Base-Promoted Isomerizations of Epoxides

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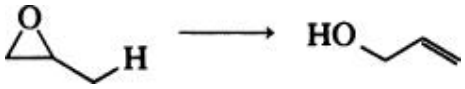
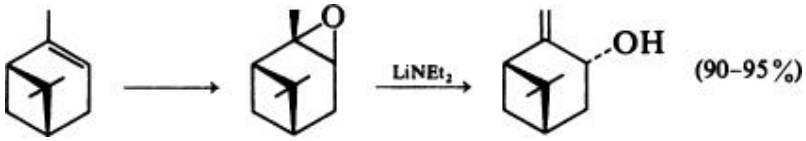
1. Introduction

Epoxides have long enjoyed popularity as synthetic intermediates because of their facile preparation, often with substantial stereochemical control, and their high chemical reactivity, a feature attributable to the ring strain of these small-ring heterocycles. (1, 2) The preponderance of synthetic applications involves nucleophilic opening of the epoxide ring, and an enormous range of nucleophilic species has been utilized for this purpose. (1, 3) The conversion of epoxides to isomeric compounds under the influence of acidic reagents has also been used preparatively for some time. (1) However, it is only relatively recently that such isomerizations have been effected by strong, non-nucleophilic bases such as lithium dialkylamides ($LiNR_2$). This chapter is concerned with the synthetic potential of these base-promoted reactions of epoxides. (4, 5)

Although several types of isomeric products are observed on treatment of epoxides with strong bases, the most interesting conversion from a synthetic point of view is the formation of allylic alcohols as indicated by the generalized transformation of Eq. 1. A specific example illustrating the remarkable selectivity often found for these reactions is the isomerization of α -pinene oxide to *trans*-pinocarveol (Eq. 2). (6) This process, coupled with the stereoselective generation of the epoxide by peracid oxidation of α -pinene, converts a simple double bond into an allylic alcohol with both positional and stereochemical control. Isolated early reports (7, 8) on the transformation of Eq. 1 have been followed by extensive studies leading to the definition of the structural features and reaction variables that determine the course of the epoxide to allylic alcohol rearrangement. This subject constitutes the major emphasis of the discussion that follows.

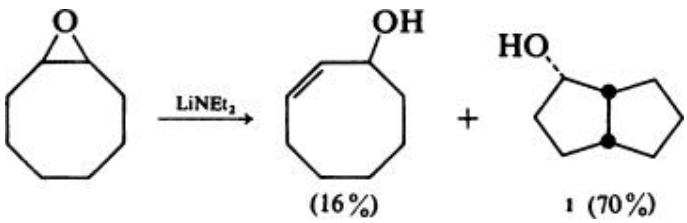


(1)



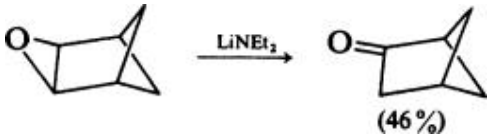
(2)

A second, much less common transformation is typified by the conversion of *cis*-cyclooctene oxide to *endo*-2-bicyclo[3.3.0]octanol (**1**), along with some of the expected allylic alcohol (Eq. 3). (9) This early observation attracted considerable attention because of the unanticipated generation of a new carbon skeleton in the isomerization process and is largely responsible for the subsequent flurry of activity in the area of base isomerization of epoxides.

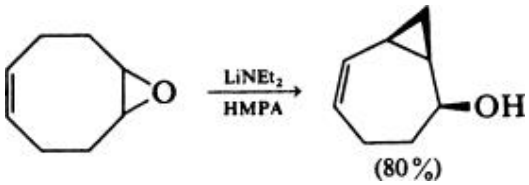


(3)

A third type of conversion also occasionally observed leads to the production of an isomeric carbonyl compound. (10)



The final isomerization pathway included in this survey involves the transformation of epoxides possessing allylic, propargylic, or benzylic methylene groups with a 1,3 relationship to an epoxide carbon into cyclopropylcarbinols by lithium amides in the presence of hexamethylphosphoramide (HMPA). (11)



This review attempts to provide the necessary information for predicting the

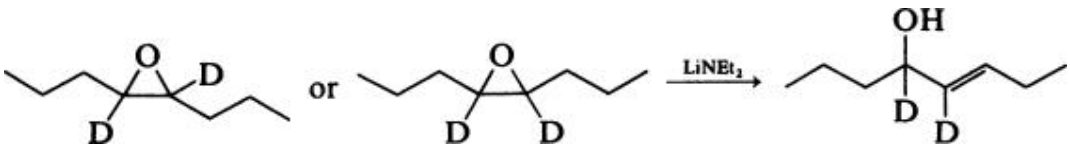
type of isomerization to be expected for a given epoxide under a specified set of conditions and, where possible, for manipulating these conditions to achieve the desired conversions. The survey is limited to the isomerizations of simple epoxides by powerful, relatively non-nucleophilic bases. Thus the significant literature concerning epoxides with proximate carbonyl functions and other anion-stabilizing substituents is not considered since the chemistry of such molecules is typical of the stabilized anions (intramolecular alkylations, Favorskii rearrangements, *etc.*) with the epoxide unit serving the trivial function of a good leaving group. (1, 4, 5) In addition to lithium amides and organolithium reagents, the recently developed dialkylaluminum amides (12) are systematically covered. Studies utilizing non-nucleophilic alkoxides (*e.g.*, potassium *tert*-butoxide), particularly in polar aprotic solvents, are also included. However, the vast literature concerning the interaction of epoxides with metal alkoxides in alcohol solvents is not reviewed since these conditions are generally conducive to nucleophilic addition and are only rarely effective in promoting the epoxide isomerizations of concern in this chapter.

2. Mechanism

Most of the mechanistic information available regarding the title reactions has been deduced from product studies and deuterium-labeling experiments designed to show the site of proton removal by the basic reagents. Little useful kinetic data are available because of the complicated nature of the commonly utilized lithium reagents. These species undoubtedly exist as aggregates, the nature of which is likely to depend strongly on the solvent systems and other reaction conditions. (13, 14) Moreover, the character of these reagents surely changes as the reaction proceeds to generate lithium alkoxides, which can themselves be involved in the aggregation process.

2.1. Allylic Alcohol Formation

The formation of allylic alcohols from the reaction of epoxides with lithium amide bases in relatively nonpolar solvents appears to proceed predominately, if not exclusively, by a β -elimination pathway. This is shown most clearly in a study of the isomerization of *cis*- and *trans*-4,5-epoxyoctanes labeled with deuterium at the two ring carbons (Eq. 4). (15) The allylic alcohol product retains almost all of the deuterium label, thereby demonstrating that the major pathway to product does not involve attack of base at a ring proton. The only reasonable mechanistic alternative consistent with this observation invokes proton removal from an adjacent carbon center (β elimination). Similar results are obtained with an appropriately deuterated *cis*-epoxycyclodecane (Eq. 5). (16) It has been noted that the loss of a small amount of the label in these experiments is consistent with a competing route to the allylic alcohol that proceeds by ring metalation, followed by α elimination and rearrangement of the resulting carbenoid species. This mechanism is illustrated in Eq. 6 for *cis*-epoxycyclodecane. However, the observation that unlabeled *cis*-epoxycyclodecane incorporates deuterium in the presence of lithium diethylamide and diethylamine-*N*-d_1 strongly suggests that the loss of label arises from reversible metalation of the epoxide ring in a process that is unrelated to its rearrangement to allylic alcohol. (16) Other instances of the reversible metalation at an epoxide ring under the conditions of the rearrangement are known. (17-20) Thus, whereas an α -elimination route to allylic alcohol cannot be excluded as a minor mechanistic contribution, this pathway has yet to be conclusively demonstrated. Consequently, a β -elimination mechanism is assumed for much of the discussion concerning allylic alcohol formation.



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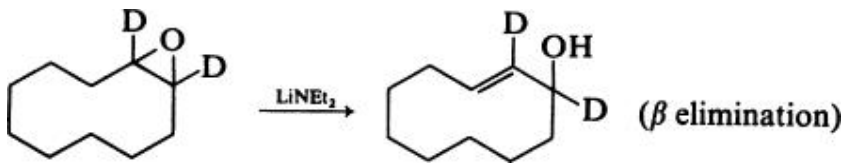

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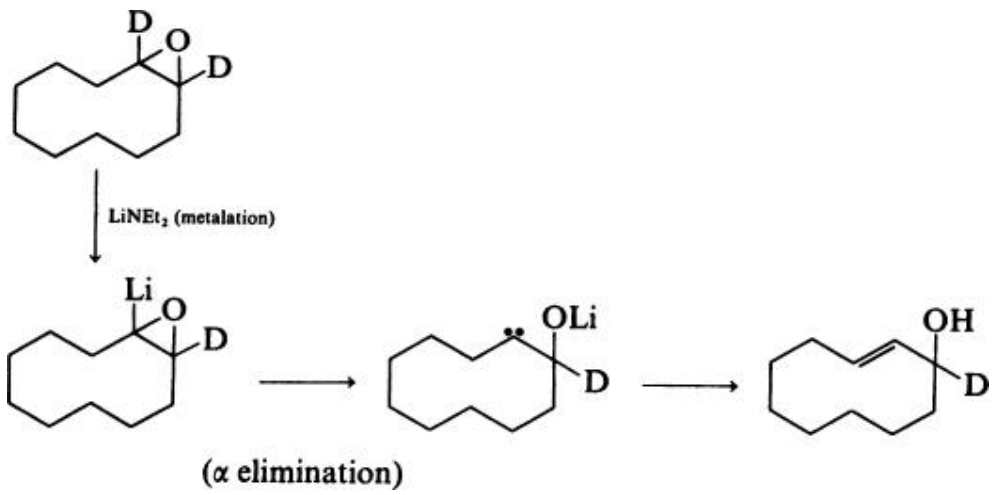
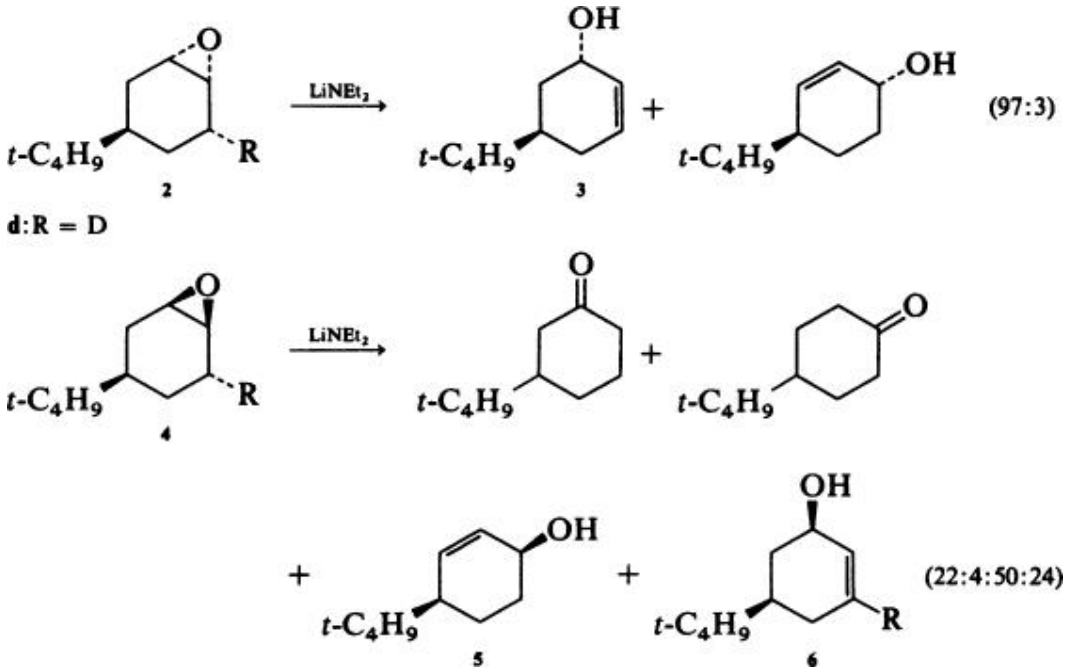
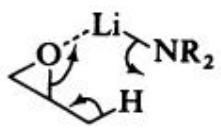


(6)

A second, crucial mechanistic point concerns the stereochemistry of the β -elimination process. This has been shown to proceed by *syn* elimination in the isomerizations of *cis*- and *trans*-4-*tert*-butylepoxycyclohexanes by lithium diethylamide. (21) The *trans* isomer **2** reacts more readily and yields only allylic alcohol products with a high degree of regioselectivity for **3**. A rather complicated deuterium-labeling experiment demonstrates that epoxide **2d** is transformed to alcohol **3** with loss of deuterium. (17) Thus the proton *syn* to the epoxide function is preferentially abstracted by the base. The more slowly reacting *cis* epoxide **4** yields considerable amounts of two cyclohexanone products and, furthermore, shows little regioselectivity in its transformation to allylic alcohols **5** and **6**. Nonetheless, labeled epoxide **4d** gives alcohol **6d** with retention of the deuterium label, indicating that *syn* elimination is also operative in this transformation.



The hypothesis that reaction occurs from a complex of the epoxide with the lithium amide reagent is extremely useful in rationalization of these results and many others discussed in this chapter. Coordination of an oxygen lone pair with an electron-deficient lithium center of the reagent gives a species whose essential features are represented by structure **7**. (The lithium amide reagent is depicted here as monomeric for simplicity, although more than one base unit may actually be involved.) Decomposition of complex **7** in a cyclic, concerted manner provides a reasonable route to allylic alcohol products. Such a process requires the removal of a *syn* hydrogen in cyclic systems such as the rigid epoxycyclohexanes **2** and **4** discussed above. Furthermore, stereoelectronic considerations suggest that β elimination should be facilitated by the availability of a conformation that permits bond reorganization to occur with a maximum of orbital overlap and a minimum of molecular deformation in the transition from reactant to product. This is achieved best from a conformation in which the more acute dihedral angle of the epoxide ring subtends the dihedral angle of the adjacent proton-bearing carbon in the fashion indicated by the Newman projection structure **8**. This situation obtains for removal of a *syn* quasi-axial proton in a half-chair conformation of epoxycyclohexane, but not for abstraction of a *syn* quasi-equatorial hydrogen. This line of reasoning explains the regio selectivity found for the *trans* epoxide **2**, since base removal of the *syn* quasi-axial proton at C_6 in the favored half-chair conformation (equatorial *tert*-butyl group) leads to the predominant allylic alcohol **3** as illustrated by structure **9**.



