted with ether (2 × 50 mL). The ether extract was concentrated in vacuo and the residue of crude 2-hydroxy-Boc-indoline was dissolved in 50 mL of tetrahydrofuran and treated with 12 N hydrochloric acid (0.5 mL). The resulting solution was stirred at room temperature until TLC (10% ethyl acetate–hexane) indicated that complete dehydration to the indole had occurred (10–30 min). Ether (100 mL) was added and the mixture was washed with 50 mL of water followed by 50 mL of saturated aqueous sodium bicarbonate, dried over sodium sulfate, and evaporated. Medium pressure silica gel chromatography (2% ethyl acetate–hexane) afforded 2.0 g (86%) of **180** as a colorless oil; IR (neat) 1728 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.57 (s, 9H), 6.41 (d, 1H, *J* = 3.4 Hz), 6.92 (ddd, 1H, *J* = 2.6, 8.8, 8.8 Hz), 7.10 (dd, 1H, *J* = 2.6, 8.8 Hz), 7.52 (d, 1H, *J* = 3.4 Hz), 8.00 (br m, 1H). Anal. Calcd for C$_{13}$H$_{14}$FNO$_2$: C, 66.37; H, 6.00; N, 5.96. Found: C, 66.12; H, 6.11; N, 5.92.
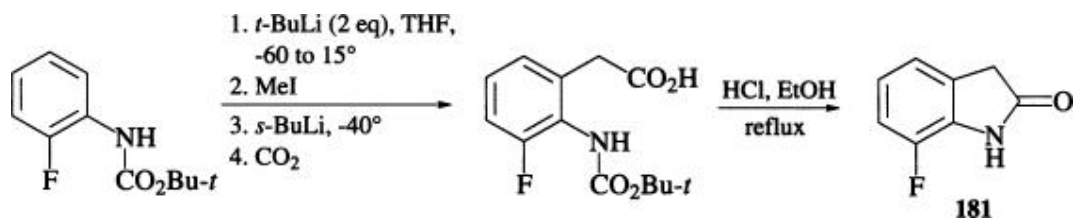
7.1.1.23. 7-Fluoroindol-2(3H)-one (181) (Preparation of an Oxindole from a Boc-Aniline by One-Pot Sequential ortho and Lateral Lithiation) (93)

A solution of *N*-(*tert*-butoxycarbonyl)-2-fluoroaniline (5.3 g, 25 mmol) in 75 mL of tetrahydrofuran was cooled to –60° and *tert*-butyllithium (35 mL of 1.7 M in pentane, 60 mmol) was added at such a rate as to maintain the internal temperature below –40°. The mixture was stirred at –60° for 1.5 hours and was then allowed to slowly warm to –15° over a 30-minute period. The solution was cooled to –45° and iodomethane (2.2 mL, 35 mmol) was added. The resulting suspension was allowed to warm to –15° over 15 minutes and was then cooled to –40°. *sec*-Butyllithium (27 mL of 1.3 M in cyclohexane, 35 mmol) was added and after 5 minutes, carbon dioxide was bubbled into the mixture for 1 minute. Water (150 mL) was added and the mixture was washed with 150 mL of ether. The aqueous layer was acidified with hydrochloric acid (ice-bath) and extracted with dichloromethane (2 × 150 mL). The combined dichloromethane extract was concentrated in vacuo and the residue was dissolved in 50 mL of ethanol. To the resulting solution was added 10% HCl in ethanol (10 mL) and the mixture was heated on a steam bath for 10 minutes. The solution was concentrated in vacuo and the solid residue was recrystallized from ethanol to afford 1.9 g (50% overall yield) of **181** as a white solid, mp 192–193°; IR (KBr) 3600–3300, 1723, 1700 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.56 (s, 2H), 6.88–7.00 (m, 3H), 9.24 (br s, 1H). Anal. Calcd for C$_8$H$_6$FNO : C, 63.57; H, 4.00; N, 9.27. Found: C, 63.82; H, 4.05; N, 9.40.
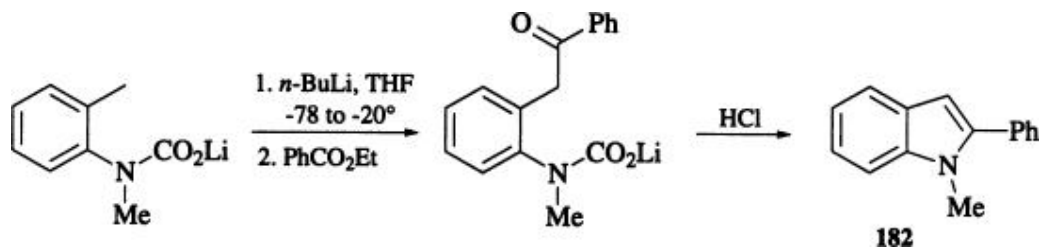
7.1.1.24. 1-Methyl-2-phenylindole (182) (Preparation of a 2-Substituted N-Methylindole by Lateral Lithiation of an N-Methyl-o-toluidine/Carbon Dioxide Adduct) (100)

A solution of *N*-methyl-*o*-toluidine (1.20 g, 10 mmol) in 30 mL of tetrahydrofuran in a Schlenk-type reactor was cooled to –70° and *n*-butyllithium (4.0 mL of 2.5 M in hexane, 10 mmol) was added dropwise. The resulting solution was kept at –70° for a few minutes, and the temperature was then allowed to rise to ca. 0°. Carbon dioxide gas was passed through the solution for about 5 minutes. The solvents were then removed under reduced

pressure to give the lithium *N*-methyl-*N*-tolylcarbamate. The atmosphere was replaced with argon and 30 mL of tetrahydrofuran was added. The solution was again cooled to –70°, and *n*-butyllithium (4.4 mL of 2.5 M in hexane, 11 mmol) was added slowly. The solution was kept at –20° for 45 minutes and was then cooled back to –70°. A solution of ethyl benzoate (10 mmol) in 5 mL of tetrahydrofuran was added and the mixture was allowed to warm to room temperature. After several hours, the mixture was concentrated in vacuo and 10 mL of 2 N hydrochloric acid was then added at 0°. The aqueous solution was neutralized with solid sodium bicarbonate and extracted with chloroform (2 × 20 mL). The extract was washed with water, dried over magnesium sulfate, and evaporated under reduced pressure. Crystallization of the residue afforded indole **182** in 60% yield, mp 98–100°; ^{1}H NMR (CDCl$_3$) δ 3.70 (s, 3H), 6.55 (s, 1H), 7.20–7.75 (m, 9H).
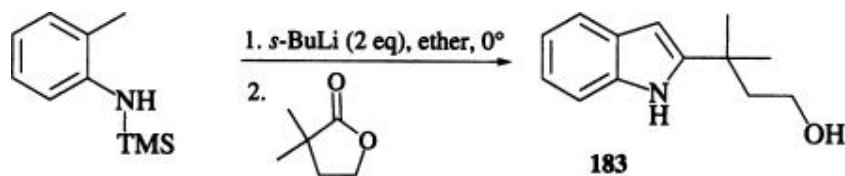
*7.1.1.25. 2-(4-Hydroxy-2-methylbut-2-yl)indole (**183**) (Preparation of a 2-Substituted Indole by Lateral Lithiation of an N-Trimethysilyl-o-toluidine) (102)*

sec-Butyllithium (17.2 mL of 1.3 M in cyclohexane, 22.3 mmol) was added dropwise to a solution of *N*-trimethylsilyl-*o*-toluidine (1.82 g, 10.1 mmol) in 40 mL of ether at 0°. The pale yellow suspension was stirred at ambient temperature for 1.5 hours, cooled to –78°, and quenched with dimethylbutyrolactone (2.02 g, 17.7 mmol) in one portion. The mixture was allowed to warm to ambient temperature and was then poured into aqueous ammonium chloride solution (50% saturated). The mixture was extracted with ether, and the combined ether extract was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. Medium pressure silica gel chromatography (hexanes–ethyl acetate, 3:2) afforded 1.29 g (63%) of the indole **183** as a colorless oil which crystallized on standing. Recrystallization from ether-hexanes gave colorless prisms, mp 96–97°; IR (CHCl$_3$) 3650–3150, 3005, 2970, 1460, 1405, 1295, 1225, 1015 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.37 (s, 6H), 1.58 (br s, 1H), 1.88 (t, 2H, *J* = 7.0 Hz), 3.56 (t, 2H, *J* = 6.9 Hz), 6.25 (m, 1H), 7.06 (dt, 1H, *J* = 1.2, 7.1 Hz), 7.12 (dt, 1H, *J* = 1.4, 7.5 Hz), 7.28 (d, 1H, *J* = 7.9 Hz), 7.53 (dd, 1H, *J* = 1.0, 7.2 Hz), 8.37 (br s, 1H); ^{13}C NMR (CDCl$_3$) δ 28.5, 33.9, 45.3, 59.9, 98.0, 110.5, 119.6, 119.9, 121.2, 128.2, 135.9, 146.6; mass spectrum, m/z 203.1300 (M$^+$ calcd for C$_{13}$H$_{17}$NO , 203.1310). Anal.

Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 77.08; H, 8.65; N,6.67.

184
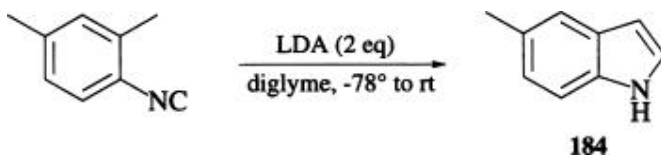
7.1.1.26. 5-Methylindole (*184*) (Preparation of an Indole by Lateral Lithiation of an o-Tolyl Isocyanide) (*104*)

To a solution of diisopropylamine (304 mg, 3 mmol) in 4 mL of diglyme was added dropwise *n*-butyllithium (1.9 mL of 1.6 M in hexane, 3 mmol) at –78°. The solution was stirred at –78° for 15 minutes and 2,4-dimethylphenyl isocyanide (197 mg, 1.5 mmol) was then added. The resulting red solution was stirred for 30 minutes at –78°, and was then allowed to warm to room temperature. The reaction mixture was quenched with aqueous ammonium chloride solution and extracted with ether. The ether extract was washed with water (3×), dried over sodium sulfate, and evaporated to a solid residue. Recrystallization from hexane furnished 5-methylindole (**184**) in almost quantitative yield, mp 57°; IR (KBr) 3400 cm^{-1}; ^{1}H NMR (CCl$_4$) δ 2.36 (s, 3H), 6.22 (m, 1H), 6.61 (m, 1H), 6.83 (br s, 2H),7.00 (br s, 1H), 7.22 (br s, 1H).

185
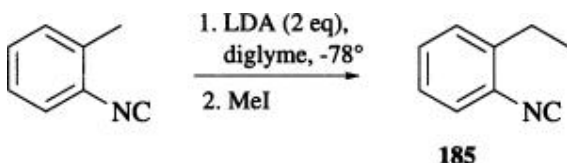
7.1.1.27. 2-Ethylphenyl Isocyanide (*185*) (Lateral Lithiation of an o-Tolyl Isocyanide Followed by Reaction with an Electrophile) (*104*)

To a stirred solution of lithium diisopropylamide (3 mmol) in 4 mL of diglyme at –78° was added *o*-tolyl isocyanide (176 mg, 1.5 mmol). After 30 minutes, iodomethane (426 mg, 3 mmol) was added dropwise. The characteristic red color of *o*-(lithiomethyl)phenyl isocyanide disappeared immediately. The reaction mixture was quenched with aqueous ammonium chloride at –78°, extracted with ether, washed with water (3×), and dried over sodium sulfate. The ether extract was evaporated and the residue was distilled using a Kugelrohr apparatus to afford **185** in 95% yield, bp 85° (10 mm); IR (neat) 2115 cm^{-1}; ^{1}H NMR (CCl$_4$) δ 1.28 (t, 3H), 2.77 (q, 2H), 7.20 (s, 4H). Anal. Calcd for C_9H_9N : C, 82.40; H, 6.92; N, 10.68. Found: C, 82.62; H, 7.09; N, 10.85.

186
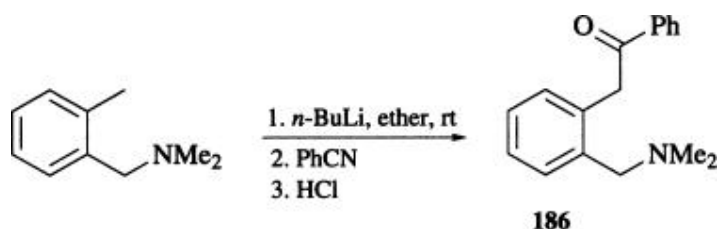
7.1.1.28. 2-(2-[(Dimethylamino)methyl]phenyl)-1-phenylethanone (186) (Lateral Lithiation of o-Methylbenzyldimethylamine and Condensation with an Aryl Nitrile) (19)

A solution of o-methylbenzyldimethylamine (11.9 g, 80 mmol) in 250 mL of ether was treated with n-butyllithium (59 mL of 1.5 M in hexane, 88 mmol) and the resulting solution was stirred at room temperature for 6 hours. A solution of benzonitrile (10.3 g, 100 mmol) in 100 mL of ether was added dropwise. The mixture was heated under reflux for 6 hours, cooled in ice, and 30 mL of water was added carefully followed by 6 mL of acetic acid. The layers were separated, the aqueous layer was extracted with ether, and the extract was combined with the original organic layer. The ethereal solution was dried over magnesium sulfate and evaporated under reduced pressure. The oily residue was heated under reflux in 250 mL of 4 N hydrochloric acid for 8 hours and allowed to stand overnight. The mixture was washed with ether, cooled, and made basic with sodium hydroxide. The product was isolated by ether extraction followed by distillation to afford 13.7 g (68%) of **186**, bp 143–146° (0.3 mm). Anal. Calcd for $C_{17}H_{19}NO$: C, 80.57: H, 7.56; N, 5.53. Found: C, 80.39; H, 7.64; N, 5.74.

187
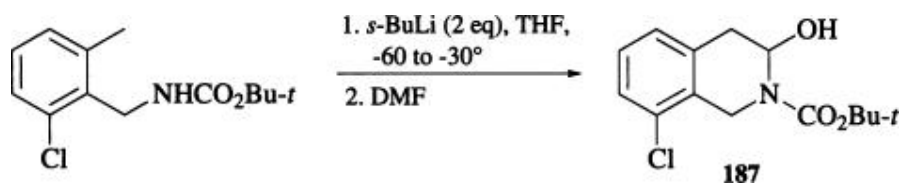
7.1.1.29. 2-(tert-Butoxycarbonyl)-8-chloro-3-hydroxy-1,2,3,4-tetrahydroisoquinoline (187) (Lateral Lithiation of an N-Boc-o-Methylbenzylamine) (47)

A solution of N-(tert-butoxycarbonyl)-2-chloro-6-methylbenzylamine (1.28 g, 5 mmol) in 10 mL of tetrahydrofuran was cooled to ca. –60° and sec-butyllithium (8.5 mL of 1.3 M in cyclohexane, 11 mmol) was added over several minutes at such a rate as to maintain the internal temperature at ca. –30°. The resulting bright orange solution was stirred for 10 minutes and DMF

(0.58 mL, 7.5 mmol) was then added. The now colorless reaction mixture was quenched with saturated aqueous ammonium chloride. The mixture was diluted with ether, washed with water and brine, and dried over sodium sulfate. Removal of solvent in vacuo gave the crude product which was purified by medium pressure silica gel chromatography (ethyl acetate–hexane) to afford 1.13 g (80%) of **187** as a white solid, mp 105–106°; IR (KBr) 3360–3200, 1670 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.53 (s, 9H), 2.95 (dd, 1H, J = 3.7, 15.8 Hz), 3.10 (dd, 1H, J = 3.7, 15.8 Hz), 3.30 (br s, 1H, -OH), 4.45 (d, 1H, J = 17.0 Hz), 4.70 (d, 1H, J = 17.0 Hz), 5.90 (m, 1H), 7.14 (m, 2H), 7.27 (m, 1H); mass spectrum, m/z 285 (M^{+2}, 7), 283 (M$^+$, 18), 229 (6), 227 (18), 211 (12), 209 (32), 192 (12), 164 (16), 148 (22), 138 (44), 57 (100). Anal. Calcd for C$_{14}$H$_{18}$ClNO$_3$: C, 59.26; H, 6.40; N, 4.94. Found: C, 58.98; H, 6.34; N, 4.92.
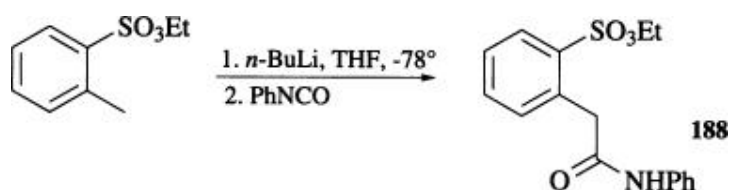
7.1.1.30. Ethyl 2-(N-Phenylcarbamoylmethyl)benzenesulfonate (188) (Lateral Lithiation of a 2-Methylbenzenesulfonate) (144)

n-Butyllithium in hexane (13.7 mmol) was added slowly to a solution of ethyl 2-methylbenzenesulfonate (2.5 g, 12.5 mmol) in 50 mL of tetrahydrofuran at –78° and the resulting mixture was stirred at –78° for 1.5 hours. Phenyl isocyanate (13.7 mmol) in 30 mL of tetrahydrofuran was added to the deep red solution and the mixture was stirred at –78° for 1 hour, allowed to warm to 0°, and stirred at 0° for 1 hour. Water was then added at 0° followed by 5% aqueous hydrochloric acid. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic portions were washed with brine, dried over magnesium sulfate, and evaporated in vacuo to afford a solid residue. Recrystallization from dichloromethane–petroleum ether gave amide **188** in 78% yield as pale yellow needles, mp 124–126°; IR (KBr) 3360, 2990, 1680, 1600, 1550, 1450, 1350, 1180, 1000, 920 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.2 (t, 3H), 4.1 (q and s, 4H), 7.1–7.6 (m, 8H), 8.0 (dd, 1H), 8.35 (1H, -NH).
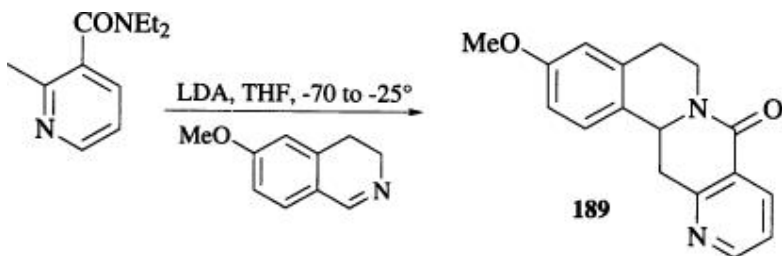
7.1.1.31. 5,8,13,13a-Tetrahydro-3-methoxy-8-oxo-6H-isoquino[2,1-g][1,6] naphthyridine (189) (Cyclocondensation of a Lithiated Tertiary Nicotinamide and a Dihydroisoquinoline) (225)

A solution of lithium diisopropylamide was prepared at –70° by addition of n-butyllithium (312 mL of 1.6 M in hexane, 0.50 mol) to diisopropylamine (74 mL, 0.53 mol) in 750 mL of tetrahydrofuran. To this solution was added a solution of N,N-diethyl-2-methylpyridine-3-carboxamide (96.0 g, 0.50 mol) and 6-methoxy-3,4-dihydroisoquinoline (80.5 g, 0.50 mol) in 200 mL of tetrahydrofuran over a 15-minute period. The resulting dark reaction mixture was allowed to warm to –25° over 30 minutes at which point a thick suspension had formed. A solution of 200 mL of concentrated hydrochloric acid in 500 mL of water was slowly added, and the layers were separated. The aqueous layer was basified with ammonium hydroxide and extracted with ethyl acetate (2×). The ethyl acetate extract was dried over sodium sulfate and concentrated in vacuo. Ether was added to the semisolid residue and filtration afforded 93 g (66%) of 189 as a white solid. An additional 25 g (84% total yield) of product was obtained by medium-pressure chromatography on silica gel (ethyl acetate) of the mother liquor, mp 115–116° (ether); IR (KBr) 1640 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.85 (m, 1H), 3.00 (m, 2H), 3.16 (dd, 1H, J = 13.8, 16.4 Hz), 3.52 (dd, 1H, J = 3.8, 16.4 Hz), 3.82 (s, 3H), 4.90 (m, 2H), 5.00 (dd, 1H, J = 3.8, 13.8 Hz), 6.75 (d, 1H, J = 2.6 Hz), 6.86 (dd, 1H, J = 2.6, 8.6 Hz), 7.20 (d, 1H, J = 8.6 Hz), 7.36 (dd, 1H, J = 4.9, 7.8 Hz), 8.38 (dd, 1H, J = 1.6, 7.8 Hz), 8.64 (dd, 1H, J = 1.6, 4.9 Hz). Anal. Calcd for C$_{17}$H$_{16}$N$_2$O$_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.79; H, 5.81; N, 10.01.
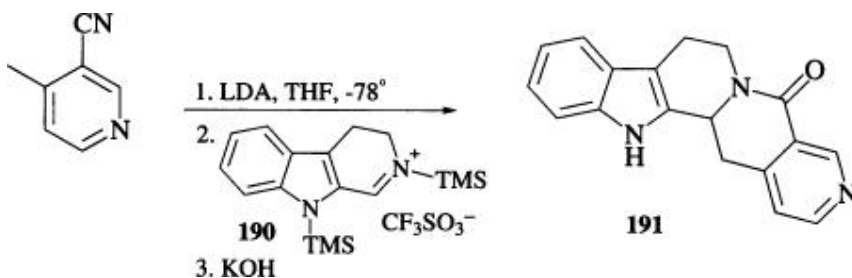
7.1.1.32. 8,13,13b,14-Tetrahydroindolo[2′,3′:3,4]pyrido[1,2-b][2,7]naphthyridin-5[7H]-one [191, (±)-Dihydronauclefine] (Addition of a Lithiated Picolyl Nitrile to an Iminium Salt) (122)

To a stirred solution of 3,4-dihydropyrido [3,4-*b*]indole (629 mg, 3.7 mmol) in 7 mL of tetrahydrofuran at –70° was added *n*-butyllithium (2.3 mL of 1.6 M in hexane, 3.7 mmol). A heavy precipitate appeared after ca. 30 minutes. Trimethylsilyl triflate (1.43 mL, 7.4 mmol) was added and the resulting suspension was stirred at –70° for 15 minutes and then at –5° for 1.5 hours. The heterogeneous mixture containing triflate salt **190** was then cooled to –70° and treated with a solution of the lithio species prepared as follows. To a solution of lithium diisopropylamide [from 0.62 mL (4.4 mmol) of diisopropylamine and 2.8 mL (4.4 mmol) of 1.6 M *n*-butyllithium in hexane] in 25 mL of tetrahydrofuran at –70° was added dropwise a solution of 3-cyano-4-methylpyridine (524 mg, 4.4 mmol) in 10 mL of tetrahydrofuran. The resulting yellow solution was transferred via cannula to the suspension of iminium salt from above. After the addition was complete, the reaction mixture was stirred for 10 minutes at –70° and then it was added to 200 mL of brine. The mixture was extracted with dichloromethane (200 mL) and the extract was dried over sodium sulfate and concentrated under reduced pressure. The residue was stirred for 10 minutes in 10 mL of ethyl acetate and the solid that separated was collected by filtration and dried in vacuo to give 700 mg (49%) of the amidine product. This material was heated under reflux in 60 mL of dioxane and 20 mL of 20% aqueous potassium hydroxide for 24 hours. The solvent was removed under reduced pressure and the residue was partitioned between dichloromethane (200 mL) and water (50 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate to give 447 mg (44% overall yield) of (±)-dihydronauclefine (**191**), mp 266–268°; ^{1}H NMR (CDCl$_3$) δ 2.90–3.00 (m, 2H), 3.05 (m, 2H), 3.45 (dd, 1H, *J* = 3.4, 16.3 Hz), 5.19 (m, 1H), 5.22 (m, 1H), 7.14 (m, 1H), 7.21 (m, 1H), 7.25 (dd, 1H, *J* = 1.1, 5.0 Hz), 7.38 (dd, 1H, *J* = 0.9, 8.0 Hz), 7.56 (d, 1H, *J* = 7.8 Hz), 8.62 (d, 1H, *J* = 5.0 Hz), 9.24 (s, 1H); high-resolution mass spectrum, calculated for C$_{18}$H$_{15}$N$_3$O : m/z 289.1215; found m/z 289.1225.

8. Tabular Survey

Tables I–XI are organized according to the sequence used in the Scope and Limitations section. Entries in Tables I–IX are ordered by increasing carbon count of the compound lithiated. Protecting groups are included in the carbon count. For a particular carbon count, entries are ordered according to increasing hydrogen count. Toluene derivatives are given priority over alkylbenzenes, and *meta* and *para* isomers are given the lowest priority. Table X (Alkyl Substituted Heterocycles) is ordered both by carbon count and by facilitating group as in the Scope and Limitations section. Table XI (Lateral Lithiations in Natural Products Synthesis) is ordered by carbon count and by the general class of the lithiated starting material. The conditions used to effect the lithiations are given in the tables; however, conditions for reactions with substrates are not given. Examples in which no substrate is added to the lithiated species are indicated by — in the substrate column, and unspecified yields are indicated by (—). The tables contain all examples that could be found in the literature through the beginning of 1994.

Abbreviations used in the tables are as follows:

Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOM	benzyloxymethyl
CBZ	carbobenzyloxy
C_4H_3O	furyl
C_4H_3S	thienyl
C_5H_4N	pyridinyl
C_6H_{11}	cyclohexyl
$C_{10}H_7$	naphthyl
diglyme	diethylene glycol dimethyl ether
DMF	*N,N*-dimethylformamide
DMPU	*N,N¢*-dimethylpropyleneurea
ether	diethyl ether
HMPA	hexamethylphosphoric triamide
LCHTBA	lithium *N-tert*-butylcyclohexylamide
LDA	lithium diisopropylamide
LDMA	lithium dimethylamide
LHMDS	lithium hexamethyldisilazide
LTMDA	lithium *N,N,N¢*-trimethylethylenediamide

LTMP	lithium 2,2,6,6-tetramethylpiperazide
MoOPH	molybdenumoxodiperoxy pyridine hexamethylphosphoric triamide complex
MOM	methoxymethyl
NPSPO	*N*-(phenylsulfonyl)-3-phenyloxaziridine
PMB	*p*-methoxybenzyl
rt	room temperature
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
THF	tetrahydrofuran
THP	2-tetrahydropyranyl
TFA	trifluoroacetic acid
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMU	1,1,3,3-tetramethylurea
Ts	*p*-toluenesulfonyl

Table I. Toluic Acid and Derivatives

View PDF

Table II. Tolyl Ketones

View PDF

Table III. Tolualdehyde Derivatives

Table IV. 2-Methylbenzyl Alcohols

Table V. Cresol and Thiocresol Derivatives

Table VI. Toluidine Derivatives

Table VII. 2-(Alkylamino)Toluene Derivatives

Table VIII. Toluenesulfonic Acid Derivatives

Table IX. Fluoro- and Trifluoromethyltoluenes

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Table X. Alkyl-Substituted Heterocycles

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Table XI. Lateral Lithiations in Natural Product Synthesis

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TABLE I. TOLUIC ACID AND DERIVATIVES
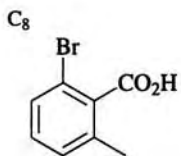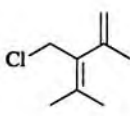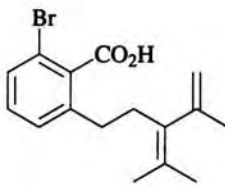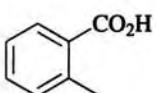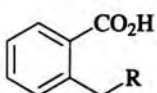
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.

A. Toluic Acids

C_8

LDA, THF, -78°, 2 h — [structure: 2-bromo-6-methylbenzoic acid] → product (84) 117

[structure: 2-methylbenzoic acid]

			R	
	LDA, THF, 0°	n-BuBr	Bu-n (69-73)	29
	LDA, THF, 0°	$CH_2=CHCH_2Br$	$CH_2CH=CH_2$ (—)	48
	LDA, THF, rt	TMSCl	TMS (—)	258
	LDA, THF, HMPA, -78° to rt	TMSCl	TMS (88)	259
	LDA, THF, -78° to rt	$(MeO)_2CO$	CO_2H (85)	256
	n-BuLi, THF, -84 to 0°, 4 h	MeI	Me (74)	31
	s-BuLi, THF, -78°, 1 h	MeI	Me (95)	32
		EtI	Et (93)	32
		$PhCH_2Cl$	CH_2Ph (80)	32

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
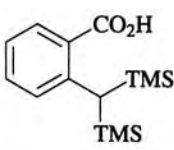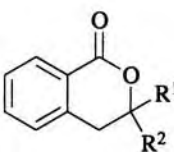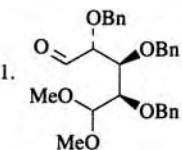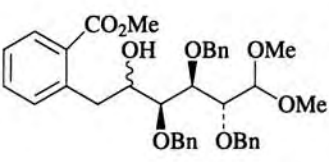
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.

| | 1. n-BuLi, THF, HMPA | 1. TMSCl
2. s-BuLi
3. TMSCl | [structure with CH(TMS)CH2TMS, CO_2H] (80) | 260 |

LDA, THF, -78°, 45 min

[isochromanone structure with R^1, R^2]

		PhCHO	R^1 = H, R^2 = Ph (40)	260a
		p-MeOC$_6$H$_4$CHO	R^1 = H, R^2 = C$_6$H$_4$OMe-p (40)	260a
		m-MeOC$_6$H$_4$CHO	R^1 = H, R^2 = C$_6$H$_4$OMe-m (40)	260a

LDA, THF, 0°, 10 min

| | | Ph_2CO | $R^1 = R^2$ = Ph (28) | 29 |
| | | p-MeOC$_6$H$_4$(Ph)CO | R^1 = Ph, R^2 = C$_6$H$_4$OMe-p (24) | 29 |

| | LTMP, THF, -78° | 1. [sugar aldehyde with OBn, OBn, MeO, OBn, MeO]
2. CH_2N_2 | [structure with CO_2Me, OH, OBn, OMe, OBn, OBn, OMe] (63) | 30 |

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
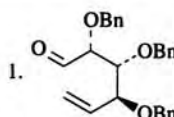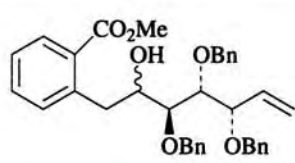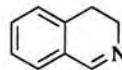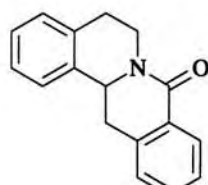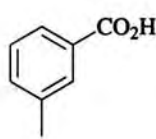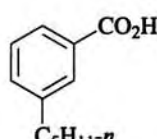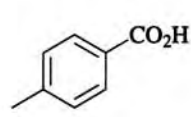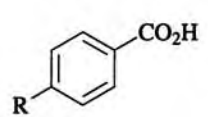
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LTMP, THF, -78°	1. 2. CH₂N₂	(—)	30
	LDA , THF, -78°, 45 min		(—)	260a
	LDA, THF, 0°	*n*-BuBr	(26)	29
	LDA, THF, 0°	*n*-BuBr	*n*-C₅H₁₁ (54-58)	29
	LDA, THF, 0°	*i*-BuCH₂Br	*i*-Bu(CH₂)₂ (51-65)	29
	LDA, THF, 0°	THPO(CH₂)₂₀Br	THPO(CH₂)₂₁ (56)	261

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
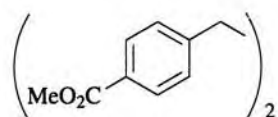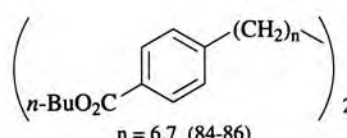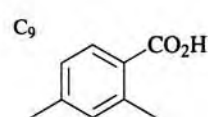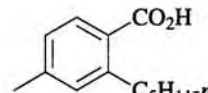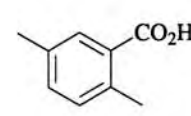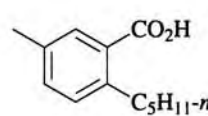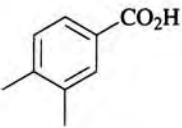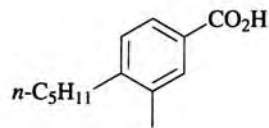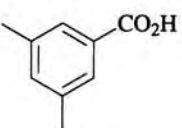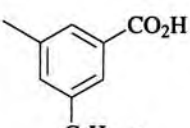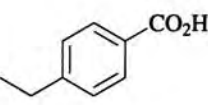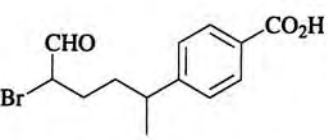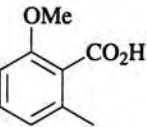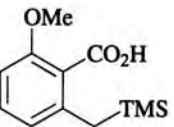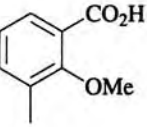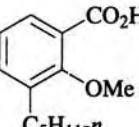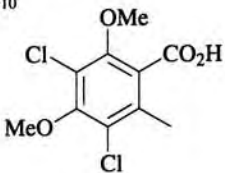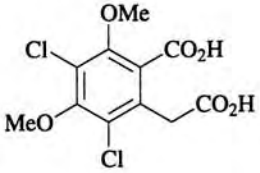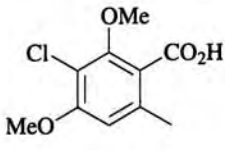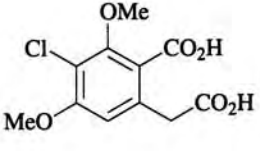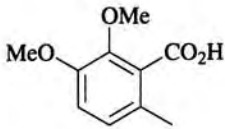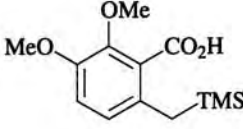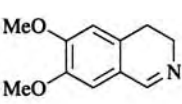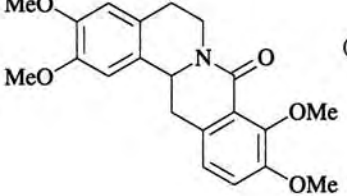
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
			R	
	LDA, THF, 0 to 5°, 20 h	1. MeOCH=CHCH₂Cl 2. Br₂	OHCCH(Br)CH₂CH₂	262
	LDA, THF, -84 to 0°, 4 h	MeI	Et (74)	31
	LDA, THF, -84 to 0°, 4 h	1. ICH₂CO₂Na 2. MeOH, H₂SO₄	MeO₂C(CH₂)₂ (20)	31
	LDA, THF, -84 to 0°, 4 h	1. I₂ 2.MeOH, H₂SO₄	(60)	31
	LDA, THF, 0°	1. Br(CH₂)ₙBr 2. C₄H₉OH, H₂SO₄	n = 6,7 (84-86)	263
C₉	LDA, THF, 0°	*n*-BuBr	(57)	29
	LDA, THF, 0°	*n*-BuBr	(67)	29

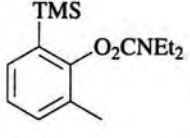TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, 0°	*n*-BuBr	(82–89)	29
	LDA, THF, 0°	*n*-BuBr	(31)	29
	LDA, THF, rt, 15 h	1. MeOCH=CHCH$_2$Cl 2. Br$_2$	(—)	262
	LDA, THF, -78°, 30 min	TMSCl	(—)	185
	LDA, THF, 0°	*n*-BuBr	(35)	29

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

Compound Lithiated	Co nditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C$_{10}$	LDA, THF, -78° to rt, 4 h	(MeO)$_2$CO	(90)	264
	LDA, THF, -78° to rt, 4 h	(MeO)$_2$CO	(81)	264
	LDA , THF, -78°, 45 min	TMSCl	(65)	260a
	LDA , THF, -78°, 45 min		(37)	260a

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TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
(structure: OMe, CO$_2$H, Me, MeO, Cl)	LDA, THF, -78° to rt, 4 h	(MeO)$_2$CO	(structure: OMe, CO$_2$H, CO$_2$H, MeO, Cl) (88)	264
(structure: MeO, OMe, CO$_2$H, Me)	s-BuLi, THF, -78°	TMSCl	(structure: MeO, OMe, CO$_2$H, TMS) (90)	185
(structure: CO$_2$H, isopropyl)	LDA, THF, HMPA, rt, 24 h	1. MeOCH=CHCH$_2$Cl 2. Br$_2$	(structure: CHO, Br, CO$_2$H) (—)	262
C$_{11}$ (indane structure: OMe, CO$_2$H)	n-BuLi, THF, -20°, 45 min	CO$_2$	(indane structure: OMe, CO$_2$H, CO$_2$H) (33)	265
(structure: Me, CO$_2$H, MOMO, Me)	1. NaH, THF 2. t-BuLi, -78°, 1 h	MeI	(structure: Me, CO$_2$H, MOMO, Et) (85)	33

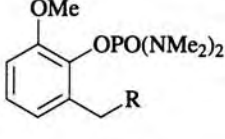TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C$_{12}$ (tetralin structure: OMe, CO$_2$H)	n-BuLi, THF, -20°, 45 min	CO$_2$	(tetralin structure: OMe, CO$_2$H, CO$_2$H) (81)	265
(naphthalene structure: OMe, OMe, CO$_2$H, Me)	LDA, THF, -78°	(MeO)$_2$CO	(naphthalene structure: OMe, OMe, CO$_2$H, CO$_2$H) (85-90)	266
(structure: Me, CO$_2$H, PhS)	LDA, THF, TMU, -15 to -5°, 40 min	CO$_2$	(structure: HO$_2$C, CO$_2$H, PhS) (96)	175
C$_{17}$ (xanthone structure: O, OMe, CO$_2$H, Me, MeO)	LDA, THF, HMPA, -78° to rt, 4 h	(MeO)$_2$CO	(xanthone structure: O, OMe, CO$_2$H, CO$_2$H, MeO) (4) + (xanthone structure: O, OMe, CO$_2$H, Me, MeO, CO$_2$H) (3)	267

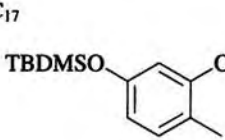TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
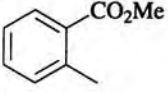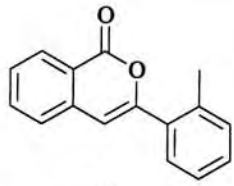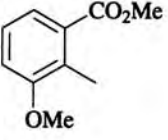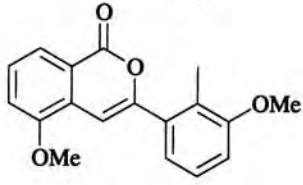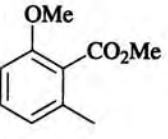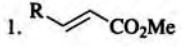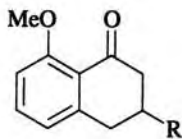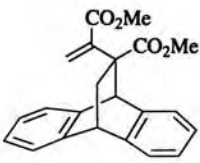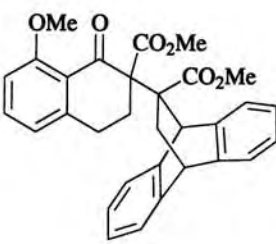
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.

B. Toluate Esters

C₉

| | LDA, THF, -78° | — | (—) | 35 |

C₁₀

| | LDA, THF, -78° | — | (—) | 35 |

| | LDA, THF, -78° | 1.   2. HCl, MeOH | R = H (41) R = Me (40) | 149 149 |

| | LDA, THF, -78° to rt | | (71) | 268 |

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
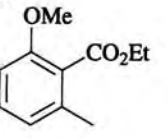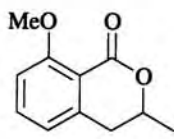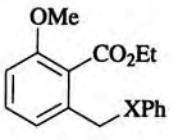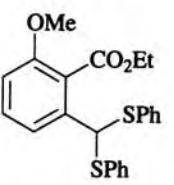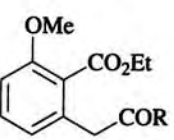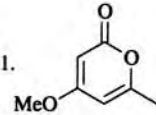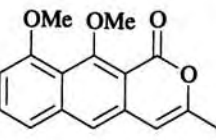
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.

C₁₁

| | LDA, THF, -78° | MeCHO | (52) | 196 |

| | LDA, THF, -78° | (PhX)₂ | X = S (87) X = Se (87) | 35 35 |

| | LDA, THF, -78° | (PhS)₂ | (83) | 35 |

| | LDA, THF, -78° | RCON(OMe)Me | R = Me (81) R = Pr-*n* (66) R = CH=CHMe (68) R = Ph (85) | 159 159 159 159 |

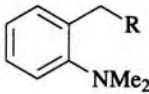| | LDA, THF, -78° to rt | 1.   2. CH₂N₂ | (48) | 154 |

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
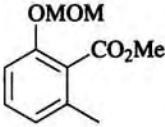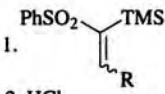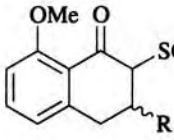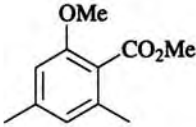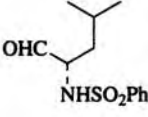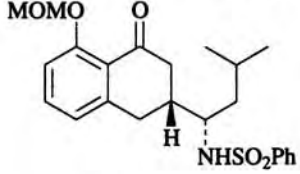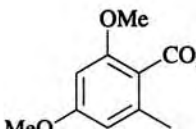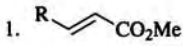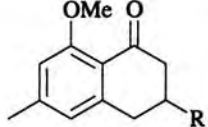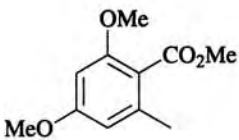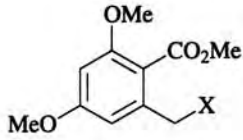
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, -78°	1. PhSO₂—TMS (R) 2. HCl	(tetralone, OMe, SO₂Ph, R) R = H (91)	152
			R = Ph (93)	152
			R = C₆H₄OMe-*o* (65)	152
			R = C₆H₄OMe-*p* (98)	152
OMOM / CO₂Me / Me (aromatic)	LDA, TMEDA, THF, -78°	OHC—(NHSO₂Ph)	(MOMO tetralone with NHSO₂Ph side chain) (—)	198
OMe / CO₂Me / Me (aromatic)	LDA, THF, -78°	1. R—CO₂Me 2. HCl, MeOH	(OMe tetralone, R) R = H (52)	149
			R = Me (51)	149
OMe / CO₂Me / Me / MeO (aromatic)	LDA, THF, -78°		(OMe, CO₂Me, MeO, CH₂X aromatic)	
	TMSCl		X = TMS (55)	197
	(PhS)₂		X = SPh (84)	35
	(PhSe)₂		X = SePh (71)	35

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
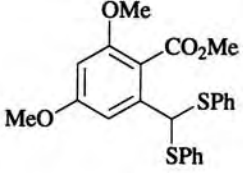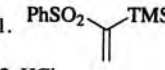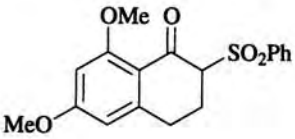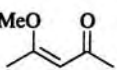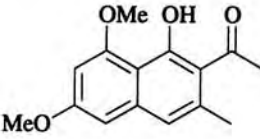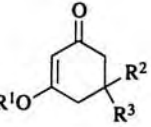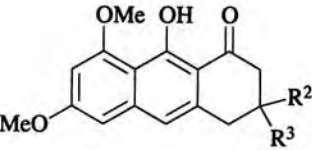
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	3 LDA, THF, -78°	(PhS)₂	(OMe, CO₂Me, MeO, CH(SPh)₂ aromatic) (85)	35
	LDA, THF, -78°	1. PhSO₂—TMS 2. HCl	(OMe, MeO tetralone, SO₂Ph) (96)	152
	LDA, THF, -78°	MeO—(enone)	(OMe, OH, MeO naphthalenone, Me) (50)	153
	LDA, THF, -78°	R¹O—(cyclohexenone, R², R³)	(OMe, OH, MeO tricyclic, R², R³)	
		R¹ = Et, R² = R³ = Me	R² = R³ = Me (64)	153
		R¹ = Me, R² = H, R³ = Me	R² = H, R³ = Me (57)	153

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, -78°	(cyclohexanone ketal substrate)	(tricyclic OMe, OH, O product) (75)	153
C_{12} (ethyl 2,4-dimethoxy-6-methylbenzoate)	LDA, THF, -78°, 15 min		(OMe, CO_2Et, CH_2X product)	
		CO_2	X = CO_2H (60)	197
		MeI	X = Me (92)	197
		$(Me)_3SnCl$	X = $Sn(Me)_3$ (72)	197
		MeCOCl	X = COMe (50)	197
	LDA, THF, -78°, 10 min	RCON(OMe)Me	(OMe, CO_2Et, CH_2COR product)	
			R = Me (82)	159
			R = Pr-*n* (58)	159
			R = CH=CHMe (58)	159
			R = Ph (61)	159

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
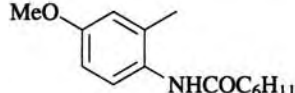
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, -78°, 15 min	RCHO	(isochromanone product) R = Me (—)	197
			R = Ph (—)	197
C_{13} (methyl 2-methoxy-tetrahydronaphthalene carboxylate)	LCHTBA, THF, HMPA, -15°	CO_2	(OMe, CO_2Me, CO_2H product) (81)	265
(ethyl 2-methoxy-dimethyl-methoxy benzoate)	LDA, THF, -78°	(cyclohexenone R^1O, R^2, R^3)	(tricyclic R^2, R^3 product)	
		R^1 = Et, $R^2 = R^3$ = Me	$R^2 = R^3$ = Me (32)	153
		R^1 = Me, R^2 = H, R^3 = Me	R^2 = H, R^3 = Me (36)	153
(ethyl 2,3,4-trimethoxy-6-methylbenzoate)	LDA, pentane, -78°	—	(OMe, CO_2Et, CH_2CO-aryl product) (—)	269

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
OMe, CO₂Et, MeO, Et (aromatic ester)	Ph–CH(CH₃)–N(Li)–CH₂CH₂OMe, THF, -78°	(Me)₂CO	OMe, O, MeO (isochromanone) 72% ee (51)	199
C₁₄ OMOM, CO₂Et, MeO, Me	LDA, THF, -78°	EtO, O (5,5-dimethylcyclohexenone)	MOMO, OH, O, MOMO (55)	153
C₂₀ MeO, CO₂Me (dioxolane fused)	LCHTBA, THF, HMPA, -15°	CO₂	MeO, CO₂Me, CO₂H (81)	265
H, MeO, CO₂Me (dioxolane fused)	LCHTBA, THF, HMPA, -15°	CO₂	H, MeO, CO₂Me, CO₂H (71)	265

114

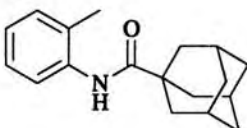TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
		C. Phthalides		
C₈ (phthalide)	LDA, THF, -40°, 30 min	CH₂=CH–CN	O, CN, OH (naphthalenone) (39)	148
	LDA, THF, -40°, 30 min	CH₂=CH–CO₂Me	OH, CO₂Me, OH (37)	148
	LDA, THF, -40°, 30 min	(CH₃)₂C=CH–CO₂Me	O, CO₂Me, (dimethyl), OH (37)	148
	LDA, THF, -40°, 30 min		O, CO₂Me, Me, OH	
		trans =CH–CO₂Me	(48)	148
		cis =CH–CO₂Me	(44)	148

115

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, -40°, 30 min	CO₂Me / CO₂Me (crotonate diester)	(45)	148
	LDA, THF, -40°, 30 min	COMe (mesityl oxide)	(20)	148
	Ph₃CNa, benzene, -10 to 40°	R^1, R^2 quinone CO₂Me	R^1 = H, R^2 = OMe (5); R^1 = OMe, R^2 = H (—)	270
	Ph₃CNa, benzene, -10 to 40°	OMe, CO₂Et naphthoquinone	(17)	271

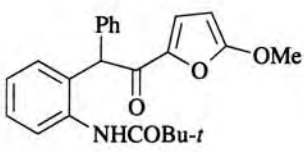## TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, -78°	CO₂	(45) CO₂H	39
	LDA, THF, -40° to rt; 2. air	1. aryl-R		
			R	
			H (75)	156
			OMe-2 (45)	156
			(OMe)₂-1,4 (46)	156
			Me-2 (40)	156
			C₄H₄-1,2 (62)	156
			OH-1, OMe-4 (26)	156
	LDA, THF, -40°, 1 h; 2. *p*-TsOH, benzene	1. R^1, SiMe₃, R^2 vinylsilane		
			R^1 — **R^2**	
			PhS — H (75)	152
			PhSO₂ — H (96)	152
			PhSO₂ — C₆H₄OMe-*o* (60)	152
			PhSO₂ — C₆H₄OMe-*p* (93)	152

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

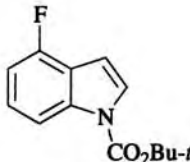| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, -78°			

R^1	R^2	I	II	
Ph	Ph	(51)	(21)	211
C_6H_4Me-*p*	Ph	(33)	(18)	211
C_6H_4OMe-*p*	Ph	(26)	(15)	211
C_6H_4OMe-*p*	C_6H_4OMe-*p*	(31)	(16)	211
Ph	C_6H_4OMe-*p*	(39)	(20)	211
C_6H_4Cl-*p*	Ph	(39)	(7)	211
Ph	CH_2Ph	(43)	(—)	211

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, -40° to rt	$C_6H_3(OMe)_2$-3,4 Me	(39) (19)	212
	LDA, THF, -40° to rt		(61)	212

TABLE I. TOLUIC ACID AND DE RIVATIVES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, -35° to rt		(55)	272
	LDA, THF, -70 to -35°, 20 min	R = Me	**I** (19) **II** (21)	273
	LDA, ether, -78°, 20 min	R = Me	**I:II** = 1:1.9 (30)	274
	LDA, ether, -78°, 20 min	R+R = CH_2	**I:II** = 1:3.4 (50)	274

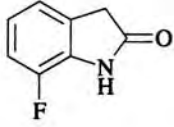TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
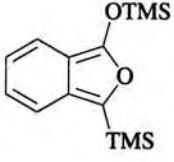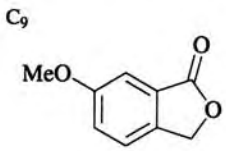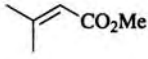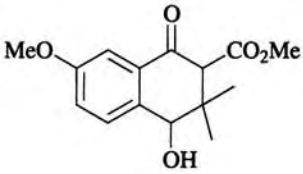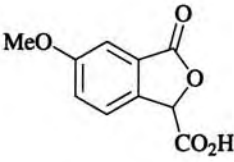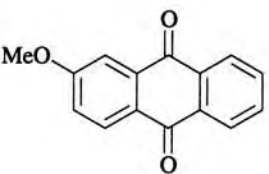
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, -78 to 0°	TMSCl	[1,3-bis-substituted isobenzofuran with OTMS and TMS] (—)	275
C₉ [6-methoxyphthalide: MeO-substituted benzofuranone]	LDA, THF, -40°, 30 min	[methyl 3-methylbut-2-enoate, Me₂C=CHCO₂Me]	[MeO-substituted bicyclic product with O, CO₂Me, two Me, and OH] (41)	148
	LDA, THF, -40°, 20 min	1. ClCO₂Et 2. KOH, heat 3. HCl	[MeO-substituted phthalide with CO₂H] (84)	276
	LDA, THF, -45° to rt	1. [benzyne] 2. air	[MeO-substituted anthraquinone] (45)	156

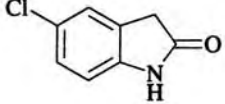TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, -45° to rt	1. [methoxy benzyne, OMe] 2. air	[dimethoxy anthraquinone, OMe and OMe] (41)	156
[4-methoxyphthalide: phthalide with OMe]	LDA, THF, -45° to rt	1. [benzyne] 2. air	[MeO-substituted anthraquinone] (51)	156
	LDA, THF, -45° to rt	1. [methoxy benzyne, OMe] 2. air	**I** [MeO anthraquinone with OMe] + **II** [MeO anthraquinone with OMe] **I + II** (60)	156

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

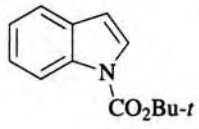| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, -45° to rt	1. [p-dimethoxybenzene] 2. air	[anthraquinone with OMe groups] (64)	156
	LDA, THF, -45° to rt	1. [anisole] 2. air	[anthraquinone with OMe groups] (40) + [anthraquinone with OMe groups] (2)	156
	LDA, THF, -40°, 30 min	[MeO2C-CH=CH-Me] CO2Me	[tetralone with CO2Me, Me, OMe, OH] (58)	148
	LDA, THF, -40°, 30 min	[MeO2C-C(Me)=CH-Me] CO2Me	[tetralone with CO2Me, gem-dimethyl, OMe, OH] (48)	148

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, -45° to rt	[maleate diester] CO2Me / CO2Me	[tetralone with two CO2Me, OMe, OH] (34)	156
	LDA, THF, -40°, 30 min	[butenolide]	[naphthofuranone with OH, OMe] (30)	156
[7-methoxyisobenzofuranone]	LDA, THF, -45° to rt	1. [p-dimethoxybenzene] 2. air	[anthraquinone with OMe groups] (50)	156
	LDA, THF, -78 to 0°	TMSCl	[methoxyisobenzofuranone with TMS] (—)	275

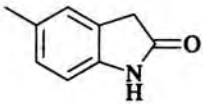TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, -40°, 1 h	MeO, MeO-3,4-dihydroisoquinoline	(87)	212
C$_{10}$ MeO, MeO-isobenzofuranone	LDA, THF, -45° to rt	1. benzene 2. Air	MeO, MeO-anthraquinone (46)	156
	LDA, THF, -45° to rt	1. 1,4-dimethoxybenzene (OMe, OMe) 2. air	MeO, MeO, OMe, OMe (64)	156
	LDA, THF, -45° to rt	1. naphthalene 2. air	MeO, MeO (32)	156

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, -50° to rt	*p*-MeOC$_6$H$_4$CH=N-Ph	MeO, MeO, N-Ph, C$_6$H$_4$OMe-*p*, OH (46) + MeO, MeO, N-Ph, C$_6$H$_4$OMe-*p*, OH (23)	211
	LDA, THF, -35° to rt	MeO, MeO-3,4-dihydroisoquinoline	MeO, MeO, H, HO, OMe, OMe (69)	212
	LDA, THF, -40° to rt	methylenedioxy-3,4-dihydroisoquinoline	O, O, H, HO, OMe, OMe (33)	212

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TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
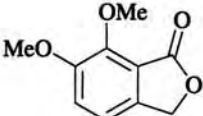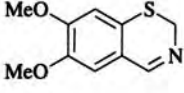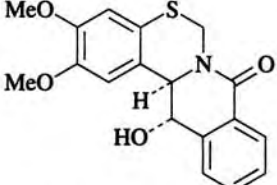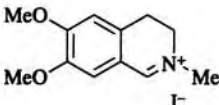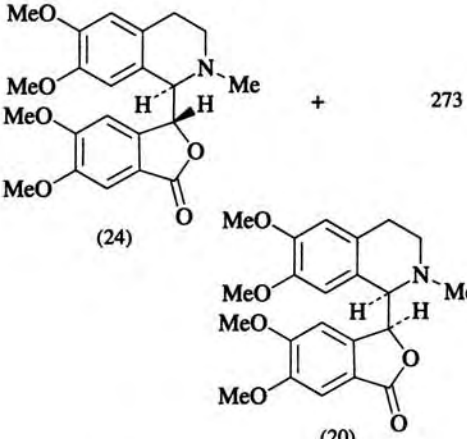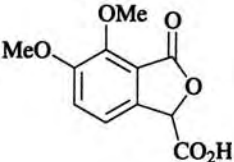
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, -35° to rt		(51)	272
			+ (24) (20)	273
	LDA, THF, -78°, 5 min	CO_2	(94)	276

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
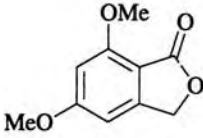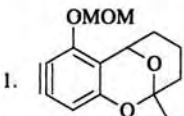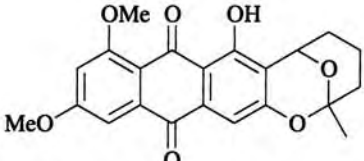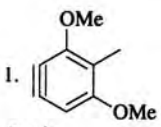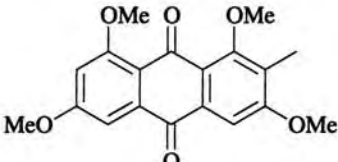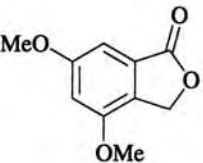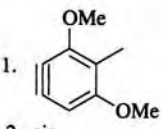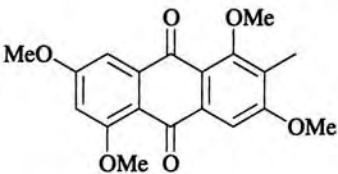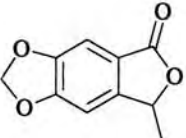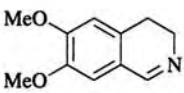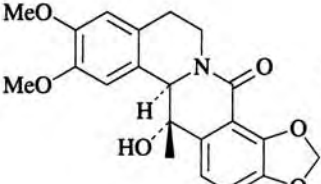
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LTMP, THF, -60°, 20 min	1. 2. HOAc	(55)	277
	LTMP, THF, -60°, 20 min	1. 2. air	(66)	277
	LTMP, THF, -60°, 20 min	1. 2. air	(—)	277
	LDA, THF, -40°, 1 h		(80)	212

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
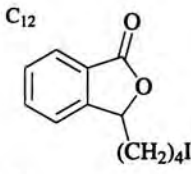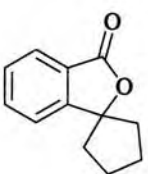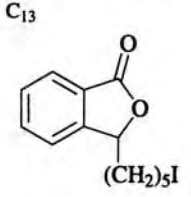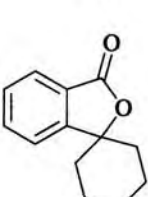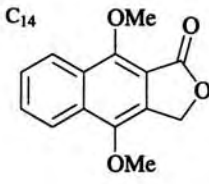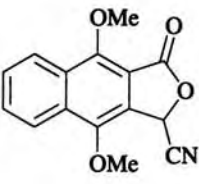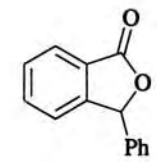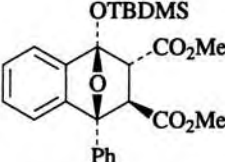
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C$_{12}$ (phthalide with (CH$_2$)$_4$I)	LDA, THF, HMPA, -70°, 30 min	—	spiro phthalide (cyclopentane) (67)	278
C$_{13}$ (phthalide with (CH$_2$)$_5$I)	LDA, THF, HMPA, -70°, 30 min	—	spiro phthalide (cyclohexane) (59)	278
C$_{14}$ (dimethoxy phthalide, OMe/OMe)	LDA, THF, -78°	1. CO$_2$ 2. HCl 3. ClSO$_2$NCO	dimethoxy phthalide with CN (—)	39
(phthalide with Ph)	LDA, THF, -78 to 0°	1. TBDMSCl 2. MeO$_2$C—CO$_2$Me	bicyclic OTBDMS, CO$_2$Me, CO$_2$Me, Ph (87)	189

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

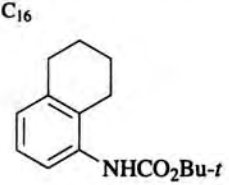| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C$_{15}$ (phthalide with C$_6$H$_4$OMe-*p*)	LDA, THF, -78 to 0°	1. TBDMSCl 2. MeO$_2$C—CO$_2$Me	bicyclic OTBDMS, CO$_2$Me, CO$_2$Me, C$_6$H$_4$OMe-*p* (78) + isomer bicyclic OTBDMS, CO$_2$Me, CO$_2$Me, C$_6$H$_4$OMe-*p* (12)	189
(MeO-substituted phthalide with Ph)	LDA, THF, -78 to 0°	1. TBDMSCl 2. MeO$_2$C—CO$_2$Me	MeO bicyclic OTBDMS, CO$_2$Me, CO$_2$Me, Ph (80) + isomer MeO bicyclic OTBDMS, CO$_2$Me, CO$_2$Me, Ph (10)	189

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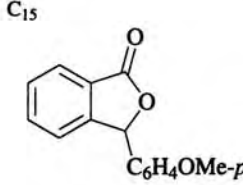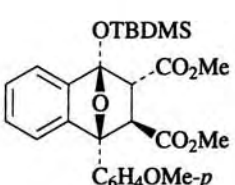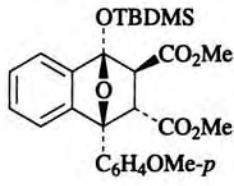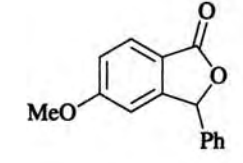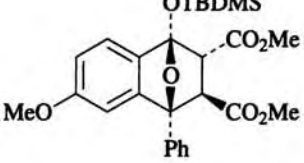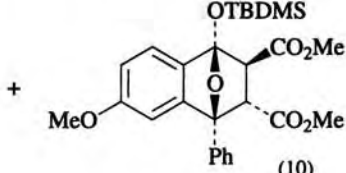
TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
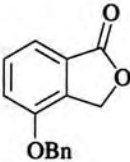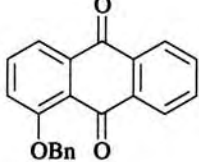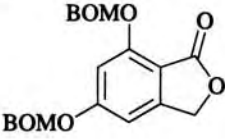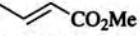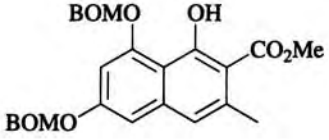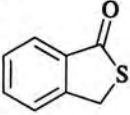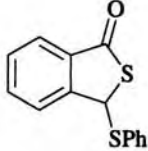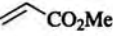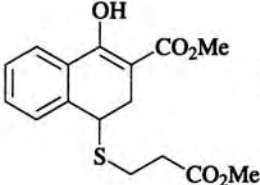
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
OBn	LDA, THF, -45° to rt	1. (benzyne) 2. air	OBn	(24)	156
C₂₂ BOMO / BOMO	LDA, THF, -40°	1. (E)-CH=CH-CO₂Me 2. MsCl, Et₃N, CH₂Cl₂	BOMO, OH, CO₂Me, BOMO, Me	(65)	228

D. Thiophthalides

C₈				
(thiophthalide)	LDA, THF, -78°, 2 h	(PhS)₂	SPh	(30)	41
	LiOBu-*t*, THF, -60°, 3 h	CH₂=CH-CO₂Me	OH, CO₂Me, S-CH₂CH₂-CO₂Me	(26)	41

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
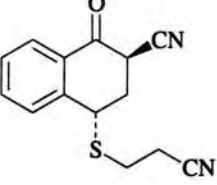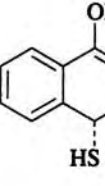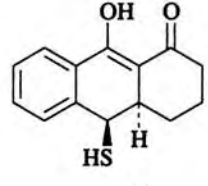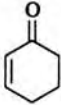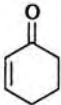
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LiOBu-*t*, THF, -60°, 3 h	CH₂=CH-CN	O, CN, S-CH₂CH₂-CN	(43)	41
			I + II **I** (OH, O, HS, H) + **II** (OH, O, HS, H)		
	LiOBu-*t*, THF, -60°, 3 h	(cyclohexenone)	**I:II** = 1:3 (27)	41
	LDA, THF, CuI, -60° to rt	(cyclohexenone)	**I:II** = 1:1 (42)	41

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C₉	LiOBu-*t*,THF, -60°		(31)	41
	LiOBu-*t*, THF, -60°		(23)	41
	LiOBu-*t*, THF, -60°		(35)	41
	LDA, THF, -60°, 1 h		(14)	41
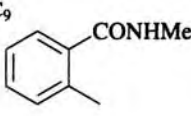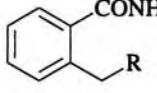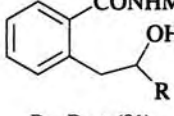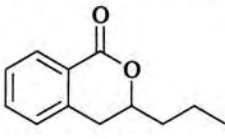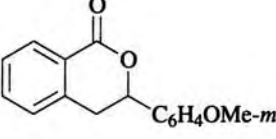
TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
		E. Secondary Toluamides		
C₉	*n*-BuLi, THF, 0°			
		D₂O	R = D (75)	42
		1. O₂ 2. Na₂SO₃	R = OH (70)	163
		TMSCl	R = TMS (92)	279
	n-BuLi, THF, reflux	RCHO		
			R = Bu-*t* (81)	214
			R = Ph (51)	43
			R = C₆H₄OMe-*o* (65)	280
			R = C₆H₄OMe-*p* (69)	280
	n-BuLi, THF, reflux, 15 min	1. *n*-BuCHO 2. 200–215°	(40)	281
	n-BuLi, ether, 0°, 45 min	*m*-MeOC₆H₄CHO	(13)	282

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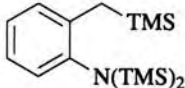TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	n-BuLi, THF, 0°			
		MeCOEt	R^1 = Me, R^2 = Et (80)	214
		(CH$_2$)$_4$CO	R^1, R^2 = (CH$_2$)$_3$ (41)	43
		(CH$_2$)$_5$CO	R^1, R^2 = (CH$_2$)$_4$ (65)	43
		Ph$_2$CO	R^1 = R^2 = Ph (93)	43
		Et$_2$CO	R^1 = R^2 = Et (81)	213
		PhCOEt	R^1 = Et, R^2 = Ph (80)	213
			R^1, R^2 = (50)	43
	n-BuLi, THF, rt, 40 min			
			R = Me (46)	283
			R = Pr-n (25)	284
			R = CH$_2$CH=CH$_2$ (21)	284
			R = Bu-i (44)	284
			R = C$_6$H$_{11}$ (2)	284
			R = CH$_2$C$_6$H$_{11}$ (26)	284

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TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
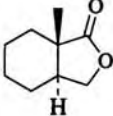
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
			R = Ph (9)	284
			R = CH$_2$Ph (37)	284
			R = (CH$_2$)$_2$Ph (5)	284
			R = (CH$_2$)$_3$Ph (34)	284
	n-BuLi, THF, 0°		(—)	52
	n-BuLi, THF, 0°, 1 h	1. RCN 2. NH$_4$Cl		
			R = Pr-i (42)	158
			R = Bu-t	158
			R = Ph (87)	158
			R = C$_6$H$_4$Me-o (66)	158
			R = C$_6$H$_4$CF$_3$-m (60)	158
			R = C$_4$H$_3$S-2 (58)	158
	n-BuLi, THF, reflux, 45 min	HCON(Me)$_2$	(32)	160

135

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
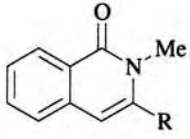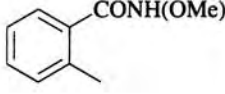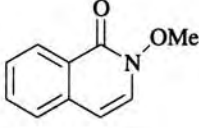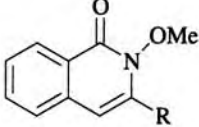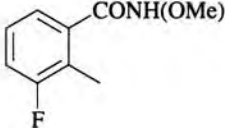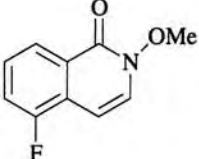
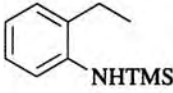| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	n-BuLi, THF, reflux, 45 min	1. RCON(Me)$_2$ 2. HCl		
			R = H (77)	160
			R = Me (58)	160
			R = Ph (73)	160
(CONH(OMe), 2-methyl)	*s*-BuLi, THF, -70°, 5 min	1. DMF 2. HCl	(60)	49
	s-BuLi, THF, -70°, 5 min	1. RCON(OMe)Me 2. HCl		
			R = (CH$_2$)$_3$CH$_3$ (75)	49
			R = (CH$_2$)$_3$CH$_2$Cl (64)	49
			R = (CH$_2$)$_4$CH$_2$Cl (81)	49
(CONH(OMe), 2-methyl, 3-F)	*s*-BuLi, THF, -70°, 5 min	1. DMF 2. HCl	(36)	49

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
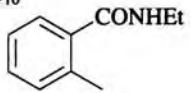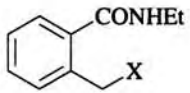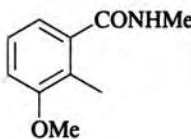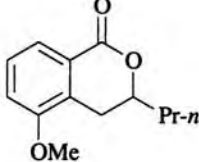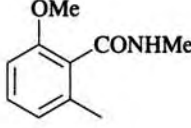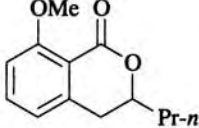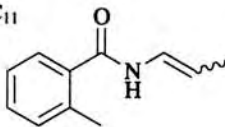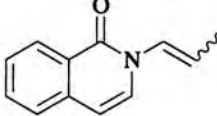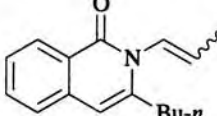
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C$_{10}$ (CONHEt, 2-methyl)				
	s-BuLi:TMEDA, THF, -78°, 30 min	MeOD	X = D (87)	168
	n-BuLi, THF	1. O$_2$ 2. Na$_2$SO$_3$	X = OH (70)	163
(CONHMe, 2-methyl, 3-OMe)	*n*-BuLi, THF, reflux, 15 min	1. *n*-PrCHO 2. 200-215°	(53)	281
(2-OMe, CONHMe, 6-methyl)	*n*-BuLi, THF, reflux, 15 min	1. *n*-PrCHO 2. 200-215°	(27)	281
C$_{11}$	*s*-BuLi, THF, -70°, 10 min	1. DMF 2. HCl	(84)	46
	s-BuLi, THF, -70°, 10 min	1. *n*-BuCON(OMe)Me 2. HOAc	(81)	46

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
(2-ethyl, CONHEt)	s-BuLi:TMEDA, THF, -78°	MeOD	(CONHEt, CHDMe) (87)	168
(2,5-(OMe)₂, CONHMe, methyl)	n-BuLi, THF, reflux, 15 min	1. n-PrCHO 2. 200-215°	(28)	281
C₁₂ (CONHBu-t, methyl)	n-BuLi:TMEDA, THF, 0° to rt, 1 h	3,4,5-(MeO)₃C₆H₂-CH₂CH₂C₆H₄CO₂Me-4	(20)	285
(CONNaBu-t, methyl)	n-BuLi, THF, HMPA, -78°, 1 h		(CONHBu-t, R)	
		Me₂CO	R = C(Me)₂OH (46)	45
		p-MeOC₆H₄CHO	R = CHOHC₆H₄OMe-p (63)	45
	n-BuLi, THF, HMPA, -78°, 1 h	DMF	(N-Bu-t isoquinolinone) (40)	45

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C₁₃	LTMP, THF, -60 to -10°, 1 h	MeI	(94)	47
C₁₅ (CONHPh, methyl)	n-BuLi, THF, 0°, 30 min	PhCOR	R = H (92) / R = Ph (95)	213 / 213
	s-BuLi, THF, -70°, 10 min	1. DMF 2. HCl	(96)	47
	n-BuLi, THF, -22°, 30 min	1. DMF 2. HCl	(70)	44
	n-BuLi, THF, -22°, 30 min	1. DMF 2. HCl	(65)	44

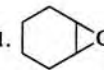TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
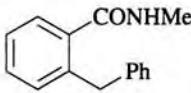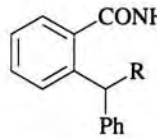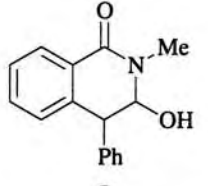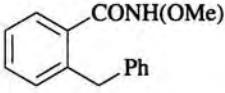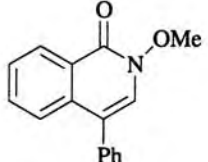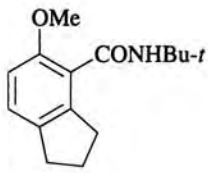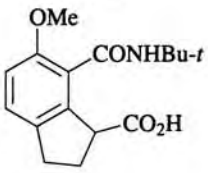
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	n-BuLi, THF, 0°, 30 min			
			R	
		Et$_2$CO	COHEt$_2$ (55)	213
		(CH$_2$)$_5$CO	COH(CH$_2$)$_5$ (40)	213
		Ph$_2$CO	COHPh$_2$ (81)	213
	n-BuLi, THF, 5°, 3 h	*t*-BuCOCl	COBu-*t* (—)	286
	n-BuLi, ether, 0°	DMF	(80)	287
	s-BuLi, THF, -70°, 5 min	1. DMF 2. HCl	(49)	49
	n-BuLi, THF, -50 to -10°, 30 min	CO$_2$	(74)	265

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
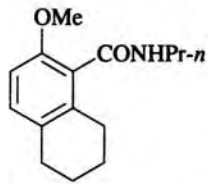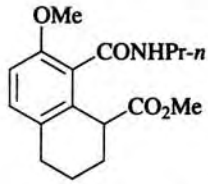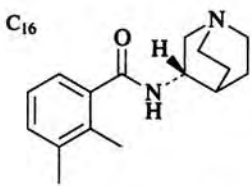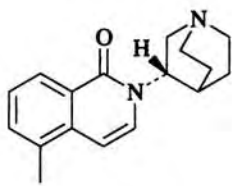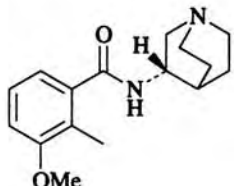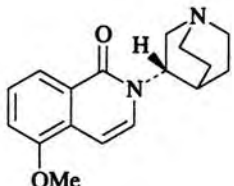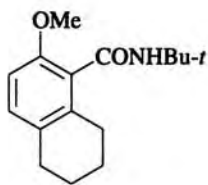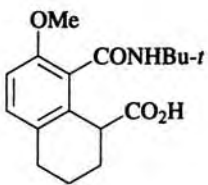
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	n-BuLi, THF, -50 to -10°, 30 min	1. CO$_2$ 2. CH$_2$N$_2$	(80)	265
C$_{16}$	*n*-BuLi, THF, -22°, 30 min	1. DMF 2. HCl	(85)	44
	n-BuLi, THF, -22°, 30 min	1. DMF 2. HCl	(93)	44
	n-BuLi, THF, -50 to -10°, 30 min	CO$_2$	(90)	265

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
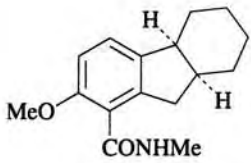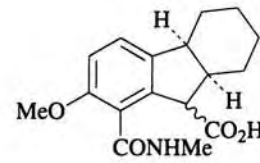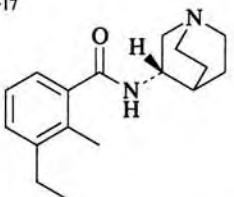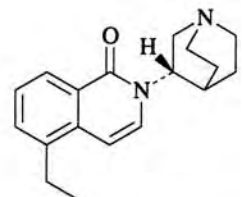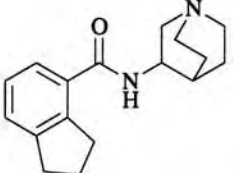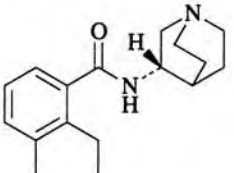
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
(MeO-substituted indane-fused hexahydro structure; CONHMe)	BuLi, THF, 0°, 1 h	CO_2	α-CO_2H (37) β-CO_2H (48)	288
C$_{17}$ (benzamide with quinuclidine, methyl, ethyl substituents)	BuLi, THF, -22°, 30 min	1. DMF 2. HCl	(81)	44
(acenaphthene-fused benzamide with quinuclidine)	BuLi, THF, -22°, 30 min	1. DMF 2. HCl	(*S*)-isomer (81) (*R*)-isomer (77)	44
(benzamide with quinuclidine, ethyl, methyl substituents)	BuLi, THF, -22°, 30 min	1. DMF 2. HCl	(—)	44

