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# METHODOLOGY FOR THE CONSTRUCTION OF QUATERNARY CARBON CENTERS

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## 1. INTRODUCTION

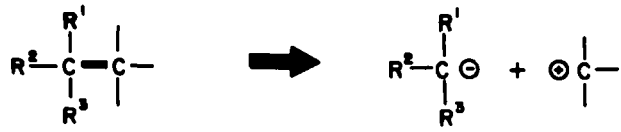
During the course of the syntheses of natural products possessing complex molecular architecture, the task of creating a quaternary carbon atom that bears alkyl appendages containing differentiated functionality and substituents is commonly encountered. Although there exists a vast armament of synthetic reactions for the formation of new carbon–carbon bonds, those constructions which allow the generation of such centers are among the most restricted in organic synthesis. This situation is partially a consequence of the limited accessibility of commercial or otherwise readily available starting materials which contain the requisite tertiary carbon atoms. One or more synthetic operations are therefore usually necessary before the reaction which will allow the creation of a fully substituted carbon atom may be executed. In addition, some care must be exercised in the selection of the two reactants to be coupled since a variety of transformations that are frequently employed for carbon–carbon bond constructions may not be applicable to the efficient creation of a quaternary carbon center. For example, the reaction of a tertiary alkyl halide with a nucleophilic carbon partner such as an enolate usually results in extensive elimination by dehydrohalogenation rather than substitution.

With certain limitations, each of the four fundamental classes of carbon–carbon bond forming processes may be employed for the elaboration of fully substituted carbon atoms from tertiary carbon centers. These include: (1) ionic constructions which may involve the participation of the tertiary carbon atom as a nucleophilic or as an electrophilic reaction partner; (2) oxidative and reductive coupling reactions; (3) rearrangement reactions; and (4) cycloaddition reactions. Those constructions that allow the connection of two simpler synthons by the formation of one or more carbon–carbon bonds are strategically the most desirable since their use generally maximizes the overall efficiency of the reaction sequence required for the assemblage of the molecular framework. If this were the only consideration, the various classes of reactions for the generation of quaternary carbon atoms might be given the following preference: (1) cycloaddition reactions wherein two new carbon–carbon bonds are produced; (2) ionic constructions, pericyclic rearrangements, and oxidative/reductive couplings in which one new carbon–carbon bond is formed; and (3) simple 1,2- and 1,3-rearrangements wherein there is no net change in the total number of carbon–carbon bonds. However, other practical factors, such as the availability of the requisite starting materials and the possibility of deleterious side reactions during the coupling of the two reactants must be carefully weighed prior to the final determination of the synthetic strategy that will be employed for the creation of a given quaternary carbon atom.

Before embarking upon a discussion of the available methodology for the elaboration of quaternary carbon centers, it is necessary to recognize that there are numerous individual examples of every type and class of reaction that allow such constructions. Consequently, in order to provide a general overview, particular emphasis will be placed upon conceptually different strategies. Whenever possible examples that illustrate the practical applications of the various synthetic methods to the syntheses of natural products will be chosen.

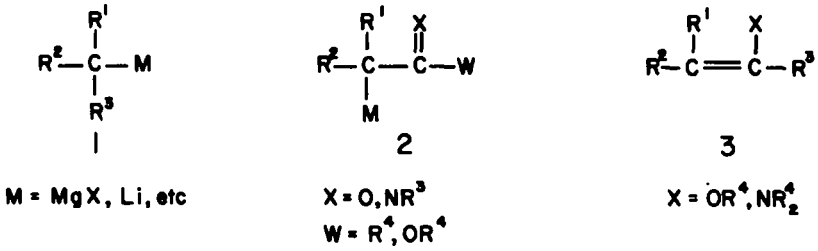
## 2. REACTIONS OF ELECTROPHILES WITH TERTIARY CARBON NUCLEOPHILES

The most widely employed synthetic strategy for the construction of quaternary carbon atoms involves the reaction of a carbon electrophile with a tertiary carbon nucleophile as depicted by the polar bond disconnection in eqn (1). The electrophiles in these reactions include a diversity of organic



(1)

substrates in which the electrophilic site may be either a saturated carbon atom (e.g. alkyl halides, epoxides, etc.) or an unsaturated carbon atom (e.g. aldehydes, ketones, carboxylic acids or their derivatives and electron deficient alkenes). The nucleophilic partners in these reactions fall into three general categories: (1) simple tertiary organometallic reagents 1 such as Grignard reagents and alkyllithium compounds; (2) resonance-stabilized tertiary carbanions 2 such as enolates and metallo enamines; and (3) heteroatom-substituted alkenes 3 such as enol ethers and enamines. Obviously, the judicious combination of electrophiles and nucleophiles as substrates in these reactions will allow the construction of quaternary

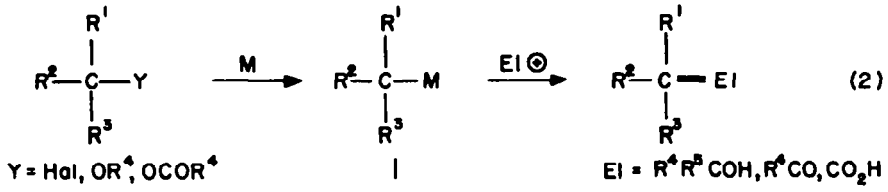


M = MgX, Li, etc

X = O, $NR^3$
W = $R^4$, $OR^4$

carbon atoms bearing alkyl substituents containing differentiated functionality. Within this context, varying the nature of the electrophile generally offers a considerable degree of flexibility since each of the tertiary carbon nucleophiles 1–3 undergo reactions with a number of different electrophilic reagents.

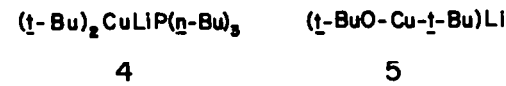
*Tertiary organometallic reagents.* Tertiary organometallic reagents may be generated by the reduction of the corresponding halide, ether or ester with a suitable metal, and the reactions of these carbanions, with unsaturated carbon electrophiles such as carbonyl compounds, carboxylic acids or their derivatives and carbon dioxide (eqn 2) are well established in synthetic organic chemistry. Since, however, the coupling of most such organometallic reagents of alkali and main group metals with alkyl halides is usually complicated by side reactions involving metal-halogen exchange and $\beta$-elimination, the discovery that



(2)

Y = Hal, $OR^4$, $OCOR^4$

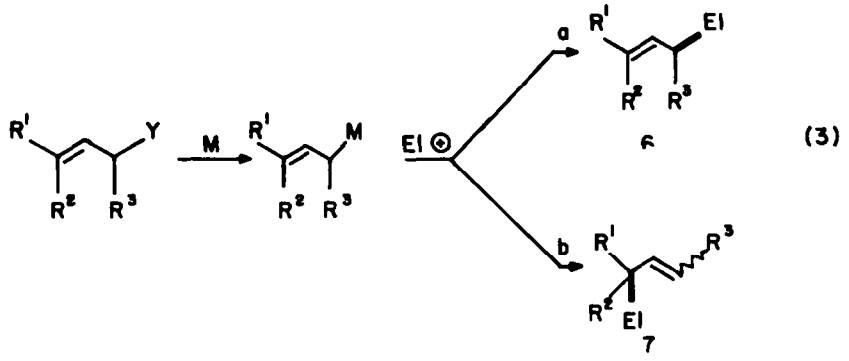
El = $R^4R^5COH$, $R^4CO$, $CO_2H$



4 5

the *tert*-alkyl complex cuprate 4[1] and the heterocuprate 5[2] serve as viable nucleophiles in substitution reactions with primary, but not secondary or tertiary, alkyl halides is of considerable importance.

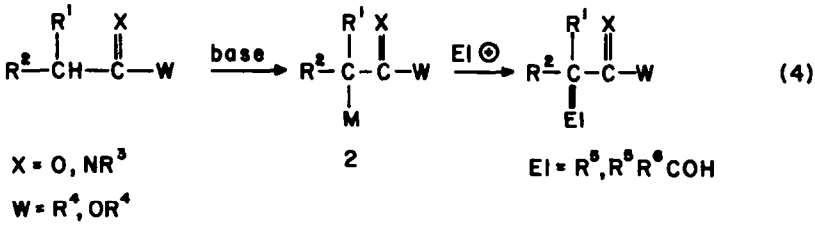
Unsymmetrical, allylic organometallic reagents which are trisubstituted at one terminus of the allyl moiety and either mono or disubstituted at the other may undergo electrophilic substitution at either terminus (eqn 3), and the ratio of the two possible products 6 and 7 depends upon the metal counterion,



(3)

the nature of the electrophile and the reaction conditions.[3-8] For example, in the reactions of prenyl-type carbanions with $sp^3$ hybridized electrophiles, a magnesium counterion tends to favor reaction at the more hindered terminus ($S_E2'$) to give compounds related to **7** (El = alkyl), but the use of copper (I) as a counterion leads to predominant attack at the less substituted terminus to give **6** (El = alkyl).[3] On the other hand, the addition of these prenyl organometallic reagents to sterically unhindered carbonyl compounds ($sp^2$ electrophiles) generally proceeds regioselectively to give the less stable and more highly branched adducts **7** (El = $R^4R^5COH$), but the actual product ratio is very dependent upon the reaction conditions and the metal counterion.[4-8] Since it is known that the addition of some allylic organometallic reagents to carbonyl compounds is reversible,[5,7,9] the less highly branched adduct **6** may be the product of thermodynamic control.

*Reasonance-stabilized tertiary carbanions.* The reaction of the tertiary, resonance stabilized carbanions derived from carbonyl and acyl compounds or derivatives thereof with carbon electrophiles is probably the most important synthetic means for the construction of quaternary carbon atoms. The

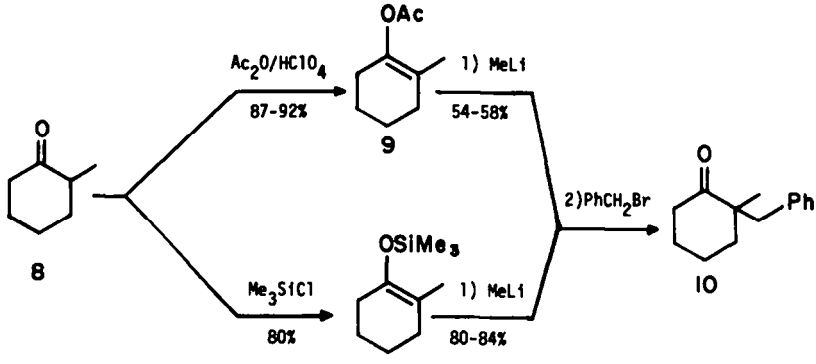


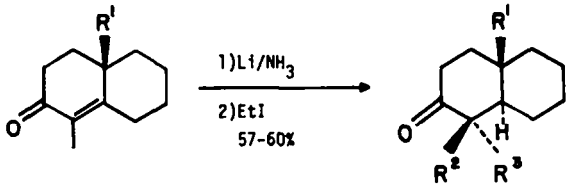
(4)

requisite carbanions **2** may be generated conveniently from readily available precursors by the: (1) direct deprotonation of the corresponding conjugate acid using strong, non-nucleophilic bases (eqn 4); (2) cleavage of the corresponding trimethylsilylenol ether or enol acetate with a suitable nucleophile; (3) metal reduction of $\alpha$-heteroatom-substituted carbonyl and acyl compounds; and (4) either conjugate reduction of or addition to $\alpha,\beta$-unsaturated carbonyl and acyl compounds. The electrophilic partners in these sequences include alkyl halides, aldehydes, ketones and electron-deficient alkenes (Michael acceptors). Although most of the ensuing discussion will focus upon tertiary carbanions stabilized by only one group, it should be recognized that carbanions bearing two stabilizing groups such as **2** ($R^2$ = CXW) usually undergo similar reactions.

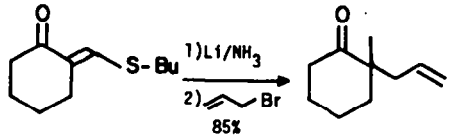
The direct alkylation of enolates of $\alpha,\alpha$-disubstituted aldehydes to give tertiary aldehydes is subject to certain limitations. For example, the alkylation of the lithium enolates of $\alpha,\alpha$-disubstituted aldehydes, generated either by cleavage of the corresponding enol acetate with methyllithium or by direct deprotonation with lithium diisopropylamide (LDA), may be complicated by the subsequent reaction of the alkylated aldehydes with the various bases present in the reaction mixture to give products of a Cannizzaro or Tishchenko reaction.[10] The alkylation of such aldehydes under phase transfer conditions is successful only with allylic and benzylic halides since the use of less reactive halides leads to extensive, base-catalyzed self-condensation reactions.[11] It has been recently reported that the reaction of the potassium enolates of aldehydes with reactive primary alkyl halides (allyl, benzyl and methyl) affords high yields of C-alkylated products, but there is competing O-alkylation when less reactive alkylating agents are used.[12]

Reactions which result in substitution alpha to a keto group have long been the subject of intensive studies,[13] and general synthetic procedures now exist for the regioselective generation and alkylation of the enolates derived from unsymmetrical ketones.[14] For example, the more substituted enolate of 2-methylcyclohexanone (8) may be prepared either from the corresponding enol acetate 9 or the trimethylsilylenol ether 11.[15] Unfortunately, the advantage gained by employing the trimethylsilylenol ether 11 as an enolate precursor to avoid polyalkylation, which occurs because of the unavoidable presence of the lithium *tert*-butoxide generated by the cleavage of the enol acetate 9, is partially offset by the occasional difficulty of producing the more substituted silyl enol ether with a high degree of selectivity. Other variants of this general theme involve the alkylation of tertiary enolates regioselectively produced by the: (1) reduction of $\alpha$-heteroatom-substituted ketones;[16,17] (2) 1,4-reduction of $\alpha,\beta$-unsaturated ketones;[18-20] and (3) conjugate addition of organocuprates to $\alpha,\beta$-unsaturated ketones.[21-24] Whenever there is substantial steric hindrance to the alkylation of the enolates produced by the conjugate addition of organocuprates to enones, problems resulting from the equilibration of the intermediate enolates by proton transfer reactions may ensue.[21-23]




12: $R^1$ = H
14: $R^1$ = Me
13: $R^1$ = H; $R^2$ = Et; $R^3$ = Me
15: $R^1$ = $R^2$ = Me; $R^3$ = Et

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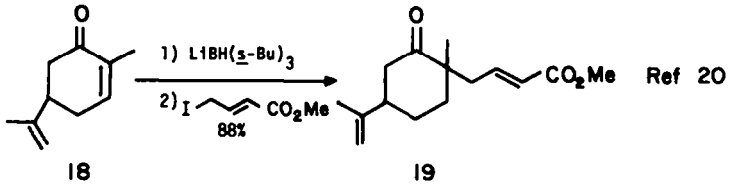


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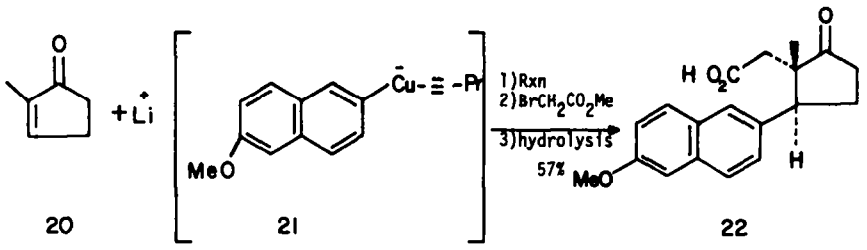
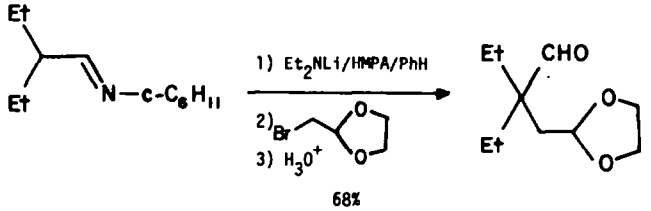



20 21 22

The alkylation of enolates frequently proceeds with a high degree of predictable stereoselectivity. Generally, the introduction of a new alkyl group onto a conformationally biased cyclohexanone enolate occurs from an axial direction via a chair-like transition state (**12**→**13**).[18] The usual exceptions to this rule arise whenever the introduction of the alkyl group by such an approach results in a 1,3-diaxial interaction between two alkyl groups (**14**→**15**).[18] Moreover, if one face of the cycloalkanone enolate is significantly more hindered than the other, alkylation proceeds preferentially from the less hindered side as exemplified by the conversion **20**→**22** which was the key step in a highly stereoselective approach to the synthesis of steroids.[24]

Some of the problems attendant to the use of enolates as nucleophilic derivatives of carbonyl compounds in substitution reactions may be expeditiously circumvented by the use of the corresponding metallo enamines (imine anions).[25] In particular, compared with enolates metallo enamines are more nucleophilic, they usually undergo exclusive C-alkylation and they exhibit a low propensity to suffer equilibration by proton transfer processes. These important, practical advantages frequently outweigh the inconvenience of performing the additional step(s) that are required for the preparation of a suitable precursor of the desired metallo enamine.

Although the metalation of $\alpha,\alpha$-dialkyl aldimines may be conveniently achieved with strong bases such as ethylmagnesium bromide[25] or *n*-butyllithium,[26] the use of lithium diethylamide in benzene/hexamethylphosphoramide (HMPA)[27,28] or lithium diisopropylamide in dimethoxyethane (DME)[10] may be preferred in certain cases. A wide variety of mono- and difunctionalized electrophiles including propargyl halides,[26] $\alpha,\omega$-dihalocompounds, 2,3-dihalopropenes and epoxides[27] may be employed as alkylating agents in reactions with metallo enamines. The exceptional reactivity and utility of metallo enamines in carbon–carbon bond forming reactions is underscored by the preparation of 1,4-dialdehyde acetals using the relatively poor alkylating agent 2-bromomethyl-1, 3-dioxolane (**23**→**24**).[28] Since the

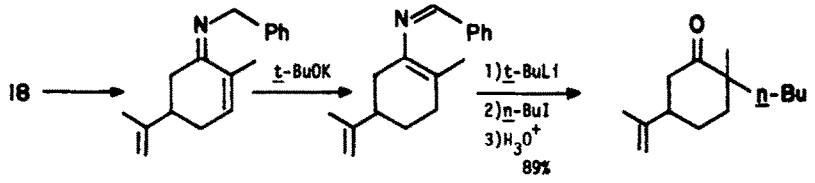



23 24

metalation and subsequent alkylation of the N,N-dimethylhydrazones of $\alpha,\alpha$-disubstituted aldehydes proceeds anomalously to give tertiary nitriles,[29] these carbonyl derivatives may not be used for the synthesis of tertiary aldehydes.

Until recently, the construction of quaternary carbon centers from the lithiated ketimines derived from unsymmetrical ketones was not feasible as the deprotonation and thus subsequent carbon–carbon bond formation occurs at the *less* substituted $\alpha$-position.[30] However, a regiospecific entry to the more substituted and apparently less stable metallo enamines of unsymmetrical ketones has been developed which involves the nucleophilic addition of organometallic reagents to 2-azadienes[31,32] as illustrated by the conversion **18**→**27**.[31a] Although alkyllithium reagents are usually utilized to produce metallo enamines from 2-azadienes in these reactions, hydride reducing agents such as L-Selectride and Super Hydride also add smoothly to 2-azadienes.[33] Dissolving metal reductions of 2-azadienes also afford metallo enamines.[31a] The metalation of **28** followed by sequential methylation and hydrolysis afforded **29** in 96% optical yield (40% chemical yield).[34] Although this sequence represents one of the few examples of the

enantioselective construction of a quaternary carbon center, the general utility of this procedure in asymmetric synthesis is severely limited by the necessary presence of an aromatic ring to facilitate the formation of the more highly substituted imine anion. However, this important experiment does firmly

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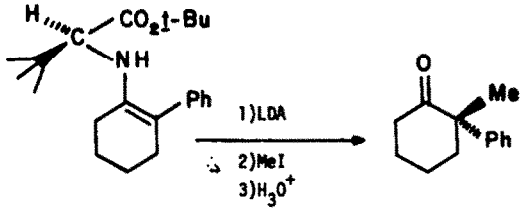
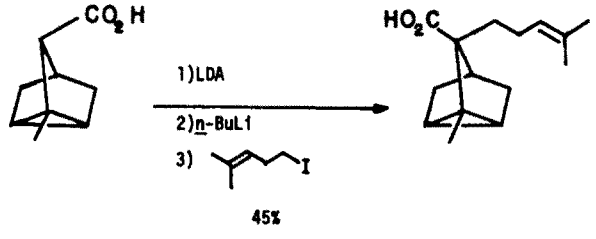



28 29

establish the feasibility of achieving asymmetric induction in reactions which lead to the formation of fully substituted carbon atoms by the alkylation of chiral imine anions. It is, therefore, tempting to speculate that the alkylation of a chiral metallo enamine that was generated from a suitable 2-azadiene might also proceed with a high degree of asymmetric induction.