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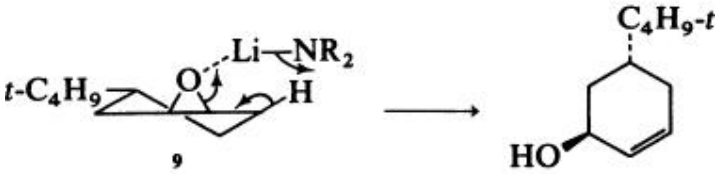

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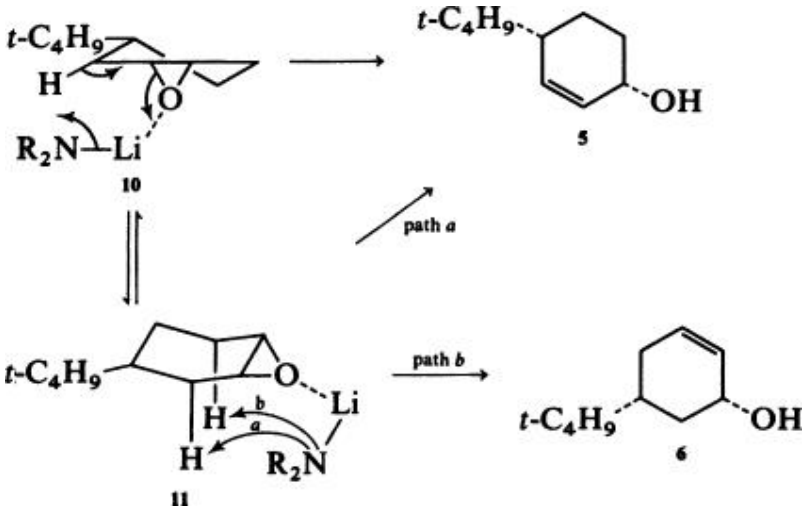
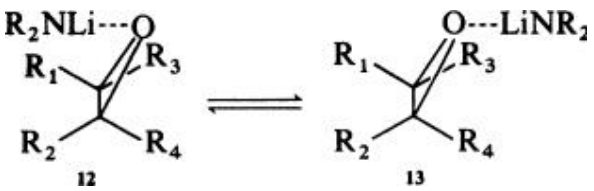
According to these arguments, the *cis* epoxide **4** should react by removal of the quasi-axial hydrogen at C_3 as shown in **10** and, indeed, the appropriate alcohol **5** is the major product from this epoxide. However, the sluggishness of this reaction suggests that the nearby *tert*-butyl group provides some steric hindrance to this process, allowing the formation of other products in significant quantities. The *syn* elimination leading to the isomeric allylic alcohol **6** most probably proceeds by way of the accessible half-boat conformation **11**, thus satisfying the stereoelectronic requirements. This conformation can also give alcohol **5** since both adjacent *syn* hydrogens have the appropriate relationship to the epoxide ring. Alternatively, product **6** could arise by *syn* elimination of a quasi-equatorial hydrogen atom from the energetically more favorable half-chair conformation; steric interference by the *tert*-butyl group hinders the otherwise favorable abstraction to yield **5**.

The proposed involvement of epoxide–base complexes in epoxide isomerizations is also useful in understanding some of the other propensities of these



reactions. In general, a given epoxide can give rise to two isomeric complexes, depending on which lone pair of the oxygen is used as the donor site. This is depicted by structures **12** and **13**. The relative stabilities of these complexes are largely determined by steric interactions between the base moiety and the *syn* substituents. The steric demands of the base are also important in this regard. Furthermore, these features are probably highly influential in determining the activation parameters for subsequent transformations of the complexes. Thus the number and steric bulk of the substituents exert significant control over the competition among potential isomerization pathways.



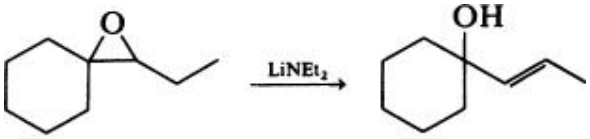
Trisubstituted epoxides (R_1, R_2, R_3 = R; R_4 = H), for example, will normally show a preference for complex **13** in which the base unit is *syn* to the single hydrogen substituent on the epoxide ring. Consequently, in the absence of other overriding effects, β elimination into the alkyl group (R_3) *cis* to the hydrogen is expected to predominate.

A second situation of some importance concerns *cis*-disubstituted epoxides (R_1, R_2 = R; R_3, R_4 = H). In this instance complex **13** with the base situated *anti* to the alkyl substituents is clearly preferred over complex **12**. However, allylic alcohol formation must proceed by way of the less stable complex if the mechanism previously elaborated is operative. Although β elimination is usually observed with this type of epoxide, it is frequently accompanied by formation of other products. This is especially true with epoxycycloalkanes whose carbocyclic rings provide additional steric destabilization of complex **12**. The other products are derived from metalated epoxide intermediates. Metalation presumably occurs from the more stable complex **13** in which the base is held in close proximity to the epoxide hydrogen atoms. Products derived from epoxide metalation are normally observed only with *cis*-disubstituted epoxides, apparently a result of slow β elimination by means of the destabilized complex **12**. Experimental illustrations of these ideas are deferred to the section entitled “Scope and Limitations.”

The concept of a *syn* β elimination from an epoxide–base complex is a useful generalization for describing most epoxide isomerizations. This is particularly

important when lithium amides are used in relatively nonpolar solvents such as hexane or ether. Alkyllithium reagents are used less frequently as bases but appear to behave similarly. The more recently introduced dialkylaluminum amides undoubtedly form complexes with even more avidity and seem to display analogous behavior. (12) However, metal alkoxides in polar, aprotic solvents probably utilize other mechanistic pathways that do not involve complexation to the degree suggested for the other bases. Kinetic studies (22, 23) of several activated epoxides that isomerize to allylic alcohols under the influence of alkoxide bases in hydroxylic solvents seem to indicate typical E-2 elimination reactions. (24, 25) Likewise, the use of more polar solvents or additives such as hexamethyl-phosphoramide profoundly influence certain reactions with lithium amides in a manner suggestive of mechanistic change. (26, 27) The ability of hexamethyl-phosphoramide to break up the base aggregates and coordinate with the electrophilic lithium species surely precludes significant association with weakly basic epoxides under these conditions. (28)

An important feature of the β -elimination reactions is the very high degree of stereoselectivity for the *trans* double-bond isomer of the allylic alcohol product. This is again illustrated most conclusively with the *cis*- and *trans*-4,5-epoxyoctanes, both of which are transformed by lithium diethylamide into *trans*-oct-5-en-4-ol (Eq. 4, p. 349). (15) The isomeric *cis* alcohol is not formed in detectable quantities in these reactions. Likewise, this reagent converts the spiroepoxide **14** exclusively to the *trans* allylic alcohol **15**. (29) Similarly, both *n*-butyllithium (30) and diethylaluminum 2,2,6,6-tetramethylpiperidide (DATMP) (31, 32) promote the conversion of either *cis*- or *trans*-epoxycyclododecane to the corresponding *trans* allylic alcohol. Of course, the *cis* isomer is formed exclusively when the double bond is endocyclic to an eight-membered or smaller ring. However, *trans*-cyclodec-2-en-1-ol is apparently the major allylic alcohol derived from *cis*- and *trans*-epoxycyclodecanes (Eq. 5). (33)



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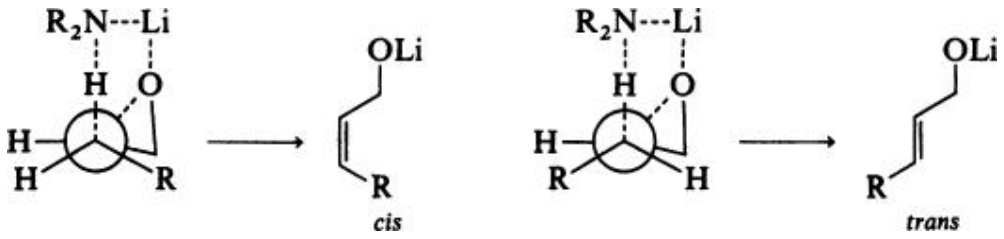
The distinct propensity for formation of a *trans* double bond in conformationally unrestricted systems appears to be a result of the *syn*-elimination mechanism. Thus extensive studies on a wide variety of elimination reactions show that the production of *trans* double bonds is generally associated with *syn* elimination.

(34)

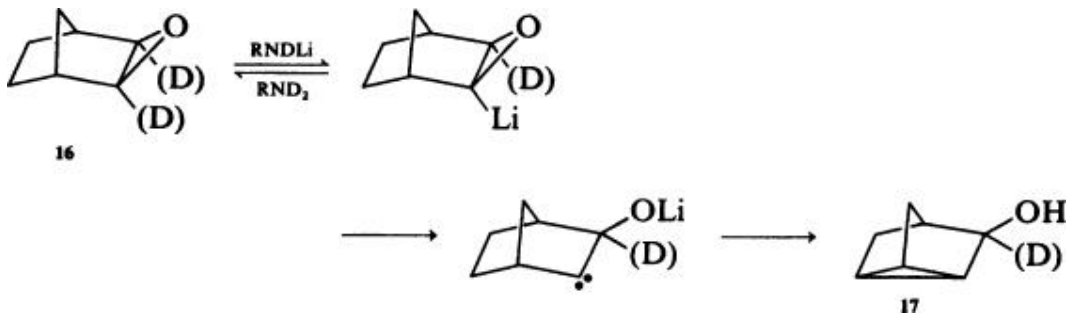
This is understandable in terms of the transition states that lead to the *cis* and *trans* olefins. Clearly, the transition state that yields the *cis* double bond experiences substantial nonbonded interaction involving the side chain R. This is not the case with the transition state that gives the *trans* double bond.



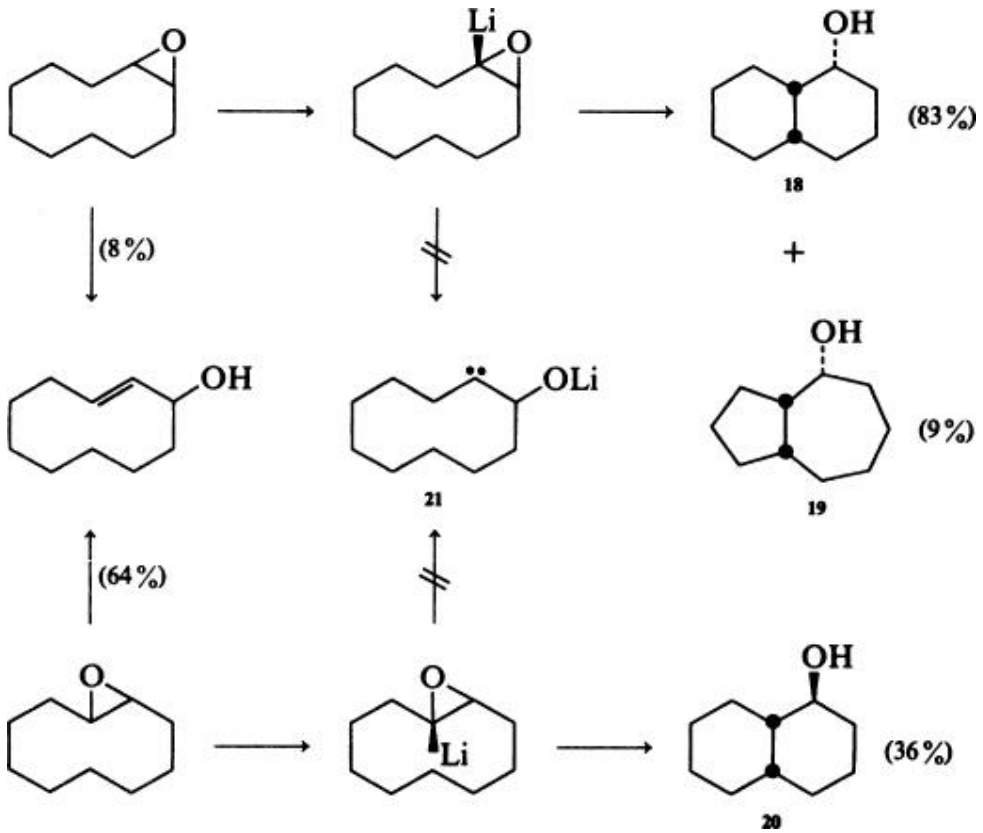
2.2. Cyclic Alcohol Formation

In a number of instances where the β -elimination process is retarded or somehow excluded, a competing cyclization such as that of *cis*-epoxycyclooctane to bicyclic alcohol **1** (Eq. 3) is observed. (9) The available evidence supports a carbenoid mechanism for these reactions. The initial step in these transformations almost certainly involves metalation of the epoxide ring. The corresponding metalated epoxide is thought to undergo α elimination and insertion of the carbenoid center into a neighboring C — H bond.

The reversible metalation of epoxides under typical reaction conditions is supported by several deuterium-labeling studies. (16, 17, 19, 20) Thus the treatment of *exo*-norbornene oxide (**16**) with lithium cyclohexylamide in the presence of an excess of cyclohexylamine-d_2 gives recovered starting material with a very substantial level (83%) of deuterium incorporation. (18) In addition, the concomitantly formed rearrangement product nortricyclanol (**17**) also shows significant label incorporation (69%), specifically at the carbinol center. The lack of appreciable amounts of deuterium elsewhere in alcohol **17** is not consistent with a mechanism triggered by base attack at another site of epoxide **16**, for example, a 1,3 elimination (35) resulting from proton removal from the unfunctionalized two-carbon bridge. The metalation of the epoxide ring most probably takes place within an epoxide–base complex similar to that proposed as an intermediate in β elimination.

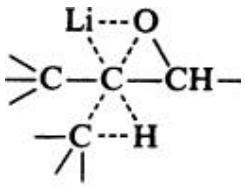


Ample precedent for the postulated carbene insertion process in the norbornane skeleton and, indeed, in many of the other ring systems where this type of cyclization occurs, is available from studies of the analogous unfunctionalized carbenes generated by alternative methods. (36) However, a complication arises with the stepwise mechanism depicted for norbornene oxide when it is applied to a detailed description of the results with the stereoisomeric *cis*- and *trans*-epoxycyclodecanes. (33) In addition to some β -elimination product, the *cis* epoxide gives *endo*-2-*cis*-bicyclo[4.4.0]decanol (**18**) along with a little *endo*-2-*cis*-bicyclo[5.3.0]decanol (**19**), whereas the *trans* epoxide produces *exo*-2-*cis*-bicyclo[4.4.0]decanol (**20**), the epimer of alcohol **18**. Thus, whereas a transannular carbene insertion mechanism satisfactorily accounts for the products from each of the epoxides when taken individually, the stereospecificity of the conversion of the isomeric epoxides to epimeric *cis*-2-bicyclo[4.4.0]decanols



clearly precludes common intermediates, most notably the free carbene species **21**. An analogous situation exists for *cis*- and *trans*-epoxycyclooctanes that stereospecifically produce the epimeric *endo*- and *exo*-2-*cis*-bicyclo[3.3.0] octanols, respectively. (9) Nonetheless, rearrangement of *cis*-epoxycyclodecane labeled with deuterium at both epoxide carbons proceeds with loss of approximately half of the label to give bicyclic alcohols **18** and **19** with the remaining deuterium at the carbinol carbons; (16) these observations complement those on the norbornene oxide rearrangement.