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
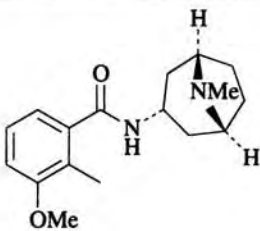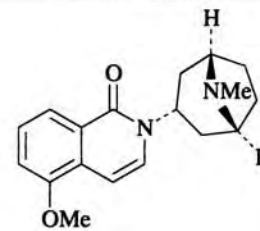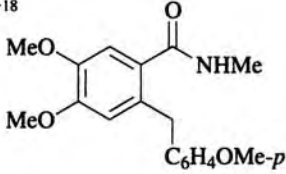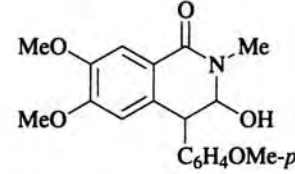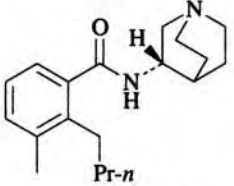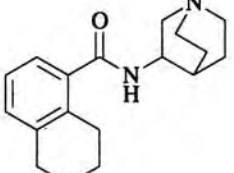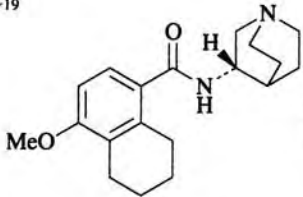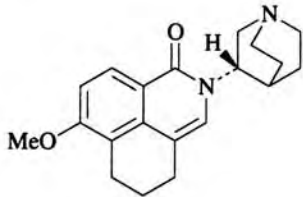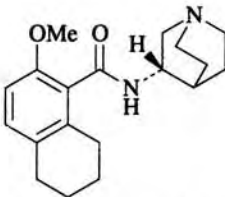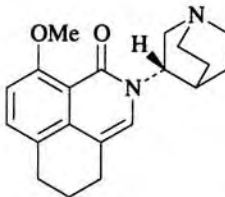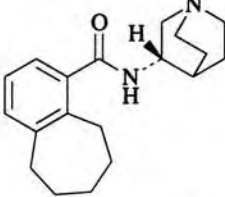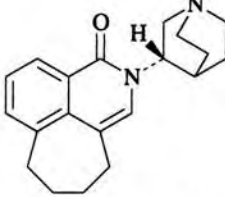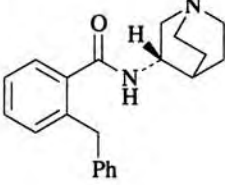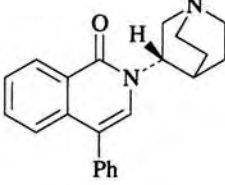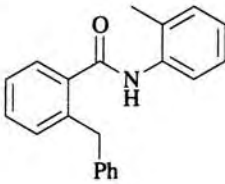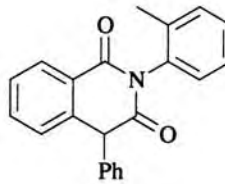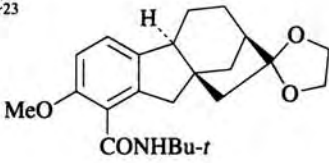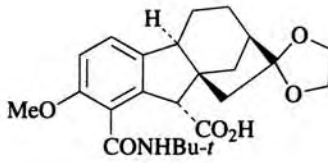
| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
(benzamide with NMe tropane, methyl, OMe substituents)	*n*-BuLi, THF, -22°, 30 min	1. DMF 2. HCl	(52)	44
C$_{18}$ (MeO, MeO benzamide NHMe, C_6H_4OMe-*p*)	*n*-BuLi, THF, 0°	DMF	(75)	287
(benzamide with quinuclidine, methyl, Pr-*n* substituents)	*n*-BuLi, THF, -22°, 30 min	1. DMF 2. HCl	(25)	44
(tetrahydronaphthalene-fused benzamide with quinuclidine)	*n*-BuLi, THF, -22°, 30 min	1. DMF 2. HCl	(*S*)-isomer (77) (*R*)-isomer (68)	44

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C$_{19}$	n-BuLi, THF, -22°, 30 min	1. DMF 2. HCl	(85)	44
	n-BuLi, THF, -22°, 30 min	1. DMF 2. HCl	(15)	44
	n-BuLi, THF, -22°, 30 min	1. DMF 2. HCl	(30)	44
	n-BuLi, THF, -22°, 30 min	1. DMF 2. HCl	(20)	44

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

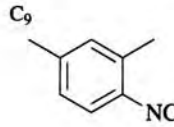| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	n-BuLi, THF, -25° to rt, 3 h	CO$_2$	(60)	92
C$_{23}$	n-BuLi, THF, -50 to -10°, 30 min	CO$_2$	(62)	265

F. Secondary Toluthioamides

| CSNHMe | n-BuLi, THF, 0°, 15 min | | CSNHMe (89) | 50 |

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
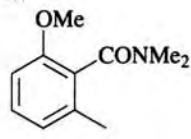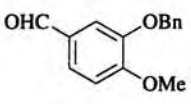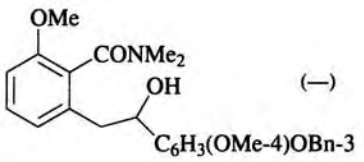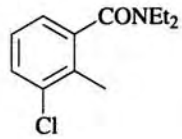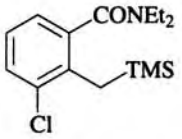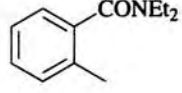
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
		G. Tertiary Toluamides		

C$_{11}$

| | LDA, THF, -78°, 40 min | | (—) | 51 |

C$_{12}$

| | s-BuLi:TM EDA, THF, -78°, 1 h | TMSCl | (83) | 166 |

	s-BuLi:TMEDA, THF, -100°	MeOD	R = D (—)	23
	s-BuLi:TMEDA, THF, -78°, 1 h	TMSCl	R = TMS (87)	166
	BuLi, THF, 0°, 45-60 min	Ph$_2$CO	R = COHPh$_2$ (50-60)	22
	LDA, THF, 0°, 30-60 min	n-BuBr	R = Bu-n (75)	22
	s-BuLi:TMEDA, THF, -78°, 1 h	1. O$_2$ 2. NaBH$_4$	R = OH (49)	164

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
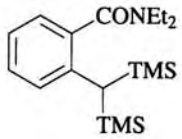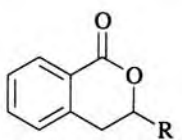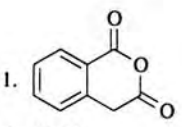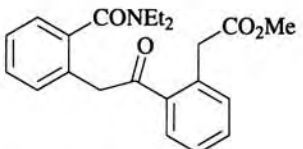
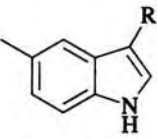| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.

	s-BuLi:TMEDA, THF, -78°, 1 h	1. TMSCl 2. s-BuLi:TMEDA 3. TMSCl	(91)	166
	LDA, THF, -78°, 1 h	1. RCHO 2. NaOH 3. HCl		
			R = C$_6$H$_4$OMe-p (65)	51
			R = C$_6$H$_4$OMe-m (40)	51
			R = C$_6$H$_4$OMe-o (45)	51
			R = Ph (30)	51
			R = C$_4$H$_3$O-2 (30)	51
			R = C$_4$H$_3$S-3 (30)	51
			R = C$_6$H$_3$(OMe-2)(OBn-3) (32)	51
	LDA, THF, -78°	1. 2. CH$_2$N$_2$	(86)	181

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
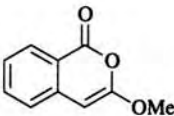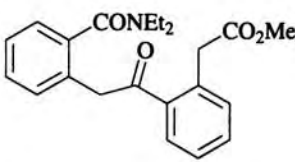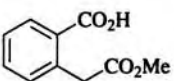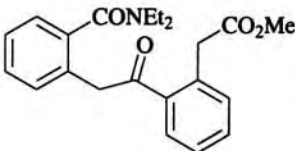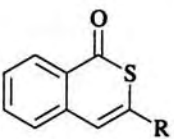
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, -78°		(56)	181
	LDA, THF, -78°		(90)	181
	LDA, THF, -78°	1. RCSOEt 2. HCl	 R = Me (51) R = Ph (71) R = C$_6$H$_4$Me-*p* (69) R = C$_6$H$_4$OMe-*p* (65) R = C$_6$H$_4$Cl-*p* (60) R = C$_6$H$_3$(OCH$_2$)-3,4 (64) R = C$_4$H$_3$S-2 (59) R = C$_6$H$_{11}$ (61)	 194 194 194 194 194 194 194 194

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
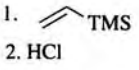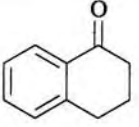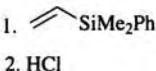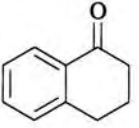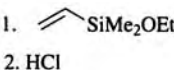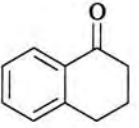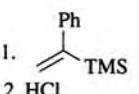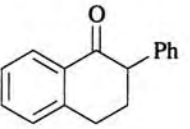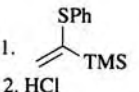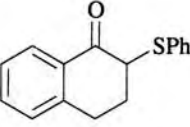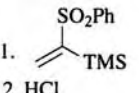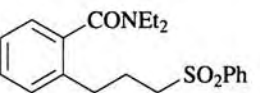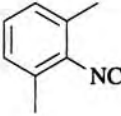
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, -78°, 1 h	1. ⟋TMS 2. HCl	(9)	152
	LDA, THF, -78°, 1 h	1. ⟋SiMe$_2$Ph 2. HCl	(19)	152
	LDA, THF, -78°, 1 h	1. ⟋SiMe$_2$OEt 2. HCl	(54)	152
	s-BuLi, THF, -78°, 1 h	1. Ph⟋TMS 2. HCl	Ph (70)	152
	s-BuLi, THF, -78°, 1 h	1. SPh⟋TMS 2. HCl	SPh (54)	152
	LDA, THF, -78°, 1 h	1. SO$_2$Ph⟋TMS 2. HCl	(75)	152

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TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, -78°		(75)	52
	LDA, THF, -70°			

$R^1 = C_6H_{11}$; $R^2 = Me$ (44)　52
$R^1 = C_5H_4N-4$; $R^2 = Me$ (30)　52
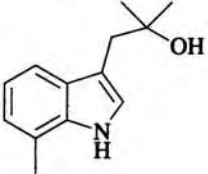$R^1 = C_6H_4Me-p$; $R^2 = Me$ (56)　52
$R^1 = C_6H_3(OCH_2O)-3,4$; $R^2 = Me$ (47)　52
$R^1 = C_6H_3(OCH_3)_2-3,4$; $R^2 = Me$ (37)　52
$R^1 = C_6H_4OMe-p$; $R^2 = Bu-n$ (42)　52
$R^1 = C_6H_4OMe-p$; $R^2 = C_6H_{11}$ (48)　52
$R^1 = C_6H_4OMe-p$; $R_2 = CH_2CH_2NMe_2$ (37)　52
$R^1 = Ph$; $R^2 = CH_2Ph$ (55)　52
$R^1 = C_6H_4Me-m$; $R^2 = C_6H_{11}$ (42)　52
$R^1 = C_6H_4OMe-p$; $R^2 = $ 1-benzyl-4-piperidinyl (24) 52

	LDA, THF, -78°		$X = CH_2$ (44)	52
			$X = CH_2CH_2$ (40)	157
			$X = CHBu-t$ ((40)	157

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

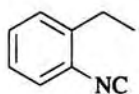| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, -78°		$R^1 = R^2 = Me$ (43)	52
			$R^1 + R^2 = CH_2$ (59)	52
	LDA, THF, -78°		(50)	216
	LDA, THF, -78°		(50)	216
	LDA, THF, -78°	1. 2. MeI	(45)	226

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
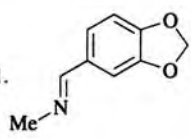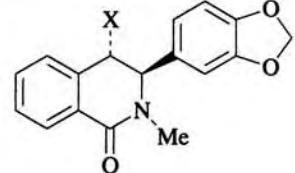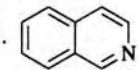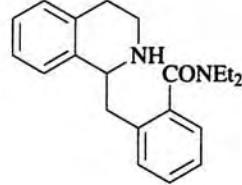
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, -78°	1. 2. electrophile		

electrophile	X	
TMSCl	TMS (32)	52
TMSCH₂Cl	CH₂TMS (58)	52
MeI	Me (62)	52
n-BuCl	Bu-n (59)	52
n-BuBr	Bu-n (53)	52
n-BuI	Bu-n (68)	52
CH₂=CHCH₂Br	CH₂CH=CH₂ (51)	52
PhCH₂Cl	CH₂Ph (59)	52
(MeO)₂CHCH₂Br	CH₂CH(OMe)₂ (54)	233

| | LDA, THF, -78° | 1.
 2. NaBH₄ | (84) | 217 |

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
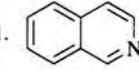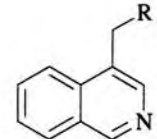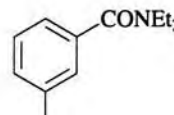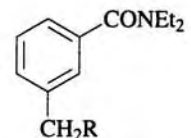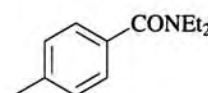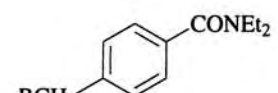
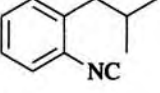| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, -78°	1. 2. RCH₂Cl	R = Ph (78)	217
			R = C₆H₄OMe-m (60)	217
			R = C₆H₄OMe-p (68)	217
			R = C₆H₄Me-o (65)	217
			R = C₆H₄(Bu-t)-p (73)	217
	LDA, THF, 0°, 30-60 min			
	Ph₂CO		R = COHPh₂ (42)	22
	n-BuBr		R = Bu-n (75)	22
	LDA, THF, 0°, 30-60 min			
	Ph₂CO		R = Ph₂COH (35-40)	22
	n-BuBr		R = n-Bu (80)	22

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TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
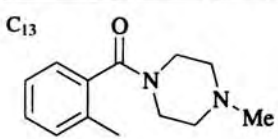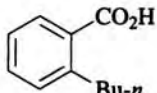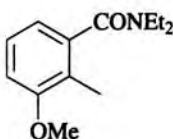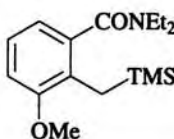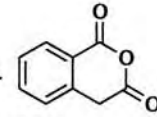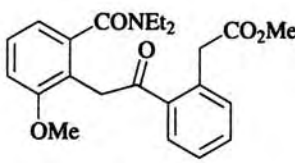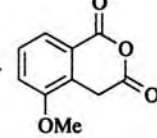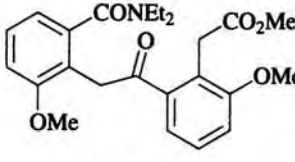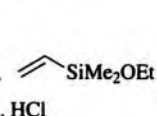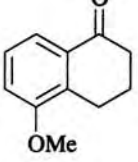
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C$_{13}$ *(2-methylphenyl 4-methylpiperazin-1-yl ketone)*	LDA, THF, -78°, 1 h	1. *n*-PrI 2. MeI 3. NaOEt 4. HCl	*(2-n-butylbenzoic acid)* (72)	53
(N,N-diethyl 3-methoxy-2-methylbenzamide)	*s*-BuLi:TMEDA, THF, -78°, 1 h	TMSCl	*(product with CONEt$_2$, CH$_2$TMS, OMe)* (68)	166
	LDA, THF, -78°	1. *(isochroman-1,3-dione)* 2. CH$_2$N$_2$	*(product 93)* (93)	181
	LDA, THF, -78°	1. *(5-methoxyisochroman-1,3-dione)* 2. CH$_2$N$_2$	*(product 61)* (61)	181
	LDA, THF, -78°, 1 h	1. $\diagup$SiMe$_2$OEt 2. HCl	*(5-methoxy-1-tetralone)* (62)	152

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

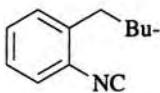| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, -78°, 1 h	1. *(1-phenyl-1-(TMS)ethylene)* 2. HCl	*(5-methoxy-2-phenyl-1-tetralone)* (43)	152
	LDA, THF, -78°, 1 h	1. *(1-SPh-1-TMS ethylene)* 2. HCl	*(5-methoxy-2-phenylthio-1-tetralone)* (35)	152
(N,N-diethyl 4-methoxy-2-methylbenzamide)	LDA, THF, -78°, 1 h	1. $\diagup$SiMe$_2$OEt 2. HCl	*(6-methoxy-1-tetralone)* (54)	152
	LDA, THF, -78°, 1 h	1. *(1-phenyl-1-TMS ethylene)* 2. HCl	*(6-methoxy-2-phenyl-1-tetralone)* (25)	152
	s-BuLi:TMEDA, THF, -78°, 1 h	1. TMSCl 2. *s*-BuLi:TMEDA 3. TMSCl	*(product with CONEt$_2$, CH(TMS)$_2$, OMe)* (75)	172

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

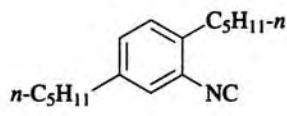| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
OMe / CONEt$_2$ / CH$_3$ (2-methyl-6-methoxy)	s-BuLi:TMEDA, THF, -78°, 1 h	TMSCl	OMe / CONEt$_2$ / CH$_2$TMS (80)	166
	LDA, THF, -78°, 1h	1. CH$_2$=CHSiMe$_2$OEt 2. HCl	(tetralone, OMe) (8)	152
	s-BuLi, THF, -78°, 20 min	MeO$_2$CC$_6$H$_4$OMe-*p*	OMe / CONEt$_2$ / CH$_2$COC$_6$H$_4$OMe-*p* (49)	51
(methylenedioxy) CONEt$_2$ / CH$_3$	LDA, THF, -70 to -45°, 10 min	(vinyl methylenedioxy benzaldehyde N-Me imine)	(isoquinolinone product) (50)	226
CONEt$_2$ / CH$_2$CH$_3$	s-BuLi:TMEDA, THF, -78°, 90 min	MeOD	CONEt$_2$ / CH(D)CH$_3$ (52)	168

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
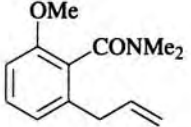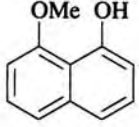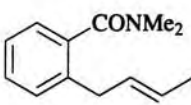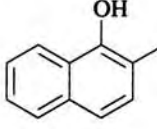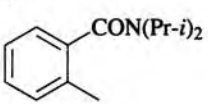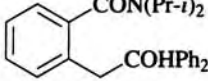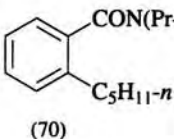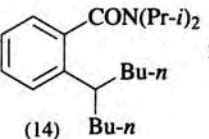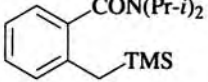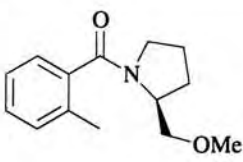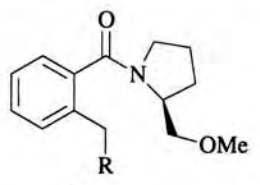
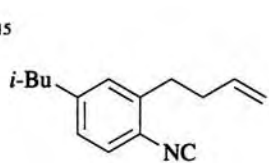| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
OMe / CONMe$_2$ / CH$_2$CH=CH$_2$	MeLi, THF, -78° to rt, 8 h	—	OMe OH (naphthol) (81)	178
CONMe$_2$ / CH$_2$CH=CHCH$_3$	MeLi, THF, -78° to rt, 8 h	—	OH (2-methylnaphthol) (50)	178
C$_{14}$ CON(Pr-*i*)$_2$ / CH$_3$	LDA, THF, 0°, 30-60 min	Ph$_2$CO	CON(Pr-*i*)$_2$ / CH$_2$COHPh$_2$ (80-90)	22
	LDA, THF, 0°, 30-60 min	*n*-BuBr	CON(Pr-*i*)$_2$ / C$_5$H$_{11}$-*n* (70) + CON(Pr-*i*)$_2$ / CH(Bu-*n*)$_2$ (14)	22
	s-BuLi:TMEDA, THF, -78°, 5 min	TMSCl	CON(Pr-*i*)$_2$ / CH$_2$TMS (88)	289

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

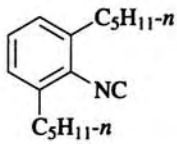| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
(structure: 2-methylbenzoyl pyrrolidine with CH2OMe)	s-BuLi, THF, -78°, 45 min		(structure: benzoyl pyrrolidine with CH2R and CH2OMe)	
			R	
		MeI	Me (77)	32
		EtI	Et (65)	32
		CH2=CHCH2Br	CH2CH=CH2 (53)	32
		CH2=CHCH2CH2Br	CH2CH2CH=CH2 (59)	32
		PhCH2Br	CH2Ph (71)	32
		PhCH2CH2Br	CH2CH2Ph (58)	32
		TMSCH2CH2OCH2Br	CH2OCH2CH2TMS (68)	32
(structure: CONEt2, Me, OMe, MeO benzene)	LDA, THF, -78°, 1 h	1. ⟋SiMe2OEt 2. HCl	(tetralone structure, MeO, OMe) (48)	152
(structure: MeO, CONEt2, Me, OMe benzene)	LDA, THF, -78°, 1 h	1. ⟋SiMe2OEt 2. HCl	(tetralone structure, MeO, OMe) (45)	152
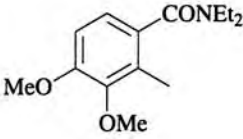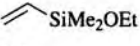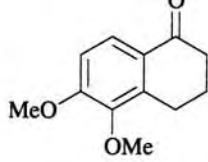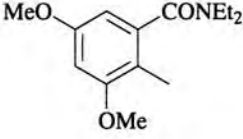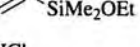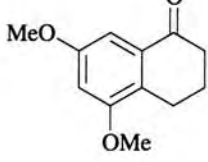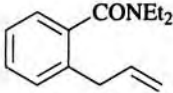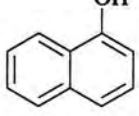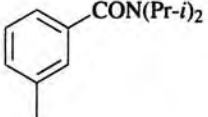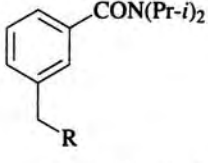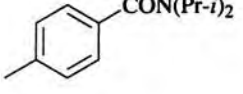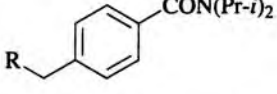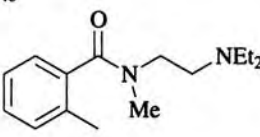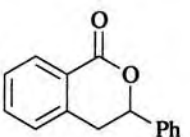
TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

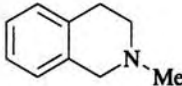| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
(structure: 2-allyl-CONEt2 benzene)	MeLi, THF, -78° to rt, 8 h	—	(1-naphthol, OH) (86)	178
(structure: m-tolyl CON(Pr-i)2)	LDA, THF, 0°, 30-60 min		(structure: CON(Pr-i)2 with CH2R)	
		Ph2CO	R = COHPh2 (3-10)	22
		n-BuBr	R = Bu-n (77)	22
(structure: p-tolyl CON(Pr-i)2)	LDA, THF, 0°, 30-60 min		(structure: RCH2-C6H4-CON(Pr-i)2)	
		Ph2CO	R = Ph2COH (80-100)	22
		n-BuBr	R = n-Bu (93)	22
		D2O	R = D (93)	23

C15

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
(structure: 2-methylbenzamide, N-Me, N-CH2CH2NEt2)	LDA, THF, -78°, 1 h	1. PhCHO 2. HCl	(isochromanone with Ph) (62)	53

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
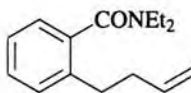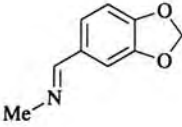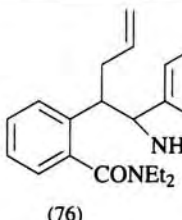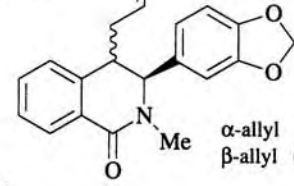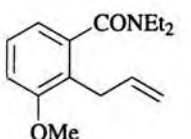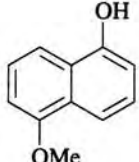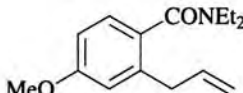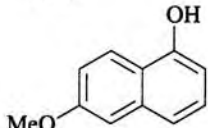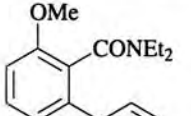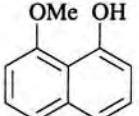
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
[structure: 2-(3-butenyl)benzamide, CONEt₂]	LDA, THF, -78°, 5 min	[structure: piperonal N-methylimine, Me–N]	[structure: product with NHMe, CONEt₂, allyl, benzodioxole] (76); [structure: isoquinolinone with allyl, benzodioxole, N-Me] α-allyl (9), β-allyl (2)	52
[structure: 3-OMe-2-allyl benzamide CONEt₂]	MeLi, THF, -78° to rt, 8 h	—	[structure: 5-OMe-1-naphthol, OH / OMe] (90)	178
[structure: 4-MeO-2-allyl benzamide CONEt₂]	MeLi, THF, -78° to rt, 8 h	—	[structure: 6-MeO-1-naphthol, OH] (64)	178
[structure: 2-OMe-6-allyl benzamide CONEt₂]	MeLi, THF, -78° to rt, 8 h	—	[structure: 8-OMe-1-naphthol, OMe OH] (35)	178

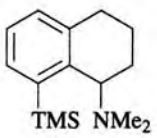TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

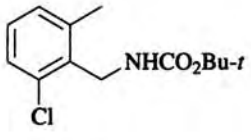| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C₁₆ [structure: TMS, CONEt₂, methylenedioxy, methyl benzamide]	s-BuLi, THF, -78°	C₆H₁₁CHO	[structure: TMS, CONEt₂, OH, CH₂CH(OH)C₆H₁₁ product] (—)	30
[structure: N-ethyl-N-(2-diethylaminoethyl)-2-methylbenzamide, O, NEt₂, Et]	LDA, THF, -78°, 1 h	n-PrI	[structure: product with O, NEt₂, Et, Bu-n] (92)	53
[structure: 2,6-diOMe-3-allyl benzamide CONEt₂, OMe/OMe]	MeLi, THF, -78° to rt, 8 h	—	[structure: OMe OH / OMe naphthol] (77)	178
[structure: 2,4-diOMe-6-allyl benzamide CONEt₂, OMe/MeO]	MeLi, THF, -78° to rt, 8 h	—	[structure: OMe OH / MeO naphthol] (62)	178
C₁₇ [structure: OMOM, CONEt₂, methyl, fused cyclopentane indane]	LTMP, THF, -78°, 15 min	(EtO)₂CHCN	[structure: MOMO, O, N–H isoquinolinone, CH(OEt)₂] (52)	230

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
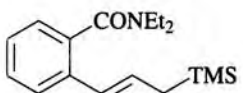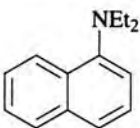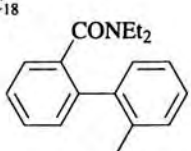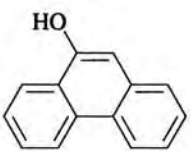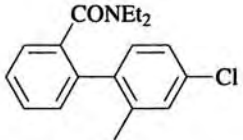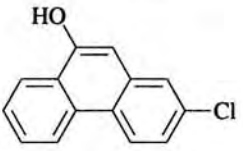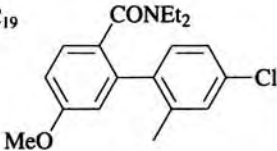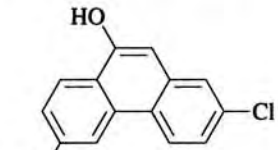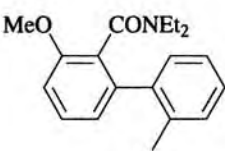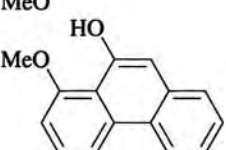
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	MeLi; THF, -78° to rt, 8 h	—	(35)	178
C18	LDA, THF, 0° to rt, 3 h	—	(92)	55
	LDA, THF, 0° to rt, 3 h	—	(96)	55
C19	LDA, THF, 0° to rt, 3 h	—	(93)	55
	LDA, THF, 0° to rt, 3 h	—	(92)	55

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
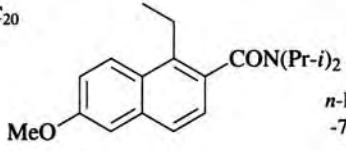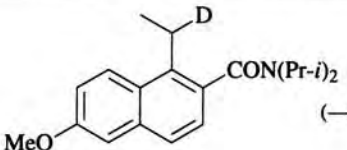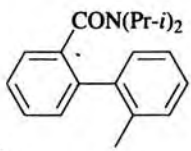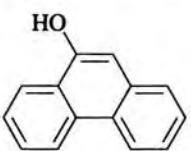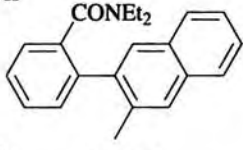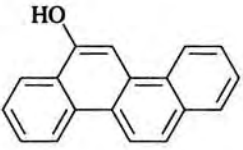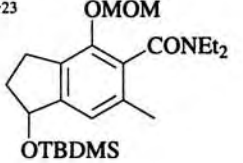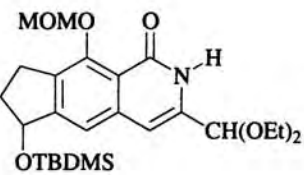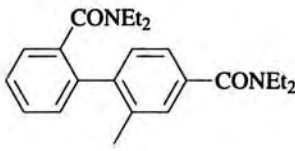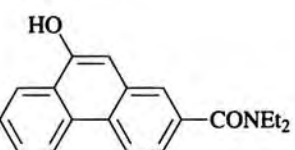
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C20	*n*-BuLi, THF, -78°, 20 min	D2O	(—)	290
	LDA, THF, 0° to rt, 3 h	—	(98)	55
C22	LDA, THF, 0° to rt, 3 h	—	(90)	55
C23	LTMP, THF, -78°, 15 min	(EtO)2CHCN	(—)	230
	LDA, THF, 0° to rt, 3 h	—	(78)	55

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
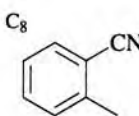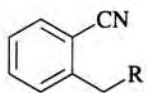
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.

H. Tolunitriles

C8 (structure: o-tolunitrile)

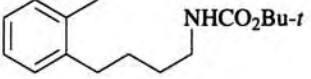|	KNH₂, NH₃, 10 min		(product structure: o-CN-benzyl-R)	

R

		i-PrI	Pr-*i* (69)	57
		n-C₅H₁₁I	C₅H₁₁-*n* (66)	57
		PhCH₂Cl	CH₂Ph (81)	57
		p-MeC₆H₄CH₂Cl	CH₂C₆H₄Me-*p* (21)	57
		PhCO₂Me	COPh (66)	57
		p-MeOC₆H₄CO₂Me	COC₆H₄OMe-*p* (46)	57
		EtCO₂Me	COEt (42)	57
		i-PrCO₂Me	COPr-*i* (51)	57
	NaNH₂, NH₃, 15 min			
		PhCH₂Cl	CH₂Ph (77)	58
		p-ClC₆H₄CH₂Cl	CH₂C₆H₄Cl-*p* (64)	58
		PhCO₂Me	COPh (40)	176
		t-BuCO₂Me	COBu-*t* (37)	210
		EtOCO₂Me	CO₂Et (25)	210
		p-MeC₆H₄CO₂Me	COC₆H₄Me-*p* (45)	210
		p-Me₂NC₆H₄CO₂Me	COC₆H₄NMe₂-*p* (48)	210
		3,4-(MeO)₂C₆H₃CO₂Me	COC₆H₃(OMe)₂-3,4 (54)	210
		3,4-(OCH₂O)C₆H₃CO₂Me	COC₆H₃(OCH₂O)-3,4 (54)	210
		Br(Me)₂CC(Me)₂Br	CH₂C₆H₄CN-*o* (52)	58
		BrCH₂CH₂Br	(CH₂)₄C₆H₄CN-*o* (67)	58

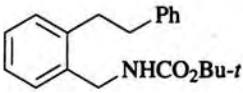TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
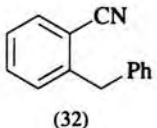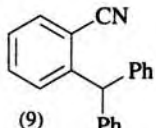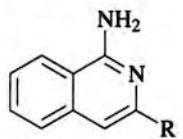
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	NaH, DME			
		PhCO₂Me	COPh (54)	210
		p-MeOC₆H₄CO₂Me	COC₆H₄OMe-*p* (41)	210
		p-ClC₆H₄CO₂Me	COC₆H₄Cl-*p* (63)	210
	KNH₂, NH₃	PhCl	(product structures: o-CN-benzyl-Ph (32) + o-CN-CHPh₂ (9))	56
	KNH₂, NH₃		(product structure: 1-amino-3-R-isoquinoline)	

R

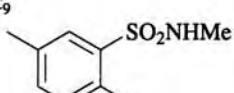| | | — | C₆H₄Me-*o* (65) | 59 |
		PhCN	Ph (65)	291
		2-NCC₅H₄N	C₅H₄N-2 (25)	291
		3-NCC₅H₄N	C₅H₄N-3 (2)	291
	LDMA, THF, HMPA, -78°, 15 min	—	C₆H₄Me-*o* (80)	60
		PhCN	Ph (70)	60
		2-NCC₅H₄N	C₅H₄N-2 (28)	60
		3-NCC₅H₄N	C₅H₄N-3 (50)	60
		1-NCC₁₀H₇	C₁₀H₇-1 (48)	60

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
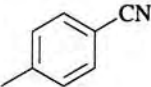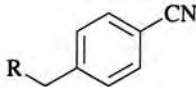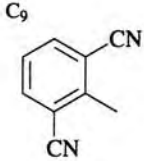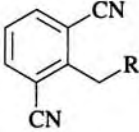
| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	NaNH₂, NH₃, 30 min			
			R	
		PhCH₂Cl	CH₂Ph (71)	58
		Br(CH₂)₂Br	(CH₂)₂C₆H₄CN-*p* (63)	58
		n-BuBr	*n*-Bu (63)	58
		p-ClC₆H₄CH₂Cl	CH₂C₆H₄Cl-*p* (86)	58
		Ph₂CO	COHPh₂ (54)	176
		Br(Me)₂CC(Me)₂Br	CH₂C₆H₄CN-*p* (55)	58
C₉	LiNH₂, NH₃	PhCH=CHCOPh	CHPhCH₂COPh	292
	LDA, THF, -78°, 2 h			
			R	
		MeI	Me (84)	62
		CH₂=CHCH₂Br	CH₂CH=CH₂ (53)	62
		MeOCH₂Cl	CH₂OMe (48)	62
a	LDA, THF, -78°, 1 h			
		D₂O	D (—)	62
		MeI	Me (81)	62

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
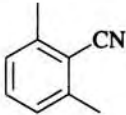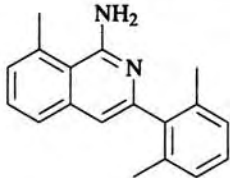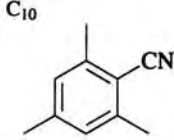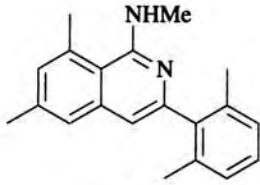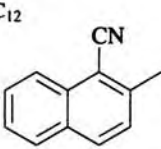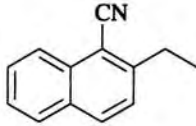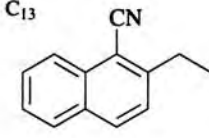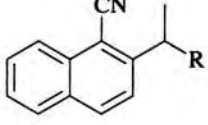
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, benzene, ether, reflux, 4 h	—	(80)	293
C₁₀	*t*-BuLi, THF, -78 to 20°, 1 h	MeI	(15)	294
C₁₂	LTMP, THF, -78°, 35 min	MeI	(85)	61
C₁₃	LTMP, THF, -78°, 35 min			
		MeI	R = Me (85)	61
		TMSCl	R = TMS (90)	61

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TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
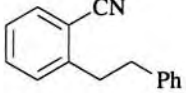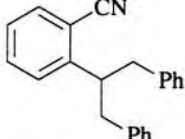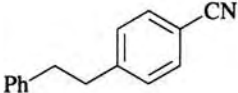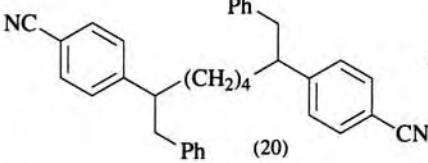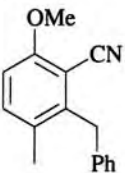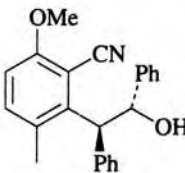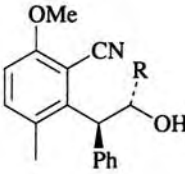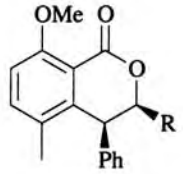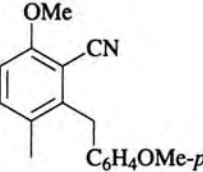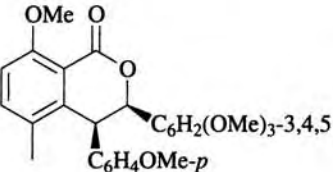
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C₁₄	NaNH₂, NH₃, 15 min	PhCH₂Cl	(44)	58
	NaNH₂, NH₃, 15 min	Br(CH₂)₄Br	(20)	58
C₁₆	LDA, THF, -78 to 0°	PhCHO, 0°, 15 min	(—)	295
	LDA, THF, -78 to 0°	RCHO, 0° to rt, 24 h		

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

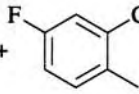| R	I	II	
Ph	(—)	(70)	295
C₆H₄OMe-*o*	(55)	(—)	295
C₆H₄F-*m*	(30)	(35)	295
C₆H₃(OMe)₂-3,4	(—)	(70)	295
C₆H₂(OMe)₃-3,4,5	(—)	(79)	295

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C₁₇	LDA, THF, -78 to 0°	3,4,5-(OMe)₃C₆H₂CHO	(54)	295

I. Tolyl Oxazolines

| C₁₁ | *n*-BuLi, ether, 0° | TMSCl | (—) | 184 |

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
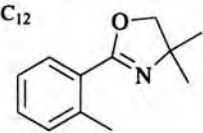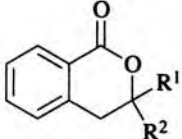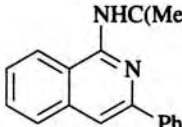
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C₁₂ (2-methylphenyl oxazoline)	*n*-BuLi, ether, 0°, 20 min		(benzyl oxazoline, CH₂R)	
		(MeS)₂	R = SMe (85)	64
		CH₂=CHCH₂Br	R = CH₂CH=CH₂ (78)	64
	n-BuLi, ether	TMSCl	R = TMS (—)	184
	n-BuLi, ether, 0°, 1 h	1. R¹COR² 2. HCl	(isochromanone with R¹, R²)	

R¹	R²	
H	Ph (72)	195
H	C₆H₄Me-*p* (80)	195
H	C₆H₄OMe-*p* (65)	195
H	C₆H₄F-*o* (78)	195
H	C₁₀H₇-1 (87)	195
H	C₁₀H₇-2 (68)	195
Me	C₁₀H₇-1 (56)	195

	n-BuLi, THF	1.PhCN 2. H⁺	(isoquinoline, NHC(Me)₂CH₂OH, 3-Ph) (—)	158

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)
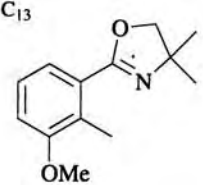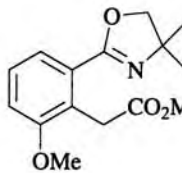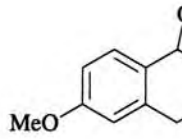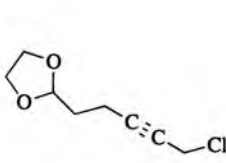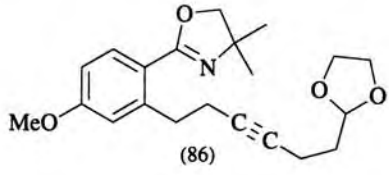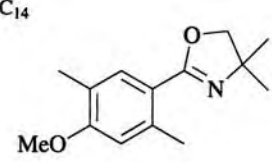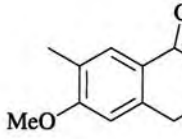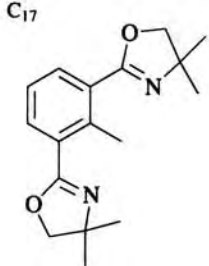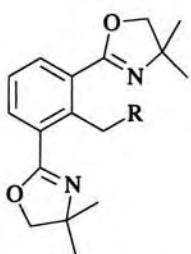
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C₁₃ (2-methyl-3-methoxyphenyl oxazoline, OMe)	*n*-BuLi, THF, 0°, 1 h	(MeO)₂CO	(CH₂CO₂Me product, OMe) (48)	192
(4-methoxy-2-methylphenyl oxazoline, MeO)	*n*-BuLi, ether, 0°	TMSCl	(CH₂TMS product, MeO) (92)	187
	n-BuLi, HMPA, −78°, 3 h	(dioxolane propargyl chloride)	(alkylation product, MeO) (86)	147
C₁₄ (methoxy dimethylphenyl oxazoline, MeO)	*n*-BuLi, THF, 0°, 1.5 h	(MeO)₂CO	(CH₂CO₂Me product, MeO) (45)	193

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C$_{17}$	*n*-BuLi, benzene, rt, 30 min			
		n-PrBr	R = Pr-*n* (84)	296
		HC≡CCH$_2$Br	R = CH$_2$C≡CH (26)	296

J. Tolyl Tetrazoles
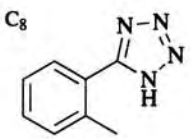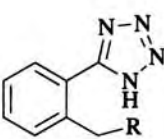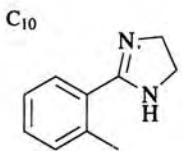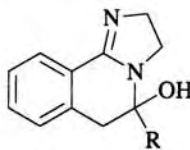
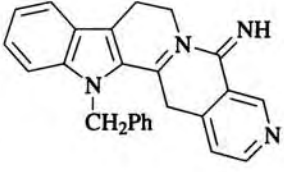| C$_8$ | *s*-BuLi:TMEDA, THF, -30°, 45 min | | | |
			R	
		MeI	Me (71)	66
		n-C$_5$H$_{11}$I	C$_5$H$_{11}$-*n* (92)	66
		PhCH$_2$Br	CH$_2$Ph (73)	66

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

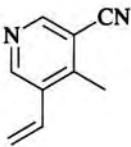| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
		K. Tolyl Imidazolines		
C$_{10}$	*n*-BuLi, THF, 35°, 4 h			
			R	
		PhCO$_2$Me	Ph (28)	297
		o-FC$_6$H$_4$CO$_2$Me	C$_6$H$_4$F-*o* (46)	297
		m-FC$_6$H$_4$CO$_2$Me	C$_6$H$_4$F-*m* (23)	297
		p-FC$_6$H$_4$CO$_2$Me	C$_6$H$_4$F-*p* (58)	297
		o-ClC$_6$H$_4$CO$_2$Me	C$_6$H$_4$Cl-*o* (56)	297
		m-ClC$_6$H$_4$CO$_2$Me	C$_6$H$_4$Cl-*m* (59)	297
		p-ClC$_6$H$_4$CO$_2$Me	C$_6$H$_4$Cl-*p* (60)	65
		2,4-Cl$_2$C$_6$H$_3$CO$_2$Me	C$_6$H$_3$Cl$_2$-2,4 (75)	65
		3,4-Cl$_2$C$_6$H$_3$CO$_2$Et	C$_6$H$_3$Cl$_2$-3,4 (47)	297
		p-MeC$_6$H$_4$CO$_2$Me	C$_6$H$_4$Me-*p* (57)	297
		m-CF$_3$C$_6$H$_4$CO$_2$Me	C$_6$H$_4$CF$_3$-*m* (27)	297
		p-MeOC$_6$H$_4$CO$_2$Me	C$_6$H$_4$OMe-*p* (35)	297
		3,4-OCH$_2$OC$_6$H$_3$CO$_2$Me	C$_6$H$_3$OCH$_2$O-3,4 (36)	297
		PhCH$_2$CO$_2$Me	CH$_2$Ph (21)	65
		PhCHOHCO$_2$Me	CHOHPh (61)	65
		3-C$_5$H$_4$NCO$_2$Me	C$_5$H$_4$N-3 (41)	297
		4-C$_5$H$_4$NCO$_2$Me	C$_5$H$_4$N-4 (37)	297
		2-C$_4$H$_3$SCO$_2$Me	C$_4$H$_3$S-2 (40)	297

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	n-BuLi, THF, 35°, 4 h		(33)	65
	n-BuLi, THF, 35°, 4 h	*p*-ClC₆H₄CO₂Me, 50°	(13)	297
	n-BuLi, THF, 35°, 4 h			
		Ph₂CO	R = COHPh₂ (66)	65
		PhSO₂F	R = SO₂Ph (28)	65

TABLE I. TOLUIC ACID AND DERIVATIVES (*Continued*)

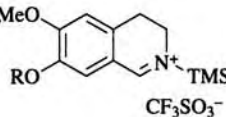| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C₁₁	*s*-BuLi:TMEDA, THF, 0°, 3 h	1. 3,4,5-(MeO)₃C₆H₂-CH₂CH₂C₆H₄CO₂Me-4 2. TsOH, C₆H₆, reflux	(32)	285
	s-BuLi:TMEDA, THF, 0°, 3 h	1. 3,4,5-(MeO)₃C₆H₂-CH₂CH₂C₆H₄CO₂Me-4 2. TsOH, C₆H₆, reflux	(32)	285
C₁₂	*s*-BuLi:TMEDA, THF, 0°, 3 h	1. 3,4,5-(MeO)₃C₆H₂-CH₂CH₂C₆H₄CO₂Me-4 2. TsOH, C₆H₆, reflux	(38)	285
C₁₃	*s*-BuLi:TMEDA, THF, 0°, 3 h	1. 3,4,5-(MeO)₃C₆H₂-CH₂CH₂C₆H₄CO₂Me-4 2. TsOH, C₆H₆, reflux	(29)	285

[a]2,6-Dicyanotoluene is produced in situ from the bis-(*N,N*-dimethylhydrazone) of 2-methylisophthalaldehyde.

TABLE II. TOLYL KETONES

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C₉	n-BuLi:TMEDA, hexane, rt, 24 h	TMSCl	(—)	68
C₁₁	n-BuLi:TMEDA, hexane, rt, 24 h	TMSCl	I:II = 77:23 (—)	68
C₁₂	LDA, THF, -78°, 5 min			

			R¹	R²	
		MeCHO	Me	H (91)	67
		p-MeC₆H₄CHO	C₆H₄Me-p	H (74)	67
		PhCH=CHCHO	CH=CHPh	H (69)	67
		Me₂CO	Me	Me (94)	67
		(CH₂)₅CO	(CH₂)₅	(64)	67
		Ph₂CO	Ph	Ph (42)	67

TABLE II. TOLYL KETONES (Continued)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C₁₃	LTMP, THF, -78°, 5 min	Me₂CO	(42)	67
C₁₄	LDA, THF, -78° to rt	—	(25)	298
C₁₆	LDA, THF, -78° to rt	—	(68)	298
C₁₈	LDA, THF, -78° to rt	—	(87)	298

TABLE III. TOLUALDEHYDE DERIVATIVES
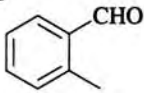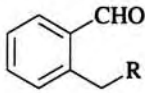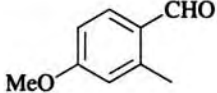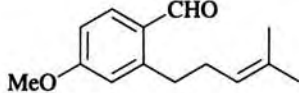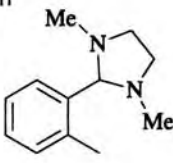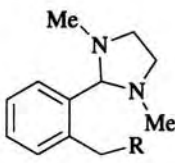
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
		A. Tolualdehyde Amido Adducts		

C$_8$

	1. LTMDA, THF 2. *n*-BuLi, -20°, 1.5 h			
		1. *n*-PrI 2. HCl	R = Pr-*n* (85)	69
		1. Me$_2$C=CHCH$_2$Br 2. HCl	R = CH$_2$CH=CMe$_2$ (74)	299

C$_9$

| | 1. LTMDA, THF
2. *n*-BuLi, -20°, 1.5 h | 1. Me$_2$C=CHCH$_2$Br
2. HCl | (54) | 299 |

B. Tolualdehyde Imidazolidines

C$_{11}$

	n-BuLi, ether, TMEDA, 25°, 1.5 h			
		n-PrBr	R = Pr-*n* (90)	71
		PhCH$_2$Br	R = CH$_2$Ph (72)	71

TABLE III. TOLUALDEHYDE DERIVATIVES (*Continued*)
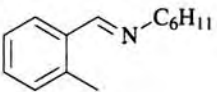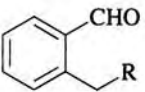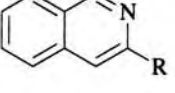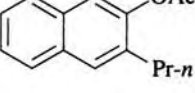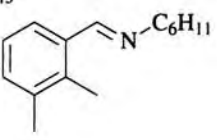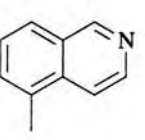
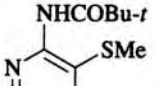| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
		C. Tolualdehyde Imines		

C$_{14}$

	LTMP, THF, -15°, 1 h			
			R	
		MeI	Me (81)	70
		n-C$_5$H$_{11}$I	C$_5$H$_{11}$-*n* (88)	70
		CH$_2$=CHCH$_2$Br	CH$_2$CH=CH$_2$ (69)	70
	LTMP, THF, -15°, 1 h	1. RCON(OMe)Me 2. NH$_4$OH		
			R = Bu-*n* (82)	208
			R = Bu-*i* (84)	208
	LTMP, THF, -20°, 1 h	1. *n*-BuCON(OMe)Me 2. KOH, MeOH 3. Ac$_2$O	(26)	180

C$_{15}$

| | LTMP, THF,
-15°, 1 h | 1. DMF
2. NH$_4$OH | (57) | 208 |

TABLE III. TOLUALDEHYDE DERIVATIVES (*Continued*)
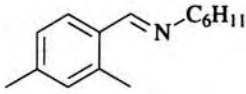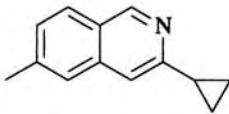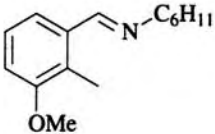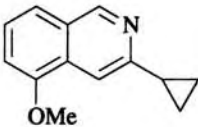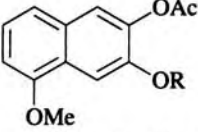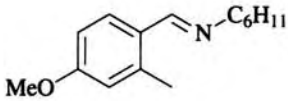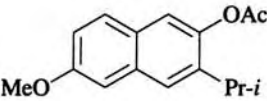
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LTMP, THF, -15°, 1 h	1. *c*-PrCON(OMe)Me 2. NH₄OH	(72)	208
	LTMP, THF, -15°, 1 h	1. *c*-PrCON(OMe)Me 2. NH₄OH	(75)	208
	LTMP, THF, -20°, 1 h	1. ROCH₂CON(OMe)Me 2. KOH, MeOH 3. Ac₂O	 R = Me (48) R = Ph (34)	180 180
	LTMP, THF, -20°, 1 h	1. *i*-BuCON(OMe)Me 2. KOH, MeOH 3. Ac₂O	(33)	180

180

TABLE IV. 2-METHYLBENZYL ALCOHOLS
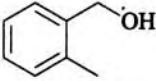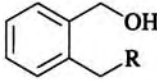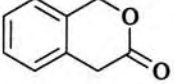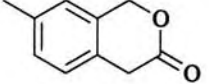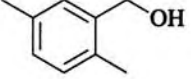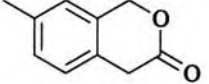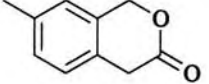
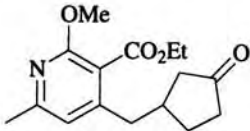| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C_8	n-BuLi, ether, rt, 24 h or reflux, 4 h			
			R	
		EtBr	Et (92)	72
		n-$C_{10}H_{21}Br$	$C_{10}H_{21}$-n (73)	72
		PhCHO	CHOHPh (62)	72
	n-BuLi, ether, -78° to rt, 24 h	TMSCl	TMS (79)	257
	n-BuLi	n-Bu_3SnCl	Sn(Bu-n)$_3$ (67)	167
	n-BuLi, THF, 0 to 45°, 4 h	$BrCH_2CH(OMe)_2$	$CH_2CH(OMe)_2$ (8)	300
	n-BuLi, THF, 0 to 45°, 4 h	$BrCH_2CH(OCH_2CH_2O)$	$CH_2CH(OCH_2CH_2O)$ (18)	300
	n-BuLi, ether, rt, 24 h or reflux, 4 h	CO_2	(56)	72
C_9	n-BuLi, ether, rt, 24 h or reflux, 4 h	CO_2	(53)	72

TABLE IV. 2-METHYLBENZYL ALCOHOLS (*Continued*)
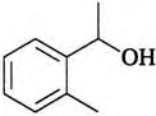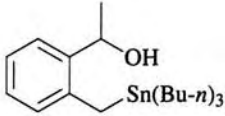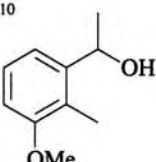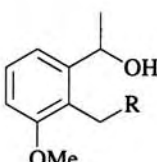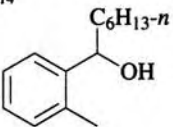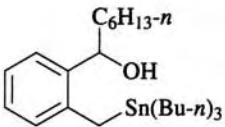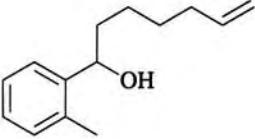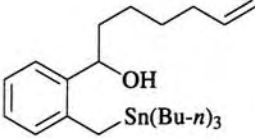
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	n-BuLi	(*n*-Bu)$_3$SnCl	(71)	167
C$_{10}$	*n*-BuLi, ether, rt, 24 h or reflux, 4 h			
		EtCHO	R = CHOHEt (45)	72
		Ph$_2$CO	R = COHPh$_2$ (59)	72
C$_{14}$	*n*-BuLi	(*n*-Bu)$_3$SnCl	(67)	167
	n-BuLi	(*n*-Bu)$_3$SnCl	(60)	167

TABLE V. CRESOL AND THIOCRESOL DERIVATIVES
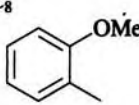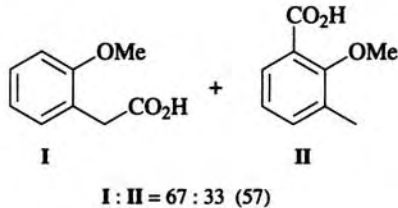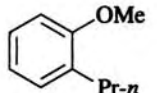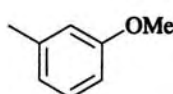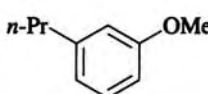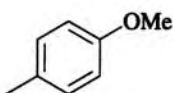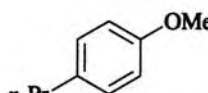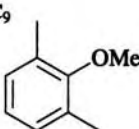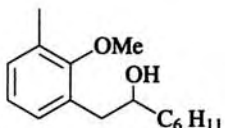
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
		A. Cresol Ethers		
C_8	n-BuLi, C_6H_{12}, reflux, 10 h	CO_2	$\mathbf{I} : \mathbf{II} = 67 : 33$ (57)	76
	n-BuLi, t-BuOK, heptane, rt, 2 h	$(EtO)_2SO_2$	(49)	77
	n-BuLi, t-BuOK, heptane, rt, 2 h	$(EtO)_2SO_2$	(80)	77
	n-BuLi, t-BuOK, heptane, rt, 2 h	$(EtO)_2SO_2$	(26)	77
C_9	n-BuLi, THF, 0°, 1 h, rt, 4 h	$C_6H_{11}CHO$	(48)	78

TABLE V. CRESOL AND THIOCRESOL DERIVATIVES (*Continued*)

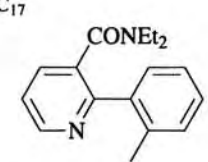| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	n-BuLi, t-BuOK, heptane, rt	(EtO)$_2$SO$_2$	(62)	77
	n-BuLi, t-BuOK, hexane, 0 to 25°, 5 h	Br(CH$_2$)$_n$Br		301

n	I	II		n	I	II
2		(2)		8	(20)	(14)
3		(2)		9	(14)	
4		(3)		10	(7)	
5		(3)		11	(4)	
6	(5)	(3)		12	(—)	
7	(11)	(2)		13	(—)	

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
OMe	n-C$_5$H$_{11}$Na, pet. ether, 45°, 6 h	CO$_2$	(—)	302

TABLE V. CRESOL AND THIOCRESOL DERIVATIVES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C$_{10}$	n-BuLi, t-BuOK, heptane, rt, 20 h	(EtO)$_2$SO$_2$	(50)	77
	n-BuLi, t-BuOK, heptane, rt, 20 h	(EtO)$_2$SO$_2$	(58)	77
C$_{11}$	n-BuLi, ether, 27°, 20 h	MeCHO	(79)	303
C$_8$ SMe				

B. Thiocresol Ethers

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	n-BuLi, ether, reflux, 4 h	CO$_2$	**I : II : III** = 29 : 68 : 3	82
	n-BuLi:TMEDA, ether, reflux, 4 h	CO$_2$	**I : II : III** = 3 : 97 : —	82

TABLE V. CRESOL AND THIOCRESOL DERIVATIVES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	n-BuLi:TMEDA (2 eq), hexane, rt, 12 h			
			R	
		MeI	Me (71)	83
		CH$_2$=CHCH$_2$Br	CH$_2$CH=CH$_2$ (68)	83
		TMSCl	TMS (71)	83
		PhCOCl	COPh (63)	83
	n-BuLi:TMEDA (2 eq), hexane, rt, 12 h	MeI (1 eq)	I:II = 50:50 (—)	83
	n-BuLi:TMEDA (2 eq), hexane, rt, 12 h	CO$_2$	(18) (51)	83
	n-BuLi:TMEDA (2 eq), hexane, rt, 12 h	PhCOCl (-80°)	(58)	83
	n-BuLi:TMEDA (2 eq), hexane, rt, 12 h	SCl$_2$	(64)	83

TABLE V. CRESOL AND THIOCRESOL DERIVATIVES (*Continued*)

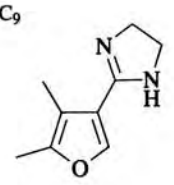| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	n-BuLi:TMEDA (2 eq), hexane, rt, 12 h			
		Me$_2$SiCl$_2$	R^1 = R^2 = Me (75)	83
		MePhSiCl$_2$	R^1 = Me, R^2 = Ph (70)	83
		Ph$_2$SiCl$_2$	R^1 = R^2 = Ph (78)	83
	n-BuLi:TMEDA (2 eq), hexane, rt, 12 h			
		Me$_2$SnCl$_2$	R^1 = R^2 = Me (61)	83
		Ph$_2$SiCl$_2$	R^1 = R^2 = Ph (56)	83
	n-BuLi:TMEDA (2 eq), hexane, rt, 12 h	SiCl$_4$	(62)	83
C$_9$			I:II =70:30 (—)	
	n-BuLi, ether, reflux, 4 h	CO$_2$	I:II =70:30 (—)	82
	n-BuLi:TMEDA, ether, reflux, 4 h	CO$_2$	I:II = 4:96 (—)	82

TABLE V. CRESOL AND THIOCRESOL DERIVATIVES (*Continued*)
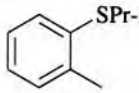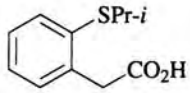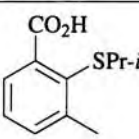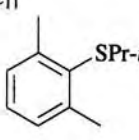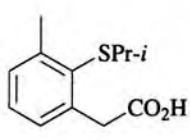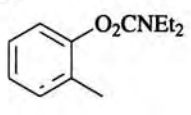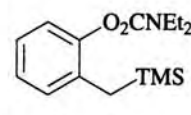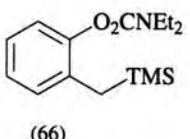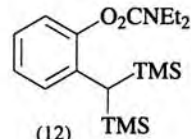
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C_{10}				
	n-BuLi, ether, reflux, 4 h	CO_2	**I:II** = 57:43 (—)	82
	n-BuLi:TMEDA, ether, reflux, 4 h	CO_2	**I:II** = 5:95 (—)	82
C_{11}	*n*-BuLi, ether, reflux, 4 h	CO_2	(100)	82

C. Cresol Dialkyl Carbamates

| C_{12} | *s*-BuLi:TMEDA, THF, -78°, 1 h | TMSCl | **I:II** = 2:1 (—) | 85 |
| | LDA, THF, -78°, 1 h | TMSCl | (66)   (12) | 85 |

TABLE V. CRESOL AND THIOCRESOL DERIVATIVES (*Continued*)
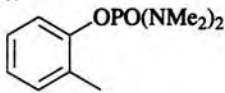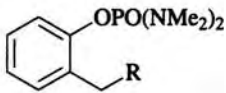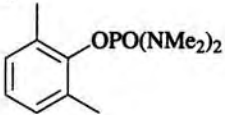
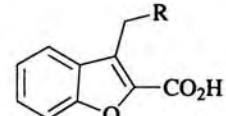| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
		D. Cresol Tetraalkylphosphorodiamidates		
C_{11}	*s*-BuLi, THF, -105°, 1 h			
			R	
		MeI	Me (81)	87
		TMSCl	TMS (55)	87
		CO_2	CO_2H (48)	87
		MeCON(OMe)Me	COMe (90)	87
		PhCHO	CHOHPh (43)	87
		p-MeOC$_6$H$_4$CHO	CHOHC$_6$H$_4$OMe-*p* (54)	87
		PhCO$_2$Me	COPh (74)	87
		p-MeOC$_6$H$_4$CO$_2$Me	COC$_6$H$_4$OMe-*p* (60)	87
		3,4-(MeO)$_2$C$_6$H$_3$CO$_2$Me	COC$_6$H$_3$(OMe)$_2$-3,4 (79)	87
	s-BuLi:TMEDA, THF, -105°, 1 h	PhCHO	CHOHPh (69)	201
C_{12}	*s*-BuLi, THF, -105°, 1 h			
		PhCO$_2$Me	R = COPh (64)	87
		MeI	R = Me (96)	87

188

189
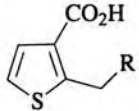
TABLE V. CRESOL AND THIOCRESOL DERIVATIVES (*Continued*)
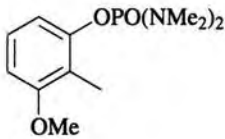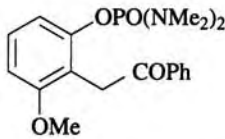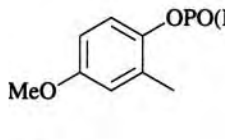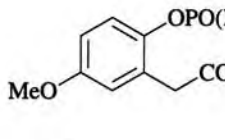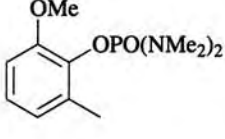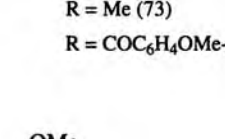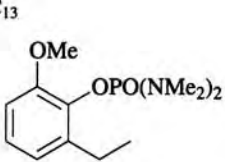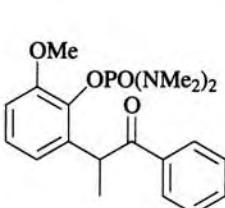
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	s-BuLi, THF, -105°, 1 h	PhCO₂Me	(67)	87
	s-BuLi, THF, -105°, 1 h	PhCO₂Me	(71)	87
	s-BuLi, THF, -105°, 1 h			
		MeI	R = Me (73)	87
		p-MeOC₆H₄CO₂Me	R = COC₆H₄OMe-p (70)	87

C₁₃

| | s-BuLi, THF, -105°, 1 h | 3,4-(OCH₂O)C₆H₃CO₂Me | (37) | 87 |

TABLE V. CRESOL AND THIOCRESOL DERIVATIVES (*Continued*)
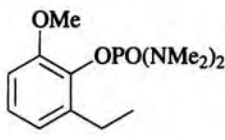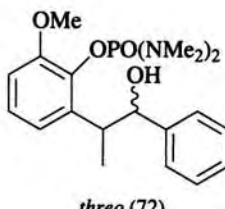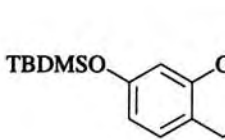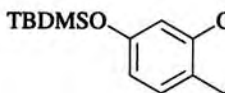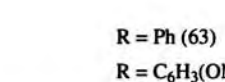
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	s-BuLi:TMEDA, THF, -105°, 1 h	3,4-(OCH₂O)C₆H₃CHO	 *threo* (72) *erythro (13)*	201

C₁₇

	n-BuLi, THF, -105°, 1 h	MeI	(52)	173
	s-BuLi:TMEDA, THF, -105°, 1 h			
		PhCO₂Me	R = Ph (63)	173
		2,4-(MeO)₂C₆H₃CO₂Me	R = C₆H₃(OMe)₂-2,4 (—)	173

TABLE V. CRESOL AND THIOCRESOL DERIVATIVES (*Continued*)
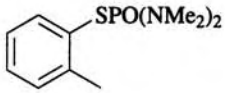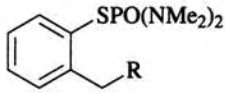
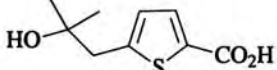| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.

E. Thiocresol Tetraalkylphosphorodiamidates

C_{11}

	s-BuLi, THF, -105°, 1 h			

			R	
		CO_2	CO_2H (96)	88
		$PhCO_2Me$	COPh (59)	88
		$3,4-(MeO)_2C_6H_3CO_2Me$	$COC_6H_3(OMe)_2-3,4$ (64)	88
		$3,5-(MeO)_2C_6H_3CO_2Me$	$COC_6H_3(OMe)_2-3,5$ (50)	88
		$4-C_5H_4NCO_2Me$	COC_5H_4N-4 (80)	88
		MeCON(OMe)Me	COMe (74)	88

TABLE VI. TOLUIDINE DERIVATIVES
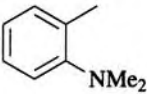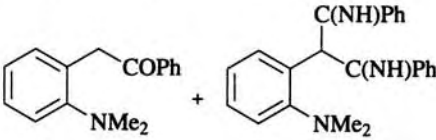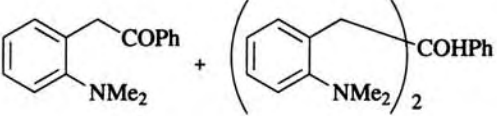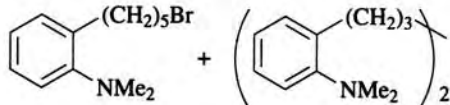
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.