The methodology for the alkylation of tertiary carboxylic acid dianions[35] (30→31),[36] ester enolates,[37-39] amide enolates[40] (32→33)[41] and nitrile anions[42] is also well established. Although these stabilized carbanions are most frequently generated from the corresponding conjugate acids by deprotonation using N,N-dialkylamide bases, they may also be prepared by a variety reductive processes[38,39] as illustrated by the synthesis of methyl callitrisate (35).[38]

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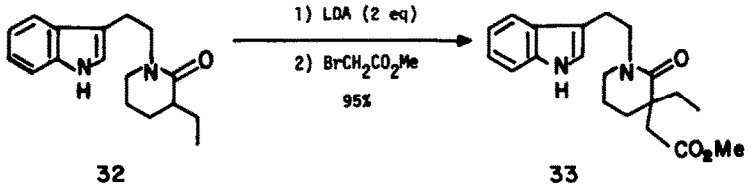


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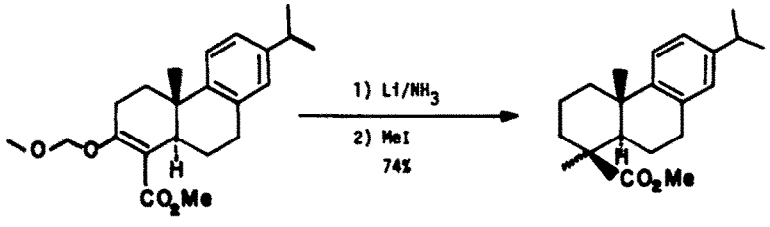


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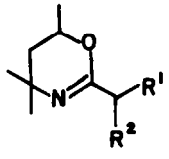
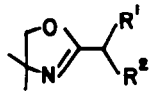
2-Isoalkyl-1, 3-oxazines **36**,[43] 2-isoalkyl-2-oxazolines **37**[44] and 2-isoalkyl-2-thiazolines **38**[45] may be readily metalated with alkyllithium reagents. However, the carbanions initially generated by the metalation of either **36** ($R^1$, $R^2$ = alkyl)[43] or **37** ($R^1$, $R^2$ = alkyl)[43,44] suffer rapid ring opening to form a ketene imine which is susceptible to further nucleophilic addition giving a metallo enamine (**39**→**40**).[43] Methylation and subsequent hydrolysis afforded the $\alpha$-trisubstituted ketone **41**. Since the deprotonation of these dihydro-1, 3-oxazines **36** ($R^1$, $R^2$ = alkyl) and these 2-oxazolines **37** ($R^1$, $R^2$ = alkyl) does not produce carbanions that are sufficiently stable to undergo efficient alkylation, these heterocycles cannot be utilized for the synthesis of tertiary aldehydes. On the other hand, the metalation of the 2-isoalkyl thiazolines **38** ($R^1$, $R^2$ = alkyl) proceeds without incident, and the anion thus obtained undergoes simple alkylation to give 2-*tert*-alkylthiazolines which may be converted to tertiary aldehydes in good overall yields (**42**→**44**).[45]



**36**



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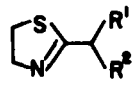
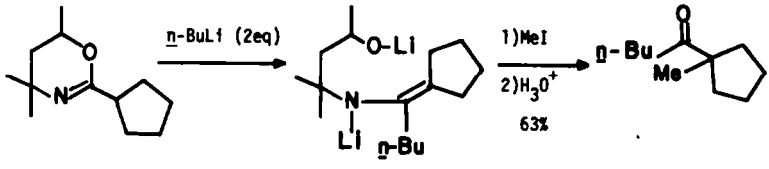
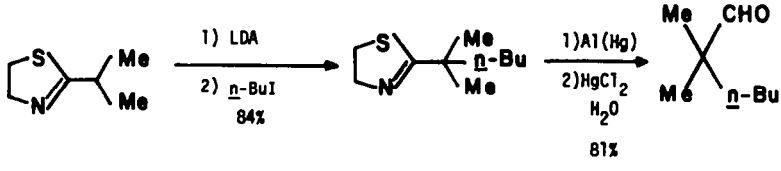


**38**

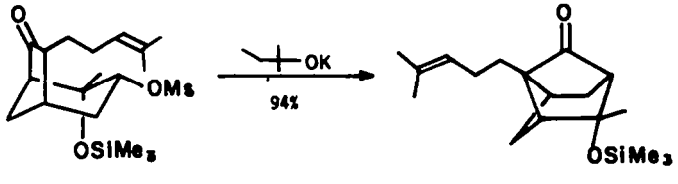



**39** **40** **41**

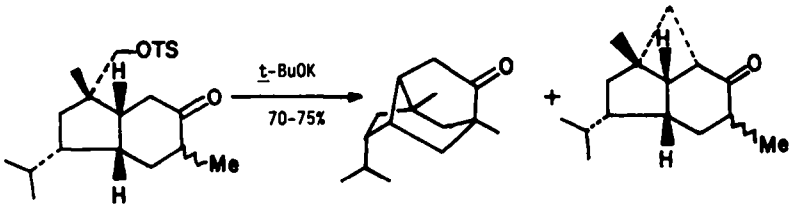



**42** **43** **44**

In addition to the rather extensive methodology which exists for the construction of quaternary carbon centers via bimolecular alkylations, there are an appreciable number of examples wherein the fully substituted carbon atom is formed by the intramolecular cyclization of an enolate to give fused,[23] bridged,[46,47] and spiro[48,49] ring systems. For example, the cyclization **45**→**46** was a key step in the first, fully stereocontrolled synthesis of $\alpha$-*trans*-bergamotene,[46] and an elegant synthesis of $\beta$-vetivone featured the highly stereoselective $\alpha'$,$\alpha'$-dialkylation of the enone **50**.[49] Interestingly, the by-product **49** formed in the cyclization **47**→**48** becomes the major product if lithium diisopropylamide is used as the base.[47]




**45** **46**

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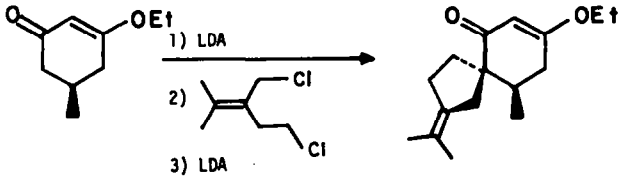
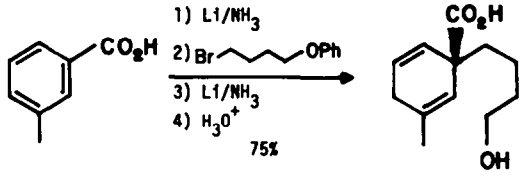


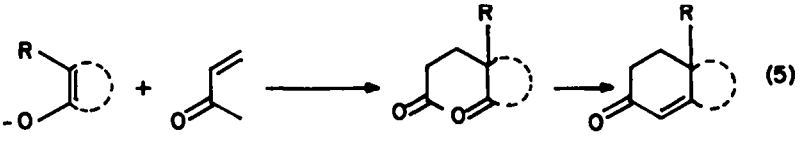

50 ~45% 51

The alkylation of the carbanions derived from $\alpha$-alkyl-$\alpha,\beta$-unsaturated aldehydes, ketones, carboxylate anions, esters and nitriles proceeds preferentially alpha to the electron withdrawing function to produce $\alpha$-trisubstituted-$\beta,\gamma$-unsaturated carbonyl and acyl compounds.[13,50-54] The requisite carbanions usually may be generated by the deprotonation of the corresponding conjugate acid, but some care may be required in the choice of the base for effecting these deprotonations. For example, the reaction of ethyl crotonate with lithium diisopropylamide resulted in the exclusive Michael-type addition of the diisopropylamide anion. However, a non-nucleophilic form of LDA, which is an apparent 1:1 complex with HMPA, acted solely as a base.[52] The Birch reduction of substituted benzoic acids such as **52** and alkylation of the anion thus produced *in situ* has lead to a facile entry to bicyclic and tricyclic hydronaphthalene sesquiterpenes.[51] Since the alkylation of enolates derived from $\alpha,\beta$-unsaturated aldehydes may be plagued by significant O-alkylation as a side reaction,[50] the use of the corresponding metallo enamines, which with few apparent exceptions undergo highly regioselective alkylation at carbon, may be preferred for the preparation of $\alpha$-trialkyl-$\beta,\gamma$-unsaturated aldehydes.[55]



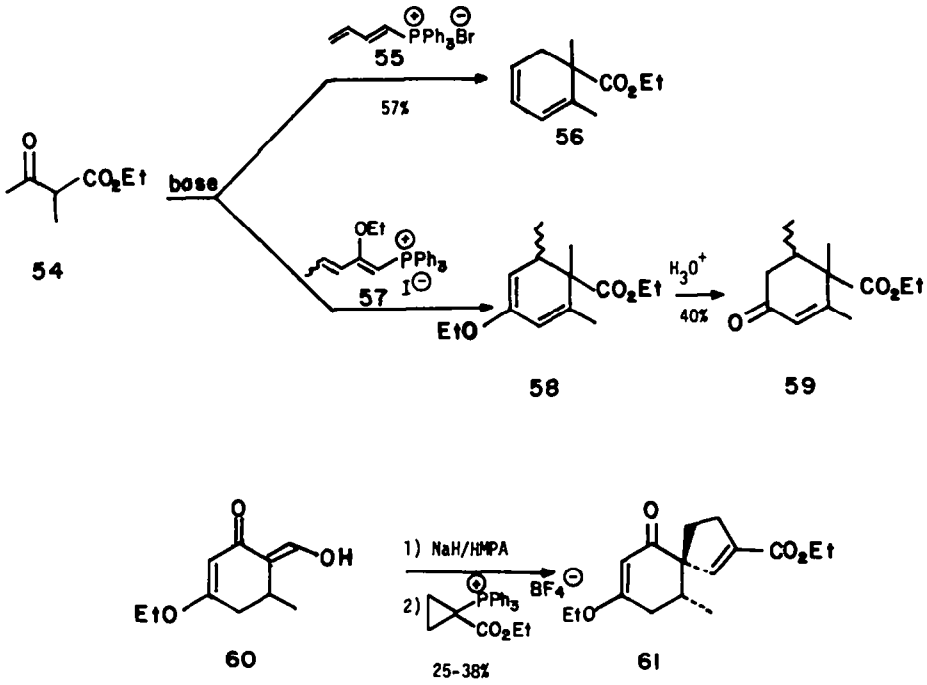

52 53

The Michael-type addition of tertiary enolates to electron deficient alkenes including $\alpha,\beta$-unsaturated ketones and esters is a highly useful procedure for the construction of quaternary carbon centers. Indeed, such a process is the first step in the Robinson annelation reaction (eqn 5) which, together with its numerous variants, has been used to great advantage for the construction of the 9-methyldecalin and 8-methyl hydroindane ring systems common to many terpene and steroid natural products.[56] A novel, alternative route for the annelation of functionalized cyclohexane rings onto pre-existing ketones has been reported which features the initial 1,4-addition of tertiary enolates to butadienyl phosphonium salts

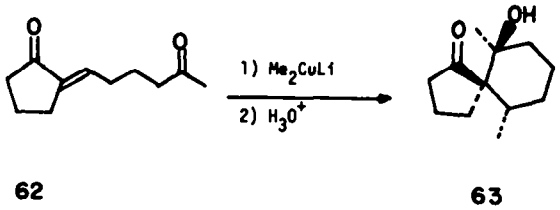


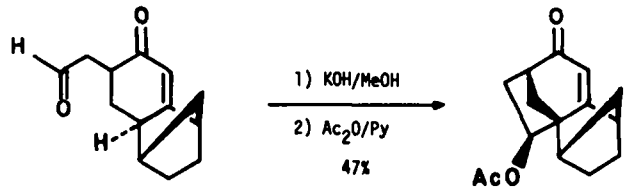
such as **55**[55,58] and **57**.[59] The resulting ketophosphoranes then suffer an intramolecular Wittig reaction to give the cyclohexadienes **56** and **58**, respectively. Vinyl sulfoxides[60,61] also undergo nucleophilic addition by tertiary enolates, thereby providing access to quaternary carbon centers bearing functionalized ethyl or vinyl substituents.

Homoconjugate additions involving the bimolecular[62,63] or intramolecular[64] opening of activated cyclopropanes by the enolates of active methylene compounds have also been observed. For example, a procedure for the annelation of functionalized five-membered rings has been discovered which features the reaction of enolates of $\beta$-dicarbonyl compounds with 1-carboethoxycyclopropyl phosphonium salts,[62,63] as illustrated by the preparation of **61**, a key intermediate in a synthesis of $\beta$-vetivone.[63]



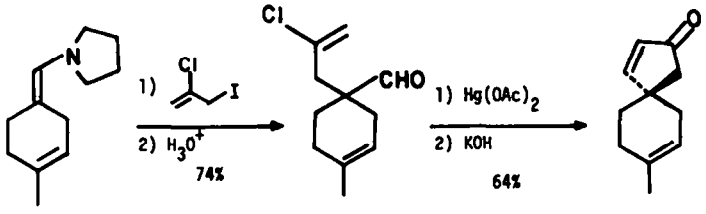

Although there are directed aldol processes which involve the reaction of aldehydes (but not ketones) with simple tertiary enolates[65] or their corresponding trimethylsilylenol ethers,[66,67] there seem to be no reports of the use of tertiary metallo enamines as nucleophilic partners in directed aldol operations.[68] (See, however, **95**→**97** and accompanying discussion for such an example.) Intramolecular aldol reactions which allow the construction of quaternary carbon centers have also been discovered (**62**→**63**[69] and **64**→**65**[70]). Since the aldol products produced in these reactions cannot undergo dehydration to give $\alpha,\beta$-unsaturated carbonyl compounds, retroaldolization of the initial $\beta$-hydroxy aldehydes or ketones may become an important side reaction. There are also a variety of transformations which are related to the aldol reaction wherein tertiary carbanions derived from $\alpha,\alpha$-disubstituted carboxylic acids, esters, amides and nitriles have been utilized as nucleophiles in reactions with carbonyl compounds.[29,71-74]



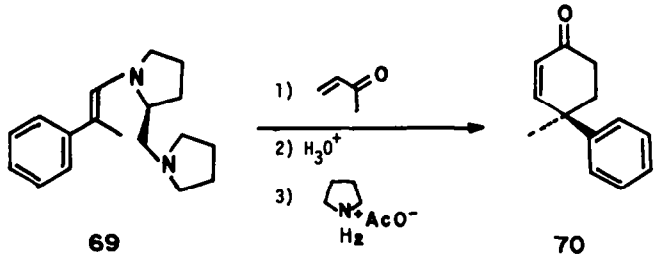



64 65

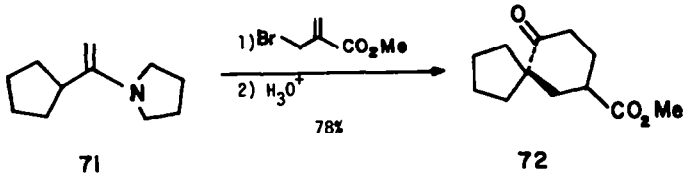
*Heteroatom-substituted alkenes.* The use of $\beta,\beta$-dialkyl, heteroatom-substituted alkenes as nucleophilic partners in carbon–carbon bond forming processes is principally restricted to enamines and enol ethers, but of the two, enamines[75] have been historically the more important synthetic intermediates. The most frequent applications of enamines to the synthesis of compounds possessing quaternary carbon centers appear to involve the annelation of functionalized cyclopentanones or cyclohexanones at a tertiary carbon atom. For example, the key step in a recent synthesis of the spirosesquiterpene acorone features a useful procedure for the spiroannelation of a cyclopentenone ring **66**→**68**.[76] The construction of cyclohexenones by the reaction of the enamines of $\alpha,\alpha$-disubstituted aldehydes with methyl vinyl ketone and derivatives or functional equivalents thereof is a well established process. If the secondary amine that is utilized in the formation of the $\beta,\beta$-disubstituted enamine is chiral, a quaternary carbon may be created with a modest degree of asymmetric induction as illustrated by the preparation of **70** in 44% optical yield.[77] A novel procedure for the synthesis of spirocyclic systems such as **72** via an $\alpha,\alpha'$-annelation process of an enamine has been described.[78]



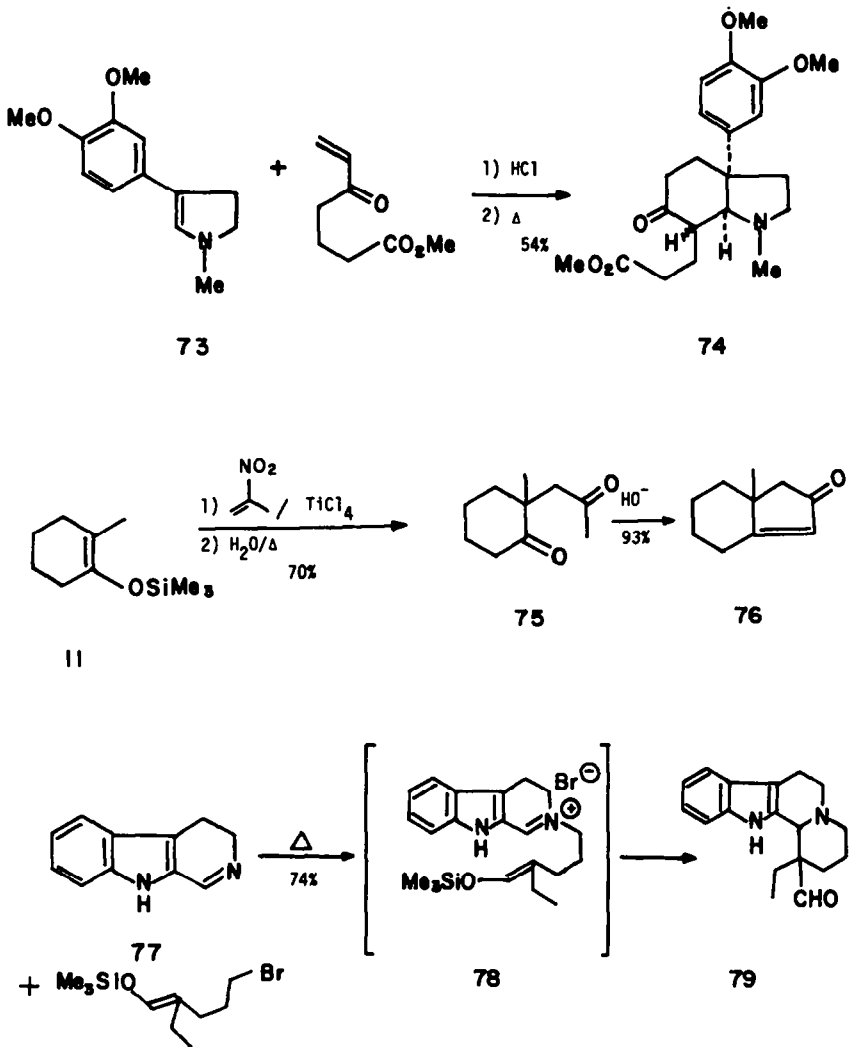

66 67 68




69 70



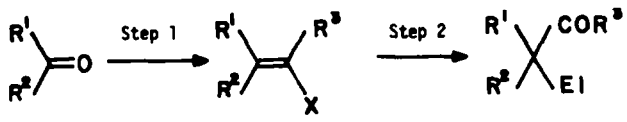

71 72




One particularly elegant and general synthetic strategy for the construction of a wide variety of alkaloid natural products possessing angularly substituted hydroindole and hydroquinoline ring systems features the reaction of endocyclic enamines with $\alpha,\beta$-unsaturated ketones[79-84] as exemplified by the preparation of **74**, a key intermediate in the synthesis of Sceletium alkaloid A-4.[81] The best results in these annelation operations are obtained when the enamine is converted to the corresponding iminium salt prior to reaction with the $\alpha,\beta$-unsaturated ketone.

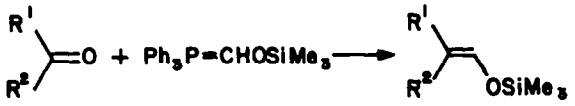
$\beta,\beta$-Dialkyl-O-trimethylsilylenol ethers may also be employed in carbon–carbon bond forming reactions which result in the creation of quaternary carbon centers.[66,67,85-87] For example, a convenient route to 1,4-dicarbonyl compounds **75** involves the reaction of trimethylsilylenol ethers with $\alpha$-,$\beta$- and $\alpha,\beta$-substituted nitroethylenes.[85] An imaginative synthesis of the alkaloid vincamine is highlighted by the intramolecular Mannich reaction of the trimethylsilylenol ether **78**.[86] Trimethylsilylenol ethers also undergo regioselective phenylthiomethylation upon reaction with chloromethyl phenylsulfide in the presence of titanium tetrachloride.[87]

*Geminal disubstitution at a carbonyl center.* The carbonyl functional group of a ketone is ideally suited for elaboration into a quaternary carbon atom by a geminal disubstitution operation in which both of the carbon–oxygen bonds are replaced by carbon–carbon bonds. One appealing strategy for achieving such a construction would involve the initial chain elongation of the carbonyl group by one carbon atom[88] employing a process for the direct olefination of a ketone to give a tertiary enolate, enamine, or metallo enamine (or precursors thereof). The subsequent reaction of these nucleophilic derivatives of carbonyl compounds generated *in situ* with carbon electrophiles would then result in the formation of a second carbon–carbon bond at the original electrophilic center, thereby completing the synthetic sequence (eqn 6).