The results can be accommodated within the mechanistic framework shown for the latter process, provided α elimination and C —H insertion are compressed into a single, concerted reaction step. Structure **22** illustrates a hypothetical



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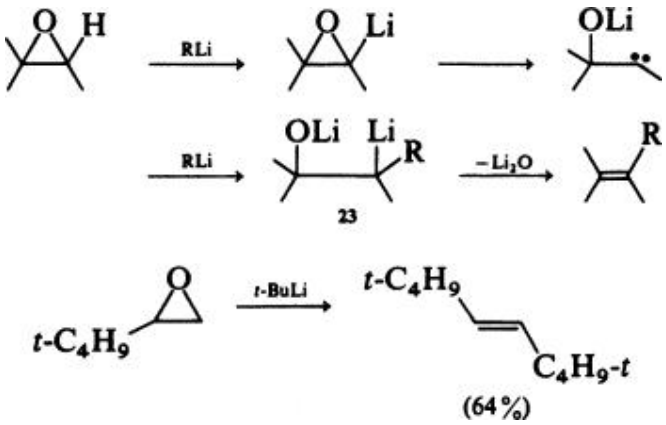
transition state for the rather complicated bonding changes implicit in this one-step process. Such “carbenoid” mechanisms (carbenelike reactions that

do not proceed by way of a free divalent carbon species) have been invoked to rationalize aspects of “carbene” chemistry where the data are inconsistent with a simple carbene intermediate. (37, 38) In the present reaction a concerted α elimination–insertion mechanism allows for the absence of crossover products from epimeric epoxycycloalkanes. It is noteworthy that cyclizations by C — H insertion occur only with epoxides in which the appropriate C — H bond is held in very close proximity to the reactive center by structural features of the molecule. Finally, the stereospecificity of the rearrangements discussed above also demonstrates that the intermediate metalated epoxides are configurationally stable to the usual reaction conditions.

The involvement of carbenes or carbenoid intermediates in the isomerization of epoxides under strongly basic conditions is supported by consideration of a side reaction that occurs on treatment of certain monosubstituted and disubstituted epoxides with alkyllithium reagents. (19, 39, 40) The overall conversion results in transformation of an epoxide into an olefin with concomitant substitution of one of the original ring hydrogen atoms with an alkyl group from the reagent (Eq. 7). A particularly efficient example of this process is the reaction of *tert*-butyllithium with *tert*-butylethylene oxide to yield *trans*-di-*tert*-butylethylene. (40) This unusual reaction has been rationalized by a mechanism proceeding by metalation of the epoxide followed by α elimination and insertion of the carbenoid center into a C — Li bond of the alkyllithium reagent. This generates intermediate **23**, which gives the observed olefin by the loss of lithium oxide. With the monoepoxide of 1,5-hexadiene, this reaction is accompanied by intramolecular trapping of the carbenoid center by the side-chain double bond to give *endo*-2-bicyclo[3.1.0]hexanol (**24**). (39) These observations supplement the evidence for the intervention of carbenoid reactions of epoxides under strongly basic conditions.



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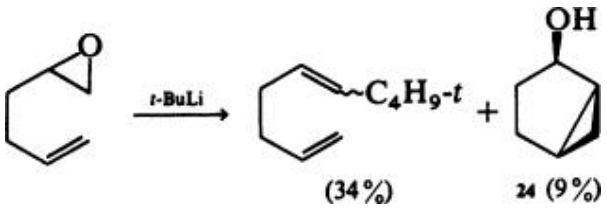
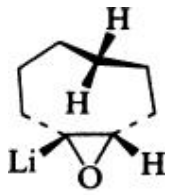
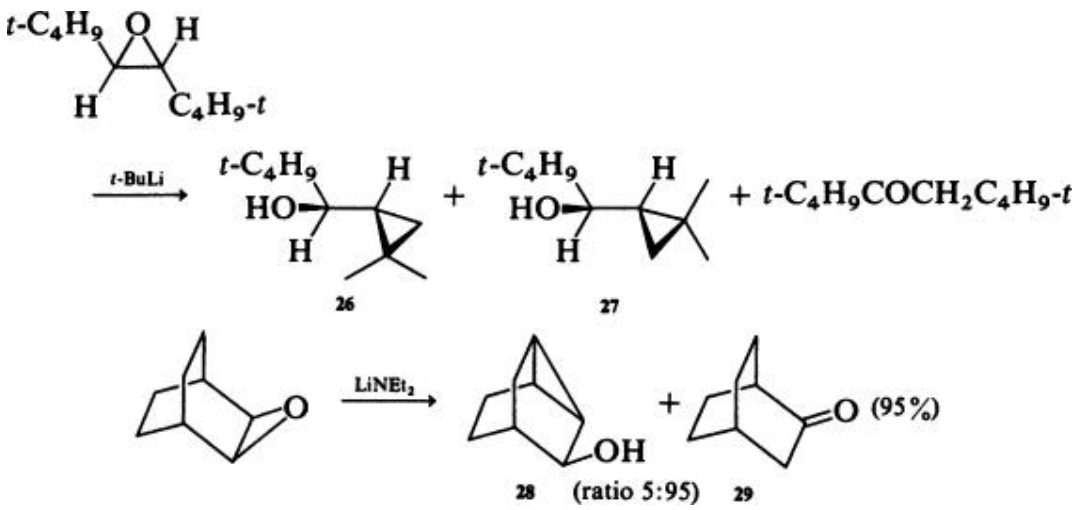


The stereochemical features of the transannular carbenoid reactions of medium-ring epoxycycloalkanes follow from the conformational properties of the metalated epoxide intermediates and the known propensity for retention of configuration in C — H insertions. (36) Thus *cis*-fused bicyclic systems are formed exclusively in these transformations as, indeed, they are in other transannular carbene insertions. (36) This is a result of the relative stabilities of the ring conformations that allow a transannular C — H bond to interact with the carbenoid center. In principle, the C — H group can approach this site in two different fashions termed “backside” and “frontside.” In the former, the C — H approaches the metalated epoxide center from a direction away from the departing oxygen; in the latter, attack is from the oxygen side of the reactive site. If the metalated epoxide moiety is so situated as to minimize steric interaction with the ring residue, the backside mode is clearly favored for these cyclic compounds as illustrated for *cis*-cyclooctene oxide in structure **25**. This defines the stereochemistry of the hydroxyl group, namely, *endo* alcohols from *cis* epoxides and



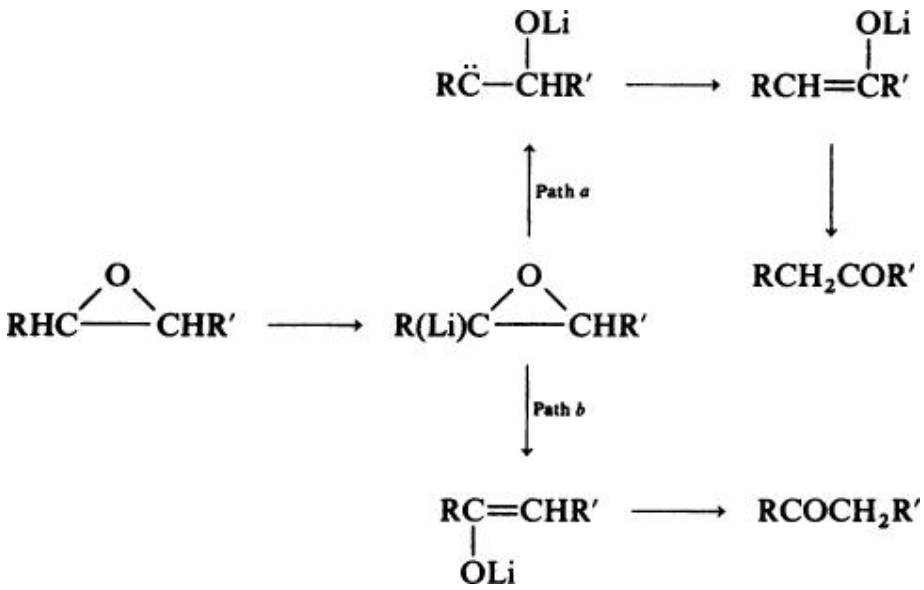
25

exo alcohols from *trans* epoxides. However, backside attack is not inherently favored, but rather is a result of specific structural features of the medium-ring compounds. Thus frontside and backside modes compete in the conversion of the acyclic epoxide *trans*-di-*tert*-butylethylene oxide into the diastereomeric cyclopropylcarbinols **26** and **27**, along with some *tert*-butyl neopentyl ketone. (39) In fact, frontside approach is observed exclusively with 2,3-epoxybicyclo[2.2.2] octane, a structurally unbiased substrate that yields tricyclic alcohol **28** as the only transannular insertion product. The major product from this epoxide is bicyclic ketone **29**. (18)

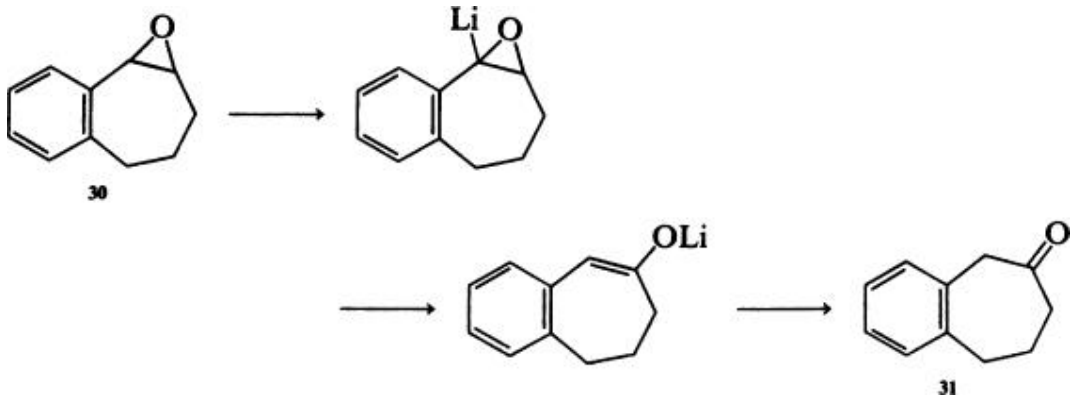


2.3. Ketone Formation

In a number of base isomerizations of epoxides, ketones are generated as primary products. This type of transformation is generally found under circumstances where neither β elimination nor transannular insertion processes are effective. It should be noted that ketones can also arise from further isomerization of allylic alcohols under the reaction conditions. Consequently, it is not always clear whether the observed ketone products are formed directly from the epoxides or are secondary products. However, several unambiguous examples of direct ketone production from epoxides have been cited above. This isomerization is also initiated by metalation of the epoxide ring. Two pathways are considered as reasonable routes to the enolate anions, which are the actual products prior to hydrolysis. The first of these proceeds by α elimination and hydrogen migration from the adjacent ring carbon as illustrated by path *a*. The alternative is an electrocyclic ring opening, sometimes referred to as β *elimination*, which is depicted in path *b*.



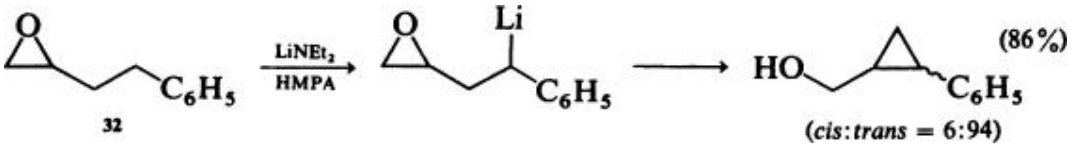
The two mechanisms predict different products when the substituents on the metalated epoxide are not the same. Unfortunately, in most instances of ketone formation there is competitive metalation at the two ring sites, obscuring the relationship between the products and the mechanism. The clean conversion of epoxide **30** to ketone **31** indicates that the α -elimination mechanism occurs in this reaction, if the reasonable assumption of metalation at the benzylic epoxide position is made. (41) In several other instances, more involved arguments can be generated to support this mechanistic possibility. (42-44) At the present time, however, adequate information is not available to enable confident prediction of the mechanism that will be followed for rearrangement of a given epoxide to an isomeric ketone.



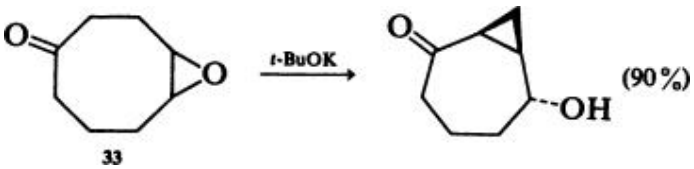
2.4. Formation of Cyclopropyl Carbinols

Relatively few examples of this type of conversion are known and little rigorous mechanistic information is available because of the rather specific structural

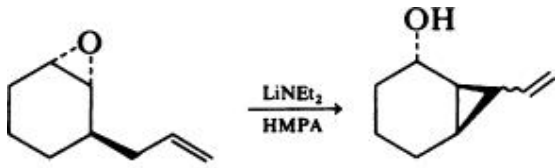
requirements and reaction conditions necessary for such reactions to occur. However, it is most likely that this kind of transformation is not truly an epoxide isomerization since the reactive site appears to be a carbanion generated by proton abstraction from an activated (allylic, benzylic, or propargylic) center. This accounts for the required structural features in the reactant and also the need for hexamethylphosphoramide, which facilitates the metalation process. An appropriately situated epoxide function then alkylates the nucleophilic carbanion in the usual fashion. This mechanism is illustrated for the conversion of the phenyl-activated epoxide **32** to the indicated cyclopropyl carbinols. (11) The high



yield in this reaction is noteworthy, in view of the fact that many monosubstituted epoxides react with lithium amides to give nucleophilic addition to the terminal carbon. The high degree of selectivity for the *trans* product is rationalized on steric grounds. Analogous intramolecular alkylations of enolates and other stabilized carbanions by epoxides are well known as routes to cyclopropanes and larger carbocyclic rings. (4, 5) A relevant example is the reaction of 4,5-epoxycyclooctanone (**33**). (45)



The S_N2-type mechanism with its inherent inversion of configuration at the site of attack on the epoxide ring requires that the reactant be able to achieve an appropriate geometry in cyclic systems. Furthermore, this process defines the stereochemistry of the products. Thus the *trans* isomer of 3-allylepoxycyclohexane (**34**) is smoothly converted to a mixture of alcohols **35** (epimeric at the vinyl group) with a *trans* relationship between the cyclopropyl and hydroxy functions. (11) The corresponding *cis* epoxide gives no cyclopropane product because of the unfavorable geometric relationship between the allyl and epoxide functions that renders an intramolecular alkylation impossible.