A. N,N-Dialkyltoluidines

C$_9$

A. *n*-BuLi, ether, hexane, rt, 40 h

B. *n*-BuLi:TMEDA, hexane, rt, 3-4 h

R	A	B	
Ph$_2$CO	COHPh$_2$	(47-61) (60-94)	89
PhCHO	CHOHPh	(41-48) (78-79)	89
PhCH$_2$Cl	CH$_2$Ph	(33) (33-42)	89
PhCH$_2$Br	CH$_2$Ph	(36-38)	89
PhNCO	CONHPh	(30)	89

A. *n*-BuLi, ether, hexane, rt, 40 h   PhCN

B. *n*-BuLi:TMEDA, hexane, rt, 3-4 h

A:	(41-43)	(—)	89
B:	(48-54)	(15-20)	89

A. *n*-BuLi, ether, hexane, rt, 40 h   PhCO$_2$Me

B. *n*-BuLi:TMEDA, hexane, rt, 3-4 h

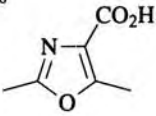|			
A:	(48-52)	(—)	89
B:	(47)	(18-20)	89

TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)

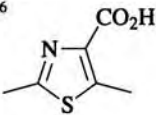| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	A. *n*-BuLi, ether, hexane, rt, 40 h	Br(CH₂)₄Br	A: (42) (—)	89
	B. *n*-BuLi:TMEDA, hexane, rt, 3-4 h		B: (10-15) (45-50)	89

B. Toluidine Carboxamides

C₁₂
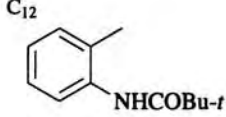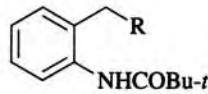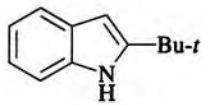
	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	n-BuLi, THF, 0°, 1.5 h		R	
		TMSCl	TMS (73)	90
		MeCHO	CHOHMe (71)	90
		CO₂	CO₂H (64)	90
	n-BuLi, THF, rt, 16 h	—	(>90)	90
	n-BuLi, THF, 15° to rt, 16 h	—	(87)	92

TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)
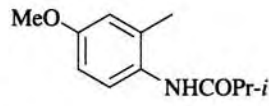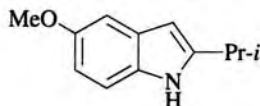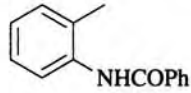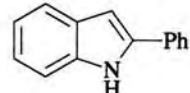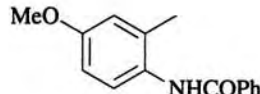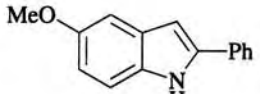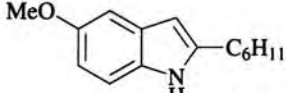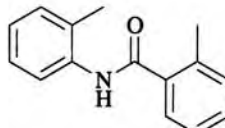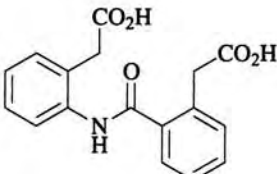
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	n-BuLi, THF, rt, 16 h	—	(49)	91
C₁₄	*n*-BuLi, THF, rt, 16 h	—	(90)	92
C₁₅	*n*-BuLi, THF, 15° to rt, 20 h	—	(80)	92
	n-BuLi, THF, rt, 16 h	—	(80)	91
	n-BuLi, THF, -25° to rt, 3 h	CO₂	(67)	92

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TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)
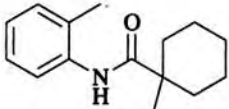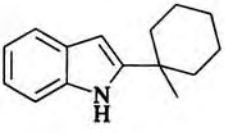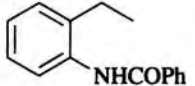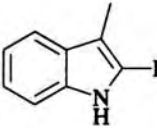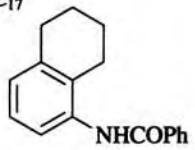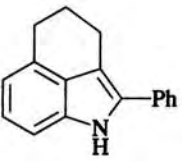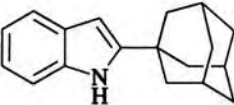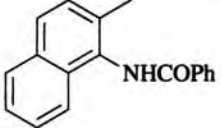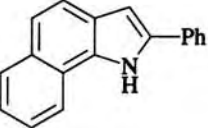
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	n-BuLi, THF, rt, 18 h	—	(76)	92
	n-BuLi, THF, 15° to rt, 48 h	—	(20)	92
C₁₇	n-BuLi, THF, 0°, 18 h	—	(41)	92
C₁₈	n-BuLi, THF, 15° to rt, 6 h	—	(59)	92
	n-BuLi, THF, 0° to rt, 16 h	—	(38)	92

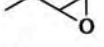TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)
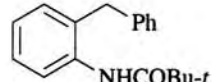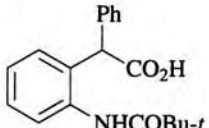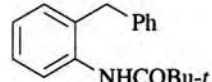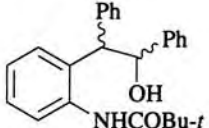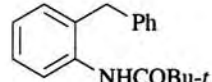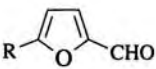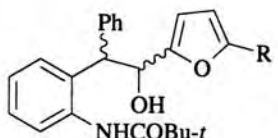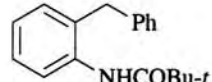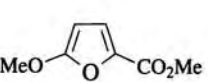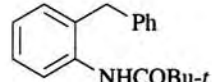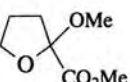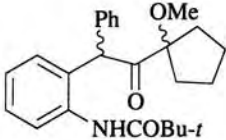
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	n-BuLi:TMEDA, THF, -20°	CO_2	(80)	304
	n-BuLi:TMEDA, THF, -20°	PhCHO	(98)	304
	n-BuLi:TMEDA, THF, -20°	R—furan—CHO	R = H (98); R = OMe (85)	207; 207
	n-BuLi:TMEDA, THF, -20°	MeO—furan—CO_2Me	(50)	207
	n-BuLi:TMEDA, THF, -20°	OMe, CO_2Me	(62)	304

TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)
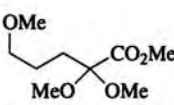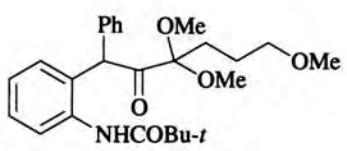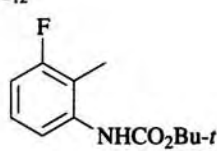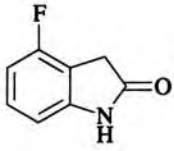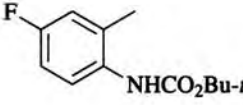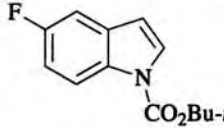
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	n-BuLi:TMEDA, THF, -20°		(73)	304

C. Toluidine tert-Butyl Carbamates

C₁₂ *(shown as C12)*

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	s-BuLi, THF, -40 to -20°, 5 min	1. DMF 2. HCl, THF	(73)	93
	s-BuLi, THF, -40 to -20°, 5 min	1. CO₂ 2. HCl, EtOH	(70)	93
	s-BuLi, THF, -40 to -20°, 5 min	1. DMF 2. HCl, THF	(86)	93

TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)
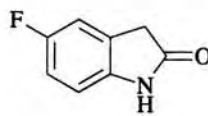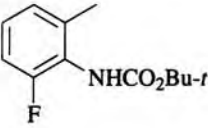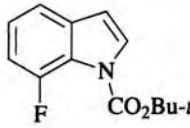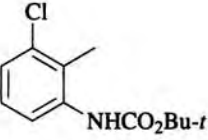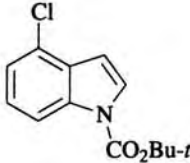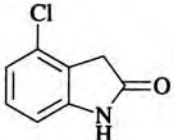
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	s-BuLi, THF, -40 to -20°, 5 min	1. CO₂ 2. HCl, EtOH	(84)	93
	s-BuLi, THF, -40 to -20°, 5 min	1. DMF 2. HCl, THF	(66)	93
	s-BuLi, THF, -40 to -20°, 5 min	1. CO₂ 2. HCl, EtOH	(80)	93
	s-BuLi, THF, -40 to -20°, 5 min	1. DMF 2. HCl, THF	(70)	93
	s-BuLi, THF, -40 to -20°, 5 min	1. CO₂ 2. HCl, EtOH	(81)	93
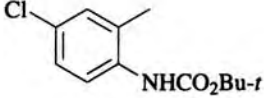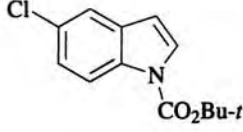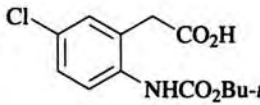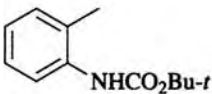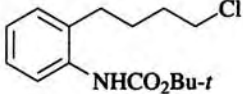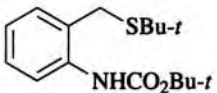
198

199

TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)

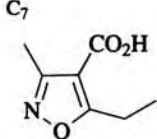| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	s-BuLi, THF, -40 to -20°, 5 min	1. DMF 2. HCl, THF	(83)	93
	s-BuLi, THF, -40 to -20°, 5 min	CO_2	(53)	93
	s-BuLi, THF, -40 to -20°, 5 min	1. CO_2 2. HCl, EtOH	(75)	93
	s-BuLi, THF, -40 to -20°, 5 min	$Cl(CH_2)_3Cl$	(98)	219
	s-BuLi, THF, -40° 20 min	$(t\text{-BuS})_2$	(86)	203

TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)
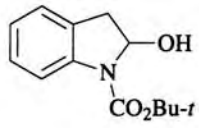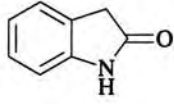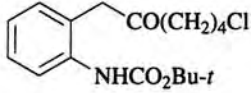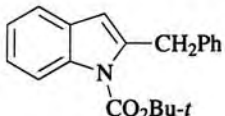
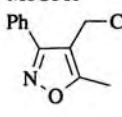| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	s-BuLi, THF, -40 to -20°, 5 min	DMF	(85)	93
	s-BuLi, THF, -40 to -20°, 5 min	1. DMF 2. HCl, THF	(80)	93
	s-BuLi, THF, -40 to -20°, 5 min	1. CO_2 2. HCl, EtOH 3. PhMe, reflux	(80)	93
	s-BuLi, THF, -40 to -20°, 5 min	$Cl(CH_2)_4CON(OMe)Me$	(62)	93
	s-BuLi, THF, -40 to -20°, 5 min	1. $PhCH_2CON(OMe)Me$ 2. TFA, CH_2Cl_2, 5 min	(60)	93

TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	s-BuLi, THF, -40 to -20°, 5 min	1. RCON(OMe)Me 2. TFA, CH$_2$Cl$_2$, 48 h	indole, 2-R; R = Me (74) / R = Ph (77)	93 / 93
C$_{13}$ 2,4-dimethyl-C$_6$H$_3$-NHCO$_2$Bu-t	s-BuLi, THF, -40 to -20°, 5 min	1. DMF 2. HCl, THF	5-methyl-1-(CO$_2$Bu-t)-indole (75)	93
	s-BuLi, THF, -40 to -20°, 5 min	1. CO$_2$ 2. HCl, EtOH 3. PhMe, reflux	5-methyl-oxindole (61)	93
MeO—(2-methyl)-C$_6$H$_3$-NHCO$_2$Bu-t	s-BuLi, THF, -40 to -20°, 5 min	1. DMF 2. HCl, THF	5-methoxy-1-(CO$_2$Bu-t)-indole (60)	93
	s-BuLi, THF, -40 to -20°, 5 min	1. CO$_2$ 2. HCl, EtOH 3. PhMe, reflux	5-methoxy-oxindole (60)	93

TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)
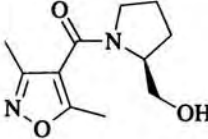
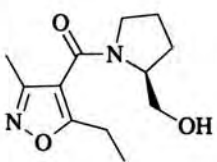| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	s-BuLi, THF, -40 to -20°, 5 min	1. RCON(OMe)Me 2. TFA, CH$_2$Cl$_2$, 5 min	5-methoxy-2-R-1-(CO$_2$Bu-t)-indole; R = (CH$_2$)$_3$Cl (60) / R = (CH$_2$)$_4$Cl (70)	93 / 93
	s-BuLi, THF, -40 to -20°, 5 min	1. n-BuCON(OMe)Me 2. TFA, CH$_2$Cl$_2$, 5 min 3. NaOH, EtOH	5-methoxy-2-Bu-n-indole (74)	93
MeO—(2-methyl)-C$_6$H$_3$-NHCO$_2$Bu-t	s-BuLi, THF, -55 to -15°, 90 min	1. DMF 2. HCl, THF	6-methoxy-1-(CO$_2$Bu-t)-indole (75)	93
(2-methyl, 6-OMe)-C$_6$H$_3$-NHCO$_2$Bu-t	s-BuLi, THF, -40 to -20°, 5 min	1. n-BuCON(OMe)Me 2. TFA, CH$_2$Cl$_2$, 5 min 3. NaOH, EtOH	7-methoxy-2-Bu-n-indole (64)	93
2-ethyl-C$_6$H$_4$-NHCO$_2$Bu-t	t-BuLi:TMEDA, THF, -40 to -20°, 4 h	1. DMF 2. HCl, THF	3-methyl-1-(CO$_2$Bu-t)-indole (80)	93

TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	t-BuLi:TMEDA, THF, -40 to -20°, 4 h	1. CO$_2$ 2. HCl, EtOH 3. PhMe, reflux	(65)	93
C$_{14}$	*s*-BuLi, THF, -55 to -15°, 90 min	1. DMF 2. HCl, THF	(88)	93
	s-BuLi, THF, -55 to -15°, 90 min	1. CO$_2$ 2. HCl, EtOH 3. PhMe, reflux	(75)	93
	t-BuLi:TMEDA, THF, -40 to -20°, 4 h	1. DMF 2. HCl, THF	(40)	93
	t-BuLi:TMEDA, THF, -40 to -20°, 4 h	TMSCl	(74)	94

TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)

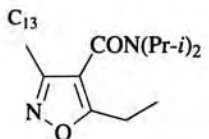| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C$_{15}$	*s*-BuLi, THF, -40°, 20 min	(RS)$_2$	R = Pr-*i* (44) R = Bu-*t* (33)	203 203
C$_{16}$	*t*-BuLi:TMEDA, THF, -30 to -20°, 45 min	DMF	(88)	93
	1. CO$_2$ 2. CH$_2$N$_2$		(70)	93
C$_{17}$	*s*-BuLi, THF, -40 to -20°, 5 min	1. DMF 2. HCl, THF	(88)	305

TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C_{18} (2-benzyl-N-Boc-aniline)	s-BuLi, THF, -40 to -20°, 5 min	1. DMF 2. HCl, THF	3-Ph-1-(CO₂Bu-t)indole (61)	93
	s-BuLi, THF, -40 to -20°, 5 min	1. CO_2 2. HCl, EtOH	3-Ph-oxindole (74)	93
	s-BuLi, THF, -40 to -20°, 5 min	1. PhCON(OMe)Me 2. TFA, CH_2Cl_2, 48 h	2,3-diphenylindole (76)	93
C_{21} (1-Boc-8-methyl-3-(N,N-di-n-propylamino)-tetrahydroquinoline)	s-BuLi, THF, -78°, 5 min	CO_2	8-(CH₂CO₂H) product N-CO₂Bu-t, N(Pr-n)₂ (—)	306

TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)

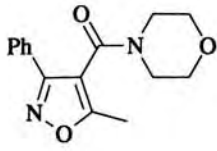### D. Toluidine N-(tert-Butoxycarbonylamino)Derivatives

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C_{13} (indoline N-NHCO₂Bu-t)	s-BuLi, THF, -40°, 45 min	MeI	3-methylindoline N-NHCO₂Bu-t (81)	95
C_{14} (tetrahydroquinoline N-NHCO₂Bu-t)	s-BuLi, THF, -40°, 45 min		4-R product N-NHCO₂Bu-t	
		MeI	R = Me (95)	95
		CO_2	R = CO_2H (81)	95
		Cl(CH₂)₄CON(OMe)Me	R = CO(CH₂)₄Cl (69)	95
C_{15} (benzazepine N-NHCO₂Bu-t)	s-BuLi, THF, -40°, 45 min		R product N-NHCO₂Bu-t	
		MeI	R = Me (76)	95
		CO_2	R = CO_2H (51)	95

TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)

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

E. Toluidine Lithium Carbamates

C7

1. *n*-BuLi, THF, -78 to 0°
2. CO2
3. *t*-BuLi, THF, -78 to -20°, 1 h

		Substrate	R	
		MeI	Me (50)	99
		Me2CHCHO	CHOHCHMe2 (48)	99
		p-MeC6H4CHO	CHOHC6H4Me-*p* (59)	99
		Ph2CO	COHPh2 (58)	99

C8

1. *n*-BuLi, THF, -70 to 0°
2. CO2
3. *n*-BuLi, THF, -70 to -20°, 45 min

		Substrate	R	
		D2O	D (95)	100
		MeI	Me (65)	100
		n-C6H13I	C6H13-*n* (48)	100
		PhCH2Br	CH2Ph (56)	100
		Me2CHCHO	CHOHCHMe2 (55)	100
		p-MeC6H4CHO	CHOHC6H4Me-*p* (80)	100
		Ph2CO	COHPh2 (89)	100
		t-BuNCO	CONHBu-*t* (63)	100
		PhNCO	CONHPh (67)	100

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

1. *n*-BuLi, THF, -70 to 0°
2. CO2
3. *n*-BuLi, THF, -70 to -20°, 45 min

		Substrate	R	
		MeCO2Et	Me (65)	100
		PhCO2Et	Ph (60)	100
		p-MeC6H4CO2Et	C6H4Me-*p* (58)	100

C9

1. *n*-BuLi, THF, -70 to 0°
2. CO2
3. *n*-BuLi, THF, -70 to -20°, 1 h

PhCO2Et

 (54)

100

F. Toluidine Trimethylsilyl Derivatives

C10

n-BuLi, ether, reflux, 5 h

PhCO2Et

 (36)

101

TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)
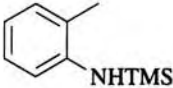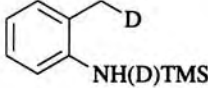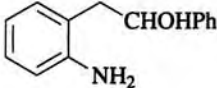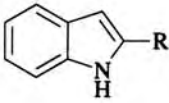
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)		Refs.
	n-BuLi	TMSCl		(—)	307
	n-BuLi, hexanes, reflux, 6 h	D$_2$O		(94)	101
	n-BuLi, hexanes, reflux, 6 h	PhCHO		(55)	101
	n-BuLi, hexanes, reflux, 6 h				
			R		
		MeCO$_2$Et	Me (60)		101
		i-PrCO$_2$Et	Pr-*i* (62)		101
		n-C$_5$H$_{11}$CO$_2$Et	C$_5$H$_{11}$-*n* (62)		101
		PhCO$_2$Et	Ph (65)		101
		Me$_2$C=CHCO$_2$Et	CH=CMe$_2$ (38)		101

TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)
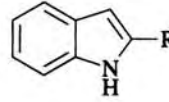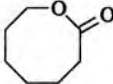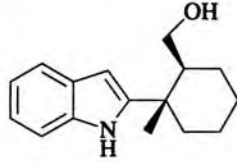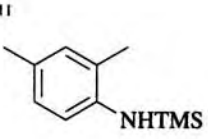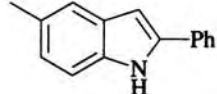
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)		Refs.
			R		
	n-BuLi, hexanes, reflux, 6 h		(CH$_2$)$_3$OH (61)		101
	s-BuLi, ether, rt		CMe$_2$CH$_2$CH$_2$OH (63)		102
	n-BuLi		(CH$_2$)$_7$OH (25)		308
	n-BuLi, hexanes, reflux, 6.5 h			(59)	101
C$_{11}$	*n*-BuLi, hexanes, reflux, 4 h	PhCO$_2$Et		(56)	101

TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)
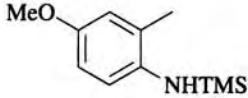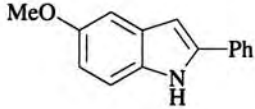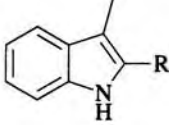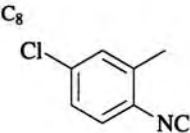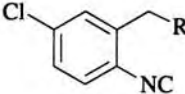
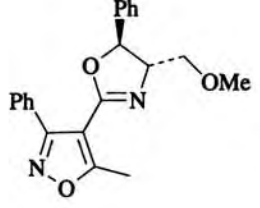| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
MeO, Me, NHTMS	*n*-BuLi, hexanes, reflux, 7.5 h	PhCO₂Et	MeO, 2-Ph indole (35)	101
Et, NHTMS	*n*-BuLi:TMEDA, hexanes, reflux, 6.5 h		3-Me-2-R indole	
		MeCO₂Et	R: Me (32)	101
		Me₂CHCO₂Et	CHMe₂ (45)	101
		PhCO₂Et	Ph (50)	101

G. Tolyl Isocyanides

C₈ Cl, Me, NC	LDA, diglyme, -78°, 30 min		Cl, CH₂R, NC	
		D₂O	R: D (—)	104
		Me₂CO	COHMe₂ (95)	104
		t-BuO₂CCH₂CH=CH₂	COBu-*t* (48)	205

TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)
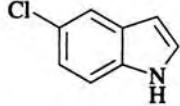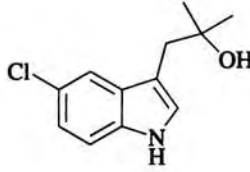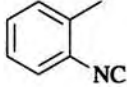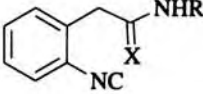
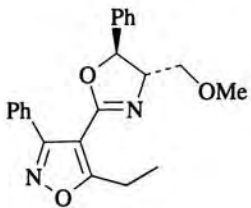| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, diglyme, -78°, 30 min	—	Cl, indole (100)	104
	LDA, diglyme, -78°, 30 min	1. epoxide (2-methyl) 2. -78° to rt	Cl, 3-(2-hydroxy-2-methylpropyl) indole (78)	104
Me, NC	LDA, diglyme, -78°, 30 min		NHR, X, NC	
		n-BuNCO	R: Bu-*n* X: O (70)	204
		t-BuNCO	Bu-*t* O (53)	204
		PhNCO	Ph O (50)	204
		C₆H₁₁NCO	C₆H₁₁ O (55)	204
		PhNCS	Ph S (82)	204
		C₆H₁₁NCS	C₆H₁₁ S (96)	204

TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, diglyme, -78°, 30 min			

	Substrate	R	
	D_2O	D (93)	104
	MeI	Me (95)	104
	$CH_2=CHCH_2Br$	$CH_2CH=CH_2$ (82)	104
	n-BuI	Bu-*n* (83)	104
	i-PrI	Pr-*i* (89)	104
	i-BuBr	Bu-*i* (78)	104
	TMSCl	TMS (95)	104
	$(MeS)_2$	SMe (67)	104
	MeO_2CCl	CO_2Me (69)	104
	MeCHO	CHOHMe (93)	220
	MeCH=CHCHO	CHOHCH=CHMe	206
	$C_4H_3OCHO-2$	$CHOHC_4H_3O-2$ (97)	206
	Me_2CO	$CHOHMe_2$ (97)	206
	MeCOPr-*c*	C(Me)OHPr-*c* (100)	206
	$Me_2C=CHCOMe$	$C(Me)OHC=CMe_2$ (93)	206
	PhCH=CHCOMe	C(Me)OHCH=CHPh (67)	206
	$MeCOC_{10}H_7-2$	$C(Me)OHC_{10}H_7-2$ (100)	206
	$MeCOC_6H_4(OCH_2CH=CH_2)-o$	$C(Me)OHC_6H_4(OCH_2CH=CH_2)-o$ (86)	206
	LDA, diglyme, H MPA, -78°, 10 h	$(EtO)_2CHCH_2Br$	$CH_2CH(OEt)_2$ (68)	104

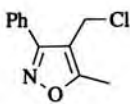TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, diglyme, -78°, 30 min		(77)	206
	LDA, diglyme, -78°, 30 min		(98)	206
	LDA, diglyme, -78°, 30 min			

	Substrate	R	
	n-$PrO_2CCH_2CH=CH_2$	Pr-*n* (57)	205
	i-$BuO_2CCH_2CH=CH_2$	Bu-*i* (55)	205
	t-$BuO_2CCH_2CH=CH_2$	Bu-*t* (57)	205
	n-$C_7H_{15}O_2CCH_2CH=CH_2$	C_7H_{15}-*n* (71)	205
	$PhO_2CCH_2CH=CH_2$	Ph (95)	205
	$Cl(CH_2)_3CO_2Et$	$(CH_2)_3Cl$ (52)	104
	MeCON⊲	Me (92)	104
	t-BuCON⊲	Bu-*t* (86)	104
		$(CH_2)_3OH$ (47)	104

TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)

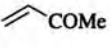| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, diglyme, -78°, 30 min	1. (epoxide) R¹ / R²	(indol-3-yl-CH₂C(R¹)(R²)OH)	
		2. LDA, -78° to rt	R¹ = Me, R² = Me (68)	104
			R¹ = H, R² = Me (65)	104
			R¹ = H, R² = Et (61)	104
	LDA, diglyme, -78°, 30 min	1. (cyclohexene oxide)	(2-(indol-3-yl)cyclohexanol) (42)	104
		2. LDA, -78° to rt		
	LDA, diglyme, -78°	1. $C_6H_{11}NCS$	(indol-3-yl–CSNHC₆H₁₁) (52)	204
		2. LDA, -78° to rt		
	LDA, diglyme, -78°	1. $CH_2=CHCH_2NCS$	(indol-3-yl–CSNHCH₂CH=CH₂) (58)	204
		2. LDA, -78° to rt		

TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)
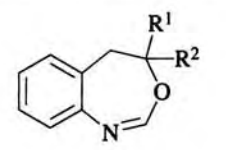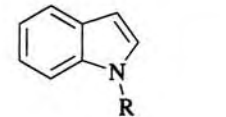
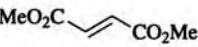| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)			Refs.
	LDA, diglyme, -78°, 30 min	1. R^1R^2CO	(benzoxazepine with R¹, R²)			
		2. Cu_2O, heat	R^1	R^2		
		MeCHO	H	Me	(90)	220
		EtCHO	H	Et	(93)	220
		$(C_4H_3O)CHO$	H	C_4H_3O	(89)	220
		PhCHO	H	Ph	(93)	220
		Me_2CO	Me	Me	(96)	220
		$(CH_2)_4CO$	-(CH₂)₄-		(93)	220
	1. LDA, diglyme, -78° to rt		(indole, N-R)			
	2. electrophile, rt		R			
		—	H (100)			104
		MeI	Me (82)			104
		n-BuBr	Bu-n (82)			104
		MeO_2CCH_2Br	CH₂CO₂Me (52)			104
		TMSCl	TMS (87)			104
		$ClCO_2Me$	CO₂Me (76)			104
		EtCOCl	COEt (79)			104

TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
			CH₂CHOHMe (72)	104
			CH₂CHOHEt	104
			CH₂COHMe₂ (65)	104
			CHOH(CH₂)₅ (18)	104
	1. LDA, diglyme, -78°, 30 min 2. MgI₂			

		Substrate	R	Refs.
		CH₂=CHCH₂Br	CH₂CH=CH₂ (80)	309
		i-PrI	Pr-*i* (20)	309
		HC≡CCH₂Br	CH₂C≡CH (62)	309
		CH₂=C(Cl)CH₂Cl	CH₂C(Cl)=CH₂ (85)	309
		n-BuBr	Bu-*n* (53)	309
		i-BuBr	Bu-*i* (47)	309
		MeCH=CH₂Cl	CH₂CH=CHMe (85)	309
		CH₂=C(Me)CH₂Cl	CH₂C(Me)=CH₂ (75)	309
		CH₂=C(CO₂Me)CH₂Cl	CH₂C(CO₂Me)=CH₂ (88)	309
		PhCH₂Br	CH₂Ph (100)	309

TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)
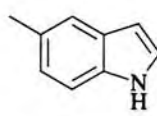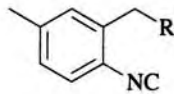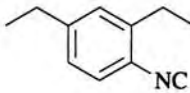
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C₉	LDA, diglyme, -78° to rt	—	(100)	104
	LDA, diglyme, -78°, 30 min			

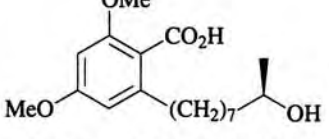|		Substrate	R	Refs.
		D₂O	D (100)	104
		MeI	Me (93)	104
		CH₂=CHCH₂Br	CH₂CH=CH₂ (98)	104
		n-BuBr	Bu-*n* (99)	104
		Me₂CO	COHMe₂ (87)	103
		Me₂C=CHCOMe	C(Me)OHCH=CMe₂ (94)	206
		MeCH=CHCO₂Me	CHMeCH₂CO₂Me (73)	218
		i-BuO₂CCH₂CH=CH₂	COBu-*i* (50)	205
		t-BuO₂CCH₂CH=CH₂	COBu-*t* (72)	205
		PhO₂CCH₂CH=CH₂	COPh (72)	205
		t-BuCON◁	COBu-*t* (85)	104
	LDA (6 eq), diglyme -78°	MeI	(64)	104

TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)
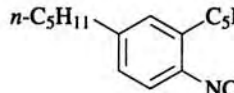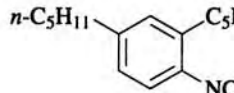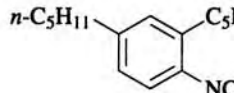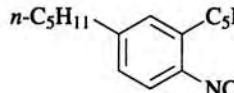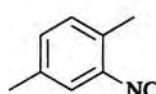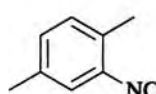
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA (6 eq), diglyme -78°.	n-BuBr	(75)	104
	LDA, diglyme, -78°, 30 min	1. 2. LDA, -78° to rt	R = H (48) R = Me (48)	104 104
	1. LDA, diglyme, -78°, 30 min 2.MgI₂			
		CH₂=CHCH₂Br	R = CH₂CH=CH₂ (87)	309
		n-BuBr	R = Bu-n (56)	309
	LDA, diglyme, -78°	D₂O	(—)	104
	LDA, diglyme, -78° to rt	—	(82)	104

TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)
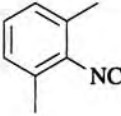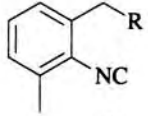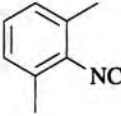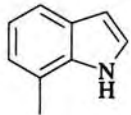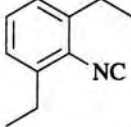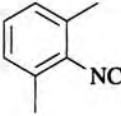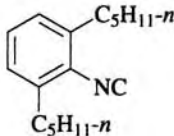
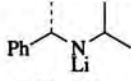| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, diglyme, -78°			
			R	
		D₂O	D (—)	104
		i-PrI	Pr-i (75)	104
		EtCHO	CHOHEt (90)	220
		PhCH=CHCOMe	C(Me)OHCH=CHPh (82)	104
		MeCH=CHCO₂Me	CMeCH₂CO₂Me (85)	218
		t-BuO₂CCH₂CH=CH₂	COBu-t (63)	205
		t-BuCON◁	COBu-t (80)	104
	LDA, diglyme, -78° to rt	—	(87)	104
	LDA(xs), diglyme, -78°, 30 min	MeI	(75)	104
	LDA(xs), diglyme, -78°, 30 min	n-BuBr	(60)	104

TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)
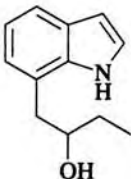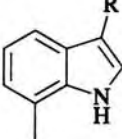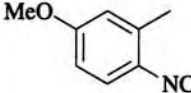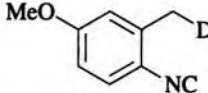
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, diglyme, -78°	1. EtCHO 2. LDA, -78° to rt	(57)	104
	LDA, diglyme, -78°, 30 min	1. (epoxide) 2. LDA, -78° to rt	(23)	104
	1. LDA, diglyme, -78° to rt 2. MgI$_2$			

		R	R	
		CH$_2$=CHCH$_2$Br	CH$_2$CH=CH$_2$ (70)	309
		PhCH$_2$Br	CH$_2$Ph (43)	309
		n-C$_8$H$_{17}$Br	n-C$_8$H$_{17}$ (20)	309
	LDA, diglyme, -78°, 30 min	D$_2$O	(—)	104

TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)
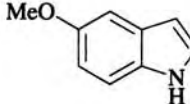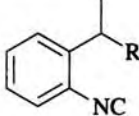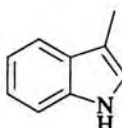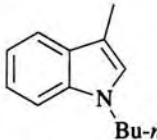
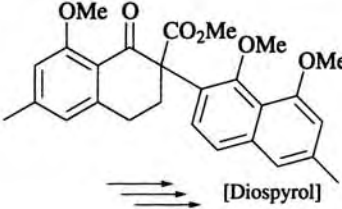| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, diglyme, -78° to rt	—	(91)	104
	LTMP, diglyme, -78°			

		R	R	
		MeI	Me (68)	104
		n-BuBr	Bu-n (72)	104
		(MeS)$_2$	SMe (75)	104
		Me$_2$CO	COHMe$_2$ (93)	220
		PhCOMe	C(Me)OHPh (89)	206
	LTMP, diglyme, -78° to rt	—	(95)	104
	LTMP, diglyme, -78° to rt	n-BuBr	(65)	104

TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)
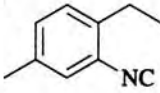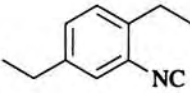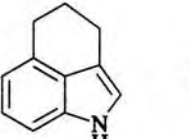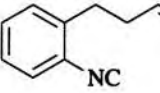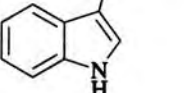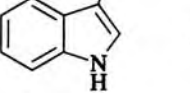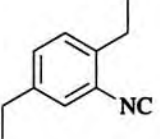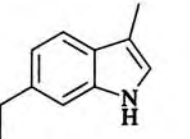
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C₁₀	LDA, diglyme, -78°	MeI	(84)	104
C₁₁	LTMP, diglyme, -78° to rt	—	(—)	104
	LTMP, diglyme, -78° to rt	—	(95)	104
	LTMP, diglyme, HMPA, -78° to rt	—	(65)	104
	LTMP, diglyme, -78° to rt	—	(39)	104

TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)
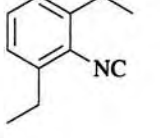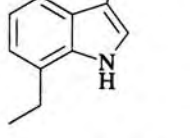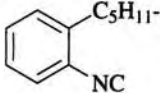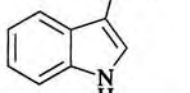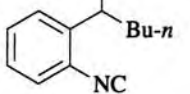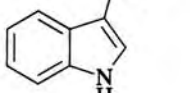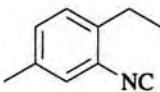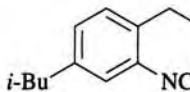
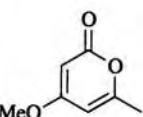| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LTMP, diglyme, -78° to rt	—	(63)	104
C₁₂	LTMP, diglyme, -78° to rt	—	(85)	104
	LTMP, diglyme, -78°	MeI	(66)	104
	LTMP, diglyme, -78° to rt	—	(78)	104
	LTMP, diglyme, -78°	*i*-PrI	(69)	104

TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)
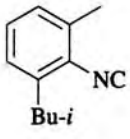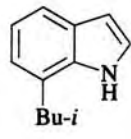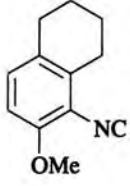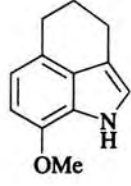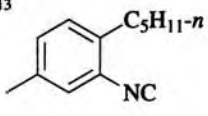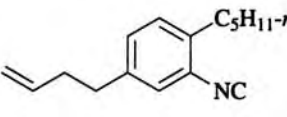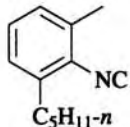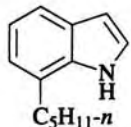
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
(2-methyl-6-isobutyl phenyl isocyanide; Bu-*i*)	LTMP, diglyme, -78° to rt	—	7-isobutylindole (74)	104
(tetrahydronaphthalene OMe isocyanide)	LTMP, diglyme, -70 to -15°, 1 h	—	(OMe tricyclic indole) (30)	310
C$_{13}$ (n-C$_5$H$_{11}$, NC, methyl phenyl isocyanide)	LTMP, diglyme, -78°	n-BuBr	(n-C$_5$H$_{11}$, C$_5$H$_{11}$-n, NC) (79)	104
	LTMP, diglyme, -78°	CH$_2$=CHCH$_2$Br	(butenyl, C$_5$H$_{11}$-n, NC) (86)	104
(2-methyl-6-pentyl phenyl isocyanide; C$_5$H$_{11}$-n)	LTMP, diglyme, -78° to rt	—	7-pentylindole (C$_5$H$_{11}$-n) (66)	104

TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)
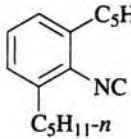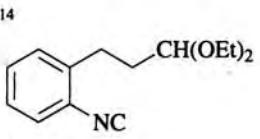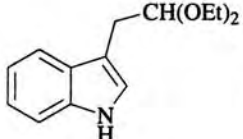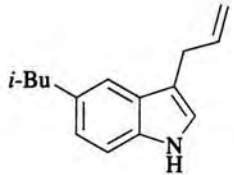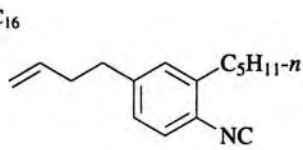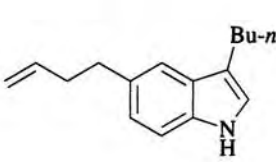
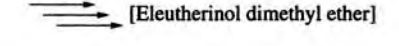| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LTMP, diglyme, -78°	n-BuBr	(C$_5$H$_{11}$-n, NC, C$_5$H$_{11}$-n) (70)	104
C$_{14}$ (CH(OEt)$_2$, NC phenyl isocyanide)	LTMP, diglyme, -78° to rt	—	3-(CH(OEt)$_2$ methyl)indole (62)	104
C$_{15}$ (*i*-Bu, butenyl, NC phenyl isocyanide)	LTMP, diglyme, -78° to rt	—	*i*-Bu, 3-allylindole (47)	104
C$_{16}$ (butenyl, C$_5$H$_{11}$-n, NC phenyl isocyanide)	LTMP, diglyme, -78° to rt	—	Bu-n, 5-butenyl-3-butylindole (30)	104

TABLE VI. TOLUIDINE DERIVATIVES (*Continued*)
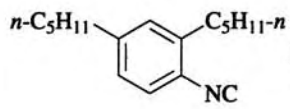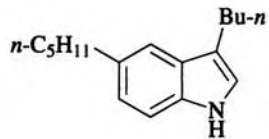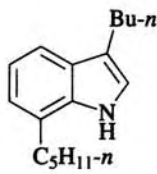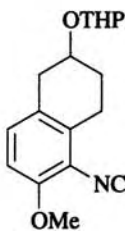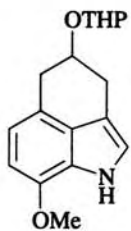
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C$_{17}$				
	LTMP,diglyme, -78° to rt	—	(30)	104
	LTMP,diglyme, -78° to rt	—	(43)	104
	LTMP, diglyme, -70 to -20°, 1.5 h	—	(50)	310

TABLE VII. 2-(ALKYLAMINO)TOLUENE DERIVATIVES
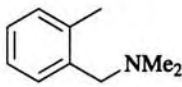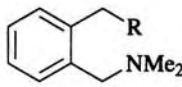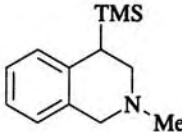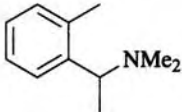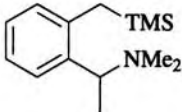
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
		A. 2-[(N,N-Dialkylamino)alkyl]toluenes		

C_{10}

			R	
	n-BuLi, ether, rt, 16 h	D_2O	D (—)	18
	n-BuLi, ether, rt, 6 h	Me_2CO	$COHMe_2$ (46)	19
		PhCHO	CHOHPh (77)	19
		Ph_2CO	$COHPh_2$ (80)	19
		PhCN	COPh (68)	19
	n-BuLi, ether, rt	TMSCl	TMS (55)	106
	n-BuLi, ether, rt, 22 h	TMSCl	TMS (96)	105

| | *n*-BuLi, THF, -75 to -40°, 2 h | TMSCl | (79) | 105 |

| | *s*-BuLi, ether, rt, 40 h | TMSCl | (95) | 105 |

TABLE VII. 2-(ALKYLAMINO)TOLUENE DERIVATIVES (*Continued*)
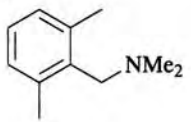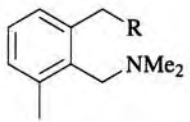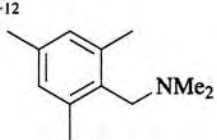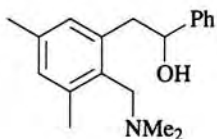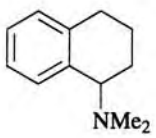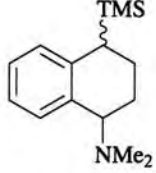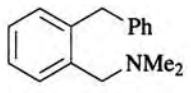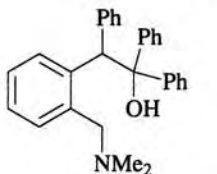
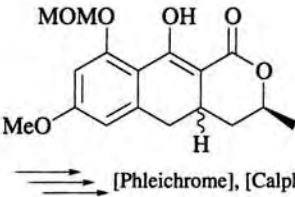| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C₁₁	*n*-BuLi, ether, rt, 6 h			
		Me₂CO	R = COHMe₂ (61)	19
		Ph₂CO	R = COHPh₂ (80)	19
C₁₂	*n*-BuLi, ether, rt, 6 h	PhCHO	(81)	19
	n-BuLi, ether, rt, 22 h	TMSCl	I (—) II (41) I:II = 1:2	105
C₁₆	*n*-BuLi, ether, rt, 6 h	Ph₂CO	(88)	19

TABLE VII. 2-(ALKYLAMINO)TOLUENE DERIVATIVES (*Continued*)
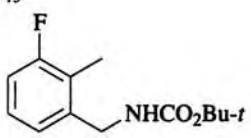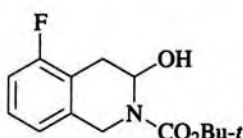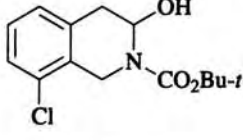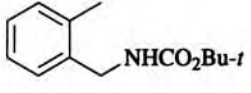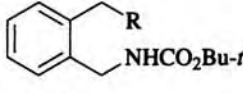
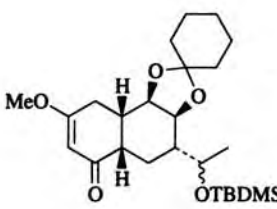| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
		B. 2-([(N-tert-Butoxycarbonyl)amino]alkyl)toluenes		
C₁₃	*t*-BuLi, THF, -60 to -25°, 20 min	DMF	(72)	47
	t-BuLi, THF, -60 to -25°, 20 min	DMF	(80)	47
	t-BuLi, THF, -60 to -25°, 20 min			
			R	
		MeI	Me (98)	108
		1. CO₂ 2. CH₂N₂	CO₂Me (70)	108
	s-BuLi, THF, -60 to -30°, 5-10 min			
		CO₂	CO₂H (90)	311
		PhCHO	CHOHPh (—)	47
		3,4-(MeO)₂C₆H₃CHO	CHOHC₆H₃(OMe)₂-3,4 (66)	47
		Ph₂CO	COHPh₂ (60)	47
		(CH₂)₅CO	COH(CH₂)₅	47

TABLE VII. 2-(ALKYLAMINO)TOLUENE DERIVATIVES *(Continued)*

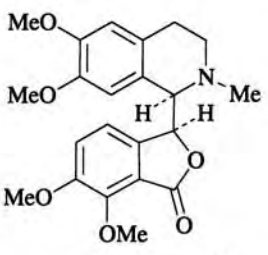| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	s-BuLi, THF, -60 to -30°, 5-10 min	DMF	(78)	47
	s-BuLi, THF, -60 to -30°, 5-10 min			
			$\underline{R}$	
		n-BuCO(OMe)Me	Bu-n (94)	47
		Cl(CH$_2$)$_4$CON(OMe)Me	(CH$_2$)$_4$Cl (95)	47
		PhCON(OMe)Me	Ph (79)	47
		3,4-(MeO)$_2$C$_6$H$_3$CH$_2$-CON(OMe)Me	CH$_2$C$_6$H$_3$(OMe)$_2$-3,4 (99)	47
C$_{14}$	s-BuLi, THF, -60 to -30°, 5-10 min	DMF	(80)	47
	t-BuLi, THF, -60 to -25°, 1.5 h			
		MeI	R = Me (80)	108
		1. CO$_2$ 2. CH$_2$N$_2$	R = CO$_2$Me (67)	108

TABLE VII. 2-(ALKYLAMINO)TOLUENE DERIVATIVES *(Continued)*

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C$_{15}$	s-BuLi, THF, -60 to -30°, 5-10 min	DMF	(60)	47
	t-BuLi, THF, -60 to -25°, 1.5 h	MeI	**I** + **II** I:II = 4:1 (82)	108
	t-BuLi, THF, -60 to -25°, 1.5 h	1. CO$_2$ 2. CH$_2$N$_2$	**I** (45) + **II** (—) CO$_2$Me I:II = 4:1	108

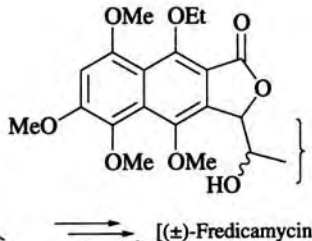TABLE VII. 2-(ALKYLAMINO)TOLUENE DERIVATIVES (*Continued*)
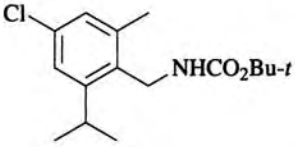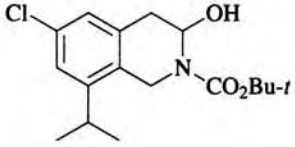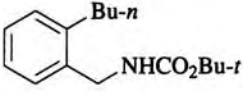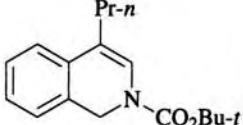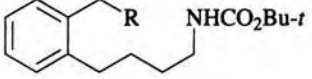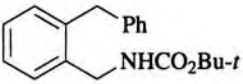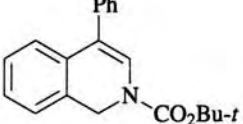
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C$_{16}$				
	t-BuLi, THF, -60 to -25°, 20 min	DMF	(97)	47
	t-BuLi, THF, -60 to -25°, 20 min	1. DMF 2. HCl	(<20)	47
	t-BuLi, THF, -60 to -25°, 6-8 h			
		MeI	R = Me (35-40)	108
		1. CO$_2$ 2. CH$_2$N$_2$	R = CO$_2$Me (35-40)	108
C$_{19}$				
	t-BuLi, THF, -60 to -25°, 20 min	1. DMF 2. HCl	(71)	47

TABLE VII. 2-(ALKYLAMINO)TOLUENE DERIVATIVES (*Continued*)
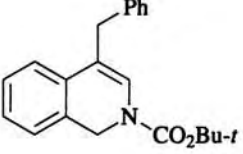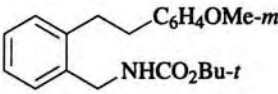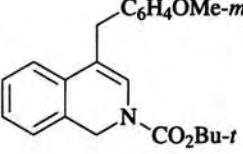
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C$_{20}$				
	t-BuLi, THF, -60 to -25°, 20 min	1. DMF 2. HCl	(42)	47
C$_{21}$				
	t-BuLi, THF, -60 to -25°, 20 min	1. DMF 2. HCl	(<20)	47

TABLE VIII. TOLUENESULFONIC ACID DERIVATIVES
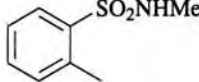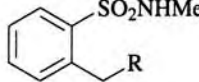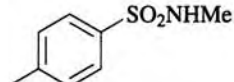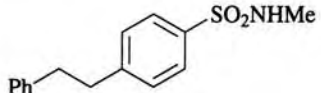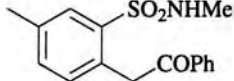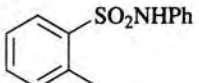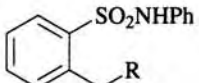
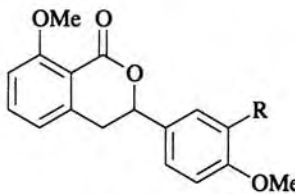| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
		A. Toluenesulfonamides		

C$_8$

	n-BuLi, THF, 0°, 30 min			
		Ph$_2$CO	R = COHPh$_2$ (91)	111
		1. PhCN 2. HCl	R = COPh (71)	110

| | NaNH$_2$, NH$_3$ | PhCH$_2$Cl | (72) | 176 |

C$_9$

| | *n*-BuLi, THF, 0°, 30 min | 1. PhCN 2. HCl | (92) | 110 |

C$_{13}$

	n-BuLi, THF, 0°, 30 min			
		Ph$_2$CO	R = COHPh$_2$ (82)	111
		1. PhCN 2. HCl	R = COPh (76)	110

TABLE VIII. TOLUENESULFONIC ACID DERIVATIVES (*Continued*)
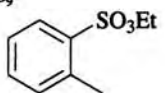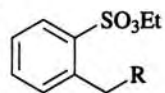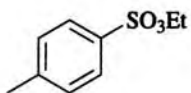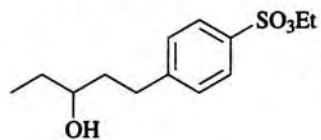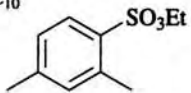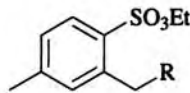
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
		B. Toluenesulfonate Esters		

C$_9$

| | *n*-BuLi, THF, -78°, 1.5 h | | | |

			R	
		EtCHO	CHOHEt (75)	114
		Me$_2$CO	COHMe$_2$ (50)	114
		PhCHO	CHOHPh (65)	114
		Ph$_2$CO	COHPh$_2$ (91)	114
		ClCO$_2$Et	CO$_2$Et (50)	114
		CO$_2$	CO$_2$H (70)	114
		PhNCO	CONHPh (78)	114
		PhSO$_2$Cl	SO$_2$Ph (50)	114

| | *n*-BuLi, THF, -78°, 1.5 h | | (40) | 114 |

C$_{10}$

| | *n*-BuLi, THF, -78°, 1.5 h | | | |

			R	
		PhCHO	CHOHPh (60)	114
		Ph$_2$CO	COHPh$_2$ (90)	114
		CO$_2$	CO$_2$H (85)	114

TABLE IX. FLUORO- AND TRIFLUOROMETHYLTOLUENES
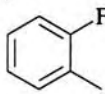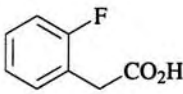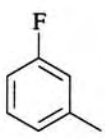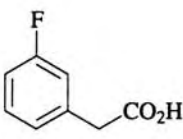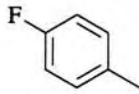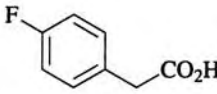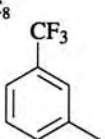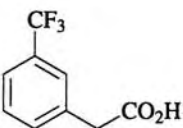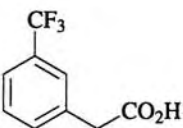
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C$_7$		*Fluorotoluenes*		
	LDA: t-BuOK, THF, -75°	CO_2	(37)	115
	LDA: t-BuOK, THF, -75°	CO_2	(62)	115
	LDA: t-BuOK, THF, -75°	CO_2	(7) + (53)	115
		Trifluoromethyltoluenes		
C$_8$				
	n-BuLi, t-BuOK, THF, -75°	CO_2	(67)	115
	LDA: t-BuOK, THF, -75°	CO_2	(67)	115

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES
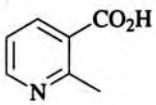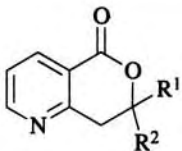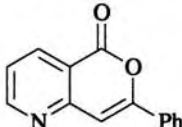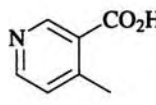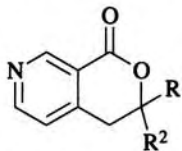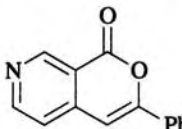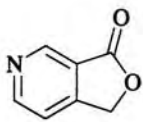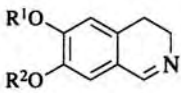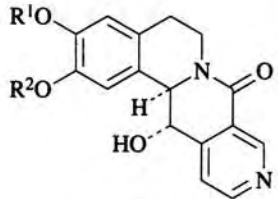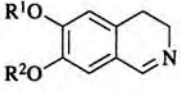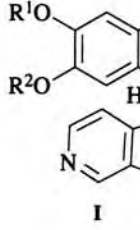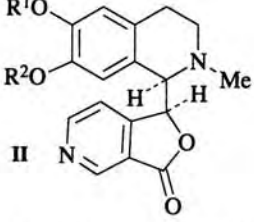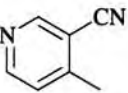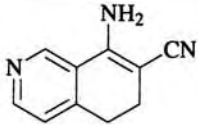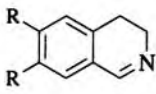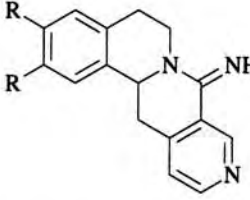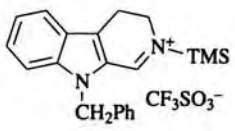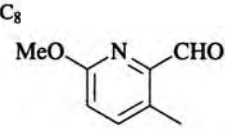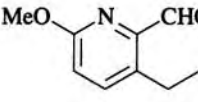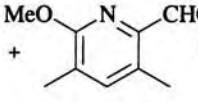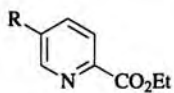
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
		A. Alkylpyridines		
C_7				
	LDA, THF, -78°	1. $(CH_2)_5CO$ 2. HCl	$R^1 + R^2 = (CH_2)_5$ (63)	117
	LDA, THF, -78°	1. p-MeOC$_6$H$_4$CHO 2. HCl	$R^1 = H, R^2 = C_6H_4OMe$-p (77)	117
	LDA, THF, -78°	1. PhCONMe$_2$ 2. H$_2$SO$_4$	(64)	117
	LDA, THF, -78°	1. $(CH_2)_5CO$ 2. HCl	$R^1 + R^2 = (CH_2)_5$ (58)	117
	LDA, THF, -78°	1. p-MeOC$_6$H$_4$CHO 2. HCl	$R^1 = H, R^2 = C_6H_4OMe$-p (50)	117
	LDA, THF, -78°	1.PhCONMe$_2$ 2.H$_2$SO$_4$	(23)	117

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, -60°, 2 h		 $R^1 = R^2 = Me$ (81) $R^1 + R^2 = CH_2$ (61)	224 224
	LDA, THF, -78°		 $R^1 = R^2 = Me$ **I** (26) **II** (9) $R^1 + R^2 = CH_2$ **I** (30) **II** (25)	224 224

240

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, -78°		(21)	222
	LDA, THF, -40°		 R = H (96) R = MeO (98)	225 119
	LDA, THF, -70°, 15 min		(78)	242
C$_8$ 	1. LTMDA, THF 2. *n*-BuLi, -78 to -45°	MeI	 **I** **II** **I:II** = 94:6 (76)	121

241

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (Continued)
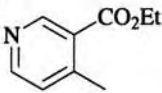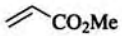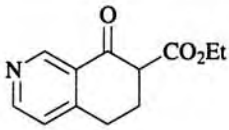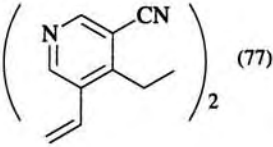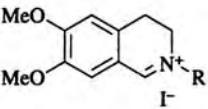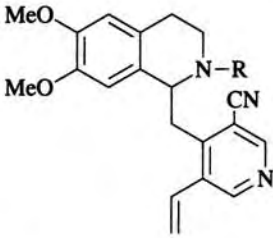
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C$_9$	LDA, THF, -78°	$CH_2=CHCO_2Me$	(58)	222
	LDA, THF, -78°, 2 h	$(PhCO_2)_2$	(77)	312
	LDA, THF, -78°			
			R	
			Me (98)	313
			$CH_2CH=CH_2$ (94)	313
			CH_2Ph (97)	313
			$CH_2C_6H_4NO_2$-o (93)	313

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (Continued)
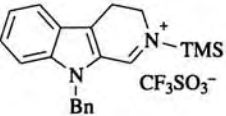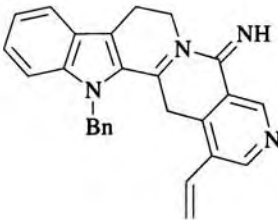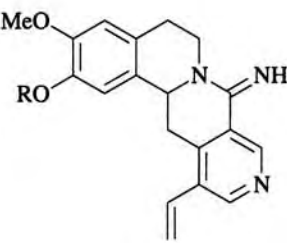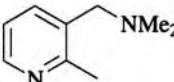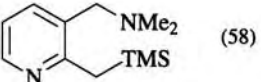
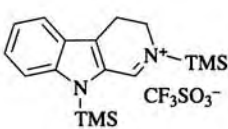| Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LHMDS, THF, -40°, 4 h			242, 314
	LHMDS, THF, -40°, 4 h		R = Me (87) R = PhCH$_2$ (98)	235, 314
	n-BuLi, THF, -78°, 2 h	TMSCl	(58)	105

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)

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

C$_{10}$

LDA, THF, -60 to -20°

R	
H (58)	225
3-MeO (84)	225
1,4-(MeO)$_2$ (41)	225
2,3-(MeO)$_2$ (65)	225
3,4-(MeO)$_2$ (39)	225
2,3-OCH$_2$O (57)	225
2,3-O(CH$_2$)$_2$O (35)	225
3-Me (57)	225
2-F (40)	225

LDA, THF, -60 to -20°

 (30) 225

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)

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

LDA, THF, -70°, 10 min

R = TMS   R = H (40)   52
R = Me   R = Me (65)   52

LDA, THF, -65°

 (97) 225

LDA, THF, -40°

 (58) 225

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)
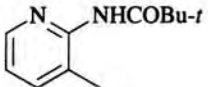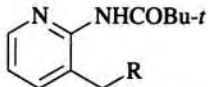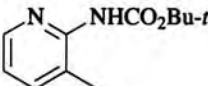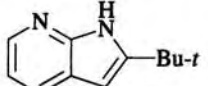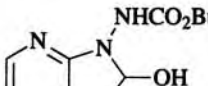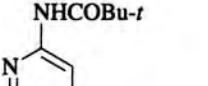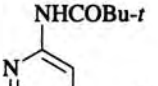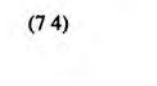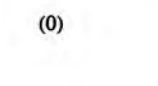
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C$_{11}$	*n*-BuLi, THF, -78° to rt			
		(MeS)$_2$	R = SMe (82)	120
		CO$_2$	R = CO$_2$H (—)	221
	n-BuLi, THF, -78° to rt	—	(83)	120
	s-BuLi, THF, -60°, 2 min	DMF	(85)	93
			+	
	n-BuLi, THF, 0°, 1h	(MeS)$_2$	(40) (51)	120
	t-BuLi, ether, -78° 3 h	(MeS)$_2$	(7 4) (0)	120

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)
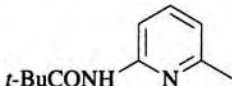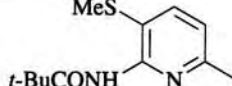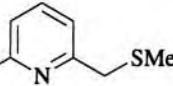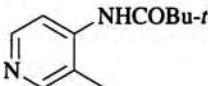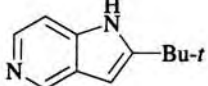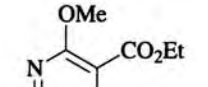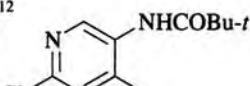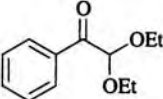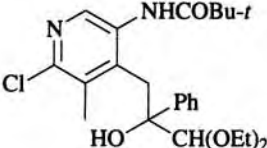
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
t-BuCONH			I + II	
	n-BuLi, THF, 0°, 1 h	(MeS)$_2$	I (59) II 27)	120
	n-BuLi, THF, 0°, 1 h	(MeS)$_2$	I (74) II (0)	120
	n-BuLi, THF, 0°, 4 h	—	(75)	120
	LDA, THF, -78°		(62)	118
C$_{12}$	*n*-BuLi, THF, -78 to 0°		(67)	223

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)
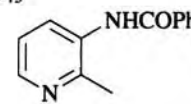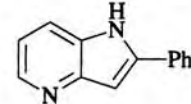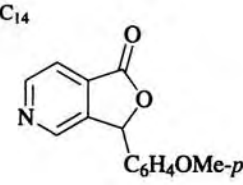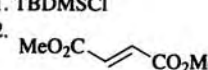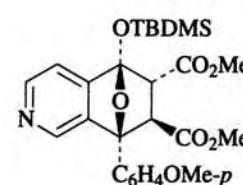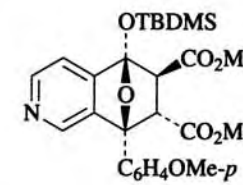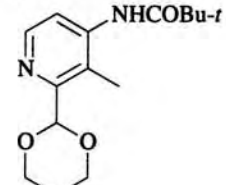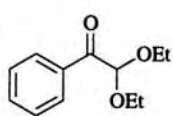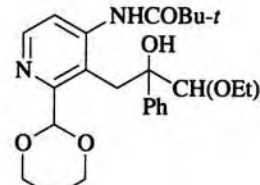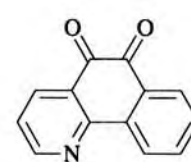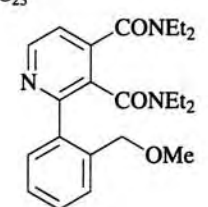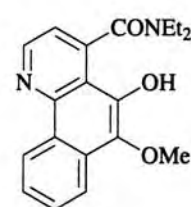
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C13	LDA, THF, -20° to rt, 16 h	—	(22)	92
C14	LDA, THF, -78 to 0°	1. TBDMSCl 2. MeO2C—CO2Me	(38) + (8)	189
C15	s-BuLi, THF, -78 to -40°		(79)	223

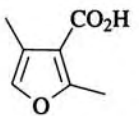248

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C17	LDA, THF, 0° to rt	1. — 2. CrO3, SiO2	(60)	182
C23	LDA, THF, 0° to rt	—	(85)	315

B. Alkylpyrroles
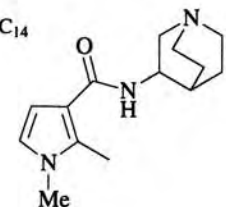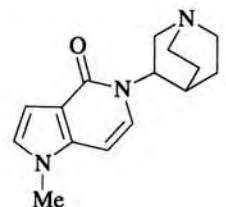
| C14 | n-BuLi, THF, -20°, 30 min | 1. DMF 2. HCl | (65) | 44 |

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TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C$_{15}$	LDA, THF, -70°, 3 min		 R^1 = OMe, R^2 = H (55) R^1, R^2 = OCH$_2$O (55)	316 48
C$_{16}$	*n*-BuLi, THF, -20°, 30 min	1. DMF 2. HCl	(30)	44
C$_{17}$	LDA, THF, -70°, 3 min		(55)	48

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C$_{20}$	*n*-BuLi, THF, -20°, 30 min	1. DMF 2. HCl	(65)	48

C. Alkylindoles

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C$_9$	1. *n*-BuLi, THF, -70°, 5 min 2. CO$_2$ 3. *t*-BuLi, THF, -70 to -20°, 45 min			
			R	
		D$_2$O	D (90)	123
		MeI	Me (52)	123
		n-BuI	Bu-*n* (58)	123
		n-C$_6$H$_{13}$I	C$_6$H$_{13}$-*n* (93)	123
		n-C$_{12}$H$_{25}$I	C$_{12}$H$_{25}$-*n* (78)	123
		n-C$_{16}$H$_{33}$I	C$_{16}$H$_{33}$-*n* (63)	123
		(CH$_2$)$_4$CO	CHOH(CH$_2$)$_4$ (58)	123
		PH$_2$CO	COHPh$_2$ (67)	123
		t-BuNCO	CONHBu-*t* (61)	123
		CO$_2$	CO$_2$H (70)	123

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	1. *n*-BuLi, THF, -70°, 15 min 2. CO_2 3. *t*-BuLi, THF, -70 to -20°, 45 min		(7)	317
	1. *n*-BuLi, THF, -70°, 15 min 2. CO_2 3. *t*-BuLi, THF, -70 to -20°, 45 min		(6) + (6)	317
C₁₀	1. *n*-BuLi, THF, -70°, 5 min 2. CO_2 3. *t*-BuLi, THF, -70 to -20°, 45 min			
		D_2O	D (88)	123
		n-C₆H₁₃I	C₆H₁₃-*n* (75)	123
		t-BuNCO	CONHBu-*t* (77)	123

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
2-ethylindole	1. *n*-BuLi, THF, -70°, 5 min 2. CO_2 3. *t*-BuLi, THF, -70 to -20°, 45 min	MeI	(95)	123
C₁₃ 2-C₅H₁₁-*n* indole	1. *n*-BuLi, THF, -70°, 5 min 2. CO_2 3. *t*-BuLi, THF, -70 to -20°, 45 min	*t*-BuNCO	(60)	123
	n-BuLi, ether, 10 to 20°, 15 min	TMSCl	(92)	183
C₁₅ 2-C₇H₁₅-*n* indole	1. *n*-BuLi, THF, -70°, 5 min 2. CO_2 3. *t*-BuLi, THF, -70 to -20°, 45 min	*t*-BuNCO	(47)	123
C₁₇	LTMP, THF, -78°, 37 min	TMSCl	(73)	183

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C$_{18}$	*n*-BuLi, THF, -20°, 30 min	1. DMF 2. HCl	(*S*)-isomer (55) (*R*)-isomer (85)	44 44
C$_{19}$	*n*-BuLi, THF, -20°, 30 min	1. DMF 2. HCl	(70)	44
C$_{20}$	*n*-BuLi, THF, -78°	MeI	(90)	318
	LDA, THF, -78°	MeO$_2$CC≡CCO$_2$Me	(53)	126

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	n-BuLi, THF, -20°, 30 min	1. DMF 2. HCl	(*S*)-isomer (70) (*R*)-isomer (85)	44 44
C$_{21}$	LDA, THF, -78°, 30 min	MeI	(47)	318
	n-BuLi, THF, -20°, 30 min	1. DMF 2. HCl	(88)	44

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TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (Continued)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, -78°, 3 h	MeO$_2$CC≡CCO$_2$Me	(57)	126
C$_{22}$	LDA, THF, -78°, 3 h	MeO$_2$CC≡CCO$_2$Me	(47)	126
C$_{23}$	LDA, THF, -78°, 3 h	MeO$_2$CC≡CCO$_2$Me	(52)	126

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (Continued)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
		D. Alkylfurans		
C$_6$	n-BuLi, THF, -20°, 1 h	1. electrophile 2. CH$_2$N$_2$		
			R	
		MeOD	D (85)	319
		EtI	Et (91)	129
		i-PrI	Pr-i (67)	129
		Cl(CH$_2$)$_3$I	(CH$_2$)$_3$Cl (82)	129
		CH$_2$=CHCH$_2$Br	CH$_2$CH=CH$_2$ (70)	129
		n-PrCHO	CHOHPr-n (79)	129
		PhCHO	CHOHPh (79)	129
		Me$_2$CO	COHMe$_2$ (84)	129
			(40)	129
C$_7$	LDA, THF, -78°, 30 min	MeI	(96)	131
	LDA, THF, -78°, 30 min		(80)	131

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)
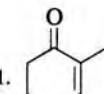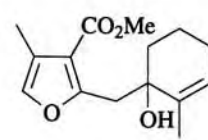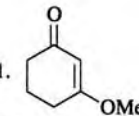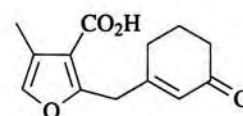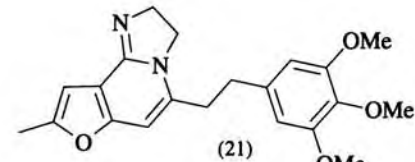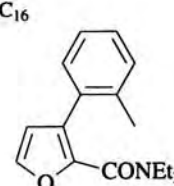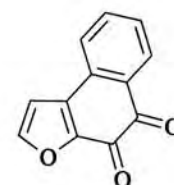
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, -78°, 30 min	1. 2. CH₂N₂	(70)	131
	LDA, THF, -78°, 30 min	1. 2. HCl	(78)	131
C₉	*n*-BuLi:TMEDA, THF, 0°, 3 h	3,4,5-(MeO)₃C₆H₂-CH₂CH₂C₆H₄CO₂Me-4	(21)	285
C₁₆	LDA, THF, 0° to rt, 3 h	1. — 2. CrO₃, H₂O, SiO₂	(50)	182

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)
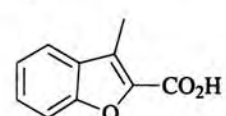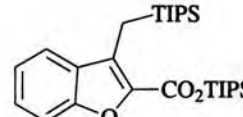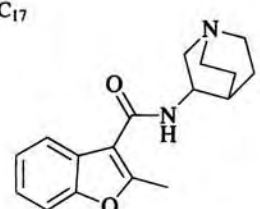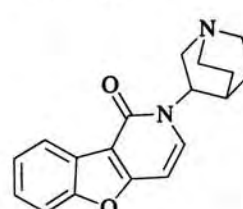
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
		E. Alkylbenzofurans		
C₁₀	LDA, THF, -10°, 30 min		**R**	
		MeI	Me (79)	134
		EtI	Et (74)	134
		TMSCl	TMS (75)	134
		n-C₆H₁₃CHO	CHOHC₆H₁₃-*n* (76)	134
		PhCHO	CHOHPh (90)	134
		PhCOMe	COH(Me)Ph (76)	134
		(epoxide)	CH₂CHOHEt (92)	134
	LDA, THF, -10°, 30 min	TIPSCl	(69)	320
C₁₇	*n*-BuLi, THF, -20°, 30 min	1. DMF 2. HCl	(10)	44

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)
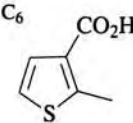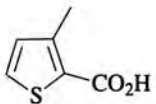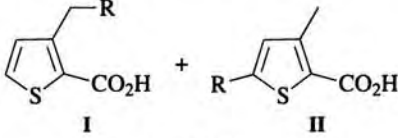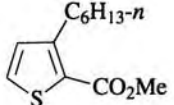
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
		F. Alkylthiophenes		

C_6

LDA, THF, -30°, 1 h

		Substrate	R	Refs.
		MeI	Me (80)	135
		n-BuBr	Bu-*n* (83)	135
		Me$_2$CHCH$_2$Br	CH$_2$CHMe$_2$ (70)	135
		PhCH$_2$Br	CH$_2$Ph (70)	135
		n-PrCHO	CHOHPr-*n* (77)	135
		Et$_2$CO	COHEt$_2$ (81)	135
		PhCHO	CHOHPh (63)	135
		PhCOMe	COH(Me)Ph (61)	135

LDA, THF, 0°, 1 h

		Substrate	Product	Refs.
		D$_2$O	R = D I:II = 74:26 (—)	136
		MeI	R = Me I:II = 65:35 (—)	136
		Me$_2$CO	R = COHMe$_2$ I:II = 62:38 (—)	136

LDA, THF, 0°, 1 h

1. *n*-C$_5$H$_{11}$Br
2. MeI, K$_2$CO$_3$, DMF

  (66) 136

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)
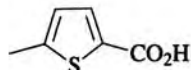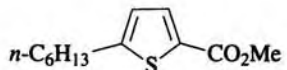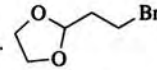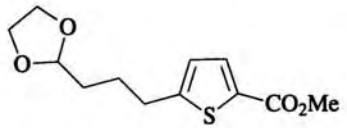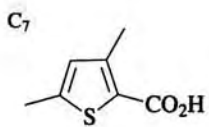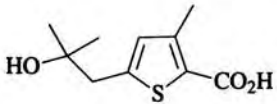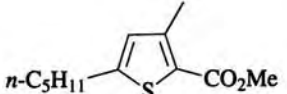
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, 0°, 1 h	1. *n*-C$_5$H$_{11}$Br 2. MeI, K$_2$CO$_3$, DMF	*n*-C$_6$H$_{13}$ — thiophene — CO$_2$Me (65)	136
	LDA, THF, 0°, 1 h	1. 2. MeI, K$_2$CO$_3$, DMF	(69)	136
	LDA, THF, 0°, 1 h	Me$_2$CO	(61)	136
C_7	LDA, THF, 0°, 1 h	Me$_2$CO	(60)	136
	LDA, THF, 0°, 1 h	1. *n*-BuBr 2. MeI, K$_2$CO$_3$, DMF	*n*-C$_5$H$_{11}$ — thiophene — CO$_2$Me (72)	136

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C₈	*n*-BuLi:TMEDA, THF, 0°, 3 h	1. 3,4,5-(MeO)₃C₆H₂-CH₂CH₂C₆H₄CO₂Me-4 2. TsOH, C₆H₆, reflux	(23)	285
C₁₀	*s*-BuLi, THF, -78°, 30 min	TMSCl	(84)	321
C₁₅	LDA, THF, 0° to rt, 3 h	1. — 2. O₂, salcomine, DMF	(74)	182
C₁₆	LDA, THF, 0° to rt, 3 h	1. — 2. CrO₃, H₂O, SiO₂	(55)	182

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, 0° to rt, 3 h	1. — 2. O₂, salcomine, DMF	(67)	182
C₁₆	*s*-BuLi, THF, -78°, 30 min	TMSCl	(93)	321

G. Alkylbenzothiophenes

C₁₇	*n*-BuLi, THF, -20°, 30 min	1. DMF 2. HCl	(20)	44

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)
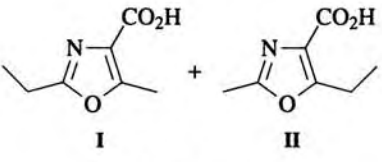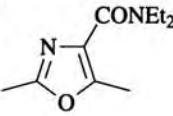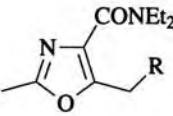
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.

H. Alkyloxazoles

C_6

| | n-BuLi, THF, -78°, 15 min | MeI | **I:II = 30:70 (71)** | 137 |

C_{10}

| | n-BuLi, THF, -78°, 30 min | | | |

			R	
		MeI	Me (98)	137
		EtI	Et (91)	137
		$CH_2=CHCH_2Br$	$CH_2CH=CH_2$ (90)	137
		PhCHO	CHOHPh (98)	137
		n-PrCHO	CHOHPr-n (15)	137

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)
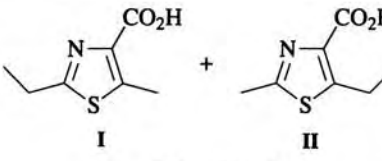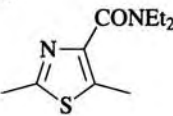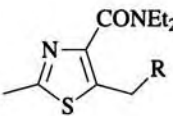
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.

I. Alkylthiazoles

C_6

| | LDA, THF, -78°, 30 min | MeI | **I:II = 59:41 (86)** | 137 |
| | n-BuLi, THF, -78°, 15 min | MeI | **I:II = 46:54 (—)** | 137 |

C_{10}

| | n-BuLi, THF, -78°, 25 min | | | |

			R	
		MeI	Me (97)	137
		EtI	Et (98)	137
		$CH_2=CHCH_2Br$	$CH_2CH=CH_2$ (96)	137
		PhCHO	CHOHPh (89)	137
		PhCOMe	C(Me)OHPh (92)	137

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)
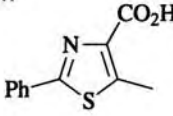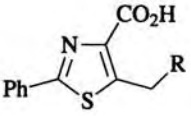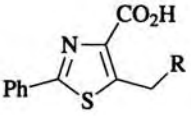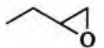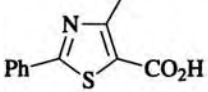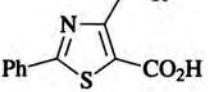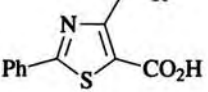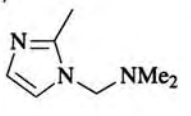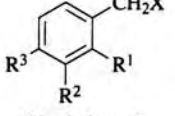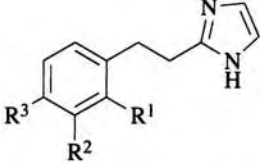
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C₁₁ 2-Ph-5-methyl-thiazole-4-carboxylic acid	LDA, THF, -78°, 30 min		2-Ph-5-(CH₂R)-thiazole-4-carboxylic acid	
			R	
		MeI	Me (86)	137
		CH₂=CHCH₂Br	CH₂CH=CH₂ (75)	137
		(epoxide)	CH₂CHOHEt (60)	137
	LDA, THF, -30°, 30 min	PhCOMe	C(Me)OHPh (51)	322
2-Ph-4-methyl-thiazole-5-carboxylic acid	LDA, THF, -30°, 5 min		2-Ph-4-(CH₂R)-thiazole-5-carboxylic acid	
			R	
		CH₂=CHCH₂Br	CH₂CH=CH₂ (84)	137
		PhCOMe	C(Me)OHPh (50)	137
		(epoxide)	CH₂CHOHEt (66)	137
	LDA, THF, -25 to -18°, 15 min	MeI	Me (89)	137

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)

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

J. Alkylimidazoles

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C₇ 2-methyl-1-(CH₂NMe₂)imidazole	n-BuLi, THF, -78°, 10 min	1. benzyl halide (X = halogen) with R¹, R², R³ substituents; 2. NaBH₄, EtOH	imidazole product with R¹, R², R³	

R¹	R²	R³	
H	H	H (59)	138
Br	H	H (57)	138
H	H	Br (60)	138
H	H	Cl (61)	138
Cl	H	Cl (50)	138
F	F	H (63)	138
H	H	MeO (57)	138
H	MeO	MeO (62)	138

K. Alkylbenzimidazoles
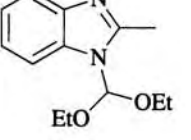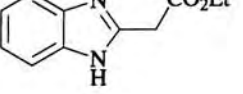
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C₁₃ 2-methyl-1-[CH(OEt)₂]benzimidazole	LDA, THF, -78°, 30 min	(EtO)₂CO	2-(CH₂CO₂Et)benzimidazole (63)	139

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)
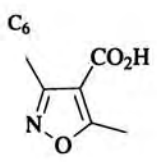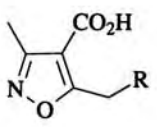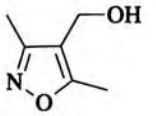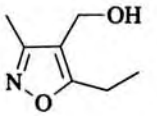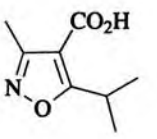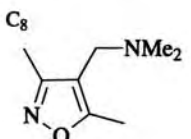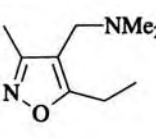
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.

L. Alkylisoxazoles

C$_6$

	n-BuLi, THF, -78°, 2 h			
			R	
		D$_2$O	D (83)	142
		MeI	Me (91)	142
		PhCH$_2$Br	CH$_2$Ph (88)	142
		n-C$_8$H$_{17}$Br	C$_8$H$_{17}$-*n* (69)	142

| | *n*-BuLi, THF, -70°, 1 h | MeI | (65) | 141 |

C$_7$

| | *n*-BuLi, THF, -70°, 1 h | MeI | (92) | 142 |

C$_8$

| | *n*-BuLi, THF, -70°, 1 h | MeI | (90) | 141 |

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)
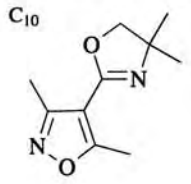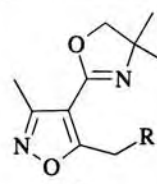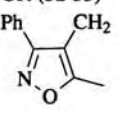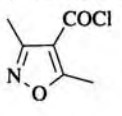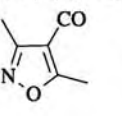
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.