(6)

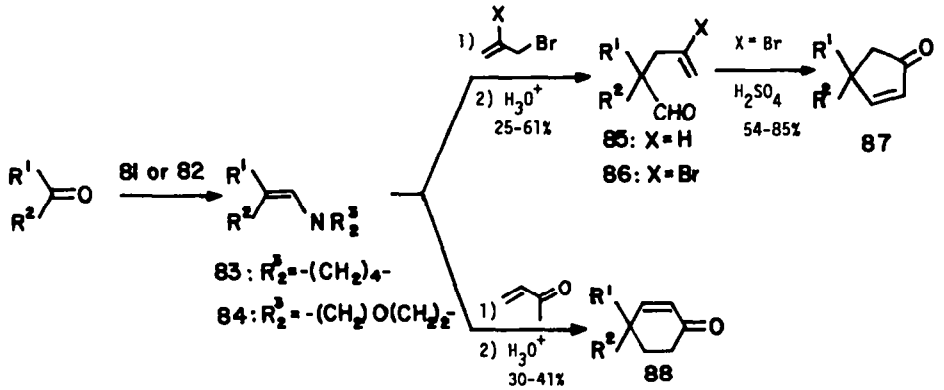
While the direct conversion of a ketone into the enolate of a higher carbonyl compound by a Wittig or related reaction remains to be reported, it has proven possible to effect the olefination of a ketone into a trimethylsilylenol ether using the phosphorane **80** (eqn 7), but this reaction has thus far been rather capricious.[89] In part the experimental difficulties encountered appear to originate from the unstable nature of the phosphorane **80**. Preliminary efforts to prepare homologs of the phosphorane **80** have been unsuccessful.[89]

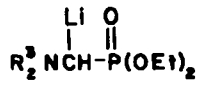



(7)

**80**

Another approach to the geminal acylation–alkylation of ketones which has been more rewarding involves the use of enamines as the key synthetic intermediates (Scheme 1).[90-92] For example, the olefination of ketones by reaction with either diethyl lithio pyrrolidinomethylphosphonate (**81**) or diethyl lithio morpholinomethylphosphonate (**82**) affords the aldehyde enamines **83**[90,91] and **84**,[92] respectively, which, *without* isolation and purification, are employed in subsequent reactions with a variety of electrophilic reagents. Thus, alkylation of the pyrrolidine enamines **83** with allyl bromide gives the $\alpha$-allyl dialkyl aldehydes **85**.[90] By merely altering the nature of the electrophile in the alkylation step, it is also possible to



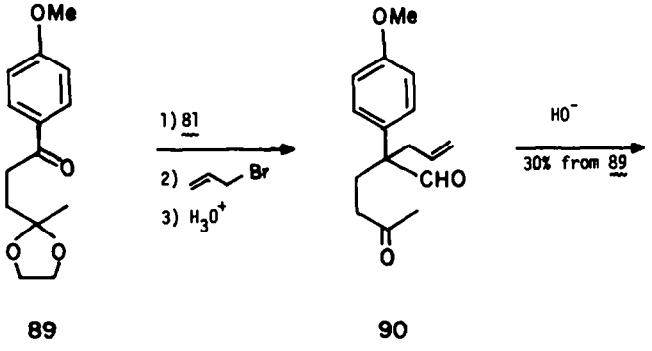
**81**: $R_2^3 = -(CH_2)_4-$

**82**: $R_2^3 = -(CH_2)_2O(CH_2)_2-$

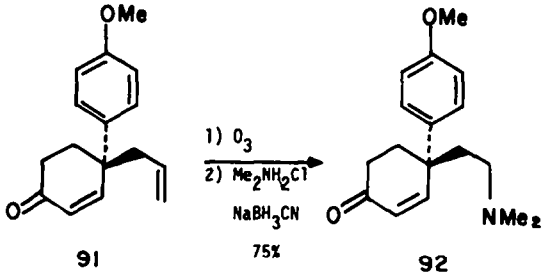
Scheme 1.

construct quaternary carbon atoms possessing alkyl appendages that are suitably functionalized for the facile transformation into cyclopentenones and cyclohexenones. Thus, reaction of the intermediate pyrrolidine enamines **83** with 2,3-dibromopropene and subsequent treatment of the aldehydes **86** thus obtained with concentrated sulfuric acid affords the 4,4-disubstituted cyclopentenones **87**.[91] 4,4-Disub-

stituted cyclohexenones **88** may be prepared by treatment of the morpholine enamines **84** with methylvinyl ketone.[92] In conformationally biased cyclohexyl systems, the alkylation of these enamine intermediates proceeds predominantly from the less hindered, equatorial face thereby resulting in a reasonable degree of stereoselectivity for the formation of the second carbon–carbon bond. A recent application of this methodology for effecting the geminal disubstitution of a ketone to the synthesis of the alkaloid O-methyljoubertiamine **92** has been described.[93,94]



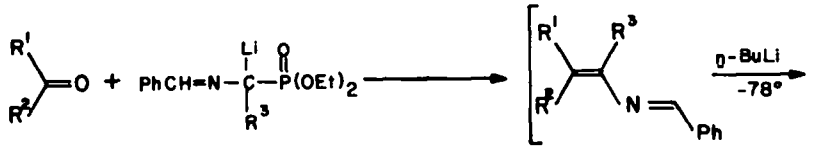

89 90



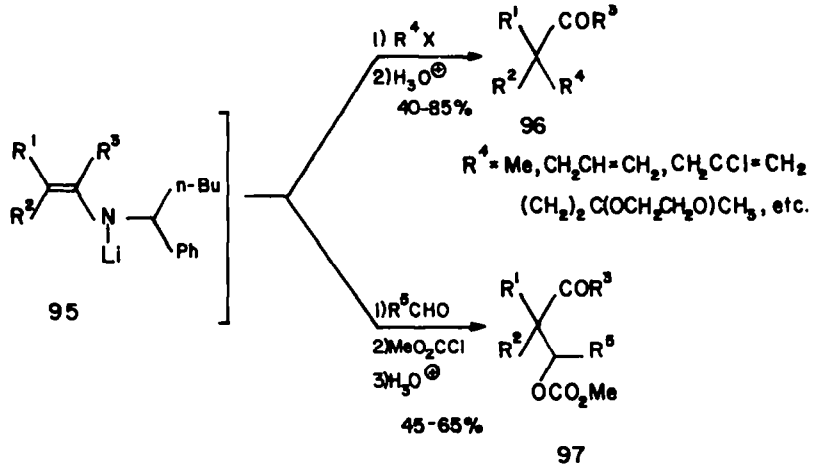

91 92

Unfortunately, the general synthetic utility of these procedures for the construction of quaternary carbon centers from ketones via enamine intermediates is somewhat limited. Coupled with the relatively low nucleophilicity of enamines, the enamines derived from $\alpha,\alpha$-disubstituted aldehydes are particularly prone to suffer deleterious N-alkylation, a reaction which is frequently irreversible. Consequently, only highly reactive electrophiles for which initial N-alkylation is reversible (e.g. allyl halides and electron deficient olefins) may be used in these sequences. Moreover, preliminary attempts to generate the more substituted enamines of unsymmetrical ketones using simple homologs of the phosphonate anions **81** and **82** have been largely unsatisfactory.[89]

A general and efficient procedure for geminal acylation–alkylation of carbonyl compounds which involves metallo enamines as nucleophilic partners has been developed and commences with the olefination of a ketone with the diethyl lithio benzylideneaminoalkylphosphonates **93** ($R^3$ = H, alkyl) (Scheme 2).

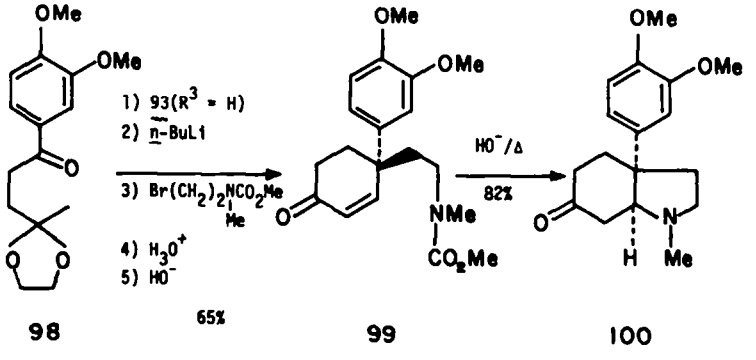



93 94



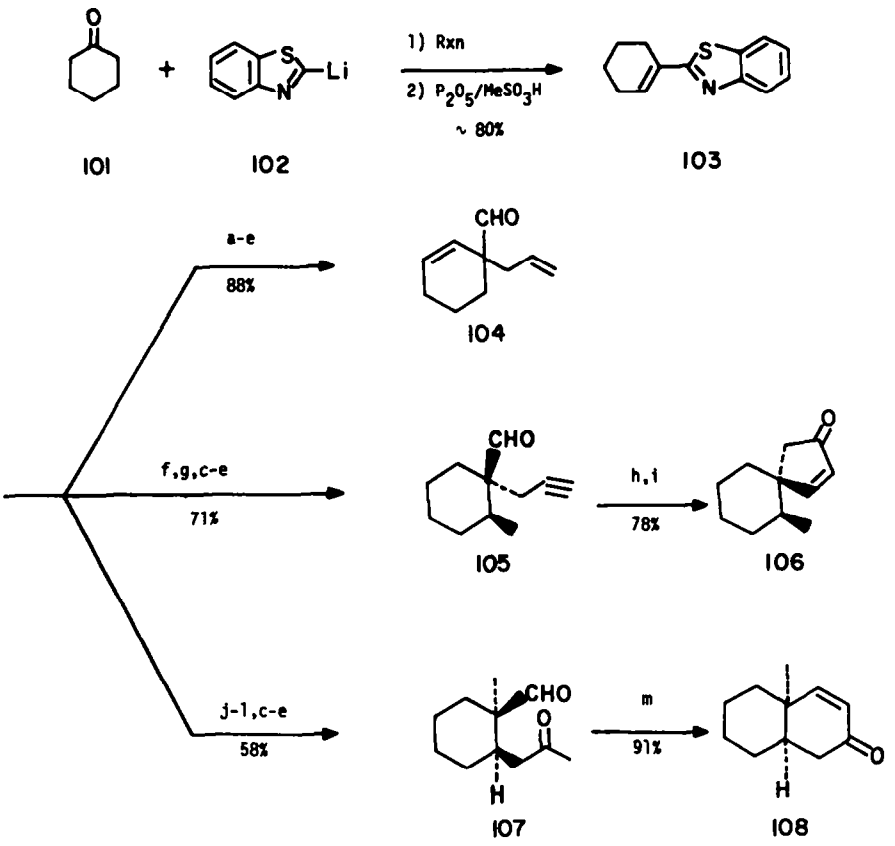

Scheme 2.

Regiospecific addition of *n*-butyllithium to the 2-azadienes **94** thus obtained produces the metallo enamines **95**. The subsequent reaction of **95** with a diverse selection of alkylating agents including methyl iodide, allyl bromide, 2,3-dichloropropene and 2-(2-bromoethyl)-1, 3-dioxolane followed by hydrolysis of the intermediate imines affords the tertiary carbonyl compounds **96** in good to excellent overall yields.[32,33] Alternatively, the directed aldol reaction of the metallo enamines **95** with aldehydes gives intermediate $\beta$-oxido imines that may be trapped either by acylation with benzoylchloride and methylchloroformate or by alkylation with bromomethyl methylether to produce the *O*-protected-$\beta$-hydroxy-aldehydes and ketones **97** in good overall yields.[33] This is apparently the first example of a directed aldol reaction involving tertiary metallo enamines. That the more highly substituted metallo enamine of an unsymmetrical ketone (**95**, $R^1$-$R^3$ = alkyl) may be regioselectively generated and trapped with electrophiles is especially noteworthy. Finally, the practical synthetic utility of this general approach to geminal acylation-alkylation is further augmented by the fact that the entire reaction sequence may be conveniently executed in a single reaction vessel without the isolation of any intermediates. The application of this methodology to a highly efficient synthesis of the *Sceletium* alkaloid mesembrine (**100**) has been completed.[94]




Another general strategy for effecting the acylation and alkylation at a carbonyl carbon atom features the elaboration of vinyl benzothiazoles **103** (Scheme 3) which may be conveniently prepared by the nucleophilic addition of 2-lithio benzothiazole (**102**) to ketones followed by dehydration.[95] The subsequent reactions of these vinyl benzothiazoles may be easily designed to allow the introduction of either one (**103**→**104**)[96] or two (**103**→**105** and **103**→**107**)[97] additional carbon substituents onto a pre-existing skeleton. By the proper choice of reagents, it is possible to incorporate alkyl substituents which possess functionality suitable for eventual annelation operations to produce cyclopentenones **106** and cyclohexenones **108**. There are several aspects of these reaction sequences which merit special mention. For example, the conversion **103**→**105** features a step in which there is net conjugate addition of methyllithium to an $\alpha,\beta$-unsaturated aldehyde. Furthermore, the transformation **101**→**108** represents a useful procedure for a modified annelation reaction wherein, unlike the Robinson annelation and related

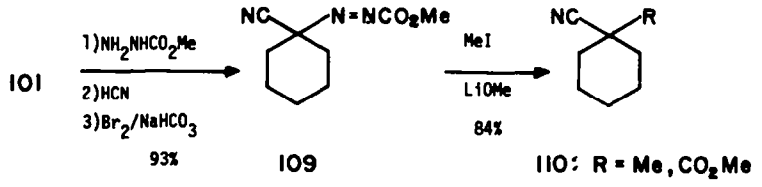
processes,[56] the β-vinyl carbon of the new cyclohexenone is not the carbonyl carbon of the original ketone.




[a]LDA; [b]$CH_2$=$CHCH_2Br$; [c]$MeOSO_2F$; [d]$NaBH_4$; [e]$AgNO_3/H_2O$; [f]MeLi; [g]$CH{\equiv}CCH_2Br$; [h]$HgSO_4/H_2O$; [i]$HO^-$; [j]$LiCH_2C(=NNMe_2)Me$; [k]MeI; [l]$CuCl_2/H_2O$; [m]p-TsOH/Δ

Scheme 3.

A method for the geminal cyanation-methylation of ketones features the methoxide-induced decomposition of methyl dialkylcyanodiazene carboxylates **109** in the presence of methyl iodide,[98] but a reasonable amount (13%) of the carbomethoxylated nitrile **110** (R = $CO_2Me$) is also unavoidably produced. A two step process involving reductive nucleophilic cyanation followed by alkylation would thus appear superior.

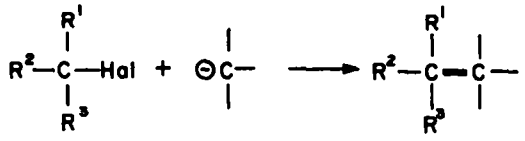



### 3. REACTIONS OF NUCLEOPHILES WITH TERTIARY CARBON ELECTROPHILES

Bimolecular nucleophilic substitution reactions at tertiary carbon atoms bearing suitable leaving groups are relatively rare processes since competing β-elimination is usually favored in such systems. Although there have been some reports of crossed coupling reactions involving organometallic reagents with tertiary alkyl halides, these reactions appear to have rather limited scope and synthetic utility. On the other hand, the conjugate addition of carbanions to β,β-disubstituted, electron deficient alkenes is

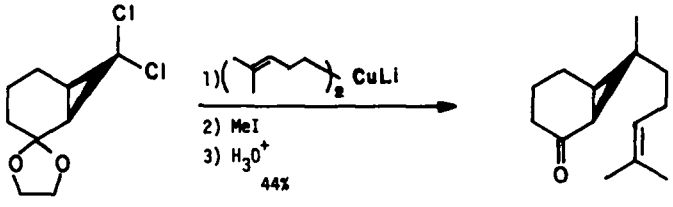
very common, and such reactions constitute a general route to quaternary carbon centers. Electrophilic additions to carbon–carbon double bonds which result in the formation of quaternary carbon atoms generally involve the trapping of a tertiary carbonium ion with an alkene or an aromatic ring, and such reactions are also quite important.

*Nucleophilic substitution reactions at tertiary carbon centers.* For purposes of the present discussion, any reaction which results in the *net replacement* of the carbon–heteroatom bond at a tertiary carbon atom by a carbon nucleophile will be considered as a nucleophilic substitution process (eqn 8), irrespective of the precise mechanism of the reaction.

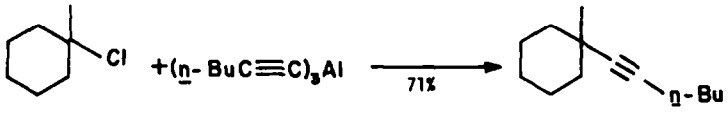


(8)

The crossed coupling reactions of monofunctional, tertiary alkyl halides with organocuprates are virtually unknown, and the only examples seem to involve halides which cannot undergo facile dehydrohalogenation.[99] Although α-halo ketones usually suffer simple reduction to enolates upon reaction with organocuprates,[100] there is a report that some highly hindered ketones may be obtained by allowing dialkyl cuprates to react with α-halo ketones.[101] The geminal dialkylation of 1,1-dihalocyclopropanes using organocuprates as nucleophilic reagents has also been reported.[102–104] Whereas the reaction of lithium dimethylcuprate with 7,7-dibromonorcarane proceeds to give 7,7-dimethylnorcarane in good yield,[102] the extension of this coupling reaction to homologous cuprates appears to proceed via initial nucleophilic substitution to give a tertiary cyclopropyl bromide which then suffers efficient metal–halogen exchange.[103,104] This side reaction, however, has been exploited in a stereoselective procedure for the geminal dialkylation of 1,1-dihalocyclopropanes as illustrated by the synthesis of **112**, an intermediate in the syntheses of sesquicarene and sirenin.[104] Although elimination, metal–halogen exchange and other side reactions appear to dominate the reactions of organocuprates and many other organometallic reagents with tertiary alkyl halides, trialkynyl alanes undergo remarkably clean reactions with tertiary alkyl chlorides or bromides to give the cross-coupled product alkynes (**113**→**114**).[105] The reaction of organocuprates[106] or preferably the boron trifluoride are complexes of copper alkyls[107] with prenyl-type halides generally proceeds regioselectively at the tertiary terminus of the allyl moiety to give a fully substituted carbon atom.



**111** **112**

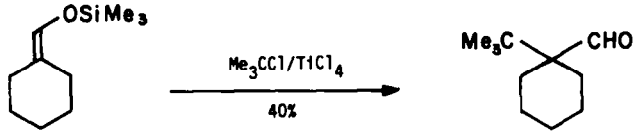


**113** **114**

The generation of quaternary carbon centers by the exhaustive methylation of tertiary alcohols,[108] ketones,[109] and carboxylic acids[110] using trimethylaluminum has been reported, but the general synthetic utility of these reactions remains to be established. Furthermore, tertiary allylic alcohols have recently been converted into geminal methyl vinyl compounds by the reaction with methylmagnesium bromide in

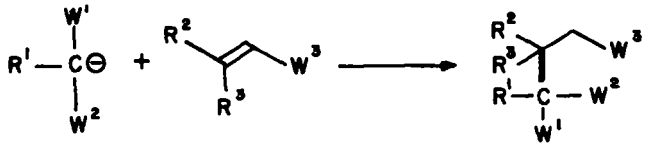
the presence of bis (triphenylphosphine) nickel chloride.[111] These nickel-catalyzed reactions proceed with predominant formation of the new carbon–carbon bond from the less hindered face of a conformationally biased molecule. There is also a modest preference for the displacement of the hydroxyl group by a methyl group without allylic inversion.

Although the direct, bimolecular alkylation of simple enolates with tertiary alkyl halides invariably results in predominant dehydrohalogenation, a successful and potentially useful strategy for effecting the *α-tert*-alkylation of carbonyl compounds and esters has been reported. These procedures involve the Lewis acid-catalyzed reactions of trimethylsilylenol ethers[112,113] and O-trimethylsilyl-O-alkyl ketene acetals[114] with *tert*-alkyl chlorides. Moreover, this technique may even be exploited for the facile construction of a carbon–carbon bond between two tertiary centers, thereby producing a compound such as **116** which possesses two contiguous quaternary centers.[112] Several intramolecular alkylations of enolates with tertiary halides[115] and of nitrile anions with tertiary epoxides[116] that result in the formation of 3- and 4-membered rings are known.




115 116

*Nucleophilic additions to electron deficient alkenes.* The construction of quaternary carbon atoms by the conjugate addition ("Michael-type") of carbon nucleophiles to a β,β-disubstituted-α, β-unsaturated carbonyl or acyl compound (eqn 9) is well entrenched in synthetic methodology. It should be recognized,



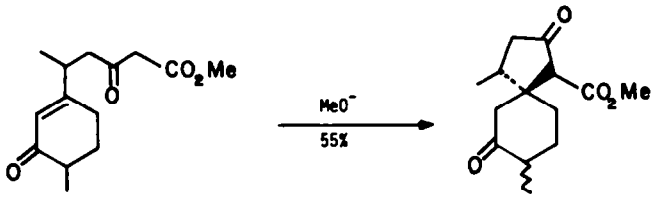

(9)

$W^{1-3}$ = $COR^4$, $CO_2R^4$, CN, etc.

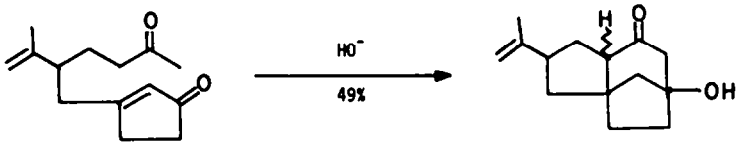
however, that the 1,4-addition of many carbon nucleophiles to β,β-disubstituted Michael acceptors is generally retarded by steric effects, and the yields of 1,4-adducts may be low as a result. Furthermore, in those conjugate addition reactions which are reversible, unfavorable steric factors present in the product may facilitate the retrograde 1,4-addition reaction, thereby precluding the formation of a quaternary center.

The nucleophilic 1,4-addition of enolates to α,β-unsaturated carbonyl and acyl compounds is an important reaction for the construction of molecules possessing 1,5-difunctionality.[13] Although bimolecular processes are the most common, intramolecular variants of this reaction are also known as illustrated by the spirocyclization of **117**.[117] A new approach for the construction of bicyclo [3.2.1] octanes features an intramolecular Michael addition followed by an intramolecular aldol reaction **119**→**120**,[118] and a related, double cyclization reaction has been utilized in the recent syntheses of patchouli alcohol and seychellene.[119]

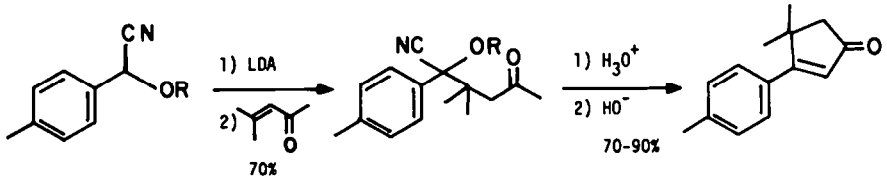
A variety of acyl and carboxyl anion equivalents[120] have been found to react with β,β-disubstituted alkenes by 1,4-addition. The net conjugate addition of acyl anion equivalents to α,β-unsaturated systems is apparently favored whenever the initial 1,2-addition is reversible. Cyanide ion reacts with α,β-unsaturated ketones in protic media to give γ-keto nitriles, and the troublesome side reactions which may sometimes occur during this process may be conveniently supressed by the use of hydrogen cyanide and triethylaluminum or diethylaluminum cyanide.[121] Moreover, the hydrocyanation of α,β-unsaturated ketones using these reagents frequently proceeds with a high degree of stereoselectivity. The 1,4-addition of a protected cyanohydrin to a β,β-disubstituted enone has been exploited for the construction of **123**, an intermediate in a synthesis of β-cuparenone.[122]




117 118

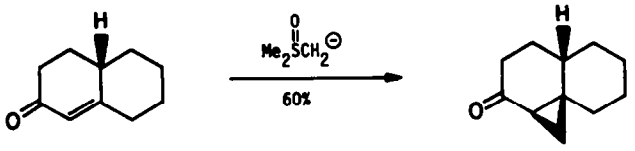



119 120

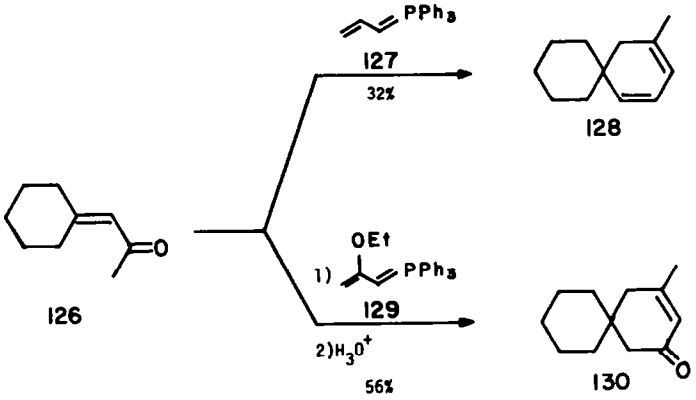



121 R = CH(CH3)OEt 122 123

The conjugate addition of sulfonium ylids to $\alpha,\beta$-unsaturated ketones is generally succeeded by the intramolecular alkylation of the resulting enolate-sulfonium salt to give $\alpha,\beta$-cyclopropyl ketones[123] as illustrated by the reaction of **124** with dimethylsulfoxonium methylide.[124] While steric hindrance may decrease the rate of cyclopropanation of enones, it need not preclude it. In this regard it may be noted that alkyl substitution at the $\alpha$-carbon atom appears to decrease the rate of cyclopropanation more appreciably than $\beta$-alkyl substitutents. The conjugate addition of allylidene triphenylphosphoranes **127**[125,126] to $\alpha,\beta$-unsaturated ketones followed by an intramolecular Wittig reaction allows the con-