34 35

3. Scope and Limitations

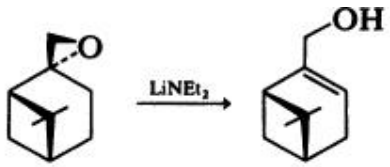
The main focus of this section is on the isomerization of epoxides to allylic alcohols (Eq. 1) as commonly effected by lithium amide bases in relatively nonpolar solvent systems. Other reaction conditions that significantly modify the chemistry taking place are specifically indicated. The discussion is subdivided according to increasing complexity of the epoxide reactant. Thus saturated epoxides are considered first, followed by epoxides possessing unsaturation (double bonds, triple bonds, or aryl groups) and finally, epoxides with other functional groups in the molecule. Departure from this classification occurs in the selection of examples only where the additional functionality has no significant influence on the transformations observed.

3.1. Saturated Epoxides

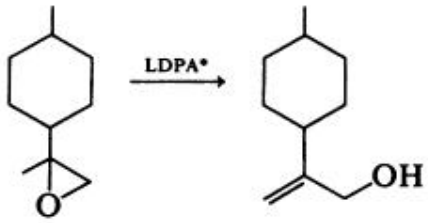
These substrates are considered according to their substitution patterns.

3.1.1.1. Terminal Epoxides

Relatively few examples of the formation of allylic alcohols from epoxides with an unsubstituted ring carbon have been recorded. Nucleophilic additions of the base to these terminal epoxides is expected to be an important competing reaction, and such behavior has been noted. (11, 39, 40, 46, 47) However, epoxides with structural features that sterically retard this side reaction appear to be suitable precursors of allylic alcohols, as illustrated with β -pinene oxide (**36**). (48) The use of more sterically encumbered bases, such as lithium diisopropylamide, shows promise in expanding the range of substrates for epoxide isomerizations to include terminal epoxides. A relevant example is given by the conversion of epoxide **37** to the corresponding primary allylic alcohol. (49) Hindered aluminum amide **38** (diethylaluminum 2,2,6,6-tetramethylpiperidide) is reported to successfully isomerize terminal epoxides such as **39** in several instances. (31, 32) However, organolithium reagents seldom are useful bases for isomerizations of such epoxides because of competing processes. (39, 40, 50) Further work designed to elaborate on the reaction conditions necessary for the synthesis of allylic alcohols from terminal epoxides is clearly warranted.

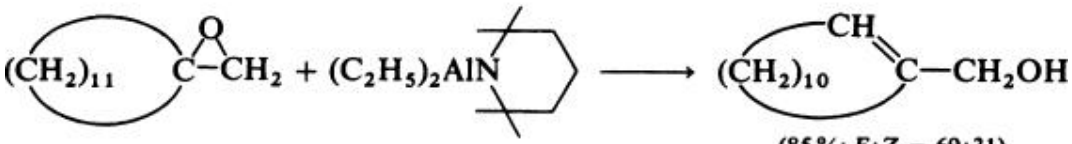


36 (81%)



(64%)

37

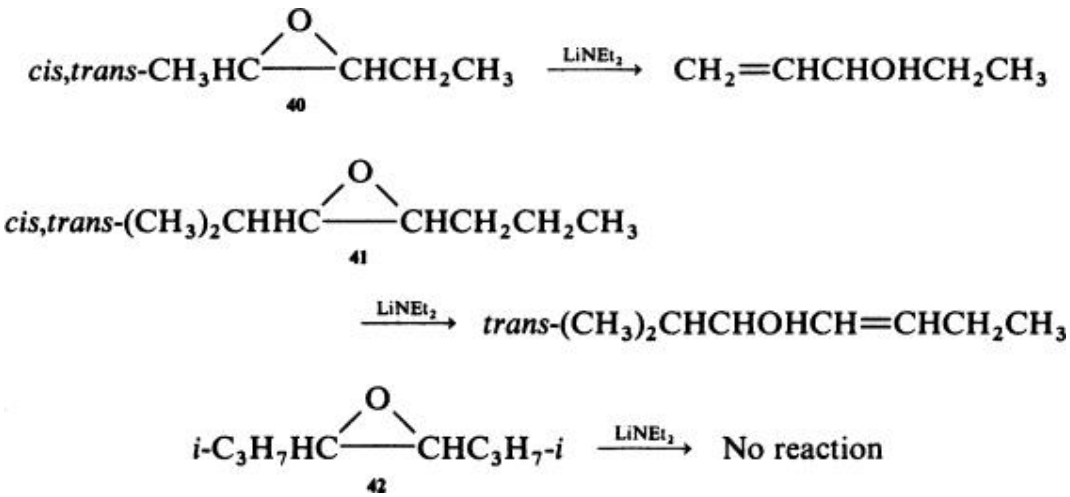


39 38 (DATMP) (85%; *E*:*Z* = 69:31)

3.1.1.2. 2,3-Disubstituted Oxiranes

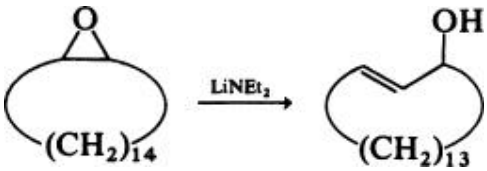
A large number of substrates in this category have been examined, including both acyclic and alicyclic epoxides. The concept of an epoxide–base complex is basic to understanding the significant selectivities observed with these epoxides. The steric requirements of the base moiety exert control over both the competition among the different types of isomerization and the regiochemistry of the β -elimination reaction.

The simple aliphatic epoxides normally undergo clean β elimination with an extraordinary degree of discrimination for proton removal from the least substituted site. (21) Thus both *cis* and *trans* isomers of epoxide **40** suffer base attack at the CH_3 group much more readily than at the CH_2 unit. Likewise, proton abstraction from a CH_2 group is preferred over that from a CH center, as illustrated with epoxide **41**. In each of these cases the indicated conversion is favored by a factor of at least 100 over the alternative mode of β elimination. In fact, removal of a methine proton is ordinarily quite difficult as indicated by the lack of reactivity of epoxide **42**. (29) As discussed previously, removal of a proton from a CH_2 group proceeds with high stereoselectivity for the *trans* allylic alcohol as observed in the isomerization of **41**.



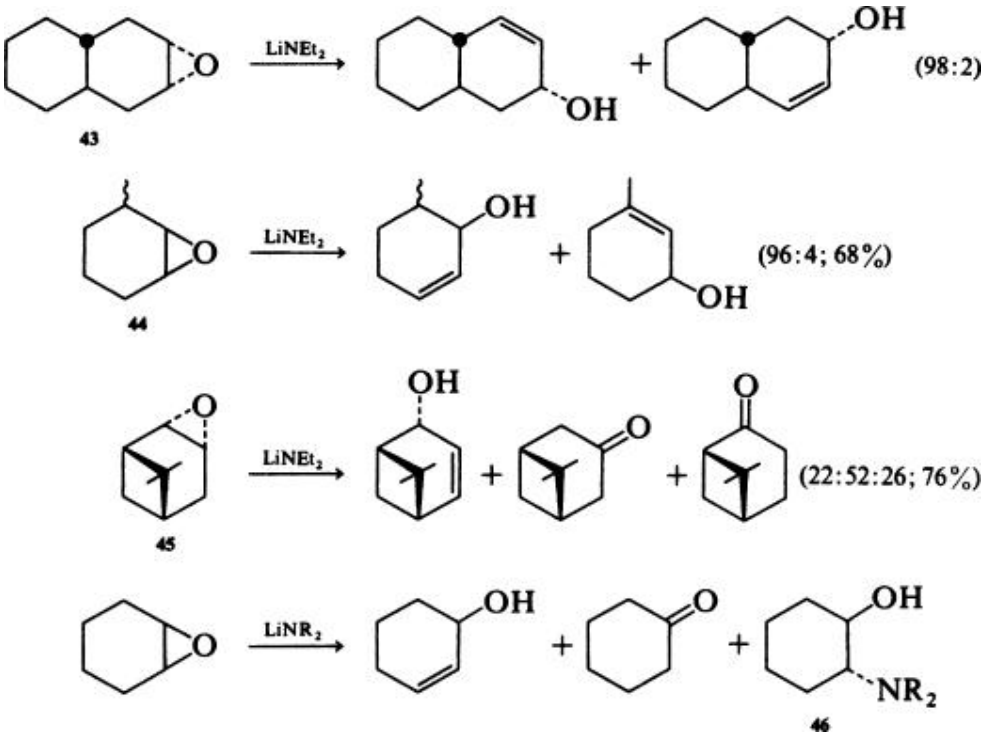
Epoxycycloalkanes show a more complicated pattern of reactivity because of the importance of transannular C — H insertion and ketone formation with this type of substrate. Because of the propensity for such epoxides to form complexes unsuitable for β elimination, plus the unfavorable stereoelectronic situation for β elimination in some medium-ring compounds, epoxide metalation and the ensuing transformations are significant processes in many instances. Both the epoxide structure and the reaction conditions can be important in determining the course of isomerization with these substrates.

As anticipated, large-ring epoxides behave much like their acyclic analogs. This is illustrated by the conversion of a mixture of *cis*- and *trans*-epoxycyclohexadecanes to the corresponding *trans* allylic alcohol. (51)

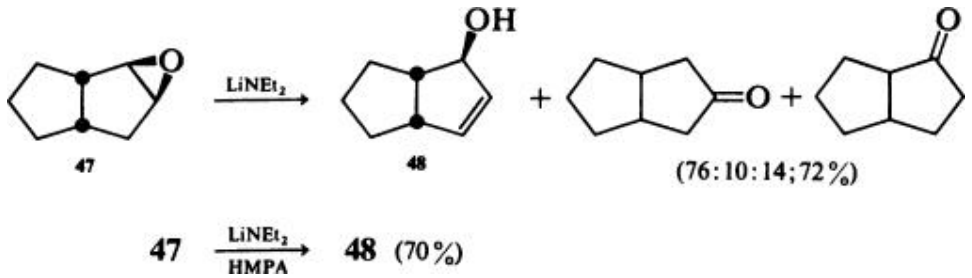


Cyclohexene oxide is smoothly converted to 2-cyclohexenol under a variety of conditions, (26, 52, 53) as are a number of more complicated analogs. (54-56) The high regioselectivity shown by the rigid *trans*-decalin system **43** is rationalized by preferential *syn* elimination of the quasi-axial β hydrogen (p. 350). (21) A mixture of *cis*- and *trans*-3-methylcyclohexene oxide (**44**) leads predominately to the epimeric 6-methyl-2-cyclohexenols, consistent with both proton abstraction from a CH_2 over a CH group and *syn* elimination. (21)

However, ketone formation is important with certain cyclohexene oxides as shown for apopinene oxide (**45**). (52) In fact, the use of sterically bulky amides results in the formation of significant amounts of cyclohexanone from cyclohexene oxide itself. (53) Thus a 62% conversion to ketone is observed with lithium 2,2,6,6-tetramethylpiperidide. This reagent favors epoxide metalation over β elimination because of steric destabilization of the requisite *syn* complex for the latter process.

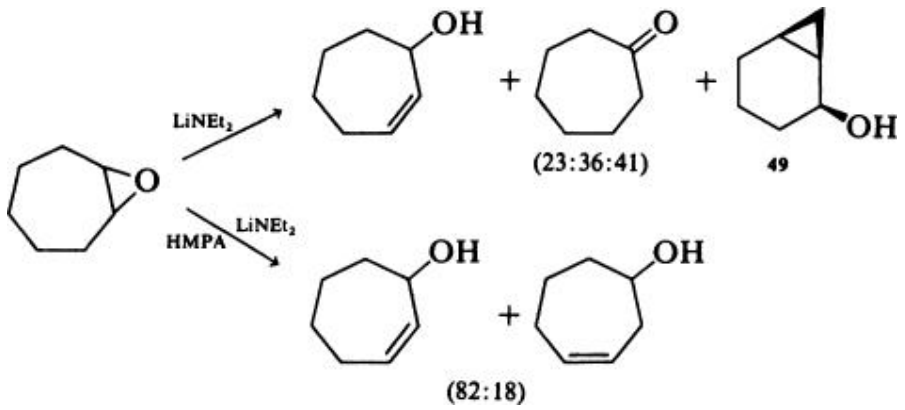


An observation of obvious relevance for synthetic applications concerns the dramatic effect of hexamethylphosphoramide on epoxide rearrangements. (26) Whereas the bulky base lithium diisopropylamide converts cyclohexene oxide to a product mixture consisting of roughly equal amounts of 2-cyclohexenol, cyclohexanone, and the nucleophilic adduct **46** under the usual reaction conditions, the addition of two equivalents of hexamethylphosphoramide to this reaction results in the exclusive formation of 2-cyclohexenol. A further example of this dramatic effect is found in the rearrangement of bicyclic epoxide **47**. This substrate yields only the allylic alcohol **48** in hexamethylphosphoramide solvent as compared to a mixture of **48** and isomeric ketones in the usual ether–hexane system. (18, 26)



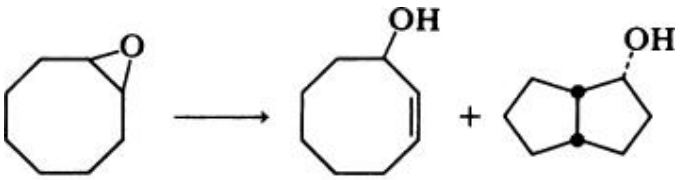
Another report on cyclohexene oxide concerns the intriguing possibility of asymmetric induction during epoxide isomerizations. (57) The use of bases prepared from optically active amines results in enrichment of the 2-cyclohexenol in one of its enantiomers. Several amine enantiomers have been used, and, depending on their structure, either the *R* or the *S* alcohol is preferentially generated in optical yields in the range 3–31%. These results, particularly with such a simple epoxide, point to great potential for asymmetric induction in epoxide isomerizations. Further exploration of this subject can be anticipated in the near future.