C$_{10}$

	n-BuLi, THF, -78°, 2 h			
			R	
		MeOD	D (82-89)	142
		MeI	Me (78-86)	142
		PhCH$_2$Br	CH$_2$Ph (91)	142
		PhCHO	COHPh (97)	142
		n-C$_8$H$_{17}$Br	C$_8$H$_{17}$-*n* (82)	142
		t-BuPh$_2$SiCl	SiPh$_2$Bu-*t* (34)	323
		(PhS)$_2$	SPh (50)	165
		[(2-C$_5$H$_4$N)S]$_2$	S(C$_5$H$_4$N-2) (55)	165
		EtO$_2$CN=NCO$_2$Et	N(CO$_2$Et)NHCO$_2$Et (75)	161
		MoOPH	OH (32-53)	142
			(72)	142
	n-BuLi, CeCl$_3$, THF, -78°, 1 h	PhCOCl	COPh (70)	324
		(2-C$_4$H$_3$O)COCl	CO(C$_4$H$_3$O-2) (65)	324
			(53)	324

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)
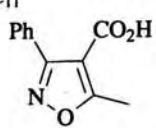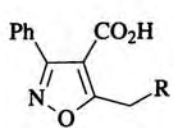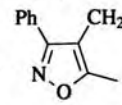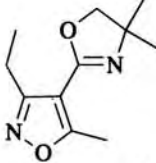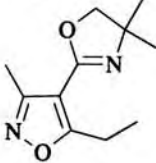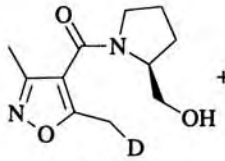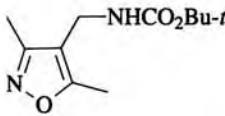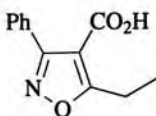
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C$_{11}$				
	n-BuLi, THF, -78°, 2 h			
		MeOD	R = D (99)	142
		MeI	R = Me (81)	142
			R = (53)	142
	n-BuLi, THF, -78°, 2 h	MeI	(74)	142
	n-BuLi, THF, -78°, 2 h	MeI	(73)	142
	n-BuLi, THF, -78°, 2 h	EtO$_2$CN=NCO$_2$Et	(78) N(CO$_2$Et)NHCO$_2$Et	161

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
			I + **II**	
	n-BuLi, THF, -78°, 2 h (added to amide)	MeOD	I:II = >95:<5 (—)	144
	n-BuLi:TMEDA, THF, -78°, 2 h (amide added to base)	MeOD	I:II = >95:<5 (—)	144
	n-BuLi, THF, -78°, 2 h	(PhS)$_2$	(66)	165
	n-BuLi, THF, -70°, 1 h	MeI	(85)	141
C$_{12}$				
	n-BuLi, THF, -78°, 2 h	MeI	(89)	142

270

271

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)
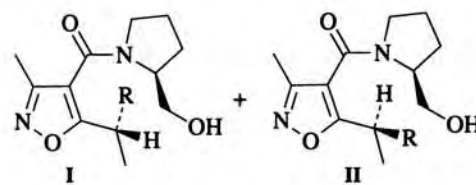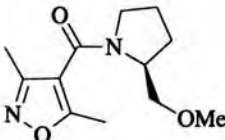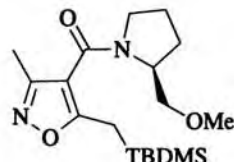
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	n-BuLi:TMEDA, THF, -78°, 2 h			
		n-BuBr	R = Bu-n (42) I:II = 13:87	162
		(PhS)$_2$	R = SPh (54) I:II = 39:61	162
		EtO$_2$CN=NCO$_2$Et	R = N(CO$_2$Et)NHCO$_2$Et I:II = 38:62	162
	n-BuLi, THF, -78°, 2 h (added to amide)	MeOD	I:II = >95:<5 (—)	144
	n-BuLi:TMEDA, THF, -78°, 1 h (amide added to base)	MeOD	I:II = 7:93 (—)	144
	n-BuLi, THF, -78°, 2 h	TBDMSCl	(32)	323

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)
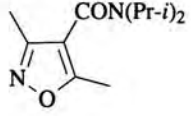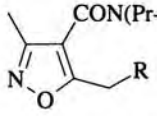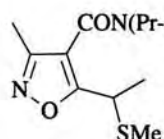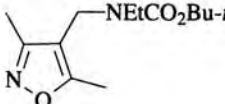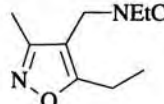
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
CON(Pr-*i*)$_2$	n-BuLi, THF, -40°, 1.5 h		CON(Pr-*i*)$_2$ R	
			R	
		MeOD	D (86)	143
		MeI	Me (55)	143
		p-BrC$_6$H$_4$CHO	CHOHC$_6$H$_4$Br-p (43)	143
		p-CNC$_6$H$_4$CHO	CHOHC$_6$H$_4$CN-p (48)	143
		o-O$_2$NC$_6$H$_4$CHO	CHOHC$_6$H$_4$NO$_2$-o (37)	143
		(2-C$_4$H$_3$O)CHO	CHOH(C$_4$H$_3$O-2) (70)	143
		(3-C$_5$H$_4$N)CHO	CHOH(C$_5$H$_4$N-3) (62)	143
	n-BuLi, THF, -78°, 2 h	(PhS)$_2$	SPh (65)	165
		EtO$_2$CN=NCO$_2$Et	N(CO$_2$Et)NHCO$_2$Et (96)	161
		t-BuO$_2$CN=NCO$_2$Bu-t	N(CO$_2$Bu-t)NHCO$_2$Bu-t (81)	161
	n-BuLi, CeCl$_3$, THF, -78°, 1 h	PhCOCl	COPh (50)	324
C$_{13}$ CON(Pr-*i*)$_2$	n-BuLi, THF, -78°, 2 h	(MeS)$_2$	CON(Pr-*i*)$_2$ (82) SMe	165
—NEtCO$_2$Bu-*t*	n-BuLi, THF, -70°, 1 h	MeI	—NEtCO$_2$Bu-*t* (86)	141

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)
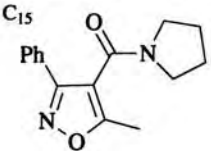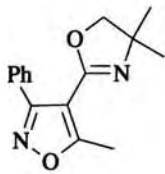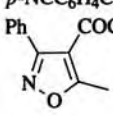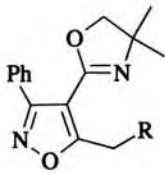
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C₁₅	n-BuLi, THF, -40°, 1.5 h			
		MeOD	R = D (90)	143
		MeI	R = Me (66)	143
		p-BrC₆H₄CHO	R = CHOHC₆H₄Br-p (48)	143
	n-BuLi, THF, -40°, 1.5 h			
		MeOD	R = D (91)	143
		MeI	R = Me (72)	143
		p-BrC₆H₄CHO	R = CHOHC₆H₄Br-p (60)	143
	n-BuLi, CeCl₃, THF, -78°, 2 h			
		PhCOCl	R = COPh (67)	324
		p-NCC₆H₄COCl	R = COC₆H₄CN-p (60)	324
			(61)	324

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)
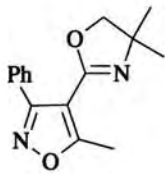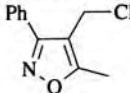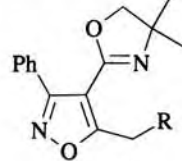
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	n-BuLi, THF, -78°, 2 h			
			R	
		MeOD	D (72)	142
		MeI	Me (86-92)	142
		o-BrC₆H₄CH₂Br	CH₂C₆H₄Br-o (98)	142
		Me₃SiCl	SiMe₃ (73)	142
		2,6-Cl₂C₆H₃CH₂Cl	CH₂C₆H₃Cl₂-2,6 (89)	142
		Cl(CH₂)₃Br	(CH₂)₃Cl	142
		PhCHO	CHOHPh (81)	142
		o-ClC₆H₄CHO	CHOHC₆H₄Cl-o (50)	142
		2,5-(MeO)₂C₆H₃CHO	CHOHC₆H₃(OMe)₂-2,5 (77)	142
		p-NCC₆H₄CHO	CHOHC₆H₄CN-p (40)	142
		p-BrC₆H₄CHO	CHOHC₆H₄Br-p (66)	142
		o-O₂NC₆H₄CHO	CHOHC₆H₄NO₂-o (50)	142
		(3-C₅H₄N)CHO	CHOH(C₅H₄N-3) (66)	142
		EtO₂CN=NCO₂Et	N(CO₂Et)NHCO₂Et (80)	161
		(MeS)₂	SMe (60-65)	165
		(PhS)₂	SPh (55-60)	165
		TBDMSCl	TBDMS (78)	323
			(67)	142

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	n-BuLi, THF, -78°, 2 h	(PhS)$_2$	(60) + (10)	165
	n-BuLi, THF, -78°, 2 h	EtO$_2$CN=NCO$_2$Et	N(CO$_2$Et)NHCO$_2$Et (74)	161
C$_{16}$	*n*-BuLi, THF, -78°, 2 h			
		MeOD	R = D (97)	142
		MeI	R = Me (93)	142
		PhCH$_2$Br	R = CH$_2$Ph (74)	142

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)		Refs.
	n-BuLi, THF, -78°; 2 h		I + II		
			R	I:II	
		PhCH$_2$Br	CH$_2$Ph (66)	27:73	162
		n-PrI	Pr-*n* (—)	34:66	162
		n-BuI	Bu-*n* (—)	23:77	162
		MeOCH$_2$Cl	CH$_2$OMe (85)	25:75	162
		PhCOCl	COPh (—)	53:47	162
		NPSPO	OH (63)	40:60	162
		EtO$_2$CN=NCO$_2$Et	N(CO$_2$Et)NHCO$_2$Et (66)	30:70	162
		(PhS)$_2$	SPh (62)	47:53	162
		[(2-C$_5$H$_4$N)S]$_2$	S(C$_5$H$_4$N-2) (63)	44:56	162
C$_{17}$	*n*-BuLi, THF, -78°, 2 h	MeI	(70)	142
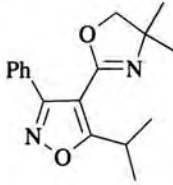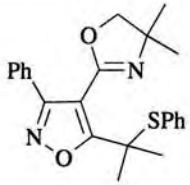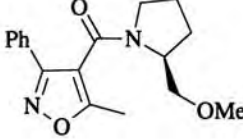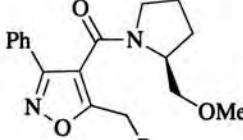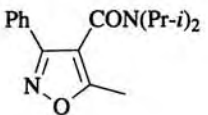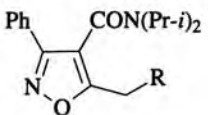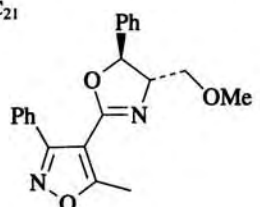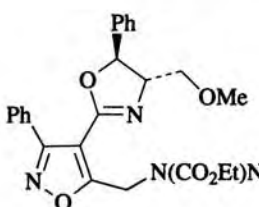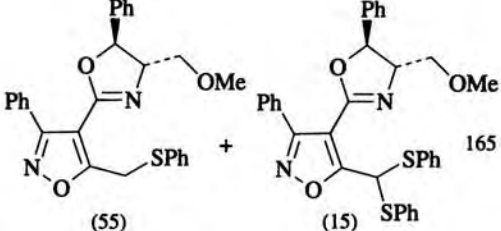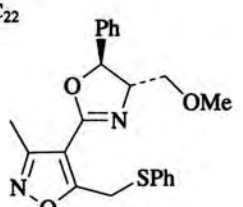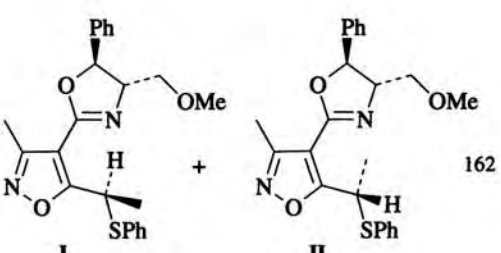
TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
(Ph, isopropyl isoxazole oxazoline structure)	n-BuLi, THF, -78°, 2 h	(PhS)$_2$	(SPh product structure) (73)	165
(Ph, methyl isoxazole pyrrolidine amide structure)	n-BuLi, THF, -40°, 1.5 h		(product structure with CH$_2$R)	
		MeOD	R = D (97)	143
		PhCH$_2$Br	R = CH$_2$Ph (56)	143
Ph CON(Pr-i)$_2$ isoxazole methyl structure	n-BuLi, THF, -40°, 1.5 h		Ph CON(Pr-i)$_2$ isoxazole CH$_2$R structure	
		MeOD	R = D (88)	143
		MeI	R = Me (70)	143
		p-BrC$_6$H$_4$CHO	R = CHOHC$_6$H$_4$Br-p (40)	143
	n-BuLi, THF, -78°, 2 h	TBDMSCl	R = TBDMS (41)	323

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C$_{21}$ (Ph oxazoline OMe, Ph isoxazole methyl structure)	n-BuLi, THF, -78°, 2 h	EtO$_2$CN=NCO$_2$Et	(product with N(CO$_2$Et)NHCO$_2$Et) (95)	161
(Ph oxazoline OMe, Ph isoxazole methyl structure)	n-BuLi, THF, -78°, 2 h	(PhS)$_2$	(mono-SPh product) (55) + (bis-SPh product) (15)	165
C$_{22}$ (Ph oxazoline OMe, methyl isoxazole CH$_2$SPh structure)	n-BuLi, THF, -78°, 2 h	MeI	**I** (diastereomer) + **II** (diastereomer); **I:II** = 59:41 (19)	162

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)
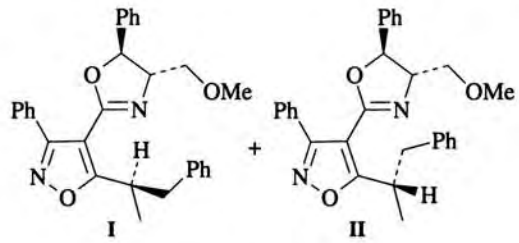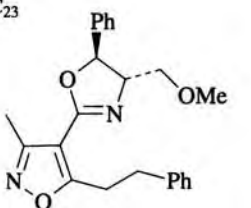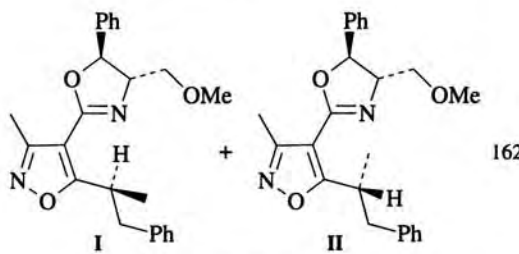
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	n-BuLi, THF, -78°, 2 h	PhCH₂Br		

			R	I:II	
		PhCH₂Br	CH₂Ph (—)	33:67	162
		n-BuBr	Bu-*n* (65)	39:61	162
		MeOCH₂Cl	CH₂OMe (85)	37:63	162
		PhCOCl	COPh (—)	53:47	162
		NPSPO	OH (82)	56:44	162
		EtO₂CN=NCO₂Et	N(CO₂Et)NHCO₂Et (81)	46:54	162

C₂₃

n-BuLi, THF, -78°, 2 h   MeI

I:II = 63:37 (66)   162

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)
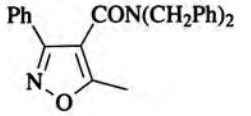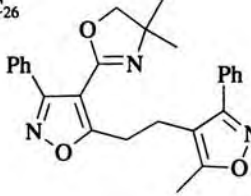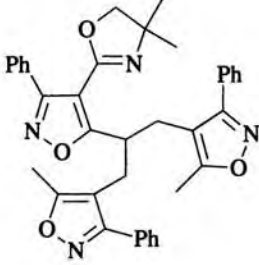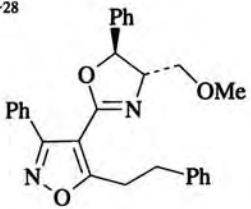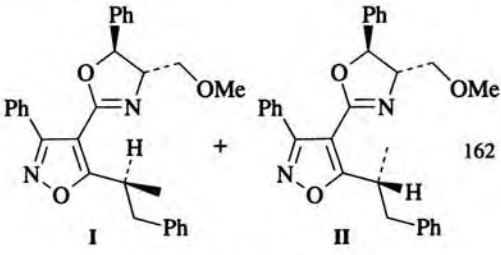
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C₂₅ 				
	n-BuLi, THF, -78°, 2 h	TBDMSCl	R = TBDMS(63)	323
	n-BuLi, THF, -40°, 1.5 h	MeI	R = Me (62)	143
C₂₆ 	*n*-BuLi, THF, -78°, 2 h		(89)	142
C₂₈ 	*n*-BuLi, THF, -78°, 2 h	MeI	 I:II = 63:37 (94)	162

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)
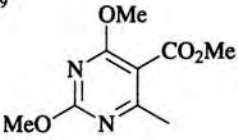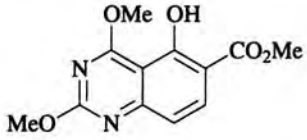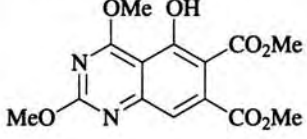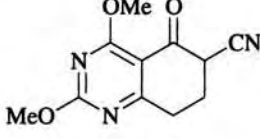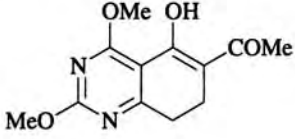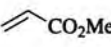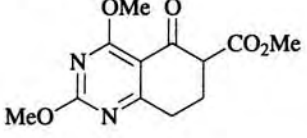
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C_9 (OMe, CO$_2$Me, MeO, methyl substituted pyrimidine)		*M. Alkylpyrimidines*		
	LDA, ether, -70°, 10 min	$HC{\equiv}CCO_2Me$	(structure) (24)	325
	LDA, ether, -70°, 10 min	$MeO_2CC{\equiv}CCO_2Me$	(structure) (38)	325
	LDA, ether, -70°, 10 min	(CH$_2$=CH)CN	(structure) (29)	325
	LDA, ether, -70°, 10 min	(CH$_2$=CH)COMe	(structure) (30)	325
	LDA, ether, -70°, 10 min	(CH$_2$=CH)CO$_2$Me	(structure) (55)	325
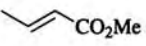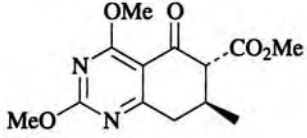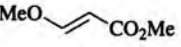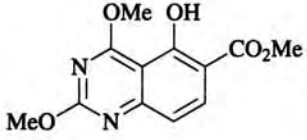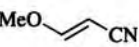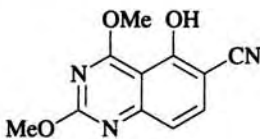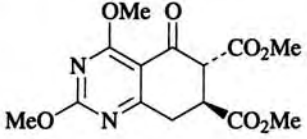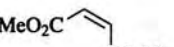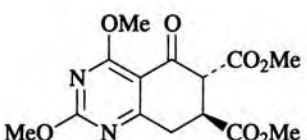
TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, ether, -70°, 10 min	$\text{CH}_3\text{CH=CH–CO}_2\text{Me}$	(structure) (47)	325
	LDA, ether, -70°, 10 min	MeO–CH=CH–CO_2Me	(structure) (37)	325
	LDA, ether, -70°, 10 min	MeO–CH=CH–CN	(structure) (28)	325
	LDA, ether, -70°, 10 min	MeO_2C–CH=CH–CO_2Me	(structure) (14)	325
	LDA, ether, -70°, 10 min	MeO_2C–CH=CH–CO_2Me	(structure) (12)	325

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)
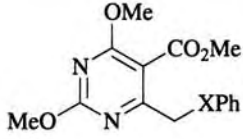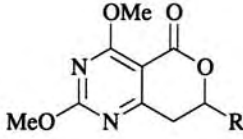
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, ether, -70°, 15 min	(PhX)$_2$		
			X = S (62)	326
			X = Se (52)	326
	LDA, ether, -70°, 15 min	RCHO		

R		
Pr-*n* (85)		326
Pr-*i* (74)		326
Ph (82)		145
C$_6$H$_4$NO$_2$-*o* (76)		145
C$_6$H$_4$OMe-*o* (62)		145
C$_6$H$_4$OMe-*m* (50)		145
C$_6$H$_4$OMe-*p* (69)		145
C$_6$H$_4$NMe$_2$-*p* (58)		145

TABLE X. ALKYL-SUBSTITUTED HETEROCYCLES (*Continued*)
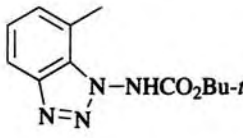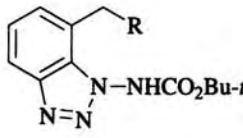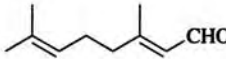
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.

N. Alkylbenzotriazoles

C$_{12}$

 | *n*-BuLi:TMEDA, -78 to 0°, 30 min | | |

		Substrate	R	Refs.
		MeI	Me (95)	146
		EtI	Et (90)	146
		CH$_2$=CHCH$_2$Br	CH$_2$CH=CH$_2$ (85)	146
		n-C$_5$H$_{11}$CHO	CHOHC$_5$H$_{11}$-*n* (55)	146
		PhCHO	CHOHPh (85)	146
		(2-C$_4$H$_3$O)CHO	CHOH(C$_4$H$_5$O-2) (81)	146
		Me$_2$CO	COHMe$_2$ (70)	146
		(CH$_2$)$_5$CO	CHOH(CH$_2$)$_5$ (62)	146
			(53)	146

TABLE XI. LATERAL LITHIATIONS IN NATURAL PRODUCT SYNTHESIS
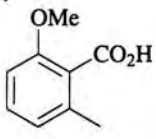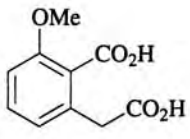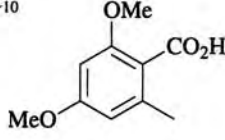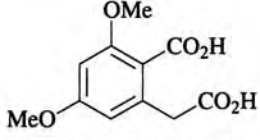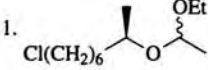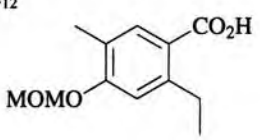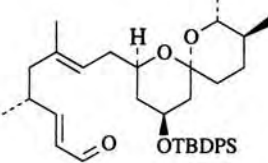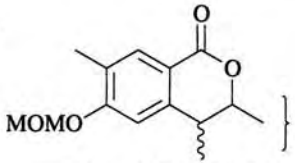
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.

A. From o-Toluic Acids

C₉

| | LDA, THF, -78° to rt | (MeO)₂CO | (90) | 190, 256 |

[β-Sorigenin]

C₁₀

| | LDA, THF, -78° to rt | (MeO)₂CO | (76) | 190 |

[α-Sorigenin]

| | LDA, THF, -15 to -10°, 3 h | 1. $Cl(CH_2)_6$ ... OEt 2. HCl | (34) | 327 |

[(R)-Lasiodiplodin]

C₁₂

| | 1. NaH, THF 2. t-BuLi, -78°, 1 h | | (74) | 33 |

[Milbemycin β₃]

TABLE XI. LATERAL LITHIATIONS IN NATURAL PRODUCT SYNTHESIS (*Continued*)
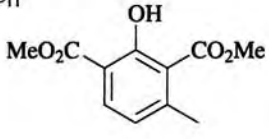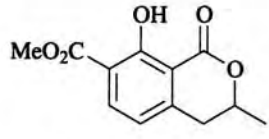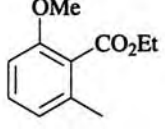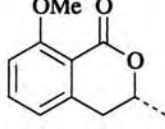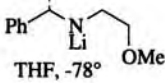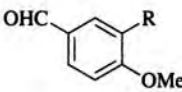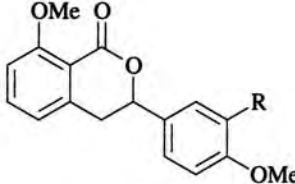
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.

B. From o-Toluate Esters

C₁₁

| | LDA, THF, HMPA, -78° | MeCHO | (69) | 36 |

[Ochratoxin A]

Mellein methyl ether

	Ph—N(Li)—iPr, THF, -78°	MeCHO	10% ee (78)	196
	Ph—N(Li)—CH₂CH₂OMe, THF, -78°	MeCHO	49-53% ee (41-51)	196
	LDA, THF, -78°, 2 h	OHC—C₆H₃(R)(OMe)		328

R = H (55) [Hydrangenol] — 328
R = OBn (50) [Phyllodulcin] — 328

TABLE XI. LATERAL LITHIATIONS IN NATURAL PRODUCT SYNTHESIS (*Continued*)
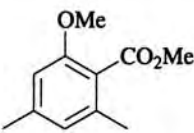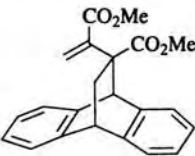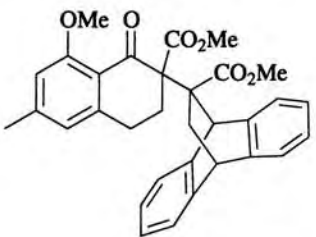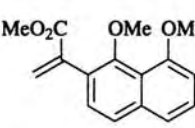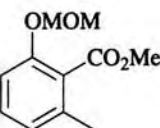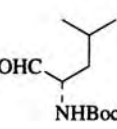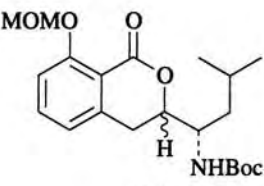
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, -78° to rt		(80) [Diospyrol]	329
	LDA, THF, -78° to rt		(74) [Diospyrol]	329
	LDA, TMEDA, THF, -78°		αH:βH = 19:81 (32) [AI-77-B]	198

TABLE XI. LATERAL LITHIATIONS IN NATURAL PRODUCT SYNTHESIS (*Continued*)
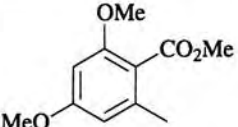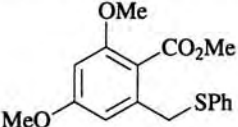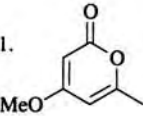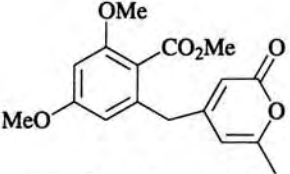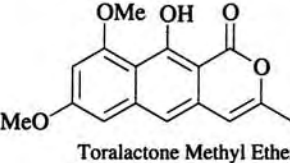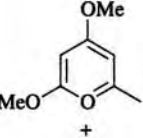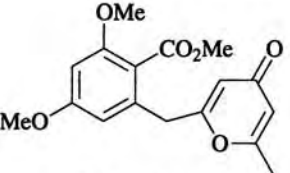
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, -78°	(PhS)₂	[(−)-Zearalenone] (60)	330
			[(R)-(+)-Lasiodiplodin] (84)	331
	LDA, THF, -78°	1. / 2. HCl	(40) [Toralactone Methyl Ether]	154
	LDA, THF, -78° to rt		(—) Toralactone Methyl Ether	154
	LDA, THF, -78°	FSO₃⁻ +	(25-35) [Alternariol]	332, 333

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TABLE XI. LATERAL LITHIATIONS IN NATURAL PRODUCT SYNTHESIS (*Continued*)
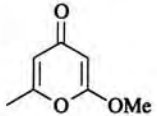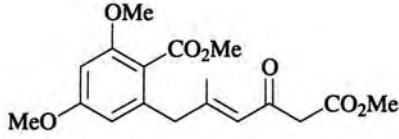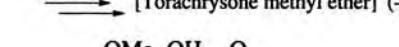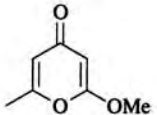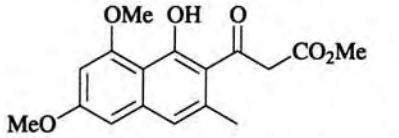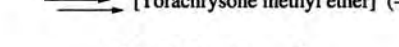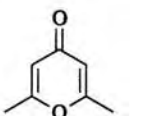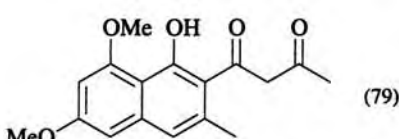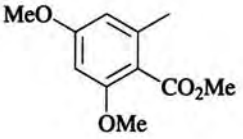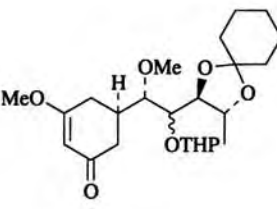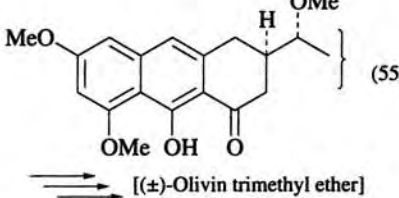
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, -78°		[Torachrysone methyl ether] (—)	155
	LDA, THF, -78° to rt		[Torachrysone methyl ether] (—)	155
	LDA THF, -78° to rt		[Eleutherinol dimethyl ether] (79)	155
	LDA, THF, -78°		[(±)-Olivin trimethyl ether] (55)	227

TABLE XI. LATERAL LITHIATIONS IN NATURAL PRODUCT SYNTHESIS (*Continued*)
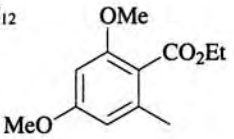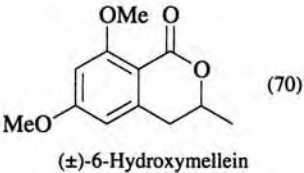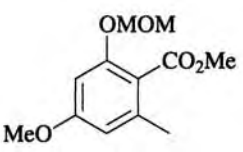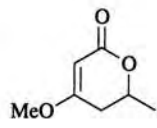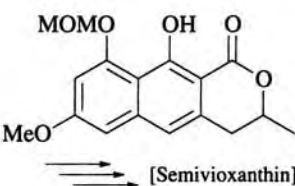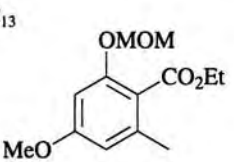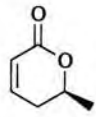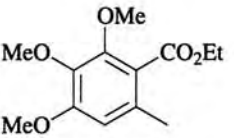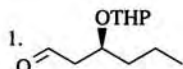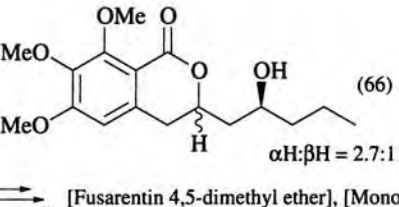
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C_{12}	LDA, THF, -78°, 15 min	MeCHO	(±)-6-Hydroxymellein (70)	197, 334
	LDA, THF, -78°		[Semivioxanthin] (68)	179
C_{13}	LDA, THF, -78°, 10 min		[Phleichrome], [Calphostin A and D] (70)	151
	LDA, pentane, THF, -78°	1. 2. TFA	αH:βH = 2.7:1 (66) [Fusarentin 4,5-dimethyl ether], [Monocerin]	269

TABLE XI. LATERAL LITHIATIONS IN NATURAL PRODUCT SYNTHESIS (*Continued*)
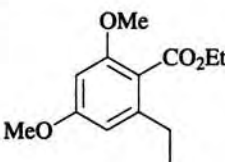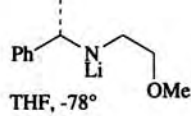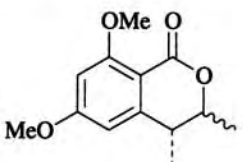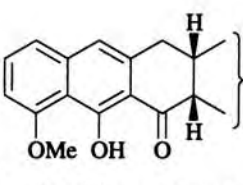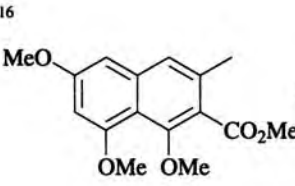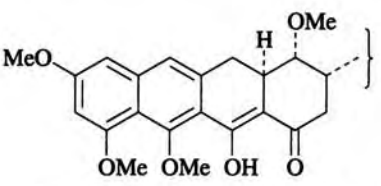
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	THF, -78°	MeCHO	(51) α–Me:β–Me = 3:1 α–Me 70% ee ⟶ β–Me 74% ee [(+)-Citrinin]	199
C$_{15}$	LDA, CeCl$_3$, THF, -78°		(62) [(±)-Pillaromycinone nucleus intermediate]	335
C$_{16}$	LDA, THF, DMPU, -78°		(150) ⟶ [Oliv in trimethyl ether (—) (natural enantiomer)]	150
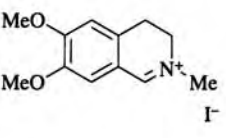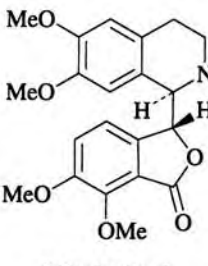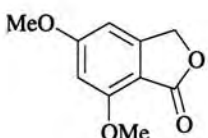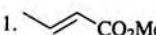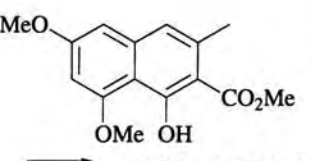
TABLE XI. LATERAL LITHIATIONS IN NATURAL PRODUCT SYNTHESIS (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C$_{10}$		*C. From Phthalides*	I Cordrastine I + II Cordrastine II	
	LDA, THF, -70°, 30 min		I (26) II (19)	273
	LDA, ether, -78°, 20 min		I:II = 1.4 : 1 (22)	274
	LDA, THF, -78° to rt	1. ⟍⟋CO$_2$Me 2. oxidation	(52) ⟶ [Olivin trimethyl ether]	150

TABLE XI. LATERAL LITHIATIONS IN NATURAL PRODUCT SYNTHESIS (*Continued*)
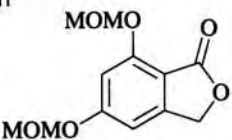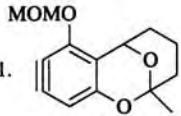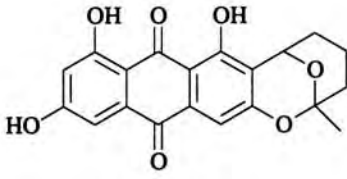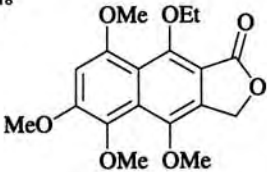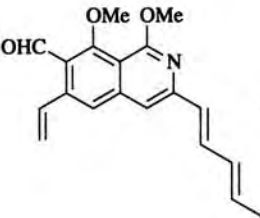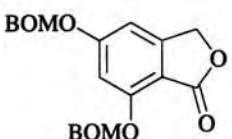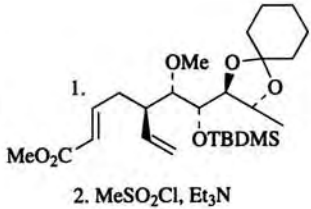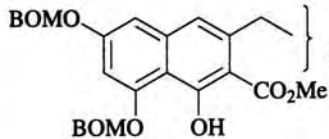
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C$_{11}$	LTMP, THF, -60°, 20 min	1. 2. HOAc	(28) (±)-Averufin	277
C$_{18}$	LDA, THF, HMPA, -78°, 3h		(54) ⟶ [(±)-Fredicamycin A)]	232
C$_{22}$	LDA, THF, -40°, 10 min	1. 2. MeSO$_2$Cl, Et$_3$N	(30-35) ⟶ [(+)-Olivin]	228

TABLE XI. LATERAL LITHIATIONS IN NATURAL PRODUCT SYNTHESIS (*Continued*)
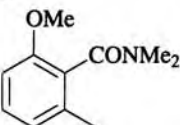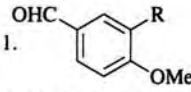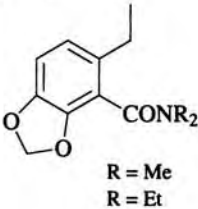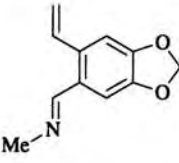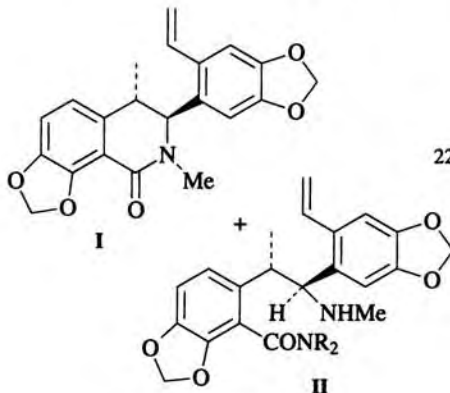
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
		D. From o-Toluamides		
C$_{11}$	s-BuLi:TMEDA, THF, -78°, 1 h	1. 2. NaOH, EtOH	R = H (35) [Hydrangenol] R = OBn (32) [Phyllodulcin]	51
C$_{12}$, C$_{14}$ R = Me R = Et	LDA, THF, -78°, 10 min		I + II R = Me I (30) II (35) R = Et I (50) II (28) ⟶ [(±)-Corydalic acid methyl ester]	226

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TABLE XI. LATERAL LITHIATIONS IN NATURAL PRODUCT SYNTHESIS (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C$_{13}$	*n*-BuLi, THF, -78°, 5 min	EtI	(74) [(+)-Perhydro-219A]	174
C$_{14}$	LDA, THF, -78°, 1 h	*p*-MeOC$_6$H$_4$CH$_2$Cl	(76) [Lunularic acid]	54
	LDA, THF, -78°		(80) [WS-5995A]	181
	s-BuLi, THF, -78°, 30 min	CO$_2$	(47) [(±)-Cordrastine I and II]	191

TABLE XI. LATERAL LITHIATIONS IN NATURAL PRODUCT SYNTHESIS (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, -70 to -45°, 2 h	1. 2.	[Oxynitidine] (68)	233
C$_{16}$	*s*-BuLi, THF, -78°		(95) [(+)-Tetrabenzyllycoricidine]	30
C$_{18}$	*n*-BuLi, THF, 0°	DMF	(72) [(±)-Latifine dimethyl ether]	336

TABLE XI. LATERAL LITHIATIONS IN NATURAL PRODUCT SYNTHESIS (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C$_{21}$	LDA, THF, 0° to rt, 3 h	1. — 2. FeCl$_3$	(50) β-Lapachone	182
C$_{23}$	LDA, THF, 0° to rt, 3 h	—	(78) [Gymnopusin]	337
C$_{11}$	*n*-BuLi, THF, -78°, 30 min	*E. From Tolyloxazolines* 1. 2. silica, CH$_2$Cl$_2$	(45) βH:αH 85:15 [AI-77-B]	338

TABLE XI. LATERAL LITHIATIONS IN NATURAL PRODUCT SYNTHESIS (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
		F. From o-Cresol Tetraalkylphosphorodiamidates		
C$_{15}$	*s*-BuLi, THF, -105°, 1h	MeI	(96) [Carinitrin]	87
	s-BuLi, THF, -105°, 1h	MeI	(99) [Eupomatenoid-1 and 13]	87
C$_{16}$	*s*-BuLi:TMEDA, THF, -105°, 1 h	3,4-(MeO)$_2$C$_6$H$_3$CHO	 X = H, OH *threo* (55) : *erythro* (16) [Carinatol and (±)-Dihydrocarinitin]	201
		3,4-(MeO)$_2$C$_6$H$_3$CO$_2$Me	X = O (44) [Carinitin]	87

TABLE XI. LATERAL LITHIATIONS IN NATURAL PRODUCT SYNTHESIS (*Continued*)
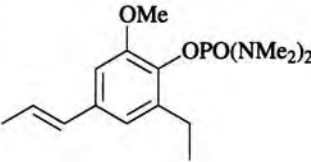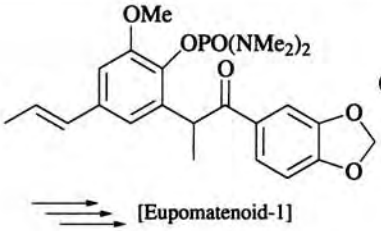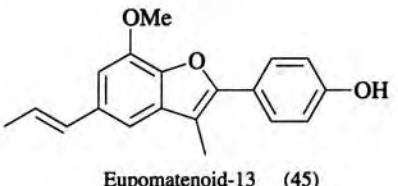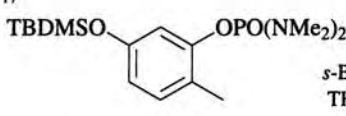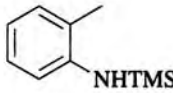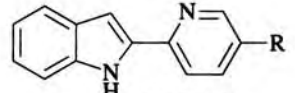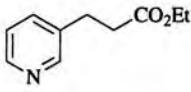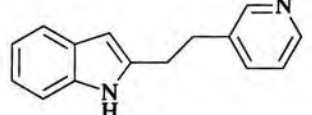
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	s-BuLi:TMEDA, THF, -105°, 1h	3,4-(OCH₂O)C₆H₃CO₂Me	(56) [Eupomatenoid-1]	87
	s-BuLi:TMEDA, THF, -105°, 1h	3,4-(OCH₂O)C₆H₃CHO	X = Y = OCH₂O *threo* (70) : *erythro* (11) [(±)-Licarin B]	201
		p-TBDMSOC₆H₄CHO	X = H, Y = OTBDMS *threo* (56) : *erythro* (8) [Neolignan from *Krameria cystisoides*]	201
	s-BuLi:TMEDA, THF, -105°, 1h	1. *p*-TBDMSOC₆H₄CO₂Me 2. HCO₂H	Eupomatenoid-13 (45)	87

TABLE XI. LATERAL LITHIATIONS IN NATURAL PRODUCT SYNTHESIS (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C₁₇	s-BuLi:TMEDA, THF, -105°, 1h			
		2-MeO-4-BnOC₆H₃CO₂Me	R = C₆H₃OMe-2-OTBDMS-4 (75) [Vignafuran] [6-Demethylvignafuran]	173
		3,5-(TBDMSO)₂C₆H₃CO₂Me	R = C₆H₃(OTBDMS)₂-3,5 (57) [Moracin M]	173
		G. From o-Toluidine Derivatives		
C₁₀	*n*-BuLi, hexanes, reflux, 6 h	R \ CO₂Et	R = H (63) R = Et (67) [Flavopereirine] [Flavocarpine] [Dihydroflavopereirine]	339
	n-BuLi, hexanes, reflux, 6 h	CO₂Et	(55) [(±)-20-Desethyl-*N*ᵦ-methylgoniomitine]	340

TABLE XI. LATERAL LITHIATIONS IN NATURAL PRODUCT SYNTHESIS (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	n-BuLi, hexanes, reflux, 6.5 h		(62) (+)-Cinchonamine	101
	n-BuLi, hexanes, reflux, 6.5 h		(32) (+)-epi-Cinchonamine	101
C₂₅	1. *n*-BuLi, ether, -78° to rt, 10 min 2. TMSCl 3. *s*-BuLi, 0°, 1 h		(27) [Penitrem D intermediate]	102
C₃₀	*n*-BuLi, THF, 0° to rt, 1.1 h	—	(83) [Penitrem D intermediate]	102

TABLE XI. LATERAL LITHIATIONS IN NATURAL PRODUCT SYNTHESIS (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
		H. From Alkylpyridines		
C₇	LDA, THF, -60°, 2 h		(43) [(±)-Alamaridine]	119, 224
	LDA, THF, -70°, 15 min		(49-78) [Nauclefine] [(±)-Normalindine]	122 234
	LDA, THF, -70°, 15 min	1. HCO₂Me 2.	(75) [Dihydronauclefine]	341

TABLE XI. LATERAL LITHIATIONS IN NATURAL PRODUCT SYNTHESIS (*Continued*)
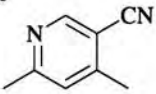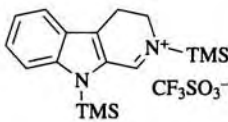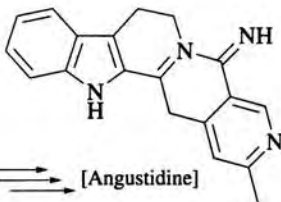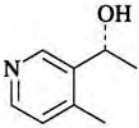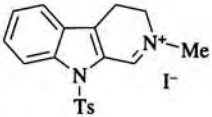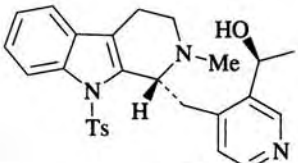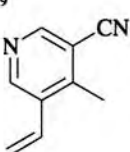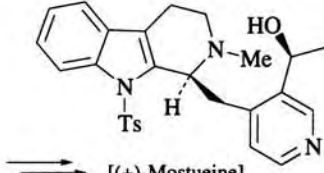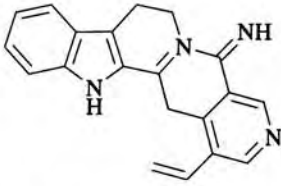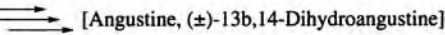
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C$_8$	LDA, THF, -70°, 15 min		(11) ⟶ [Angustidine]	122
	1. KOBu-*t*, THF, -10° 2. LDA, -78°		(26) + (36) ⟶ [(+)-Mostueine]	116
C$_9$	LDA, THF, -78°		(63) ⟶ [Angustine, (±)-13b,14-Dihydroangustine]	122

TABLE XI. LATERAL LITHIATIONS IN NATURAL PRODUCT SYNTHESIS (*Continued*)
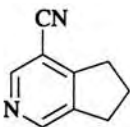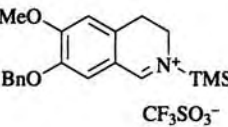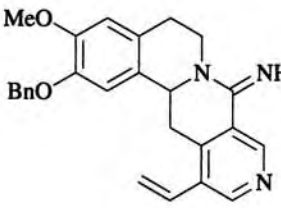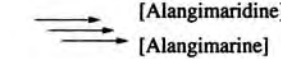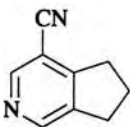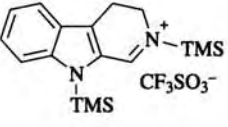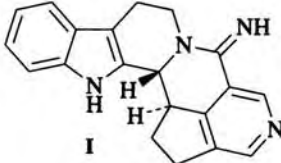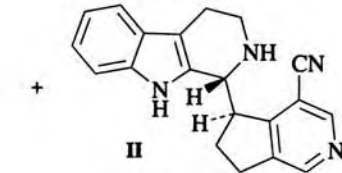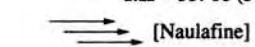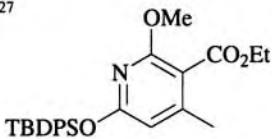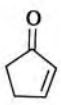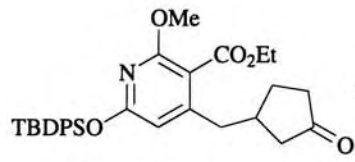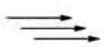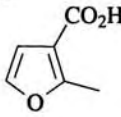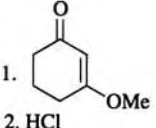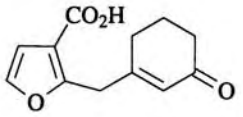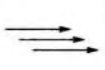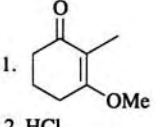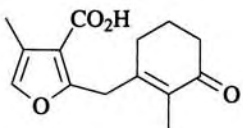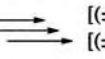
Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
	LDA, THF, -78°		(83) ⟶ [Alangimaridine] ⟶ [Alangimarine]	235
	LDA, THF, -78°, 20 min		I + II I:II = 33: 66 (58) ⟶ [Naulafine]	122

TABLE XI. LATERAL LITHIATIONS IN NATURAL PRODUCT SYNTHESIS (*Continued*)

Compound Lithiated	Conditions	Substrate	Product(s) and Yield(s) (%)	Refs.
C_{27}	LDA, THF, -78°, 20 min		(85) [(±)-Fredericamycin A]	231

I. From Alkylfurans

C_6	LDA, THF, -78°, 30 min	1. 2. HCl	(70) [(±)-Isoalantolactone] [(±)-Dihydrocallitrisin] [(±)-Septuplinolide]	130
C_7	LDA, THF, -78°, 30 min	1. 2. HCl	(74) [(±)-Furanoeremophilan-14, 6α-olide] [(±)-Furanoeremophilan-3,6-dione]	131

9. Acknowledgments

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The Intramolecular Michael Reaction

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1. Introduction

Like its intermolecular counterpart, the intramolecular Michael reaction involves the addition of a nucleophile, often referred to as the donor, to an acceptor, usually an olefin bearing one or more functional groups capable of stabilizing a carbanion.

Strictly speaking, the term Michael reaction refers to the 1,4-, or conjugate, addition of a carbanion to an acceptor under basic conditions. However, just as the scope of a previous review dealing with the Michael reaction was expanded to encompass a wide range of acceptors and noncarbon-centered donors, (1) so too has the scope of this chapter. Furthermore, reactions occurring under both basic and acidic conditions are discussed.

As suggested by the name, the intramolecular Michael reaction most often leads to the formation of a ring, either carbo- or heterocyclic.
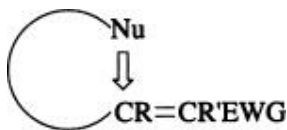
However, there are many examples of sequential, or tandem, Michael reactions wherein the first inter- or intramolecular Michael reaction is followed directly by an intramolecular variant leading to the formation of more than one ring. (2, 3) In other instances, a nucleophile is delivered to the β -carbon atom of an acceptor in a process which does not lead to the production of a ring. These transformations are referred to as heteroconjugate addition reactions. (4)

inter- followed by intramolecular

(25%)

heteroconjugate addition

(87%)
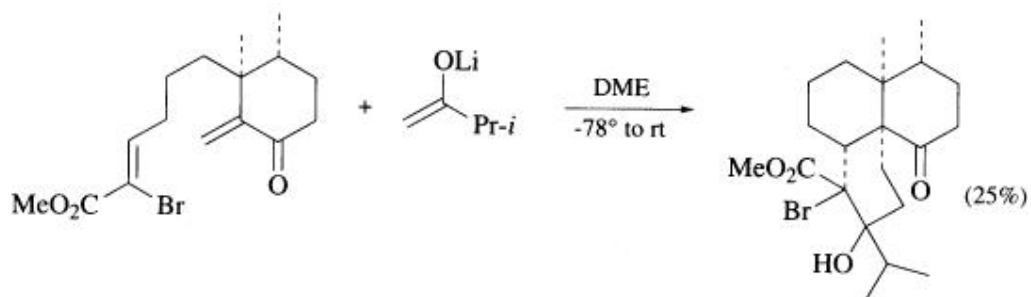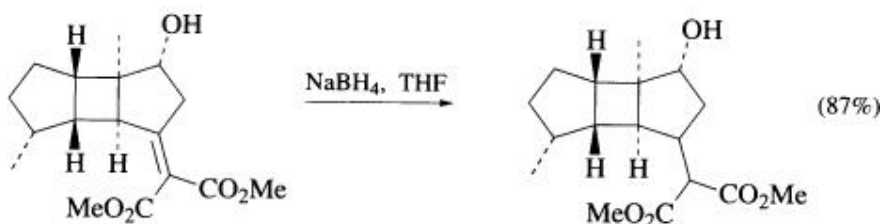
In contrast to the intermolecular counterpart, the intramolecular Michael reaction has been formally reviewed only once. (5) Two contemporary publications, however, have focused on the reaction and serve to highlight recent developments. (6, 7) The first example dates back to 1898 when Guthzeit reported that on standing at room temperature for a year, or upon treatment with a "small amount" of pyridine, ethyl α -carboxyglutaconate transforms to the "bimeric" ester **2**. (8-10) Subsequent reinvestigation by Ingold and co-workers led to the revised structure **3** and to the

CO_2Et

EtO_2C CO_2Et

1

CO_2Et

EtO_2C CO_2Et

EtO_2C CO_2Et

EtO_2C

2

+ 1

EtO_2C
EtO_2C CO_2Et

EtO_2C CO_2Et

CO_2Et

EtO_2C
EtO_2C CO_2Et

EtO_2C CO_2Et

CO_2Et

3
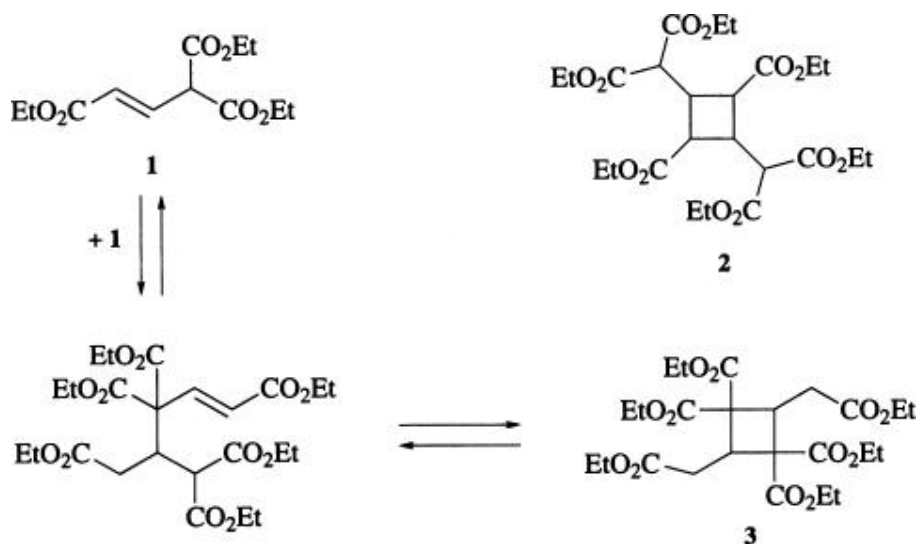
suggestion that it arose via an initial inter- followed by an intramolecular Michael reaction. (11)

The first systematic study of the intramolecular Michael reaction appeared in 1945 and focused upon examination of the transformation illustrated below. (12, 13) Thus, treatment of a variety of substituted ethyl coumarinates with sodium alkoxide in alcohol solvent leads to coumarins. Of particular interest is the fact that the reaction proceeds efficiently even when the β carbon of the acceptor is substituted with two sterically demanding groups. This apparent lack of retardation by double substitution at the β carbon contrasts sharply with the intermolecular Michael reaction and appears to be general.

R^1 CO_2Et

R^2

O CO_2Et

$\xrightarrow{\text{NaOR, ROH}}$

R^1

R^2 CO_2Et

CO_2Et

O

Another example highlighting the susceptibility of sterically hindered systems to participate in intra- but not intermolecular Michael reactions comes from studies concerning the mode of activation of the antibiotics calicheamicin and esperamicin. Thus, while thiolate, cyanide, and cuprate all failed to add intermolecularly to **4**, treatment of **5** with diethylamine and 1,4-cyclohexadiene in THF afforded a 71% yield of thiophene **7**. The purpose of the cyclohexadiene, of course, was to serve as a hydrogen atom source in the cycloaromatization of the initial Michael adduct **6**. (14)
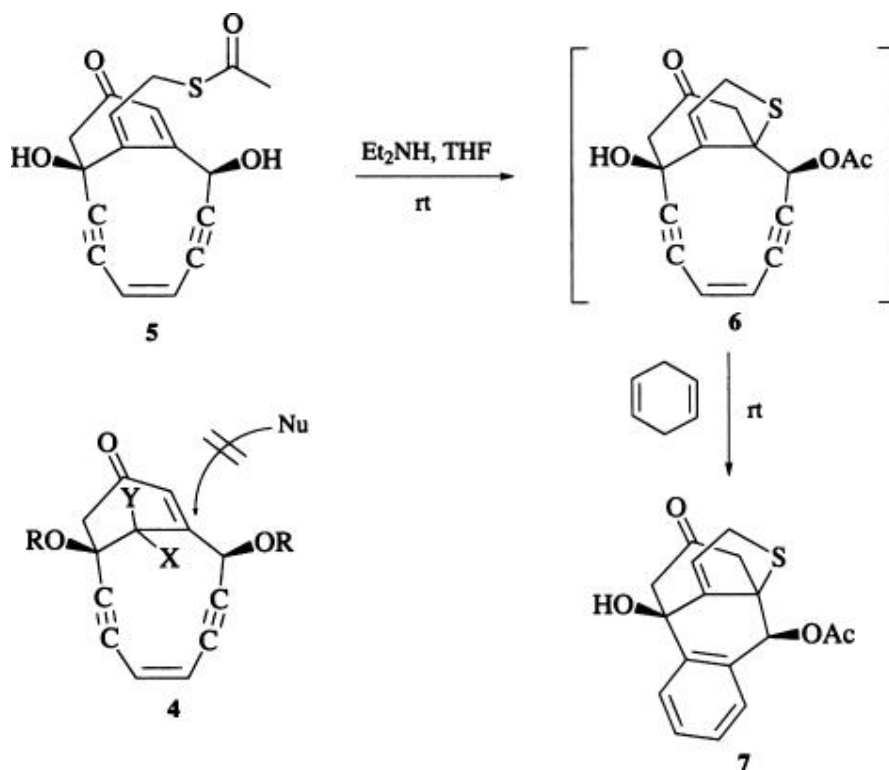
Access to the tetracyclic precursor **9** of a taxol analog was achieved via an intramolecular Michael addition to the relatively hindered βcarbon of enone **8**. (15)
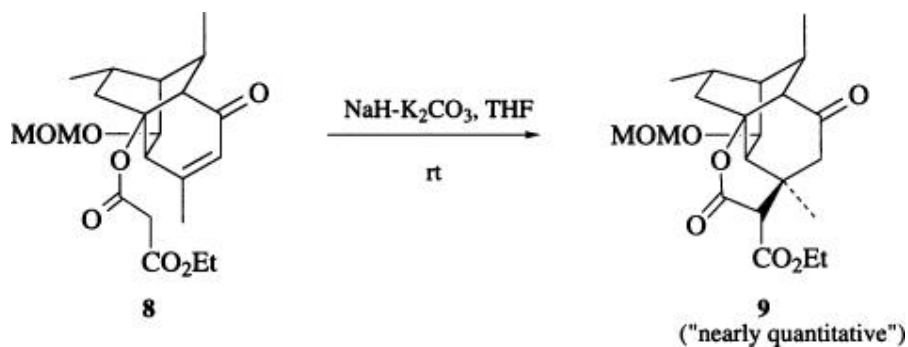
The intramolecular Michael reaction again formed the subject of publications appearing in 1951, (16) 1957, (17) and 1962. (18, 19) During the 1960s, comparatively little study or use of the reaction was reported. A notable and historically significant exception, however, was Corey's use of it in a total synthesis of longifolene. (20)
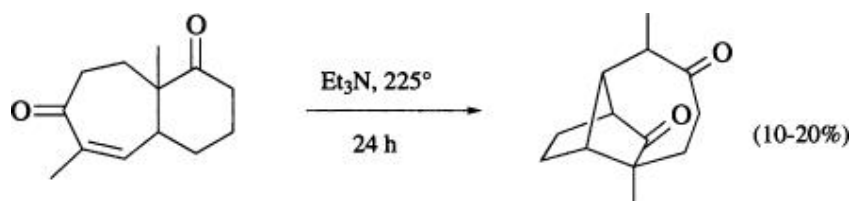
This approach to the construction of tricyclic systems is similar to that suggested mechanistically in the base-induced conversion of santonin to santonic acid. (20, 21)
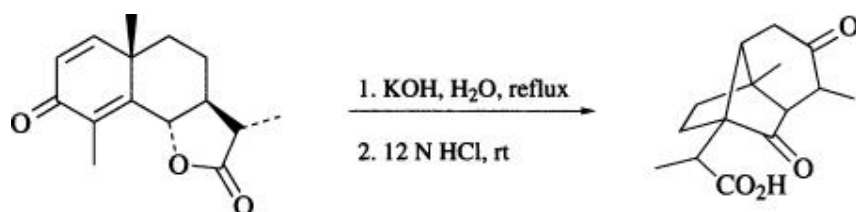
The 1970s and 1980s witnessed a dramatic increase in uses of the intramolecular Michael reaction. Much of the chemistry discussed in this chapter focuses upon material discovered during this time period.

2. Mechanism and Stereochemistry

2.1.1.1. Geometry of Closure
As the following discussion illustrates, the facility with which a substrate undergoes intramolecular Michael cyclization is dependent upon (a) the size of the ring being created, (b) the geometry at the reacting terminus, and (c) the *endo* or *exo* nature of the closure being investigated. (22, 23)

The geometric restraints associated with the intramolecular Michael reaction, especially the formation of five-membered rings, are reasonably well defined. The propensity for the conjugated ester shown below to undergo a base-initiated 1,2-addition–elimination to the ester carbonyl carbon (a 5-exo, trig closure) rather than an intramolecular Michael reaction (a 5-endo, trig closure) exemplify the constraints. (22, 23)
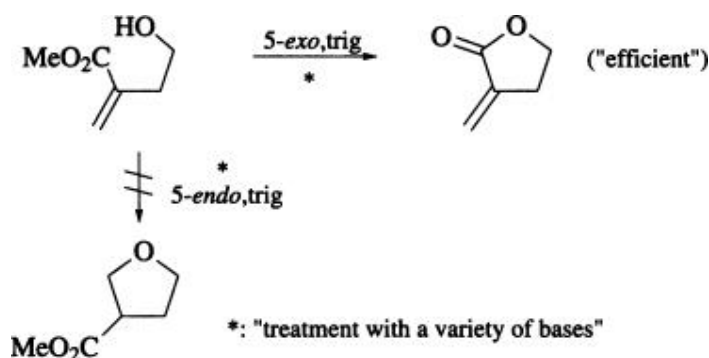
The same tendency is noted in the failure of the amino diester **10** to form amine **11** rather than produce lactam **12**, despite the fact that primary amines readily undergo intermolecular 1,4 in preference to 1,2 addition to α -substituted

10 → base, 25° → **12** (100%)

11
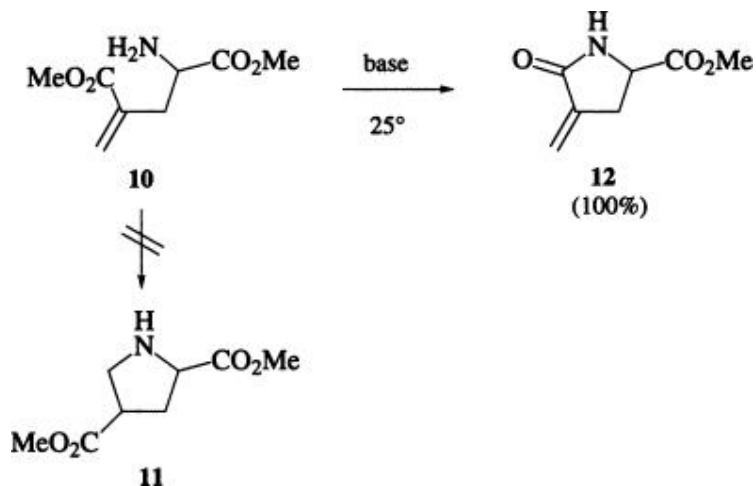
acrylic esters. (22, 23) Presumably, the restrictive geometry imposed by the existence of the two sp^2-hybridized carbons as members of the ring being formed in the 5-endo, trig cyclization does not allow the reacting centers to approach one another with the geometry required for sigma bond formation.

These limitations can sometimes be removed by simply choosing to conduct the desired cyclization under acidic rather than basic conditions. An example is illustrated below. (24)

13 → HCl, AcOH → (88%)
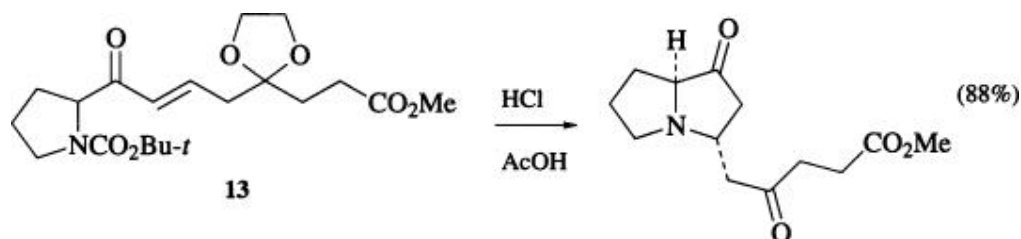
It has been suggested that the reaction does not involve a 5-endo, trig closure. Instead, the protonated enone **14**, derived from **13** via loss of the *tert*-butoxycarbonyl unit, deketalization, and isomerization, is considered the reactive intermediate leading to a geometrically preferable 5-exo, trig process.

14
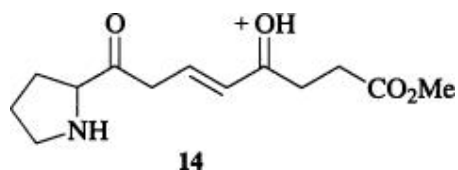
Similarly, while enones **15** and **16** fail to undergo a base-initialized intramolecular Michael reaction, the reaction occurs satisfactorily when acid

catalyzed. (25, 26) The success of the latter conditions has been attributed to the reduction in the rotational barrier around the enone double bond of the conjugate acid **17**, thus allowing access to conformations which are geometrically similar to the product.

15, R = Me
16, R = (CH₂)₄

17
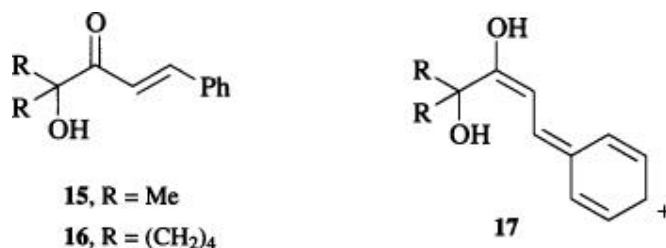
While 5-endo, trig cyclizations are rare, they are by no means unknown. Excellent yields of tetrahydrofurans and good yields of pyrrolidines and cyclopentane derivatives have been obtained by treating vinyl sulfones with catalytic quantities of potassium hydride in THF. (27)

R^1	R^2	Yield (%)
Ph	H	81
Et	Et	88
n-C₅H₁₁	n-C₅H₁₁	85
–(CH₂)₄–		84

(65%)

(65%)
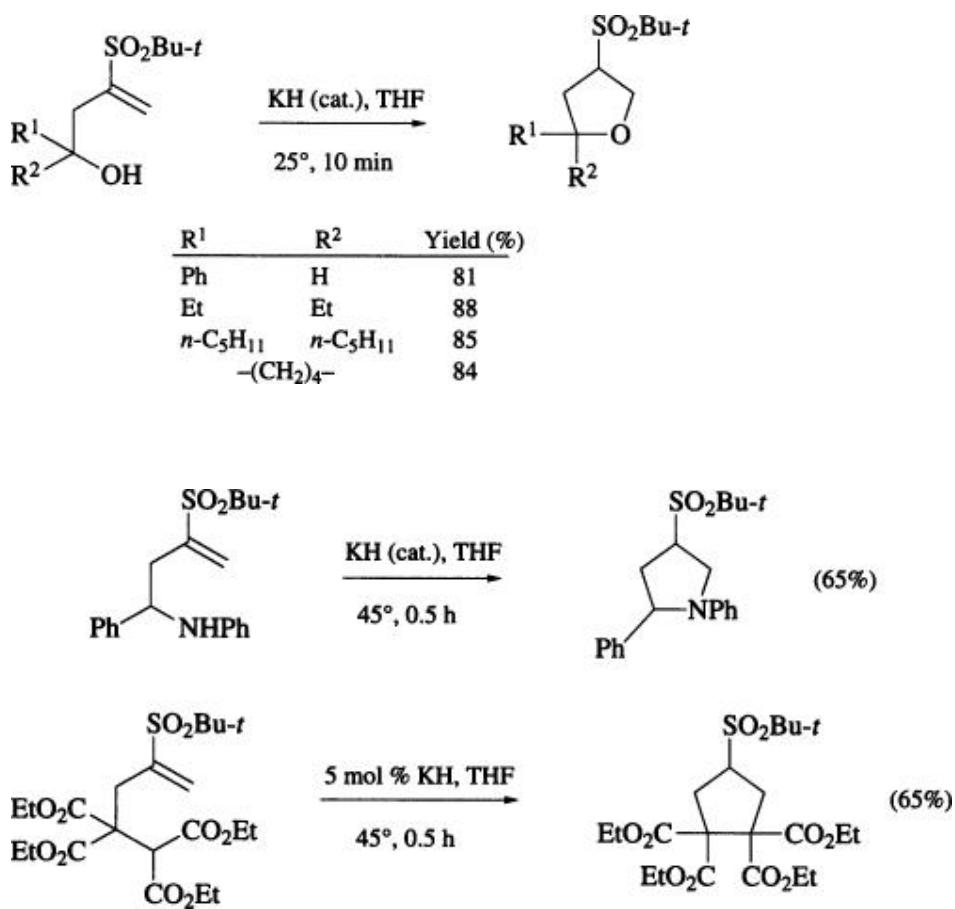
A similar example is illustrated below.
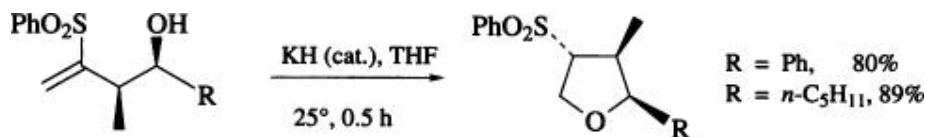
Interestingly, the corresponding sulfoxide failed to undergo cyclization under the same conditions.

An attempt was made to qualitatively compare the differences in the rate of 5-endo, trig cyclization with an anion accelerated sigmatropic rearrangement of order [1,3] or [3,3]. Thus treatment of hydroxy sulfone **18** with one equivalent
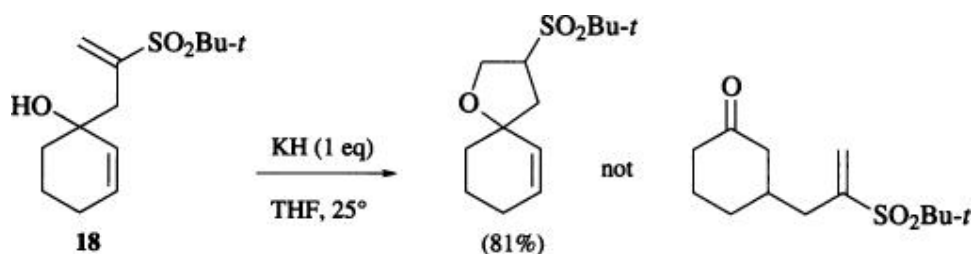
of potassium hydride in THF at 25° led only to the tetrahydrofuran; none of the expected sigmatropically rearranged keto sulfone was detected. (28) A more relevant comparison would have been available if both products had formed. Nonetheless, considering the speed of known anion accelerated [1,3] and [3,3] shifts, the present observation suggests that 5-endo, trig cyclization may be a much faster process than anticipated.

To our knowledge, no suggestion has been made to account for the ease with which the systems discussed in the preceding paragraphs undergo 5-endo, trig cyclization. It is tempting, however, to suggest that the cyclopentene synthesis outlined below is driven enthalpically by the formation of an α , β -unsaturated amide and entropically by the extrusion of the phenylsulfonyl anion. (29)

R^1	R^2	Yield (%)
H	CON(Me)Ph	(33)
Me	CO$_2$Me	(59)
Me	CN	(22)
Me	CON(Me)Ph	(65)
TMS	CO$_2$Me	(57)
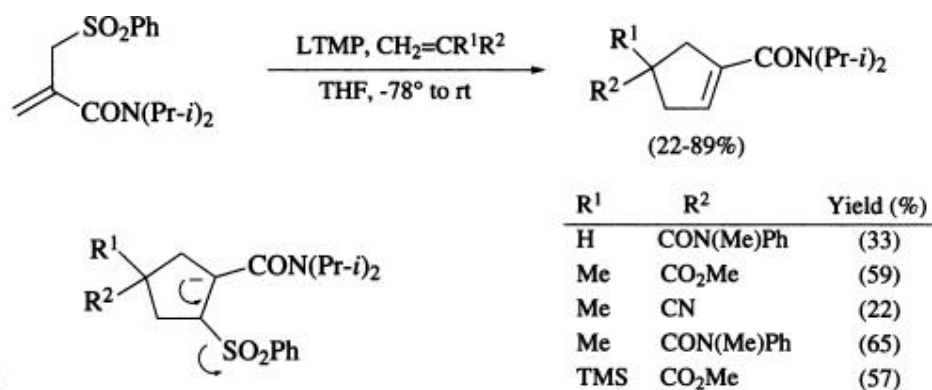
Perhaps an equilibrium between open and closed forms exists (*cf.* ref. 27), and the equilibrium is shifted toward the cyclized material by an irreversible β-elimination of phenylsulfinate.

While the 5-endo trig pathway is geometrically unfavorable, 5-endo dig cyclizations occur with facility. For example, treatment of hydroxy ynone **19** with sodium hydride in refluxing methanol provided the natural product bullatenone **20** in 93% yield. (25) The same product was produced in a 79% yield upon treatment
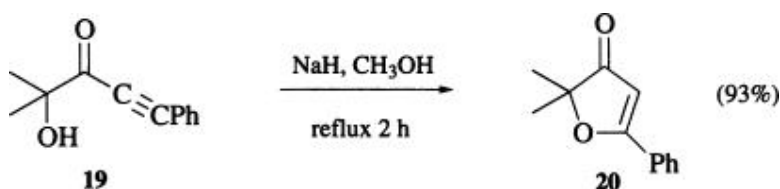
of **19** with catalytic *p*-toluenesulfonic acid, albeit after 19 hours of refluxing in methanol.

Inclusion of one additional carbon between potentially reactive centers eases geometric constraints; both acid and base initiated 6-endo trig Michael additions occur. (25) This is illustrated by the chalcone to chromanone conversion.
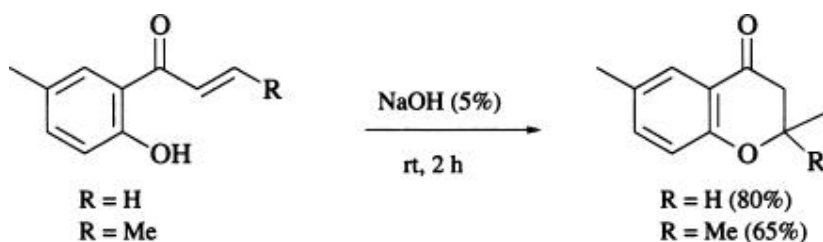
The mere fact that a six-membered ring is to be formed does not, however, guarantee success. Interesting and important examples which dramatically illustrate this point stem from several independent efforts to use the reaction in the construction of the carbocyclic six-membered ring found in the antitumor agent quadrone. (30-32)

$R = CO_2Me$, $R' = (CH_2)_3CHO^{31}$

21a, $R = Me$, $R' = (CH_2)_3CHO$

$R = Me$, $R' = CH_2COCH_2CO_2Me$ } as enolates

$R = Me$, $R' = CH_2CH_2CH=N(Me)O$; (1,3-dipolar)

$R = Me$, $R' =$ [structure with OH, S, I⁻, N⁺, Me, OH]

[Ref. 30]

... all failed to undergo intramolecular Michael cyclization under all conditions tried.
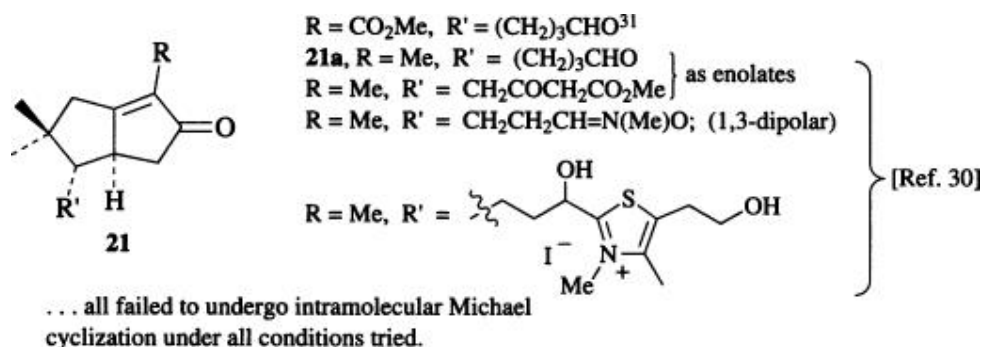
It has been suggested that the failure of **21** (structure shown above, the enolate **21b** below) to undergo cyclization relates to the existence of unfavorable torsional strain imposed about the C5 to C6 bond as the transition state for s -bond formation is reached. (30, 33)

Similarly, [structure with CO₂Me, O, H, CHO] failed to undergo an intramolecular Michael reaction[31,34]
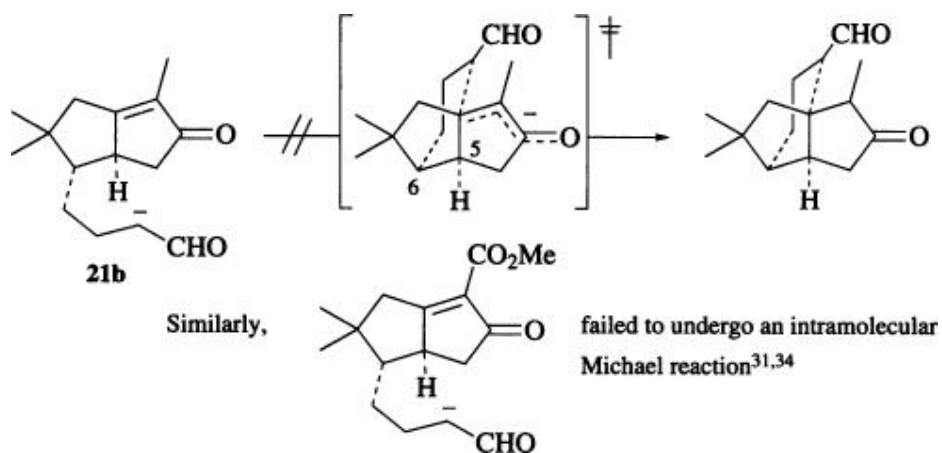
The successful cyclization of keto enone **22**, ultimately leading to a total synthesis of cedrene, stands in marked contrast to these results. (35)

22   KOBu-*t* / *t*-BuOH, 25°, 15 min   (73%)
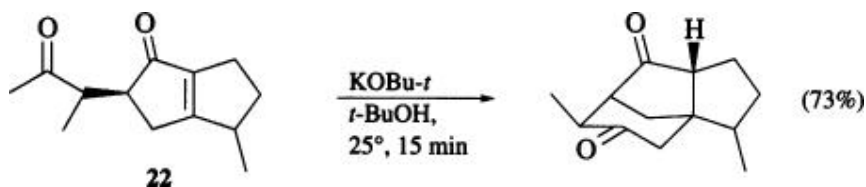
2.1.1.2. Kinetic vs. Thermodynamic Control of Stereochemical Outcome

In many instances, the intramolecular Michael reaction is conducted under the same conditions as those used in the classical intermolecular version (e.g., catalytic metal alkoxide in alcohol solvent). Accordingly, each step of the sequence is reversible, and it is not surprising to discover that stereoselectivity is subject to those factors usually associated with both kinetically and thermodynamically controlled processes. Consequently, prediction of the stereochemical outcome of a given transformation is often complicated by the fact that a change in reaction conditions often leads to a change in product ratios. For example, after one hour at 55°, the reaction of equimolar quantities of pelletierine, benzaldehyde, and sodium hydroxide in water leads to quinolizidinones **23** and **24** in a 58% yield and a ratio of 5:2. (36) Lengthening the reaction time to 14 hours changes the product ratio to 3:4. The same trend is observed when the reaction is conducted for varying lengths of time in methanol. That is, the ratio of compounds **23** and **24** varies from 5:2 after one hour to 1:6 after 14 hours. These results are rationalized by suggesting that the intramolecular Michael reaction emanating from intermediate **25** is reversible and leads, at early reaction times, to a product ratio reflecting kinetic rather than thermodynamic control. Prolonged reaction times evidently drive the reaction toward the thermodynamically more stable product **24**.

PhCHO, NaOH

MeOH, 55°, 14 h

25

23   +   **24**

(56% total)   **23**:**24** = 1:6
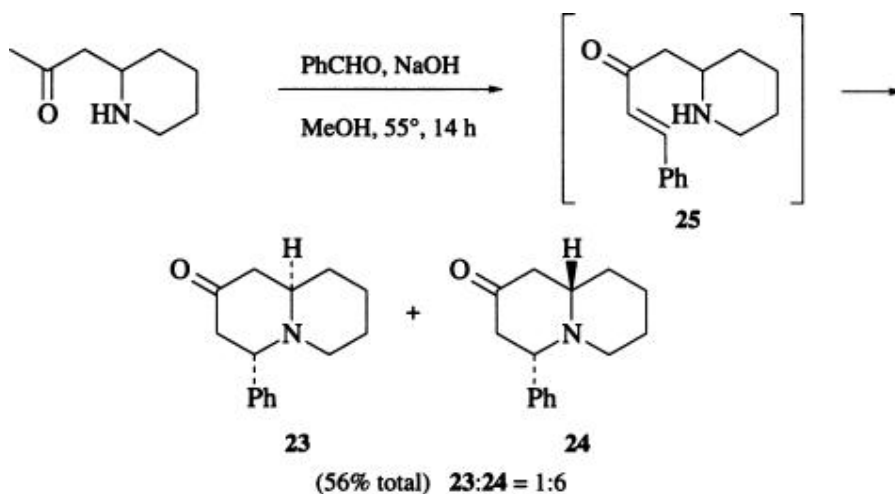
In some instances, kinetics and thermodynamics operate cooperatively and afford high levels of stereoselectivity, and occasionally stereospecificity. For example, treatment of enone **26** with potassium carbonate in ethanol affords a high yield of the diketoester **27**. (37) This result is in accord with expectations based
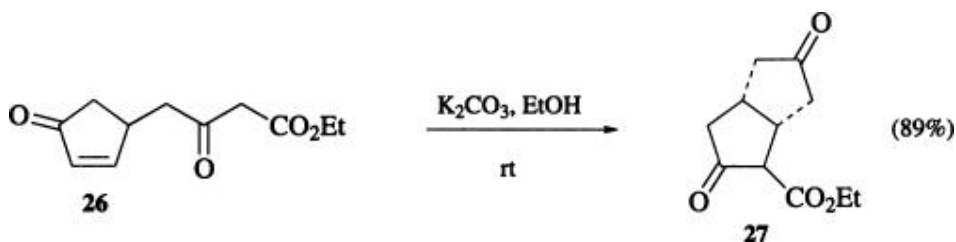
on the ~7 kcal/mol difference in strain energies between *cis*- and *trans*-fused bicyclo[3.3.0]octane, the former being preferred. Of course, the strain energy difference may also be manifest in the transition state leading to **27**, making it the preferred product on kinetic as well as thermodynamic grounds.

2.1.1.3. Stereoelectronic Control of Stereochemical Outcome
Stereoelectronic factors often play an integral role in affecting the stereochemical outcome of intramolecular Michael reactions. The conversion of malonic ester **28** to the bicyclic lactone **29**, an important intermediate to vernolepin, is illustrative; the
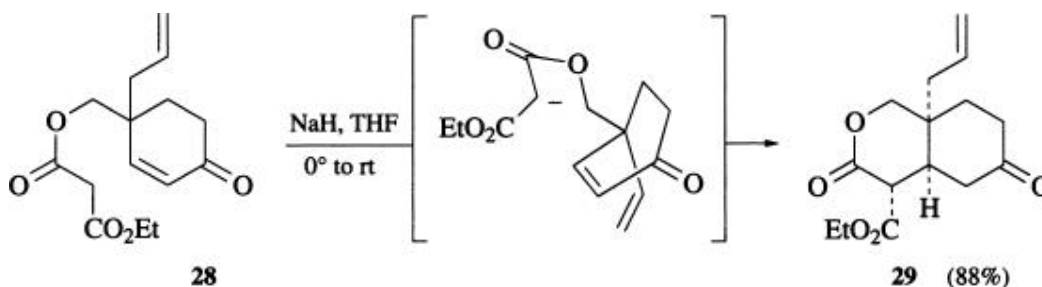
malonyl anion approaches the β carbon of the enone in that fashion which leads to the most efficient overlap of the donor and acceptor units (an axial approach). (38)

2.1.1.4. Steric Factors
Steric factors also play a role. For example, treatment of the unsaturated ketonitrile **30** with potassium *tert*-butoxide in *tert*-butyl alcohol leads to the formation of the *cis*-hydrindanone **31** only. (39)

30 → **31** (85%)

t-BuOK, t-BuOH
rt to 65–70°
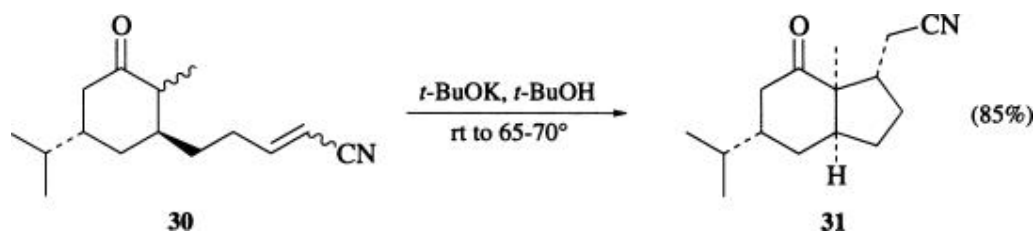
The formation of **31**, rather than any of several stereoisomers, is readily explained by suggesting that, of the possible transition states **32–34**, **32** is of lowest energy since it does not experience the energy-raising side chain interactions that are present in **33**, or the H-H interaction that is found in **34**.