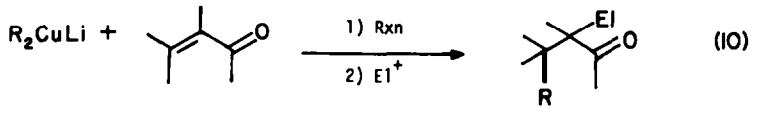



124 125



struction of substituted cyclohexadienes onto pre-existing enones. When heteroatom-substituted allylidene phosphoranes such as **129** are employed in these reactions, 2-heteroatom-substituted cyclohexadienes are produced which may be conveniently converted into cyclohexenones by acid-catalyzed hydrolysis.[127]

One of the most important recent developments in synthetic methodology has been the use of organometallic compounds as reagents for the formation of new carbon–carbon bonds. It appears that preformed organocuprates are frequently the reagents of choice for effecting the conjugate addition of simple alkyl residues to an $\alpha,\beta$-unsaturated system (eqn 10) although the copper (I) catalyzed conjugate addition of Grignard reagents may sometimes be employed effectively for such transformations.[128] The conjugate addition of alkyl groups to particularly unreactive substrates such as $\beta,\beta$-disubstituted $\alpha,\beta$-unsaturated esters may be achieved using organo copper reagents complexed with boron trifluoride.[129] The alkyl moiety may contain a variety of functional groups including carbon–carbon double bonds,

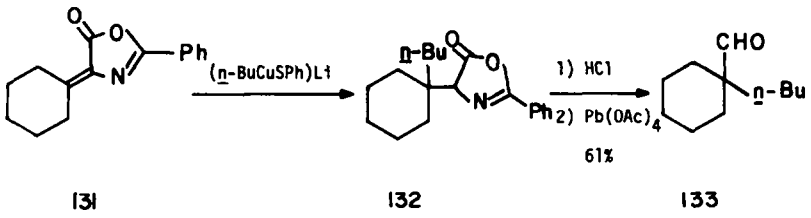


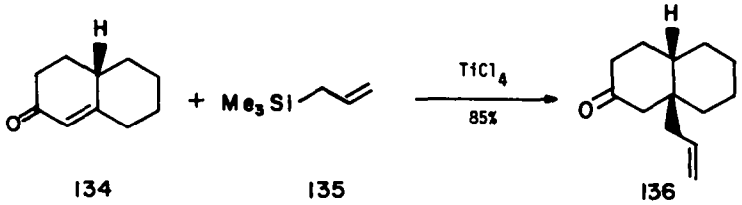
(10)

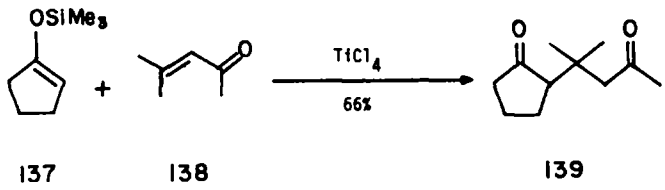
protected alcohols and protected carbonyl groups. Moreover, the enolates which are regioselectively produced upon the conjugate addition of the organocuprate reagent may be trapped with a variety of alkylating agents[21,22] and carbonyl compounds,[69,130] but some difficulty arising from enolate equilibration may be encountered if the alkylation step is slow.

Electron deficient alkenes other than simple $\alpha,\beta$-unsaturated ketones or carboxylic acid derivatives also undergo conjugate addition reactions with organocuprates. For example, the alkylidene azlactone **131**, which may be readily prepared from cyclohexanone, undergoes regioselective, nucleophilic addition with hetero cuprates to give **132**.[131] Sequential treatment of **132** with aqueous acid and lead tetraacetate then produces the tertiary aldehyde **133**. The net conversion of cyclohexanone to **133** thus represents a process for the geminal acylation–alkylation of a carbonyl group by the substitution of both of the carbon–oxygen bonds with nucleophilic reagents. While $\beta,\beta$-disubstituted $\alpha,\beta$-unsaturated aryl sulfones suffer nucleophilic addition with organocuprate reagents, the related ethylenic sulfides and ketene dithioacetals do not.[132]

Alkyl derivatives of other main group elements may also be employed in carbon–carbon bond forming reactions in conjugate additions to $\beta,\beta$-disubstituted-$\alpha,\beta$-unsaturated carbonyl compounds. For example, alkynyl boranes have been found to transfer alkynyl groups to $\alpha,\beta$-unsaturated ketones which may adopt a cisoid conformation, including mesityl oxide, to give $\gamma,\delta$-acetylenic ketones,[133a] whereas in the presence of a nickel catalyst organoaluminum acetylenides add to $\alpha,\beta$-unsaturated ketones that are fixed in the s-trans conformation.[133b] The conjugate addition of alkyl groups to $\beta,\beta$-disubstituted enones may be effected by their nickel catalyzed reaction with trialkylalanes.[134] In the presence of titanium tetrachloride, allylsilanes **135** transfer an allyl group with inversion of the allyl moiety to $\alpha,\beta$-unsaturated ketones.[135] 1,5-Dicarbonyl compounds may be conveniently prepared by the related, titanium tetrachloride-catalyzed reaction of trimethylsilylenol ethers **137**[136] or O-trimethylsilyl-O-alkyl ketene acetals[137] with $\beta,\beta$-disubstituted enones.

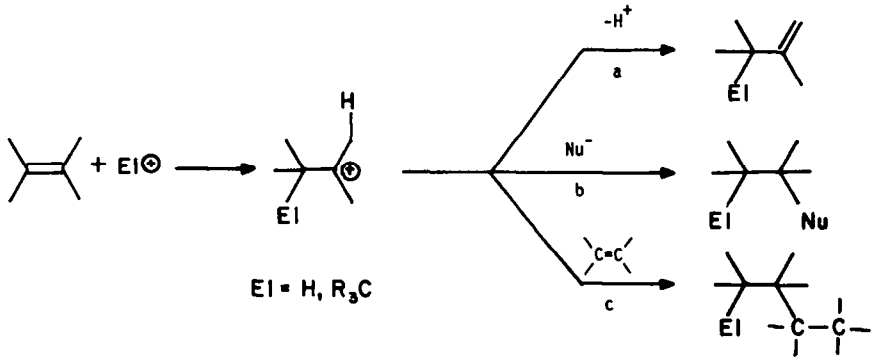




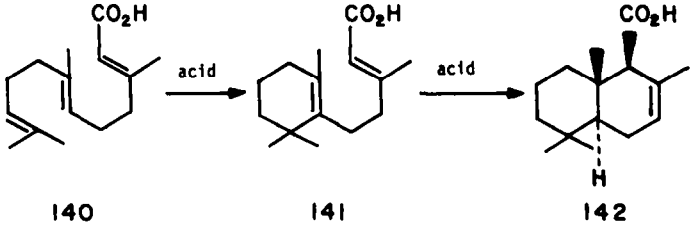

137 138 139

*Electrophilic additions to carbon–carbon double bonds.* The formation of new carbon–carbon bonds by electrophilic additions to alkenes formally involves a two step process which is usually initiated by the interaction of an electrophile such as a proton or a carbonium ion with a tri- or tetrasubstituted carbon–carbon double bond to produce a tertiary carbonium ion (Scheme 4). The carbocation thus produced may then suffer: (a) loss of a proton to give an alkene; (b) attack by a heteroatom nucleophile; or (c) attack by a carbon nucleophile such as a carbon–carbon double bond. While examples of both intramolecular (cation-initiated olefinic cyclizations) and bimolecular (Friedel–Crafts alkylations) capture such tertiary carbonium ions by carbon nucleophiles are known, the intramolecular processes appear to possess the greatest utility for the synthesis of natural products.




Scheme 4.

An important process for the construction of a quaternary carbon atom concomitant with carbocyclic ring formation involves the intramolecular trapping of a tertiary carbonium ion by a carbon–carbon double or triple bond.[138] One of the earliest examples of this type of reaction was the acid-catalyzed cyclization of farnesic acid (**140**) to drimanic acid (**142**) via monocyclofarnesic acid (**141**),[139] an overall process which results in the formation of two quaternary carbons and two 6-membered rings. It has now been generally established that polyenic substrates possessing *trans* double bonds disposed in a 1,5-relationship may be induced to undergo highly stereoselective cationic cyclizations to give polycyclic products having the all *trans* configuration. These important transformations, in which as many as four rings may be produced, appear to mimic the biogenetic conversion of squalene into lanosterol and have been utilized in a number of biomimetic total syntheses of steroid and terpenoid natural products.

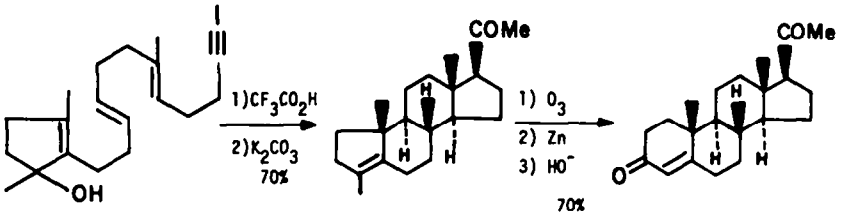



140 141 142

Although the most frequently employed initiators in these cationic, polyolefin cyclizations have been trisubstituted double bonds and allylic alcohols or acetals,[138] cationic cyclizations have recently been reported wherein $\alpha,\beta$-unsaturated ketones,[140] $\alpha,\beta$-epoxyketones,[141] and ketene dithioacetals[142] have served as initiating functions. These latter examples are of particular importance since they allow the introduction of a carbonyl group at C-4 of a steroid or related nucleus. The use of unconjugated carbon–carbon double bonds or aromatic rings[138] and allenes[143] as terminators in these cyclization reactions generally affords a 6-membered ring in the final closure step. Since 5-membered rings are

frequently present in natural products (as in the steroid D ring), it is especially significant that suitably disposed methyl- or phenylacetylenic[144] and styryl end groups allow the formation of a 5-membered ring. For example, the use of a methyl acetylene as a terminating function has been exploited in an elegant, biomimetic synthesis of progesterone **145**.[145] Vinyl chlorides may also be employed as terminators in cationic cyclizations leading to the formation of fused cycloalkanones.[146]

Other applications of cationic cyclizations have been described. For example, the annelation of a cyclopentanone ring by treatment of the ketone-propargyl alcohol adduct **146** with sulfuric acid is both regio- and stereoselective and apparently involves the electrocyclic, conrotatory closure of a hydroxypentadienylcation.[147] Although unsaturated diazoketones undergo an acid-catalyzed intramolecular cyclization,[148–150] electronic stabilization, such as aryl $\pi$ bond participation, of the intermediate cationic species appears necessary in order to ensure regioselective, carbon–carbon bond formation as evidenced by the lack of regioselectivity in the cyclization of **148**.[148] The cationic cyclization of nitrogen-containing olefinic substrates is also feasible as illustrated by the construction of the morphinane skeleton **152**.[151]

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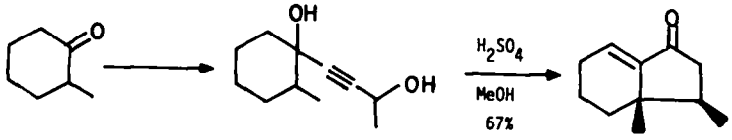


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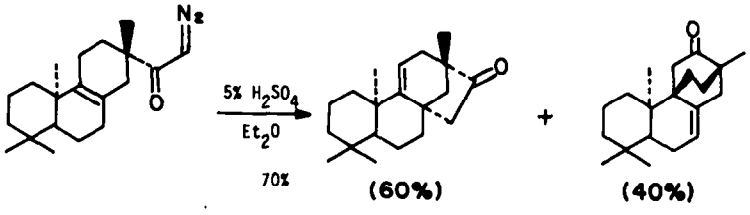


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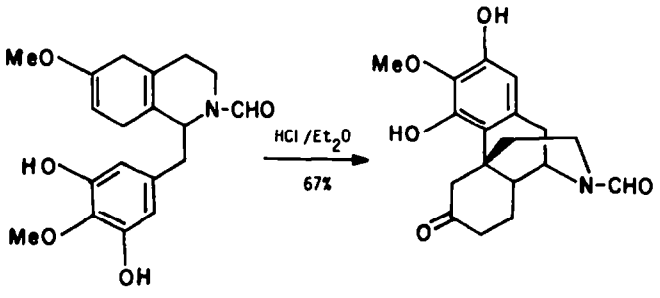


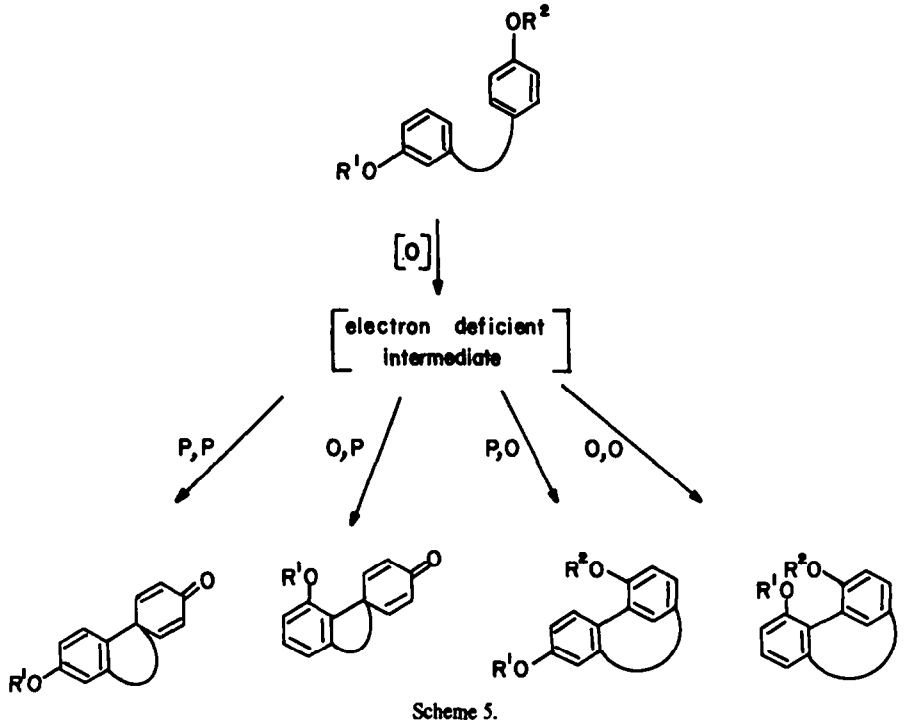

151 152

## 4. OXIDATIVE AND REDUCTIVE COUPLING REACTIONS

Since they are generally effective only for the construction of symmetrical dimers, oxidative and reductive coupling processes are rarely synthetically useful in bimolecular reactions. Even if symmetrical coupling products are desired, yields of the dimers are frequently low whenever two contiguous quaternary carbon atoms are produced. However, such coupling reactions, especially those involving oxidation, may be expeditiously employed for the union of two dissimilar synthons in cyclization reactions.

*Bimolecular coupling reactions.* The dimerizations of ketone enolates[152] or their derived trimethylsilylenol ethers[153] to produce symmetrical 1,4-diketones may be conveniently effected with chemical oxidants, but these reactions typically do not proceed in high yield when quaternary carbon atoms are formed. The oxidative coupling of $\alpha,\alpha$-disubstituted ester enolates may be induced either electrochemically[154] or with chemical oxidants.[155] The reductive dimerization of symmetrical $\alpha,\alpha'$-dibromoketones[156] and $\alpha$-bromoesters[157] proceeds in fair to good yields even when the coupling results in the generation of two contiguous quaternary carbon atoms.

*Intramolecular oxidative coupling of phenolic and nonphenolic substrates.* The intramolecular, oxidative coupling of phenolic and nonphenolic $\alpha,\omega$-diaryl alkanes has long been recognized as the key step in the biosynthesis of many classes of natural products.[158,159] Unfortunately, the effective utilization of these coupling reactions for the chemical synthesis of natural products has, until recently, been frequently plagued by low yields and the obtention of complex product mixtures. There are two important features of these oxidative cyclizations that deserve mention (Scheme 5). Firstly, it is necessary to generate the electron deficient intermediate (most likely a radical cation) under conditions that minimize deleterious side reactions such as polymerization which result from the intermolecular coupling of either the initial substrate or of the cyclized product. Moreover, it should be recognized that the products of these reactions are sometimes more readily oxidized than the starting materials. Secondly, effective regiocontrol of the coupling process is essential so that the formation of the new carbon–carbon bond affords the

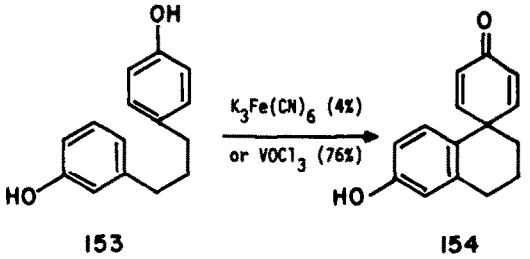



Scheme 5.

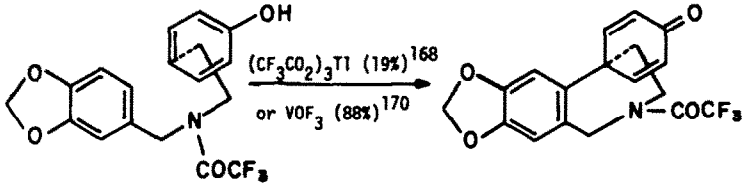
desired substitution pattern in the product. Obviously, all coupling processes do not lead to the formation of a quaternary carbon atom. Although chemical oxidants have been historically utilized in these coupling reactions,[160–168] electrochemical oxidation has recently proven to be a highly effective experimental technique.[169,170] The Pschorr reaction and the photochemical dehydrohalogenation of aryl halides[171] appear to be generally unsatisfactory for the synthesis of natural products containing quaternary carbon centers since the yields of coupled products in such reactions is usually low.

The intramolecular, oxidative coupling of diphenolic substrates may be readily effected with one electron oxidants such as potassium ferricyanide, ferric chloride or manganese dioxide,[158] but the yields in these reactions have been characteristically low owing to appreciable polymerization and over oxidation. However, the use of two electron oxidants such as vanadium oxytrichloride[160,161] and thallic trifluoroacetate,[162] each of which may form covalent bonds to oxygen prior to the actual oxidation, has led to markedly improved results (e.g. **153**→**154**).[161] The complex of ferric chloride in dimethylformamide appears to give better yields of coupled products and less polymerization than ferric chloride alone.[163] The presence of a basic nitrogen atom during these chemical, oxidative couplings is usually deleterious, and notrogen is thus generally protected as an amide. While it appears that the para–para coupling mode is preferred in the oxidative coupling of diphenolic substrates, this reaction pathway may be precluded by the expeditious use of suitable blocking groups such as bromine, which may be removed with lithium aluminum hydride.[164] The use of blocking groups, however, adds steps to the synthetic sequence, and other, more effective means of achieving the requisite regiocontrol for the coupling process are required. In this regard it appears that thallic trifluoroacetate exerts a remarkable influence in directing para-ortho coupling, an effect which has been attributed to a coordination phenomenon.[162]

The oxidative, intramolecular coupling of monophenolic substrates has been investigated as an attractive *in vitro* modification of the biosynthetic process since a high concentration of oxidant would be unnecessary, and the coupled products would not be phenolic and thereby not as susceptible to further oxidation. Although thallic trifluoroacetate,[161,165,166] vanadium oxytrichloride[161] and vanadium oxytrifluoride[167] may each be used as chemical oxidants to induce this transformation, the latter two seem to be more effective as illustrated by the oxidative cyclization of **155**. In several applications of monophenolic oxidative coupling reactions to alkaloid synthesis, amine boranes have been employed as protecting groups for the basic nitrogen.[165,167]

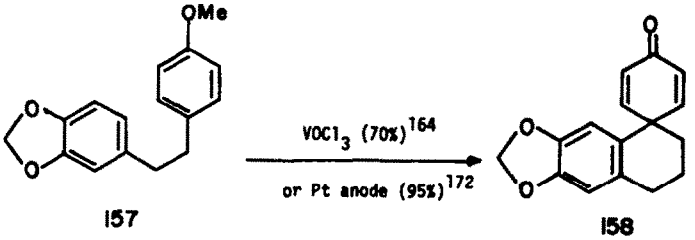



153 154

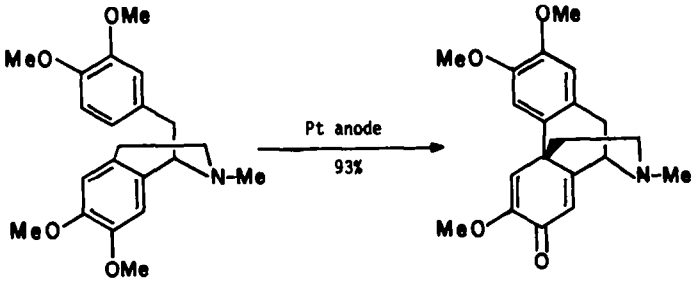



155 156

Whereas the oxidative coupling of nonphenolic substrates may be effected with chemical oxidants such as vanadium oxytrichloride[161] or vanadium oxytrifluoride,[168] anodic oxidation[169,170] appears to give superior results as illustrated by the cyclization **157**→**158**. The electrochemical cyclization of laudanosine (**159**) to give the morphinandienone **160** in 93% yield is particularly noteworthy.[170]




157 158

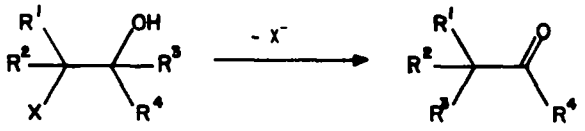



159 160

## 5. REARRANGEMENT REACTIONS

Synthetic reactions which allow the construction of quaternary carbon centers by rearrangement modes are becoming increasingly important in organic synthesis. These rearrangement reactions may be classified into two general categories depending upon the net change in the number of carbon–carbon bonds. Thus, there are simple molecular reorganizations in which there is no change in the total number of carbon–carbon bonds, and there are others wherein an additional carbon–carbon bond is produced. Rearrangements of the first type generally involve [1, 2] or [1, 3] shifts whereas those of the second type are usually pericyclic reactions such as [2, 3] or [3, 3] sigmatropic rearrangements. It should be recognized that molecular rearrangements which do result in the formation of a new carbon–carbon bond may result in the more convergent construction of the target skeletal framework since two simple synthons may be connected by these processes. The synthesis of carbocyclic spiro compounds via rearrangement routes has been reviewed.[172]