A new competing reaction, namely, transannular C — H insertion, is a significant process with medium-ring epoxides of 7- to 10-membered carbocycles. Thus cycloheptene oxide yields bicyclic alcohol **49** in addition to cycloheptanone and 2-cycloheptenol on base isomerization. (52) The use of hexamethylphosphoramide as solvent does suppress the first two products, but significant amounts of 3-cycloheptenol are also formed. (26)



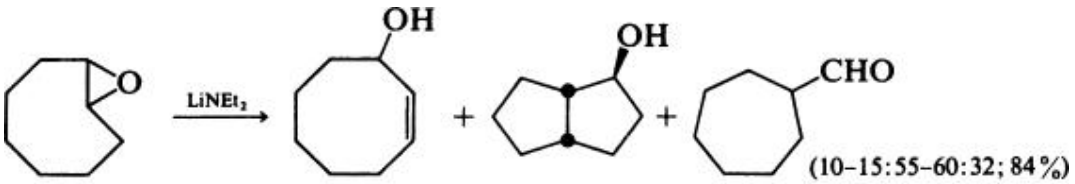
Some very useful information concerning epoxide rearrangements is provided by the transformations of *cis*-epoxycyclooctane, which have been studied extensively. Interestingly, the initial observation that bicyclic alcohol **1** is the

major product of this epoxide, in fact, depends on the presence of lithium bromide in the lithium diethylamide reagent. (9, 58) When *salt-free* lithium diethylamide is used, 2-cyclooctenol is the predominant product. (42, 58) However, the bulkier base lithium diisopropylamide converts this epoxide almost exclusively to bicyclic alcohol **1**. (58) On the other hand, this same base in hexamethylphosphoramide results in the slow but complete isomerization to 2-cyclooctenol. (26) The allylic alcohol is also the major product when the reaction is conducted with potassium *tert*-butoxide in dimethyl sulfoxide. (59) Finally, *n*-butyllithium is an effective reagent for the generation of bicyclic alcohol **1**. (42)



$LiNEt_2$	20:80 (−)
LDPA	2:98 (80%)
LDPA-HMPA	100: 0 (70%)

The conformationally rigid *trans*-epoxycyclooctane yields 2-cyclooctenol, bicyclic alcohol **50**, and cycloheptanecarboxaldehyde on treatment with lithium diethylamide. (9) A favorable geometry for β elimination is difficult to achieve with this compound, allowing for competitive epoxide metalation and subsequent transformations. The high degree of stereospecificity in the rearrangements of the isomeric *cis*- and *trans*-epoxycyclooctanes to the epimeric bicyclic alcohols is discussed in connection with the analogous reactions of the epoxycyclodecanes (p. 354). (33) Transannular C —H insertions are not reported for larger carbocycles.

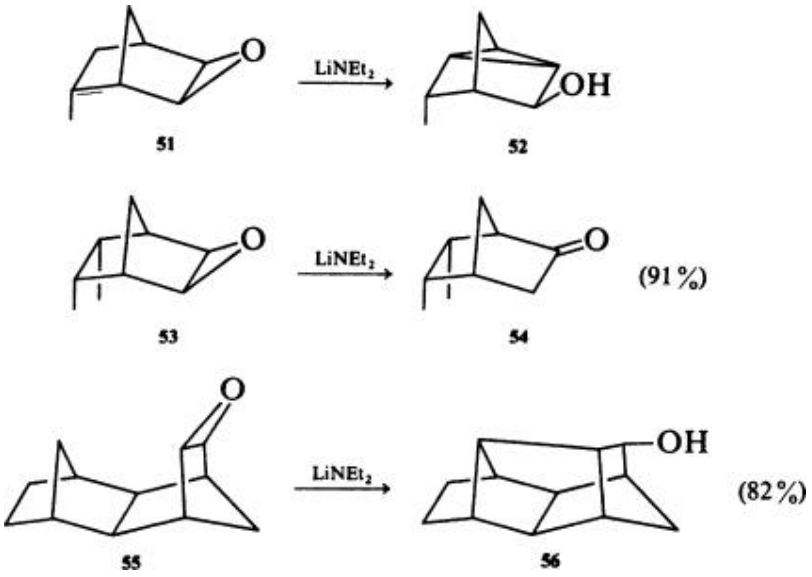


(10–15:55–60:32; 84%)

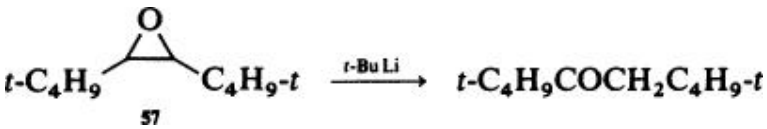
50

The second class of epoxides that give C — H insertions are bridged bicyclic derivatives that are precluded from β elimination by Bredt's rule restrictions. The structures of these compounds, like the medium-ring carbocycles, are often favorable for transannular carbenoid reactions. Norbornene oxide and its

derivatives are particularly prone to such transformations. (18, 60) Thus the *endo*-5-methyl compound **51** behaves analogously to the parent system in isomerizing to the tricyclic alcohol **52**. (18) However, bicyclic epoxide **53** yields ketone **54** as the only significant rearrangement product. (18) Ketone formation is also the principal process with epoxides in the bicyclo[2.2.2]octane and bicyclo[2.1.1]hexane systems. (10, 18) The striking transformation of tetracyclic epoxide **55** into alcohol **56** is noteworthy in that insertion occurs into a proximate C — H unit that is several bonds removed from the carbenoid center. (61)



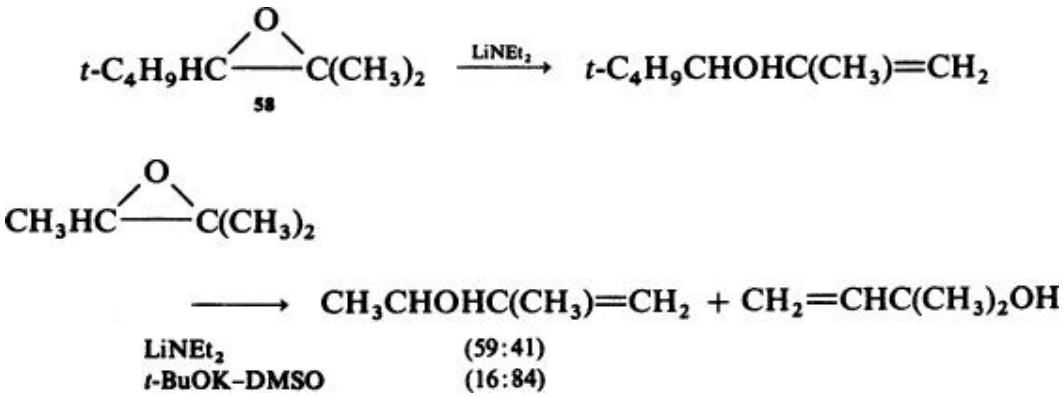
These results emphasize the stringent geometric requirements for C — H insertion. This process is efficient only when the structure of the molecule holds a C — H bond in close proximity to the metalated epoxide carbon in a rigid or readily accessible conformation. With substrates that do not fulfill this prerequisite, metalation is usually followed by ketone formation. Isomerization of epoxides to ketones is observed with normal-ring and large-ring epoxycyclo-alkanes that are not susceptible to transannular carbenoid reactions. Significant ketone formation is normally confined to cyclic epoxides and is enhanced by conditions that favor epoxide metalation, namely, the use of bulky lithium amides or alkyllithiums as isomerizing agents. A notable exception to this generalization is found with the di-*tert*-butylethylene oxides. The *cis* isomer **57** is converted to *tert*-butyl neopentyl ketone under forcing conditions with *tert*-butyllithium as the base. (62) This ketone is also produced from the *trans* epoxide that gives carbenoid insertion into the C — H bonds of the adjacent *tert*-butyl group as the principal reaction. (39)



3.1.1.3. Trisubstituted Epoxides

This class of substrate is also well studied, and a number of important applications in synthesis are recorded in the literature. Allylic alcohols are the only significant isomerization products normally observed from these epoxides, which apparently are not easily metalated. The major allylic alcohol is usually derived from the more stable epoxide–base complex.

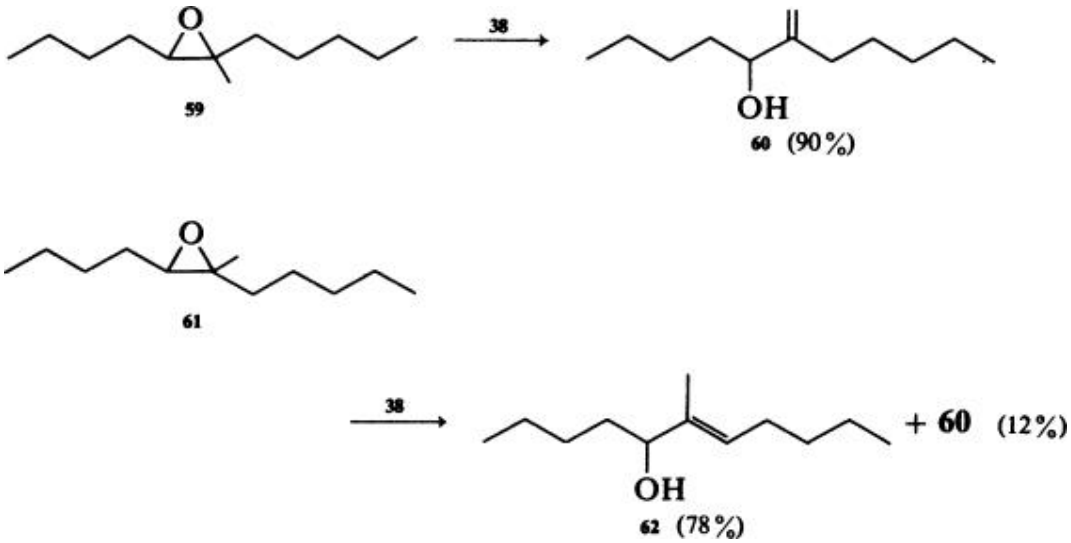
For example, epoxide **58** gives the only possible β -elimination product in good yield. (52) The complications introduced by the availability of more than one β -elimination pathway are illustrated by the isomerization of trimethyloxirane with lithium diethylamide. (21) The low degree of regioselectivity in this reaction indicates that base attack at the *gem*-dimethyl and monomethyl centers is reasonably competitive. Interestingly, potassium *tert*-butoxide in dimethyl sulfoxide reacts slowly with this epoxide to give a product mixture that is



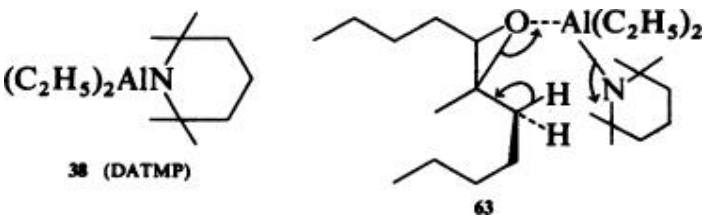
enriched in the isomer derived from proton removal at the single methyl group. (46) Although this point has not received experimental attention, bulkier amide bases are expected to favor β elimination at the *gem*-dimethyl center since they should favor the less hindered complex.

The sterically hindered diethylaluminum 2,2,6,6-tetramethylpiperidide (**38**) offers some useful advantages as a base for the isomerization of trisubstituted epoxides. Thus, the *Z* epoxide **59** is converted cleanly to alcohol **60** by proton abstraction from the CH_3 substituent. (31, 32) On the other hand, the *E* epoxide **61** gives only a minor amount of alcohol **60**, and the major product is the isomeric alcohol **62** formed by base attack at the CH_2 of the alkyl group *cis*

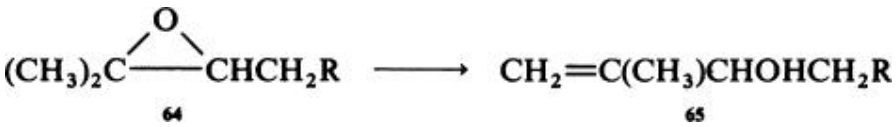
to the hydrogen substituent. It is noteworthy that elimination toward the other CH_2 group is not observed for either of these epoxides. These results indicate a predisposition for reaction by means of the least crowded complex that overcomes the usual selectivity for elimination toward a CH_3 group.



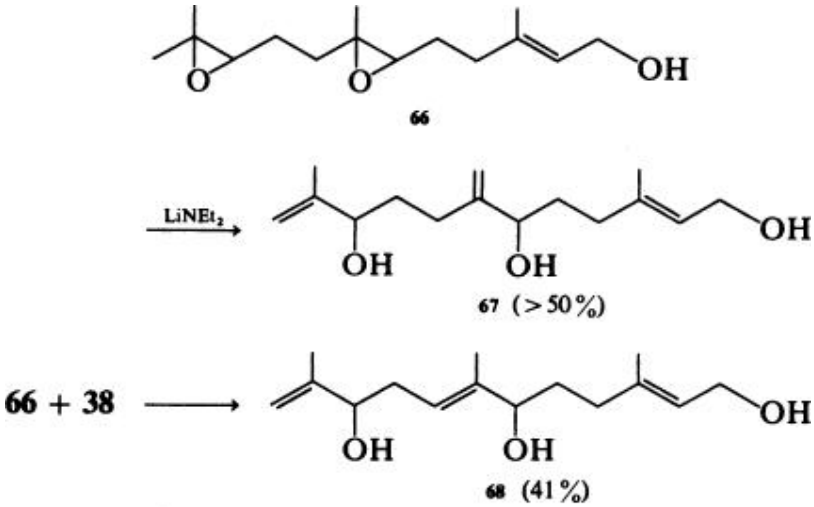
An important aspect of the reaction of epoxide **61** is the high degree of stereoselectivity for the *E* form of the trisubstituted double bond in **62**. This suggests that isomerization proceeds by way of conformation **63** of the complex in which the side-chain residue is oriented away from the sterically demanding base moiety. Such high discrimination is unusual in the generation of trisubstituted olefins.



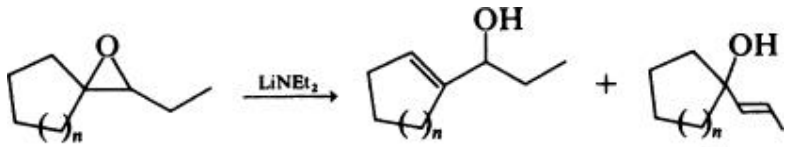
A number of terpenoid epoxides of partial structure **64** are converted to allylic alcohols of type **65** in good yields by the aluminum amide **38**. (32) A related transformation by use of lithium diisopropylamide proceeds equally selectively, (63) but an isomerization analogous with that for this base is reported to give some of the allylic alcohol derived from attack at the CH_2 substituent. (64)



A striking example illustrating the difference between lithium diethylamide and aluminum amide **38** is found in the reactions of the farnesol diepoxide **66**. Lithium diethylamide is reported to give exclusive proton abstraction from the CH_3 group at both sites to yield **67**. (65) However, the use of **38** results in the formation of the isomeric triol **68**. (32) Thus it appears that, whereas the aluminum amide reaction is controlled by the more stable complex, the less hindered lithium amide selects proton removal from a CH_3 group over that from a CH_2. This difference is of obvious interest in synthetic applications.