32 vs. **33** vs. **34**
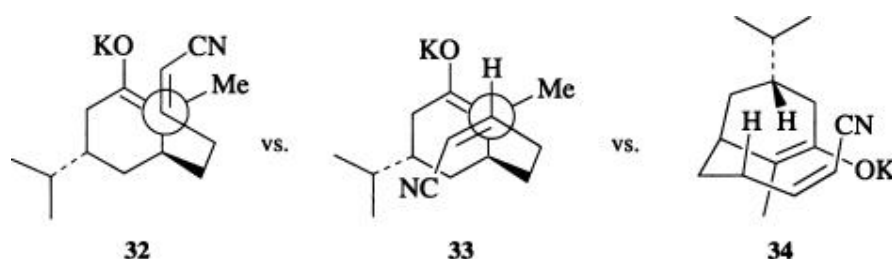
Another example illustrating the role of steric factors is the conversion of the β-ketoester **35** to a 30:1 mixture of products **36** and **37** in 88% yield. (40)

35 → **36** + **37**
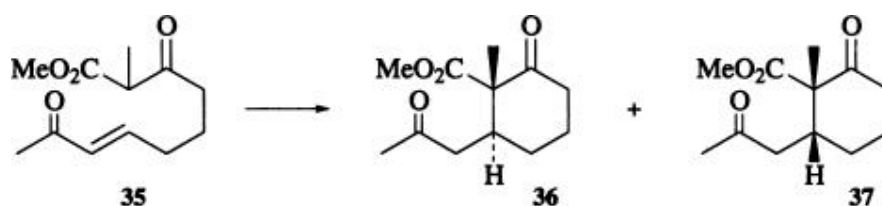
Conditions	36:37	Yield (%)
NaH (cat.), C_6H_6, 15 min, rt	30:1	(88)
KOBu-t, t-BuOH	1:1	(—)

The high degree of stereoselectivity is explained by suggesting that energy-raising steric interactions between the chelate ring and the acceptor chain are lower in transition state formulation **38** than in **39**, and that the former leads preferentially

38 **39**
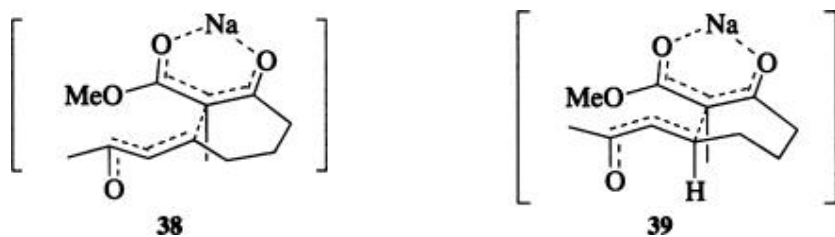
to **36** in a kinetically controlled process. Notice that in a polar medium (potassium *tert*-butoxide, *tert*-butyl alcohol), stereoselectivity is greatly reduced.

Similarly, the efficient conversion of ketoenoate **40** to a mixture of products wherein diastereomer **41** predominates is believed to occur in a fashion that minimizes nonbonded interactions in the transition state. (41)

Conditions	41	42
K$_2$CO$_3$, EtOH, reflux, 1 h	(73%)	(15%)
NaH, dioxane, reflux, 45 min	(51%)	(26%)
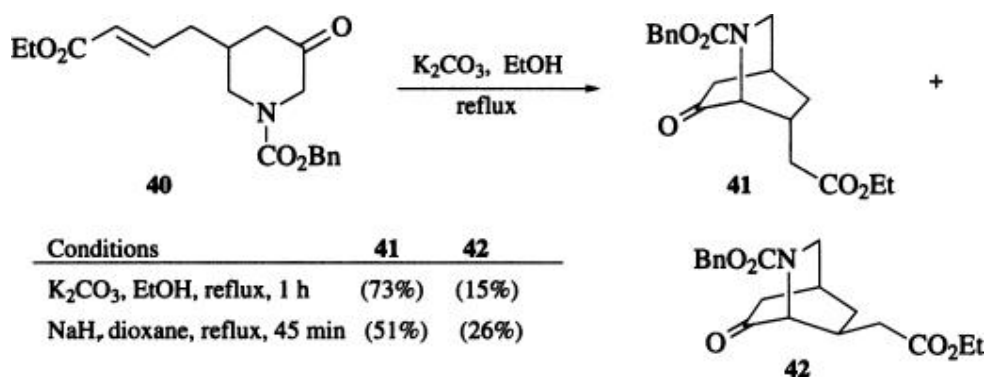
In the example portrayed below, the authors cite avoidance of allylic 1,3-strain as the means to fix the preferred reacting conformations about the enolate and the acceptor subunits. Only a single stereoisomer was isolated. (42)
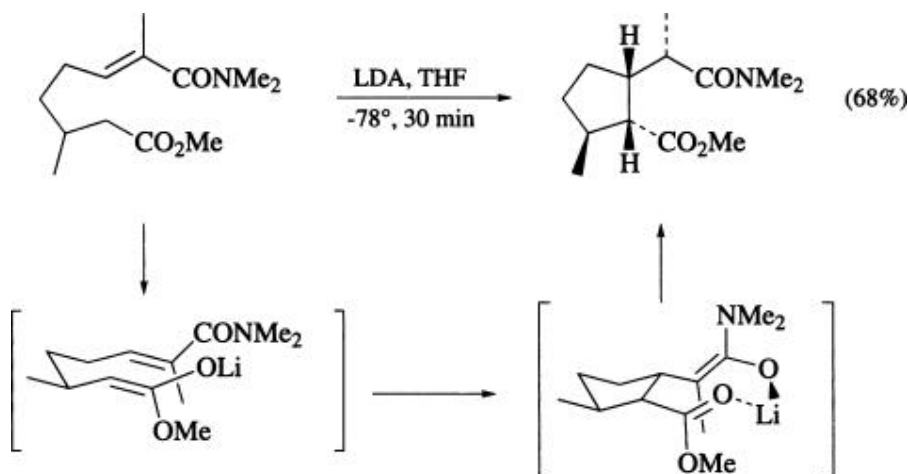
2.1.1.5. Stereochemical Control: Intramolecular Michael Followed by Aldol Condensation

When an intramolecular Michael reaction is followed by an aldol condensation, the sequence provides an excellent protocol for the preparation of *trans*-hydrindenones. (43) The *trans/cis* ring junction product ratio resulting from such Michael-aldol sequences varies markedly as a function of the counterion of

63%
trans fused / *cis* fused 25:1
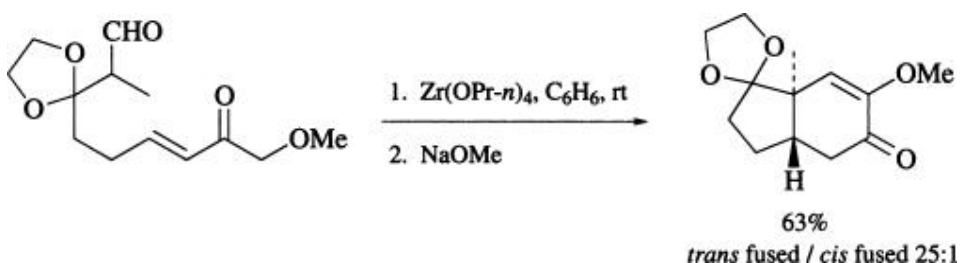
the base used to initiate the reaction, as well as the nature of the solvent. (43) Zirconium *n*-propoxide in dry benzene is the base/solvent system best suited to afford *trans*-fused products. As illustrated below, the ratio varies in accord with a pattern wherein those metals that form stronger bonds with oxygen lead to larger amounts of the *trans* product. This being so, it is reasonable to note the increase in the *trans/cis* ratio upon changing from methanol, a solvent that can efficiently solvate the metal, to benzene which is poorly solvating.

Base	Solvent	*trans/cis*
Ba(OH)$_2$	MeOH	3:1
Ca(OH)$_2$	MeOH	10:1
Mg(OMe)$_2$	MeOH	12:1
Al(OBu-t)$_3$	MeOH	20:1
Zr(OPr-n)$_4$	C$_6$H$_6$	25:1
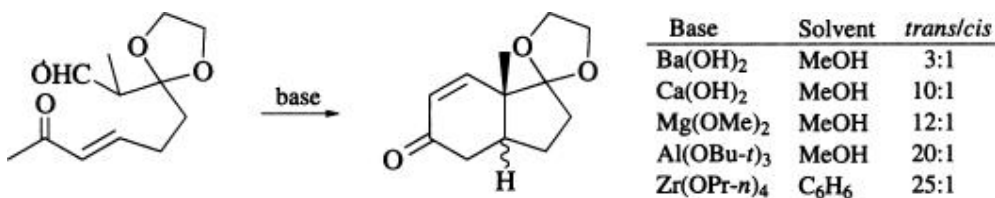
Assuming kinetic control, then, the stereochemical results illustrated above are consistent with the transition state models **43** and **44**. The latter is assumed to

43

44

be of lower energy, the thought being that electron repulsion and eclipsing interactions are minimized.

These observations concerning the nature of the factors responsible for stereochemical control served as the foundation upon which a total synthesis of retigeranic acid was based. (44)

1. Zn(OPr-n)$_4$, C$_6$H$_6$, LiOH, 22°, 12 h

2. (CF$_3$CO)$_2$O, DBU, DMAP, CH$_2$Cl$_2$, -78° to rt

+ 1 : 1 mixture of isomers

(80%) 10:1:1)
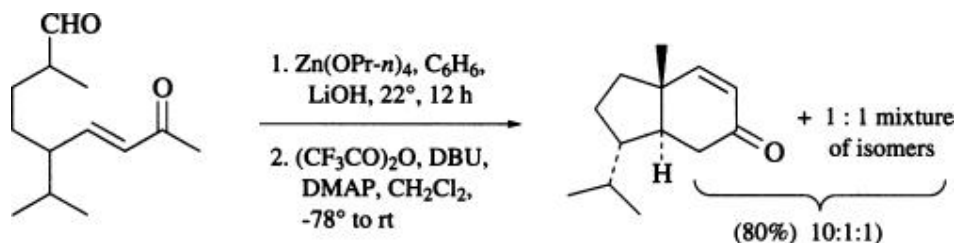
The scope of the process has been expanded through the use of a variety of standard chiral auxiliaries; (45) useful amounts of asymmetric induction have been achieved, and the process has been applied to the construction of 11-ketosteroids. (46)

NaH, C$_6$H$_6$
rt, 15 min

I   (89-95%)   II

R*	I:II
	1:12-14
OBu-t	> 40:1
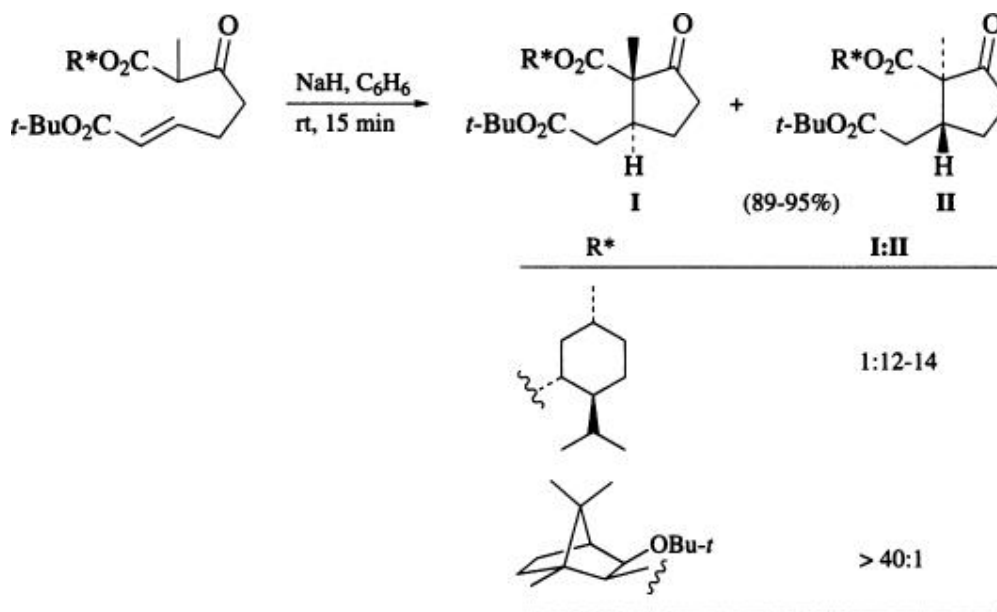
2.1.1.6. Chelation Control

Chelation of the entering nucleophile with another functional group which is also pendant to the starting material can lead to a stereocontrolled

intramolecular Michael reaction. For example, both sulfoxides **45** and **46** undergo efficient cyclization upon treatment with potassium hydride in
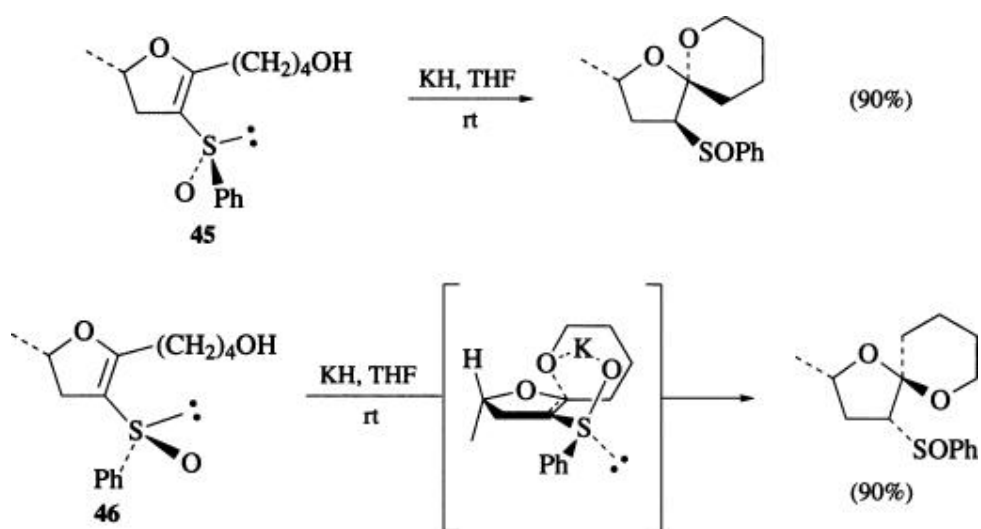
tetrahydrofuran at room temperature; in each instance, only one product is isolated in 90% yield. (47) It is believed that chelation between the side-chain oxido anion and the sulfoxide oxygen controls the direction of approach of the former to the unsaturated sulfoxide.

Enone **47** undergoes sequential intramolecular Michael reactions when treated with 1.3 equivalents of lithium hexamethyldisilazide in tetrahydrofuran at temperatures ranging from –78° to ambient. The observed stereospecificity was suggested to arise as a consequence of chelation control. The same product was isolated, albeit in only 10% yield, when the reaction was carried out in THF-HMPA, that is, under conditions where one would expect the metal to be preferentially coordinated by HMPA. (48)
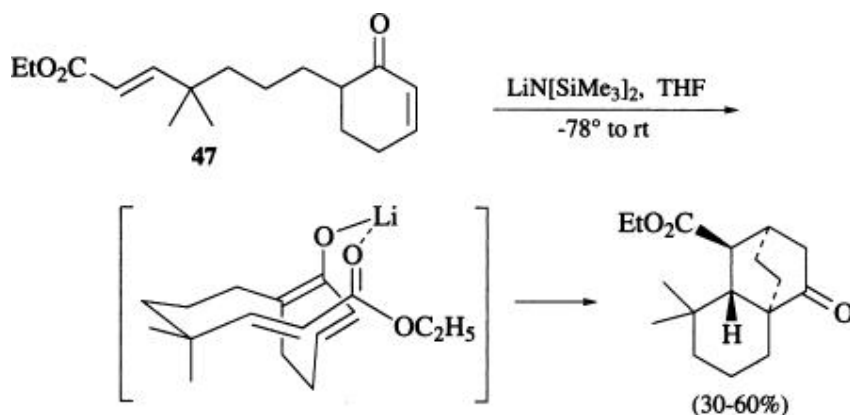
3. Scope and Limitations

3.1. Retro Intramolecular Michael Reactions

The Michael reaction is reversible. An interesting example, conducted under acidic conditions and illustrating its use in the construction of spirocyclic compounds, is illustrated. (49)
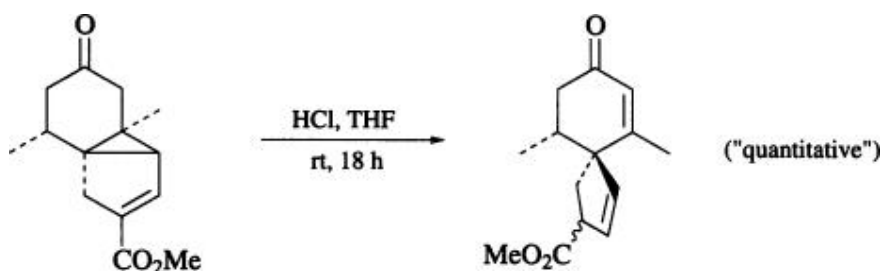
One can imagine situations where the addition of a nucleophile could be used formally to "protect" the acceptor from attack. Here, the nucleophile should also be a good leaving group; often, it is heteroatom-centered (e.g., N, S, or O). (50) If it is carbon-centered, then the carbon should be substituted with one or more anion stabilizing groups. This "self-protection protocol" proved particularly expedient in the example below since the protection/deprotection operations arose as a natural consequence of the methodology used in the assembly of **48**, (51) a labile intermediate related to lycorine.
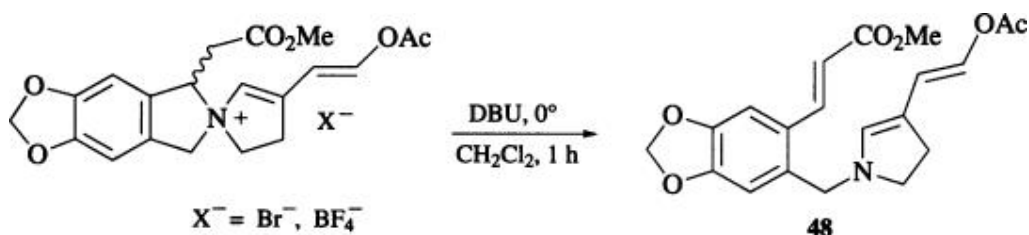
An example stemming from efforts to prepare leukotrienes is illustrated. (52)
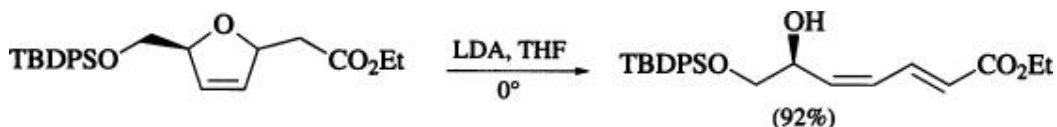
Often, especially when using phosphonate anions rather than phosphonium

ylides, five- and six-membered ring lactols undergo Horner–Emmons olefination only to be followed in situ by an intramolecular Michael cyclization. (53)

(53%)
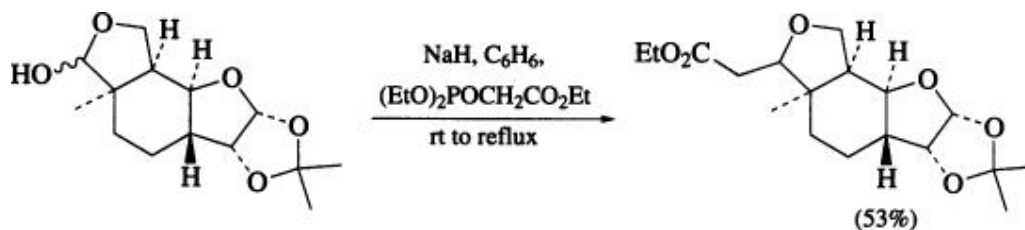
The resulting tetrahydrofuran or pyran can be thought of as a "self-protected" ω-hydroxy-α, β-unsaturated ester (ketone, nitrile, etc.). The following example, leading to the formation of an important intermediate used in a novel synthesis of the sesquiterpene $\triangle^{9,12}$-capnellene, exemplifies the idea. (54)
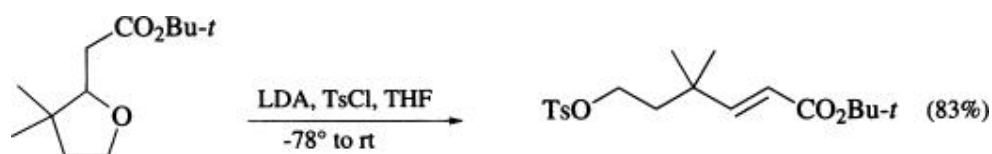
3.2. Sequential Reactions

The terms "sequential" or "tandem" Michael reaction are used to describe an inter- or intramolecular version followed directly by one or more intramolecular Michael reactions. Posner uses the term MIMIRC (Michael–Michael–ring Closure) as a descriptor. (2, 55)

As many as four successive Michael reactions have been carried out successfully. The example shown begins with one of the intermolecular variety, and finishes with three consecutive intramolecular Michael reactions. (56)

$(C_{11}H_7O_2CH_3)$ (excess)   (20%)

Nu = $C_{11}H_7O_2CH_2$
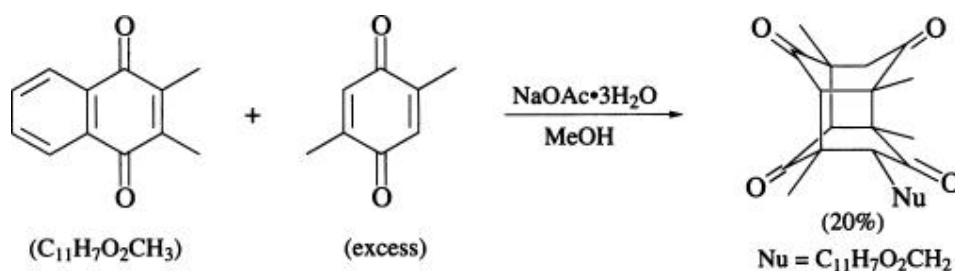
A sequential Michael process involving two components, one of which serves twice as a Michael acceptor, provides a clever and facile means of bridging the α and α' carbons of a cyclic ketone with a three-carbon bridge. In the example shown, a Dieckmann condensation leads to the formation of a tricyclic diketo diester related to clovane. (57)
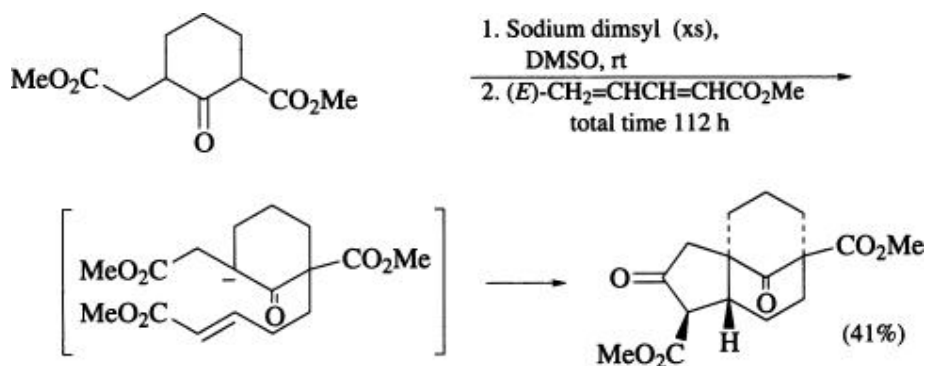
Sequential reactions have been used creatively in the construction of a variety of ring systems, including, for example, those of the natural products eriolanin, (58) atisiranone, (59) and atisine. (60)

used en route to eriolanin

several steps to atisiran-15-one

several steps to atisine
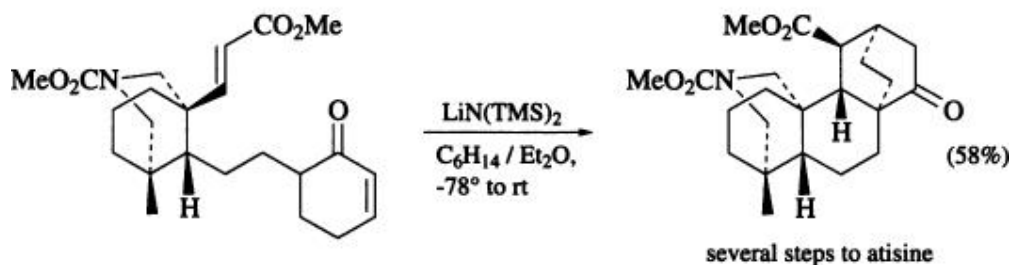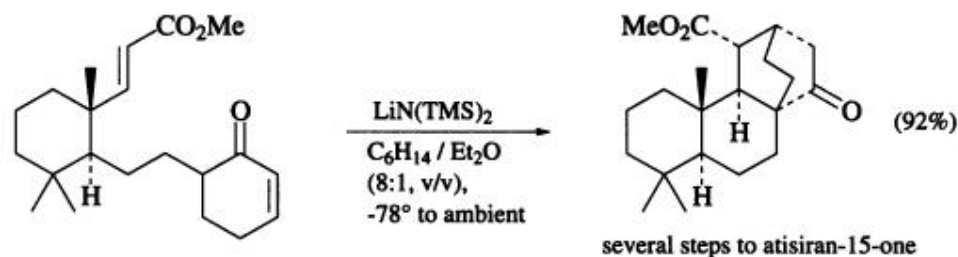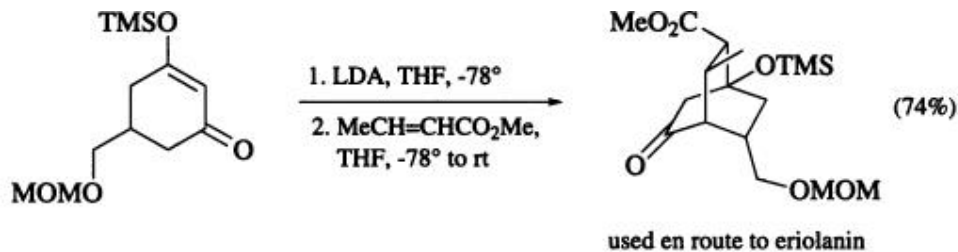
Three-membered rings are formed readily when the kinetic enolate of cyclohexenone, or a substituted derivative thereof, reacts with a Michael acceptor whose anion stabilizing unit serves as a leaving group after the initial Michael reaction has occurred. (61-63)
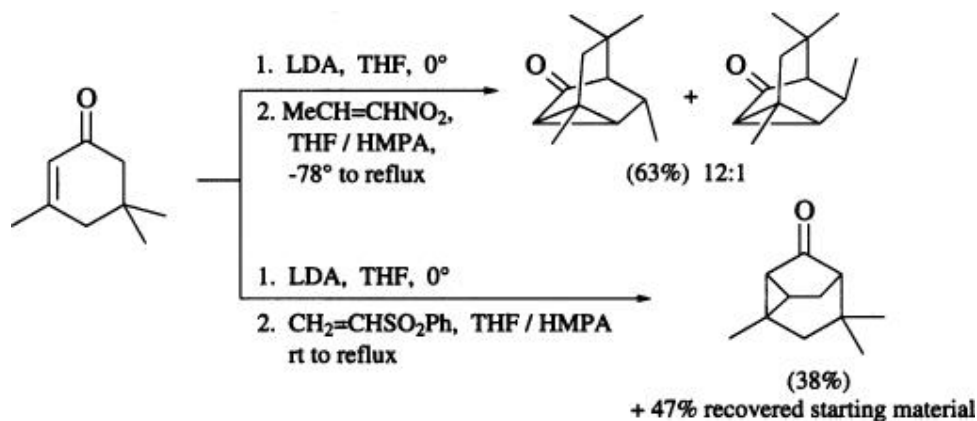
This basic concept has been applied to total synthesis; one example is illustrated. (64-67)

toward trachyloban-19-oic acid
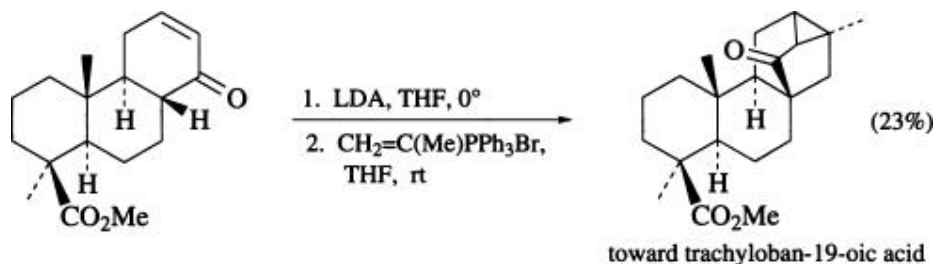
A similar strategy has been applied to the total synthesis of several eremophilane sesquiterpenes, including ishwarane. (68)

(20%)   + 37% starting material   (20%)

toward ishwarane
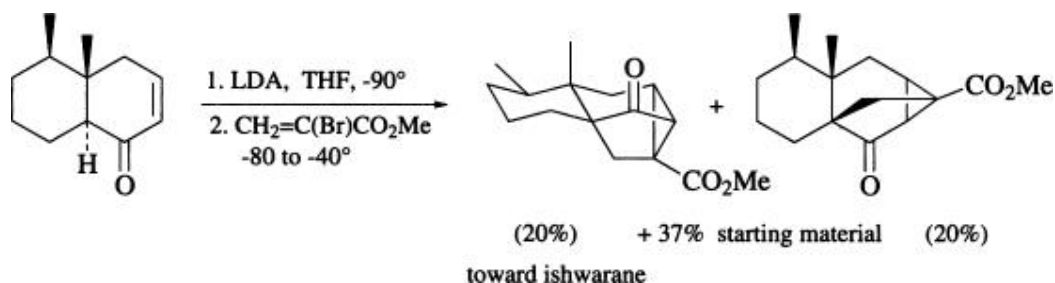
A nice example of stereocontrol in a sequential Michael sequence is portrayed below. Here it was reasoned that the preferred reacting conformation is that which places the large silyl ether groups antiperiplanar and the α , β -unsaturated ester moieties gauche to one another. In this manner the π faces of the acceptor units are rendered homotopic. The authors use the expression "rotamer distribution control" to refer to the control of ground state rotamer distribution in a manner that leads to such differentiation. (69) The conjugate addition of a variety of Grignard reagents occurs stereospecifically; an intramolecular Michael reaction leads to the five-membered rings shown.

R	Yield (%)
CH$_2$=CH	(94)
Me	(92)
Et	(77)
Ph	(40)
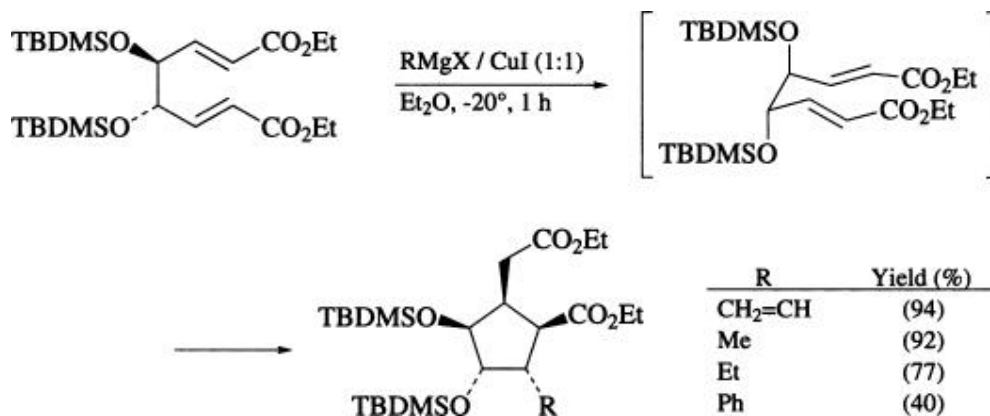
One powerful variation of the sequential sequence begins with an intermolecular addition of the kinetic enolate derived from an α , β-unsaturated ketone to either the same or a different α ,β -unsaturated ketone (or aldehyde or ester). Overall, two new carbon–carbon σ bonds are formed. As shown, the yields are not always high, but considering the significant increase in architectural complexity attendant to such a simple procedure, the transformations are remarkable. (70)

1. LDA, THF, −70°, 70 h
2. warm to rt

(65-70%)

LDA, THF
−70° to rt

(62%)

LDA, THF
−70° to rt

(9%)

−CHO   LDA, THF

+ endo

Temp	exo:endo
−70°	8:1
−20°	1.5:1
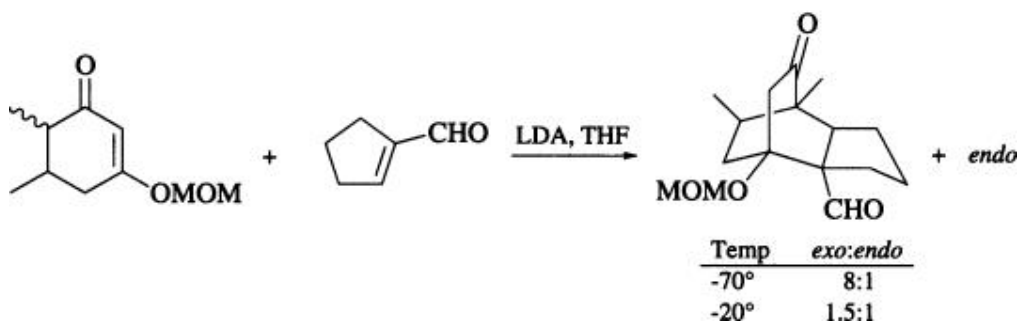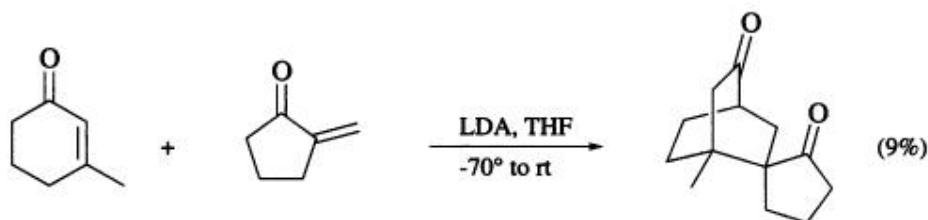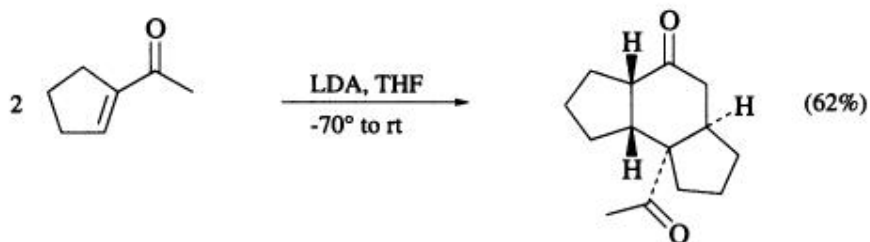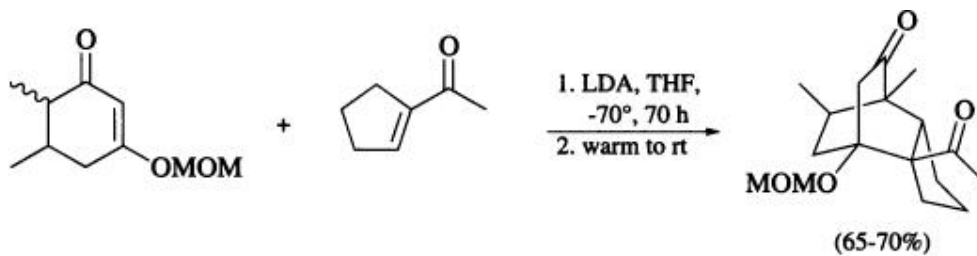
Sequential Michael additions can be achieved under basic conditions, as the examples considered thus far make abundantly clear, or under acidic conditions,

Et₂AlCl, CH₂Cl₂
−80 to 25°
overnight

(43%)
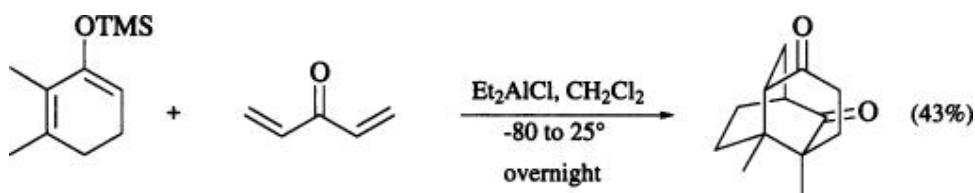
though there are far fewer examples. One, illustrated above, features three consecutive Lewis acid promoted Michael additions and leads to the sesquiterpene seychelene. (71)

3.2.1.1. Sequential Reactions: A Lewis Acid Promoted Intramolecular Michael or Diels–Alder Reaction?

Each of the base-initiated reactions illustrated above bears similarity to the Lewis acid promoted Diels–Alder reaction of a silyl dienol ether with a dienophile. (48, 72-74)
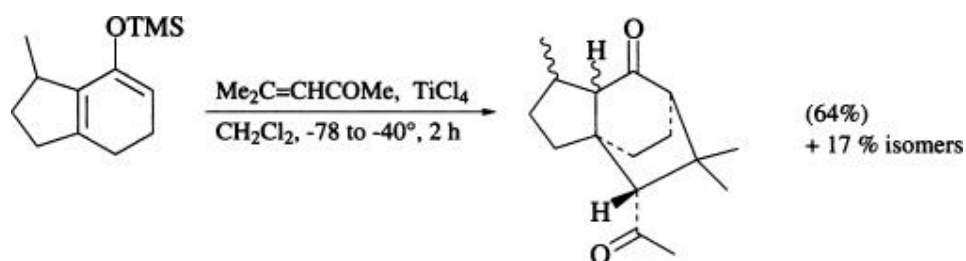
The two processes may in fact be used to complement one another. For example, attempted Diels–Alder cycloaddition with triene **49** did not afford the desired adduct,
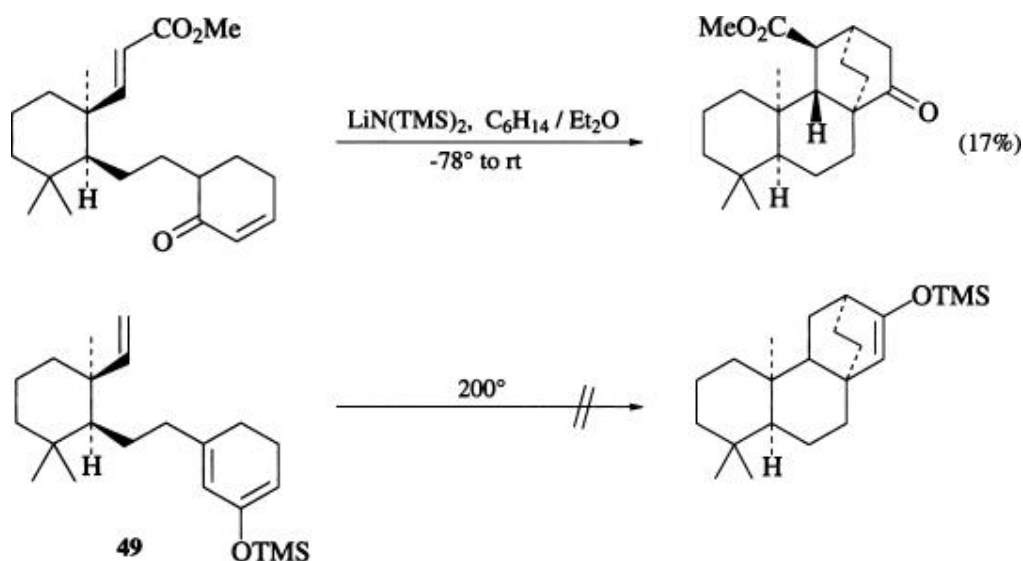
whereas the ring system was produced, although in only 17% yield, via a sequential Michael reaction. One should be cautious in comparing the two reactions, however, since in one case the dienophile is unactivated. (74-76)

Most authors have expressed a preference for classification of the base initiated processes as sequential Michael rather than anion accelerated Diels–Alder reactions. (70, 77, 78) The mildness of the reaction conditions as

well as the isolation of products resulting from the formation of only one σ bond (i.e., after only one Michael reaction has occurred) have been cited as evidence in support of the former classification. However, since the degree of acceleration expected in such an anion accelerated Diels–Alder reaction has never been measured, it seems risky to point to the use of "mild reaction conditions" as being supportive of either of the mechanistic alternatives.

3.2.1.2. Sequential Reactions with Alkene Acceptors

Sequential Michael reactions allow one to "stitch" a carbon or a heteroatom between the two Michael acceptor units. Most often, six-membered rings are formed. The reaction conveniently leads to usable yields of spirocyclic compounds, (79) as well as to simple substituted cyclohexanones, (80) and has even been used to form seven-membered rings, albeit with variable yields. (81)
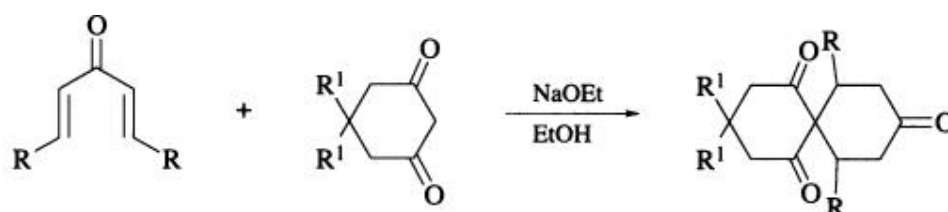
R	R¹	Conditions	Yield (%)
Ph	H	reflux	(45)
Ph	Me	reflux	(40)
H	H	rt	(33)
H	Me	rt	(40)

$R = Me, H$
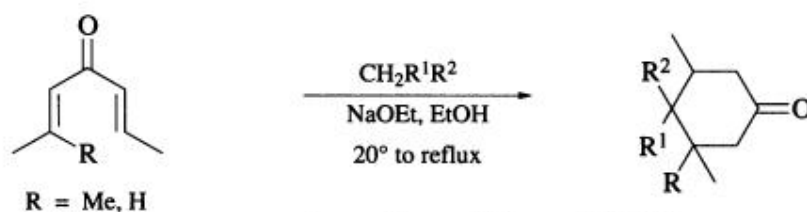
R	R¹	R²	Yield (%)
Me	CO_2Et	CN	(62)
Me	NO_2	H	(59)
Me	Ts	CN	(65)
H	Ts	CN	(52)
Me	CO_2Et	CO_2Et	(0)
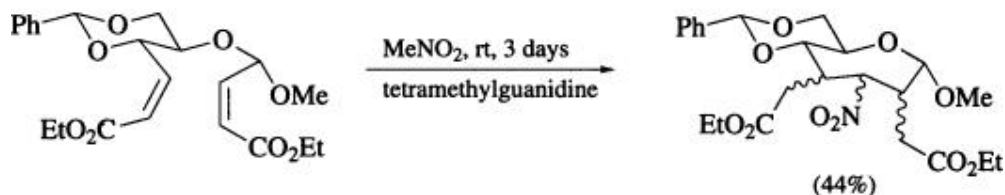
3.2.1.3. Sequential Reactions with Alkyne Acceptors

When one of the alkene acceptors is replaced with a triple bond, substituted cyclohexenones are formed. A classic example involves the reaction of 7-chloro-4,6-dimethoxy coumaranone with methoxyethynyl propenyl ketone in the presence of potassium *tert*-butoxide in diethylene glycol dimethyl ether, leading to the formation of the antifungal antibiotic griseofulvin. (20)

griseofulvin (—)
60:40 mix with *epi*-griseofulvin
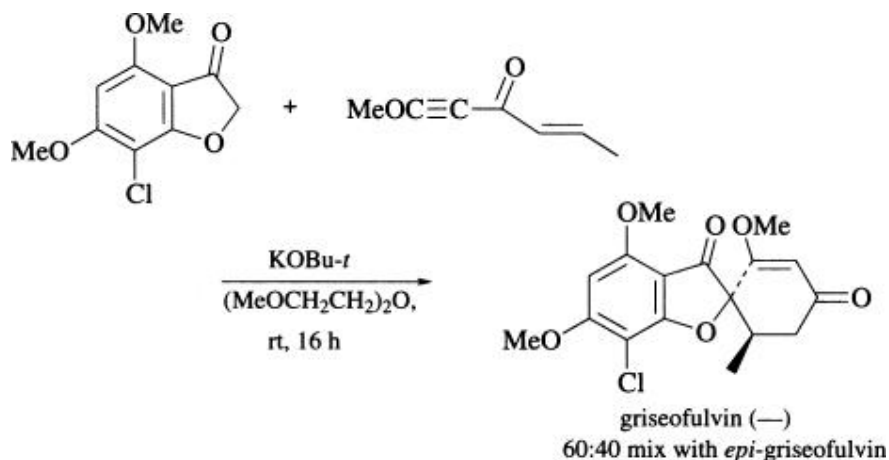
The reaction is presumably kinetically controlled and proceeds stereospecifically via that pathway which allows maximal orbital overlap in the transition state leading to the formation of the second C - C bond. (20)

A similar process, used as a test case for the griseofulvin synthesis, occurs in ~70% yield. (20)
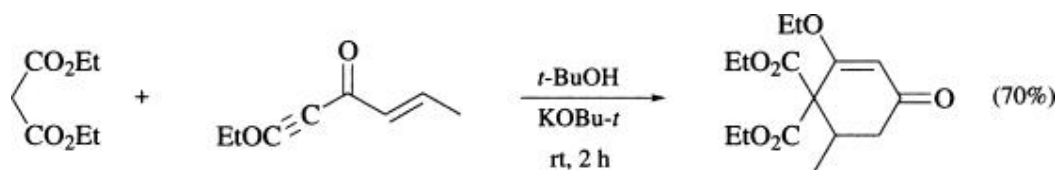
Activated alkynes, while not used frequently, make excellent Michael acceptors. (20, 82, 83) For example, treatment of ketoalkyne **50** with 4–8 equivalents of triethylamine in refluxing toluene for 12 hours afforded bicycle **51** in 65–70% yield. (84)

50   Et₃N, PhMe, reflux 12 h   **51**

(65-70%); a 30% enantiomeric excess
was obtained by using using (–)-quinine.
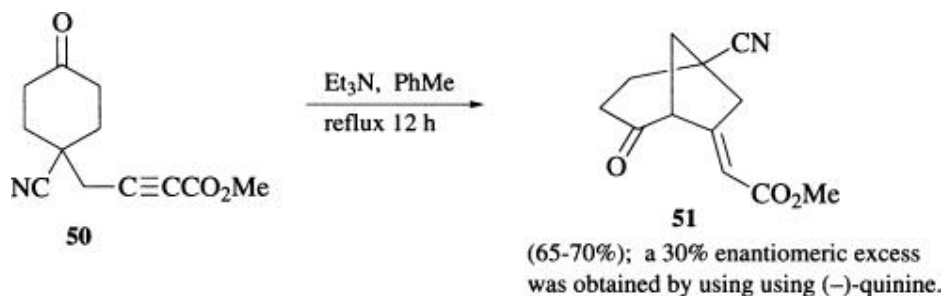
By virtue of the use of an alkynoate, the product contains an α , β -unsaturated ester that can be further functionalized.

In the example cited, a series of straightforward manipulations, including a retro-Michael reaction (**52** to **53**), converted **51** to aldehyde **54** which upon treatment with 2–3 equivalents of 3,4-dimethyl-5-(2¢-hydroxyethyl)thiazolium iodide (Stetter salt; (85, 86)) and 50 equivalents of triethylamine in refluxing 2-propanol afforded the tricyclic ketone **55**, a key intermediate to hirsutic acid, in 67% yield. (84)

52   NaOMe, MeOH, rt, 3 h   **53** (77%)   several steps

54   Stetter salt (2.3 eq), Et₃N (50 eq), i-PrOH, reflux 5 h   **55** (67%)
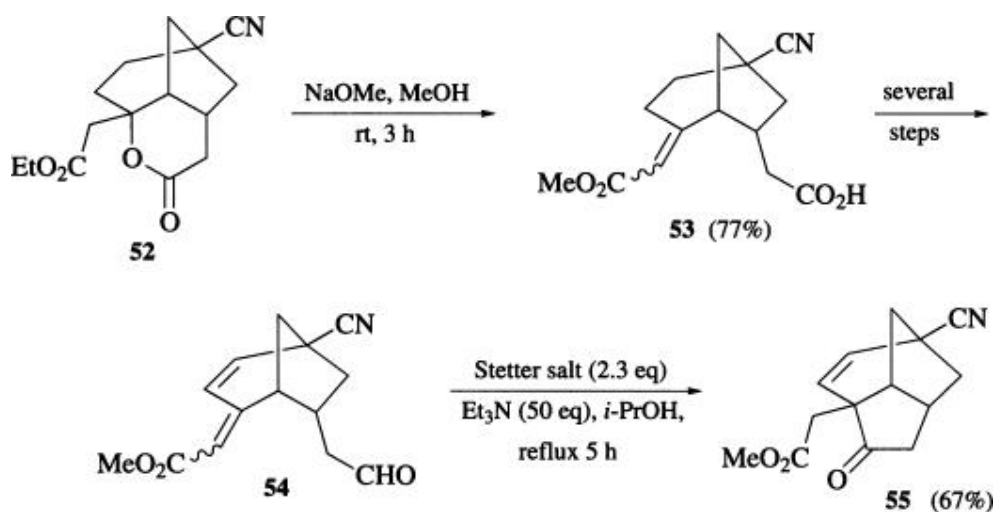
A most interesting example of the use of an ynoate in an intramolecular Michael reaction is illustrated; it originated from efforts to assemble the natural product bilobalide. (87, 88) Of particular interest to the former is the suggestion that what formally amounts to a 5-endo dig intramolecular Michael reaction, probably occurs via an electron transfer-protonation (from diisopropylamine) sequence leading to diyl **56** which subsequently engages in σ -bond formation.
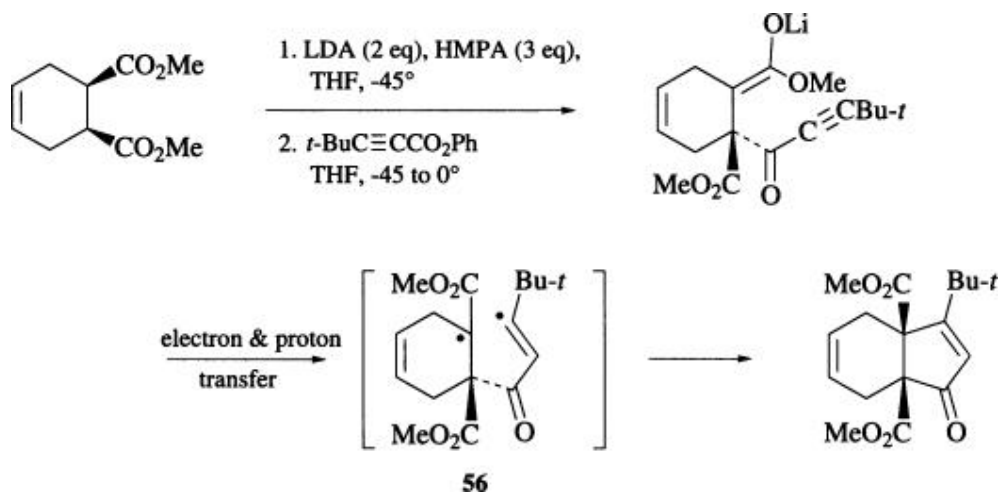
The intramolecular Michael cyclization onto an activated alkyne is used in the preparation of 9- and 10-membered rings. (83, 89, 90)
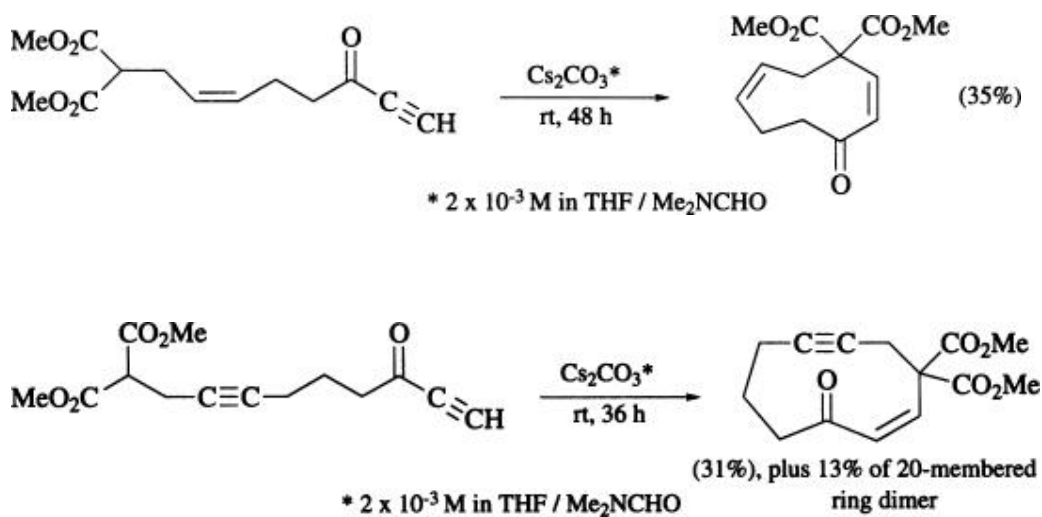
The thermodynamic enolates of β-keto esters also undergo intramolecular Michael addition to alkynones. (91, 92) With substrates bearing a leaving group on the terminal carbon, the anion produced in the intramolecular Michael reaction undergoes alkylation leading to the formation of tricyclic diketones. (91) Alternatively, the enolate can be intercepted in an aldol-like manner.

Cs$_2$CO$_3$, DMF
65°, 20 min

(80%)   (< 5%)

R = CO$_2$Me

Cs$_2$CO$_3$, DMF
40°

(29%)   R = CO$_2$Me

(20%)
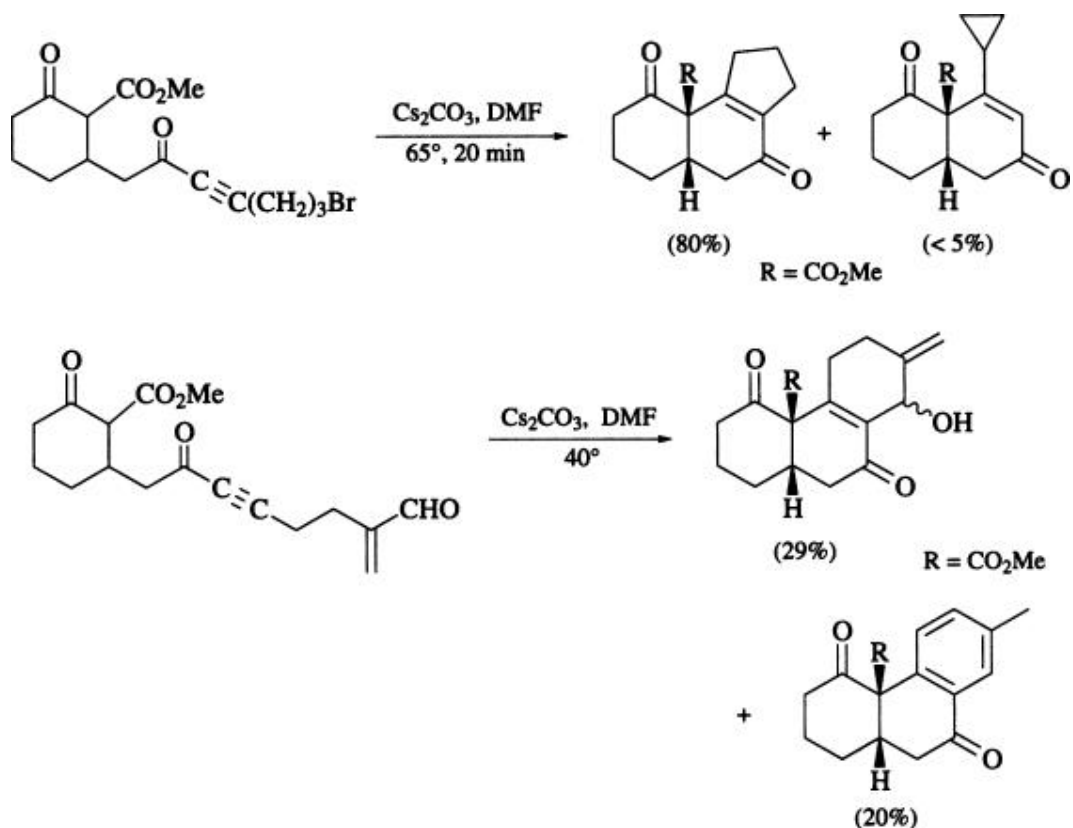
3.2.1.4. Sequential Reactions with Allene Acceptors (see p. 341, top)
Allenes that are activated toward conjugate addition by a nitrile unit undergo
sequential Michael additions when treated with 1,2-diamines. (93) The initial
conjugate addition occurs readily to afford an α , β -unsaturated nitrile, (94)
which reluctantly (temperatures of ca. 300° are required) undergoes the
intramolecular Michael reaction. (95)

3.3. Lewis Acid Promoted Cyclizations
3.3.1.1. Addition of Silyl Enol Ethers
The sesquiterpene seychellene has been constructed by using an
intramolecular variation of the Mukaiyama reaction, that is, a Lewis acid
promoted addition of a silyl enol ether to an enone. (96) While the use
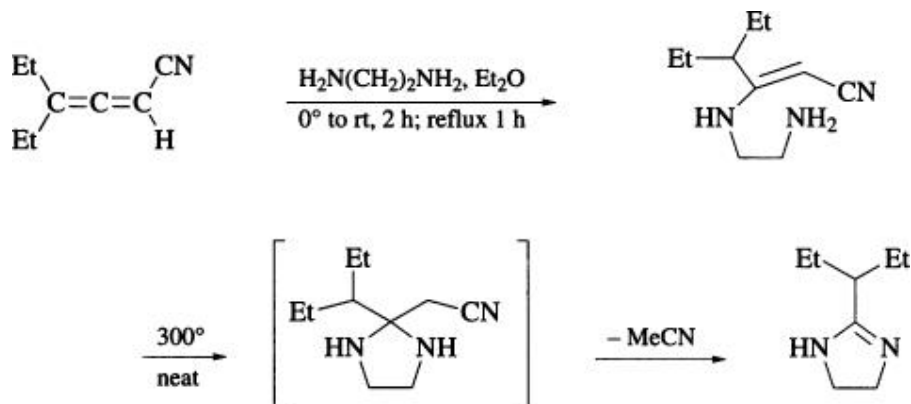
of a variety of different Lewis and protic acids (TiCl$_4$, SnCl$_4$, AlCl$_3$, BF$_3$·Et$_2$O, BF$_3$, MgBr$_2$, HF, HCl, CF$_3$CO$_2$H) failed to convert **57** (3:1 mixture of *endo* and *exo* isomers) to **58** in yields exceeding 5%, the use of a mixture of TiCl$_4$ and Ti(OPr-*i*)$_4$ in methylene chloride proved satisfactory. Considering the fact that only the *exo* isomer can participate in the desired process, the 31% isolated yield of **58** is noteworthy.
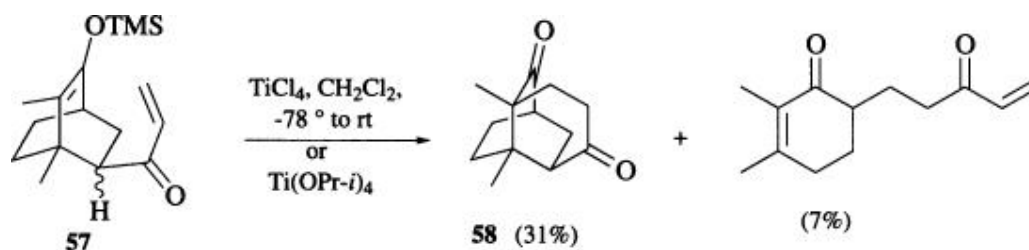
Organotin reagents are useful nucleophiles for the construction of carbon–carbon bonds through their addition to Lewis acid activated enones. (97) For example, fused and spirocyclic ring systems have been prepared from cyclic conjugated enones bearing the tin unit attached to either C3 or C4 of the enone. Yields range from 68 to 92%; the reactions are conducted in dichloromethane in the presence of 1% titanium tetrachloride at temperatures ranging from −78 to 40°.
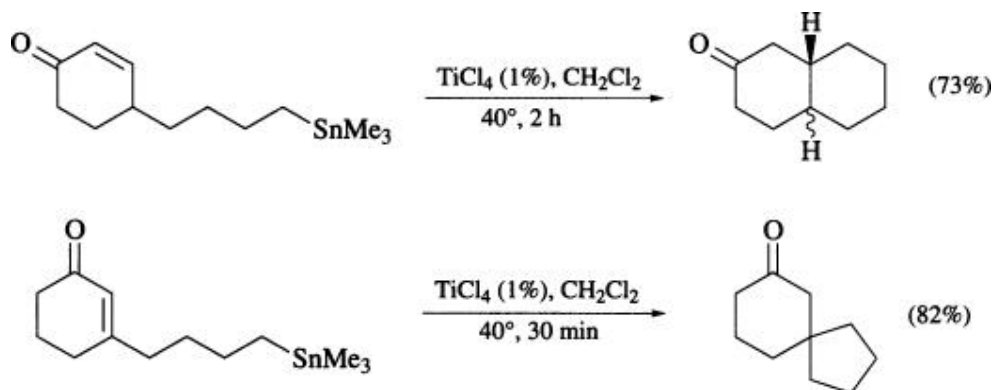
Iodoesters add conjugately to enones upon exposure to trimethylsilyl iodide. Several pathways can be proposed to account for the transformation. In one, the iodo ester is converted to a silyl ketene acetal; a second equivalent of the silyl halide then serves as a Lewis acid, activating the enone toward conjugate addition. The methodology has been applied advantageously to the construction of quassinoids. (98)
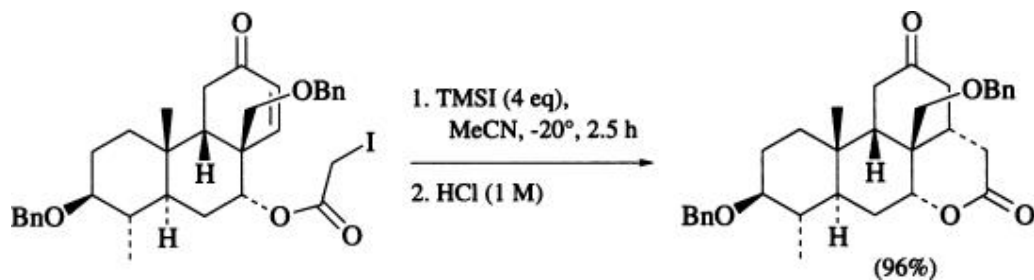
3.3.1.2. Addition of Allylic or Propargylic Silanes

The intramolecular Sakurai reaction, involving the addition of an allylic or propargylic silane to cyclic enones, can be conducted in the presence of a Lewis acid catalyst (EtAlCl$_2$ or TiCl$_4$) or fluoride ion. (99) The reaction has been explored in considerable detail and has proven exceptionally useful. Excellent reviews exist, and the reader is referred to them for detail. (99-104)

4. Comparison with Other Methods

4.1. Free-Radical Cyclizations

Of the alternative methods for accomplishing the equivalent of an intramolecular Michael reaction, those using free radical chemistry are particularly significant and have proven to be of considerable synthetic utility. (105-112) The reader is referred to existing excellent reviews for detail. (113-115)
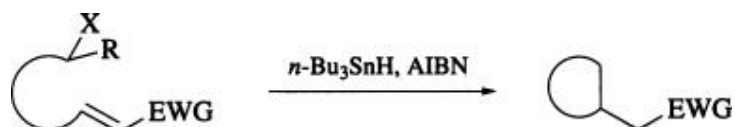
EWG = electron withdrawing group
X = Br, I (radical may also be derived from a vinyl iodide)

4.2. Reductive Methods

Samarium diiodide has become a popular and useful reducing agent which allows one to accomplish a variety of different transformations, (115a) including, for example, cyclization between the β carbon of an electron-deficient alkene and a remotely tethered aldehyde or ketone, that is, between two electrophilic centers. (116) Electrochemical variants of this process exist, though the use of this technique has not become nearly so widespread as has the samarium diiodide version. (117, 118) For the same substrates the stereoselectivity obtained electrochemically is generally inferior to that obtained using samarium(II) or using a vanadium(II) reductant. (116, 117, 119)

EWG = electron withdrawing group

* SmI$_2$, THF, MeOH (or with V[II]), or
  +2 e (electrochemically), proton donor, supporting electrolyte

5. Experimental Procedures
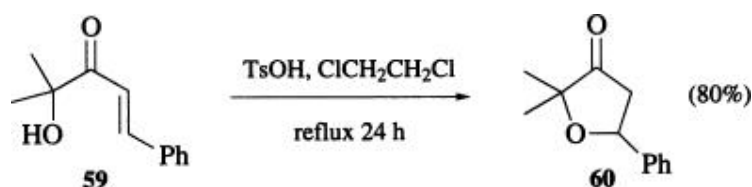
5.1.1.1. 2,2-Dimethyl-5-phenyltetrahydro-3-furanone (Acid-initiated 5-Endo trig Cyclization) (25)

A solution of 2.0 g (10.5 mmol) of enone **59** and 500 mg (2.64 mmol) of p-toluenesulfonic acid monohydrate in 75 mL of 1,2-dichloroethane was heated at reflux for 24 hours. The solution was diluted with methylene chloride and washed with dilute sodium hydroxide, water, and brine. The solution was dried over MgSO$_4$ and the solvent was removed in vacuo to afford 2.3 g of viscous oil. Filtration through 60 g of silica gel gave 1.60 g (8.4 mmol, 80%) of pale yellow solid **60**: mp 34–36°. IR (neat) 2980, 1750, 1180, 1120, 780, 720 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.34 (broad s, 5H, aromatic), 5.13 (dd, X of ABX, J_{AX} = 7, J_{BX} = 10, 1H, methine), 2.85 and 2.35 (AB of ABX, J_{AX} = 7, J_{BX} = 10, J_{AB} = 18, 2H, methylene), 1.38 (s, 3H, CH$_3$), 1.30 (s, 3H, CH$_3$); mass spectrum m/z 190, 172, 162, 132, 104, 78, 77.
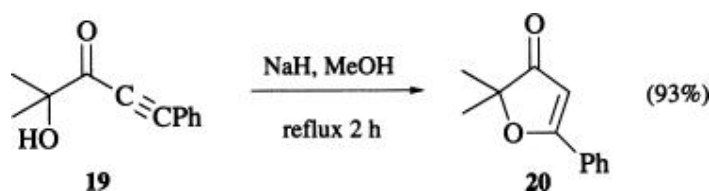
5.1.1.2. 2-Phenyl-4-oxo-5,5-dimethyldihydrofuran (Base-initiated 5-Endo, dig Cyclization) (25)

To a solution of 84 mg (0.44 mmol) of ynone **19** in 5 mL of methanol was added 12 mg (0.50 mmol) of oil-free sodium hydride. The solution was heated at reflux for 2 hours, cooled, and the methanol was removed in vacuo. The residue was partitioned between water and methylene chloride. The organic phase was dried over MgSO$_4$, and the solvent was removed in vacuo to afford 77 mg (0.41 mmol, 93%) of **20** as a pale yellow solid. Recrystallization from hexanes gave an analytical sample: mp 66–67°; IR (CHCl$_3$) 3000, 1685, 1605, 1590, 1565 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.4–8.0 (m, 5H, aromatic), 5.98 (s, 1H,

vinyl), 1.50 (s, 6H, CH₃); UV λ $_{max}$ (EtOH) 215, 242, 298, ε $_{298}$ = 17,750. Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.69; H, 6.54.
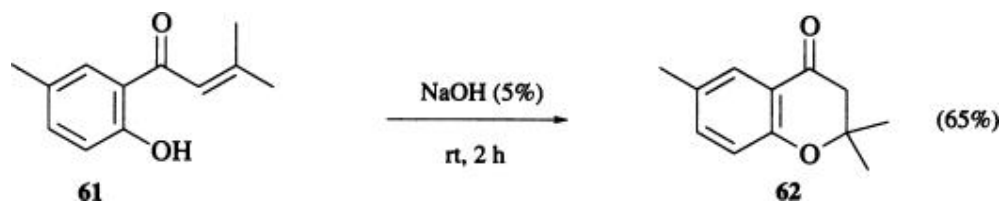
5.1.1.3. Sodium Hydroxide Catalyzed 6-endo, trig Cyclization (25)

A solution of the phenylate of **61** was prepared by dissolving 0.150 g (0.78 mmol) of **61** in 10 mL of 5% aqueous sodium hydroxide. The resulting bright yellow solution rapidly faded to become colorless, and after standing at room temperature for 2 hours the solution was diluted with water and extracted twice with ether, which was subsequently washed with brine and dried (MgSO⁴) to give 0.100 g (65%) of **62** as a light yellow oil: IR (CCl₄) 2990 (s), 1695 (s), 1620 (s) cm⁻¹; ¹H NMR (CDCl₃) δ 1.52 (s, 6H), 2.33 (s, 3H), 2.7 (s, 2H), 6.7 (d, 1H, J = 8 Hz), 7.18 (2 d, 1H, J = 2 and 8 Hz), 7.58 (br d, 1H, J = 2 Hz).

63, R = MeOCH₂
64, R = H
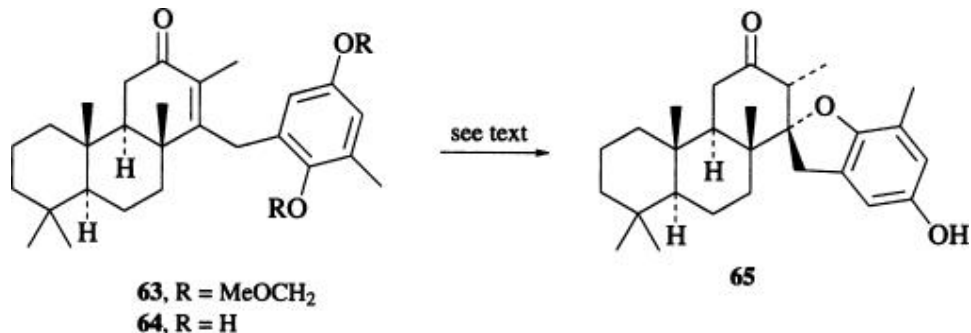
5.1.1.4. Lewis Acid Mediated Cyclization of a Phenol onto a Hindered Acceptor (120)

To a solution of racemic **63** (0.83 g, 1.67 mmol) in dry dichloromethane (30 mL) was added dropwise boron tribromide (1.6 mL, 16.7 mmol) at –78° under argon. The mixture was allowed to warm to –10° within 3 hours. Then the mixture was hydrolyzed with water (15 mL) at 0°. After stirring at room temperature for 12 hours, the mixture was extracted with ether (3 × 30 mL). The combined organic extracts were washed with water and brine, dried with anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel chromatography. Elution with n-hexane/ether (3:2) gave

racemic **65** (0.31 g, 45%) after recrystallization from ether/*n*-hexane as colorless flakes; further elution gave racemic **64** (0.19 g, 28%) as a colorless solid. For **65**, mp 247.0–251° (dec); IR (film) 3330, 1700, 1465, 1210, 1140 cm^{-1}. ^{1}H NMR (90 MHz, CDCl$_3$) δ 0.82 (s, 6H, 2 CH$_3$), 0.90 (d, 3H, $J = 6.5$ Hz, 2¢-CH$_3$), 0.91 (s, 3H, CH$_3$), 1.17 (s, 3H, CH$_3$), 1.21–1.80 (m, 11H), 2.10 (s, 3H, C7-CH$_3$), 1.90–2.52 (m, 3H), 2.59 (q, 1H, $J = 6.5$ Hz, C2¢-H), 2.91 (d, 1H, $J = 16.5$ Hz, C2-H), 3.37 (d, 1H, $J = 16.5$ Hz, C2-H), 4.32 (m, 1H, OH), 6.42 (br s, 2H, aromatic). Anal. Calcd for C$_{27}$H$_{38}$O$_3$: C, 78.98; H, 9.33. Found: C, 78.64; H, 9.32.

*5.1.1.5. Protic Acid-Catalyzed Cyclization of Racemic **64** (120)*
To a solution of racemic **64** (100 mg, 0.10 mmol) in dry THF (5 mL) was added 6 N hydrochloric acid (1 mL) at room temperature under argon. After stirring at room temperature for 3 days, the mixture was extracted with ether (3 × 10 mL). The combined organic extracts were washed with water and brine, dried with anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel chromatography. Elution with *n*-hexane/ether (1:1) gave racemic **65** (25 mg, 25%) with recovery of racemic **64** (33 mg, 33%).
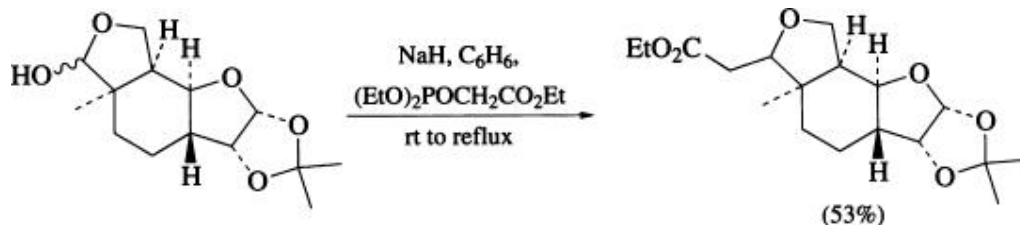
5.1.1.6. Reaction of (2R,3R,3aR,6S,-7S,7aR)-7-(Hydroxymethyl)-2,3-(isopropylidenedioxy)-6-methyl-6-(oxomethyl)octahydrobenzo[3,4-b]furan 6,7-Lactol with Triethyl Phosphonoacetate (Horner–Emmons–Wadsworth Reaction Followed by Intramolecular Michael Cyclization) (53)
To a suspension of sodium hydride prewashed with hexane (67 mg, 50% oil dispersion, 1.4 mmol) in 4 mL of dry benzene under argon was added, via syringe, triethyl phosphonoacetate (0.24 mL, 1.2 mmol). After 5 minutes, the lactol (150 mg, 0.6 mmol) in dry benzene (1 mL) was added. The reaction mixture was refluxed for 1 hour, cooled, quenched with water, and washed with brine. The organic layer was dried (Na$_2$SO$_4$) and evaporated, and the residue was purified by chromatography on silica gel (diethyl ether, R_f 0.64) to afford the Michael adduct (100 mg, 53%) as a solid material: IR 3500, 2890, 1720 (ester) cm^{-1}; ^{1}H NMR (80 MHz) δ 1.00–1.84 (m, 17H, C(CH$_3$)$_2$, H3, H9, H10, CO$_2$CH$_2$CH$_3$, CH$_3$), 2.39 (d, 2H, H11), 2.53–2.84 (m, 1H, H5), 3.68–4.33

(m, 6H, H4, H6, H8, CO$_2$CH$_2$CH$_3$), 4.58 (dt, 1H, H2), 5.75 (d, $J_{1,2}$ = 4.5, 1H, H1); MS, m/z 326 ([M$^+$ + 1] - CH$_3$), 325 (M$^+$ -CH$_3$).
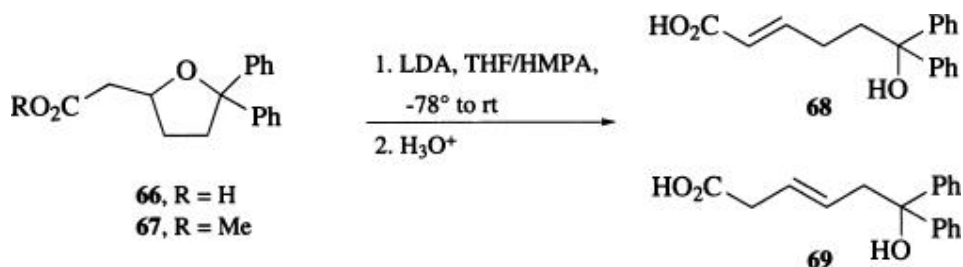
5.1.1.7. Preparation of 6-hydroxy-6,6-diphenyl-2-hexenoic acid (68) and 6-6-hydroxy-6,6-diphenyl-3-hexenoic acid (69) (A Retro Reaction: Ring Opening of THF- and THP-Acetic Acids with Excess LDA) (121)

To a cold (–78°) solution of LDA (3.5 mmol) in THF (8 mL) was added a solution of 66 (0.282 g, 1 mmol) in THF (2 mL) and HMPT (1 mL). After stirring overnight (–78° to room temperature) and adding acetic acid (at –78°), the reaction mixture was poured into water, acidified with 1 N HCl, and extracted with ether. The crude product after usual workup was purified by preparative TLC (silica gel PF254, ethyl acetate/pentane 35:65), furnishing 69 (0.21 g 74%).