[1, 2] *Rearrangements.* A variety of [1, 2] molecular reorganizations including the pinacol[173] or Tiffeneau–Demjanov[174] (eqn 11) and the Favorski or quasi-Favorski (eqn 12)[175] rearrangements may lead

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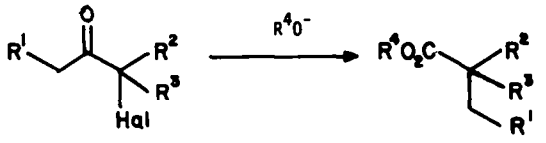
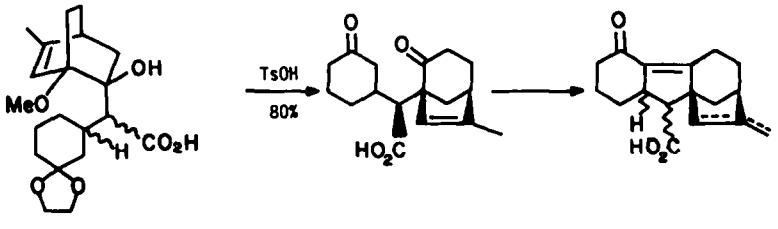
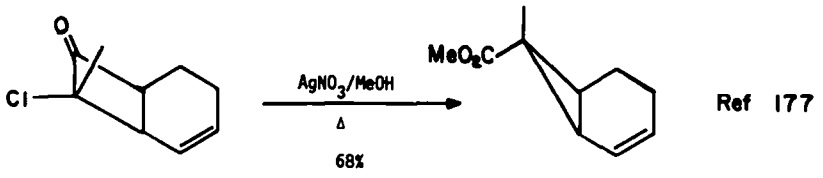



(12)

to the creation of a quaternary carbon atom. It should be noted that there is usually no net change in the number of carbon–carbon bonds in these rearrangements. One recent application of a semipinacol reaction features the rearrangement/cyclization **161**→**163**, a key sequence in a novel approach to the gibberellin skeleton.[176]

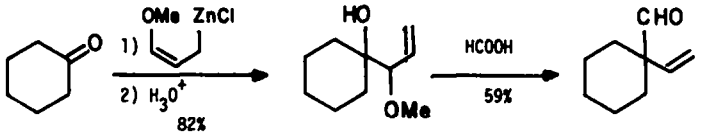



161 162 163



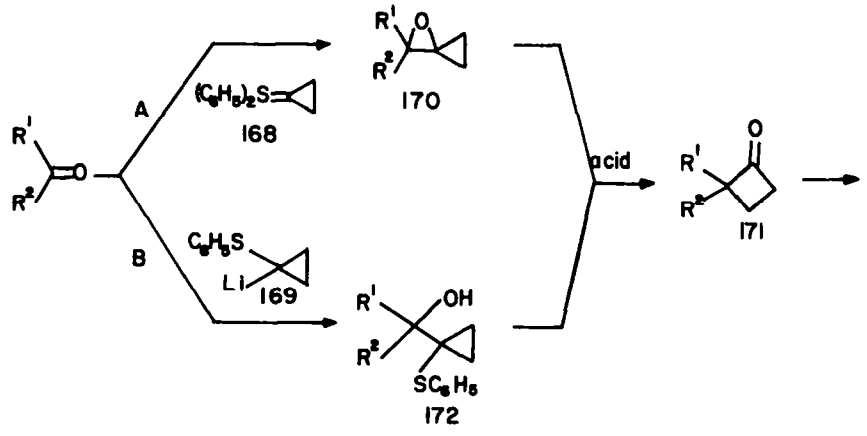

164 165

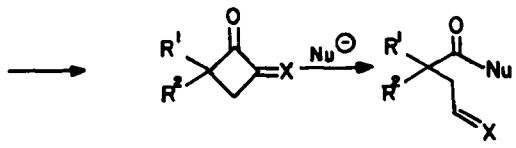
*Geminal disubstitution via* [1, 2]-*rearrangements.* The semipinacol rearrangement has recently been exploited as the key step in several reaction sequences which result in the construction of quaternary carbon atoms by net geminal disubstitution at a carbonyl function. Although the conversion **101** → **167**




101 166 167

represents a simple illustration of this process,[178] one of the most general synthetic approaches to the geminal secoalkylation at a carbonyl carbon features the conversion of a ketone functional group into a 2,2-disubstituted cyclobutanone **171**, and two efficient procedures for effecting this spiroannelation reaction have been developed (Scheme 6).[179–184] For example, the reaction of diphenylsulfonium cyclopropylid (**168**) with ketones produces oxaspiropentanes **170** (Method A)[179–181] via an unusually facile $S_N2$ displacement at a cyclopropyl carbon. Coupled with the presence of an oxygen atom, the substantial strain energy in these oxaspiropentanes renders them highly susceptible to undergo an acid-catalyzed, semipinacolic rearrangement to produce the key intermediate cyclobutanones **171**. The alternate route to these cyclobutanones features the sequential addition of 1-lithio cyclopropylphenylsulfide (**169**) to carbonyl compounds followed by the sulfur-directed, acid-catalyzed ring expansion of the intermediate cyclopropyl carbinols **172** thus produced (Method B).[181–183] These two procedures are complementary with respect to the reactivity of the two reagents **168** and **169** toward different carbonyl compounds. Thus though the anion **169** added smoothly to $\alpha,\beta$-unsaturated ketones and hindered ketones, the less reactive ylid **168** did not. Moreover, the stereochemical outcome of the rearrangements of conformationally biased derivatives of **170** and **172** is complementary. There is also a modified procedure for the stereoreversed formation of cyclobutanones from the oxaspiropentanes **170**.[184]





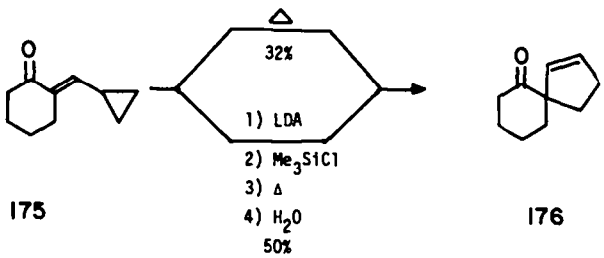
173 174

X = $Br_2$, $-S(CH_2)_3S-$

Scheme 6.

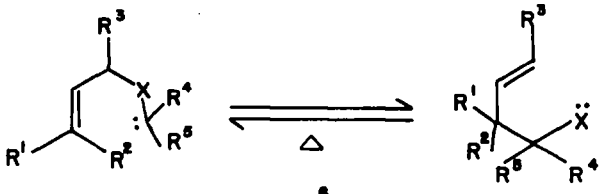
The nucleophile-induced cleavage of these intermediate cyclobutanones **171** to produce quaternary carbon atoms bearing differentially functionalized alkyl substituents requires the presence of anion stabilizing groups, even though the release of the strain energy in the four-membered ring provides a strong driving force for the ring scission. When geminal dibromo or dithio substituents are introduced at the $\alpha'$-position [e.g. **173**, X = $Br_2$, $-S(CH_2)_3S-$], the intermediate carbanion produced by the rupture of the cyclobutanone ring is sufficiently stabilized that the cleavage becomes exceptionally facile and may be triggered with a variety of nucleophiles. The use of a dithiane moiety as the anion stabilizing function seems generally preferred since: (1) the geminal dibromo cyclobutanones **173** (X = $Br_2$) may suffer ring contraction via a semibenzylic acid rearrangement; (2) the selective bromination of the cyclobutanone ring in the presence of other functional groups such as double bonds may not be feasible; and (3) the versatility of the dithiane group as an acyl anion equivalent allows additional elaboration of the side chains. The applications of this general methodology for the net reductive, nucleophilic acylation–alkylation at a carbonyl center to the synthesis of natural products such as acorenone B,[185] the trichothecanes,[186] and the gibberellins[187] have been described.

[1, 3]-*Rearrangements.* Although the thermal rearrangement of vinyl cyclopropanes to give cyclopentenes is not commonly used in synthetic organic chemistry, this reaction may be used for the annelation of cyclopentenes onto pre-existing rings. For example, the rearrangement of $\beta$-cyclopropylenones such as **175** provides a facile entry to spirobicyclic systems.[188]



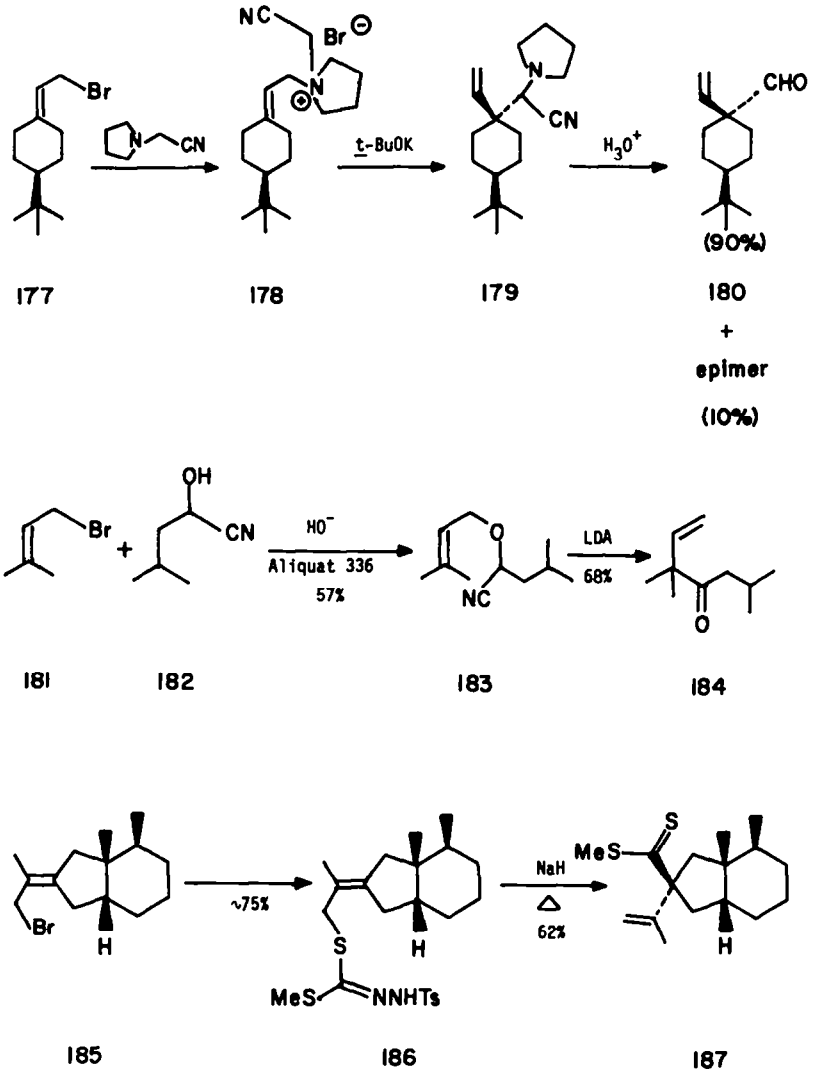

175 176

[2, 3]-*Sigmatropic rearrangements.* [2, 3]-Sigmatropic rearrangements constitute an exceptionally important class of bond reorganization processes that have substantial application in organic synthesis. Those [2, 3] rearrangements which are generally applicable for the construction of quaternary carbon centers are depicted in general terms in eqn (13) where X = NR,[189,190] O,[191,192] and S.[178,193–195] Since there is a net increase in the total number of carbon–carbon bonds, these rearrangements may be used advantageously for the connection of two synthetically simpler precursors, thereby resulting in the construction of a more complex molecular framework.

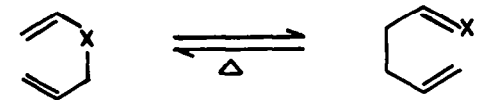


X = $NR^6$, O, S (13)

From the standpoint of practical synthetic applications, [2, 3] sigmatropic rearrangements have been most frequently employed to generate a geminal vinyl-acyl or vinyl-carboxyl functional array as illustrated by the preparation of **180**,[189] **184**[192] and **187**.[178] These particular reaction sequences effect the net $S_N2'$ reaction of an allyl halide with an acyl or carboxyl anion equivalent, but this simple formalism does not apply to all [2, 3] rearrangements. There are several other features of these concerted, molecular reorganizations which are noteworthy. Although it is generally feasible to utilize such reactions for the construction of specific olefin geometries, this fact apparently has not been exploited in those rearrangements that result in the creation of a quaternary carbon center. [2, 3] Sigmatropic rearrangements which occur on a conformationally-biased carbon framework appear to proceed preferentially across the less hindered face of the molecule, resulting in the formation of the quaternary carbon atom with a high degree of stereoselectivity (e.g. **178**→**179** and **186**→**187**). Moreover, it appears that comparable levels of stereoselectivity are observed for the different classes of [2, 3] sigmatropic rearrangements depicted in eqn (13) (X = NR, O, S).[178]

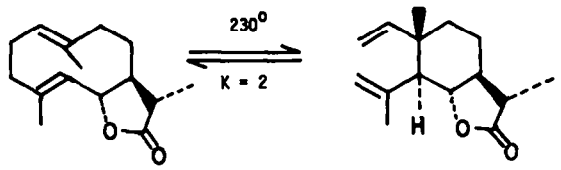



[3, 3]-*Sigmatropic rearrangements.* [3, 3] Sigmatropic rearrangements (eqn 14) constitute another synthetically important class of molecular reorganization processes, the most common of which are the Cope[196] (X = C) and Claisen (X = O) or the hetero-Claisen rearrangements (X = NR,S).[197] With the exception of the Cope rearrangement, each of these pericyclic reactions results in the formation of a new carbon–carbon bond, and these reactions may thus be advantageously used for the construction of more complex molecules by the connection of two simpler synthons.

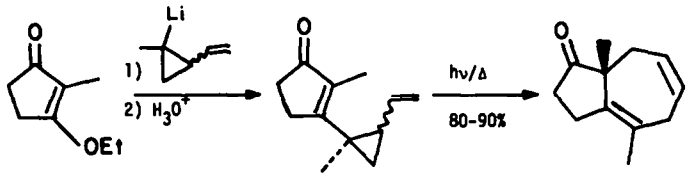


X = C,O, NR,S (14)

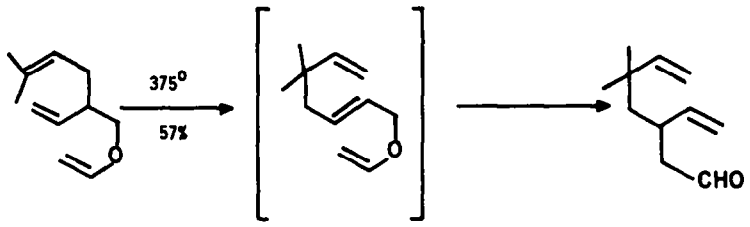
The Cope rearrangement has its greatest synthetic utility when one of the two isomeric compounds is considerably favored at equilibrium. The driving force for this shift in equilibrium might be provided by an increase in conjugation or a release of steric, angle, or torsional strain. The balance between the two isomers may be relatively close as illustrated by the interconversion between dihydrocostunolide (**188**) and saussurea lactone (**189**).[198] The homo-Cope rearrangement of substituted divinylcyclopropanes to give cycloheptadienes is driven by the release of ring strain in the cyclopropane ring.[199-202] This reaction has recently been exploited as an efficient means for the construction of the pseudoguaiane **192**, a common intermediate in the total syntheses of damsinic acid and confertin.[200b] An imaginative approach for shifting an unfavorable Cope equilibria has been reported, wherein an initial, reversible Cope rearrangement triggers an irreversible Claisen rearrangement **193**→**195**.[203]



**188** **189**



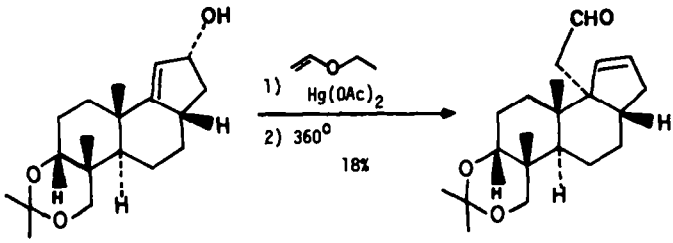
**190** **191** **192**



**193** **194** **195**

The early development of the Claisen rearrangement in synthetic organic chemistry involved the thermal reorganization of allyl vinyl ethers to give γ,δ-unsaturated aldehydes, the driving force for the rearrangement being provided by the formation of a carbonyl group. Typically the requisite allyl vinyl ethers are produced *in situ* by heating a mixture of an allylic alcohol in a low boiling vinyl ether in the presence of a Lewis acid as illustrated by the construction of the highly hindered quaternary carbon in **197**, an intermediate in the synthesis of aphidicolin.[204] A number of useful variants of this simple process have been developed that involve the alteration of the nature of the substituents appended to the vinyl ether moiety, thereby allowing the synthesis of substituted γ,δ-unsaturated carboxylic acid derivatives. Some of the common modifications include the reaction of amide acetals[205-207] or ortho esters[208,209] with

allylic alcohols to give $\gamma,\delta$-unsaturated amides or esters, respectively. Interestingly, the rearrangement **200**→**202** proceeds via a boat transition state.[209] A highly useful alternative method for the preparation of $\gamma,\delta$-unsaturated carboxylic acid derivatives features the [3,3] sigmatropic rearrangements of allylic esters via their enolates or their trialkylsilylenol ether derivatives.[210–212]

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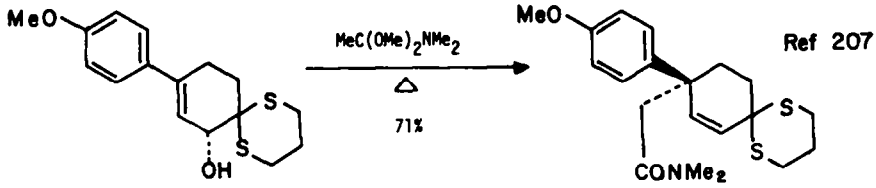


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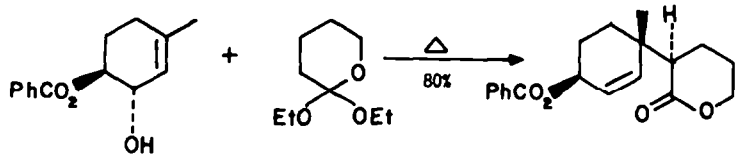


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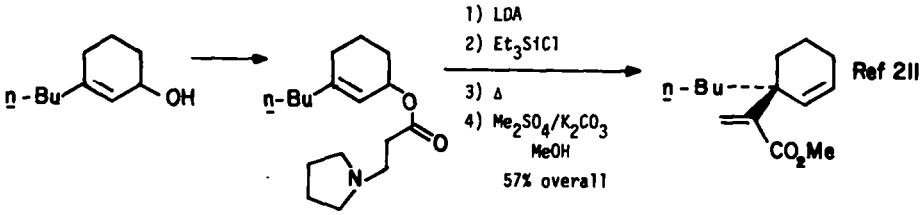


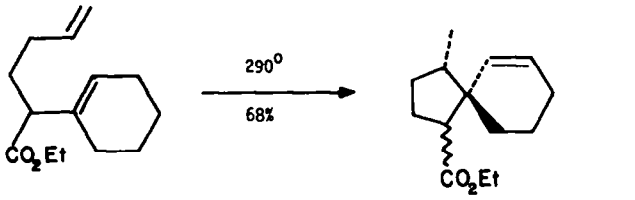

203 204 205

Several general comments regarding these Claisen rearrangements, which formally effect the net $S_N2'$ displacement of an alcohol function with an enolate, are in order. The procedures for the preparation of the intermediate allyl vinyl ethers and the allyl ketene acetal derivatives usually require the use of large excesses of the appropriate enol ether, ortho ester, or amide acetal. Unfortunately, these reagents are not always readily accessible in large quantity. In certain instances, especially cyclohexenyl systems, elimination to produce 1,3-dienes may prove to be a major side reaction. When the ortho ester variant of the Claisen reaction is employed, it is, therefore, necessary to use weak acids to promote the reversible alcohol exchange reaction. Although amide acetals undergo facile exchange in the absence of acid catalysis, elimination may still occasionally prove troublesome.[206] In view of the aforementioned problems which may attend the synthesis of the requisite 1,5-diene intermediates by exchange

reactions, the rearrangement of the enolates or the corresponding trialkylsilylenol ethers derived from allyl esters appears especially attractive. This methodology requires no prior equilibration of an allylic alcohol with an excess of the appropriate reagent, and the rearrangements themselves proceed under relatively mild conditions. Finally, despite the rather high temperatures that may sometimes be required to effect Claisen rearrangements, these molecular reorganizations are moderately sensitive to steric factors. On conformationally biased carbon frameworks, there is a slight energy preference for the rearrangement to proceed across the less hindered face of the molecule.[213] However, the degree of stereoselectivity in these reactions is neither as great nor as independent of the class of compound undergoing rearrangement as compared to the related [2, 3] sigmatropic rearrangements.[178]

Both the aza-Claisen[214,215] and the thio-Claisen[216] rearrangements have been employed for the construction of quaternary carbon centers. In general, aza-Claisen rearrangements require either high temperatures, nitrogen quaternization or the use of Lewis acid catalysts such as titanium tetrachloride. The complex side reactions of the tertiary thioaldehydes produced by thio-Claisen rearrangements may be conveniently supressed by the presence of mercuric oxide.

*Intramolecular ene reactions.* The thermal cyclization of 1,6- and 1,7-dienes and the corresponding enones or dienols via an intramolecular ene reaction[217] may be used for the construction of fused- and spirocyclic ring systems containing quaternary carbon atoms. For example, the key step in an elegant approach to the acorane spirosesquiterpenes was the thermal cyclization **206**→**207**.[218] A magnificent example of the thermal cyclization of unsaturated carbonyl compounds, which proceed via initial enolization followed by an intramolecular ene reaction, is the double cyclization **208**→**210**.[219]

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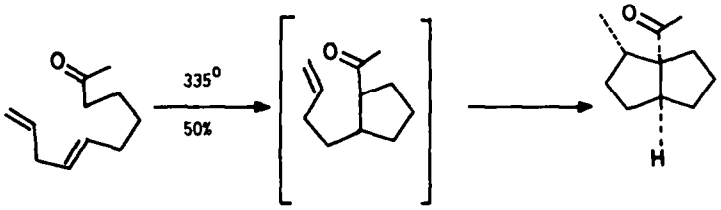
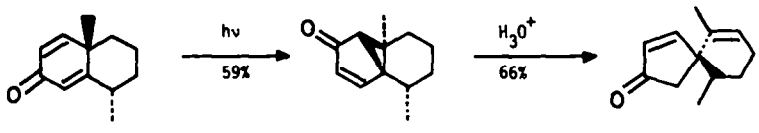


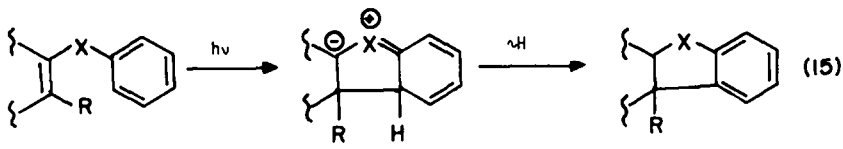

208 209 210

*Photochemical rearrangements and cyclizations.* The photochemical rearrangement of cyclic, cross conjugated dienones, followed by the solvolytic cleavage of the intermediate cyclopropyl ketones is a general procedure for the preparation of substituted spiranes.[172] This reaction has been particularly useful for the construction of the spiro [4.5] decane ring system as illustrated by the synthesis of **213**,[220] a key intermediate in a synthesis of β-vetivone.