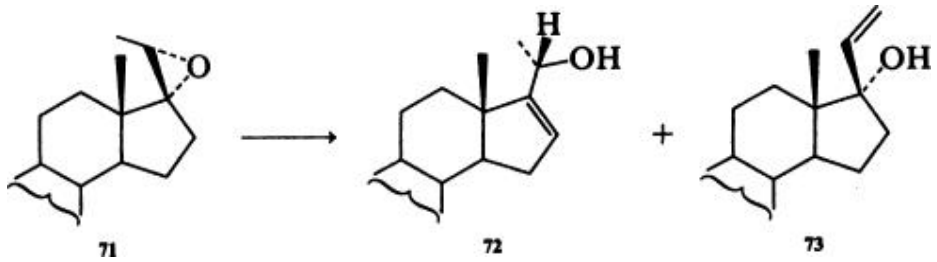
The isomerizations of the spiroepoxides of structure **69** by lithium diethylamide represent a competition between two different CH_2 groups. (29) With one notable exception, it is the endocyclic CH_2 that participates preferentially in the elimination process. This is once again consistent with reaction by way of the sterically favored complex. The exception is the cyclohexyl derivative **69** (n = 2) that is slowly isomerized by elimination into the ethyl substituent to give **70**. In this reaction the conformational preference of the cyclohexane ring does not allow a readily accessible geometry that fulfills the stereoelectronic requirements for β elimination. Consequently, proton abstraction from the conformationally mobile ethyl group is the preferred pathway despite the necessity for proceeding by way of the more hindered epoxide–base complex. The other spiroepoxides have no serious problem in achieving an optimum geometry for elimination into the ring.



$n = 0$	83:17; 66%
$n = 1$	100:0; 84%
$n = 2$	5:95; 69%
$n = 3$	98:2; 76%
$n = 4$	100:0; 74%
$n = 8$	100:0; 66%

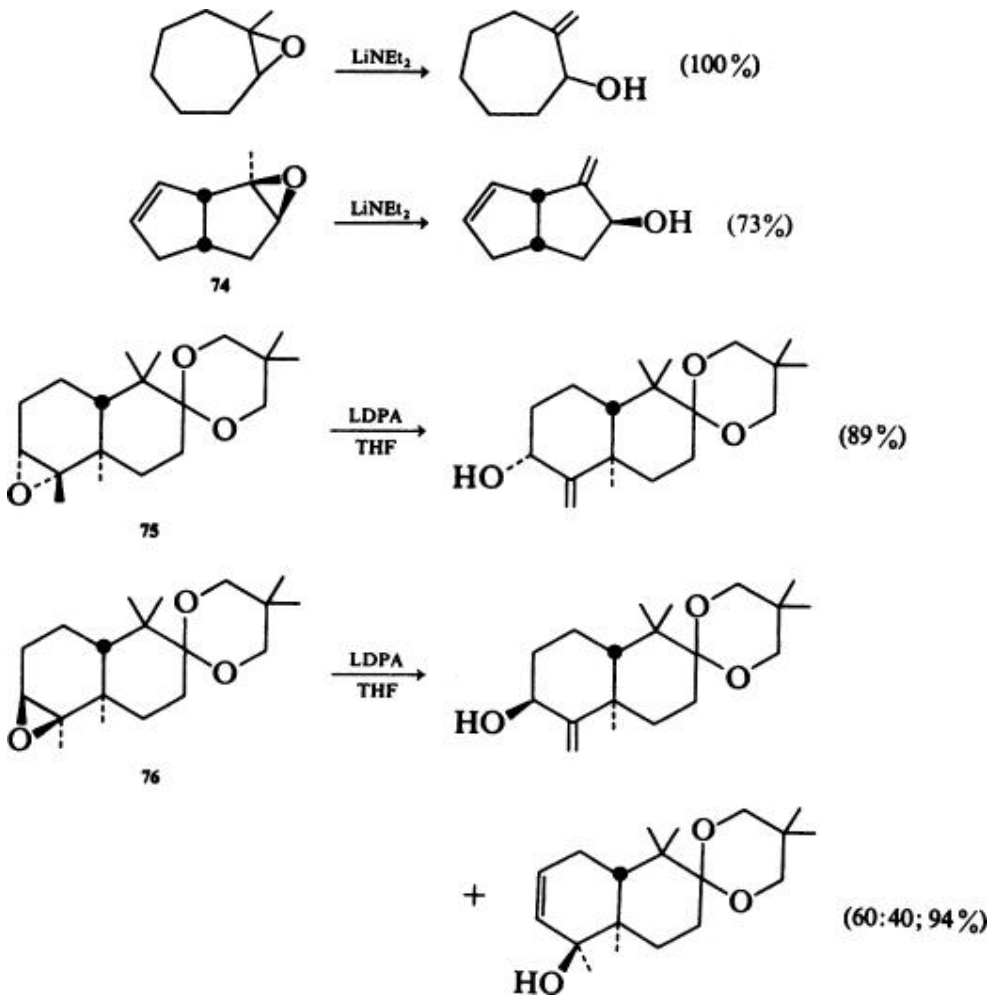
The lower homologs of **69**, with a methyl group in place of the ethyl side chain, show poor regioselectivity between elimination into the ring and into the methyl group. (29) The tendency for reaction from the less hindered complex is counter-balanced by that for proton removal from a CH_3 over a CH_2 group in this case. The cyclohexyl system is an exception again, yielding only elimination toward the CH_3 substituent.

The use of HMPA can influence the regioselectivity of β elimination with epoxides of this type. This is illustrated by the synthetically relevant example of steroid epoxides of partial structure **71**. (66) In this case a mixture of alcohols **72** and **73** is obtained on treatment with lithium diethylamide under the usual conditions, whereas only **72** is observed in the presence of two equivalents of hexamethylphosphoramide. The results with added hexamethylphosphoramide appear to implicate attack of the base at the most accessible site without prior complexation.



The 1-methylepoxycycloalkanes are an interesting class of cyclic epoxides whose base-promoted reactions are frequently utilized in synthesis. Proton removal from the CH_3 group by way of the more stable complex is normally anticipated for these substrates. Thus 1-methylepoxycycloheptane can be

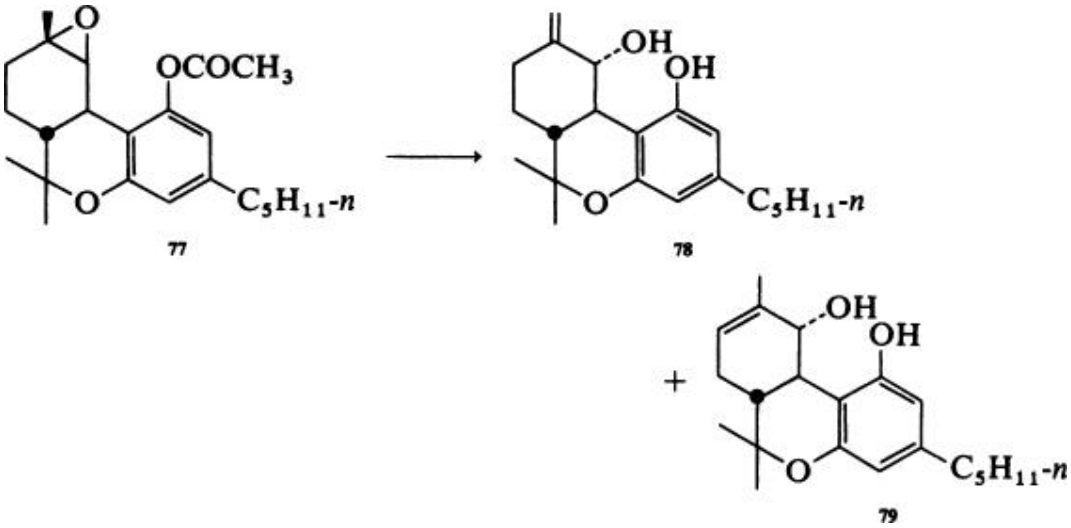
converted cleanly to 2-methylenecycloheptanol. (67) However, such conversions must be monitored closely to achieve good yields and purities of the methylenecycloalkanols since the intermediate alkoxides are especially susceptible to further isomerization. Further examples of relevant transformations are shown for epoxides **74** and **75**. (68, 69)



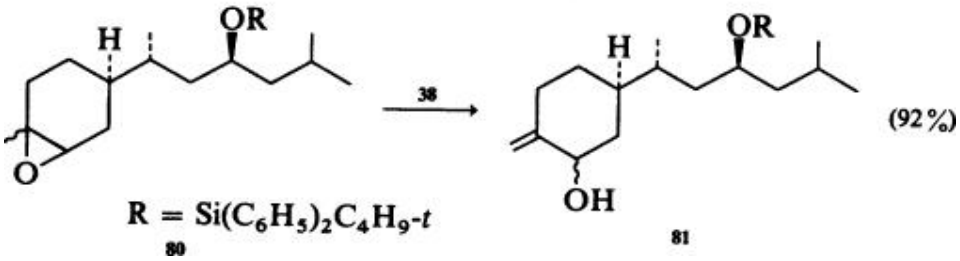
Structural features in more complicated epoxides can, however, overcome the selectivity for elimination into the CH_3 group. This is demonstrated with epoxide **76** (a stereoisomer of **75**) that gives competitive base attack at the CH_3 and ring CH_2. (69) The use of the basic solvent tetrahydrofuran in this study may be a significant feature leading to these results. Other examples that show little selectivity are known. (70-73)

The nature of the base can exert a significant influence on the course of the isomerization of epoxides of this type. In the conversion of epoxide **77**, lithium

diethylamide gives a mixture of alcohols **78** and **79** in a 17:83 ratio. (74) The use of lithium *tert*-butyltrimethylsilylamide, on the other hand, favors the desired compound **78** by an 80:20 ratio. Other amides of intermediate steric bulk result in roughly equal amounts of the two alcohols. These observations imply an important steric effect, although it is not clear in this case whether this operates on the regioselectivity of the β elimination or on the secondary isomerization of alcohol **78** to its endocyclic isomer **79**.

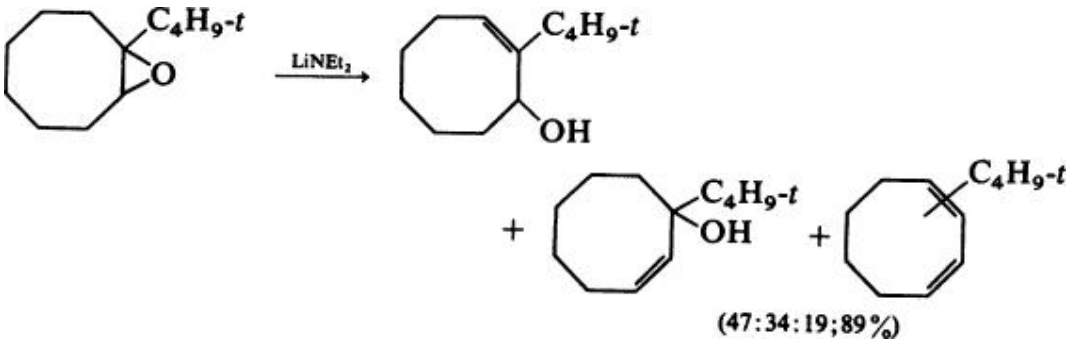


Another informative study concerns the isomerization of **80**, an epoxide that gives complex product mixtures with lithium amides. (75, 76) In this reaction the amide diethylaluminum 2,2,6,6-tetramethylpiperidide (**38**) yields the *exo*-methylene isomer **81** cleanly. This result suggests more widespread application of aluminum amides with trisubstituted epoxides that give complex product mixtures with lithium amides.

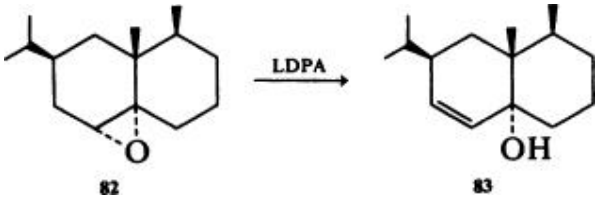


Little information is available concerning 1-alkylepoxycycloalkanes with alkyl groups other than methyl, despite the synthetic potential for isomerizations of

such substrates. However, the reaction of 1-*tert*-butylepoxycyclooctane is interesting in that only products from β elimination are found. (67) This reversal of character of the eight-membered ring, which usually undergoes transannular insertion, is attributed to the difficulty of metalation as a result of steric retardation.



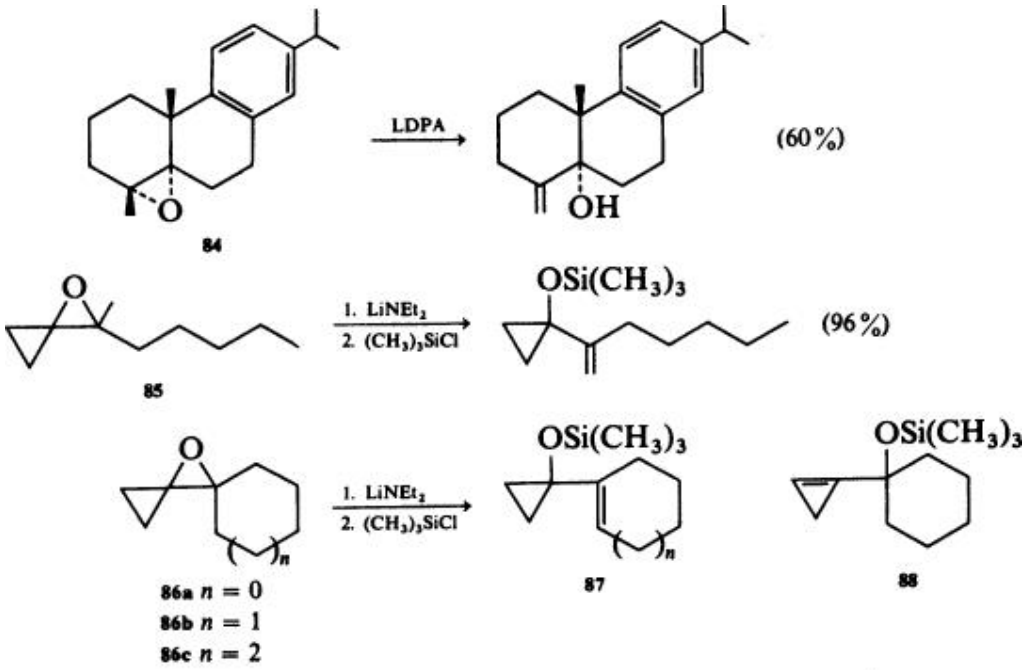
Finally, bicyclic compound **82**, whose epoxide ring is fused to one cyclohexane unit and spiro to the second, is converted solely to the endocyclic olefin **83** rather than the other possible allylic alcohol. (77) Removal of a *syn* proton in the fused ring is preferred over β elimination into the spiro cyclohexane. This is reasonable on the basis of stereoelectronic considerations and parallels the behavior of the spiro epoxides discussed earlier.