If acid 66 (1 mmol) was treated with LDA (2 mmol), it gave a mixture of 68 and 69 (68/69 = 66:34). When treated with 2.2 mmol of LDA, it gave 68 (mp 137–138.5°) and 69 in equal portions, from which 69 was separated by fractional crystallization (from ether).

IR (α , β -unsaturated product 68; KBr) 2500–3300, 1680, 1640, 1595, 1490, 1450, 1425, 1350, 1310, 1290, 1250, 1200, 1060, 960, 910, 880, 780, 750, 640, 600 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 2.33 (m, 4H, 2H-[4 and 5]), 5.76 (d, 1H, J = 16 Hz, H-C[3]), 7.0 (m, 1H, H-C[2]), 7.33 (m, 10H, aromatic). Anal. Calcd for C$_{18}$H$_{18}$O$_3$: C, 76.57; H, 6.43. Found: C, 76.46; H, 6.56.

Spectral data for β , γ -unsaturated product 69: IR (film) 2500–3500, 1710, 1655, 1600, 1495, 1450, 1180, 1100, 1060, 1010, 750, 700 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 3.06 and 3.13 (2 d, J = 6 Hz, 4H, 2 H-C[2]) and 2 H-C[5]), 5.6 (m, 2H, CH = CH), 7.3 (m, 10H, aromatic).
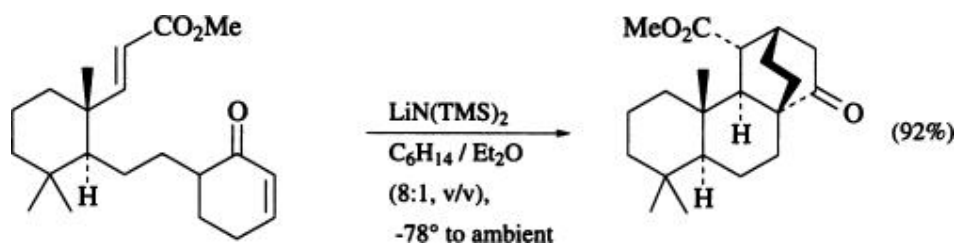
5.1.1.8. Methyl (–)-(3S,4R,4aR,4bS,8aS,10aR)-1,2,3,4,4a,4b,5,6,7,8,8a,9,10,10a-Tetradecahydro-4b,8,8-trimethyl-1-oxo-3,10a-ethanophenanthrene-4-carboxylate (Sequential Michael Reactions: Inter- Followed by Intramolecular) (122)

To a stirred solution of lithium hexamethyldisilazide, prepared from 1,1,1,3,3,3-hexamethyldisilazane (160 mg, 0.991 mmol) and butyllithium (63 mg, 0.991 mmol) in dry *n*-hexane (20 mL) at –78° under argon, was added a solution of the α , β -unsaturated ester (250 mg, 0.762 mmol) in dry diethyl ether (3.3 mL). After being stirred for 1 hour at –78°, the mixture was allowed to warm to room temperature during 30 minutes, and was then stirred for 1 hour. The reaction mixture was poured onto silica gel (50 g) at room temperature and diethyl ether (100 mL) was added. The resulting mixture was filtered and the filtrate was evaporated to give a solid, which was purified by silica gel chromatography. Elution with *n*-hexane/ethyl acetate (20:3, v/v) afforded the tetracyclic compound illustrated (230 mg, 92%) as needles, mp 145–148°. IR 1725, 1715 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ0.82, 0.88, 1.02 (each 3H, 3 × CH$_3$), 0.90–2.65 (m, 19H), 3.61 (s, 3H, OCH$_3$). MS, m/e 332 (M$^+$). Anal. Calcd for C$_{21}$H$_{32}$O$_3$: C, 75.85; H, 9.7. Found: C, 75.8; H, 9.6.
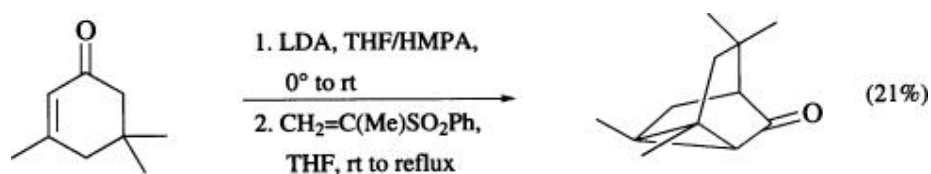
5.1.1.9. 1,2,4,4-Tetramethyltricyclo[3.2.1.0^{2,7}]octan-6-one. (Sequential Reactions: Bicycloannulation) (63)

To a solution of 0.77 mL (0.55 g, 5.4 mmol) of diisopropylamine and 3 mg of 2,2¢-bipyridyl in 4 mL of THF at 0° was added dropwise, with stirring, 3.9 mL (5.1 mmol) of 1.3 M *n*-butyllithium over 10 minutes. To the resulting crimson solution at 0° was added dropwise, with stirring, a solution of 0.47 mL (0.50 g, 3.6 mmol) of isophorone in 4 mL of THF over 1 hour. After the solution had been allowed to stir at 0° for an additional 15 minutes, 2.5 mL of HMPA was

added, and the mixture was allowed to warm to room temperature. To the resulting deep purple solution was added dropwise, with stirring, a solution of 0.76 g (4.2 mmol) of isopropenyl phenyl sulfone in 10 mL of THF over 1 hour. The solution was then heated and refluxed for 2 hours, after which it was partitioned between saturated aqueous $NaHCO_3$ and petroleum ether (boiling range 30–60°). The aqueous phase was extracted with petroleum ether, and the combined extracts were washed with water, aqueous $CuSO_4$ (saturated solution diluted with an equal portion of water), and brine and dried over Na_2SO_4. The solvent was distilled through a Vigreux column on a steam bath, and the residual oil was subjected to preparative GC (200°) to give the tricyclooctanone shown above: 0.132 g (21%); colorless oil; IR 1721 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ 1.47–2.07 (m, 5H), 1.31 (s, 3H), 1.27 (m, 1H), 1.11 (s, 3H), 1.02 (s, 3H), 0.91 (s, 3H), MS, m/e (relative intensity) 178 (M$^+$, 12), 150 (18), 135 (55), 119 (11), 107 (100), 91 (33), 79 (35). High-resolution MS, calcd for $C_{12}H_{18}O$: 178.1358. Found: 178.1358.

6. Tabular Survey

An effort has been made to cover the literature entirely through June 1992, but additional entries published between July and September 1992 have been included where possible. Because many intramolecular Michael reactions occur as part of a larger synthetic work, often the reaction is not included in abstract material and thus does not appear in *Chemical Abstracts*. Frequently, Michael reactions are referred to as conjugate additions and/or 1,4 additions, and search efforts have been expanded to include other terminologies whenever possible. Retro- (or reverse) intramolecular Michael reactions have been included in the tables, although these reactions are seldom found in abstracts under this heading, and a thorough search of the retro version of the reaction is bound to be incomplete. Although searches of the indices of the major journals have been made in addition to manual and on-line searches of *Chemical Abstracts*, many of the references cited were found by other methods, leading to the conclusion that omissions are, unfortunately, inevitable.

The tables are arranged according to the following guidelines:

1. Nucleophile type (i.e., sulfur, oxygen, nitrogen, and carbon).
2. For a given nucleophile, tables are subdivided according to acceptor type (i.e., α , β -unsaturated sulfoxide, sulfone acceptor, etc.). For simplicity and to aid a researcher in finding a particular example, entries are organized according to increasing carbon count in the product rather than the starting material. Because many of the reactions are condensations, it is difficult to know which of the starting materials to count. Excluded from the count are carbons in:
   a. Alcohols that esterify carboxylic acids, and carboxylic acids that esterify alcohols;
   b. Alcohol-protecting groups such as silyl, benzylic, and THP ethers; and
   c. Nitrogen-protecting groups such as amides, urethanes, and benzylic groups.

   Arbitrarily, acetals and ketals, as well as sugar anomeric acetals, are not excluded.
3. If the starting material contains a sulfoxide or a sulfone group, the substituents on the S atom are not included in the carbon count.
4. The table containing double (or sequential) Michael reactions contains only the examples where two intramolecular closures occur. The examples that involve an intermolecular reaction followed by an intramolecular closure are shown throughout other tables and have been pointed out in footnotes to the tables.
5. Retrograde Michael reactions are tabulated separately according to the

above guidelines for a hypothetical addition reaction.

6. Molecules that contain a ferrocene nucleus are tabulated in a separate table following the guidelines listed above.

Product structures often reflect subsequent reactions which follow the intramolecular Michael reaction. The observed products are shown and the nature of many subsequent reactions (aldol, elimination, subsequent Michael reaction, substitution, etc.) are indicated in the footnotes to the table.

A dash (—) by itself in the column listing conditions indicates that no conditions were provided. If a yield is not reported but a product is isolated, a dash (—) appears in the yield column. A zero (0) in the yield column indicates that the reaction did not proceed.

Although closures of compounds containing allylsilanes onto the Michael acceptor fall within the boundaries of this chapter, such compounds are not included in the tables since the allysilane chemistry has been reviewed extensively in recent years. For leading references see Refs. 101-104.

Standard solvents and reagents such as THF, DMF, *n*-BuLi, and so on are not included in the table of abbreviations.

Table I. Sulfur Donor, Miscellaneous Acceptor

View PDF

Table II. Oxygen Donor, α , β -Unsaturated Sulfoxide or Sulfone Acceptor

View PDF

Table III. Oxygen Donor, α , β -Unsaturated Ketone or Alkynyl Ketone Acceptor

Table IV. Oxygen Donor, α , β -Unsaturated Ester, Nitrile, Aldehyde, or Acid Acceptor

Table V. Nitrogen Donor, α , β -Unsaturated Sulfoxide, Sulfone, or Sulfoximide Acceptor

Table VI. Nitrogen Donor, α , β -Unsaturated Carbon or Nitrogen Group Acceptor

Table VII. Nitrogen Donor, α , β -Unsaturated Ketone or Alkynyl Ketone Acceptor

Table VIII. Carbon Donor, α , β -Unsaturated Sulfoxide or Sulfone Acceptor

Table IX. Carbon Donor, α , β -Unsaturated Carbon or Nitrogen Group Acceptor

Table X. Carbon Donor, α , β -Unsaturated Ketone or Alkynyl Ketone Acceptor

Table XI. Carbon Donor, Ferrocenes and Miscellaneous Acceptor

Table XII. Intramolecular Double, or Sequential, Michael Reactions

Table XIII. Retro Intramolecular Michael Reactions

Table I. SULFUR DONOR, MISCELLANEOUS ACCEPTOR

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{6-8}$ H$_2$N—S, NH$_2$Br, CO$_2$Et	1. KOH, H$_2$O, reflux 8 h 2. H$^+$	CO$_2$H n = 1 (60) n = 2 (69) n = 3 (<5)	123
C$_7$	H$_2$S, piperidine	(—)	124
R^{1}O$_2$C, Cl, NH, R^2, O R^1 R^2 Me Me Et Me	KSH, MeOH, 50–60°, 2 h	R^{1}O$_2$C, S, NH, R^2, O (48) (—)	125,125a
AcS, CO$_2$Me	1. NaOMe, MeOH 2. LAH 3. MsCl, C$_5$H$_5$N 4. PhSeNa	S, SePh (82)	126

351

Table I. SULFUR DONOR, MISCELLANEOUS ACCEPTOR (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

KOH, H$_2$O, reflux 8 h; H$^+$

123

	R	R^1	R^2	
C$_7$	OMe	H	Me	(76)
C$_8$	OEt	Me	H	(75)
C$_{11}$	OEt	(CH$_2$)$_5$	H	(71)

CS$_2$, NaOH, DMF, H$_2$O, rt, 2 h; X

127-129

	R	R^1	X	
C$_9$	H	Na•nH$_2$O	—	(67)
	Cl	Na•nH$_2$O	—	(58)
	Br	Na•nH$_2$O	—	(55)
C$_{10}$	Me	Na•nH$_2$O	—	(95)
	H	Me	(MeO)$_2$SO$_2$	(95)
	Cl	Me	(MeO)$_2$SO$_2$	(95)
C$_{11}$	Me	Me	(MeO)$_2$SO$_2$	(98)
	H	Et	(EtO)$_2$SO$_2$	(93)

128 (for the Na•nH$_2$O rows), 127 (for the Me/Et rows)

C$_9$

CH$_2$(CO$_2$Me)$_2$, *t*-BuOK, THF, -70 to 20°, 10 h

 (82)

130

1. KOH, H$_2$O, reflux 8 h
2. H$^+$

 (78)

123

K$_2$CO$_3$ (0.1 M)

131

	R	R^1	
C$_{10}$	H	Me	(82)
	p-Cl	Me	(92)
	m-Cl	Me	(89)
	o-Cl	Me	(93)
	p-Br	Me	(88)
C$_{11}$	H	Et	(94)
	p-Cl	Et	(92)
	o-Cl	Et	(90)
	p-Br	Et	(90)
	p-Me	Me	(86)
C$_{12}$	*p*-Me	Et	(85)
C$_{13}$	H	*n*-Bu	(96)
C$_{15}$	H	C$_6$H$_{11}$	(86)

Table I. SULFUR DONOR, MISCELLANEOUS ACCEPTOR (*Continued*)

354

355

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

	R
C_{10}	CO_2Me
	CO_2Et
C_{11}	$COMe$

1. Thiourea, EtOH, reflux 1-3.7 h
2. NH_4Cl, 85°, 1 h

(61)
(63)
(27)[a]

132

C_{10-11}

1. KOH, H_2O, reflux 8 h
2. H^+

n = 1 (69)
n = 2 (73)

123

$PhC\equiv CCOCH_2R^1$

1. NaH, DMF, CS_2, rt, 2 h
2. R^2X, 3 h[b]

R^1	R^2	I	II
H	Bn	(46)	(11)
H	p-$BrC_6H_4CH_2$	(72)	(18)
H	Me	(55)	(13)
Me	Me	(43)	(11)

C_{11}
C_{12}
C_{13}

133

C_{11}

Et_3N (cat.), CH_2Cl_2, H_2S, rt, overnight

(59)

134

Et_3N (1 eq), CH_2Cl_2, H_2S, rt, overnight

(85)

134

C_{12}

HCl (2 N), THF, rt, 2 h

(75)

135

	R^1	R^2	R^3
C_{13}	Me	Me	H
C_{18}	H	Ph	Me
	Ph	H	Me
C_{19}	H	Ph	Et

H_2S, AcONa•$3H_2O$, EtOH, reflux 4-15 h

I + II	I:II
(81)	100:0
(26)	0:100
(25)	100:0
(28)	0:100

136

	R^1	R^2	R^3
C_{23}	Ph	Ph	H

H_2S, Triton B, EtOH, reflux 15 h

I + II	I:II
(38)	100:0

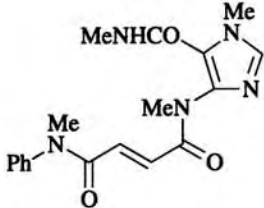136

Table I. SULFUR DONOR, MISCELLANEOUS ACCEPTOR (*Continued*)
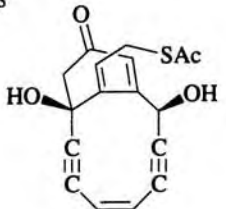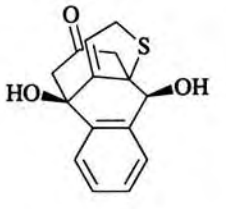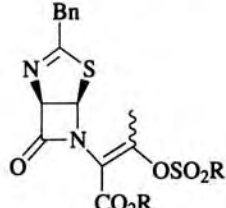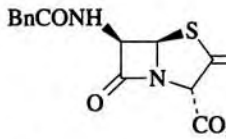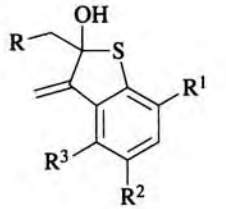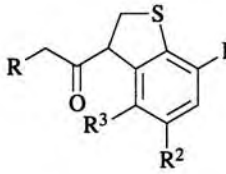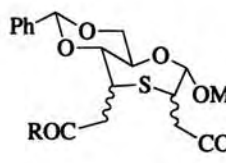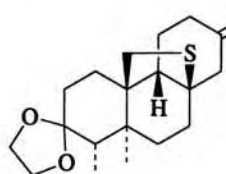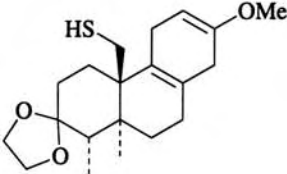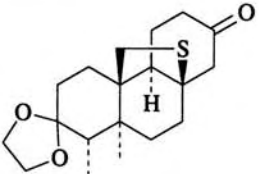
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₁₅	Et₃N, THF, , rt, 15.5 h	(71)	14
	Et₃N, DMF, -20°, 0.2-0.5 h		137

		R	R¹	
	HCl (10%)	Me	Me	(80)
	HClO₄ (60%)	Me	CF₃	(75)
	HClO₄ (60%)	Ph₂CH	CF₃	(66)
	HClO₄ (60%)	PMB	Me	(55)

138

		R	R¹	R²	R³	
C₁₆	KOH (aq), rt, 3 min	p-ClC₆H₄O	H	Cl	H	(95)
	KOH (aq), warm 5 min	p-ClC₆H₄O	H	H	H	(86)
	KOH (aq), rt, 3 min	p-ClC₆H₄O	H	Br	H	(94)
	KOH, EtOH, warm 3.5 min	p-ClC₆H₄O	Cl	H	Cl	(92)
C₁₇	KOH (aq), rt, 5 min	p-ClC₆H₄O	H	OMe	H	(91)
	KOH (aq), rt, 30 min	p-ClC₆H₄O	H	Me	H	(94)
	KOH (aq), rt, 5 min	p-MeC₆H₄O	H	Cl	H	(95)
C₁₈	KOH (aq), warm 5 min	p-MeC₆H₄O	Me	H	H	(85)
	KOH (aq), rt, 3 min	p-ClC₆H₄O	H			(93)

C₁₈₋₁₉	H₂S, Py, Et₃N, 6 h	R = Me (33) R = OEt (41)	81
C₁₉	MeOK, MeOH, rt, 18 h	(20)	139

Table I. SULFUR DONOR, MISCELLANEOUS ACCEPTOR (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	PPTS, Py, rt, 1 h	(27)	139

[a] Two other products were also characterized.
[b] X was not specified.

Table II. OXYGEN DONOR, α, β–UNSATURATED SULFOXIDE OR SULFONE ACCEPTOR

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	A. α, β–Unsaturated Sulfoxide Acceptor		

C$_{15}$
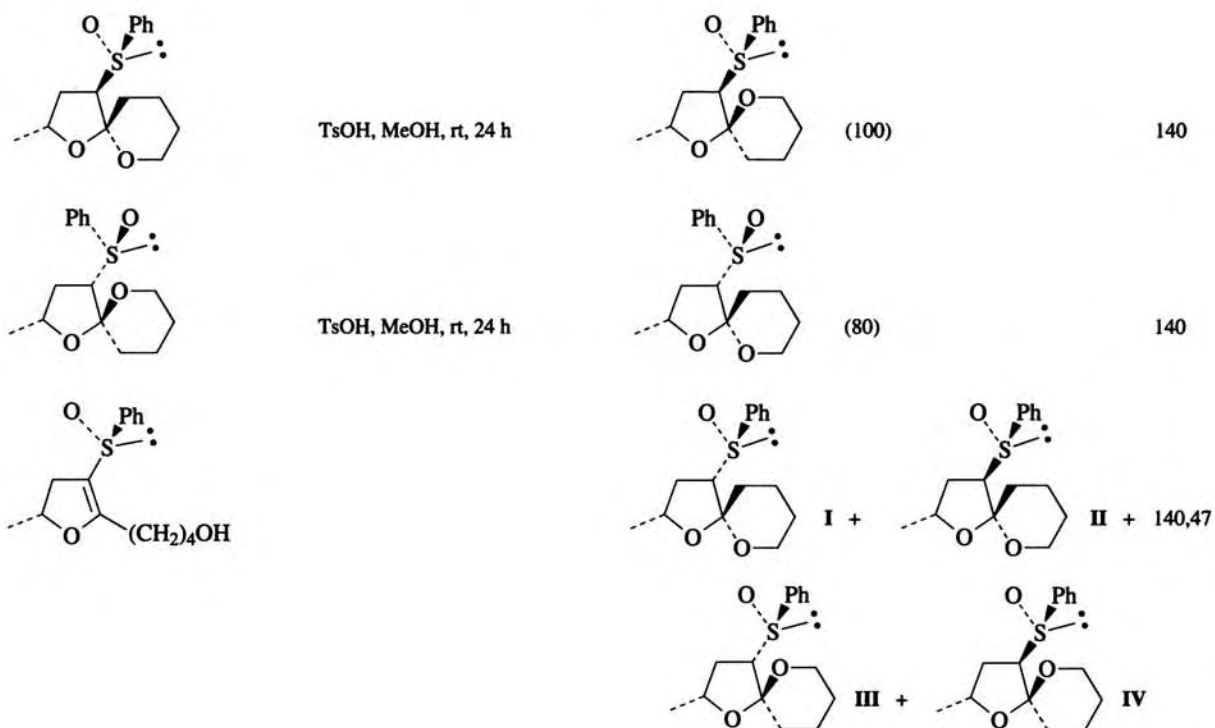
| | TsOH, MeOH, rt, 24 h | (100) | 140 |

| | TsOH, MeOH, rt, 24 h | (80) | 140 |

I + II + 140,47

III + IV

Substrate	Conditions	Product(s) and Yield(s) (%)		Refs.
		I + II + III + IV	**I:II:III:IV**	
	TsOH, MeOH, rt, 24 h	(87)	36:0:51:13	
	TsOH, CH$_2$Cl$_2$, rt, 24 h	(100)	46:0:51:3	
	ZnCl$_2$, CH$_2$Cl$_2$, rt, 24 h	(85)	73:0:16:11	
	ZnBr$_2$, CH$_2$Cl$_2$, rt, 24 h	(77)	73:0:22:11	
	MgCl$_2$, CH$_2$Cl$_2$, rt, 24 h	(83)	24:0:74:2	
	HgCl$_2$, CH$_2$Cl$_2$, rt, 24 h	*a*	36:5:51:8	
	n-BuLi, THF, reflux 2 h	(82)	0:86:14:0	
	NaH, THF, reflux 2 h	(93)	0:94:6:0	
	KH, THF, rt, 0.5 h	(90)	0:100:0:0	
	NaH, THF-C$_6$H$_{14}$, reflux 2 h	(92)	0:98:2:0	
	NaH, DME, reflux 2 h	(90)	0:94:6:0	
	NaH, DMF, reflux 2 h	(80)	31:38:21:0	
	NaH, DMSO, reflux 2 h	(85)	18:4:36:42	

I + II + 140,47

III + IV

		I + II + III + IV	**I:II:III:IV**	
	TsOH, MeOH, rt, 24 h	(84)	37:11:10:42	
	TsOH, CH$_2$Cl$_2$, rt, 24 h	(100)	13:6:1:80	
	ZnCl$_2$, CH$_2$Cl$_2$, rt, 24 h	(83)	38:1:5:56	
	ZnBr$_2$, CH$_2$Cl$_2$, rt, 24 h	(80)	52:3:6:38	
	MgCl$_2$, CH$_2$Cl$_2$, rt, 24 h	(86)	1:45:1:53	
	HgCl$_2$, CH$_2$Cl$_2$, rt, 24 h	*a*	18:22:23:37	
	n-BuLi, THF, reflux 2 h	(81)	0:4:96:0	
	NaH, THF, reflux 2 h	(92)	0:2:98:0	
	KH, THF, reflux 2 h	(90)	0:0:100:0	
	NaH, THF-C$_6$H$_{14}$, reflux 2 h	(92)	0:0:100:0	
	NaH, DME, reflux 2 h	(89)	0:3:97:0	
	NaH, DMF, reflux 2 h	(78)	22:11:8:59	
	NaH, DMSO, reflux 2 h	(83)	37:13:6:44	

C$_{16}$
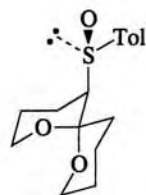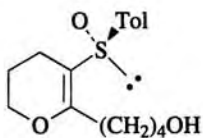
	KH, THF, 0° to rt, 1 h	(66)	141, 142
	NaH, THF, 0°; rt, 40 min	(77)	
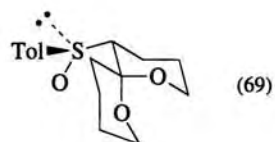
TsOH, MeOH, rt, 24 h   (69)   141, 142
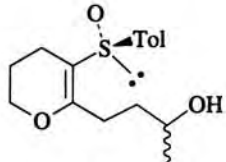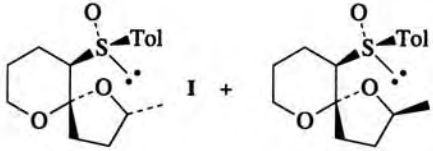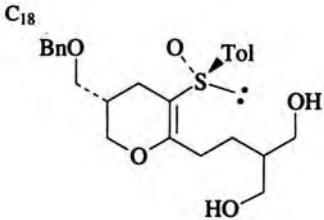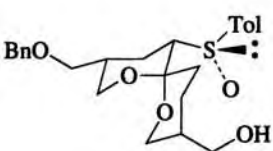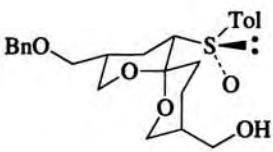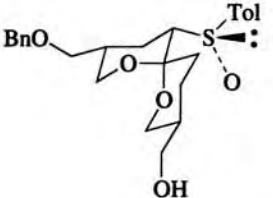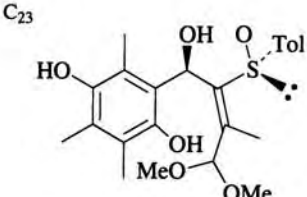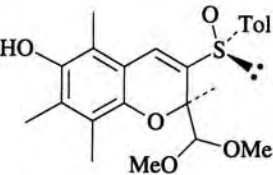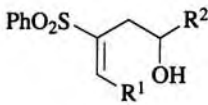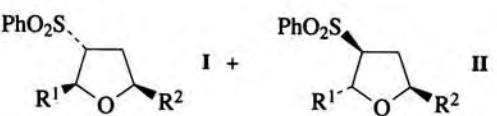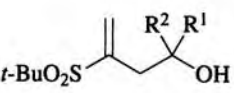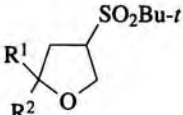
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

KH, THF, rt

I + II

R:S		I + II	I:II
47:53		(76)	48:52
15:85		(85)	18:82
76:24		(74)	73:27
58:42		(86)	55:45
—		(95)	47:53
—		(93)	47:53

143

C₁₈

KH, THF, rt

(87)

144

TsOH, MeOH, rt

(61)

144

C₂₃

NaOMe, MeOH, reflux 3 h

(96)

145

B. α, β–Unsaturated Sulfone Acceptor

t-BuOK, *t*-BuOH, THF, 25°, 1–90 min

I + II

146

	R¹	R²		I + II	I:II
C₁₂	Me	Me		(81)	57:43
	CH₂OBn	Me		(0)	—
	Me	CH₂OBn		(86)	64:36
C₁₄	*i*-Pr	Me		(0)	—
C₁₇	Me	(CH₂)₂C(Me)O(CH₂)₂O		(61)	50:50
	Ph	Me		(18)	100:0
	Me	Ph		(76)	67:33
C₁₉	2,4-(MeO)₂C₆H₃	CH₂OBn		(76)	67:33
	2,4-(MeO)₂C₆H₃	Me		(60)	80:20
C₂₁	Me	*n*-C₁₀H₂₁		(81)	57:43
C₂₄	2,4-(MeO)₂C₆H₃	Ph		(19)	80:20

KH (cat.), THF, rt, 10 min

27

Table II. OXYGEN DONOR, α, β–UNSATURATED SULFOXIDE OR SULFONE ACCEPTOR (*Continued*)
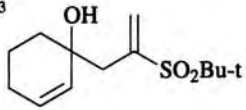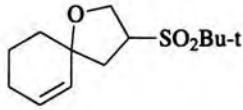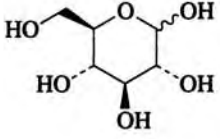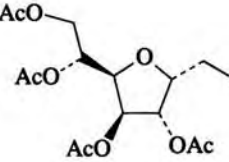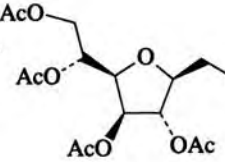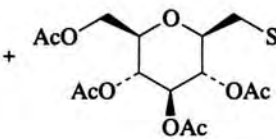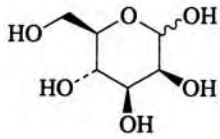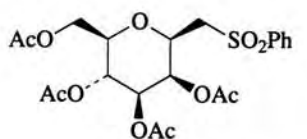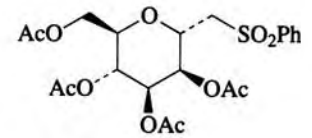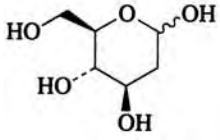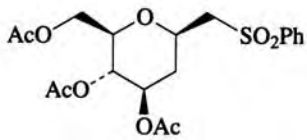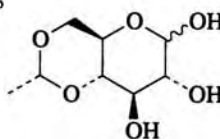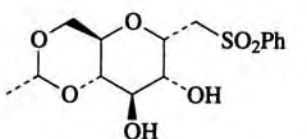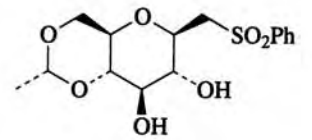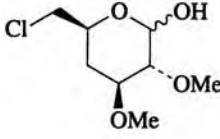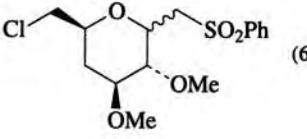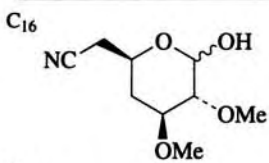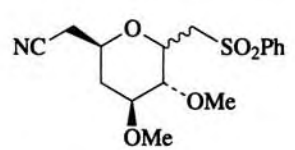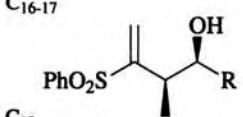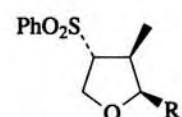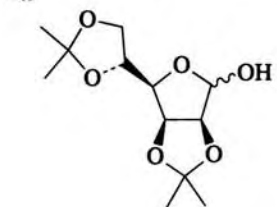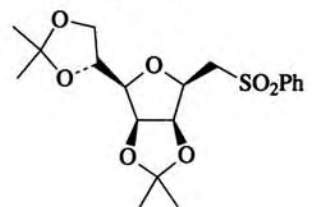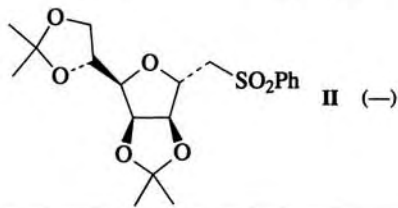
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

	R^1	R^2	
C$_{12}$	Et	Et	(88)
	-(CH$_2$)$_4$-		(84)
C$_{14}$	Ph^b	H	(81)
C$_{18}$	n-C$_5$H$_{11}$	n-C$_5$H$_{11}$	(85)

C$_{13}$

KH, THF, rt, 10 min   (81)   27

1. (EtO)$_2$P(O)CH(Na)SO$_2$Ph, Py
2. Ac$_2$O, Py

(53)   +   (18)

+   **I**   (10)   147

1. (EtO)$_2$P(O)CH(Na)SO$_2$Ph, Py   **I** (50)   147
2. NaOMe, MeOH
3. Ac$_2$O, Py

1. (EtO)$_2$P(O)CH(Na)SO$_2$Ph, Py
2. Ac$_2$O, Py

(—)   +   147

(—)

1. (EtO)$_2$P(O)CH(Na)SO$_2$Ph, Py
2. Ac$_2$O, Py

(80)   147

C$_{15}$

(EtO)$_2$P(O)CH(Na)SO$_2$Ph, THF^c

(60)   +   147

(20)

(EtO)$_2$POCH(Na)SO$_2$Ph

(60)   147, 148

Table II. OXYGEN DONOR, α, β–UNSATURATED SULFOXIDE OR SULFONE ACCEPTOR (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{16}$	(EtO)$_2$POCH(Na)SO$_2$Ph	(76)	147, 148
C$_{16\text{-}17}$	KH (cat.), THF, rt, 30 min	R = *n*-C$_5$H$_{11}$ (89) R = Ph (80)	28
C$_{19}$	(EtO)$_2$POCH(Na)SO$_2$Ph, Py	**I** (—) + **I:II** = 1:5 **II** (—)	147

^{a} The products were not isolated.
^{b} The mixture of α and β isomers can be converted to the β isomer by treatment with MeOH and NaOMe.
^{c} When the sulfoxide was used instead of the sulfone, only decomposition occurred.

Table III. Oxygen Donor, α, β–Unsaturated Ketone or Alkynyl Ketone Acceptor
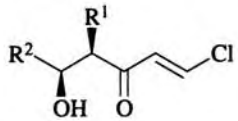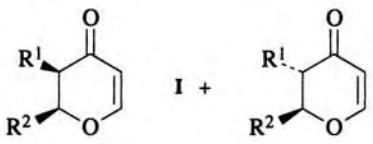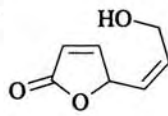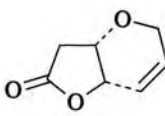
	Substrate	Conditions	Product(s) and Yield(s) (%)			Refs.

A. α, β-Unsaturated Ketone Acceptor

	R^1	R^2			I + II	I:II	
C_6	H	$BnOCH_2$	i-Pr$_2$NEt (0.6 eq), CH$_2$Cl$_2$, -78 to -15°, 15 h		(66)	—	
C_7	Me	$BnOCH_2$	i-Pr$_2$NEt (0.8 eq), CH$_2$Cl$_2$, -78 to -22°, 15 h		(62)	74:26	
C_8	H	n-Pr	i-Pr$_2$NEt (0.8 eq), CH$_2$Cl$_2$, -78 to -15°, 15 h		(60)	—	
C_9	Me	n-Pr	i-Pr$_2$NEt (1 eq), CH$_2$Cl$_2$, -78 to 20°, 30 min		(44)	70:30	
	Me	n-Pr	i-Pr$_2$NEt (1 eq), CH$_2$Cl$_2$, -78 to -15°, 15 h		(80)	68:32	
	Me	n-Pr	i-Pr$_2$NEt (0.1 eq), CH$_2$Cl$_2$, -78 to -15°, 15 h		(73)	89:11	
	Me	n-Pr	i-Pr$_2$NEt (0.6 eq), CH$_2$Cl$_2$, -78 to -15°, 15 h		(82)	91:9	
	Me	n-Pr	i-Pr$_2$NEt (0.8 eq), CCl$_4$, -78 to -15°, 15 h		(90)	95:5	
	Me	n-Pr	i-Pr$_2$NEt (0.8 eq), PhMe, -78 to -15°, 15 h		(55)	90:10	
C_{12}	Me	C_6H_{11}	i-Pr$_2$NEt (0.8 eq), CH$_2$Cl$_2$, -78 to -15°, 15 h		(62)	93:7	

The "TMSOTf" condition and reference "149" apply to the first block.

	Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_7		MeSO$_3$H	(48)	150

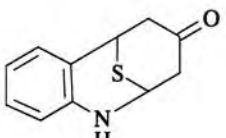Table III. OXYGEN DONOR, α, β–UNSATURATED KETONE OR ALKYNYL KETONE ACCEPTOR (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	TMSOTf, *i*-Pr₂NEt, CH₂Cl₂	(60)	151
C₈			152
	¹O₂, CH₂Cl₂, -40°, 1 h; silica gel, rt, 16 h[a]	(60)	
	¹O₂, CH₂Cl₂, silica gel, rt, 1 h[a]	(97)	
		I + II I:II	153

	R	Conditions	I + II	I:II
C₈	OEt	Et₃N, EtOH, reflux 16 h	(77)	33:67
	OEt	Et₃N, reflux 12 h	(73)	100:0
C₉	Me	NaOH (2% aq), EtOH, reflux 8 h	(66)	100:0

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₉ HO(CH₂)₃	Al₂O₃, CHCl₃	(56)	154
	1. NaOH (1% aq), 0° 2. H⁺	(50)	154a
	HCl (1 N), THF, rt, 16 h	(76) + (12)	155

	R		Yield	
		1. ¹O₂, CH₂Cl₂, -78°, 1 h 2. DMS[a]		152
C₉	OEt		(71)	
C₁₀	Me		(79)	

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₁₀	1. TFA, H₂O 2. Dowex 50W, H₂O 3. Ac₂O, Py, DMAP	(26)	156

Table III. OXYGEN DONOR, α, β–UNSATURATED KETONE OR ALKYNYL KETONE ACCEPTOR (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

First entry (cyclohexane-1,3-dione + hydroxyfuranone):

	R	Conditions	Yield
C_{10}	H	NaOH (2% aq), EtOH, reflux 2 h	(50)
C_{11}	Me	Et₃N, EtOH, reflux 1 h	(60)

Reference: 153

Second entry (NaOMe, MeOH, THF, rt) giving products I + II:

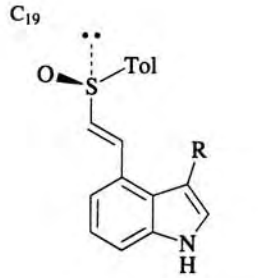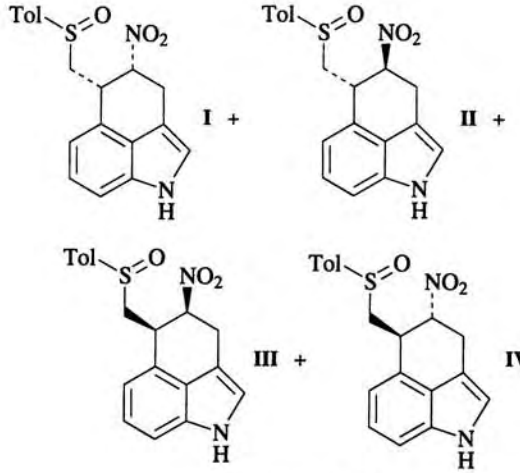|	R^1	R^2	R^3	R^4	Time (h)	I + II	I:II
C_{10}	Me	H	Me	Me	—	(29)	—
C_{11}	C(OH)Me₂	H	Me	H	2	(90)	100:0
C_{12}	t-Bu	H	Me	H	1.5	(82)	59:41
	t-Bu	H	Me	H	96	(—)	100:0
C_{13}	t-Bu	H	Me	Me	2	(77)	—
C_{14}	Me	H	Ph	H	—	(15)	—
	Me	Ph	H	H	—	(23)	—
	C(OH)Me₂	-(CH₂)₄-		H	2	(90)	100:0
C_{15}	Ph	H	Me	Me	1	(71)	—
C_{16}	t-Bu	-(CH₂)₄-		Me	3	(82)	74:26
	t-Bu	-(CH₂)₄-		Me	48	(—)	90:10
	t-Bu	-(CH₂)₄-		Me	70	(—)	100:0

Reference: 121

C_{11} entry:

(MeO)₂POCH₂COMe, CsCO₃, THF, reflux 24 h — (81) — Refs. 157, 157a

TBDMSO entry:

1. Ph₃P=CHCOMe, MeCN, 70°
2. K₂CO₃, MeOH, 0°[b]

(—) α:β = 6:1 — Ref. 158

Chromanone entry:

	R	Conditions	Yield
C_{11}	H	NaOH (5% aq), rt, 2 h	(80)
	H	NaOMe, MeOH, rt, 4 h	(93)
C_{12}	Me	NaOMe, MeOH, rt, 4 h	(65)
	Me	NaOH (5% aq), rt, 2 h	(65)

Reference: 25

C_{12} entry (dibenzofuran-type product):

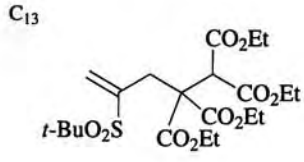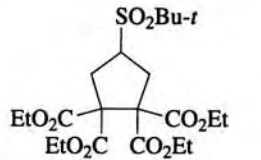| Conditions	Yield	Refs.
HCl, EtOH, H₂O, rt, 18 h	(70)	159
Piperidine, MeOH, reflux	(78)	159

Table III. OXYGEN DONOR, α, β–UNSATURATED KETONE OR ALKYNYL KETONE ACCEPTOR (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{12}

| | *n*-Bu₄NF, THF | (0) | 160 |
| | HBF₄ (20% aq), Et₂O, reflux 24 h[c] | (40) | |

	R			
C_{12}	H	NaOMe, MeOH, reflux 19 h	(0)	25
	H	TsOH, Cl(CH₂)₂Cl, reflux 24 h	(80)	161
	p-Cl	TsOH, Cl(CH₂)₂Cl, reflux 24 h	(65-80)	162
	m-Cl	TsOH, Cl(CH₂)₂Cl, reflux 24 h	(65-80)	162
	p-OH	NaOMe, MeOH, reflux 24 h	(0)	163
	p-OH	TsOH, Cl(CH₂)₂Cl, reflux 4 h	(91)	163
C_{13}	*p*-Me	TsOH, Cl(CH₂)₂Cl, reflux 24 h	(65-80)	163
	m-Me	TsOH, Cl(CH₂)₂Cl, reflux 24 h	(65-80)	163
	p-OMe	TsOH, Cl(CH₂)₂Cl, reflux 24 h	(65-80)	26

NaOMe, MeOH, THF, rt

121

	R^1	R^2	R^3	Time (h)		
C_{12}	*t*-Bu	Et	H	1.5	(62)	
C_{13}	*t*-Bu	*i*-Pr	H	1.5	(78)	
	Me	Ph	H	4	(63)	
C_{14}	Me	Ph	Me	4	(65)	
	Ph	Et	H	3	(68)	
C_{15}	Ph	*i*-Pr	H	2	(72)	
C_{16}	*t*-Bu	Ph	H	0.5	(82)	
C_{18}	Ph	Ph	H	6	(94)	
C_{22}	Ph	Ph	CH₂=CH(CH₂)₂	4	(65)	

C_{12}

1. Hg(ClO₄)₂•3H₂O, THF, CHCl₃, rt, 15 min
2. AcOH, reflux 1 h

I   **I + II** (41)   **II**

164

1. Hg(ClO₄)₂•3H₂O, THF, CHCl₃, rt, 15 min
2. AcOH, reflux 1 h

I + II (41)

164

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. Hg(ClO₄)₂•3H₂O, THF, CHCl₃, rt, 15 min 2. AcOH, reflux 1 h	(40)	164
	1. Hg(ClO₄)₂•3H₂O, THF, CHCl₃, rt, 15 min 2. AcOH, reflux 1 h	" (39)	164
C₁₃	1. DBU, CH₂Cl₂, 0° to rt 2. H₂, Pd/C	 **I + II** (14), **I:II** 0:100	164a
	DBU, CH₂Cl₂, 0° to rt	**I + II** (59), **I:II** 100:0	164a
	1. NaOH (aq), THF 2. CrO₃•2Py	(36)	165, 166
	K₂CO₃, MeOH, H₂O, rt, 2 h	(88)	167
	1. ZnBr₂, CH₂Cl₂ 2. CSA (cat.), C₆H₆	(71)	168
	1. Swern oxidation 2. NaOMe, MeOH, rt	(62)	169
	K₂CO₃, MeOH, rt, 2.75 h	(40)	170
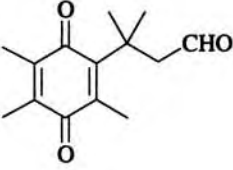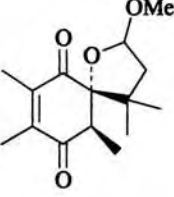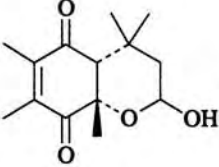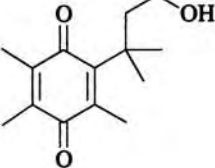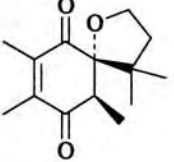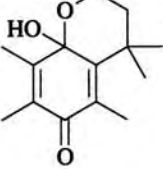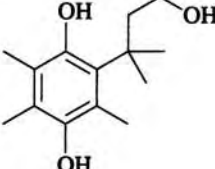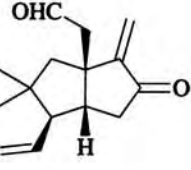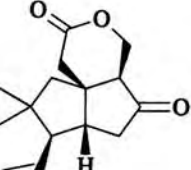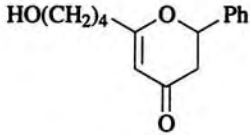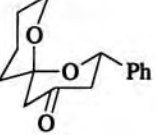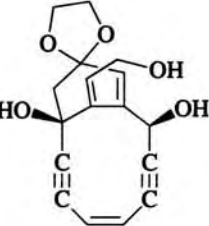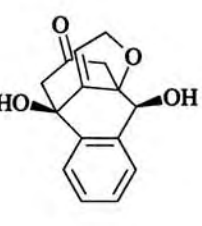
374

375

Table III. OXYGEN DONOR, α, β–UNSATURATED KETONE OR ALKYNYL KETONE ACCEPTOR (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	H_2SO_4 (2% aq), Me_2CO, 45°	(60)	171
	1. Me_3NO, DMA, 25°, 16 h 2. $(CO_2H)_2$, H_2O, MeOH, dioxane, K_2CO_3	(29)	167
	TsOH, C_6H_6, reflux	(73)	172
C14	H_2SO_4 (2% aq), Me_2CO, 50°, 72 h	(65)[d]	170
	NaOMe, MeOH, 20°	(91)	165, 166
C14-21	TsOH, C_6H_6, H_2O, reflux 2 h	R = Me (93) R = n-C_8H_{17} (91)	173
C14			174

NaOAc buffer, dioxane, 25°, 24 h   (82)
MeOH, 25°, 20 h   (6)
MeOH (50% aq), 25°, 20 h   (30)
MeOH (25% aq), 25°, 20 h   (58)
Phosphate buffer, MeOH, 25°, 20 h   (46)
AcOH, MeOH   (0)
KOAc, MeOH   (0)

Table III. OXYGEN DONOR, α, β–UNSATURATED KETONE OR ALKYNYL KETONE ACCEPTOR (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	NaOH, MeOH, 25°, 15 min	(64)	175, 176
	NaOH, MeCN, H₂O, 25°, 1 h	(63)	175, 176
	NaOH, MeOH, 2-3 min	(—)	175, 176
	NaOH, MeOH, 25°, 4 h	" (58)	175, 176
	O₂, NaOH (5% aq), MeOH, rt, 5 h	" (77)	175, 176
C₁₅			
	1. NaOH (aq), THF 2. Jones reagent	(52)	165, 166
HO(CH₂)₄	Al₂O₃, CHCl₃	Ph (82)	154
	CSA, THF (aq), , rt, 8 h	(58)	14
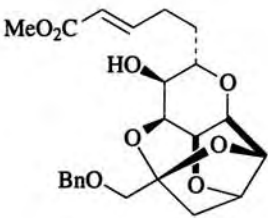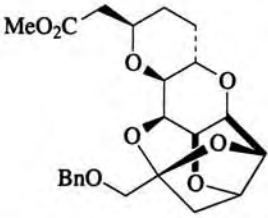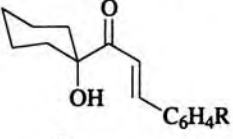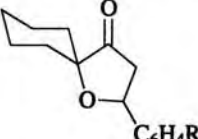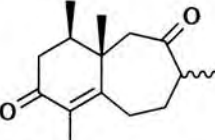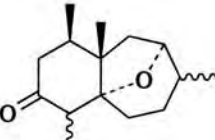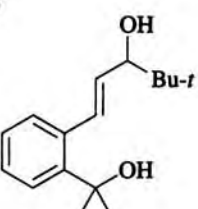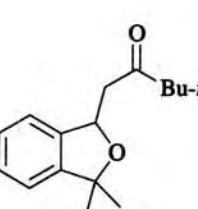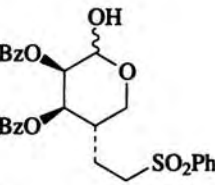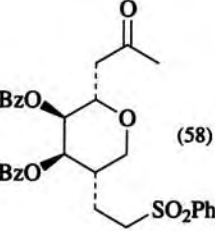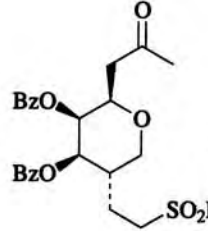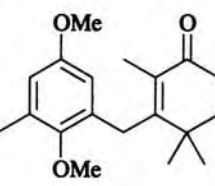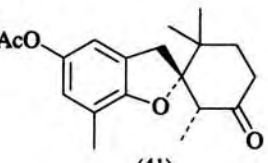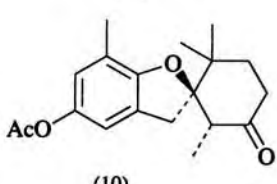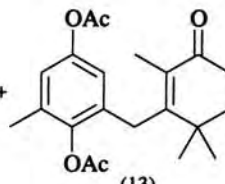
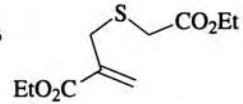| Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	BnMe₃NOMe, MeOH, MeOAc	(73)	156

R
H	NaH, THF, 0° to rt, 5 h	(0)	25
H	TsOH, C₆H₆, reflux 24 h	(10)	
p-OMe	NaH, THF, 0° to rt, 9 h	(0)	
p-OMe	NaOMe, MeOH, reflux 15 h	(0)	
p-OMe	TsOH, C₆H₆, reflux 12 h	(46)	

C₁₅

| | NaBH₄ | (75) | 177 |

C₁₆

| | MnO₂, CH₂Cl₂, rt, 1.5 h | (100) | 25 |

| | Ph₃P=CHCOMe, MeCN, reflux 48 h; DBU (cat.), 0°, 1 h | (58) + (12) | 178 |

C₁₇

| | 1. BBr₃, CH₂Cl₂, -65° to rt 2. THF, HCl, 120 h 3. Ac₂O, Py, 24 h | (41) + (10) + (13) | 179 |

Table III. OXYGEN DONOR, α, β–UNSATURATED KETONE OR ALKYNYL KETONE ACCEPTOR (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

I + II in I:II

	R^1	R^2			
C_{17}	H	H	Na$_2$CO$_3$, EtOH	(80)	29:71
	H	H	Cs$_2$CO$_3$, EtOH	(80)	29:71
	H	H	NaOH, EtOH	(10)	50:50
	H	H	NaHCO$_3$, Na$_2$CO$_3$, EtOH	(84)	33:67
	H	H	PhONa, EtOH	(75)	37:63
	H	H	Et$_3$N, DMSO	(70)	40:60
	H	H	Et$_3$N, EtOH	(60)	>96:4
C_{18}	OMe	Br	Na$_2$CO$_3$, EtOH	(10)	50:50
	OMe	Br	Et$_3$N, EtOH	(75)	54:46
	OMe	Br	Piperidine, EtOH	(70)	33:67
	OMe	Br	Morpholine, EtOH	(84)	83:17
	OMe	Br	DMAP, EtOH	(90)	66:34
	OMe	Br	Proton sponge, EtOH	(90)	60:40

C_{18}

NaH, THF, 25°, 7 d^e | (25) + (60) | 181

NaOH, CHCl$_3$, MeOH, rt, 1 h | (—) | 182

1. Ph$_3$P=CHCOMe, Cl(CH$_2$)$_2$Cl, 75°, 48 h
2. K$_2$CO$_3$, MeOH, rt, 1 h | (64) | 158

C_{19}

1. AcOH, H$_2$O
2. MeOK, MeOH | (25) | 139

C_{20}

HClO$_4$ (70%), THF, rt, 15 min | (70) | 183

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	NaH, DMF, 60°, 6 h[f]	" (74)	183
C$_{24}$	EtOH, rt, 4 h	R = NO$_2$ (—) R = Cl (—)	184
C$_{27}$	HCl (aq), THF, rt, 3 d	(25)	120

B. Alkynyl Ketone Acceptor

C$_{19}$	1. HF (48%), MeCN, rt 2. NaHCO$_3$	(—)	185

[a] The reaction occurred by attack of $^1O_2$ on the furan nucleus, leading, after reduction with DMS, to an open-chain intermediate which closed to the final products by intramolecular Michael reaction.

[b] Only the product ratios were reported.

[c] The product was a 60:40 mixture of isomers.

[d] The literature shows the product as
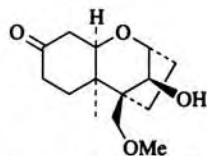
[e] Racemization occurred by an intramolecular Michael addition of the 4-alkoxide group to the α, β-unsaturated carboxylate, leading to an achiral intermediate which was in equilibrium with the R and S configuration of the alkoxide.

[f] The reaction proceeded via elimination followed by an intramolecular Michael reaction.

Table IV. OXYGEN DONOR, α, β–UNSATURATED ESTER, NITRILE, ALDEHYDE, OR ACID ACCEPTOR
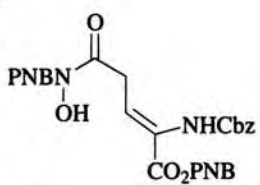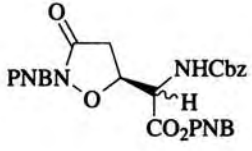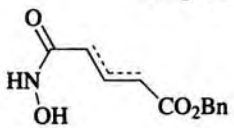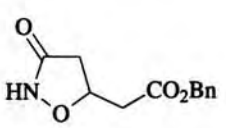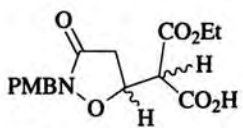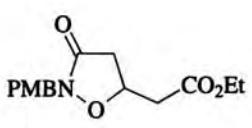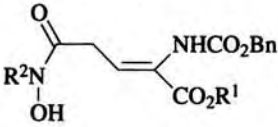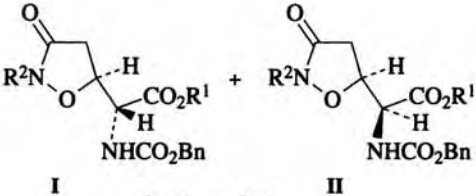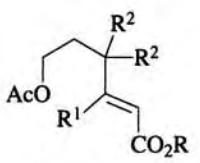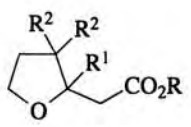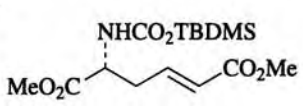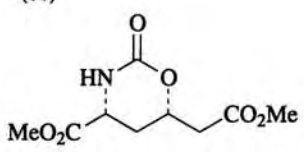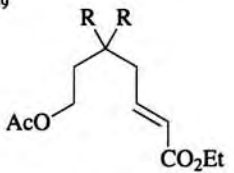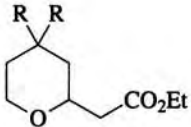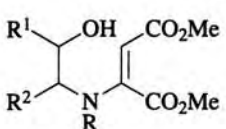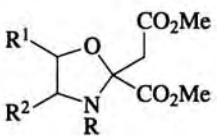
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
		A. α,β-Unsaturated Ester Acceptor	

C₅

| | NaHCO₃ (aq) | (100) | 186 |

| | *a* | (0) | 187 |

| | Et₃N, C₆H₆, rt, 24 h[b] | (99) | 187 |

| | Reflux 40 min | I + II | 187 |

R¹	R²		I + II	I:II
Bz	PMB	NaHCO₃ (sat.)	(83)	50:50
o-O₂NC₆H₄CH₂	PMB	NaHCO₃ (sat.)	(95)	—
H	H	NaOH (1 N)	(86)	100:0

| | NaOEt, EtOH, rt, 8 h | | 188 |

	R	R¹	R²	
C₆	Et	H	H	(64)
C₇	Me	Me	H	(90)
C₈	Et	H	Me	(79)
C₁₁	Et	H	-(CH₂)₅-	(80)

C₇

| | TBAF, THF, 0°, 1-3 h | (0) | 189 |

C₇₋₉

| | NaOEt, EtOH, rt, 8 h | R = H (68) | 188 |
| | | R = Me (82) | |

| | MeOH, H₂O, reflux | | 190 |

	R	R¹	R²	
C₈	Et	H	H	(40)
C₁₂	Ph	H	H	(40)
C₁₄	Me	Ph	Me	(60)

	Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_8$

AcO–⋯–CH=CH–CO$_2$Et   NaOH, EtOH, rt, 8 h   (cycloheptane-O–CH$_2$CO$_2$Et) (0)^c 188

OH ... N(CBz) pyrrolidinofuran with OH, OH   1. Ph$_3$P=CHCO$_2$Et 2. Ac$_2$O   AcO ... (lactone fused pyrrolidinofuran) (—)   191

C$_{8-9}$

AcO–⋯(–)$_n$–CH=CH–CO$_2$Et   NaOEt, EtOH, rt, 8 h   (tetrahydrofuran)(–)$_n$–CH$_2$CO$_2$Et   n = 1 (67) n = 2 (85)   188

OH cyclopentane with CH=CH–CO$_2$R^3, R^1, R^2 NaH, Et$_2$O, 25°, 1-3 h   I (bicyclic furan with CO$_2$R^3) + II (diastereomer)   192

	R^1	R^2	R^3	From	I:II^d
C$_9$	H	H	Me	*cis*	66:33
				trans	66:33
C$_{10}$	OH	CH$_2$OBn	Et	*cis*	9:91
				trans	91:9
C$_{13}$	(ring)		Me	*cis*	50:50
				trans	50:50

	R^1	R^2	R^3	From	I:II^d
C$_{17}$	OH	(R)-CH=CHCHOHC$_5$H$_{11}$-n	Et	*cis*	17:83
				trans	86:14
C$_{18}$	OTHP	(S)-CH=CHCH(OTHP)Ph	Me	*cis*	66:33
				trans	66:33

R^1–(aminophenol with OH, NHR^2)   1. BrCH$_2$CH=CHCO$_2$Me, NaHCO$_3$, MeOH, rt 2. K$_2$CO$_3$, MeOH, rt, 20 min   R^1–(benzoxazine with CH$_2$CO$_2$Me, N-R^2)   193

	R^1	R^2		
C$_{10}$	H	H	(95)	
	H	Bn	(93)	
	Cl	Bn	(90)	
	NO$_2$	Bn	(91)	
C$_{11}$	Me	Bn	(95)	

R^1–(phenol with OH, and N(R^2)C(O)CH=CH–CO$_2$R^3)   K$_2$CO$_3$, EtOH, rt, 1 h   R^1–(benzoxazinone with CH$_2$CO$_2$R^3, N-R^2, =O)   193

	R^1	R^2	R^3	
C$_{10}$	H	H	Et	(80)
	H	Bn	Et	(90)
	Cl	H	Et	(26)
C$_{11}$	Me	H	Et	(42)
C$_{10}$	H	H	Me	(50)

C$_{10}$	H	H	Me	Piperidine acetate, warm 30 min (50)

Table IV. OXYGEN DONOR, α, β–UNSATURATED ESTER, NITRILE, ALDEHYDE, OR ACID ACCEPTOR (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{10}$ 	K$_2$CO$_3$, MeOH, rt, 20 min	(100)	193
	1. H$^+$ 2. Ph$_3$P=CHCO$_2$Et	("good")	191
	(MeO)$_2$P(O)CH$_2$R, CsCO$_3$, THF, reflux 24 h	R = CO$_2$Me (76) 94% de^e R = CO$_2$Et (61) 98% de	157, 157a, 194
C$_{11}$	K$_2$CO$_3$, EtOH, rt, 1 h	(0)	195
	EtONa, EtOH, rt, 8 h	(28)	188
	K$_2$CO$_3$, EtOH, rt, 1 h	(39)	195
	K$_2$CO$_3$, EtOH, rt, 1 h		195

	R^1	R^2	R^3	
C$_{11}$	H	H	H	(17)
	H	Bn	H	(95)
	Cl	Bn	H	(93)
C$_{12}$	H	Me	H	(91)
C$_{13}$	H	Bn	Me	(50)
C$_{14}$	H	*i*-Pr	H	(93)
C$_{16}$	H	*i*-Pr	Me	(71)
C$_{17}$	H	C$_6$H$_{11}$	H	(87)
C$_{19}$	H	(CH$_2$)$_2$Ph	H	(90)
C$_{23}$	H	Bn	Ph	(12)
	Cl	Bn	Ph	(17)
C$_{26}$	H	*i*-Pr	Ph	(92)
	Cl	*i*-Pr	Ph	(68)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{12}$	1. KOH, MeOH, H$_2$O reflux 6 h 2. HCl (aq) 3. CH$_2$N$_2$	(47) + (31)	196

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	K$_2$CO$_3$, EtOH, rt, 4 d		195

	R^1	R^2	
C$_{12}$	Bn	H	(70)
C$_{13}$	Me	H	(50)
C$_{15}$	*i*-Pr	H	(65)
C$_{18}$	Bn	Ph	(55)
C$_{19}$	Me	Ph	(30)
C$_{21}$	*i*-Pr	Ph	(40)

C$_{13}$

	NaOMe, MeOH	(80)	150

	K$_2$CO$_3$		195
	EtOH, rt, 5 d	(6)	
	18-Crown-6, CH$_2$Cl$_2$, reflux 3 d	(9)	

C$_{13}$

	NaCl, DMSO, 160°, 6 h	(8)	197

C$_{15}$

	MeI, K$_2$CO$_3$, Me$_2$CO, reflux 6 d	(61)	198

	NaBH$_4$, EtOH	(60)	38, 199

C$_{16}$

	Basic conditions	(—)	200

	K$_2$CO$_3$, EtOH, rt, 1 h	R = H (55)	193
		R = *p*-Cl (95)	

Table IV. OXYGEN DONOR, α, β–UNSATURATED ESTER, NITRILE, ALDEHYDE, OR ACID ACCEPTOR (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{17}	(EtO)$_2$POCH$_2$CO$_2$Et, NaH, C$_6$H$_6$, reflux 1 h	(53)	53
	Spontaneous	(—)	200
	NaOMe, MeOH, rt, 1 h	(45) + (45)	200, 201
	K$_2$CO$_3$, EtOH, rt, 1 h	**I** + **II**	195

	R^1	R^2		I + II	I:II
C_{17}	Ph	Bn		(94)	50:50
	o-ClC$_6$H$_4$	Bn		(83)	0:100
C_{18}	Ph	Me		(62)	76:24
C_{19}	Ph	Et		(38)	68:32
C_{20}	Ph	i-Pr		(96)	50:50
C_{23}	Ph	C$_6$H$_{11}$		(30)	100:0
C_{25}	Ph	(CH$_2$)$_2$Ph		(90)	53:47

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{19}	NaBH$_4$, dioxane, rt, 14 h	(61) +	200, 201

Table IV. OXYGEN DONOR, α, β–UNSATURATED ESTER, NITRILE, ALDEHYDE, OR ACID ACCEPTOR (*Continued*)
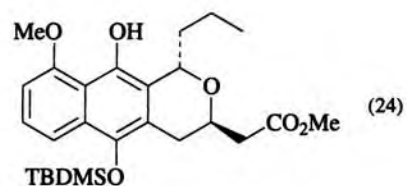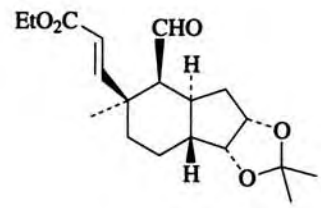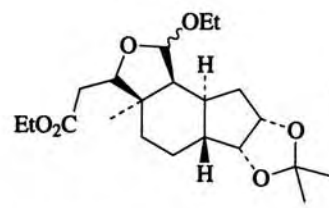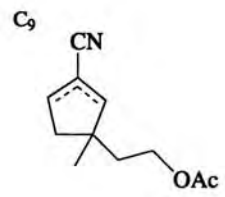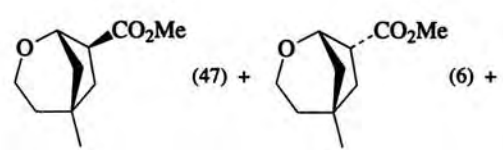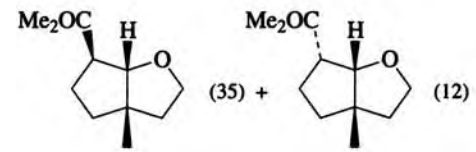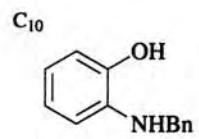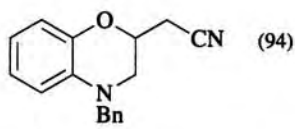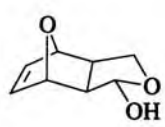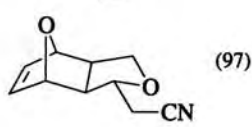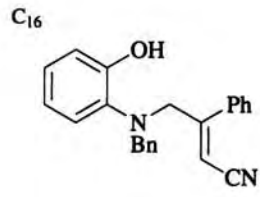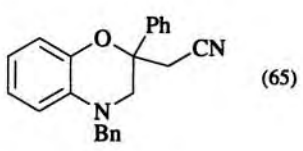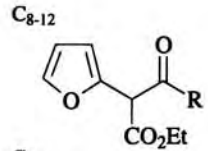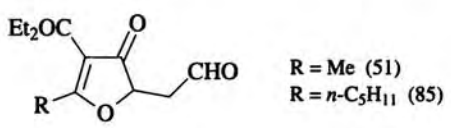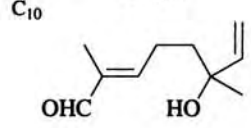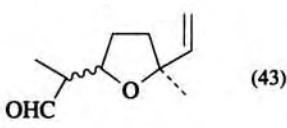
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
		MeO / OH / propyl / O / CO₂Me / TBDMSO (24)	
EtO₂C, CHO, H (decalin-dioxolane substrate)	NaOEt, EtOH, 23°, 15 min	OEt / H / EtO₂C / O / O (82)	53

B. α, β-Unsaturated Nitrile Acceptor

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₉ (CN cyclopentene with CH₂CH₂OAc, Me)	1. KOH, HO(CH₂)₂OH, H₂O, reflux 3 d 2. CH₂N₂	O / CO₂Me (47) + O / CO₂Me (6) + Me₂OC / H / O (35) + Me₂OC / H / O (12)	202
C₁₀ (OH / NHBn benzene)	1. BrCH₂CH=CHCN, NaHCO₃, MeOH, 24 h 2. Et₃N, 1 h	O / CN / N / Bn (94)	193
(oxabicyclic diol, O / OH)	(EtO)₂POCH₂CN, THF, Cs₂CO₃, reflux 24 h	O / O / CN (97)	157, 157a, 194
C₁₆ (OH / N(Bn) / Ph / CN)	K₂CO₃, MeOH, CH₂Cl₂, 10 min	Ph / O / CN / N / Bn (65)	193

C. α, β-Unsaturated Aldehyde Acceptor

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₈₋₁₂ (furan / C(=O)R / CO₂Et)	1. ¹O₂, CH₂Cl₂, -78°, 1 h 2. DMS^f	Et₂OC / O / CHO / R–O	R = Me (51) R = n-C₅H₁₁ (85)	152
C₁₀ (OHC / HO diene)	Et₃N	OHC / O (tetrahydrofuran, vinyl) (43)	203
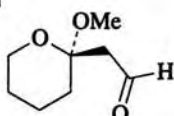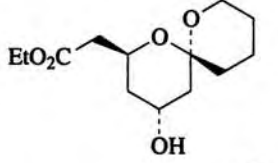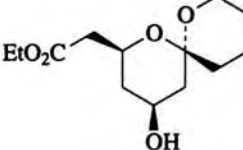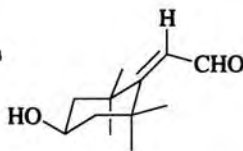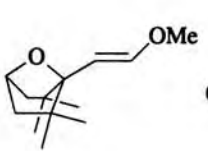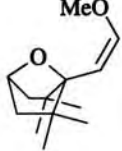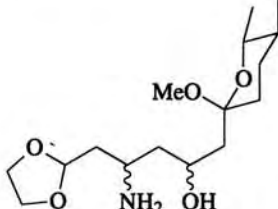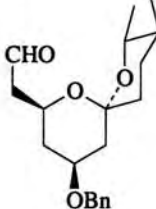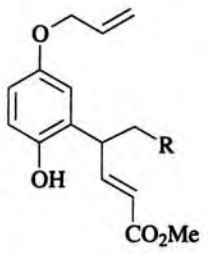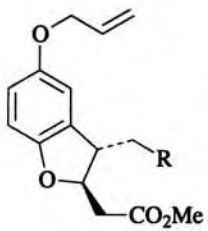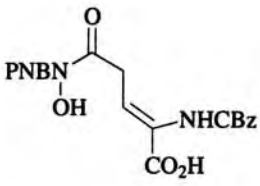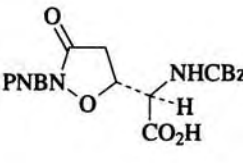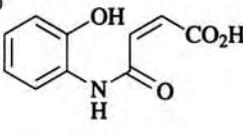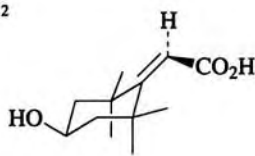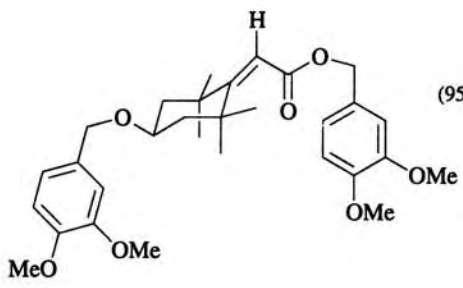
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{11}	1. MeCOCH$_2$CO$_2$Et, LDA, THF, 37 min 2. NaBH$_4$, MeOH, 20 min 3. TsOH, C$_6$H$_6$, 3.5 h	(31) + (8)	204
C_{13}	NaH, MeI, THF, 25°, 12 h	(24) + (12)	181
	1. KH, BnI, 0° 2. MeI (xs), 25° 3. TsOH, 25°	(24-30)	205, 204
C_{14-16}	Piperidine, MeOH, reflux	R = OMOM (77) R = Et (—)	159

D. α, β-Unsaturated Acid acceptor

C_5	NaOH (aq), reflux	(86)	186
C_{10}			206
	Piperidine acetate, rt, 18 h Morpholine, rt, 18 h	(0) (0)	

Table IV. OXYGEN DONOR, α, β–UNSATURATED ESTER, NITRILE, ALDEHYDE, OR ACID ACCEPTOR (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{12}$	3,4-(MeO)$_2$C$_6$H$_3$CH$_2$Cl, DMF, NaH, 0°, overnight[g]	(95)	181

[a] The reaction conditions were not specified.

[b] The reaction occurred via the sequence decarboxylation, retro Michael, and Michael reaction.

[c] Only a product from the intermolecular Michael addition of ethoxide was obtained in 72% yield.

[d] The yields were not specified.

[e] The % de was determined from the ^{1}H NMR spectrum of the crude mixture.

[f] The reaction occurred by attack of ^{1}O$_2$ on the furan nucleus, leading, after reduction with DMS, to an open-chain intermediate which closed to the final product by an intramolecular Michael reaction.

[g] Racemization occurred by intramolecular Michael addition of the 4-alkoxide group to the α, β-unsaturated carboxylate, leading to an achiral intermediate which was in equilibrium with the *R* and *S* configuration of the alkoxide.

Table V. NITROGEN DONOR, α, β–UNSATURATED SULFOXIDE, SULFONE, OR SULFOXIMIDE ACCEPTOR
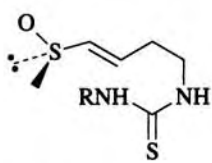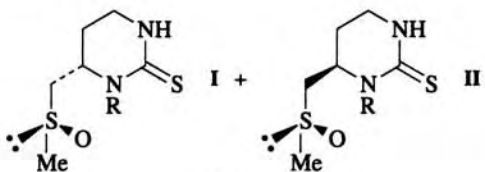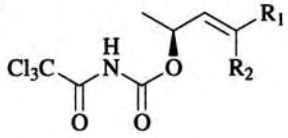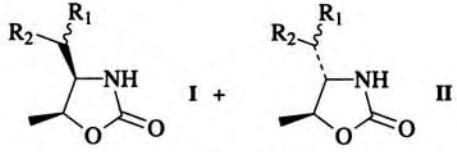
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

A. α, β-Unsaturated Sulfoxide Acceptor

	R		I + II	
C$_6$	H	NH$_3$, EtOH, 40°, 8 d	(—)	
	H	NH$_3$, CHCl$_3$, 25°, 30 d	(0)	
	H	MeNH$_2$, 25°, 1 h	(60)	
C$_7$	Me	NH$_3$, EtOH, 20°, 48 h	(—)	
	Me	NaOH (0.5 N), 25°, 1 h	(—)	
	Me	MeNH$_2$, MeOH, 25°, 2 h	(—)	
C$_{12}$	Ph	NH$_3$, EtOH, 24 h	(—)	
	Ph	Soda glass tube, EtOH, 40°, 10 d	(—)	
	Ph	Soda glass tube, EtOH, 80°, 24 h	(—)	

C$_{11}$

R^1	R^2		I + II	I:II
S(O)Ph^a	H		(81)	62:38
S(O)Ph^b	H		(93)	89:11
H	S(O)Ph^a		(98)	>100
H	S(O)Ph^b		(100)	95:5

Conditions: K$_2$CO$_3$, MeOH, CH$_2$Cl$_2$, rt, 0.5-3 h

Ref. 208

Table V. NITROGEN DONOR, α, β–UNSATURATED SULFOXIDE, SULFONE, OR SULFOXIMIDE ACCEPTOR (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

Triton B   I + II   209

	R	Conditions	From	I:II[c]
C$_{13}$	Ph	CH$_2$Cl$_2$, -40°, 40 h	*trans*	91:9
	Ph	PhMe, 0°, 1 h	*trans*	83:17
	Ph	MeOH, -40°, 40 h	*trans*	70:30
	Ph	CH$_2$Cl$_2$, -40°, 40 h	*cis*	16:84
	Ph	PhMe, 0°, 1 h	*cis*	21:79
	Ph	MeOH, -40°, 40 h	*cis*	30:70
C$_{22}$	Trisyl	CH$_2$Cl$_2$, -40°, 40 h	*trans*	93:7
	Trisyl	PhMe, 0°, 1 h	*trans*	89:11
	Trisyl	MeOH, -40°, 40 h	*trans*	72:28

C$_{18}$

BnEt$_3$NOH, CH$_2$Cl$_2$, -40°, 8 h   (47) +   210

R =

(14)

C$_{20}$

Triton B, -40°, 40 h   I + II   211, 209

	From	I + II	I:II
CH$_2$Cl$_2$	*trans*	(65-75)	42:58
MeOH	*trans*	(65-75)	38:62
CH$_2$Cl$_2$	*cis*	(96)	83:17
MeOH	*cis*	(96)	84:16
LiOH, MeOH, H$_2$O, 0°, 1 h	*trans*	(65-75)	37:63

B. α, β-Unsaturated Sulfone Acceptor

K$_2$CO$_3$, MeOH, CH$_2$Cl$_2$, 25°, 0.5-3 h   I + II   208

	R	R^1	R^2	I + II	I:II
C$_{11}$	Cl$_3$CCO	SO$_2$Ph	H	(75)	86:14
	Cl$_3$CCO	H	SO$_2$Ph	(83)	~130
C$_{12}$	Cl$_3$CCO	SO$_2$Ph	SMe	(86)	>100
C$_{18}$	Cl$_3$CCO	SO$_2$Ph	STol	(86)	>100
C$_{11}$	H	TMS	SO$_2$Ph	(71)	~120

t-BuOK, THF, 0°, 6-30 min[d]

Table V. NITROGEN DONOR, α, β–UNSATURATED SULFOXIDE, SULFONE, OR SULFOXIMIDE ACCEPTOR (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₁₃ (OTBDMS, Ts, SMe, OH)	1. CCl₃COCNO, CH₂Cl₂, 0° 2. K₂CO₃, MeOH, CH₂Cl₂, 4 h	(98)	212
C₁₇	1. CCl₃COCNO, CH₂Cl₂, 0° 2. K₂CO₃, MeOH, CH₂Cl₂, 4 h	(73)	212
C₂₀ Ph, SO₂Bu-*t*, PhNH	KH (cat.), THF, 25°, 10 min	(65)	27

C. α, β-Unsaturated Sulfoximide Acceptor

			213
	R¹ R²		
C₁₀	Me H	DMSO, 64 h	(60)
	Me 4-Cl	DMSO, 64 h	(27)
	Me 3,4-Cl₂	DMSO, 64 h	(2)
	Me 4-NO₂	DMSO, 64 h	(0)
	Me 2-NO₂	Me₂CO, 64 h	(0)
	R¹ R²		
C₁₅	Ph H	DMSO, 64 h	(84)
	Ph 3,4-Cl₂	Me₂CO, 64 h	(3)
	Ph 4-NO₂	Me₂CO, 64 h	(0)
	Ph 2-NO₂	Me₂CO, 64 h	(0)
C₁₆	Bn 3,4-Cl₂	DMSO, 64 h	(3)
	Bn 3,4-Cl₂	Me₂CO, 64 h	(31)
		NaOH (5% aq), warm 1 h	214
	R¹ R²		
C₁₀	Me H		(66)
	Me 4-Cl		(71)
	Me 3,4-Cl₂		(66)
	Me 4-NO₂		(64)
	Me 4-Cl-3-ClSO₂		(53)
	Me 4-Cl-3-H₂NSO₃		(75)
C₁₅	Ph 3,4-Cl₂		(86)
	Ph H		(87)
C₁₆		MeNH₂ (xs), Me₂CO, 2.5 h	(61)	213

Substrate	Conditions	Product(s) and Yield(s) (%)		Refs.