211 212 213

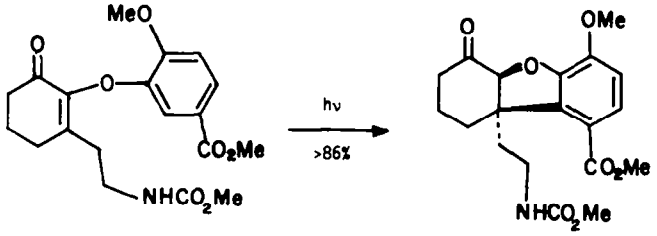
An imaginative strategy for effecting aromatic ring substitution via the photoarylation of heteroatom-substituted alkenes has been developed.[221-224] The general process (eqn 15) may be characterized as a photochemically initiated, electrocyclic reaction which originates from the arrangements of an available




(15)

X = NR', O, S

electron pair on a nitrogen, oxygen or sulfur atom and the electrons from at least one aromatic $\pi$ bond. These photoreactions, which proceed with high chemical and photochemical efficiency, are seemingly quite general and are compatible with the presence of a variety of other functional groups. The practical synthetic utility of this methodology has been recently substantiated by its use for the construction of **215**, an intermediate in a synthesis of the *Amaryllidaceae* alkaloid lycoramine.[223]



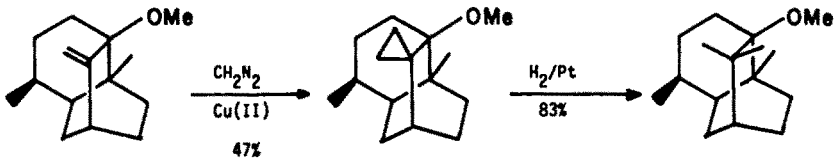

214 215

## 6. CYCLOADDITION REACTIONS

The bimolecular and intramolecular cycloadditions to alkenes possessing at least one geminally disubstituted carbon result in the simultaneous formation of two new carbon–carbon bonds concomitant with the construction of a quaternary carbon atom, and therefore such processes are particularly important synthetic reactions. Moreover, these cycloaddition reactions generally proceed with a high degree of predictable stereoselectivity. Even the most cursory examination of the literature quickly reveals a prodigious number of examples of such reactions. While the mere formation of a carbocyclic ring may be the principal objective of the cycloaddition, the ensuing discussions will focus primarily upon those individual cases in which the initial cycloadduct is further elaborated in a synthetically useful fashion. Ring cleavage and rearrangement operations are frequently encountered in these sequences. It is convenient to classify these cycloadditions according to the number of carbon atoms involved.

[1C + 2C]-*Cycloaddition reactions.* The addition of carbenes or carbenoids to carbon–carbon double bonds by either a bimolecular or an intramolecular process is well established as a general method for the construction of substituted cyclopropanes.[225] Although the formation of a cyclopropane ring may itself be the final objective of these cyclopropanation reactions, certain cyclopropanes may undergo a number of subsequent transformations to give products which no longer contain 3-membered rings. For example, the hydrogenolysis of 1,1-disubstituted cyclopropanes proceeds smoothly to afford a *gem*-dimethyl group as illustrated by the preparation of **218**.[119] The acid-induced fission of alkyl cyclopropyl ethers, which may be conveniently prepared by carbene transfer to enol ethers, affords $\alpha$-alkylated carbonyl compounds.[226-228] Thus, treatment of the methoxycyclopropane **220** with aqueous acid produces the angularly methylated 1-decalone **221**.[226] Since the direct alkylation of 1-decalones proceeds predominantly at C-2 rather than at the bridgehead, this sequence offers an attractive approach to angular methylation, and it has been recently employed in an elegant synthesis of valeranone.[227] The $\beta$-alkoxy cyclopropyl ketones produced by the copper-catalyzed addition of $\alpha$-diazomethyl ketones to enol ethers suffer ring cleavage upon treatment with acids to give 1,4-dicarbonyl compounds which may be converted into cyclopentenones as illustrated by the preparation of the spirane **68**,[228] a key intermediate in two recent syntheses of the sesquiterpene acorone.[26,76] The regioselective ring-opening of certain cyclopropyl ketones and esters by a

retrograde Michael reaction may be induced by acid[229,230] or base[231,232] to give $\gamma,\delta$-unsaturated compounds (**226**→**227**).[229] Cyclopropyl ketones generally undergo regioselective scission of the cyclopropane bond which has the best overlap with the $\pi$ orbitals of the carbonyl group upon dissolving metal reduction[233] (**229**→**230**).[230]

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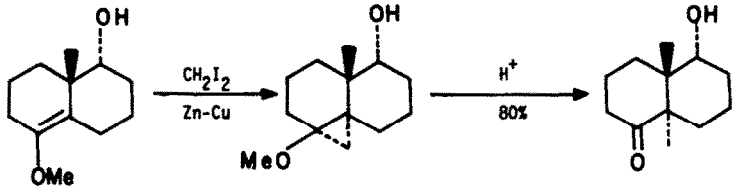


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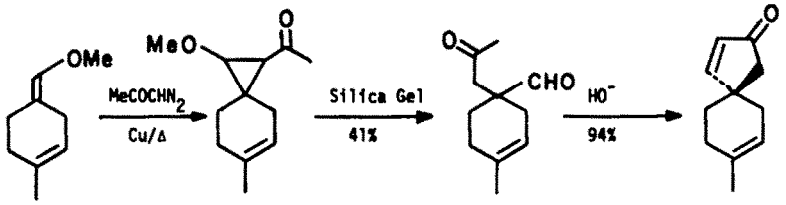


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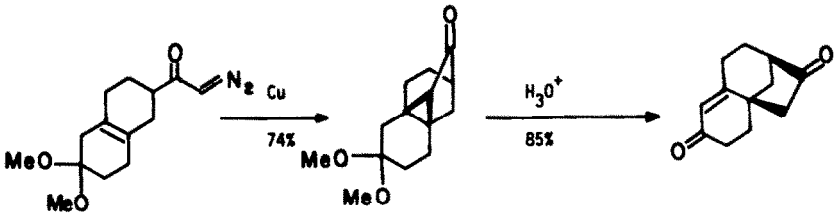


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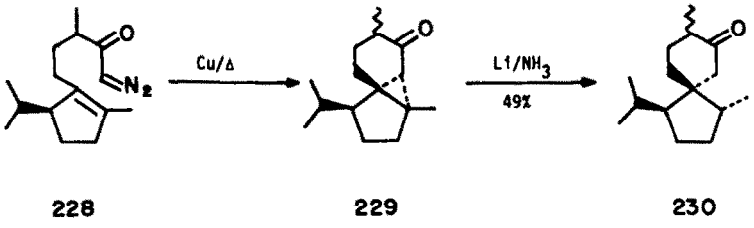


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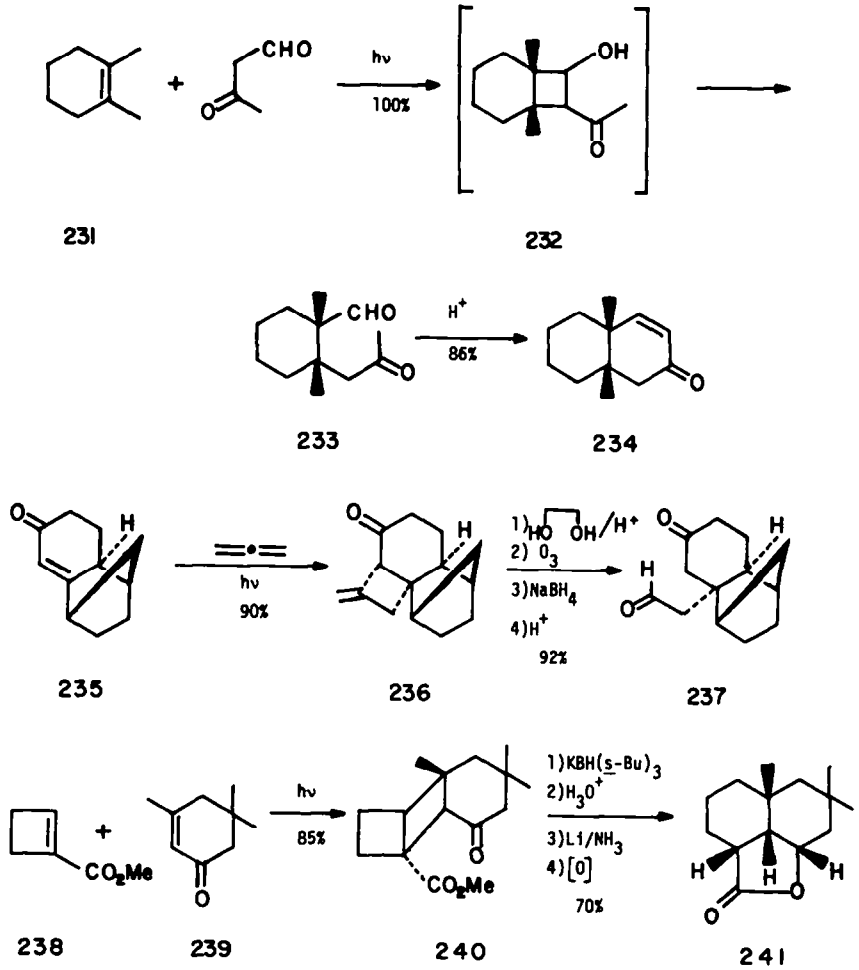
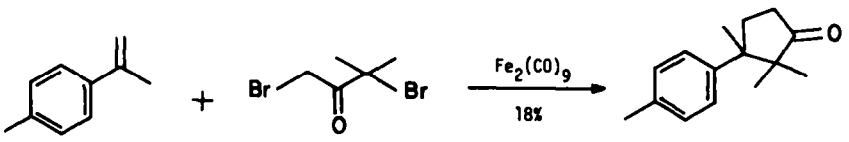
[2C + 2C]-*Cycloaddition reactions.* The photochemical [2 + 2] cycloaddition reaction of alkenes is a highly effective method for the construction of cyclobutanes, and both bimolecular and intramolecular

reactions are known.[234] Although a number of natural products possess a cyclobutane ring, some of the more interesting synthetic applications of photochemical [2+2] cycloadditions for the generation of quaternary carbon atoms entail the further elaboration of these cyclobutane intermediates. These synthetic operations, like those involving cyclopropane intermediates, exploit the strain energy present in the small ring to facilitate the ring cleavage, thereby yielding products which no longer possess a four-membered ring but which do retain the quaternary carbon atom(s) created by the cycloaddition reaction.

One example of this general strategy features the photochemical cycloaddition of alkenes and enolizable $\beta$-dicarbonyl compounds or their enol derivatives[235,236] to give substituted 2-acylcyclobutanol derivatives such as **232** which suffer facile ring fragmentation by a retro aldol process. The 1,5-dicarbonyl compounds thus produced are excellent precursors of cyclohexenones, and the overall sequence thus allows the annelation of a cyclohexenone onto a carbon–carbon double bond (**231** → **234**).[235] The considerable synthetic potential of this technique is, however, somewhat limited by the fact that the reaction of an unsymmetrical alkene with an unsymmetrical $\beta$-dicarbonyl compound can lead to the formation of four possible 1,5-dicarbonyl products. The photocycloadditions of allene to $\alpha,\beta$-unsaturated carbonyl compounds may be effectively employed for the introduction of angular acetonyl,[237] acetaldehyde,[238] or acetic acid[239] side chains via intermediate 2-acylcyclobutanol or 2-acylcyclobutanone derivatives as illustrated by the preparation of **237**.[238] An imaginative procedure for the photochemically mediated annelation of cyclohexanes onto alkenes features the elaboration of the cycloadducts that are obtained from the photochemical reaction of methyl cyclobutenecarboxylate with enones (**238** → **241**).[240] A novel synthesis of isocomene has been reported wherein three contiguous quaternary carbon centers are produced by an intramolecular [2+2] photocycloaddition. The cyclobutane ring formed by this process is then transformed into a cyclopentane by a 1,2-rearrangement of a cyclobutyl carbinyl carbon.[240a]



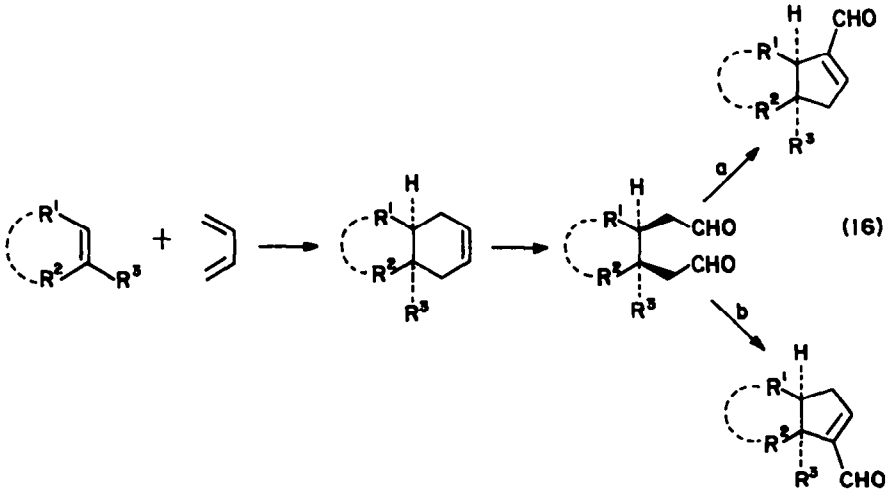
[3C + 2C]-*Cycloaddition reactions.* The use of 1,3-dipolar cycloaddition reactions for the construction of 5-membered carbocyclic systems is rather limited owing to the paucity of 1,3-dipoles with an all carbon framework. However, treatment of $\alpha,\alpha'$-dibromoketones with diiron nonacarbonyl produces an apparent oxyallyl cationic intermediate which undergoes smooth cycloadditions with alkenes[241] and enamines[242] to give cyclopentanones as illustrated by the facile synthesis of $\alpha$-cuparenone (**243**).[243]




242 243

[4C + 2C]-*Cycloaddition reactions.* Although the importance of the Diels–Alder reaction as a method for the stereoselective synthesis of 6-membered rings has long been recognized,[244] there has been a recent renaissance of interest in the development of new synthetic applications of the Diels–Alder reaction for the construction of complex molecular architecture. One of the focal points of some of these studies has been an investigation of the thermally-induced cycloaddition reactions of dienes and dienophiles which bear heteroatom substituents at the unsaturated carbon centers. Furthermore, the general utility of the intramolecular Diels–Alder reaction, which allows the simultaneous construction of two new rings, has been securely established.[245] Whenever either of the termini of the diene or the dienophile possesses two geminal alkyl substituents, a quaternary carbon will be produced concomitantly with the formation of a fused-, spiro-, or bridged-bicyclic 6-membered ring system. The enormous significance of the Diels–Alder reaction in organic chemistry is dramatically underscored by the prodigious number of total syntheses of natural products in which a [4C + 2C] cycloaddition is the key step, and a comprehensive review of these examples is not within the scope of this Report. Consequently, recent, representative examples will be chosen which are illustrative of some of the general ways that the initially produced cycloadducts may be further elaborated once the quaternary carbon atom has been created.

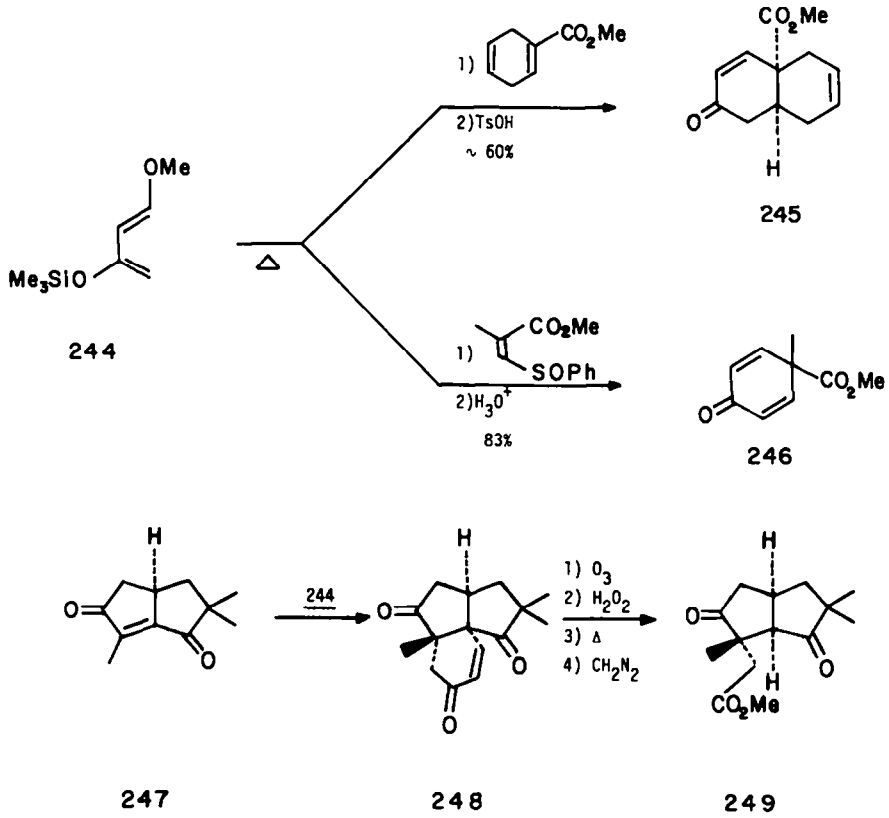
For example, oxidative cleavage of the carbon–carbon double bond of the product cyclohexene affords a 1,6-dicarbonyl compound which may undergo a variety of subsequent transformations, including two modes of cycloaldolization (eqn 16). This overall sequence thus allows the net, vicinal




(16)

*cis*-addition of two functionalized alkyl groups to a carbon–carbon double bond, the relative stereochemistry between the quaternary carbon and the adjacent carbon being secured by the Diels–Alder reaction. Although numerous examples of the application of this general strategy for the stereoselective annelation of a functionalized cyclopentene ring onto a double bond may be found, its recent use in the total syntheses of gibberellic acid[246] and serratinine, a *Lycopodium* alkaloid,[247] is representative.

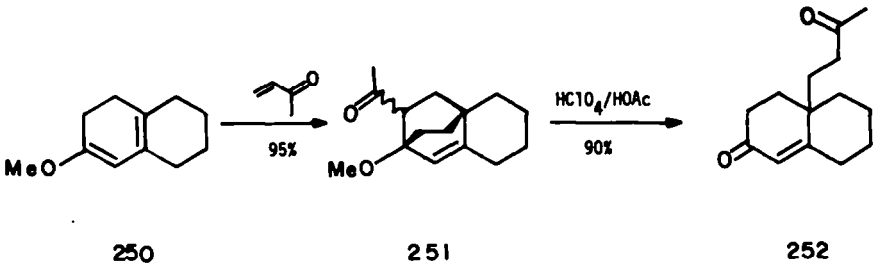
There has been considerable effort directed toward the synthesis of heteroatom-substituted dienes for use in Diels–Alder reactions.[248-250] If these heteroatoms are strategically positioned on the diene moiety, the cyclohexenes obtained in the cycloaddition step may be conveniently elaborated into functionalized cyclohexanones as illustrated by the syntheses of **245**[251] and **246**[252]. The preparation of the *cis*-decalone derivative **245**, a key intermediate in a synthesis of the sesquiterpene vernolepin, clearly establishes the utilization of heteroatom-substituted dienes as a general methodology for the regio- and stereoselective *cis*-annelation of a cyclohexanone derivative onto a carbon–carbon double bond. An application of the Diels–Alder reaction to the stereospecific alkylation of enones is illustrated by the conversion **247**→**249**, a sequence in an approach to the synthesis of coriolin.[253] While this transformation may be perceived as a mere modification of that depicted in eqn (16), it may also be more broadly envisioned as a general protocol for the stereoselective, *cis*-introduction of two alkyl substituents alpha and beta to the carbonyl carbon of an enone. An alternative procedure to the vicinal $\alpha,\beta$-dialkylation of enones involves the initial conjugate addition of an organocuprate reagent followed by the alkylation of the intermediate enolate, but this approach does not guarantee the obtention of the *cis*-stereochemical relationship between the new alkyl substituents.[254]




The bicyclo [2.2.2] octanes that are produced by the Diels–Alder reactions of 1,3-cyclohexadienes with a variety of dienophiles may be conveniently transformed by subsequent molecular reorganization involving either a fragmentation[255,256] to give cyclohexanes or fused cyclohexanes (**251**→**252**)[256] or a pinacolic rearrangement to give bicyclo [3.2.1] octanes.[176,257-259] Since the CD ring system of a number of diterpenes and diterpene alkaloids is a substituted bicyclo [3.2.1] octane, a general approach for its construction by an initial Diels–Alder reaction followed by the subsequent rearrangement of a suitable bicyclo [2.2.2] octane intermediate would be very useful. The viability of one such route to bicyclo [3.2.1] octanes is admirably illustrated by the conversion **253**→**257**, the key sequence in an elegant synthesis of stachenone.[258]

An imaginative approach to the construction of the *Hasubanan* alkaloid skeleton **260** features the use of a Diels–Alder reaction for the formation of the requisite quaternary carbon atom and the tetracyclic ring system in tandem with the allylic sulfoxide-allylic sulfenate [2, 3] sigmatropic rearrangement.[260] This

general strategy for coupling a cycloaddition process with a pericyclic rearrangement reaction should have broad synthetic applicability.