3.1.1.4. Tetrasubstituted Epoxides

Data are available for only a few substrates of this type, but the selectivities appear to follow the principles already elaborated for less highly substituted epoxides. Thus selective proton abstraction from a CH_3 group is observed with epoxide **84**. (78) Likewise, base attack is highly regioselective for a CH_3 over a CH_2 group with the interesting spiro epoxide **85**. (79) Excellent yields of the highly reactive cyclopropanol can be obtained if the product is converted directly into the trimethylsilyl derivative. The bis–spiro epoxides **86a** and **86c** undergo similar transformations to yield cyclopropanols **87a** and **87c**. (79) Elimination into the three-membered ring is not competitive because of the highly strained nature of the cyclopropene derivative that would result.

Interestingly, the cyclohexane analog **86b** does yield some of this product, alcohol **88**, illustrating once again the resistance to elimination into the spiro cyclohexane moiety.

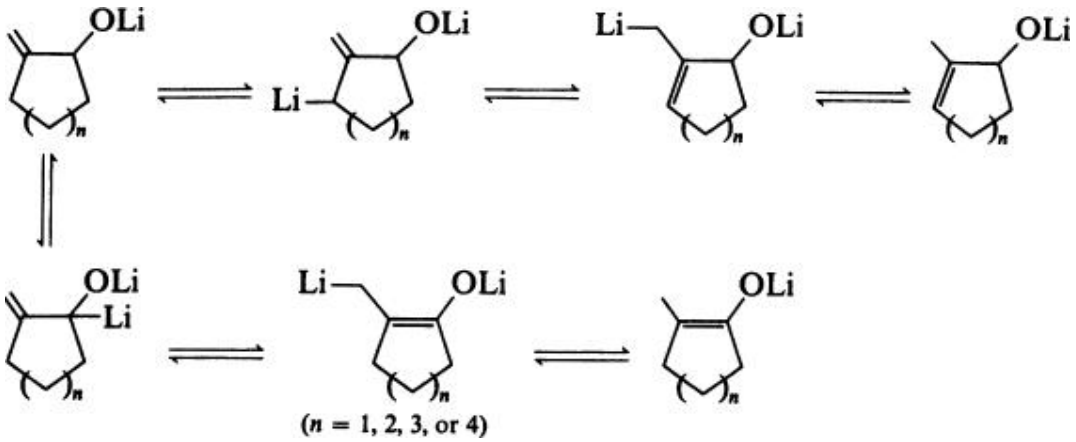


3.1.1.5. Side Reactions

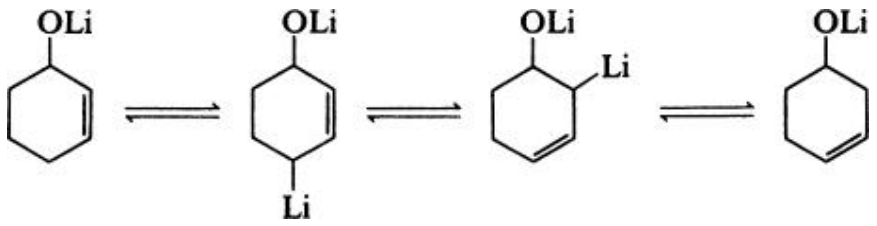
Nucleophilic addition of the base to the epoxide ring probably occurs to some extent in most isomerization reactions. The addition products formed in this manner from amide bases are conveniently removed from the neutral products during processing of the reaction mixture as a result of their basic properties. As a consequence, these materials are rarely examined in synthetic conversions, where they pose no great inconvenience apart from decreasing the yields of the desired isomerization products. Base adducts have been characterized in a number of reactions using lithium amides. (11, 15, 44, 47, 52)

This side reaction is expected to be subject to the usual considerations that govern S_N2-type substitutions. (3) Thus an increase in the number and steric size of the substituent groups on the epoxide ring should retard nucleophilic attack. Likewise, an increase in the steric encumberment of the lithium amide should be detrimental to the nucleophilic addition process. It appears that these steric effects are usually more critical for nucleophilic processes than for the competing proton-abstraction events that lead to epoxide rearrangement.

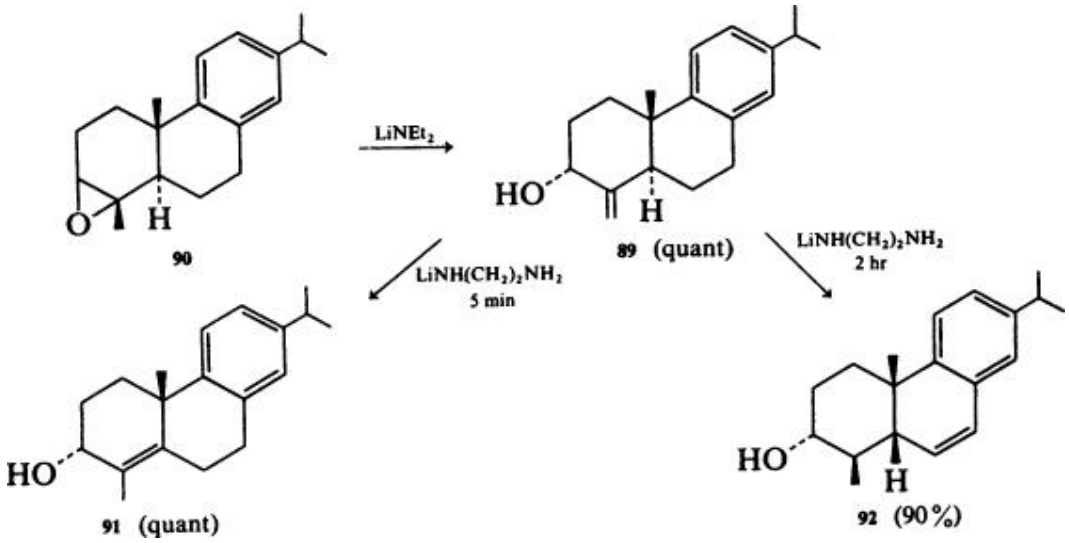
In a number of instances the initially formed allylic alcoholates are subject to further isomerizations under the reaction conditions. (21, 43, 67, 70) For reasons that remain obscure, this is especially true of the reactions of 1-methylepoxycycloalkanes. Thus lithium salts of the primary products, 2-methylenecycloalkanols, are transformed into the precursors of 2-methyl-2-cycloalkenols and 2-methylcycloalkanones. (67, 70) This reaction pathway is indicated by studies of the evolution of product mixtures with time and by independent transformations of the allylic alcohols. The most obvious explanation of these secondary isomerizations invokes allylic metalation of the intermediate alkoxides followed by allylic rearrangement and reprotonation. This is illustrated for the 2-methylenecycloalkanols. A similar process accounts for the slow conversion of 1-penten-3-ol to 3-pentanone. (21) In a number of other reactions complex product mixtures probably result from secondary isomerizations. (67, 71, 74, 76, 80)



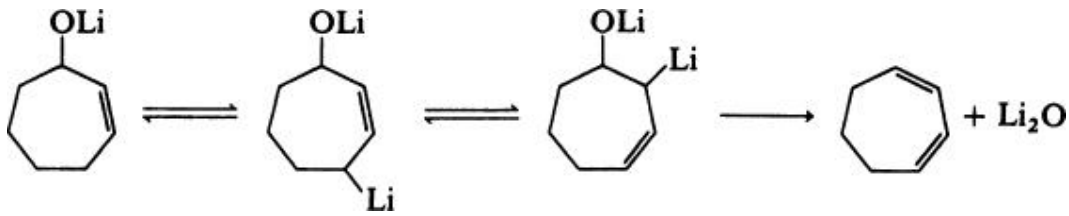
The formation of small amounts of 3-cyclohexenol during the rearrangement of cyclohexene oxide is another side reaction that must proceed by a related mechanism. (53) Thus metalation of the lithium salt of 2-cyclohexenol, followed by rearrangement and protonation, results in double-bond migration away from the alkoxide function. This reaction appears to be favored by hexamethylphosphoramide, a solvent that greatly enhances the prospects for metalation. This is illustrated with epoxycycloheptane, which gives 2-cycloheptenol contaminated with significant amounts of 3-cycloheptenol when hexamethylphosphoramide is used. (26)



Analogous transformations of allylic alcohols can sometimes be performed efficiently on a synthetic scale by using the lithium salt of ethylenediamine as the base. (78, 81) This is demonstrated in the reactions of alcohol **89**, the clean isomerization product of the lithium diethylamide treatment of epoxide **90**. Reaction of alcohol **89** with the lithium salt of ethylenediamine for a brief period of time gives isomeric alcohol **91**, whereas longer reaction times yield alcohol **92**, which is presumably the thermodynamically favored product. These further isomerizations have considerable synthetic potential in their own right.

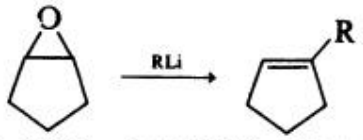


In a few instances conjugated dienes are found as minor products from epoxycycloalkanes, as in the formation of cycloheptadiene from cycloheptene oxide. (51, 52) These dienes are secondary products derived from the allylic alcohols and are favored by high temperatures and prolonged reaction times. A reasonable mechanism invokes allylic metalation as the initial event, but decomposition of the key intermediate gives lithium oxide and the diene. The elimination of lithium oxide as a driving force for reactions is proposed in several other instances. (40)



Finally, it should be mentioned that certain terminal and cyclic epoxides react with organolithium reagents at higher temperatures to give substituted olefins in low to moderate yields according to the transformation indicated below. (20, 39, 40, 50, 82) Thus 1,2-epoxybutane gives olefins of the indicated structure on prolonged heating with various alkyllithium reagents. The yields appear to increase with the size of the alkyl group of the reagent; the *trans* isomers of the product are preponderant. In a similar fashion cyclopentene oxide is converted to the analogous trisubstituted olefins. This reaction is less prevalent for the medium-ring and bicyclic epoxides that undergo transannular insertions. (50) In certain situations this conversion constitutes a satisfactory synthesis of substituted olefins.

R (yield): *t*-C_4H_9 (57%), *n*-C_4H_9 (35%), *i*-C_3H_7 (35%), C_2H_5 (12%)



R (yield): *t*-C_4H_9 (49%), *n*-C_4H_9 (41%), C_6H_5 (16%), CH_3 (7%)

3.1.1.6. Influence of the Base

A number of examples are cited in the survey of epoxide types in which the nature of the base system plays an important role in determining the course of a reaction. However, relatively little attention is usually given to the choice of an appropriate base in experimental work. Consequently, it is worthwhile summarizing some of the factors that appear to be significant in deciding on a reagent for a specific transformation. Because of a lack of systematic study on representative substrates, there is a fair amount of speculation in the generalizations that follow. Nonetheless, these hypotheses should be useful in devising experimental conditions for controlling isomerizations.

Lithium amides are the most widely used reagents, and in a variety of situations these bases function effectively. A range of amides with different substituents are easily prepared from readily available materials. Lithium diethylamide is often the reagent of choice for promoting β eliminations. This amide generally favors allylic alcohol formation even for the epoxycycloalkanes, which have a tendency to undergo epoxide metalation. The high selectivity for the sequence $CH_3 > CH_2 > CH$ is of substantial importance in determining the regiochemistry of β elimination with lithium diethylamide. There are indications that this strong preference can overcome the propensity for reaction from the more stable complex in some instances. Sterically smaller bases may enhance this tendency, whereas more bulky amides are expected to favor the product derived from the more stable complex.

Nucleophilic addition of the base to the epoxide is occasionally a problem. The use of bulkier lithium amides such as lithium diisopropylamide is indicated in such circumstances.

Increase in the steric hindrance of the reagent also results in a shift toward metalation with epoxycycloalkanes. This leads to ketone formation or transannular insertion depending on the structure. Thus bulky amides should be adopted or avoided according to the desired outcome of the isomerization.

A detailed study of the isomerization of cyclohexene oxide provides some useful insight into the influence of the amide structure. (53) The only important products from this substrate are 2-cyclohexenol, cyclohexanone, the nucleophilic adduct, and occasionally a little 3-cyclohexenol. Monoalkylamides, with the exception of lithium *tert*-butylamide, give large amounts of nucleophilic addition and are, therefore, of limited utility in synthesis. These reactions are slow and usually result in noticeable secondary isomerization of the allylic alcohol to 3-cyclohexenol. The dialkylamides function more rapidly and tend to give less nucleophilic addition. The best conversions to 2-cyclohexenol are achieved with the rarely used di-*n*-propylamide and di-*n*-butylamide that are a little more efficient than lithium diethylamide. Both nucleophilic adducts and cyclohexanone are important products with amides of intermediate steric bulk such as lithium diisopropylamide. With severely hindered amides such as lithium 2,2,6,6-tetramethylpiperidide, nucleophilic addition is minimal, but cyclohexanone is the major product. Thus the less congested amides favor allylic alcohol, whereas ketone formation is promoted by bulky bases. A similar effect is noted for *cis*-epoxycyclooctane, where the competition is between β elimination and transannular insertion.

Hindered amides are also suggested for the isomerization of 1-methylepoxycycloalkanes. These bases should show more selectivity for β

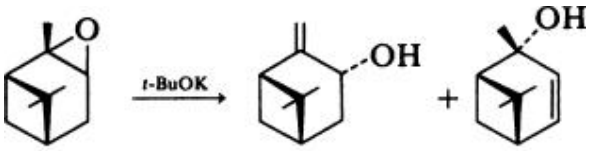
elimination into the CH_3 group and limit secondary isomerization with this type of substrate. Bulky amides are also expected to modify the regiochemistry of elimination with other trisubstituted epoxides by directing reaction through the more stable complex.