I   II

		I + II	**I:II**	
C$_{19}$ R =	Triton B, CH$_2$Cl$_2$, 0°, 1 h	(88-96)	26:74	
	Triton B, CH$_2$Cl$_2$, -40°, 40 h	(88-96)	28:72	
	Triton B, MeOH, 0°, 1 h	(88-96)	58:42	
	LiOH, MeOH, H$_2$O, 0°, 1 h	(88-96)	65:35	
C$_{29}$ R =	Triton B, CH$_2$Cl$_2$, 0°, 1 h	(88-96)	71:29	
	Triton B, CH$_2$Cl$_2$, -40°, 40 h	(88-96)	68:32	
	Triton B, MeOH, 0°, 1 h	(88-96)	54:46	
	LiOH, MeOH, H$_2$O, 0°, 1 h	(88-96)	65:35	

[a] A sulfoxide with *S* configuration was used.

[b] A sulfoxide with *R* configuration was used.

[c] Only the product ratios were reported.

[d] The TMS group was eliminated during the reaction.

TABLE VI. NITROGEN DONOR, α, β–UNSATURATED CARBON OR NITROGEN GROUP ACCEPTOR
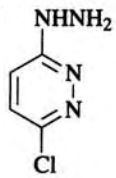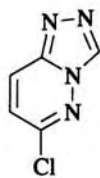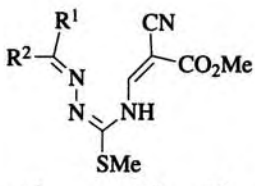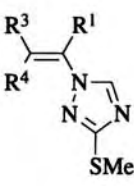
	Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

A. α, β-Unsaturated Ester Acceptor

C_5

EtOCH=C(CO$_2$Et)$_2$. MeCN, 3 h   (75)   216

	R^1	R^2	R^3	R^4			
C_5	H	Me	H	H	Cl$_3$CCO$_2$H, PhMe, reflux 30 min	(2)	
C_{11}	Ph	Me	H	H	AcOH, 90°, 1.5 h	(82)	217
	o-ClC$_6$H$_4$	Me	H	H	"	(52)	
	o-BrC$_6$H$_4$	Me	H	H	"	(72)	
	o-MeC$_6$H$_4$	Me	H	H	"	(57)	
	o-O$_2$NC$_6$H$_4$	Me	H	H	"	(31)	
C_{12}	Ph	Et	Me	H	"	(59)	
C_{13}	Ph	n-Pr	Et	H	"	(59)	
	Ph	i-Pr	Me	Me	"	(69)	
C_{17}	Ph	Bn	Ph	H	"	(65)	

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

	R¹			R²		
C₅	Me	AcOH, 90°, 1.5 h		Me	(35)	217
C₁₀	Ph	"		Me	(77)	
	Ph	PhCO₂H, PhMe, 90°, 1.5 h		Ph	(36)	
	2,6 -Cl₂C₆H₃	AcOH, 90°, 1.5 h		Me	(76)	
	3-O₂NC₆H₄	"		Me	(84)	
C₁₁	4-MeOC₆H₄	"		Me	(66)	

	R	Conditions	From	I + II	I:II	Refs.
C₆	Me	*t*-BuOK, THF, 0°, 25 min	trans	(66)	84:16	218-220
C₁₁	Ph	*t*-BuOK, THF, 0°, 30 min	trans	(85)	92:8	
	Ph	*t*-BuOK, THF, 0°, 30 min	trans	(68)	88:12	
	Ph	*t*-BuOK, THF, 0°, 30 min	cis	(75)	>100:1	
C₇	[structure]	*t*-BuOK, THF, 0°, 30 min	trans	(79)	>95:5	
	,, O₂CNH₂	*t*-BuOK, THF, 0°, 20 min	cis	(90)	98:2	

C₆₋₈

BnNH₂, Et₃N, EtOH, reflux 36 h

n = 1 (63)
n = 2 (59)
n = 3 (<5)   123

C₆

NaH, THF, 4°, 19 h

(52)   +   (20)   221

	R¹	R²	R³	Conditions	From	I + II	I:II	Refs.
C₇	Me	H	Me	NaH, THF, rt, 1 h	trans	(53)	91:9	218a-220
	Me	H	Me	NaH, THF, rt, 1 h	cis	(70)	>95:5	
	Me	OAc	Et	*t*-BuOK, THF, 0°, 2 min	trans	(52)	95:5	
	Me	OTBDMS	Et	*t*-BuOK, THF, 0°, 10 min	trans	(90)	97:3	
	Me	OTES	Me	*t*-BuOK, THF, 0°, 20 min	cis	(73)	>99:1	
	Me	OTES	Et	*t*-BuOK, THF, 0°, 20 min	trans	(74)	98:2	
C₁₀	3-Butenyl	H	Me	NaH, THF, rt, 1.5 h	trans	(70)	91:9	
C₁₁	Me	*t*-BuO	Et	*t*-BuOK, THF, 0°, 20 min	trans	(91)	88:12	
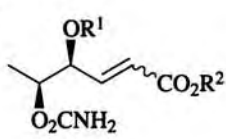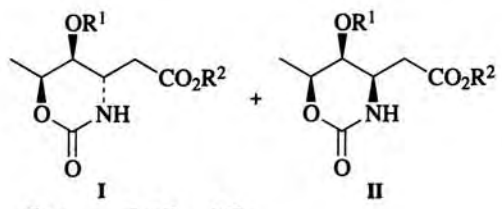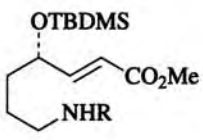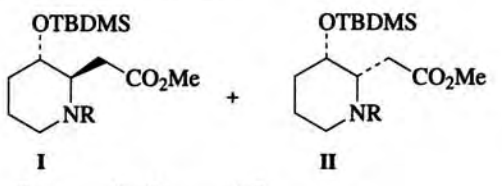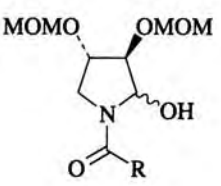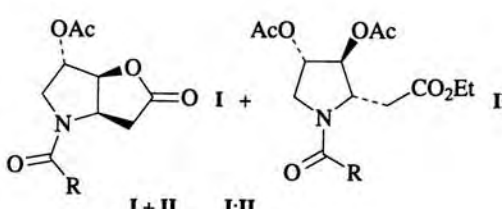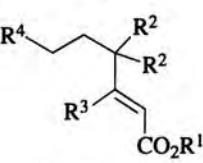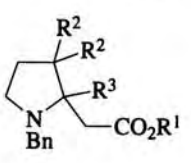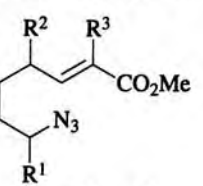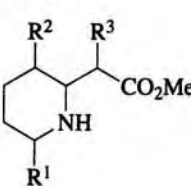
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₇

t-BuOK, THF, 0°, 20 min

I + II

R¹	R²
TES	Me
TBDMS	Et
TES	Et

From	I + II	I:II
cis	(73)	>99:1
trans	(53)	66:33
trans	(75)	84:16

222, 220

t-BuOK, THF

I + II

222a

R		
t-BuO₂C	-50°, 5 min	
Ac	-36°, 15 min	
t-BuO₂C	-42°, 5 min	
t-BuO₂C	rt, 12 min	
Ac	-48°, 15 min	
CF₃CO	K₂CO₃, MeOH, rt, 20 h	

From	I + II	I:II
cis	(81)	96:4
cis	(56)	98:2
trans	(81)	<1:99
trans	(61)	14:86
trans	(68)	13:87
trans	R = H (89)	59:41

1. (EtO)₂P(O)CH₂CO₂Et, NaH, DME, rt, 39 h
2. EtSH, BF₃•Et₂O
3. Ac₂O, Py, DMAP

I + II

223-225

	R
C₇	OEt
	OEt^a
C₁₃	Ph

I + II	I:II
(52)	40:60
(71)	23:77
(54)	50:50

BnNH₂, Et₃N, R¹OH, reflux 36 h

123

	R¹	R²	R³	R⁴
C₇	Me	H	Me	I
C₈	Et	Me	H	Br
C₁₁	Et	–(CH₂)₅–	H	I

(71)	
(64)	
(68)	

Ph₃P, THF, H₂O

226

	R¹	R²	R³	
C₇	H	H	H	-50°
C₈	H	H	Me	rt
	H	Me	H	rt
	Me	H	H	rt

(60)
(86)
(83)
(82)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_7$

t-BuOK, THF, 0°

 I + **II**   219, 220, 227

R	I + II	I:II
TBDMS	(90)	~27:1
CONH$_2$	(98)	23:1

Ph$_3$P, THF, H$_2$O, -50°

 (78)   226

C$_8$

NH$_2$OH, H$_2$O, rt, 3.5 h

 (72)   228

1. H$_3$N(Cl)CH$_2$CO$_2$Et, MeOH, 0°, 1 h
2. NaBH$_3$CN, MeOH, 0°, 3 h

 (54) + (36)   229

BnNH$_2$, EtOH, 80°, 48 h

    R = TBDMS (0)   69
R = TMS (57)

Catalase, phosphate buffer, EtOH, 20-25°, 4 h

    230

	R^1	R^2	
C$_8$	H	H	(—)
C$_{10}$	Me	Me	(—) } (78-85)
C$_{15}$	H	PhCO	(—)

Catalase, phosphate buffer, EtOH, 20-25°, 4 h

    230

	R^1	R^2	
C$_8$	H	H	(88)
C$_{10}$	Me	Me	(—) } (75-80)
C$_{15}$	H	PhCO	(—)

C$_8$

EtOCH=C(CN)CO$_2$Et, EtOH

 (81)   216
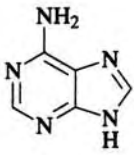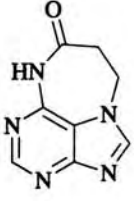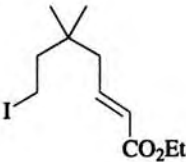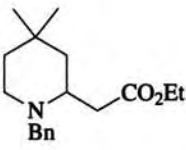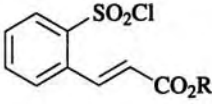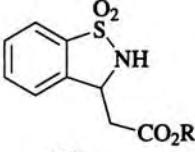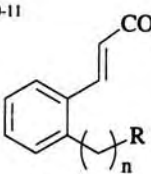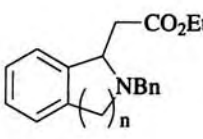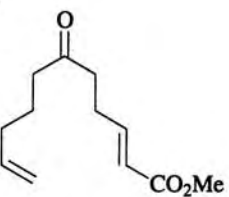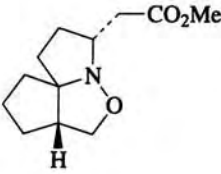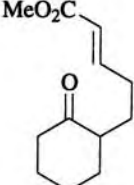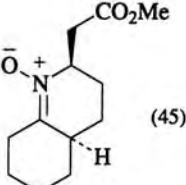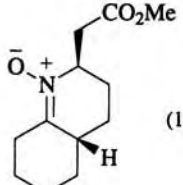
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	DMSO, 60°, 24 h		231
	Acrylic anhydride Vinyl acrylate	(13) (26)	

C$_9$

	BnNH$_2$, Et$_3$N, EtOH, reflux 36 h	(66)	123
  $\dfrac{R}{Me}$ Et *n*-Pr *i*-Pr *n*-Bu *s*-Bu	NH$_4$OH, overnight	 (46) (40) (14) (24) (32) (32)	232

C$_{10-11}$

  $\dfrac{R \quad n}{Br \quad 1}$ I $\quad$ 2	BnNH$_2$, Et$_3$N, EtOH, reflux 36 h	 (69) (0)[b]	123

C$_{11}$

	NH$_4$OH•HCl, xylene, AcOH, 140°, 16 h[c]	(82)	228
	NH$_2$OH, H$_2$O, rt, 3.5 h	(45) + (13)	228

TABLE VI. NITROGEN DONOR, α, β–UNSATURATED CARBON OR NITROGEN GROUP ACCEPTOR (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Reflux		233
	NaH, EtOH, 45 min[d]	(70)	
	H$_2$O, 2 h	(90)	
	EtOH, 24 h	(82)	
	Py, 24 h	(83)	
	C$_6$H$_6$, 8 h	(0)	
	AcOH, EtOH, 8 h	(0)	
	AcOPr, 8 h	(0)	
	N-Methylmaleimide, PhMe, 110°, 3 h[c]	(90)	228
C$_{12}$	TsNCO, 0°	(45) + (45)	234
C$_{15}$	Na$_2$CO$_3$, HMPT, rt, 24 h[e]	(9) + (18)	235
C$_{17}$	Xylene, reflux	(57)	236
C$_{18}$	RNH$_2$, EtOH, rt, 10-12 d	R = H (69) R = *n*-Bu (0)	81

B. α, β-Unsaturated Nitrile Acceptor

C$_6$	Ph$_3$P, THF, H$_2$O, -50°	(74)	226
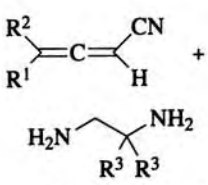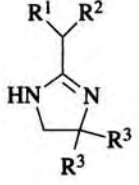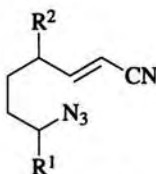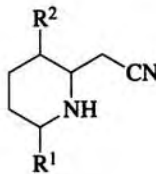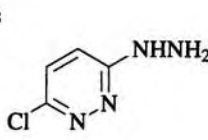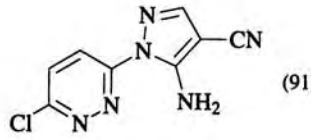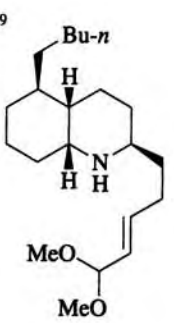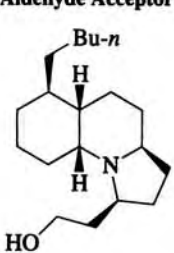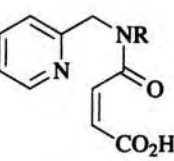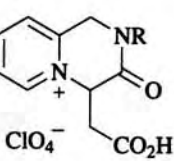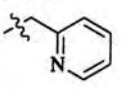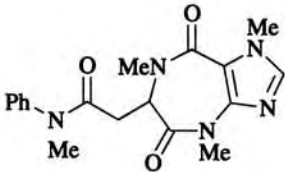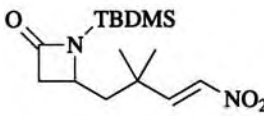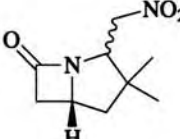
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

	1. EtOH, rt, 1 h		93, 95
	2. heat 3 h		
	3. rt, 12 d^f		

	R^1	R^2	R^3	
C_6	Me	Me	H	(72)
C_7	Me	Et	H	(68)
	n-Pr	H	H	(80)
C_8	Et	Et	H	(80)
	Me	Me	Me	(76)
C_9	Me	Et	Me	(82)
	n-Pr	H	Me	(85)
C_{10}	Et	Et	Me	(83)

| | Ph$_3$P, THF, H$_2$O | | 226 |

	R^1	R^2		
C_7	H	H	-50°	(83)
C_8	H	Me	rt	(71)
	Me	H	rt	(77)

C_8

| | EtOCH=C(CN)$_2$, EtOH | (91) | 216 |

C. α, β-Unsaturated Aldehyde Acceptor

C_{19}

	1. HCl (1 N), THF, rt, 1 h^g	(46)	237
	2. NaOMe, MeOH, 1 h		
	3. NaBH$_4$, 0.5 h		

D. α, β-Unsaturated Acid Acceptor

| | NaClO$_4$, H$_2$O, 65° | R = H (—) | 238 |
| | | R = (—) | |

TABLE VI. NITROGEN DONOR, α, β–UNSATURATED CARBON OR NITROGEN GROUP ACCEPTOR (*Continued*)

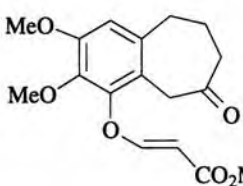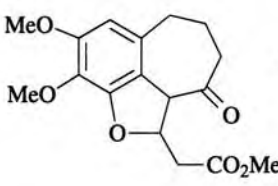| Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

E. α, β-Unsaturated Amide Acceptor

| | H₂O, reflux 2 h | (76) | 233 |

F. Nitroalkene Acceptor

	MeOH, 0°		239
	KF, 15 min	(78)	
	HCl, silica gel	(—)	

---

[a] KH was used instead of NaH.

[b] Only product from elimination of **I** was obtained in 90%.

[c] The reaction occured via an intramolecular Michael reaction followed by a 1, 3-dipolar cycloaddition.

[d] Other reaction conditions were reported which did not lead to the product. Under aqueous basic conditions (aq NaOH, rt, 2 h, 71%), the ester functionality in the product hydrolyzes to an acid.
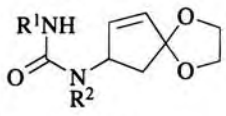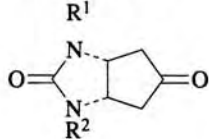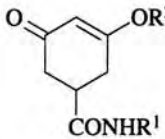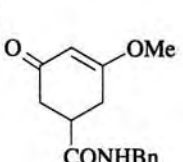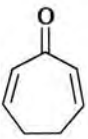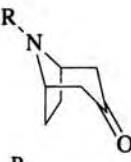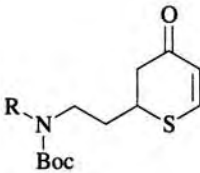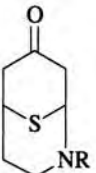
[e] The substrate was formed in situ by rearrangement of
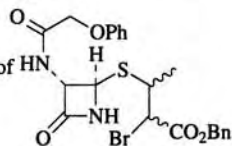
[f] The intermolecular Michael reaction is followed by isomerization of the double bond, intramolecular Michael reaction, and elimination of MeCN.

[g] The crude amine was used immediately after removal of the trichloroethoxycarbamate unit.

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

A. α,β-Unsaturated Ketone Acceptor

	R¹	R²			
C$_6$	H	Bn	HCl (2 N), THF, rt, 1 h	(98)	135
C$_{14}$	H	n-C$_8$H$_{17}$	"	(75)	
C$_{18}$	Ph	Ph	HCl (cat.), CHCl$_3$, rt, 30 min	(100)	
	Ph	Ph	DMSO, 60°, 30 min	(100)	

	R¹	R²			
C$_7$	Bn	Me	1. LiAlH$_4$, THF, reflux 12 h 2. H$_2$SO$_4$ (25%), rt, 24 h	(42)	240, 241
C$_8$	Me	Me	1. LiAlH$_4$, THF, reflux 18 h 2. H$_2$SO$_4$ (25%), rt, 90 min	(63)	
	Me	Et	1. LiAlH$_4$, THF, reflux 8 h 2. HCl (10%), 3 h	(30)	

C$_7$	1. LAH, THF 2. H$_2$SO$_4$ (aq), 0°, 1.5 h	(52)	242

		R		
C$_7$	RNH$_2$, MeOH, rt, 30 min	Bn	(59)	243-245
C$_8$	"	Me	(64)	
	RNH$_2$, EtOH, rt, 2 h	Me	(55)	
C$_9$	RNH$_2$, MeOH, rt, 30 min	Et	(56)	
C$_{10}$	RNH$_2$•HCl, Na$_2$CO$_3$, MeOH, rt	(S)-1-Carbomethoxyethyl	(75)	
	"	(S)-1-Carbo-tert-butoxyethyl	(80)	
C$_{11}$	"	(S)-2-Butyl	(70)	
C$_{12}$	"	(S)-1-Carbomethoxyisobutyl	(65)	
C$_{13}$	RNH$_2$, Et$_2$O, rt, 3 h	Ph	(91)	
	"	4-ClC$_6$H$_4$	(73)	
	"	4-O$_2$NC$_6$H$_4$	(45)	
C$_{14}$	"	4-MeOC$_6$H$_4$	(93)	
	"	4-MeC$_6$H$_4$	(68)	
C$_{15}$	RNH$_2$, MeOH, rt	(S)-α-Cyclohexylethyl	(65)	
	"	(S)-α-Phenylethyl	(70)	
	RNH$_2$•HCl, Na$_2$CO$_3$, MeOH, rt	(S)-1-Carbomethoxybenzyl	(70)	
	RNH$_2$, MeOH, reflux	3,5-(MeO)$_2$C$_6$H$_3$	(70)	
	"	2,5-(MeO)$_2$C$_6$H$_3$	(50)	
C$_{16}$	RNH$_2$•HCl, Na$_2$CO$_3$, MeOH, rt	(S)-1-Carbomethoxy-2-phenylethyl	(75)	
C$_{17}$	RNH$_2$, MeOH, reflux	α-Naphthyl	(50)	
C$_{19}$	"	p-Biphenylyl	(60)	

		246

422

423

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_7 | R = H

1. CF_3CO_2H, CH_2Cl_2, 20 min
2. K_2CO_3, MeOH, 4 h

$(85)^a$

C_8 | Me

1. CF_3CO_2H, CH_2Cl_2, 1 h
2. K_2CO_3, MeOH, overnight

(95)

C_8

I + [structure] II

I + II	**I:II**
(—)	20:80
(70)	<1:99

Et_3N, C_6H_6, reflux
Na_2CO_3 (sat.), Me_2CO, rt, 1 h

247

MnO_2, CH_2Cl_2, 25°

(78)

248

Na_2CO_3 (sat.), Me_2CO, H_2O, rt, 1 h

I (83)

247

C_{8-9}

RNH_2, MeOH, rt, 30 min

R = Me (53)
R = Bn (62)

244, 124

C_9

H_2SO_4 (2 N), reflux 2.5 h

(75)

249

1. Et_3N, EtOH, rt, 12 h
2. CH_2N_2, Et_2O

(—)

153

—

(—)

250

1. CF_3CO_2H, CH_2Cl_2, 5 min
2. Et_3N, THF, 6 h
3. Ac_2O, Et_3N, overnight

(56)

246

C_{10}

Na_2CO_3 (5%), rt, 30 min

(54)

153

1. NaOH, EtOH, rt, 72 h
2. CH_2N_2, Et_2O

(60)

153

TABLE VII. NITROGEN DONOR, α, β–UNSATURATED KETONE OR ALKYNYL KETONE ACCEPTOR (*Continued*)
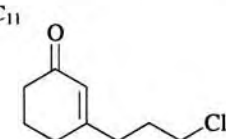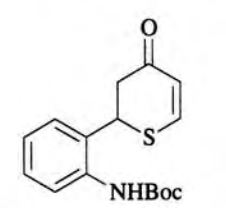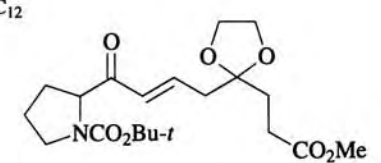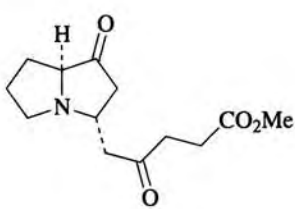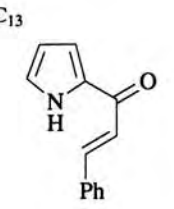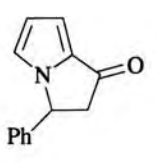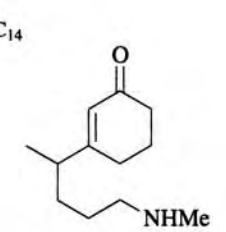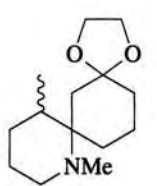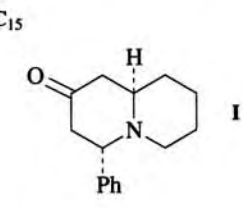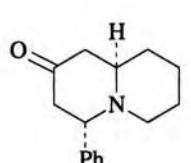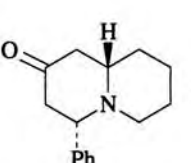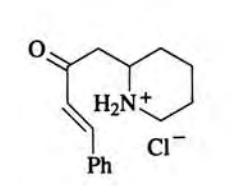
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₁₁	BnNH₂, TsOH, (CH₂OH)₂, C₆H₆, reflux 5 h	(33)	251
	1. CF₃CO₂H, CH₂Cl₂, 30 min 2. K₂CO₃, CH₂Cl₂, 30 min	(—)	246
C₁₂	HCl, AcOH	(88)	24
C₁₃	KOH, MeCN, rt, 20 min	(0)	252
C₁₄	TsOH, C₆H₆, (CH₂OH)₂, reflux	(22)	253

C₁₅

	I:II
NaOH, MeOH (aq), 55°, 22 h[b]	10:90
MeOH (aq), 55°, 22 h	17:83
MeOH, 55°, 17 h	30:70
HCl, MeOH (aq), 55°, 25 h	—
Et₃N, THF, 55°, 17 h	—

NaOH, 55°, 1-90 h	I + II	I:II	
H₂O	(70)	79:21	254, 36
H₂O	(69)	40:60	
H₂O	(64)	4:96	
MeOH (aq)	(62)	77:23	
MeOH (aq)	(67)	46:54	
MeOH (aq)	(61)	30:70	
MeOH (aq)	(79)	17:83	
Et₃N, THF, 55°, 16 h	(66)	88:12	

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

	R¹	R²			
C₁₅	H	H	TsOH, C₆H₆, reflux 6 h	(—)	255
C₁₆	H	Me	"	(—)	
C₁₇	Me	H	"	(62)	
	Me	H	NaOH, dioxane, warm 30 min	(34)	
	Me	H	BnNH₂, MeCN, warm 2 h	(70)	
	Me	H	*t*-B uOK, *t*-BuOH, reflux 30 min	(35)	
	Me	H	Dioxane, HCl (3 N), reflux 30 min	(52)	

C₁₅

TsOH, C₆H₆, reflux	(—)	255

HCl (20%), AcOH, reflux 9.5 h	(53)	256

NaOH (1 N), EtOH, 3-45 min[c]		257

	R¹	R²	
C₁₆	H	2-Thienyl	(51)
C₁₇	Me	2-Thienyl	(71)
C₁₈	H	Ph	(72)
	H	*p*-ClC₆H₄	(50)
C₁₉	Me	Ph	(60)
	Me	*p*-ClC₆H₄	(65)

C₁₇

H₂O, reflux 1 h	(90)	233

Na₂CO₃ (aq), CHCl₃	(54)	258

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{18}$

Zn, THF, NH$_4$OAc, 25°, 40 h

(65)

259

PhNCS, Et$_3$N, CH$_2$Cl$_2$, rt, 72 h

(40)

135

C$_{19}$

K$_2$CO$_3$, MeOH, rt

R = CO$_2$Et (0)
R = COCF$_3$ (90)

260

d

(2)

261

TsOH, (CH$_2$OH)$_2$, C$_6$H$_6$, reflux 3 h

(100)

251

R = β-(3,4-dimethoxyphenyl)ethyl

C$_{20}$

p-Ph(O)$_n$SC$_6$H$_4$

MeNH

p-Ph(O)$_n$SC$_6$H$_4$

247

	n^e	
Na$_2$CO$_3$ (sat.), Me$_2$CO, rt, 0.5 h	2	(96)
Et$_3$N, Me$_2$CO, reflux 2 h	2	(78)
Na$_2$CO$_3$ (sat.), Me$_2$CO, 5°, 15 min	0	(95)

p-PhO$_2$SC$_6$H$_4$
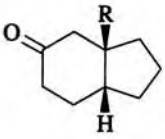
MeNCO, Et$_3$N, CH$_2$Cl$_2$, rt, 6 h

p-PhO$_2$SC$_6$H$_4$

(10)

247

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{21}

Amine, 260°
hv (254 nm), EtOH, 20 h[f]

(0) 262
(93) 263

264

R^2 =   R^3 =

	R^1		R^4	I + II	I:II
C_{38}	H	ClSO_2NCO, CH_2Cl_2, rt, 5.5 h	H	(10)	40:60
	CONH_2	*t*-BuOK, THF, 5°, 30 min	H	(64)	0:100
	CONH_2	(TMS)_2NNa, THF, 0°	H	(—)	0:100
	CONH_2	NaH, THF, 0°	H	(—)	0:100
C_{39}	COimidazole	MeNH_2 (40% aq), MeCN, 35°, 2.5 h	Me	(84)	0:100
C_{41}	COimidazole	PrNH_2, MeCN (aq), 35°, 3.5 h	Pr	(91)	0:100
	CONHPr	*t*-BuOK, THF, 0°	Pr	(—)	0:100
C_{42}	COimidazole	BnNH_2, MeCN (aq), 35°, 4.5 h	Bn	(84)	0:100
	CONHPr	(TMS)_2NNa, THF, 0°	Pr	(—)	0:100
	CONHPr	NaH, THF, 0°	Pr	(—)	0:100
	CONHPr	DBU, THF, rt	Pr	(75)	0:100
	CONHPr	Tetramethylguanidine, THF, rt	Pr	(10)	0:100
	CONHPr	Et_3N, THF, 0°	Pr	(0)	—
	CONHPr	*n*-PrNH_2	Pr	(0)	—

B. Alkynyl Ketone Acceptor

C_{15}

MeOH, reflux

(—) 25

[a] This was the overall yield of the *N*-acyl derivative after treatment of the initial product with Ac_2O.

[b] The yields were not specified. The isomerization occurred via a retroMichael followed by an intramolecular Michael reaction.

[c] The starting material underwent hydrolysis, leading to an acyclic intermediate which closed to give the Michael adduct.

[d] The reaction conditions were not specified.

[e] The starting material isomerized before closure.

[f] Irradiation of the reaction mixture caused isomerization of the double bonds, followed by the intramolecular Michael reaction.

TABLE VIII. CARBON DONOR, α, β–UNSATURATED SULFOXIDE OR SULFONE ACCEPTOR

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

A. α, β-Unsaturated Sulfoxide Acceptor

C₁₄ — *t*-BuOK, THF — (0) — 265

C₁₆ — *t*-BuOK, THF, rt, 72 h — (62) — 265

C₁₈ — *t*-BuOK, THF, rt, 24 h — (33) — 265

C₁₉ — NaBH₄, CHCl₃, MeOH, reflux — I + II + 266

III + IV

R		
(E)-CH=CHNO₂		
CH₂CH₂NO₂		

	Total	I:II:III:IV
(E)-CH=CHNO₂	(72)	36:46:1:17
CH₂CH₂NO₂	(61)	23:61:0:16

B. α, β-Unsaturated Sulfone Acceptor

C₁₃ — KH (cat.), 45°, 0.5 h — (65) — 27

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₁₆, C₁₈, C₂₂ (R = H, CH₂=CH, Ph)	n-BuLi, THF, -78°	(99), (62), (83)	267
C₁₈	CsF, MeCN, 80°	(75-87)	268
(R¹ = t-Bu, R² = H; t-Bu, TsN(Me)(CH₂)₂; Ph, TsN(Me)(CH₂)₂)	n-BuLi, THF, -78°, 0.5 h	(81)ᵃ, (0)ᵇ, (0)ᵇ	267
C₁₉	n- or t-BuLi, THF, -78°	(73)ᶜ	267
	n- or t-BuLi, THF, -78°	(69)ᵈ	267
C₂₁	PhS(O)₂CH₂PO(OEt)₂, n-BuLi, THF, -78° to rt	(67) + (17)	269
C₂₄	n-BuLi (2.2 eq), THF, -78°	(45) (60)ᵉ	270

436

437

TABLE VIII. CARBON DONOR, α, β−UNSATURATED SULFOXIDE OR SULFONE ACCEPTOR (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₂₈	*t*-BuLi, THF, -78 to 0°	(49)	267

[a] An 11% yield of the debrominated product was also obtained.

[b] Only debrominated product was obtained.

[c] The reaction occurred via an intramolecular Michael reaction followed by an intramolecular alkylation reaction.
Some debrominated, deconjugated product was also obtained.

[d] A 23% yield of debrominated, deconjugated product was also obtained.

[e] The reaction occurred via an intramolecular Michael reaction followed by an intramolecular alkylation. A 10% yield
of debrominated, deconjugated product was also obtained.

TABLE IX. CARBON DONOR, α, β–UNSATURATED CARBON OR NITROGEN GROUP ACCEPTOR

Substrate	Conditions	Product(s) and Yield(s) (%)		Refs.

A. α,β-Unsaturated Ester Acceptor

	n	R			
C_6	3	H	n-BuLi, THF, -100°	(78)	
C_7	3	Me	"	(0)	
	4	H	"	(82)	
	4	H	n-BuLi, THF, -78°	(52)	
	4	H	n-BuLi, THF, -8°	(14)	
	4	H	sec-BuLi, THF, -100°	(22)	
	4	H	t-BuLi, THF, -100°	(68)	
	4	H	MeLi, THF, -100°	(0)	
C_8	4	Me	n-BuLi, THF, -100°	(86)	
	5	H	"	(14)	

C_6

NaOEt, EtOH	(—)	(—)	272
NaH, THF, reflux	(65)	(35)	

C_7

1. NaOEt (cat.), C_6H_6, rt, 0.5 h	(89) +	(5)	273
2. NaOEt, EtOH, reflux 2 h			

TABLE IX. CARBON DONOR, α, β–UNSATURATED CARBON OR NITROGEN GROUP ACCEPTOR (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_8$ (diester with CO$_2$Et groups)	1. LSA, THF, -78°, 1 h 2. AcOH	(cyclopentane with HNBn, CO$_2$Et, CH$_2$CO$_2$Et) (78)	274

C$_8$ (diester substrate with CO$_2$R^1, R^2, CO$_2$R^1)

Products I and II (cyclopentene with CO$_2$R^1, CO$_2$R^1, H, R^3) 274
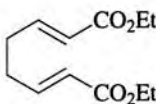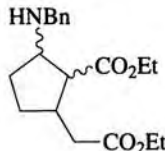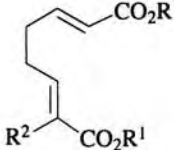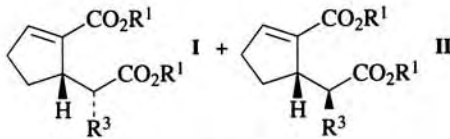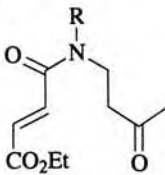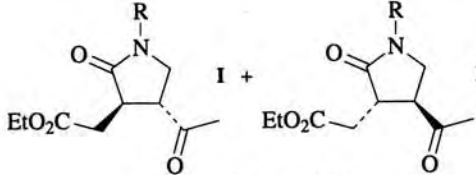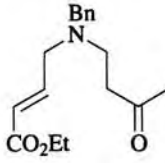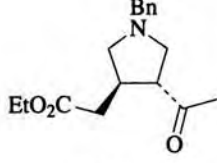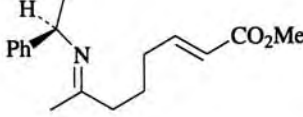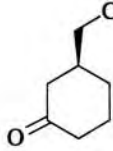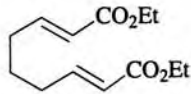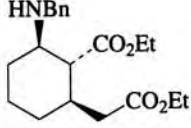
	R^1	R^2		R^3	I + II	I:II
C$_8$	Et	H	1. LSA, THF, -78°, 1 h 2. AcOH 3. MeI, K$_2$CO$_3$, EtOH, rt, 7 h 4. SiO$_2$, xylene, reflux	H	(65)	—
C$_9$	Et	Me	"	Me	(64)	26:74
	Me	H	1. LSA, THF, -78°, 1 h 2. MeI, -78°, 3 h; rt, overnight 3. MeI, K$_2$CO$_3$, EtOH, rt, 7 h 4. SiO$_2$, xylene, reflux	Me	(69)	61:39

C$_8$ (amide substrate with R, CO$_2$Et)

| | THF, MS 5 Å, 5° | Products I + II (pyrrolidinones with R, EtO$_2$C, acetyl) | 275 |

R	Conditions	I + II	I:II	
Bn	(R)-(+)-1-Phenylethylamine	(89)	100:0	63% ee
Tr	"	(95)	100:0	65% ee
Bn	(S)-(–)-1-Phenylethylamine	(84)	0:100	63% ee
Tr	"	(—)	0:100	—

| (substrate with Bn, N, CO$_2$Et, O) | (R)-(+)-1-Phenethylamine, THF, MS 5 Å, 5-10° | (pyrrolidine with Bn, N, EtO$_2$C, acetyl) (—) 62% ee | 276 |

(imine substrate with H, Ph, N, CO$_2$Me)		(cyclohexanone with CO$_2$Me)	277
	DMF, 80°, 40 h; H$^+$	(63) 21% ee	
	THF, 12 Kbar, 20°, 60 h; H$^+$	(61) 16% ee	
	MgBr$_2$, Et$_2$O, 0°, 5 min; H$^+$	(65) 50% ee	

| C$_9$
 (diester with CO$_2$Et groups) | 1. LSA, THF, -78°, 1 h
 2. AcOH | (cyclohexane with HNBn, CO$_2$Et, CH$_2$CO$_2$Et) (93) | 274 |

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C9

NaH, C6H6

R¹	R²	I + II	I:II
Me	(–)-Menthyl	(85-95)	69:31
t-Bu	(–)-Menthyl	(85-95)	84:16
Me	8-Phenylmenthyl	(85-95)	80:20
t-Bu	8-Phenylmenthyl	(85-95)	93:7

Me		(85-95)	77:23
t-Bu		(85-95)	81:19
Me		(85-95)	6:94
t-Bu		(85-95)	2:98

45

	I + II	I:II
K2CO3, EtOH, reflux 30 min	(88)	83:17
NaH, dioxane, reflux 4.5 h	(77)	66:33

278, 41

From	I + II	I:II
trans	(88)	75:25
trans	(88)	80:20
trans	(82)	76:24
trans	(91)	76:24
trans	(82)	77:23
trans	(87)	72:28
cis	(—)	>300:1

n-BuLi, THF, -78°
t-BuLi, THF, -78°
n-BuLi, THF, LiI, -100°
n-BuLi, THF, LiI, -78°
n-BuLi, BF3•Et2O, -78°
n-BuLi, TMEDA, -78°
n-BuLi, THF, -100°

279

RMgBr, CuI, Et2O, -20°, 1 hᵃ

C9	R		
	Me	(92)	>99% de
C10	CH2=CH	(94)	>99% de
	Et	(77)	>99% de
C14	Ph	(40)	>99% de

69

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
			276, 280, 281
	Pyrrolidine, THF, rt, 12 h	(80)	
	(R)-(+)-1-Phenylethylamine, THF, 5°	(80) 80% ee	
	(R)-(+)-1-Phenylethylamine, THF, MS 5 Å, 5°	(78) 90% ee	
	(S)-(–)-1-Phenylethylamine, THF, MS 5 Å, 5°	(83) 91% ee	276, 280

C$_{9-10}$

n		I + II	I:II	
1	t-BuOK, t-BuOH, rt	(—)	50:50	
2	"	(—)	50:50	
1	NaH, C$_6$H$_6$, rt, 15 min	(85)	96:4	
2	"	(88)	97:3	

C$_9$

			277
	C$_6$H$_6$, 80°, 8 h; H$^+$	(65) 58% ee	
	THF, 12 Kbar, 20°, 60 h; H$^+$	(61) 62% ee	
	MgBr$_2$, Et$_2$O, 35°, 20 h; H$^+$	(62) 29% ee	

C$_{10}$

	Pyrrolidine, AcOH, C$_6$H$_6$, rt	(36)	282

	1. LSA, THF, -78°, 1 h 2. AcOH	(0)^b	274

	C$_6$H$_6$, 80°, 6 h; H$^+$	(62) 86% ee	277
	THF, 12 Kbar, 20°, 60 h; H$^+$	(63) 92% ee	
	MgBr$_2$, Et$_2$O, 35°, 100 h; H$^+$	(0)	

	LDA, THF, -78°, 30 min	(68)	42

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

n-BuLi, THF, Et$_2$O, C$_6$H$_{14}$, -100°   283

	R^1	R^2		
C$_{11}$	H	I	—	(43)
	H	I	TMSCl	(85)
	H	Br	"	(0)
C$_{12}$	OMe	I	"	(92)

NaOMe, EtOH, rt or reflux   13, 12

	R^1	R^2	R^3	R^4	R^5	
C$_{11}$	H	H	H	H	Et	(77)
C$_{12}$	H	H	OMe	H	Et	(—)
C$_{13}$	H	Me	H	Me	Et	(—)
C$_{15}$	Et	Me	H	Me	Et	(—)
	-(CH$_2$)$_3$-		H	Me	Et	(82)
C$_{17}$	Ph	H	H	H	Me	(—)

C$_{11}$

NaOMe, MeOH, reflux   (—)   13

Warm 30 min   206

R			R^1	
Me	Piperidine acetate		Piperidinyl	(—)
Et	Morpholine acetate		Morpholinyl	(—)

NaOMe, MeOH, 6-12 h^c I +   II   284

	R^1	R^2	I + II	I:II
C$_{11}$	Me	H	(65)	>98:2
C$_{12}$	Me	Me	(73)	71:29
C$_{16}$	Ph	H	(81)	>98:2
C$_{17}$	Ph	Me	(83)	95:5

C$_{11}$

NaOMe, MeOH   (—)   13

446

447

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

DMSO-d_6, 80°, 67 h[d] — (3) — 285

n-BuLi, THF, Et$_2$O, C$_6$H$_{14}$, -100°, 1 h — 286

	R^1	R^2	R^3	R^4	
C$_{11}$	OMe	H	H	H	(68)
	H	H	OCH$_2$O		(68)
C$_{12}$	H	Me	Me	H	(60)
	OMe	H	Me	H	(69)
	OMe	H	H	Me	(71)

C$_{12}$

KH, PhMe, 90°, 8 h — (69) — 287

NaOMe, MeOH — (—) — 13

— 197

	R^1	R^2		
C$_{12}$	*n*-C$_5$H$_{11}$	H	LiH, THF, reflux, 20 h	(trace)
	n-C$_5$H$_{11}$	H	NaH, DME, reflux, 20 h	(12)
	n-C$_5$H$_{11}$	H	NaH, dioxane, reflux, 20 h	(15)
	n-C$_5$H$_{11}$	H	NaH, DME, DMSO, reflux, 20 h	(trace)
	n-C$_5$H$_{11}$	H	(TMS)$_2$NNa, C$_6$H$_6$, reflux, 20 h	(trace)
	n-C$_5$H$_{11}$	H	t-BuOK, BuOH, reflux, 20 h	(trace)
	n-C$_5$H$_{11}$	H	t-BuOK, DME, reflux, 20 h	(trace)
	n-C$_5$H$_{11}$	H	Pyrrolidine, TiCl$_4$, C$_6$H$_6$, reflux, 20 h	(trace)
	n-C$_5$H$_{11}$	H	Pyrrolidine, TiCl$_4$, PhMe, reflux, 20 h	(8)
	n-C$_5$H$_{11}$	H	Pyrrolidine, TiCl$_4$, xylene, reflux, 20 h	(24)
	n-C$_5$H$_{11}$	H	Pyrrolidine, TsOH, xylene, reflux, 20 h	(15)
	n-C$_5$H$_{11}$	H	Pyrrolidine, AcOH, C$_6$H$_6$, reflux, 20 h	(6)
	n-C$_5$H$_{11}$	H	Morpholine, TiCl$_4$, xylene, reflux, 20 h	(0)
C$_{14}$	*n*-C$_5$H$_{11}$	CO$_2$Et	NaH, C$_6$H$_6$, reflux, 20 h	(73)
	EtC≡CCH$_2$	CO$_2$Et	"	(68)

C$_{12}$

(EtO)$_2$P(O)CH(Me)CO$_2$Et, NaH, DMF, 0° — (32) + (16) + 288

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

450

(16) + (16)

| | | | |

C_{12} $\dfrac{n}{1}$
C_{13} 2
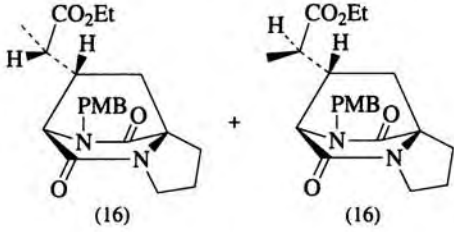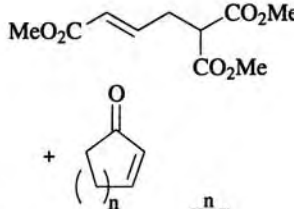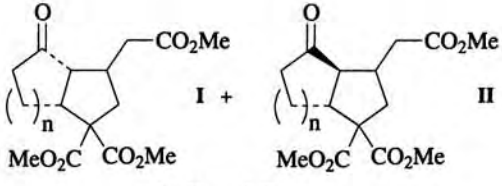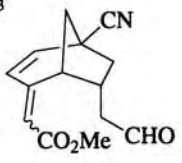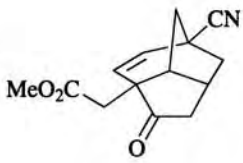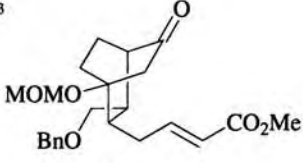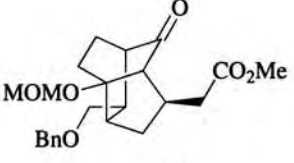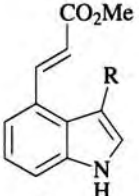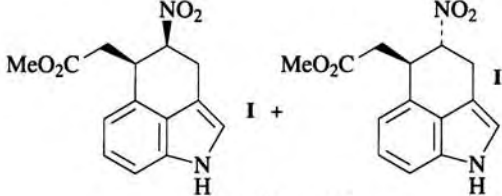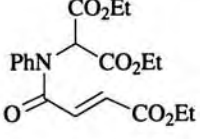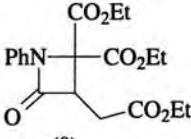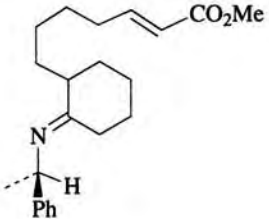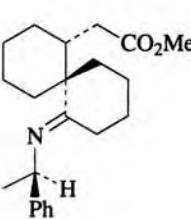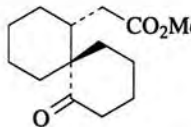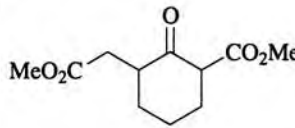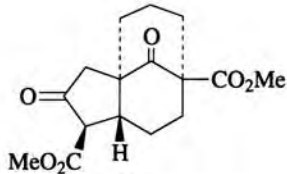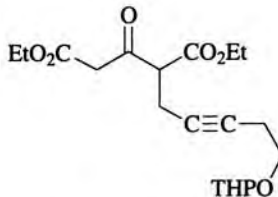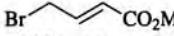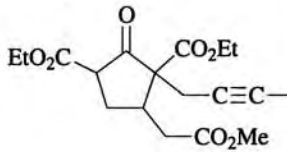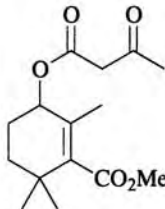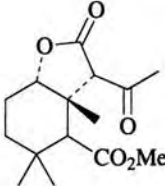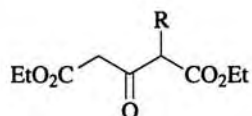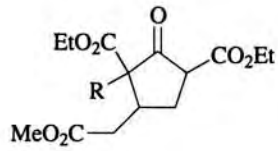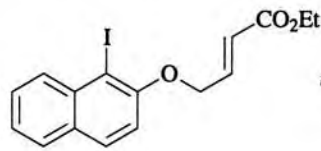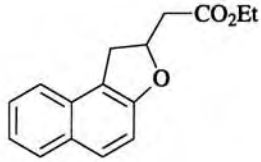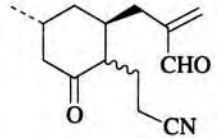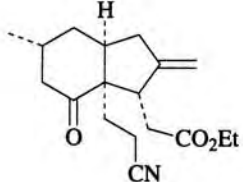
NaOMe, MeOH, 6-12 h[c]

I + II

I + II	I:II
(62)	>98:2
(55)	10:90

284

C_{13}

3,4-Dimethyl-5-(2'-hydroxyethyl)-
  thiazolium iodide, *i*-PrOH,
  Et$_3$N, heat 5 h

(67)

84

C_{13}

t-BuOK, THF, -78°

(99)

289

R	
(*E*)-CH=CHNO$_2$	NaBH$_4$, MeOH, warm
CH$_2$NMe$_2$	KF, 18-C-6, MeCN, MeNO$_2$, reflux

I + II

I + II	I:II
(79)	100:0
(87)	18:82

266

Et$_3$N
Piperidine

(0)
(—)

290

DMF, 120°, 12 h

(85)

291
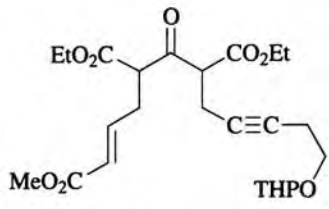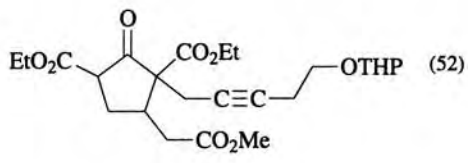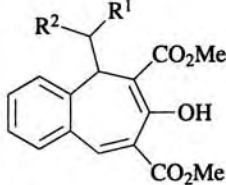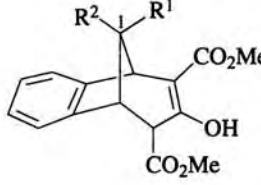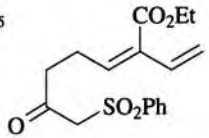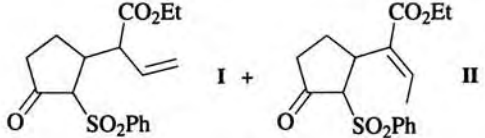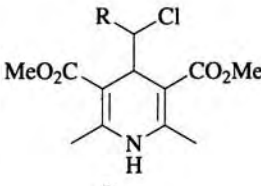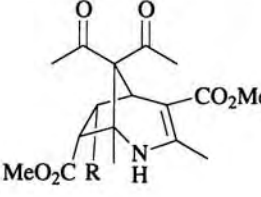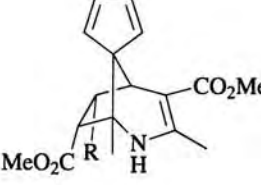
451

TABLE IX. CARBON DONOR, α, β–UNSATURATED CARBON OR NITROGEN GROUP ACCEPTOR (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. PhMe, 24 h 2. H_3O^+	(—)	291
C_{14} 	, dimsyl sodium, DMSO, rt, 112 h[e]	(41)	57, 2
	Br⌇CO₂Me, NaH, PhMe, 0° to rt, 2 h; 80°, 20 h	(52)	292
	K_2CO_3, EtOH, rt, 4 h	(0)	293

R		
$n\text{-}C_5H_{11}$	Mg(OMe)$_2$, MeOH, reflux, 10 h	(62)
$n\text{-}C_5H_{11}$	LiOH, MeOH, reflux, 10 h	(trace)
$n\text{-}C_5H_{11}$	K_2CO_3, MeOH, reflux, 10 h	(trace)
$n\text{-}C_5H_{11}$	NaH, THF, 20 h	(26)
$n\text{-}C_5H_{11}$	Mg(OEt)$_2$, EtOH, reflux, 10 h	(96)
$n\text{-}C_5H_{11}$	LiOH, EtOH, reflux, 10 h	(trace)
EtC≡CCH$_2$	Mg(OMe)$_2$, MeOH, reflux, 10 h	(68)
EtC≡CCH$_2$	LiOH, MeOH, reflux, 10 h	(72)
EtC≡CCH$_2$	K_2CO_3, MeOH, reflux, 10 h	(53)
EtC≡CCH$_2$	NaH, THF, 10 h	(29)
EtC≡CCH$_2$	Mg(OEt)$_2$, EtOH, reflux, 10 h	(92)
EtC≡CCH$_2$	LiOH, EtOH, reflux, 10 h	(75)

Ref: 197

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	n-BuLi, THF, Et$_2$O, C$_6$H$_{14}$, -100°, 1 h	(68)	286
	1. Ph$_3$P=CHCO$_2$Et, EtOH, overnight 2. NaOEt, EtOH, 30 min	(90)	269

TABLE IX. CARBON DONOR, α, β–UNSATURATED CARBON OR NITROGEN GROUP ACCEPTOR (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

NaH, PhMe, 0°, 30 min — (52) — 292

NaOMe, MeOH — 294

	R¹	R²	Time (h)	
C₁₄	H	NO₂	0.5	(89)
	NO₂	NO₂	1	(46)
C₁₅	NO₂	CO₂Me	1	(80)
	Me	NO₂	2	(33) epimers at 1
C₁₆	CO₂Me	CO₂Me	2	(93)
	CO₂Me	CO₂Me	12	(84)
C₁₇	COMe	CO₂Me	0.5	(84)
	COMe	CO₂Me	2	(83)
C₂₀	Ph	NO₂	0.75, rt; 1 h reflux	(55) epimers at 1

C₁₅

NaH, reflux — I + II — 295

	I + II	I:II
PhMe, 4 h	(80)	33:66
Xylene, 2 h	(80)	19:81
DME, 1 h	(85)	75:25
Diglyme, 2 h	(75)	0:100
bis(2-Ethoxyethyl) ether, 3 h	(70)	0:100

Na(acac), DMF — 296, 297

	R		
C₁₅	H	60°, 10 h	(85)
C₁₆	Me	65°, 2 h	(13)
	Me	100°, 6 h	(74)

CpNa, DMF, 60° — 296, 297

	R		
C₁₅	H	6 h	(68)
C₁₆	Me	10 h	(38)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

296, 297

	R	R^1		
C$_{16}$	H	H	1,3-Cyclohexanedione-Na, DMF, 70°, 10 h	(90)
C$_{17}$	Me	H	1,3-Cyclohexanedione-Na, DMF, 90°, 10 h	(60)
C$_{18}$	H	Me	Dimedone-Na, DMF, 65°, 8 h	(82)
C$_{19}$	Me	Me	Dimedone-Na, DMF, 90°, 10 h	(68)

C$_{15}$

t-BuOK (cat.), *t*-BuOH, rt, 30 min

(45) + (30) + (5)   298

DMAD (1 eq), reflux 2 d

I + II + III + IV   E = CO$_2$Me   V

299

	R^1	R^2		I	II	III	IV	V
C$_{15}$	H	Me	EtOH	(34)	(54)	(—)	(—)	(—)
C$_{16}$	Me	Me	EtOH	(19)	(19)	(—)	(—)	(—)
	Me	Me	*n*-C$_5$H$_{11}$OH	(17)	(13)	(—)	(—)	(—)
	Me	Me	MeCN	(4)	(—)	(14)	(10)	(8)
	Me	Me	Dioxane	(4)	(—)	(14)	(21)	(8)
	Me	Me	Dioxane, DMAD (2 eq)	(4)	(—)	(9)	(35)	(14)
	Me	Me	PhMe	(2)	(—)	(11)	(44)	(—)
C$_{20}$	H	Ph	EtOH	(27)	(42)	(—)	(—)	(—)

NaH, DMF, -78°

I + II   300

	R		I + II	I:II
C$_{15}$	H		(88)	100:0 >90% de
C$_{16}$	Me		(—)	0:100

456

457

TABLE IX. CARBON DONOR, α, β–UNSATURATED CARBON OR NITROGEN GROUP ACCEPTOR (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₁₅ R = H C₁₆ R = OMe	KF, 18-C-6, MeCN, MeNO₂	I + II I + II : I:II (84)ᶠ : 25:75 (74)ᶠ : 11:89	266
C₁₆	t-BuOK, t-BuOH, reflux	(—)	301
	NaOMe	(70)	296
C₁₆ Me C₁₈ CH(CO₂Me)₂ C₁₉ n-Bu	C₁₆ Me₂CuLi, 12 min, -78° C₁₈ CH₂(CO₂Me)₂, MeONa, 13 min, 20° C₁₉ Bu₂CuLi, 12 min, -30°	R Me (15) CH(CO₂Me)₂ (1)ᵈ n-Bu (3)	302
C₁₆	Na(acac), DMF, 90°	(80)	296, 297
E = CO₂Me	DMAD, EtOH, reflux 20 h	(—)	299
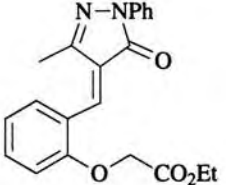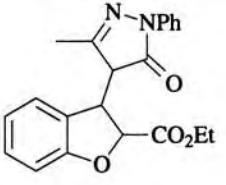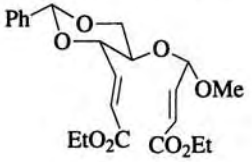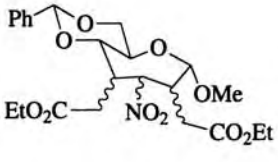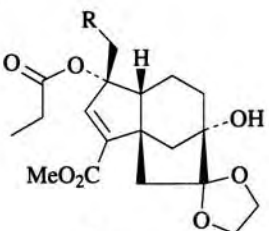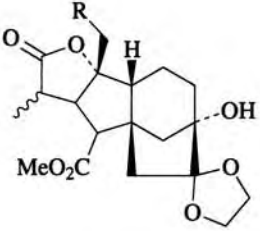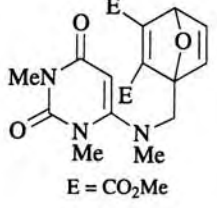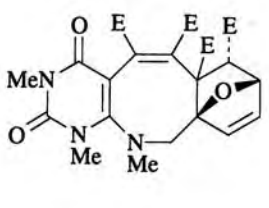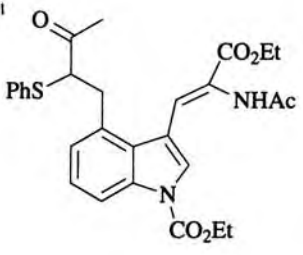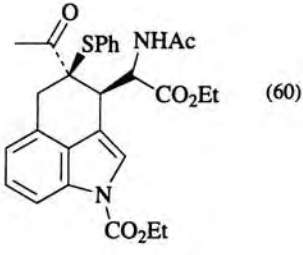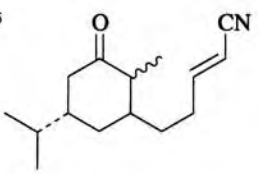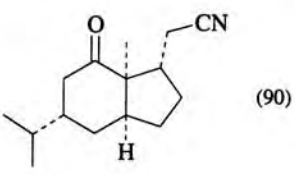
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{17}$	NaOMe, MeOH, reflux 2 h	(71)	13
C$_{18}$	*i*-PrOTiCl$_3$, Et$_3$N, CH$_2$Cl$_2$, -78°, 5 h	(88)	303
	KH, DMF, -20°, 0.5 h	(91)	304
			305

	R			
C$_{18}$	H	Several conditions	(0)	
C$_{19}$	CO$_2$Me	NaOMe, MeOH, rt, 8.3 h	(60)	

C$_{19}$	NaH, THF	(—)	306
	Pyrrolidine, THF	(85)	306
	NaOEt, EtOH, rt, 1.5 h	(63)	281, 307
	Pyrrolidine, THF, rt, 15 h	(80)	281, 307

460

461

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	NaOEt, EtOH	(0)	12
	Tetramethylguanidine, MeNO$_2$, rt, 3 d^g	(44)	81

C$_{20}$

			308-310
$\underline{R}$ HC≡C CH$_2$=CH	— 1. KH, DMF, -20°, 20 min 2. Et$_3$NHAc quench -40°	(0) (—) ~2:1 mixture of isomers	
E = CO$_2$Me	DMAD, dioxane, reflux 20 h	(83)	299

C$_{21}$

	DBU, *t*-BuOH, heat	(60)	311

B. α, β-Unsaturated Nitrile Acceptor

C$_{15}$

	t-BuOK, *t*-BuOH, 65-70°, 2 h	(90)	39

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C. α, β-Unsaturated Aldehyde Acceptor

C_{14}

	K$_2$CO$_3$, EtOH, rt, 4 h	(63)[h]	293, 312,
	NaH, DMF, 20°, 8 h	(60)	313
	t-BuOK, C$_6$H$_6$, reflux 3 h	(60-66)	

D. α, β-Unsaturated Acid Acceptor

C_{11}

| | Morpholine acetate | (0) | 206 |

E. α, β-Unsaturated Amide Acceptor

C_7

| | *n*-BuLi, THF, -100° | (15) | 271 |

| | LiTMP, THF, -78° to rt; | | 29 |
| | rt, 24 h | | |

	R^1	R^2		
C_7	H	CONMePh	(33)	
	TMS	CO$_2$Me	(57)	
C_8	Me	CO$_2$Me	(59)	
	Me	CN	(22)	
	Me	CONMePh	(65)	
	Me	CO$_2$C$_6$H$_{11}$	(89)	

C_{11}

	t-BuOK	(0)	314
	NaH	(0)	
	DBU, dioxane, reflux	(65)	

C_{12}

| | Et$_3$N | (0) | 290 |

TABLE IX. CARBON DONOR, α, β–UNSATURATED CARBON OR NITROGEN GROUP ACCEPTOR (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

NaOMe, MeOH, reflux

(0)

13

315, 316

	R^1	R^2			
				I + II	**I:II**
C_{16}	H	Ph	KOH, EtOH, reflux, 30 min	(95)	90:10
C_{17}	CO_2Bu-t	Ph	Et_3N, MeOH, 25°, 7 d	(100)	0:100
C_{18}	CO_2Bu-t	m-MeOC$_6$H$_4$	Et_3N, MeOH, rt, 48-120 h	(—)^i	12:88
	CO_2Bu-t	m-MeOC$_6$H$_4$	MeONa, MeOH, rt, 2.7 h	(—)^i	13:87
	CO_2Bu-t	m-MeOC$_6$H$_4$	MeONa, MeOH, H$_2$O, rt, 2 h	(—)^i	13:87
	CO_2Bu-t	m-MeOC$_6$H$_4$	t-BuOK, t-BuOH, rt, 1 h	(—)^i	45:55
	CO_2Bu-t	m-MeOC$_6$H$_4$	t-BuOK, t-BuOH, rt, 12 h	(—)^i	50:50
	CO_2Bu-t	m-MeOC$_6$H$_4$	t-BuOK, PhMe, rt, 6 h	(—)^i	25:75

F. α, β-Unsaturated Nitro Acceptor

C_8

NaH, t-BuOH, THF

n = 0 (0)
n = 2 (100)

317

C_{10}

TsOH, morpholine, C$_6$H$_6$, reflux 20 h

(32)

318

319

R		
Me	LDA, THF, -78°	(0)
Me	LiHMDS, THF, -78°	(0)
Me	LiHMDS, THF, -100°; quench at -50°	(67)
Me	LiHMDS, THF, -100°; quench at -40°	(55)
Me	LiHMDS, THF, -100°; quench at -20°	(48)
p-O$_2$NC$_6$H$_4$CH$_2$	LiHMDS, THF, -100°; quench at -50°	(57)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. LiHMDS, THF, -100°; quench at -80° 2. PhSeCl, 15 min	(71)	319

[a] The reaction occurred by intermolecular addition of the cuprate to the enone followed by intramolecular closure of the resulting anion on the enoate.

[b] Only the product from intermolecular addition of the amine was obtained in 59% yield.

[c] The reaction occurred via an intermolecular Michael reaction followed by an intramolecular Michael reaction.

[d] Four other products were also isolated.

[e] The reaction occurred via an intermolecular 1,6-Michael addition followed by an intramolecular Michael reaction and a Dieckman condensation.

[f] Some product from the intermolecular conjugate addition of the nitromethane anion was also obtained.

[g] The reaction with bulkier anions (methyl cyanoacetate, malononitrile) gave only the product from intermolecular addition of the nucleophile.

[h] The product from intramolecular Michael reaction followed by aldol condensation was also obtained in 14% yield.

[i] The authors report a quantitative yield of crude product.

TABLE X. CARBON DONOR, α, β–UNSATURATED KETONE OR ALKYNYL KETONE ACCEPTOR
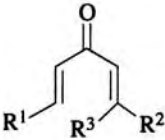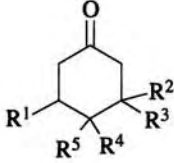
| | Substrate | | Conditions | Product(s) and Yield(s) (%) | | Refs. |

A. α, β-Unsaturated Ketone Acceptor

320, 321, 80

	R^1	R^2	R^3		R^4	R^5	
C_9	Me	Me	Me	$CH_2R^4R^5$, NaOEt, EtOH, reflux	NO_2	H	(59)
C_{11}	Me	Me	Me	"	CO_2Et	CN	(62)
C_{16}	Me	Me	H	"	Ts	CN	(52)
C_{17}	Me	Me	Me	"	Ts	CN	(65)
C_{20}	Ph	Ph	H	$CH_2R^4R^5$, NaOH (10%), MeOH, reflux	CO_2Me	CO_2Me	(62)
	Ph	Ph	H	"	CO_2Et	CO_2Et	(98)
	p-ClC$_6$H$_4$	p-ClC$_6$H$_4$	H	"	CO_2Me	CO_2Me	(80)
C_{22}	p-MeOC$_6$H$_4$	p-MeOC$_6$H$_4$	H	"	CO_2Et	CO_2Et	(84)
	p-MeOC$_6$H$_4$	p-MeOC$_6$H$_4$	H	"	CO_2Me	CO_2Me	(81)
	PhCH=CH	Ph	H	$CH_2R^4R^5$, NaOH (10%), MeOH, rt	CO_2Me	CO_2Me	(76)
C_{25}	Ph	Ph	H	"	CN	Ph	(85)
	Ph	Ph	H	"	CN	p-ClC$_6$H$_4$	(83)
	Ph	Ph	H	"	CN	p-O$_2$NC$_6$H$_4$	(85)
	Ph	Ph	H	"	CN	Ph	(45)
C_{26}	Ph	p-MeOC$_6$H$_4$	H	"	CN	p-ClC$_6$H$_4$	(86)
	Ph	p-MeOC$_6$H$_4$	H	"	CN	p-O$_2$NC$_6$H$_4$	(80)
C_{27}	p-MeC$_6$H$_4$	p-MeC$_6$H$_4$	H	"	CN	p-O$_2$NC$_6$H$_4$	(88)
	p-MeC$_6$H$_4$	p-MeC$_6$H$_4$	H	"	CN	p-ClC$_6$H$_4$	(85)
	p-MeOC$_6$H$_4$	p-MeOC$_6$H$_4$	H	"	CN	p-O$_2$NC$_6$H$_4$	(78)
C_{20}	Ph	Ph	H	$CH_2R^4R^5$, C$_6$H$_6$, ion exchange resin, reflux	CO_2Me	CO_2Me	(92)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_8$

1. Hg(OAc)$_2$, AcOH
2. NaBH(OMe)$_3$

 (58)

322

BnNH

CH$_2$=CHNO$_2$, rt

 (—)

323

	R^1	R^2		I + II	I:II	
C$_8$	H	Me	THF, *n*-BuLi, -100°	(—)	—	
C$_{13}$	H	Ph	THF, *n*-BuLi, -100°	(—)	—	
C$_{29}$	Et	CH(PPh$_3$)CO$_2$Et	THF, *n*-BuLi, -78°	(88)	77:33	
	Et	CH(PPh$_3$)CO$_2$Et	THF, *n*-BuLi, -100°	(90)	77:33	
	Et	CH(PPh$_3$)CO$_2$Et	THF, *t*-BuLi, -78°	(93)	83:17	
	Et	CH(PPh$_3$)CO$_2$Et	THF, *t*-BuLi, LiI, -78°	(—)	88:12	
	Et	CH(PPh$_3$)CO$_2$Et	THF, *t*-BuLi, LiI, -78°	(—)	86:14	
	Et	CH(PPh$_3$)CO$_2$Et	THF, *n*-BuLi, BF$_3$•Et$_2$O, -78°	(—)	81:19	

279, 271

Cs$_2$CO$_3$

324

C$_9$ MeCN, rt   R = H, n = 1 (0)

C$_{11}$ THF, DMF, rt   R = Me, n = 2 (0)

C$_9$

L-Proline, DMF, rt, 48 h^a

 (87)

325

K$_2$CO$_3$, EtOH, rt, 3 h

 (89)

37

1. Hg(OAc)$_2$, AcOH
2. NaBH(OMe)$_3$

 (50)

322

TiCl$_4$, CH$_2$Cl$_2$
20°, 30 min

97

	R
C$_9$	H
C$_{10}$	Me

(—)
(68)

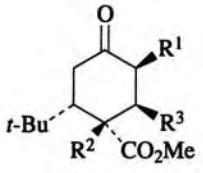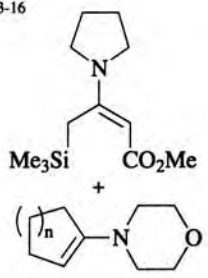TABLE X. CARBON DONOR, α, β–UNSATURATED KETONE OR ALKYNYL KETONE ACCEPTOR (*Continued*)

Substrate					Conditions	Product(s) and Yield(s) (%)				Refs.
R¹	R²	R³	R⁴	R⁵		R⁶	R⁷	R⁸		

1. LDA, THF, -78°
2. HMPA, rt to reflux, 16 h — 62-64, 326

	R¹	R²	R³	R⁴	R⁵		R⁶	R⁷	R⁸	
C₉	H	Me	H	H	H	R⁶CH=CHNO₂	H	—	—	(3)
C₁₁	H	Me	Me	Me	H		H	—	—	(2)
	Me	H	H	H	Me		Me	—	—	(42)
C₁₂	H	Me	Me	Me	H		Me	—	—	(58)
C₁₃	Me	H	C₃H₅*	H	H		Me	—	—	(3)
	Me	H	C₃H₅*	H	Me		H	—	—	(13)
C₁₅	Me	H	H	H	Me		C₅H₉O*	—	—	(25)
C₉	H	Me	H	H	H	R⁶CH=C(R⁷)SO₂C₆H₄R⁸-*p*	H	H	Cl	(19)
C₁₁	H	Me	Me	Me	H		H	H	Cl	(7)
	H	Me	Me	Me	H		H	H	NO₂	(0)
	H	Me	Me	Me	H		H	H	H	(38)
C₁₂	Me	H	C₃H₅*	H	H		H	H	H	(5)
	H	Me	H	H	Pr-*i*		H	H	H	(1)
	H	Me	Me	Me	H		H	Me	H	(21)
	H	Me	Me	Me	H		H	Me	Cl	(2)
C₁₃	Me	H	C₃H₅*	H	Me		H	H	H	(17)
	Me	H	C₃H₅*	H	Me		H	H	Cl	(20)
	Me	H	C₃H₅*	H	Me		H	H	NO₂	(1)
C₁₄	Me	H	C₃H₅*	H	Me		H	Me	Cl	(20)

$C_3H_5* = $ (structure) $C_5H_9O* = $ (structure)

Substrate				Conditions	Product(s) and Yield(s) (%)	Refs.
	R¹	R²	R³			
C₉	H	H	H	LDA, CH₂=CHCO₂Me, THF, C₆H₁₄, -23°, 2 h	(90)	78, 77
C₁₀	Me	H	H		(81)	
	H	Me	H		(98)	
C₁₂	H	Me	Me		(98)	
	Me	H	Me		(91)	
C₉	H	H	H	LiCA, CH₂=CHCO₂Me, THF, -23°, 45 min	(90)	78, 77
C₁₂	H	Me	Me		(98)	
	R¹	R²	R³	LDA, CH₂=CHCOMe, THF, -78°; rt, 12 h		78
C₁₁	Me	H	H		(81)	
	H	Me	H		(70)	
C₁₃	Me	H	Me		(70)	
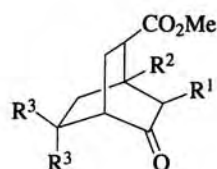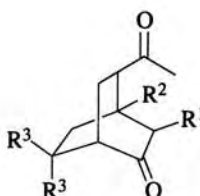
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473

TABLE X. CARBON DONOR, α, β–UNSATURATED KETONE OR ALKYNYL KETONE ACCEPTOR (*Continued*)

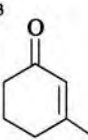| Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
			62, 63, 66, 68, 327, 328

	R^1	R^2	R^3	R^4			R^5	R^6	
C_{10}	H	H	H	H	1. LDA, HMPT, THF, -30°, 1 h		CO_2Me	Me	(28)
					2. , -20° to rt, 1 h				
C_{11}	H	Me	H	H			CO_2Me	Me	(55)
C_{13}	H	Me	Me	Me	(The base was LiCA)		CO_2Me	Me	(20)
C_{14}	Me	H	C_3H_5*	H			CO_2Me	Me	(23)
C_9	Me	H	H	H	LDA, PPh₃ , THF, -10°		H	H	(10)
C_{11}	H	Me	Me	Me			H	H	(22)
C_{12}	Me	H	H	C_3H_5*			H	H	(18)
C_{11}	H	Me	Me	Me	LDA, SO₂Ph , THF, HMPA, rt; reflux 2 h		H	H	(38)
C_{12}	Me	H	H	C_3H_5*			H	H	(5)
C_{12}	H	Me	Me	Me	LDA, SO₂Ph , THF, HMPA, rt		Me	H	(21)

C_3H_5* =

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Cs₂CO₃, MeCN, rt, 1 h		324

	n		I + II	I:II
C_{10}	1		(70)	100:0
C_{11}	2		(89)	100:0

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C_{10}	TiCl₄, CH₂Cl₂ 40°, 30 min	(82)	97
	TiCl₄, CH₂Cl₂, 20°, 30 min	(73)	97
	TiCl₄, CH₂Cl₂		97

	R		I + II	I:II
C_{10}	H	-78°, 30 min	(92)	33:67
	H	40°, 2 min	(92)	97:3
C_{11}	Me	40°, 1 h	(0)	—

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₁₀

LDA, (acrylate) CO₂R

I + II   329

R	I + II	de (%)
(–)-Menthyl	(71)	33
(–)-8-Phenylmenthyl	(91)	50
Ethyl (–)-lactyl	(90)	50
(menthyloxy structure)	(67)	10
Me₂C₆H₃–N / PhO₂S (structure)	(80)	64

(acrylate) CO₂R
R = Et-(–)-lactyl

I +   II   329

	I + II	I:II
Et₂AlCl	(76)	80:20
TiCl₄	(85)	75:25

t-BuOK, *t*-BuOH, 5-25°, 30 min   (0)   330

1. Hg(OAc)₂, HgO, MeOH
2. NaBH(OMe)₃   ~OAc (73)   322

1. Hg(OAc)₂, AcOH
2. NaBH(OMe)₃   " (70)   322

L-Proline, DMF, 60°   (40) + (40)   325

1. Hg(OAc)₂, AcOH
2. NaBH(OMe)₃   (60)   322

I + II   331

From	I + II	I:II
LiOH, MeOH[b]	*trans*	(—)	8 0:20
1. NaOMe (cat.), MeOH 2. NaOMe, Et₂O	*trans*	(80)	75:25
KOH, MeOH	*trans*	(—)	66:34
1. Zr(OPr)₄, C₆H₆, rt, 1 h; LiOH, MeOH, H₂O, overnight 2. DMAP, CH₂Cl₂, -40°; TFA, DBU, 0°	*trans*	(90)	98:2
LiOH, MeOH; TFAA, DBU	*cis*	(70)	66:33

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	t-BuOK, *t*-BuOH, rt NaH, C$_6$H$_6$, rt, 15 min	 $\dfrac{\text{I + II} \quad \text{I:II}}{(\text{—}) \quad 50:50}$ $(90) \quad 100:0$	40
	KOAc, EtOAc, EtOH, 50-70°	(—)	332
	1. NaH, DMF, -40 to -20° 2. AcOH, -20°, 20 h	(56)	333
	K$_2$CO$_3$, EtOH, rt, 40 h; HCl (aq), heat^c	(45)	330
C$_{10\text{-}11}$ C$_{11}$	1. LDA, THF, HMPA, R$\diagdown$NO$_2$, -78° 2. To reflux when R = H	 R = H (22) R = Me (39)	63, 326
	Diethyl malonate, *t*-BuOK, *t*-BuOH, rt, 2 h	(70)	19, 334
	1. Hg(OAc)$_2$, AcOH 2. NaBH(OMe)$_3$ 3. KOH, H$_2$O, MeCN 4. Jones oxidation	(44)	322
	Cs$_2$CO$_3$, rt		324
C$_{11}$ C$_{12}$	$\dfrac{n}{1}$ 2 2	MeCN, 4 h THF, DMF, 5 h MeCN, 5 h	$\dfrac{\text{I + II} \quad \text{I:II}}{(88) \quad 100:0}$ $(40) \quad 66:33$ $(57) \quad 83:17$	

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

	R¹	R²	R³			
C$_{11}$	H	H	H	TiCl$_4$, Ti(OPr-i)$_4$	(trace)	71
C$_{12}$	Me	H	H		(5)	
C$_{13}$	H	H	Me		(3)	
	Me	Me	H		(20)	
C$_{14}$	H	Me	Me		(30)	
C$_{11}$	H	H	H	Et$_2$AlCl	(trace)	
C$_{12}$	Me	H	H		(13)	
C$_{13}$	H	H	Me		(13)	
	Me	Me	H		(43)	
C$_{14}$	H	Me	Me		(34)	

C$_{11}$

CO$_2$Me, LDA, THF, -78 to -20°, 8 h

(74)   58

TBAF, THF, rt, 30 min

(64)   335

1. Hg(OAc)$_2$, AcOH
2. NaBH(OMe)$_3$

(10)   322

Cs$_2$CO$_3$, rt   324

	n	R¹	R²		I + II	I:II
C$_{11}$	1	H	Me	(2.0 eq), MeCN, 1 h	(71)	29:71
	1	Me	H	(2.0 eq), MeCN, 24 h	(27)	50:50
C$_{12}$	2	H	Me	(0.2 eq), THF, DMF, 2 h	(95)	20:80
	2	H	Me	(0.2 eq), MeCN, 2 h	(97)	33:66
	2	Me	H	(0.2 eq), MeCN, 144 h	(27)	40:60

C$_{11}$ + C$_{14-15}$

Pd(OAc)$_2$, THF, reflux

I +   II   336

	Substrate	Conditions	Product(s) and Yield(s) (%)		Refs.