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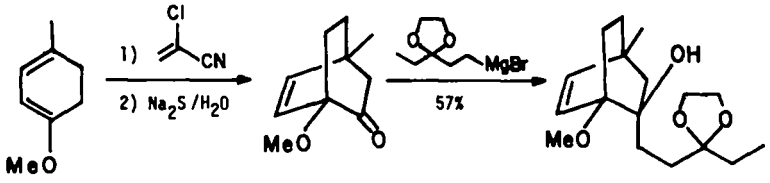


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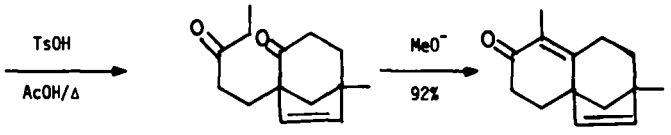
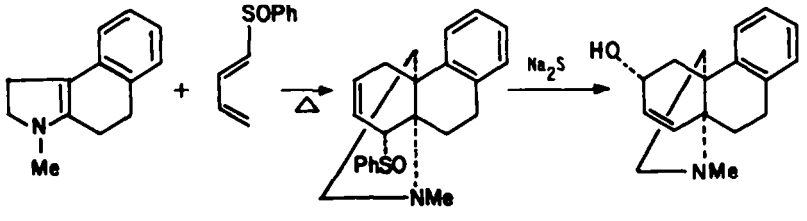
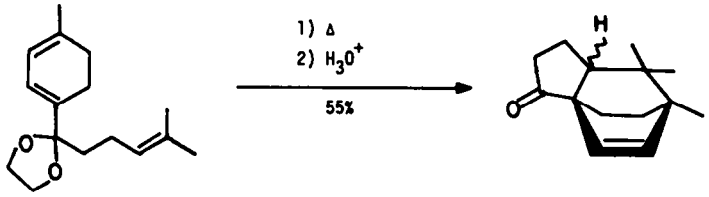



256 257

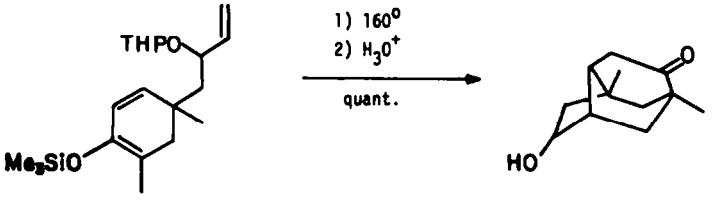



258 259 260

The intramolecular variant of the Diels–Alder reaction is being utilized with ever increasing frequency for the convergent, stereoselective syntheses of natural products containing quaternary carbon centers.[245,261-267] For example, the intramolecular cycloadditions of **261** and **263** were key steps in recent syntheses of the terpenes khusimone[261] and 9-isocyanopupukeanane,[262] respectively. The formation of the decalin **266**, which bears an angular methyl group, upon thermolysis of **265** is noteworthy,[264] and this cycloaddition reaction represents a facile, stereoselective entry to the eremophilane and valencane sesquiterpenes. An elegant route to tetracyclic diterpenes has been developed which features the intramolecular cycloaddition of the *O*-quinodimethane **269**.[266] The significant entropic assistance in these intramolecular cycloaddition reactions is dramatically substantiated by the recent observation that the endocyclic enamido diene **274** undergoes smooth conversion to the tricyclic hydrolulolidine **275**,[267] a synthon of the CDE ring system of the *Aspidosperma* alkaloids and of the BCD ring of the *Amaryllidaceae* alkaloid lycorine. This appears to be one of the first examples of the cycloaddition reaction between an enamide and an unactivated 1,3-diene.[268]




261 262

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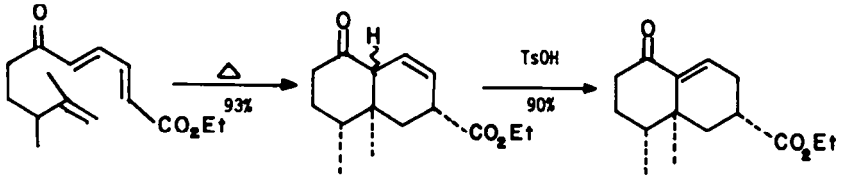


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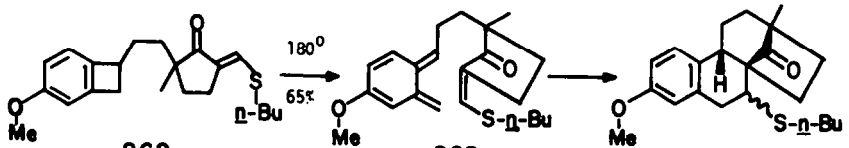


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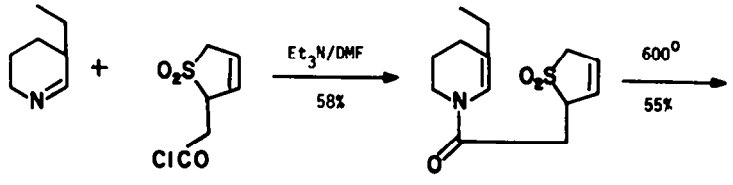


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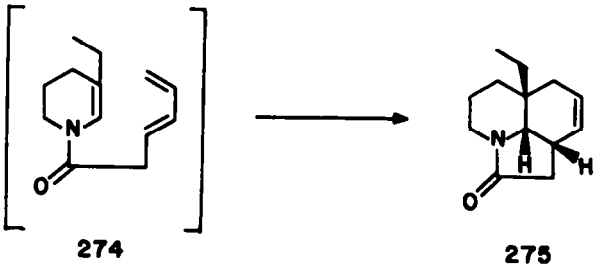

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## 7. CONCLUSIONS

Though the creation of the quaternary carbon atoms present in many molecules may pose a significant synthetic challenge, there exist a number of reactions that may be effectively employed for such constructions. The most commonly utilized methods for the formation of a fully substituted carbon atom involve the reaction of a tertiary carbon nucleophilic partner with a suitable carbon electrophile. However, nucleophilic additions to $\beta,\beta$-disubstituted, electron deficient olefins and cycloadditions to geminally disubstituted alkenes are also viable synthetic processes for the generation of a quaternary carbon atom. Molecular reorganizations, especially sigmatropic rearrangement reactions, are being used with increasing frequency. The utilization of oxidative and reductive coupling reactions is largely limited in practice to the biomimetic, intramolecular oxidative coupling of phenolic and nonphenolic substrates. Although there is a conspicuous paucity of methodology for the enantioselective elaboration of fully substituted carbon atoms, future investigations will undoubtedly unveil synthetic procedures designed to effect this important construction.

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## REFERENCES

[1]G. M. Whitesides, W. F. Fischer, Jr., J. San Filippo, Jr., R. W. Bashe and H. O. House, *J. Am. Chem. Soc.* **91**, 4871 (1969).
[2]G. H. Posner and C. E. Whitten, *Tetrahedron Letters* 1815 (1973).
[3]F. Derguini-Boumechal, R. Lorne and G. Linstrumelle, *Ibid.* 1181 (1977).
[4]D. Seyferth, K. R. Wursthorn and R. E. Mammarella, *J. Org. Chem.* **42**, 3104 (1977).
[5]V. Rautenstrauch, *Helv. Chim. Acta* **57**, 496 (1973).
[6]Y. Okude, S. Hirano, T. Hiyama and H. Nozaki, *J. Am. Chem. Soc.* **99**, 3179 (1977).
[7]F. Barbot and P. Miginiac, *Tetrahedron Letters* 3829 (1975).
[8]T. E. Stanberry, M. J. Darmon, H. A. Fry and R. S. Lenox, *J. Org. Chem.* **41**, 2052 (1976).
[9]R. A. Benkeser, M. P. Siklosi and E. C. Mozdzen, *J. Am. Chem. Soc.* **100**, 2134 (1978).
[10]H. O. House, W. C. Liang and P. D. Weeks, *J. Org. Chem.* **39**, 3102 (1974).
[11]H. K. Dietl and K. C. Brannock, *Tetrahedron Letters* 1273 (1973).
[12]P. Groenewegen, H. Kallenberg and A. van der Gen, *Ibid.* 491 (1978).
[13]For a general discussion of the alkylation of ketone enolates see in H. O. House, *Modern Synthetic Reactions* (2nd EDN.), Chapt. 9 and refs. therein. Benjamin, Menlo Park, California, (1972).
[14]For an excellent discussion of the regiospecific generation and alkylation of enolates derived from unsymmetrical ketones see: J. d'Angelo, *Tetrahedron* **32**, 2979 (1976).
[15]H. O. House, M. Gall and H. D. Olmstead, *J. Org. Chem.* **36**, 2361 (1971). For improved procedures see R. D. Miller and D. R. McKean, *Synthesis* 730 (1979) and I. Fleming and I. Paterson, *Ibid.* 736 (1979).
[16]A. J. Birch, J. E. T. Corrie, P. L. Macdonald and G. Subba Rao, *J. Chem. Soc.* Perkin I, 1186 (1972).
[17]R. M. Coates, H. D. Pigott and J. Ollinger, *Tetrahedron Letters* 3955 (1974).
[18]R. S. Matthews, S. J. Girgenti and E. A. Folkers, *Chem. Commun.* 708 (1970).
[19]R. M. Coates and R. L. Sowerby, *J. Am. Chem. Soc.* **93**, 1027 (1971).
[20]J. M. Fortunato and B. Ganem, *J. Org. Chem.* **41**, 2194 (1976).
[21]R. K. Boeckman, Jr., *Ibid.* **38**, 4450 (1973).
[22]R. M. Coates and L. O. Sandefur, *Ibid.* **39**, 275 (1974).
[23]G. H. Posner, J. J. Sterling, C. E. Whitten, C. M. Lentz and D. J. Brunelle, *J. Am. Chem. Soc.* **97**, 107 (1975).
[24]C. M. Lentz and G. H. Posner, *Tetrahedron Letters* 3769 (1978); G. H. Posner, M. J. Chapdelaine and C. M. Lentz, *J. Org. Chem.* **44**, 3661 (1979).
[25]G. Stork and S. R. Dowd, *J. Am. Chem. Soc.* **85**, 2178 (1963).
[26]D. A. McCrae and L. Dolby, *J. Org. Chem.* **42**, 1607 (1977).
[27]J. F. Le Borgne, *J. Organomet. Chem.* **122**, 123, 129, 139 (1976).
[28]J. F. Le Borgne, T. Cuvigny, M. Larchevêque and H. Normant, *Tetrahedron Letters* 1379 (1976).
[29]J. F. Le Borgne, T. Cuvigny, M. Larchevêque and H. Normant, *Synthesis* 238 (1976).
[30]See R. R. Fraser, J. Banville and K. L. Dhawan, *J. Am. Chem Soc.* **100**, 7999 (1978) and Refs. therein.
[31]aP. A. Wender and M. A. Eissenstat, *Ibid.* **100**, 292 (1978); bP. A. Wender and J. M. Schaus, *J. Org. Chem.* **43**, 782 (1978).
[32]S. F. Martin and G. W. Phillips, *Ibid.* **43**, 3792 (1978).
[33]S. F. Martin, G. W. Phillips, T. A. Puckette and J. A. Colapret, unpublished results.
[34]S. I. Hashimoto and K. Koga, *Tetrahedron Letters* 573 (1978).
[35]P. E. Pfeffer, L. S. Silbert and J. M. Chirinko, Jr., *J. Org. Chem.* **37**, 451 (1972).
[36]S. A. Monti and S. D. Larsen, *Ibid.* **43**, 2282 (1978).
[37]R. J. Cregge, J. C. Herrmann, C. S. Lee, J. E. Richman and R. H. Schlessinger, *Tetrahedron Letters* 2425 (1973).
[38]S. C. Welch, C. P. Hagan, J. H. Kim and P. S. Chu, *J. Org. Chem.* **42**, 2879 (1977).
[39]S. Kamata, S. Uyeo, N. Haga and W. Nagata, *Synth. Comm.* **3**, 265 (1973).
[40]P. Hullot, T. Cuvigny, M. Larchevêque and H. Normant, *Can. J. Chem.* **54**, 1098 (1976).
[41]J. L. Herrmann, R. J. Cregge, J. E. Richman, G. R. Kieczykowski, S. N. Normandin, M. L. Quesada, C. L. Semmelhack, A. J. Poss and R. H. Schlessinger, *J. Am. Chem. Soc.* **101**, 1540 (1979).
[42]A. Debal, T. Cuvigny and M. Larchevêque, *Synthesis* 391 (1976).
[43]A. I. Meyers, E. M. Smith and M. S. Ao, *J. Org. Chem.* **38**, 2129 (1973) and Refs. therein.
[44]C. Lion and J. E. Dubois, *Tetrahedron* **29**, 3417 (1973).

[45]A. I. Meyers and J. L. Durandetta, *J. Org. Chem.* **40**, 2021 (1975).
[46]S. D. Larsen and S. A. Monti, *J. Am. Chem. Soc.* **99**, 8015 (1977).
[47]E. J. Corey, M. Behforouz and M. Ishiguro, *Ibid.* **101**, 1608, (1979).
[48]For review of synthesis of carbocyclic spiro compounds via intramolecular alkylation routes see A. P. Krapcho, *Synthesis* 383 (1974).
[49]G. Stork, R. L. Danheiser and B. Ganem, *J. Am. Chem. Soc.* **95**, 3414 (1973).
[50]S. A. G. de Graaf, P. E. R. Oosterhoff and A. van der Gen, *Tetrahedron Letters* 1653 (1974).
[51]J. A. Marshall and P. G. M. Wuts, *J. Org. Chem.* **42**, 1794 (1977); **43**, 1086 (1978).
[52]J. L. Herrmann, G. R. Kieczykowski and R. H. Schlessinger, *Tetrahedron Letters* 2433 (1973); See also J. L. Herrmann, G. R. Kieczykowski, R. F. Romanet and R. H. Schlessinger, *Ibid.* 4715 (1973).
[53]G. R. Kieczykowski, R. H. Schlessinger and R. B. Sulsky, *Ibid.* 4647 (1975).
[54]R. L. Cargill, D. F. Bushey and J. J. Good, *J. Org. Chem.* **44**, 300 (1979) and Refs. therein.
[55]G. R. Kieczykowski, R. H. Schlessinger and R. B. Sulsky, *Tetrahedron Letters* 597 (1976).
[56]For reviews see [a]M. E. Jung, *Tetrahedron* **32**, 3 (1976); [b]R. E. Gawley, *Synthesis* 777 (1976).
[57]P. L. Fuchs, *Tetrahedron Letters* 4055 (1974).
[58]G. Büchi and M. Pawlak, *J. Org. Chem.* **40**, 100 (1975).
[59]S. F. Martin and S. R. Desai, *Ibid.* **43**, 4673 (1978).
[60]K. Seki, T. Ohnuma, T. Oishi and Y. Ban, *Tetrahedron Letters* 723 (1975); Y. Ban, T. Ohnuma, K. Seki and T. Oishi, *Ibid.* 727 (1975).
[61]G. A. Koppel and M. D. Kinnick, *J. Chem. Soc.*, Chem. Commun. 473 (1975).
[62]P. L. Fuchs, *J. Am. Chem. Soc.* **96**, 1607 (1974).
[63]W. G. Dauben and D. J. Hart, *Ibid.* **99**, 7307 (1977).
[64]S. Danishefsky, J. Dynak, E. Hatch and M. Yamamoto, *Ibid.* **96**, 1256 (1974).
[65]H. O. House, D. S. Crumine, A. Y. Ternaishi and H. D. Olmstead, *Ibid.* **95**, 3310 (1973).
[66]T. Mukaiyama, K. Banno and N. Naraska, *Ibid.* **96**, 7503 (1974).
[67]R. Noyori, K. Yokoyama, J. Sakata, I. Kuwajima, E. Nakamura and M. Shimizu, *Ibid.* **99**, 1265 (1977).
[68a]G. Wittig and H. Reiff, *Angew. Chem.* **80**, 8 (1968); *Ibid.* Internat. Ed. Engl. **7**, 7 (1968); [b]G. Wittig, *Topics in Current Chemistry* **67**, 1 (1976).
[69]F. Näf, R. Decorzant and W. Thommen, *Helv. Chim. Acta* **58**, 1808 (1975).
[70]K. Wiesner, A. Deljac, T. Y. R. Tsai and M. Przybylska, *Tetrahedron Letters* 1145 (1970).
[71]G. W. Moersch and A. R. Burkett, *J. Org. Chem.* **36**, 1149 (1971).
[72]M. W. Rathke, *Org. Reactions* **22**, 423 (1975).
[73]P. Hullot, T. Cuvigny, M. Larchevêque and H. Normant, *Can. J. Chem.* **55**, 266 (1977).
[74]T. Cuvigny, P. Hullot and M. Larchevêque, *J. Organomet. Chem.* **57**, C36 (1973).
[75]For comprehensive reviews of enamine chemistry see: [a]*Enamines: Synthesis, Structure and Reactions*, (Edited by A. G. Cook), Marcel Dekker, New York (1969); [b]M. E. Kuehne, *Synthesis* 510 (1970).
[76]S. F. Martin and T. S. Chou, *J. Org. Chem.* **43**, 1027 (1978).
[77]T. Sone, S. Terashima and S. Yamada, *Chem. Pharm. Bull.* **24**, 1273 (1976) and Refs. therein.
[78]D. J. Dunham and R. G. Lawton, *J. Am. Chem. Soc.* **93**, 2074 (1971).
[79]R. V. Stevens, R. K. Mehra and R. L. Zimmerman, *Chem. Commun.* 877 (1969).
[80]R. V. Stevens, L. E. DuPree, Jr. and P. L. Loewenwtein, *J. Org. Chem.* **37**, 977 (1972).
[81]R. V. Stevens, P. M. Lesko and R. Lapalme, *Ibid.* **40**, 3495 (1975) and Refs. therein.
[82]S. L. Keely, Jr., A. J. Martinez and F. C. Tahk, *Tetrahedron* **26**, 4729 (1970).
[83]D. A. Evans, C. A. Bryan and G. M. Wahl, *J. Org. Chem.* **35**, 4122 (1970).
[84]C. P. Forbes, G. L. Wenteler and A. Wiechers, *Tetrahedron* **34**, 487 (1978).
[85]M. Miyashita, T. Yanami and A. Yoshikoshi, *J. Am. Chem. Soc.* **98**, 4679 (1976).
[86]W. Oppolzer, H. Hauth, P. Pfäffli and R. Wenger, *Helv. Chim. Acta* **60**, 1801 (1977).
[87]I. Paterson and I. Fleming, *Tetrahedron Letters* 995 (1979); See also I. Paterson, *Ibid.* 1519 (1979).
[88]For a review of methodology for the chain extension of a carbonyl functional group see S. F. Martin, *Synthesis* 633 (1979).
[89]S. F. Martin and G. W. Phillips, unpublished results.
[90]S. F. Martin and R. Gompper, *J. Org. Chem.* **39**, 2814 (1974).
[91]S. F. Martin, T. S. Chou and C. W. Payne, *Ibid.* **42**, 2520 (1977).
*Note added in proof.* Recent results obtained in other laboratories [N. L. J. M. Broekkof, F. L. Jonkers and A. van der Gen, *Tetrahedron Letters* 2433 (1979) and R. E. Koenigkramer and H. Zimmer, Abstr. 178th National ACS Meeting, Washingon, DC ORGN 67] have indicated that the reaction of carbonyl compounds with phosphonates such as **81** and **82** may not be as straightforward as was originally envisioned. While it is evident that such carbanions add readily to carbonyl compounds, the subsequent elimination to produce the enamines **83** and **84** may not always readily occur. The morpholine enamines **84** were generally partially purified by flash distillation prior to reaction with methyl vinyl ketone (see Ref. 88, p. 645 for details), and the pure enamines could be isolated by fractional distillation. The pyrrolidine enamines **83** could also be isolated, albeit in lower yield, in a similar fashion. It might also be noted that the yields of **85** do not appear to change substantially if the reaction mixture obtained after the addition of **81** to a ketone was heated at reflux prior to the addition of allyl bromide.
[92]S. F. Martin, *Ibid.* **41**, 3337 (1976).
[93]S. F. Martin and T. A. Puckette, *Tetrahedron Letters* 4229 (1978).
[94]S. F. Martin, T. A. Puckette and J. A. Colapret, *J. Org. Chem.* **44**, 3391 (1979).
[95]E. J. Corey and D. L. Boger, *Tetrahedron Letters* **5**, (1978).
[96]E. J. Corey and D. L. Boger, *Ibid.* 9 (1978).
[97]E. J. Corey and D. L. Boger, *Ibid.* 13 (1978).
[98]F. E. Ziegler and P. A. Wender, *J. Org. Chem.* **42**, 2001 (1977).
[99]For a review of the substitution reactions of organo cuprates see G. H. Posner, *Org. Reactions* **22**, 253 (1975).
[100]G. H. Posner and J. J. Sterling, *J. Am. Chem. Soc.* **95**, 3076 (1973).
[101]J. E. Dubois, C. Lion and C. Moulineau, *Tetrahedron Letters* 177 (1971).
[102]E. J. Corey and G. H. Posner, *J. Am. Chem. Soc.* **89**, 3911 (1967).
[103]E. J. Corey and G. H. Posner, *Ibid.* **90**, 5615 (1968).
[104]K. Kitatani, T. Hiyama and H. Nozaki, *Ibid.* **98**, 2362 (1976).