<table>
<tr><td></td><td>R</td><td></td><td colspan="2">I + II   I:II</td><td></td></tr>
<tr><td>C₁₄</td><td>H</td><td>PPh₃, 0.5 h</td><td colspan="2">(68)   37:63</td><td></td></tr>
</table>

C_{14}

	R		I + II	I:II	
	H	PPh$_3$, 0.5 h	(68)	37:63	
	H	0.2 h	(71)	33:67	
C_{15}	Me	0.2 h	(69)	25:75	

NaOEt, EtOH, reflux 45 min — 337-339, 79

	R^1	R^2	
C_{11}	H	H	(33)
C_{13}	H	Me	(22)
C_{16}	H	(CH$_2$)$_5$	(28-31)
C_{19}	2-Furyl	H	(20)
	2-Thiophenyl	H	(18)
C_{21}	2-Furyl	Me	(27)
	2-Thiophenyl	Me	(25)
	5-Me-2-furyl	H	(—)
C_{23}	Ph	H	(45)
C_{25}	Ph	Me	(40)
	p-MeOC$_6$H$_4$	H	(50)
C_{28}	Ph	(CH$_2$)$_5$	(72)

C_{12}

1. AcOH (aq), 45°, 4 h^b
2. Et$_2$NH, rt, 13 h

(98) — 340

TMSI, MeCN, -20°, 2.5-3 h — 341

	R^1	R^2	R^3	
C_{12}	Me	H	H	(79)
	Me	H	NO$_2$	(0)
C_{13}	Et	H	H	(76)
C_{17}	Ph	H	H	(100)
C_{18}	Ph	OMe	H	(99)

C_{12}

Cs$_2$CO$_3$, MeCN, rt — 324

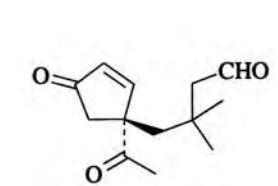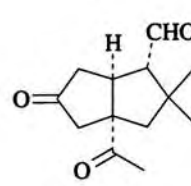|	R^1	R^2		I + II	I:II
	H	Me	18 h	(50)	10:90
	Me	H	96 h	(2)	10:90

TsOH, CH$_2$Cl$_2$

(70) — 342

TABLE X. CARBON DONOR, α, β–UNSATURATED KETONE OR ALKYNYL KETONE ACCEPTOR (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
			343
	KF, MeOH, reflux	(66)	
	NaH, THF, reflux 30 min	(60-65)	
	NaH, THF, rt, 2 h	(89)	199
	Cs$_2$CO$_3$, MeCN, rt, 48 h	I + II	324

		I + II	I:II
C$_{12}$	1	(14)	100:0
C$_{13}$	2	(25)	50:50

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{12}$	NaOH, EtOH, H$_2$O[b]	(—)	344
	t-BuOK, t-BuOH, rt, 30 min	(75)	18
	Cs$_2$CO$_3$, THF, DMF, rt, 60 h		83
	high dilution	(0)	
	"pseudo" high dilution	(27)	
	Pd(OAc)$_2$, PPh$_3$, MeCN, 40°, 7 h	(21) + (41)	336
			345, 346

	R		
C$_{12}$	H	Pyrrolidine, MeOH, 25°, 24 h	(70)
	H	t-BuOK, t-BuOH, 30°, 18 h[b]	(35)
C$_{13}$	CN	Et$_2$NH, MeOH, H$_2$O, 70°, 2 h	(40)

TABLE X. CARBON DONOR, α, β–UNSATURATED KETONE OR ALKYNYL KETONE ACCEPTOR (*Continued*)
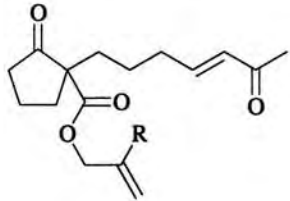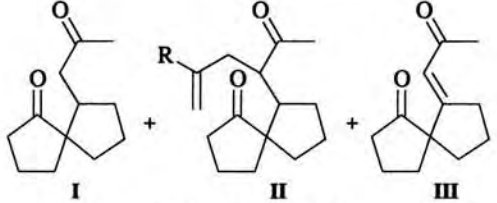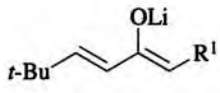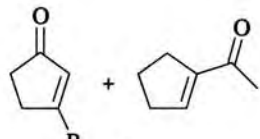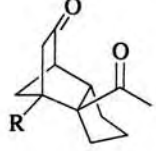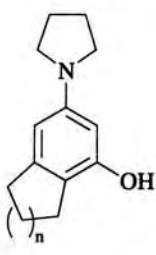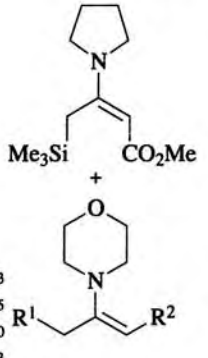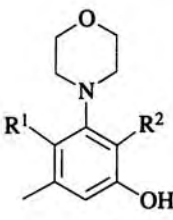
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

	R		I + II + III	I:II:III
$C_{12} + C_{15}$	H	Pd(OAc)$_2$, PPh$_3$, MeCN, 40°, 10 h	(69)	100:0:0
	H	Pd(OAc)$_2$, DPPE, MeCN, 40°, 15 h	(81)	100:0:0
	H	Pd(OAc)$_2$, DPPE, MeCN, 80°, 0.5 h	(83)	93:7:0
	H	Pd(OAc)$_2$, DPPE, MeCN, 80°, 1 h	(36)	50:0:50
	H	Pd(PPh$_3$)$_4$, MeCN, rt, 1 h	(84)	100:0:0
	H	Pd(OAc)$_2$, PPh$_3$, THF, 40°, 4 h	(69)	93:7:0
	H	Pd(OAc)$_2$, PPh$_3$, THF, 80°, 0.5 h	(62)	26:74:0
	H	Pd(PPh$_3$)$_4$, THF, rt, 1 h	(47)	34:66:0
	H	Pd(PPh$_3$)$_4$, THF, 80°, 0.2 h	(66)	27:73:0
$C_{12} + C_{16}$	Me	"	(78)	17:83:0

			R^1	R^2	R^3	
C_{12}		Methyl crotonate	H	H	Me	(87)
		Methyl methacrylate	H	Me	H	(20)
C_{13}		Methyl crotonate	Me	H	Me	(49)

	R	LDA, THF, -70°, 73.5 h		70
C_{12}	H		(10)	
C_{13}	Me		(32)	

C_{13-16}

	TFA, Cl(CH$_2$)$_2$Cl, reflux 24 h	n = 1 (64)	348
		n = 2 (63)	
		n = 3 (59)	
		n = 4 (67)	

		R^1	R^2	TFA, 100°, 48 h		348
C_{13}		Me	Me		(41)	
C_{15}		Et	Et		(37)	
C_{20}		–(CH$_2$)$_9$–			(—)	
C_{23}		–(CH$_2$)$_{12}$–			(—)	

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

LiHMDS, 1.45 h

	R¹			R²	R³	
C₁₃	H	C₆H₁₄, Et₂O, -78° to rt		H	H	(32)
C₁₄	H			H	Me	(52)
	H			Me	H	(46)
C₁₄	Me	C₆H₁₄, 0°		H	H	(79)
C₁₅	Me			H	Me	(62)
	Me			Me	H	(52)

C₁₃

LDA, THF, -78°, 73.5 h

(9)   70

LDA, THF, -78°, 73.5 h

(33)   70

LDA, THF,
PPh₃
0° to rt

(36)   66

1. Hg(OAc)₂, AcOH
2. NaBH(OMe)₃

(70)   322

KOH, MeOH, reflux 2 hᵈ

(50)   350

C₆H₆, 22°, 12 h

I + II + 44

III

	I + II + III	I:II:III
NaOMe; (CF₃CO)₂O, DBU, DMAP	(80)	61:21:18
Mg(OMe)₂; (CF₃CO)₂O, DBU, DMAP	(51)	80:12:8
Zr(OPr-*n*)₄; (CF₃CO)₂O, DBU, DMAP, CH₂Cl₂, -78 to 22°, 2 h	(80)	83:9:8
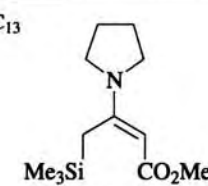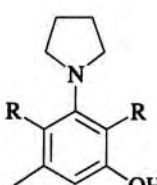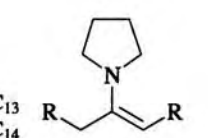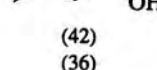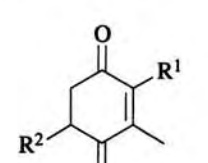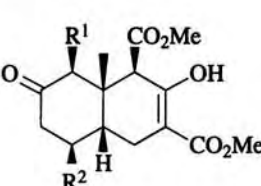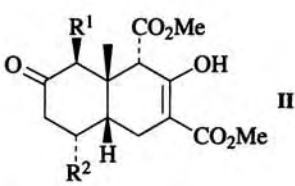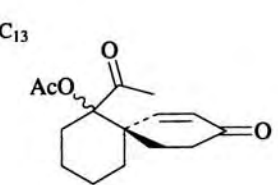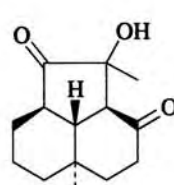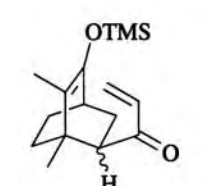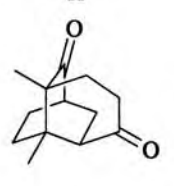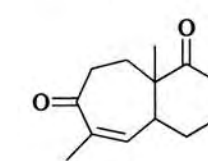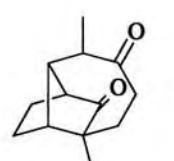
TABLE X. CARBON DONOR, α, β–UNSATURATED KETONE OR ALKYNYL KETONE ACCEPTOR (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	t-BuOK, *t*-BuOH, 30°, 50 h[b]	(86) + (11)	351
	Na, MeOH, rt, 1 h	(—)	352
	1. Zr(OPr-*i*)₄, C₆H₆, rt 2. NaOMe	(61) + (2)	43
	NaOH, EtOH, 5 min[e]	(84)	172

	R¹	R²	R³	R⁴		I + II	I:II
C₁₃	H	OMe	H	H	DBU, EtOH, reflux 24 h	(60)	—
C₁₄	H	Me	Me	H	"	(94)	50:50
	H	OMe	Me	H	"	(95)	58:42
	Me	Me	H	H	DBU, CH₂Cl₂, rt, 24 h	(73)	—
C₁₅	Me	Me	Me	H	"	(69)	36:64
	Me	Me	H	Me	"	(74)	—
	Me	Me	CO₂Et	H	Et₃N, CH₂Cl₂, rt, 24 h	(60)	0:100
	Me	OMe	Me	H	DBU, EtOH, reflux 24 h	(77)	96:4
C₁₉	H	OMe	Ph	H	"	(80)	72:28
	H	Me	Ph	H	"	(89)	67:33
C₂₀	Me	Me	Ph	H	"	(51)	40:60
C₁₄	H	Me	Me	H	KF, Al₂O₃, THF, rt, 2 h	(95)	67:33
	H	OMe	Me	H	"	(86)	64:36
C₁₅	Me	Me	Me	H	"	(95)	96:4
	Me	OMe	Me	H	"	(97)	98:2
	Me	Me	CO₂Et	H	"	(—)	—
C₁₉	H	OMe	Ph	H	"	(84)	43:57
	H	Me	Ph	H	"	(88)	60:40
C₂₀	Me	Me	Ph	H	"	(97)	79:21
	Me	OMe	Ph	H	"	(77)	79:21

353, 354

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C_{13}

+

	R
C_{13}	Me
C_{14}	Et

TFA, 100°, 48 h

(42)
(36)

348

C_{13}

	R^1	R^2
C_{13}	H	H
C_{14}	H	Me
	Me	H

Dimethyl 3-oxoglutarate, KF, DMSO, 2 d

    I +

I	**II**
(40)	(1)
(22)	(11)
(—)	(0)

    II

355

C_{13}

KOH, MeOH, reflux 4-5 h[b]

(27)

350

TiCl$_4$, Ti(OPr-i)$_4$, CH$_2$Cl$_2$, -78 to 25°, 17 h[f]

(31)

96, 72

Et$_3$N, (CH$_2$OH)$_2$, 225°, 24 h, sealed tube

(10-20)

20

Morpholine, TsOH, C$_6$H$_6$, reflux 11 h

TAMA, THF, reflux

DATA, THF, reflux

(92)

(82)

(81)

356

TABLE X. CARBON DONOR, α, β–UNSATURATED KETONE OR ALKYNYL KETONE ACCEPTOR (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. LiOH, 0.5 h 2. HCl, reflux 3. (CH₂OH)₂	(83)	357
	t-BuOK, *t*-BuOH, 25°, 15 min	(73)	358
	NaOMe, MeOH, rt*g*	(45)	359, 330
	LDA, THF, -78°, 73.5 h	I + II	70

	R¹	R²		I + II	I:II
C₁₄	CHO	H		(51)	11:89
C₁₅	COMe	H		(65-70)	100:0
C₁₆	COMe	OMe		(28)	100:0

C₁₄

	LDA, THF, -78°, 73.5 h	(62)	70

	COR, rt, 18-42 h	I + II + III	347

	From *cis:trans*	R	I + II	I:II:III
C₁₄	0:100	Me	(5)	100:0:0
C₁₉	10:90	Ph	(71)	62:16:22
	THF, HMPA 10:90	Ph	(79)	73:11:16
	99:1	Ph	(79)	47:9:44

C₁₄	THF		
C₁₉	THF		
	THF, HMPA		
	THF		

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₁₄

LDA, THF, -78°, 73.5 h

(27)

70

NaOH, EtOH, H₂O, 25°, 2 h[b]

(38) + (11)

344

C₁₄₋₁₇

t-BuOK, *t*-BuOH

R = CO₂Me (93)

R = (0)

35

C₁₅

1. LDA, THF, -90°, 30 min
2. (Br, CO₂Me) -80 to -40°, 3 h

(12) + (20)

68

	R¹	R²			
C₁₅	H	H	Al₂O₃, Et₂O, reflux, 4 h[h]	(67)	90:10
	H	H	LiH, THF, rt, 10 h	(55)	97:3
	H	H	LDA, THF, rt, 11 h	(70)	96:4
	H	H	NaH, THF, rt, 18 h	(63)	97:3
	H	H	Al₂O₃, Et₂O, rt, 25 min	(73)	97:3
	H	H	Al(OPr-*i*)₃, CH₂Cl₂, rt, 18 h	(70)	97:3
	H	H	KH, THF, 0°, 4 h	(0)	—
	H	H	Ti(OPr-*i*)₄, CH₂Cl₂, rt, 24 h	(0)	—
	H	H	DMAP, CH₂Cl₂, rt, 78 h	(13)	65:35
	H	H	Triton B, pyridine, rt, 18 h	(8)	62:38
	H	H	DBU, THF, rt, 12 h	(50)	76:24
C₁₇	OMe	Cl	Al₂O₃, Et₂O, reflux, 6 h[h]	(66)	100:0

II + III **II:III**

II +

III

360, 361

C₁₅

1. KOH, H₂O, reflux
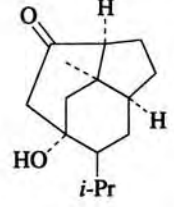2. HCl (12 N), rt

(—)

21

KH, THF, -40°, 4 h

(68)

362

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. (Imidazolyl)$_2$CO, THF, rt 2. EtO$_2$CCH$_2$CO$_2$H, Mg(OEt)$_2$ 3. K$_2$CO$_3$, EtOH	(80)	363, 364
	LDA, THF, -78°, 73.5 h	(13)	70
	1. Hg(OAc)$_2$, AcOH 2. NaBH(OMe)$_3$	(77)	322
	1. *t*-BuOK, *t*-BuOH, 0° 2. H$^+$	**I** + **II**	365

	R^1
C$_{15}$	Me
C$_{16}$	Et
C$_{17}$	*n*-Pr
	i-Pr
C$_{19}$	Cyclopentyl

R^2	R^3	I + II	I:II
H	H	(100)	100:0
H	Me	(—)	50:50
H	Et	(—)	11:89
Me	Me	(100)	100:0
–(CH$_2$)$_4$–		(100)	100:0

C$_{15}$	*t*-BuOK, *t*-BuOH, 30°, 40 h[b]	(48)	366
	HCl (2 N), EtOH, reflux 3 h	(—)	366
C$_{16}$	R^{2}CH$_2$CN, Et$_2$NH[i]		367

R^1		R^2	
Me	MeCN, reflux	CN	(51)
Et	EtOH, rt	CN	(95)
Me	MeCN, reflux	CO$_2$Me	(61)

498

499

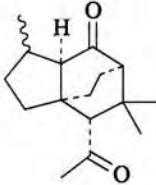TABLE X. CARBON DONOR, α, β–UNSATURATED KETONE OR ALKYNYL KETONE ACCEPTOR (*Continued*)
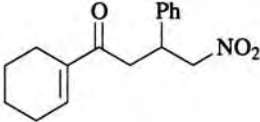
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. LDA, THF, HMPA 2. TMSCl 3. , TiCl$_4$, CH$_2$Cl$_2$, -78 to -40°^{i}	(64)	73
	MeONa, MeOH rt reflux	 $\dfrac{I + II}{(65)}$ $\dfrac{I:II}{3:97}$ (88) 20:80	368

	R^1	R^2		R^3	
C$_{16}$	COMe	H	NaH, THF, 0°, 1 h	H	(80)
	COMe	OH	KHCO$_3$, K$_2$CO$_3$, MeOH rt, 48 h	H	(—)
C$_{17}$	COCH$_2$CO$_2$Me	H	"	CO$_2$Me	(50)

C$_{16}$			
	KOH, EtOH, reflux 30 min	(86) + (14)	315
	TMSI, MeCN, -20°	(25)	341

C$_{17}$			
	LDA, CO$_2$Me , -23°	(~ quant)	370
	MeSO$_3$H, rt, 24 h	(<2)	371

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	t-BuOK, DME, rt, 20 h	(5)	19, 334
	LDA, THF, -78°, 73.5 h[j]	(68)	70
	NaH, K₂CO₃, THF, rt	(~ quant)	15
C₁₇₋₁₈	*t*-BuOK, *t*-BuOH, rt, 40 h	R = H (80) R = Me (80)	372
	Cinnamyl chloride, Et₃N, C₆H₆, reflux 6 h		373
C₁₈ R¹ = H, R² = Me		(45)	
H, Et		(36)	
Cl, Et		(67)	
Br, Et		(72)	
NO₂, Et		(85)	
C₁₉ Me, Et		(24)	
CO₂Et, Et		(76)	
C₁₈	OC(CH₂CO₂Et)₂, Et₂NH, EtOH[i]	(96)	374
	SiO₂, HCl	(66)	375
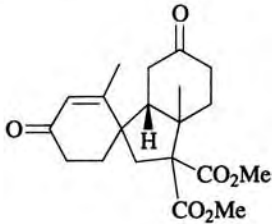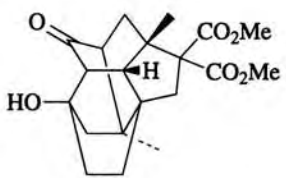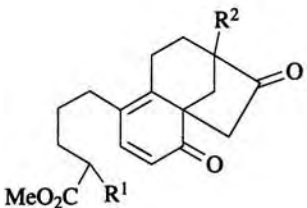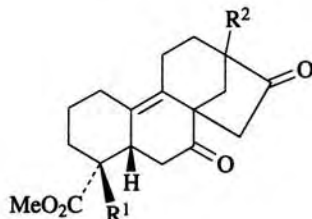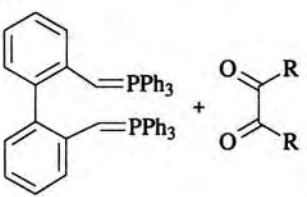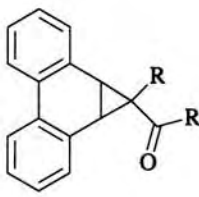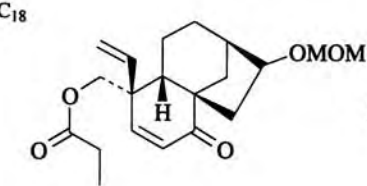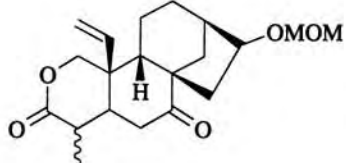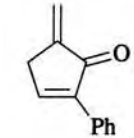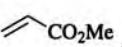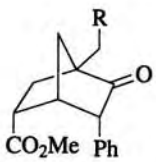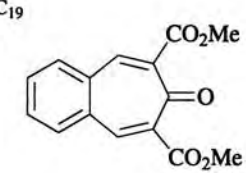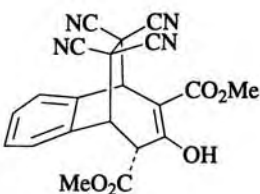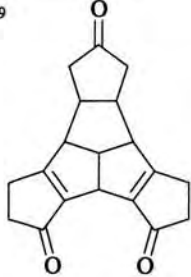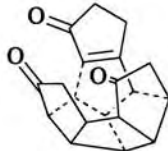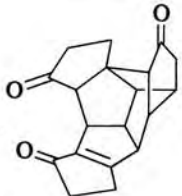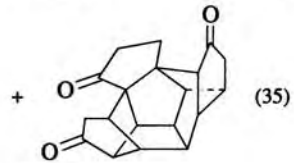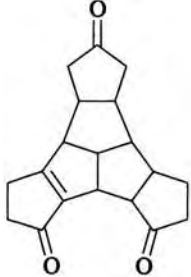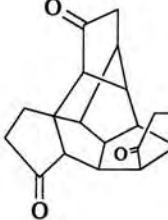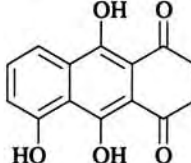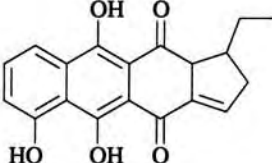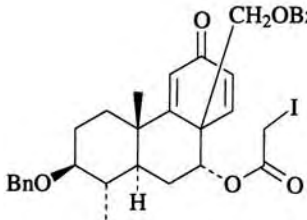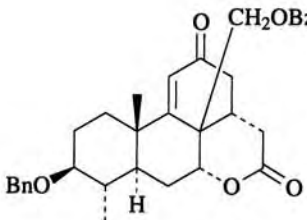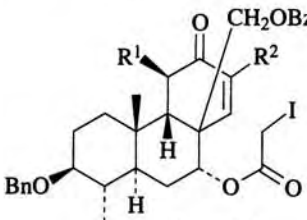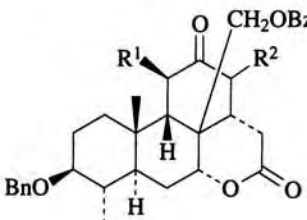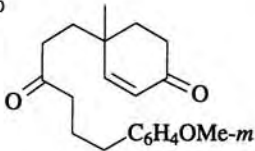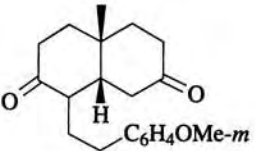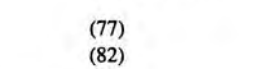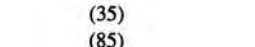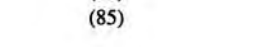
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

TsOH, C_6H_6[b]   (—)   375

376-378, 308

	R^1	R^2			
C_{18}	CO_2Me	H	NaOMe, MeOH, 4 h	(100)	
	Me	H	$BnN^+Me_3OH^-$, CH_2Cl_2	(—)	
	Me	H	LiOMe, $LiClO_4$, Et_2O	(—)	
C_{20}	CO_2Me	OMOM	DMF, NaH	(62)	

C_{18-28}

Dioxane, reflux

R = Me (25)
R = Ph (60)

379

C_{18}

KH, DMF, -30°, 2 h   (60)   380

1. RNa, THF, -78°, 1.5 h

2. $\diagup\diagup CO_2Me$, rt, 2 h[j]

381

	R	
C_{19}	$C(Me)_2CO_2Me$	(40)
	$C(OMe)_2CO_2Me$	(25)
C_{23}	$CH(Ph)CO_2Me$	(48)
C_{24}	$C(Me)(Ph)CO_2Me$	(41)

C_{32}

(67)

C_{19}

$(NC)_2CHCH(CN)_2$, Et_2NH, MeCN, rt, 90 min[j]
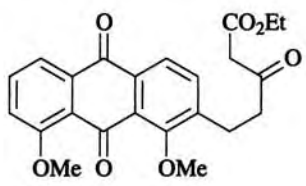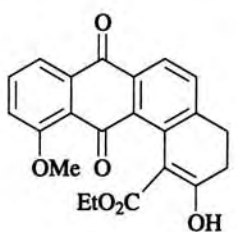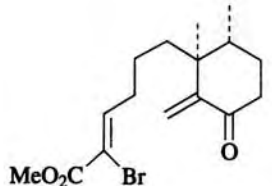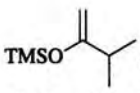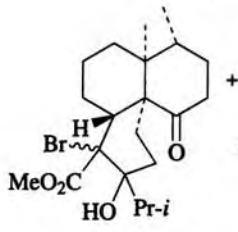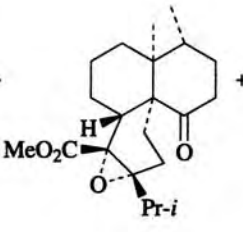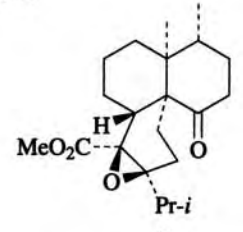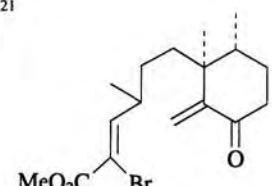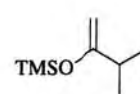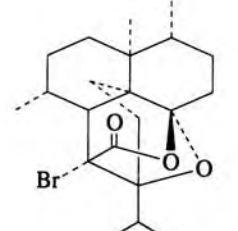
(73)   367

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₁₉	KOH, MeOH, 100°, sealed tube	(22) + (22) + (35)	382
	Na₂CO₃, MeOH, H₂O	(quant)	382
	Piperidinium acetate, pent-2-enal, EtOH	(62)	383
	TMSI, Et₃N, MeCN, -20°	(75)	341
	TMSI, Et₃N, MeCN, -20°		341

R¹	R²		
H	H	3 h	(96)
Br	H	2 h	(0)
OAc	H	1.75 h	(65)
OAc	Me	1.75 h	(0)

C₁₉

C₂₀

C₂₀

			384, 385

NaH, C₆H₆, reflux, 4 h (77)
LDA, THF, -78° to rt, 3 h (82)
Piperidine, C₆H₆, reflux, 4 h (35)
t-BuOK, *t*-BuOH (85)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	NaH, DMF, 80°, 3 h	(46)	386
	TMSO, MeLi, DME, -78°, 1 h; rt, 10 h	(25) + (15) + (7)	3, 387, 388

C$_{21}$

	TMSO, MeLi, DME, -78° to rt	(30)	3, 387, 388

			386

	R		
C$_{21}$	H	NaH, DMF, 115°, 2 h	(35)
C$_{22}$	OMe	NaH, DMF, 100°, 20 min	(<3)

C$_{21}$

	MeOK, MeOH, rt, 15 min	(14)	139

508

509

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

MeNO$_2$, NaOMe, MeOH, rt, 7 d[i,k]; IR-120, 0.5 h   (15)   81

KOH, EtOH, rt, 16 h   (—)   17

C$_{21-26}$

CsF, MeCN, rt, overnight   R = CN (43)   R = SO$_2$Ph (77)   389

C$_{22}$

t-BuOK   (9)   390

	R			
C$_{24}$	5-Me-2-furyl	AcOH, 100°, 1 h	*trans*	(66)
C$_{26}$	Ph	"	*trans*	(63)
C$_{28}$	*p*-MeOC$_6$H$_4$	"	*trans*	(62)
C$_{24}$	5-Me-2-furyl	NaOH, EtOH	*cis*	(74)
C$_{26}$	Ph	"	*cis*	(86)
C$_{28}$	*p*-MeOC$_6$H$_4$	"	*cis*	(54)
C$_{24}$	5-Me-2-furyl	CH$_2$Cl$_2$, (–)-quinine, 40°, 3 d	*trans*	(25)
C$_{26}$	Ph	"	*trans*	(30)
C$_{28}$	*p*-MeOC$_6$H$_4$	"	*trans*	(40)

339

C$_{24}$

t-BuOK, *t*-BuOH, rt, 30 min   (75)   391

R = (*S*)-CHMe(CH$_2$)$_2$CH=CMe$_2$

510

511
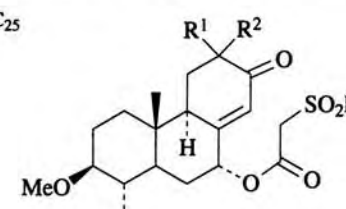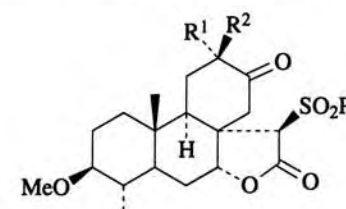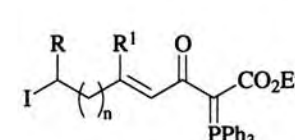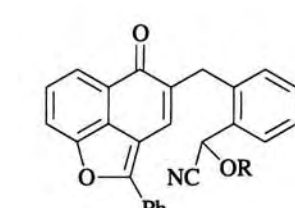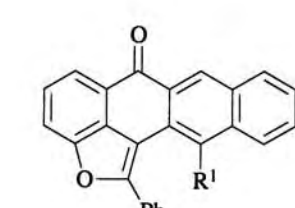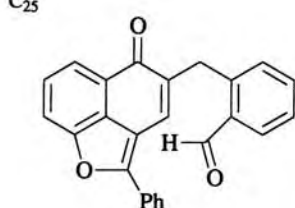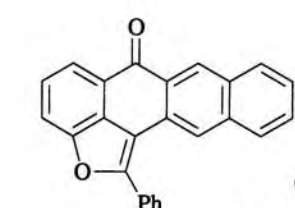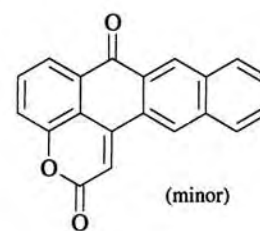
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C$_{25}$

R^1	R^2		
H	H	MeCN or CH$_2$Cl$_2$	(84)
Cl	H	CH$_2$Cl$_2$	(91)
H	Cl	CH$_2$Cl$_2$	(83)

CsF, 25°, 12-24 h — Ref. 392

n-BuLi^l, THF, -100 to -78°, 4-38 min; X — Ref. 393

	n	R	R^1	X	R^2	
C$_{25}$	1	H	H	H$_2$O	H	(77)
C$_{26}$	2^m	H	H	MeOH	H	(85)
	2^l	H	H	MeI	Me	(73)
C$_{27}$	3	H	H	MeOH	H	(77)
	2	H	Me	EtOH	H	(75)
C$_{28}$	4	H	H	MeOH	H	(44)
	3	H	Me	EtOH	H	(76)
	3^n	Me	H	MeOH	H	(0)

NaH, DMSO, 2 h — Ref. 394

	R	R^1	
C$_{25}$	Ac	OH	(95)
C$_{26}$	Bz	CN	(96)

C$_{26}$

R
THP

NaOBu-*t*, Et$_2$O, reflux — Ref. 394

(62)

C$_{25}$

NaCN, H$_2$O, EtOH, reflux 35 min — Ref. 394

(major) +

(minor)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

n-BuLi^l, THF, -78°, 4-15 min; X

393

	n	R	X	R^1	
C$_{27}$	1	H	H$_2$O	H	(87)
	1^l	H	BnBr	Bn	(91)
	1^{l,o}	H	BrCH$_2$CO$_2$Me	MeO$_2$CCH$_2$	(67)
C$_{28}$	1	Me	MeOH	H	(93)
C$_{29}$	2	H	MeOH	H	(91)
	2	H	EtI	Et	(78)

C$_{28}$

KOH, EtOH, rt, 16 h   (25)   17

≡ C$_{11}$H$_7$O$_2$CH$_2$Na = RNa

2,5-Dimethyl-1,4-benzoquinone, NaOAc, MeOH

(20)   56

2,6-Dimethyl-1,4-benzoquinone, NaOAc, MeOH

(—)   56

C$_{29}$

Et$_3$N, AcOH, reflux 1 h

(95)   395

, base

(—)   56

TABLE X. CARBON DONOR, α, β–UNSATURATED KETONE OR ALKYNYL KETONE ACCEPTOR (*Continued*)
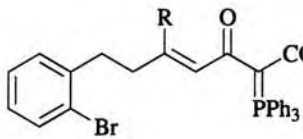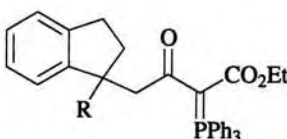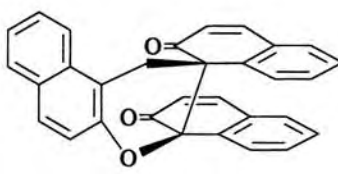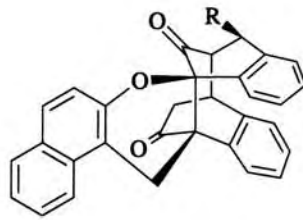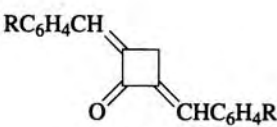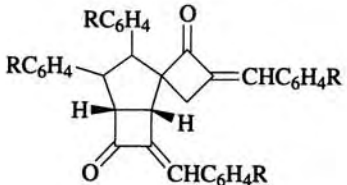
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

THF, -78° 393

	R		
C$_{31}$	H	*n*-BuLi (1 eq), 3 min	(0)
	H	*n*-BuLi (2 eq), 10 min	(0)
C$_{32}$	Me	*n*-BuLi (1 eq), 20 min	(72)
	Me	*n*-BuLi (2 eq), - 100°, 20 min	(—)

I +

II

396

		·R	I + II	I:II
C$_{32}$	MeONa, MeOH, THF, rt, 30 min	OMe	(43)	88:12
C$_{33}$	EtONa, EtOH, THF, rt, 30 min	OEt	(34)	85:15
C$_{34}$	*i*-PrONa, *i*-PrOH, THF, rt, 30 min	OPr-*i*	(33)	82:18
	CH$_2$(CO$_2$Et)$_2$, *t*-BuOK, *t*-BuOH	CH(CO$_2$Et)$_2$	(53)	100:0
	CH$_2$(CO$_2$Me)$_2$, *t*-BuOK, *t*-BuOH	CH(CO$_2$Me)$_2$	(52)	100:0
	NCCH$_2$CO$_2$Me, *t*-BuOK, *t*-BuOH	CH(CN)CO$_2$Me	(48)	100:0
	NCCH$_2$CO$_2$Et, *t*-BuOK, *t*-BuOH	CH(CN)CO$_2$Et	(52)	100:0

NaOH (aq), EtOH^i 397

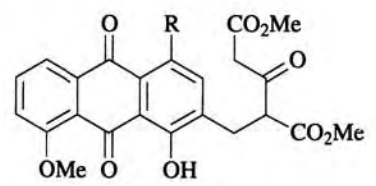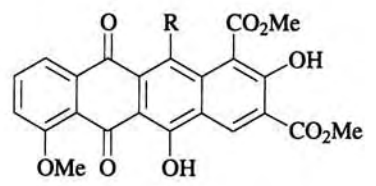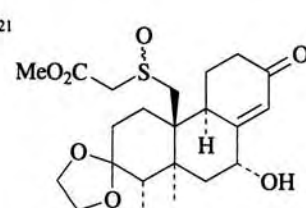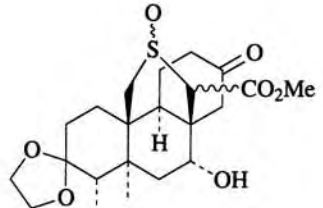|	R		
C$_{36}$	H	45°, 10 min	(23)
	p-Cl	50°, 30 min	(—)
C$_{40}$	*p*-Me	"	(32)
	p-OMe	"	(—)
C$_{44}$	3,4-(OMe)$_2$	"	(1)
	p-Me$_2$N	"	(—)

TABLE X. CARBON DONOR, α, β–UNSATURATED KETONE OR ALKYNYL KETONE ACCEPTOR (*Continued*)
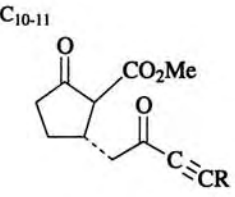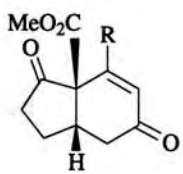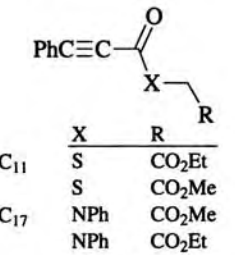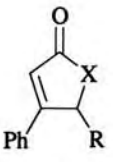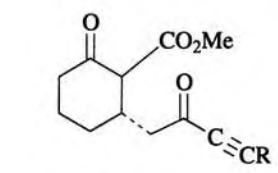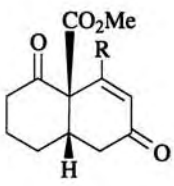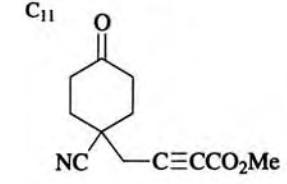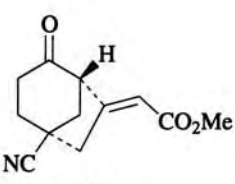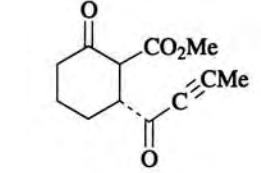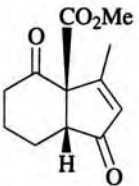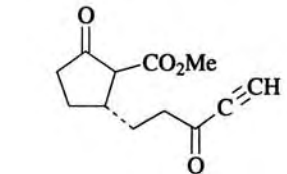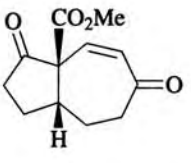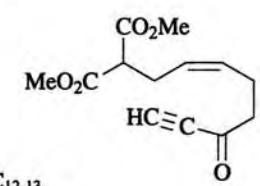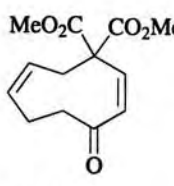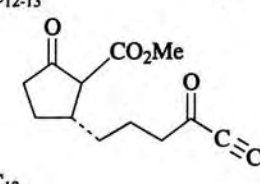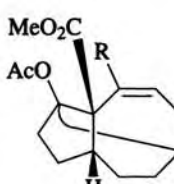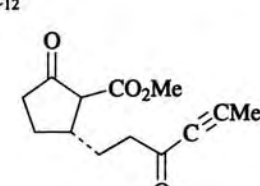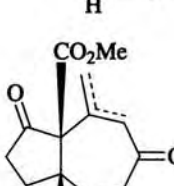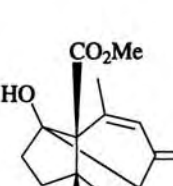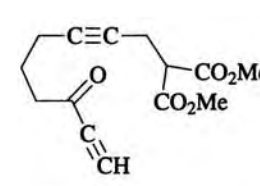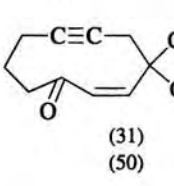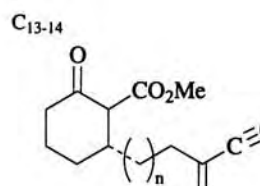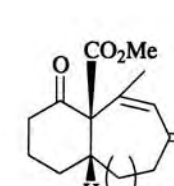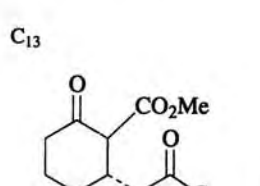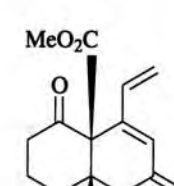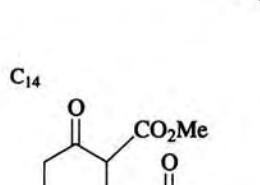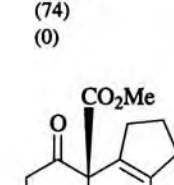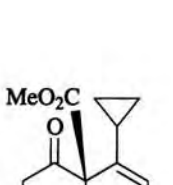
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
		B. α,β-Unsaturated Alkynyl Ketone Acceptors	

C$_{10-11}$

Cs$_2$CO$_3$, MeCN, 0.5-2 h

R = H (55)
R = Me (87)

92

LiH, DMF, rt, 2 h

	X	R	
C$_{11}$	S	CO$_2$Et	(82)
	S	CO$_2$Me	(80)
C$_{17}$	NPh	CO$_2$Me	(90)
	NPh	CO$_2$Et	(80)

398,
398a

Cs$_2$CO$_3$, THF, DMF,
2-5 h

	R	
C$_{11}$	H	(47)
C$_{12}$	Me	(89)
C$_{14}$	(CH$_2$)$_3$OAc	(75)

92

C$_{11}$

Et$_3$N, PhMe, reflux 12 h

(65-70)

84

Cs$_2$CO$_3$, THF, DMF,
0.75 h

(82)

92

Cs$_2$CO$_3$, MeCN, 1 h

(13)

92
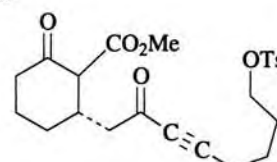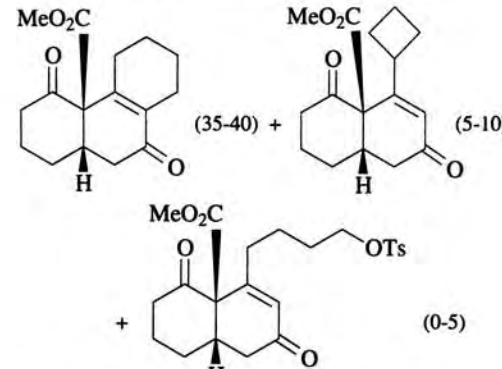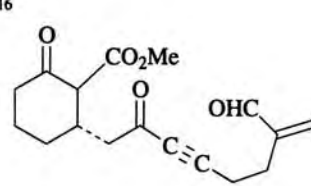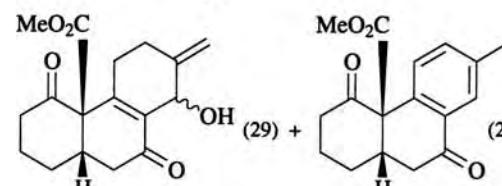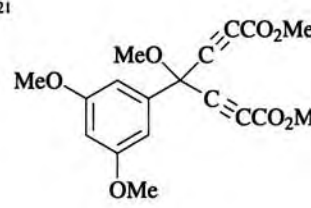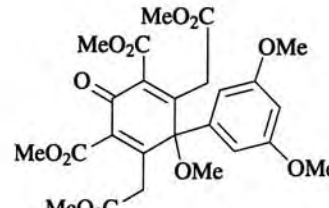
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Cs$_2$CO$_3$, THF, DMF, rt, 48 h	(35)	83
C$_{12-13}$			
C$_{12}$	1. Cs$_2$CO$_3$, MeCN, 30-96 h 2. Ac$_2$O^b, AcOH, BF$_3$•OEt$_2$	R = H (7) R = Me (1)	92
	Cs$_2$CO$_3$, MeCN, 30 h	(7) + (3)	92
	Cs$_2$CO$_3$, THF, DMF, rt, 36 h High dilution "Pseudo" high dilution	(31) (50)	83
C$_{13-14}$	Cs$_2$CO$_3$, THF, DMF, 16-72 h	n = 1, 2 (0)	92
C$_{13}$	Et$_3$N, 23°, 3 h MeCN CH$_2$Cl$_2$	(74) (0)	399
C$_{14}$	Cs$_2$CO$_3$, DMF, 65°, 20 min	I + II	91

For the C$_{14}$ entry:

R	I + II	I:II
OTs	(75)	80:20
I	(60)	100:0 ^{p}
Br	(85)	94:6 ^{p}

TABLE X. CARBON DONOR, α, β–UNSATURATED KETONE OR ALKYNYL KETONE ACCEPTOR (*Continued*)

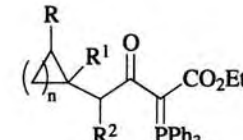| Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{15}$	KHMDS, 18-C-6, THF, DMF, -78 to 65°	(35-40) + (5-10) + (0-5)	91
C$_{16}$	Cs$_2$CO$_3$, DMF, 40°	(29) + (20)	91
C$_{21}$	LDA, (MeO$_2$CCH$_2$)$_2$CO, DME^i	(55)	400

^{a} When D-proline was used, the other enantiomer was obtained.

^{b} The reaction proceeds via an intramolecular Michael reaction followed by an intramolecular aldol condensation.

^{c} The product resulted from decarboxylation of the β-ketoester.

^{d} The reaction occurred by an oxy-Cope reaction followed by an intramolecular Michael reaction.

^{e} The reaction occurred via a retro-Michael reaction followed by intramolecular Michael reaction.
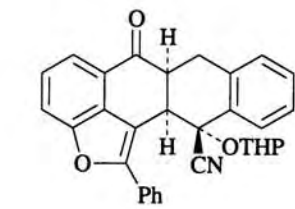
^{f} Lewis acids (TiCl$_4$, SnCl$_4$, AlCl$_3$, BF$_3$•Et$_2$O, MgBr$_2$) and protic solvents (HF, HCl, CF$_3$CO$_2$H) under a variety of conditions (temperature, time) gave only up to 5% yield of the desired compounds.
  Poorer results were obtained with LiNH$_2$/NH$_3$ and TBAF/THF.

^{g} The decarboxylated product was obtained.

^{h} **I** was generated from
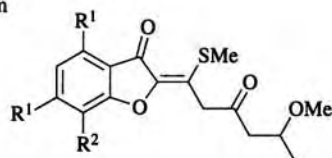
^{i} The reaction occurred by an intermolecular, then an intramolecular, Michael reaction.

^{j} A 2:1 mixture of isomers was obtained.

^{k} The reaction did not work with bulkier nucleophiles like methyl cyanoacetate and malononitrile.

^{l} In some cases *t*-BuLi was used.

^{m} When "Br" was used instead of "I", the product resulting from the conjugate addition of *n*-BuLi to enone, followed by displacement of Br, was obtained.

^{n} The product of *n*-BuLi conjugate addition to enone followed by displacement of Br was obtained.
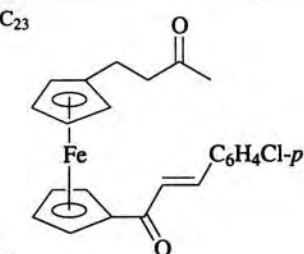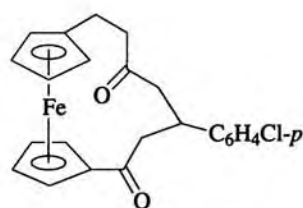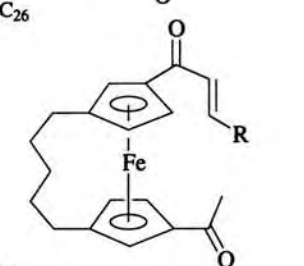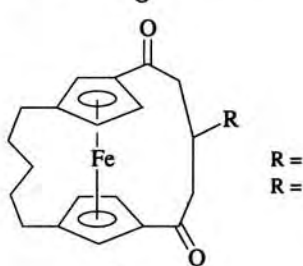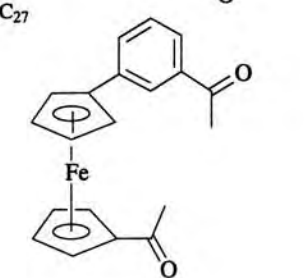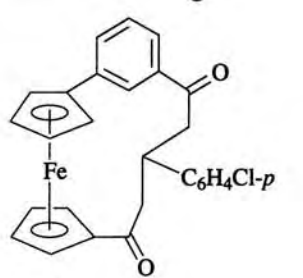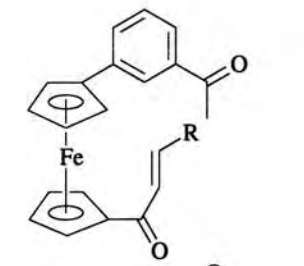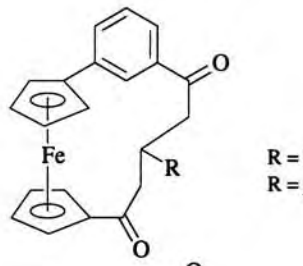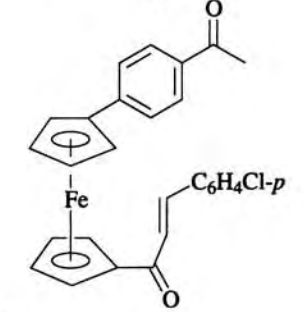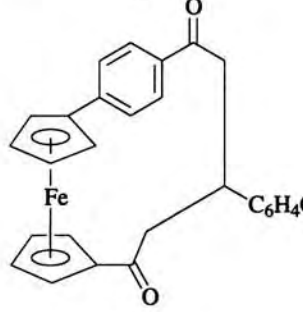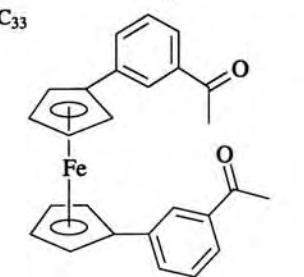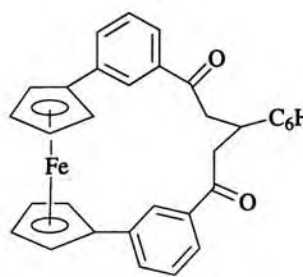
^{o} Another product was also obtained in 32% yield.

^{p} The *O*-alkylated product was also obtained.

TABLE XI. CARBON DONOR, FERROCENES AND MISCELLANEOUS ACCEPTORS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

C₂₁

	NaOH, EtOH, 20–60°	R = Ph (—)	401–404
	NaOH, EtOH, 20–60°	p-ClC₆H₄ (92)	
	AcOH, H₂SO₄, rt, 20 h	p-ClC₆H₄ (68)	
	MeOH, HCl, rt, 20 h	p-ClC₆H₄ (95)	
	Et₂O, BF₃•OEt₂, dioxane, rt, 20 h	p-ClC₆H₄ (85)	
	TFA, rt, 20 h	p-ClC₆H₄ (21)	
	MeONa, MeOH, 20–80°	(—)	401, 402
	MeONa, MeOH, 20–80°	C₆H₄Cl-p (82)	401–404
	KOH, EtOH, reflux 1 h	(14)	404

Condition A: Al₂O₃, pH 6.5–7.5
Condition B: KOH, EtOH, reflux   405, 406
                                         406a

	R	R¹	Condition	Time	Yield	
C₂₁	H	H	A	7 d	(26)	
			B	1 h	(86)	
C₂₂	Me	H	A	10 d	(33)	
			B	1 h	(68)	
C₂₃	Me	Me	A	14 d	(12)	
			B	2 h	(—)	
C₂₇	Ph	H	A	12 h	(100)	
			B	0.5 h	(100)	
	RC₆H₄	H	A	"	"	R = p-F, p-Cl, p-Br, m-Cl, m-Br, m-I
			B	"	"	
C₂₈	RC₆H₄	H	A	"	"	R = p-Me, m-Me, p-MeO, m-MeO
			B	"	"	

524

525

Substrate	Conditions		Refs.

C₂₃

NaOH, EtOH, reflux 1 h

(36)

404

C₂₆

NaOH, EtOH, reflux

R = Ph (24)
R = *p*-ClC₆H₄ (43)

407

C₂₇

p-ClC₆H₄CHO, NaOH,
MeOH, reflux

(17)

408

p-ClC₆H₄CHO, NaOH,
DMF, heat

" (33)

408

NaOH, EtOH,
reflux 30 min

R = Ph (—)
R = *p*-ClC₆H₄ (0)

401, 408

NaOH, EtOH,
reflux 30 min

(17)

401, 408

C₃₃

p-ClC₆H₄CHO, NaOH,
MeOH, reflux

(6)

408

p-ClC₆H₄CHO, NaOH,
DMF, heat

" (25)

408
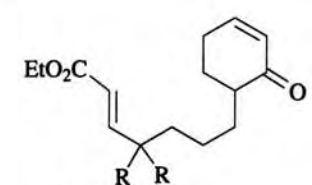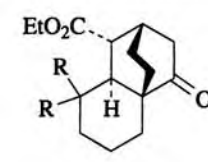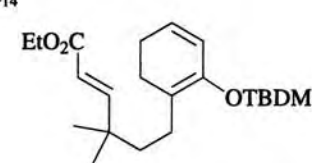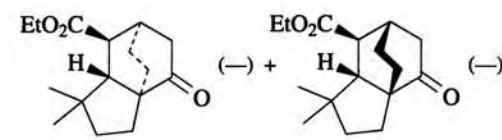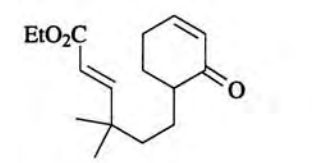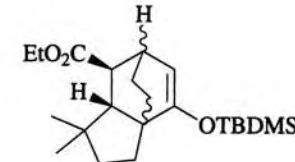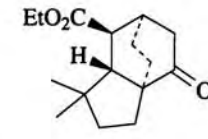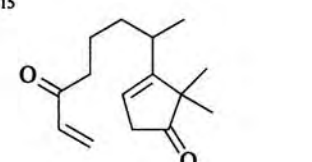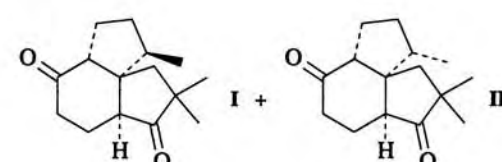
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

Conditions:

CHO with R^1, R^2, R^3, DMF, NaOH, 80-90°, 4 h

R^1	R^2	R^3	
H	H	Cl	(80)
H	H	H	(30)
H	H	OMe	(28)
H	H	Me	(32)
H	—OCH$_2$O—		(48)
H	OMe	OMe	(21)
OMe	OMe	OMe	(24)

C_{33}
C_{34}
C_{35}
C_{36}

408, 409

TABLE XII. INTRAMOLECULAR DOUBLE, OR SEQUENTIAL, MICHAEL REACTIONS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

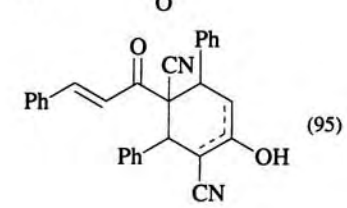|	R^1	R^2	R^3		**I**	**II**	
C$_9$	H	H	Et	ZnCl$_2$, Et$_3$N, TMSCl, PhMe, 185°, 10 h, sealed tube	(55)	(—)	
C$_{10}$	Me	H	Et	"	(72)	(7)	
C$_{15}$	Ph	H	Et	"	(75)	(11)	
C$_{10}$	Me	H	Et	TBDMSTf, Et$_3$N, CH$_2$Cl$_2$, 20°	(78)	(5)	
	Me	H	Et	TBDMSTf, Et$_3$N, CH$_2$Cl$_2$, -78°	(75)	(0)	

ZnCl$_2$, Et$_3$N

	R		**I + II**	**I:II**	
C$_{10}$	H	TMSCl, PhMe, 185°, 10 h, sealed tube	(55)	—	
	H	TBDMSTf, CH$_2$Cl$_2$, -78°, 1 h	(92)	—	
C$_{11}$	Me	TMSCl, PhMe, 185°, 10 h, sealed tube	(75)	23:77	
C$_{16}$	Ph	"	(79)	69:31	

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

			411, 74
C$_{13}$		R = H	
	LiHMDS, hexane, -78° to rt, 2 h	(50)	
	NaH, THF, 66°, 24 h	(—)	
	LiHMDS, THF, -78° to rt	(13)	
C$_{15}$	NaH, THF, 66°, 24 h	(0)	
	LiHMDS, THF, -78° to rt, 20 h	(60)	
	LiHMDS, THF, HMPA, -78° to rt, 20 h	(10)	
	LDA (2 eq), THF, -78°, 2 h	(22)	
	LDA (1.3 eq), THF, -78°, 16 h	(24)	
	LDA (1.3 eq), THF, -78 to -20°, 2 h	(45)	

C$_{14}$

BF$_3$•Et$_2$O	(—) + (—)	412

TBDMSTf, Et$_3$N, CH$_2$Cl$_2$, rt, 5 min^a	(37)	412

		413, 414
LiHMDS, hexane, Et$_2$O, 2.5 h	(64)	
LiHMDS, hexane, 3 h	(53)	
LDA, THF, 3 h	(57)	
LiCA, THF, 6 h	(26)	
LiNEt$_2$, THF, 4.5 h	(30)	

C$_{15}$

I + II   415, 416

	I + II	I:II
1. TMSCl, Et$_3$N, ZnCl$_2$ 2. Sealed tube, PhMe, 160°, 24 h, sealed tube	(100)	65:35
1. TMSCl, Et$_3$N, ZnCl$_2$ 2. Sealed tube, CH$_2$Cl$_2$, 160°, 24 h, sealed tube	(62)	84:16
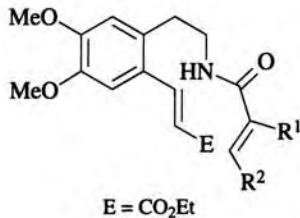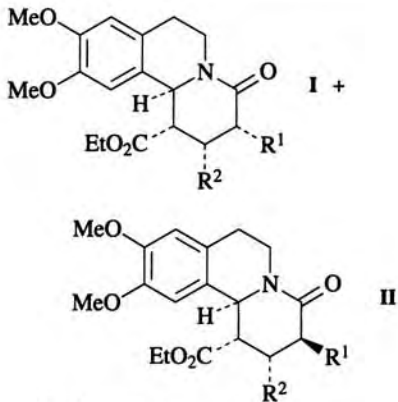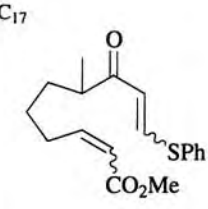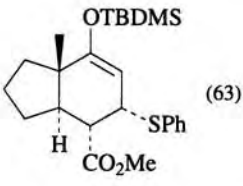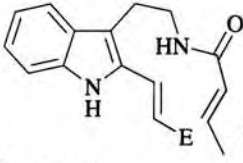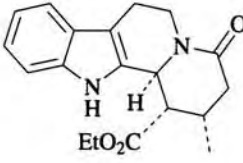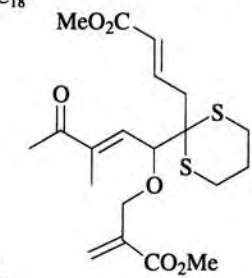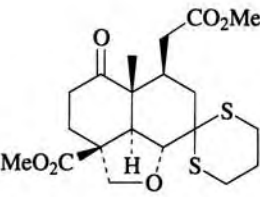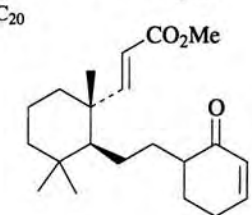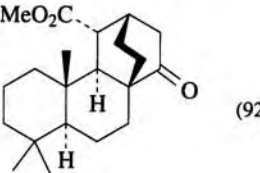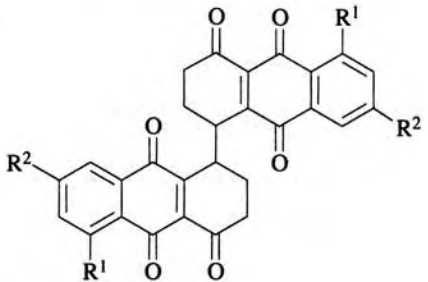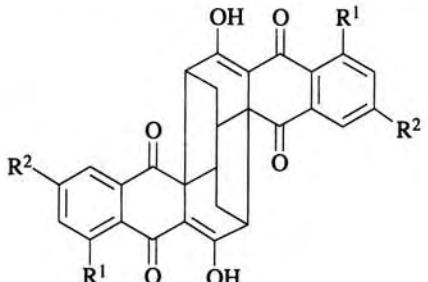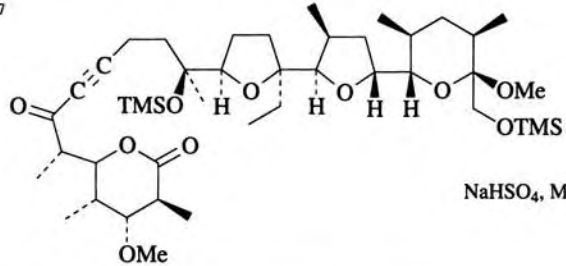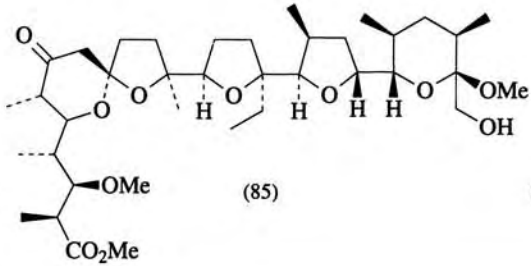
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.

E = CO₂Et

	R¹	R²		I + II	I:II	
C₁₆	H	H	ZnCl₂, Et₃N, TMSCl, PhMe, 185°, 10 h	(44)	—	
C₁₇	H	Me	"	(52)	100:0	
C₁₈	Me	Me	ZnCl₂, Et₃N, TMSCl, *o*-Cl₂C₆H₄, reflux, 16 h	(66)	38:62	
C₂₂	H	Ph	ZnCl₂, Et₃N, TMSCl, *o*-Cl₂C₆H₄, 185°, 10 h	(48)	100:0	
	H	Ph	TBDMSTf, Et₃N, CH₂Cl₂, rt, 1 h	(83)	100:0	
	H	Ph	TMSTf, Et₃N, CH₂Cl₂, rt, 1 h	(75)	100:0	

C₁₇

TBDMSTf, Et₃N, CH₂Cl₂, rt, 45 min   (63)   417

ZnCl₂, Et₃N, TMSCl, *o*-Cl₂C₆H₄, reflux 16 h   (66)   410

E = CO₂Et

C₁₈

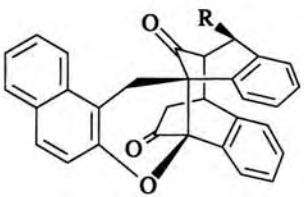Several conditions   (0)   305

C₂₀

LiHMDS, C₆H₁₄, Et₂O, -78° to rt   (92)   122

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	LiHMDS, C$_6$H$_{14}$, Et$_2$O, $-78°$ to rt[b]	(17)	59, 122
	LiHMDS, C$_6$H$_{14}$, Et$_2$O, $-78°$, 0.5 h; rt, 1.5 h	(58)	418, 60

C$_{23}$

	I + II + III	I:II:III
LDA	(0)	—
LiHMDS	(0)	—
1. TMSCl, ZnCl$_2$, Et$_3$N, PhMe, 160°, 12 h	(63)	50:25:25
2. HClO$_4$, THF		

C$_{25}$

TBDMSTf, Et$_3$N, CH$_2$Cl$_2$, -78 to 5°, 2 h

421–423

	I + II	I:II
R =	(92)	100:0
R =	(78)	80:20

TABLE XII. INTRAMOLECULAR DOUBLE, OR SEQUENTIAL, MICHAEL REACTIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	Pyridine, 3 d		424

	R¹	R²	
C₂₈	H	H	(—)
	OH	H	(—)
C₃₀	OH	Me	(—)

C₃₇

NaHSO₄, MeOH   (85)   88

a The TBDMS dienol ether was also isolated in 45% yield.

b When the α, β-unsaturated aldehyde was used, the reaction the did not work.

TABLE XIII. RETRO INTRAMOLECULAR MICHAEL REACTIONS
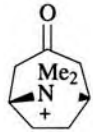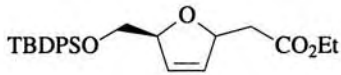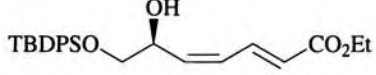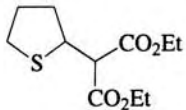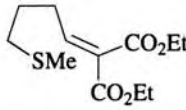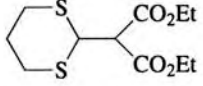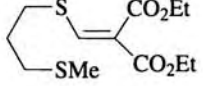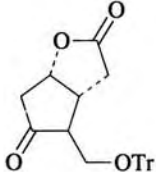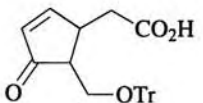
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₇			
	KOH	Cycloheptadienes (mixture)　(—)	124
	KOH	Cycloheptadienes (mixture)　(—)	124
TBDPSO...O...CO₂Et	LDA, THF, 0°	TBDPSO...OH...CO₂Et　(92)	52
C₈			
...S...CO₂Et / CO₂Et	1. NaH, THF, reflux 2. MeI	SMe...CO₂Et / CO₂Et　(36)ᵃ	50
...S...S...CO₂Et / CO₂Et	1. NaH, THF, 20° 2. MeI	S...CO₂Et / SMe...CO₂Et　(62)	50
...O...O...OTr	KOAc, H₂O, rt	...CO₂H...OTr　(—)	332

TABLE XIII. RETRO INTRAMOLECULAR MICHAEL REACTIONS (*Continued*)
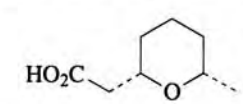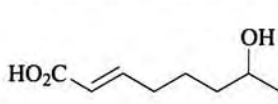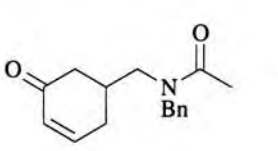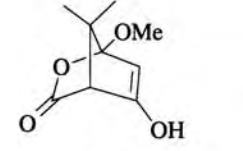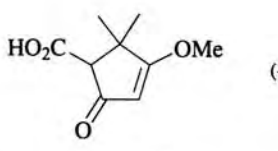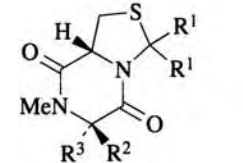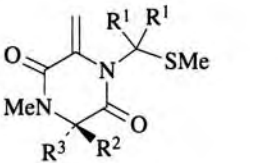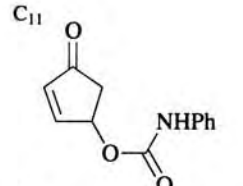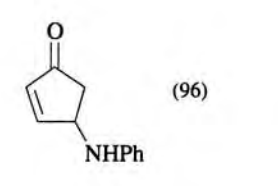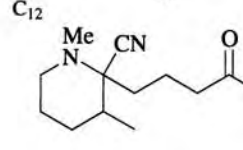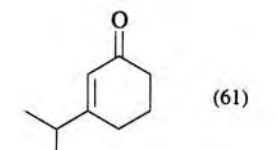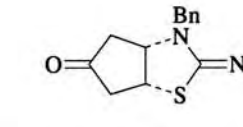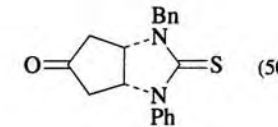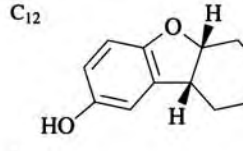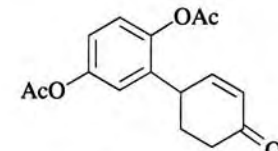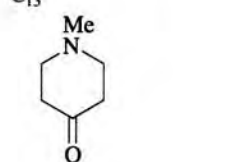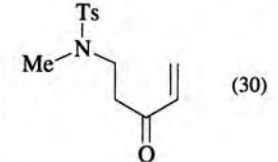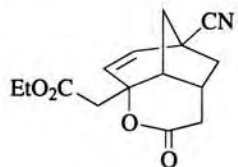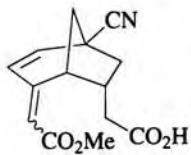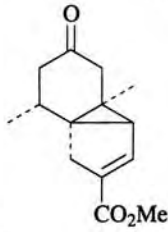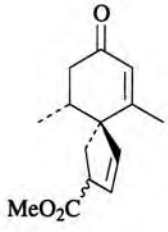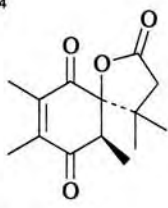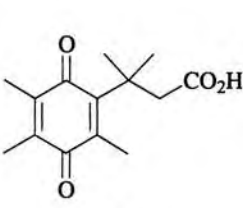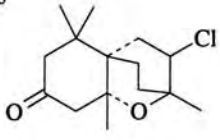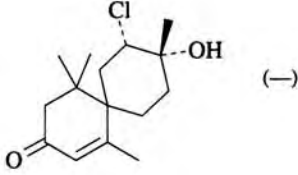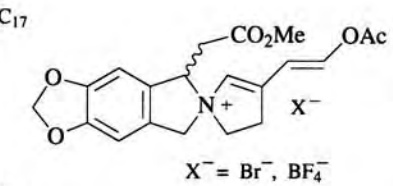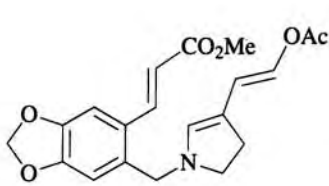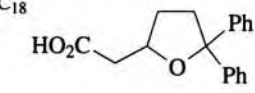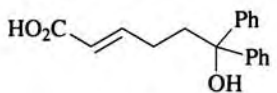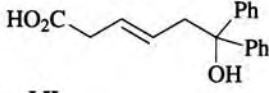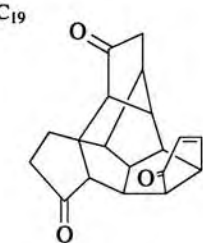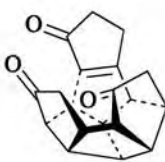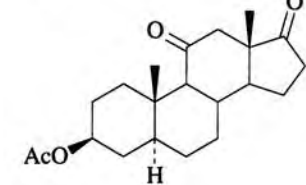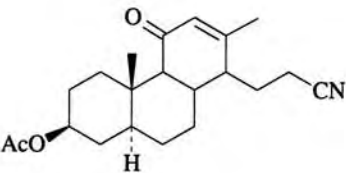
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₉	LDA, THF, -78 to 0°, 4 h	(80)	121
	Ac₂O, reflux 10 min	(—)	242
	rt	(—)	154a
	MeI, Ag₂O (xs), Me₂CO, rt		425

	R¹	R²	R³	
C₁₁	Me	Me	OH[b]	(100)
	Me	OH[b]	Me	(100)
	H	*n*-Pr	OH[b]	(100)
C₃₀	H	(CH₂)₃OCPh₃	OH[b]	(100)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C₁₁	Et₃N, CHCl₃[c]	(96)	135
C₁₂	TsOH, C₆H₆, reflux	(61)	253
	Et₃N, DMSO, 60°, 10 min[d]	(50)	135
C₁₂	Ac₂O, NaOAc, reflux	(79)	159
C₁₃	1. TsCl, PhMe, heat 1 h 2. *i*-PrNEt₂, PhMe, heat 0.5 h	(30)	426
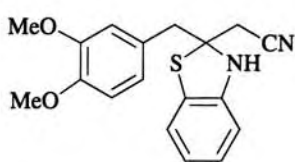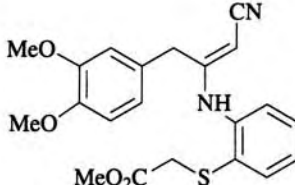
TABLE XIII. RETRO INTRAMOLECULAR MICHAEL REACTIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	NaOMe, MeOH, rt, 3 h	(77)	84
	HCl, THF rt, 18 h	(quant)	49
C$_{14}$	NaHCO$_3$ (5%), MeCN, 25°, 3 h	(86)	174
C$_{15}$	NaOMe, MeOH, 25°, 5 h	(—)	427
C$_{17}$	DBU, 0 ° CH$_2$Cl$_2$, 1 h	(—)	51
X$^-$ = Br$^-$, BF$_4^-$			
C$_{18}$	THF, -78° to rt, overnight	**I** +	121
		II	

	I + II	**I:II**
LDA (3.5 eq)	(74)	100:0
LDA (2 eq)	(—)	66:34
LDA (2.2 eq)	(—)	50:50

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{19}$	Acid or base	(0)	382
	NaN$_3$, CHCl$_3$, H$_2$SO$_4$ 0°, 30 min	(—)	17

TABLE XIII. RETRO INTRAMOLECULAR MICHAEL REACTIONS (*Continued*)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C$_{20}$	1. NaH, THF, 0°, 45 min 2. Br⁀CO$_2$Me , rt, 75 min	(93)	428

^{a} The alkylated product was also produced in 54% yield.

^{b} The OH group was transformed into OMe in the product under the reaction conditions.

^{c} The reaction occurred via a Michael addition of the nitrogen nucleophile, followed by a retro Michael
reaction to give a carbamic acid, which decarboxylated to the final product.

^{d} The reaction occurred via a retro Michael reaction, followed by closure of the nitrogen nucleophile, instead of sulfur, onto the enone.

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Abbreviations

Ac: acetyl

aq: aqueous

Bn: benzyl

BOC: *tert*-butoxycarbonyl

Bz: benzoyl

CBZ: benzyloxycarbonyl

CSA: camphorsulfonic acid

DATA: dibenzylammonium trifluoroacetate

DBU: 1,5-diazabicyclo[5.4.0]undec-5-ene

DMA: dimethylacetamide

DMAD: dimethyl acetylenedicarboxylate

DMAP: 4-*N,N*-dimethylaminopyridine

DMS: dimethyl sulfide

DPPE: 1,2-bis(diphenylphosphino)ethane

HMPA: hexamethylphosphoric triamide

KHMDS: potassium hexamethyldisilylazide

LiCA: lithium isopropylcyclohexylamide

LiHMDS: lithium hexamethyldisilylazide

LSA: *N*-benzyltrimethylsilylamide

LiTEMP: lithium tetramethylpiperidide

MEM: methoxyethoxymethyl

MOM: methoxymethyl

Ms: mesyl or methanesulfonyl

Piv: *tert*-butylcarbonyl

PMB: *p*-methoxybenzyl

PNB: *p*-nitrobenzyl

PPTS: pyridinium *p*-toluenesulfonate

sat.: saturated

TAMA: *N*-methylanilinium trifluoroacetate

TBAF: tetrabutylammonium fluoride

TBDMS: *tert*-butyldimethylsilyl

TBDMSTf: *tert*-butyldimethylsilyl trifluoromethanesulfonate

TBDPS: *tert*-butyldiphenylsilyl

TES: triethylsilyl

TFA: trifluoroacetic acid

TFFA: trifluoroacetic anhydride

THP: tetrahydropyranyl

TMS: trimethylsilyl

Tol: tolyl

Tr: *N-tert*-butoxycarbonyl tryptophyl

Trisyl: 2,4,6-triisopropylphenyl

Triton B: benzyl trimethylammonium hydroxide

TsOH: *p*-toluenesulfonic acid