[105]E. Negishi and S. Baba, *Ibid.* **97**, 7385 (1975).
[106]K. Oshima, H. Yamamoto and H. Nozaki, *Bull. Chem. Soc. Jap.* **48**, 1567 (1975).
[107]K. Maruyama and Y. Yamamoto, *J. Am. Chem. Soc.* **99**, 8068 (1977).
[108]D. W. Harney, A. Meisters and T. Mole, *Aus. J. Chem.* **27**, 1639 (1974).
[109]A. Meisters and T. Mole, *Ibid.* **27**, 1655 (1974).
[110]A. Meisters and T. Mole, *Ibid.* **27**, 1665 (1974).
[111]B. L. Buckwalter, I. R. Burfitt, H. Felkin, M. Joly-Goudket, K. Naemura, M. F. Saloman, E. Wenkert and P. M. Wovkulich, *J. Am. Chem. Soc.* **100**, 6445 (1978).
[112]T. H. Chan, I. Paterson and J. Pinsonnault, *Tetrahedron Letters* 4183 (1977).
[113]M. T. Reetz and W. F. Maier, *Angew. Chem.* **90**, 50 (1978); *Ibid.* Internat. Ed. Engl. **17**, 48 (1978). See also M. T. Reetz, I. Chatziiosifidis, U. Löwe and W. F. Maier, *Tetrahedron Letters* 1427 (1979).
[114]M. T. Reetz and K. Schwellnus, *Ibid.* 1455 (1978).
[115a]R. B. Bates, G. Büchi, T. Matsuura and R. R. Shaffer, *J. Am. Chem. Soc.* **82**, 2327 (1960); [b]G. Büchi, W. Hofheinz and J. V. Paukstelis, *Ibid.* **88**, 4113 (1966).
[116]G. Stork and J. F. Cohen, *Ibid.* **96**, 5270 (1974).
[117]A. R. Pinder, S. J. Price and R. M. Rice, *J. Org. Chem.* **37**, 2202 (1972).
[118]A. Alexakis, M. J. Chapdelaine and G. H. Posner, *Tetrahedron Letters* 4209 (1978).
[119]K. Yamada, Y. Kyotani, S. Manabe and M. Suzuki, *Tetrahedron* **35**, 293 (1979).
[120]For a review of nucleophilic acylation see O. W. Lever, Jr., *Ibid.* **32**, 1943 (1976).
[121]W. Nagata, M. Yoshioka and M. Murakami, *J. Am. Chem. Soc.* **94**, 4654 (1972) and Refs. therein.
[122]A. Casares and L. A. Maldonado, *Synth. Commun.* **6**, 11 (1976).
[123]See in B. M. Trost and L. S. Melvin, Jr., *Sulfur Ylides, Emerging Synthetic Intermediates* pp. 79–100. Academic Press, New York, (1975).
[124]F. Rocquet and A. Sevin, *Bull. Soc. Chim. Fr.* **881**, 888 (1974).
[125]G. Büchi and H. Wüest, *Helv. Chim. Acta* **54**, 1767 (1971).
[126]W. G. Dauben, D. J. Hart, J. Ipaktschi and A. P. Kozikowski, *Tetrahedron Letters* 4425 (1973).
[127]S. F. Martin and S. R. Desai, *J. Org. Chem.* **42**, 1664 (1977).
[128a]G. H. Posner, *Org. Reactions* **19**, 1 (1972); [b]H. O. House, *Accts. Chem. Res.* **9**, 59 (1976).
[129]Y. Yamamoto and K. Maruyama, *J. Am. Chem. Soc.* **100**, 3240 (1978).
[130]K. K. Heng and R. A. J. Smith, *Tetrahedron* **35**, 425 (1979).
[131]R. Lohmar and W. Steglich, *Angew. Chem.* **90**, 493 (1978), *Ibid.* Internat. Ed. Engl. **17**, 450 (1978).
[132]G. H. Posner and D. J. Brunelle, *J. Org. Chem.* **38**, 2747 (1973).
[133a]J. A. Sinclair, G. A. Molander and H. C. Brown, *J. Am. Chem. Soc.* **99**, 954 (1977); [b]R. T. Hansen, D. B. Carr and J. Schwartz, *Ibid.* **100**, 2244 (1978).
[134]L. Bagnell, E. A. Jeffery, A. Meisters and T. Mole, *Aust. J. Chem.* **28**, 801 (1975).
[135]A. Hosomi and H. Sakurai, *J. Am. Chem. Soc.* **99**, 1673 (1977). See also A. Hosomi, H. Hashimoto, H. Kobayashi and H. Sakurai. *Chem. Letters* 245 (1979).
[136]K. Narasaka, K. Soai and T. Mukaiyama, *Ibid.* 1223 (1974).
[137]K. Saigo, M. Osaki and T. Mukaiyama, *Ibid.* 163 (1976).
[138a]For reviews see W. S. Johnson, *Accts. Chem. Res.* **1**, 1 (1968); [b]W. S. Johnson, *Bioorgan. Chem.* **5**, 51 (1976).
[139]P. A. Stadler, A. Eschenmoser, H. Schinz and G. Stork, *Helv. Chim. Acta* **40**, 2191 (1957); and Refs. therein.
[140]J. L. Cooper and K. E. Harding, *Tetrahedron Letters* 3321 (1977).
[141a]E. Huq, M. Mellor, E. G. Scovell and J. K. Sutherland, *J. Chem. Soc.* Chem. Commun. 526 (1978); [b]M. Mellor, A. Santos, E. G. Scovell and J. K. Sutherland, *Ibid.* 528 (1978).
[142]R. S. Brinkmeyer, *Tetrahedron Letters* 207 (1979).
[143]K. E. Harding, J. C. Cooper and P. M. Puckett, *J. Am. Chem. Soc.* **100**, 993 (1978).
[144]W. S. Johnson, L. R. Hughes, J. A. Kloek, T. Niem and A. Shenvi *Ibid.* **101**, 1279 (1979).
[145]M. B. Gravestock, W. S. Johnson, B. E. McCarry, R. J. Parry and B. E. Ratcliffe, *Ibid.* **100**, 4274 (1978).
[146]For a review of chloro-olefin annelation see: P. T. Lansbury, *Accts. Chem. Res.* **5**, 311 (1972).
[147]T. Hiyama, M. Shinoda and H. Nozaki, *J. Am. Chem. Soc.* **101**, 1599 (1979).
[148]P. Ceccherelli, M. Tingoli, M. Curini and R. Pellicciari, *Tetrahedron Letters* 4959 (1978).
[149a]I. A. Blair, A. Ellis, D. W. Johnson and L. N. Mander, *Aust. J. Chem.* **31**, 405 (1978) and Refs. therein; [b]L. N. Mander and S. G. Pyne, *J. Am. Chem. Soc.* **101**, 3373 (1979).
[150]U. R. Ghatak, S. K. Alam and J. K. Ray, *J. Org. Chem.* **43**, 4598 (1978).
[151]H. C. Beyerman, J. van Berkel, T. S. Lie, L. Maat, J. C. M. Wessels, H. H. Bosman, E. Buurman, E. J. M. Bijsterveld and H. J. M. Sinnige, *Recl. Trav. Chim. Pays Bas.* **97**, 127 (1978).
[152]Y. Ito, T. Konoike, T. Harada and T. Saegusa, *J. Am. Chem. Soc.* **99**, 1487 (1977).
[153]Y. Ito, T. Konoike and T. Saegusa *Ibid.* **97**, 649 (1975).
[154]M. Tokuda, T. Shigei and M. Itoh, *Chem. Letters* 621 (1975).
[155]J. Brocksom, N. Petragnani, R. Rodrigues and H. LaScala Teixeira, *Synthesis* 396 (1975).
[156]C. Chassin, E. A. Schmidt and H. M. R. Hoffmann, *J. Am. Chem. Soc.* **96**, 606 (1974).
[157]C. Fouquey and J. Jacques, *Synthesis* 306 (1971).
[158a]*Oxidative Coupling of Phenols* (Edited by W. I. Taylor and A. R. Battersby). Marcel Dekker, New York (1967); [b]A. I. Scott, *Quart. Rev.* **19**, 1 (1965).
[159]T. Kametani and K. Fukumoto, *J. Heterocyclic Chem.* **8**, 341 (1971); *Synthesis*, 657 (1972).
[160]M. A. Schwartz and R. A. Holton, *J. Am. Chem. Soc.* **92**, 1090 (1970).
[161]M. A. Schwartz, B. F. Rose, R. A. Holton, S. W. Scott and B. Vishnuvajjala, *Ibid.* **99**, 2571 (1977).
[162]M. A. Schwartz and I. S. Mami, *Ibid.* **97**, 1239 (1975).
[163]E. Kotani, N. Takeuchi and S. Tobinaga, *Tetrahedron Letters* 2735 (1973).
[164]T. Kametani, K. Yamaki, H. Yagi and K. Fukumoto, *J. Chem. Soc.* (C) 2602 (1969).
[165]M. A. Schwartz, B. F. Rose and B. Vishnuvajjala, *J. Am. Chem. Soc.* **95**, 612 (1973).
[166]K. Tomoika, K. Koga and S. Yamada, *Chem. Pharm. Bull.* **25**, 2681 (1977).
[167]S. M. Kupchan, O. P. Dhingra and C. K. Kim, *J. Org. Chem.* **43**, 4076 (1978).
[168]S. M. Kupchan, O. P. Dhingra, C. K. Kim and U. Kameswaran, *Ibid.* **43**, 2521 (1978).

[169]E. Kotani, N. Takeuchi and S. Tobinaga, *J. Chem. Soc.* Chem. Commun. 550 (1973).
[170]L. L. Miller, R. F. Stewart, J. P. Gillespie, V. Ramachandran, Y. H. So and F. R. Stermitz, *J. Org. Chem.* 43, 1580 (1978); and Refs. cited.
[171]T. Kametani and K. Fukumoto, *Accts. Chem. Res.* 5, 212 (1972).
[172]A. P. Krapcho, *Synthesis* 425 (1976).
[173]C. J. Collins, *Quart. Rev.* 14, 357 (1960).
[174]P. A. S. Smith and D. R. Baer, *Org. Reactions* 11, 157 (1960).
[175]A. S. Kende, *Org. Reactions* 11, 261, (1960); A. A. Akhrem. T. K. Ustynyuk and Y. A. Titov, *Russ. Chem. Rev.* 39, 732 (1970).
[176]S. A. Monti and S. -C. Chen, *J. Org. Chem.* 44, 1170 (1979).
[177]K. E. Harding and J. W. Trotter, *Ibid.* 42, 4157 (1977).
[178]D. A. Evans, C. L. Sims and G. C. Andrews, *J. Am. Chem. Soc.* 99, 5453 (1977). However, for several examples in which the [2,3] sigmatropic rearrangement proceeds with only a slight degree of stereoselectivity see T. Nakai and Mikami, *Chem. Letters* 1081 (1979).
[179]B. M. Trost, M. J. Bogdanowicz and J. Kern, *Ibid.* 97, 2218 (1975).
[180]B. M. Trost, M. Preckel and L. M. Leichter, *Ibid.* 97, 2224 (1975).
[181]B. M. Trost, *Accts. Chem. Res.* 7, 85 (1974).
[182]B. M. Trost, D. E. Keeley, H. C. Arndt, J. H. Rigby and M. J. Bogdanowicz, *J. Am. Chem. Soc.* 99, 3080 (1977).
[183]B. M. Trost, D. E. Keeley, H. C. Arndt and M. J. Bogdanowicz, *Ibid.* 99, 3088 (1977).
[184]B. M. Trost and P. H. Scudder, *Ibid.* 99, 7601 (1977).
[185]B. M. Trost, K. Hiroi and N. Holy, *Ibid.* 97, 5873 (1975).
[186]B. M. Trost and J. H. Rigby, *J. Org. Chem.* 43, 2938 (1978).
[187]B. M. Trost and L. H. Latimer, *Ibid.* 43, 1031 (1978).
[188]E. Piers, C. K. Lau and I. Nagakura, *Tetrahedron Letters* 3233 (1976) and Refs. therein.
[189]L. N. Mander and J. V. Turner, *J. Org. Chem.* 38, 2915 (1973).
[190]D. Michelot, R. Lorne, C. Huynh and S. Julia, *Bull Soc. Chim. Fr.* (2) 1482 (1976) and Refs. therein.
[191a]J. E. Baldwin, J. DeBarnadis and J. E. Patrick, *Tetrahedron Letters* 353 (1970); [b]V. Rautenstrauch, *Chem. Commun.* 4 (1970).
[192]B. Cazes and S. Julia, *Bull Soc. Chim. Fr.* (2) 925, 931 (1977).
[193]E. Hunt and B. Lythgoe, *J. Chem. Soc*, Chem. Commun, 757 (1972).
[194]J. E. Baldwin and R. Tzodikov, *J. Org. Chem.* 42, 1878 (1977).
[195]C. Huynh, V. Ratovelomanana and S. Julia, *Bull. Soc. Chim. Fr.* (2) 710 (1977).
[196]For a review see S. J. Rhodes and N. R. Raulins, *Org. Reactions* 22, 1 (1975).
[197]For a review see [a]F. E. Ziegler, *Accts. Chem. Res.* 10, 227 (1977); [b]G. B. Bennett, *Synthesis* 589 (1977); and [c]E. Winterfeldt, *Fortschr. Chem. Forsch.* 16, 75 (1970).
[198a]T. C. Jain, C. M. Banks and J. E. McCloskey, *Tetrahedron Letters* 841 (1970); [b]P. A. Grieco and M. Nishizawa, *J. Org. Chem.* 42, 1717 (1977).
[199]J. P. Marino and L. J. Browne, *Tetrahedron Letters* 3241, 3245 (1976).
[200a]P. A. Wender and M. P. Filosa, *J. Org. Chem.* 41, 3490 (1976); [b]P. A. Wender, M. A. Eissenstat and M. P. Filosa, *J. Am. Chem. Soc.* 101, 2196 (1979).
[201]E. Piers and I. Nagakura, *Tetrahedron Letters* 3237 (1976).
[202a]E. Piers, I. Nagakura and H. E. Morton, *J. Org. Chem.* 43, 3630 (1978); [b]E. Piers and E. H. Ruediger, *J. Chem. Soc. Chem. Commun.* 166 (1979).
[203]F. E. Ziegler and J. J. Piwinski, *J. Am. Chem. Soc.* 101, 1611 (1979).
[204]J. E. McMurry, A. Andrus, G. M. Ksander, J. H. Musser and M. A. Johnson, *Ibid.* 101, 1330 (1979).
[205]D. J. Dawson and R. E. Ireland, *Tetrahedron Letters* 1899 (1968).
[206]H. Muxfeldt, R. S. Schneider and J. B. Mooberry, *J. Am. Chem. Soc.* 88, 3670 (1966).
[207]H. F. Strauss and A. Wiechers, *Tetrahedron* 34, 127 (1978).
[208]F. E. Ziegler and G. B. Bennett, *J. Am. Chem. Soc.* 93, 5930 (1971).
[209a]C. B. Chapleo, P. Hallett, B. Lythgoe, I. Waterhouse and P. W. Wright, *J. Chem. Soc.* Perkin I, 1211, (1977); [b]R. J. Cove, B. Lythgoe, D. A. Metcalfe and I. Waterhouse, *Ibid.* 1218 (1977).
[210]R. E. Ireland, R. H. Mueller and A. K. Willard, *J. Am. Chem. Soc.* 98, 2868 (1976).
[211]W. C. Still and M. J. Schneider, *Ibid.* 99, 948 (1977).
[212]J. E. Baldwin and J. A. Walker, *J. Chem. Soc.* Chem. Commun. 117 (1973).
[213]H. O. House, J. Lubinkowski and J. J. Good, *J. Org. Chem.* 40, 86 (1975).
[214]P. M. McCurry, Jr. and R. K. Singh, *Tetrahedron Letters* 3325 (1973).
[215]R. K. Hill and H. N. Khatri, *Ibid.* 4337 (1978). and Refs. therein.
[216]E. J. Corey and J. I. Shulman, *J. Am. Chem. Soc.* 92, 5522 (1970).
[217]For reviews see [a]W. Oppolzer and V. Snieckus, *Angew, Chem.* 90, 506 (1978); Internat. Ed. Engl., 17, 476 (1978); [b]J. M. Conia and P. LePerchec, *Synthesis* 1 (1975).
[218]W. Oppolzer, K. K. Mahalanabis and K. Battig, *Helv. Chim. Acta* 60, 2388 (1977).
[219]F. Leyendecker, J. Drouin and J. M. Conia, *Tetrahedron Letters* 2931 (1974).
[220a]J. A. Marshall and P. C. Johnson, *J. Org. Chem.* 35, 192 (1970); [b]P. J. Kropp, *J. Am. Chem. Soc.* 87, 3914 (1965).
[221]A. G. Schultz and I. C. Chiu, *J. Chem. Soc.* Chem. Commun. 29 (1978).
[222]A. G. Schultz, R. D. Lucci, W. Y. Fu, M. H. Berger, J. Erhardt and W. K. Hagmann, *J. Am. Chem. Soc.* 100, 2150 (1978).
[223]A. G. Schultz, Y. K. Yee and M. H. Berger, *J. Am. Chem. Soc.* 99, 8065 (1977).
[224]A. G. Schultz, W. Y. Fu, R. D. Lucci, B. G. Kurr, K. M. Lo and M. Boxer, *Ibid.* 100, 2140 (1978)
[225]See in W. Kirmse, *Carbene Chemistry*, (2nd Edn.) pp. 85–128, 267–362. Academic Press, New York. (1971).
[226]R. E. Ireland, D. R. Marshall and J. W. Tilley, *J. Am. Chem. Soc.* 92, 4754 (1970).
[227]E. Wenkert, D. A. Berges and N. F. Golob, *Ibid.* 100, 1263 (1978) and Refs. therein.
[228]E. Wenkert, B. L. Buckwalter, A. A. Craveiro, E. L. Sanchez and S. S. Sathe, *Ibid.* 100, 1267 (1978).
[229]D. J. Beames, J. A. Halleday and L. N. Mander, *Aust. J. Chem.* 25, 137 (1972).
[230]J. F. Ruppert, M. A. Avery and J. D. White, *J. Chem. Soc.* Chem. Commun. 978 (1976).
[231]J. J. Sims and V. K. Honwad, *J. Org. Chem.* 34, 496 (1969).
[232]P. Deslongchamps, J. Lafontaine, L. Ruest and P. Soucy, *Can. J. Chem.* 55, 4117 (1977).
[233a]T. Norin, *Acta Chem. Scand.* 19, 1289 (1965); [b]W. G. Dauben and R. E. Wolf, *J. Org. Chem.* 35, 2361 (1970) and Refs. therein.
[234]For reviews of the synthetic applications of photochemical cycloadditions see [a]P. G. Bauslaugh, *Synthesis* 287 (1970); [b]H. Meier,

*Houben-Weyl, Methoden der Organischen Chemie* (Edited by E. Muller), Vol. 4/5b, pp. 898–941. Georg Thieme Verlag, Stuttgart (1975).
[235]S. W. Baldwin and R. E. Gawley, *Tetrahedron Letters* 3969 (1975).
[236]S. W. Baldwin, R. E. Gawley, R. J. Doll and K. H. Leung, *J. Org. Chem.* **40**, 1865 (1975) and Refs. therein.
[237]K. Wiesner, V. Musil and K. J. Wiesner, *Tetrahedron Letters* 5643 (1968).
[238]K. Wiesner, P. -T. Ho, W. -C. Liu and M. N. Shanbhag, *Can. J. Chem.* **53**, 2140 (1975).
[239]K. Wiesner, S. Uyeo, A. Philipp and Z. Valenta, *Tetrahedron Letters* 6279 (1968).
[240]P. A. Wender and J. C. Lechleiter, *J. Am. Chem. Soc.* **100**, 4321 (1978). See also G. L. Lange and F. C. McCarthy, *Tetrahedron Letters* 4749 (1978).
[240a]M. C. Pirrung, *J. Am. Chem. Soc.* **101**, 7130 (1979).
[241]Y. Hayakawa, K. Yokoyama and R. Noyori, *J. Am. Chem. Soc.* **100**, 1791 (1978).
[242]Y. Hayakawa, K. Yokoyama and R. Noyori, *Ibid.* **100**, 1799 (1978).
[243]Y. Hayakawa, F. Shimizu and R. Noyori, *Tetrahedron Letters* 993 (1978).
[244]For reviews see [a]A. S. Onischenko, *Diene Synthesis*. Davey, New York (1964); [b]W. Carruthers, *Some Modern Methods of Organic Synthesis*, (2nd Edn.), Cambridge University Press (1978); and Refs. therein.
[245]W. Oppolzer, *Angew. Chem.* **89**, 10 (1977); *Angew. Chem.* Internat. Ed. Engl., **16**, 10 (1977).
[246]E. J. Corey, R. L. Danheiser, S. Chandrasekaran, P. Siret, G. E. Keck and J. -L. Gras, *J. Am. Chem. Soc.* **100**, 8031 (1978).
[247]T. Harayama, M. Ohtani, M. Oki and Y. Inubushi, *J. Chem. Soc.* Chem. Commun. 827 (1974); *Chem. Pharm. Bull.* **21**, 25, 1061 (1973).
[248]L. E. Overman and P. J. Jessup, *J. Am. Chem. Soc.* **100**, 5179 (1978); and Refs. therein.
[249]B. M. Trost, S. A. Godleski and J. Ippen, *J. Org. Chem.* **43**, 4559 (1978).
[250a]S. Danishefsky and T. Kitahara, *J. Am. Chem. Soc.* **96**, 7807 (1974); [b]S. Danishefsky, C. F. Yan and P. M. McCurry, Jr., *J. Org. Chem.* **42**, 1819 (1977); [c]S. Danishefsky, R. K. Singh and R. B. Gammill, *Ibid.* **43**, 379 (1978).
[251]S. Danishefsky, P. F. Schuda, T. Kitahara and S. J. Etheredge, *J. Am. Chem. Soc.* **99**, 6066 (1977).
[252]S. Danishefsky, R. K. Singh and T. Harayama *Ibid.* **99**, 5810 (1977).
[253]S. Danishefsky and S. J. Etheredge, unpublished results.
[254]For example see in G. H. Posner and C. M. Lentz, *J. Am. Chem. Soc.* **101**, 934 (1979) and Refs. therein.
[255]K. P. Dastur, *Ibid.* **96**, 2605 (1974) and Refs. therein.
[256]A. J. Birch and B. McKague, *Aust. J. Chem.* **23**, 341 (1970).
[257]S. A. Monti, S. -C. Chen, Y. -L. Yang, S. -S. Yuan and O. P. Bourgeois, *J. Org. Chem.* **43**, 4062 (1978).
[258]S. A. Monti and Y. L. Yang. *Ibid.* **44**, 897 (1979).
[259]For other routes to bicyclo [3.2.1] octanes from bicyclo [2.2.2] octanes see: [a]Y. Yamada, H. Nagaska and M. Kimura, *Synthesis* 581 (1977); [b]K. S. Atwal, R. Marinibettolo, I. H. Sanchez, T. Y. R. Tsai and K. Wiesner, *Can. J. Chem.* **56**, 1102 (1978).
[260]D. A. Evans, C. A. Bryan and C. L. Sims, *J. Am. Chem. Soc.* **94**, 2891 (1972).
[261]G. Buchi, A. Hauser and J. Limacher, *J. Org. Chem.* **42**, 3323 (1977).
[262]H. Yamamoto and H. L. Sham. *J. Am. Chem. Soc.* **101**, 1609 (1979).
[263]W. Oppolzer and R. L. Snowden, *Tetrahedron Letters* 3505 (1978); See also F. Näf and G. Ohloff, *Helv. Chim. Acta.* **57**, 1868 (1974).
[264]F. Näf, R. Decorzant and W. Thommen, *Ibid.* **62**, 114 (1979).
[265]S. R. Wilson and D. T. Mao, *J. Am. Chem. Soc.* **100**, 6289 (1978).
[266]T. Kametani, K. Suzuki, H. Nemoto and K. Fukumoto, *J. Org. Chem.* **44**, 1036 (1979).
[267]S. F. Martin, S. R. Desai and G. W. Phillips, unpublished results.
[268]For another example, see S. F. Martin, T. Chou and C. Tu, *Tetrahedron Letters* 3823 (1979).