The amide diethylaluminum 2,2,6,6-tetramethylpiperidide (**38**) shows high regioselectivity with trisubstituted epoxides, indicating that this large, congested reagent displays a very pronounced preference for β elimination by way of the least hindered complex. Consequently, this reagent is suggested when it is important to maximize this regiochemistry, in spite of the inconvenience involved in its preparation. Significantly, neither epoxide metalation nor secondary isomerizations are found with aluminum amide **38**. Nucleophilic additions of diethylaluminum 2,2,6,6-tetramethylpiperidide are also unimportant, although less hindered variants of this species are reported to add to epoxides in a useful synthetic preparation of amino alcohols. (83) Amide **38** does not isomerize normal-ring and medium-ring epoxycycloalkanes presumably because of the severe destabilization of the more hindered complex that is required for β elimination. Diethylaluminum 2,2,6,6-tetramethylpiperidide is generally used in benzene since the reaction is retarded by basic solvents such as ether and tetrahydrofuran that can compete with the epoxide for complex formation. (31, 32)

There is a pronounced effect of hexamethylphosphoramide on epoxide rearrangements promoted by lithium amides that strongly favors formation of allylic alcohols as illustrated above. (11, 26, 42, 84) Hexamethylphosphoramide acts to break up base aggregates and undoubtedly renders base–epoxide complexation ineffective. (28) Under these conditions β elimination is the only important pathway for isomerization. The mechanism for this process is probably of the typical E-2 variety. (24, 25) This hypothesis lifts the restriction for *syn* elimination and predicts regioselectivities determined by steric approach control of the attacking base and relative product stabilities. As a consequence, the regio-chemistry of hexamethylphosphoramide-mediated isomerizations may differ appreciably from the usual lithium amide reactions in nonpolar solvents. This should lead to useful product modifications in some instances. However, the addition of hexamethylphosphoramide is most useful for suppression of the metalation process with epoxycycloalkanes that tend to yield ketones or transannular insertion products.

Isomerizations promoted by potassium *tert*-butoxide in dipolar aprotic solvents such as pyridine, dimethyl sulfoxide, and dimethylformamide have been recorded. (46, 59, 85) However, *t*-butanol is seldom a suitable solvent with this base. (86) Elevated temperatures are required for these conversions, and it is difficult to drive the reactions to completion since the alcohol generated in the

reaction appears to inhibit isomerization. The reaction conditions of these isomerizations are not likely to favor the complexation phenomena proposed for lithium amides. Mechanistic details are probably more akin to those of amide–hexamethylphosphoramide reagents. Thus β elimination is the dominant process even with epoxycyclooctane. (26) The regioselectivity is consistent with base attack at the more accessible proton adjacent to the epoxide ring. For example, the difference in the product distribution from trimethyloxirane with potassium *tert*-butoxide and lithium diethylamide is detailed above. The isomerization of α-pinene oxide, which gives exclusively *trans*-pinocarveol with lithium diethylamide, yields a mixture of this alcohol and the isomeric allylic alcohol **93** with potassium *tert*-butoxide in dimethyl sulfoxide or dimethylformamide. (85) Whereas reasonably clean isomerizations are observed in a few cases with regioselectivities different from or better than those obtained with lithium amides, the potassium *tert*-butoxide isomerizations are not, in general, very useful synthetically. The lithium amide–hexamethylphosphoramide reagent, if carefully controlled to minimize secondary isomerizations, may result in more facile conversions with similar product distributions.



93

Organolithium reagents are also used to effect epoxide rearrangements. For the most part, these reagents give results that are at best equivalent to those achieved with amide bases. Furthermore, unlike the situation with the latter, the byproducts formed from nucleophilic addition of organolithium reagents are a nuisance to remove from the desired isomerization products. However, *n*-butyllithium in hydrocarbon solvents does show a strong bias for metalation of *cis*-epoxycycloalkanes. Thus normal-ring and large-ring epoxides yield appreciable amounts of the corresponding cycloalkanones in addition to allylic alcohols. (42, 51) Medium-ring epoxides are converted almost exclusively to ketones and bicyclic alcohols by transannular insertion under these conditions. There are some obvious synthetic advantages to the use of *n*-butyllithium when the desired products result from the metalated epoxide.

The hindered *tert*-butyllithium reagent displays an enhanced propensity for epoxide metalation that can be used to advantage with substrates that are particularly susceptible to nucleophilic attack or are unreactive to the usual bases. An example of the latter is *trans*-di-*tert*-butylethylene oxide, which is not

affected by prolonged treatment with lithium diethylamide at elevated temperatures but does yield isomeric products with *tert*-butyllithium (p. 357). (39)

Finally, limited information regarding the use of aluminum isopropoxide (87-89) and the reagent obtained from isopropylcyclohexylamine and methylmagnesium bromide (90) suggest the need for further evaluation of these bases for epoxide isomerizations.

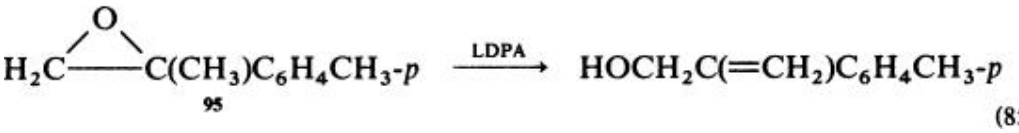
3.2. Unsaturated Epoxides

In many instances the presence of unsaturation in a substrate, particularly if it is remote from the epoxide site, has little effect on the rearrangement reactions. Several examples of this behavior are cited in the discussion on saturated epoxides. However, the activating effect of double bonds, triple bonds, and aryl groups can have a profound influence on the course of rearrangements when these functions are more proximate to the epoxide. Secondary isomerizations are also often promoted by this type of activation. Of course, the position of the activating group relative to the epoxide unit is an important consideration with these epoxides.

3.2.1.1. α Unsaturation

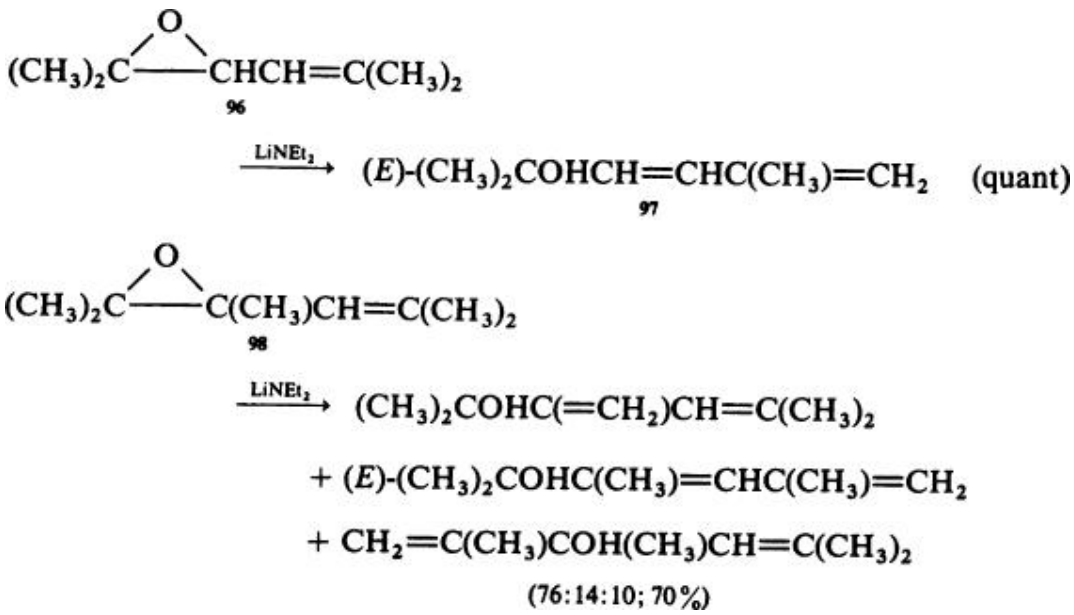
Rather diverse behavior is found for epoxides that are directly bonded to an activating group, and a consistent pattern of reactivity is not presently discernible. Epoxides **94** and **95**, which do not have acceptable alternative modes of isomerization, display typical β -elimination reactions. (91, 92) The high yields of these lithium diisopropylamide rearrangements are note-worthy for terminal epoxides, probably reflecting some assistance of the unsaturated function in the elimination process.

(76%)

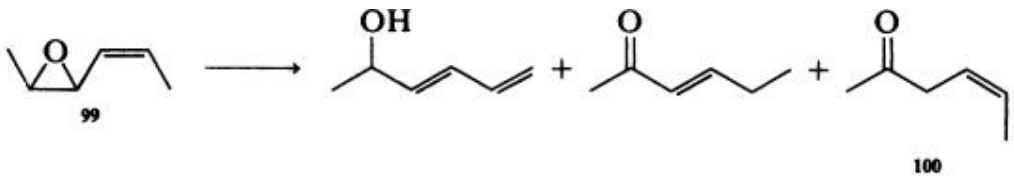


(85%)

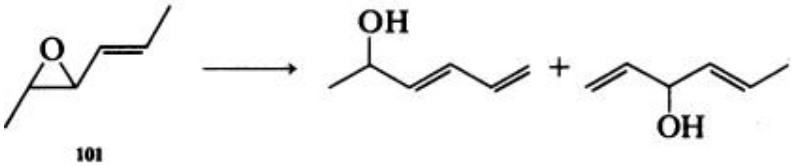
On the other hand, appropriately substituted vinyl epoxides can undergo 1,4 eliminations. Thus epoxide **96** is cleanly and rapidly converted to the *trans* dienol **97** by lithium diethylamide. (44) There is little mechanistic information available about the 1,4-elimination process. Consequently, the involvement of complexes and the geometric requirements for this reaction remain to be fully explored. The preference for 1,4 elimination disappears in the isomerization of epoxide **98**, where the additional methyl substituent must somehow retard this pathway, perhaps by forcing the double bond away from a favorable elimination geometry. (44)



The *cis* epoxide **99** gives mainly 1,4 elimination with lithium diethylamide. (44) Interestingly, the use of the diisopropylamide diverts most of the isomerization to the β , γ -unsaturated ketone **100**. The *cis* double bond in **100** suggests that it is a primary product derived from epoxide metalation, most probably at the carbon adjacent to the double bond. The *trans* epoxide **101** reacts more slowly with the diethylamide to yield predominantly the nucleophilic adduct. This side reaction can be avoided with lithium diisopropylamide; epoxide **101** gives mainly elimination products, albeit without significant regioselectivity for the 1,4 mode over the 1,2 process.



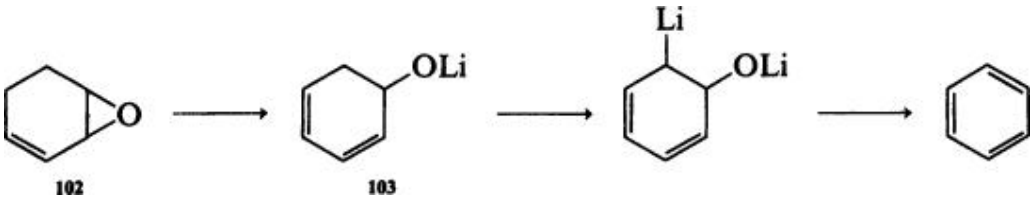
$LiNEt_2$ 99:1:0 (70%)
LDPA 26:10:64 (70%)



+ aminoalcohols + enones

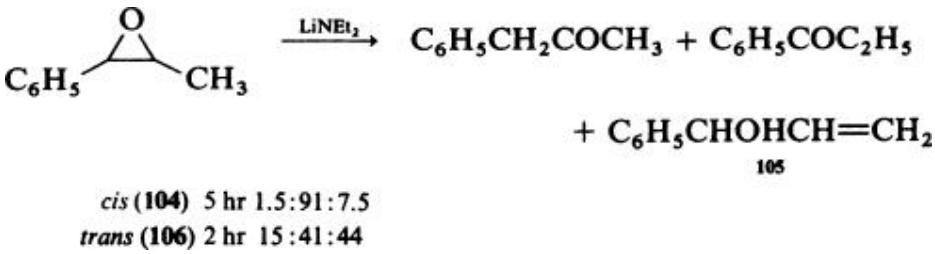
$LiNEt_2$ 15:6:71:8 (80%)
LDPA 54:30:5:21 (75%)

The reaction of 3,4-epoxycyclohexene (**102**) with lithium diethylamide very rapidly leads to a quantitative yield of benzene. (44) This conversion undoubtedly proceeds by 1,4 elimination to give the lithium salt of benzene hydrate (**103**), followed by metalation and loss of Li_2O in a process similar to that that transforms allylic alcohols into dienes. Benzene hydrate can be isolated as the major product, along with some of the nucleophilic adduct, when methyllithium is used as the reagent. (93)

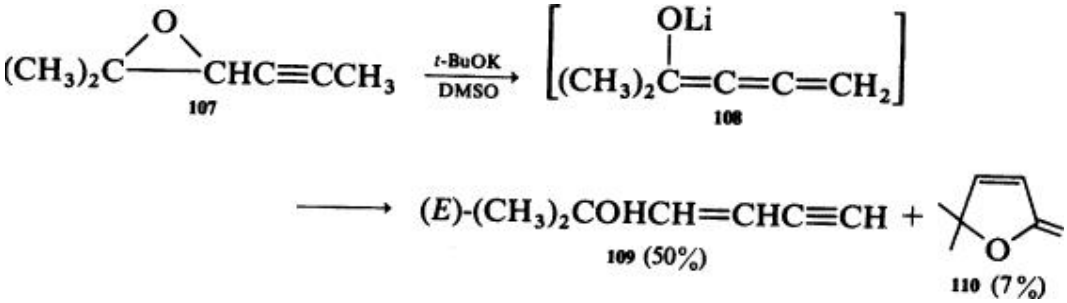


Isomerization of *cis*- β -methylstyrene oxide (**104**) leads to a mixture of propiophenone, a small amount of phenylacetone, and allylic alcohol **105**. (43) Propiophenone results from a facile secondary isomerization of alcohol **105** under the reaction conditions. Phenyl activation for this process is clearly important. The *trans* isomer **106** is more reactive and gives more phenylacetone and alcohol **105**. It is reasonable that the faster reaction results in less rearrangement of **105** to propiophenone, but the more effective

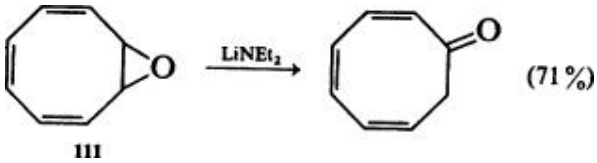
isomerization of the *trans* epoxide to phenylacetone is puzzling since metalation leading to ketone formation normally occurs best with *cis* epoxides.



Epoxides with α-acetylenic substitution undergo selective 1,4 elimination, as illustrated by the isomerization of **107** by use of potassium *tert*-butoxide in dimethyl sulfoxide under mild conditions. The initial cumulene product **108** is not observed because of its facile tautomerization to vinylacetylene **109** and cyclization to furan derivative **110**. (94)

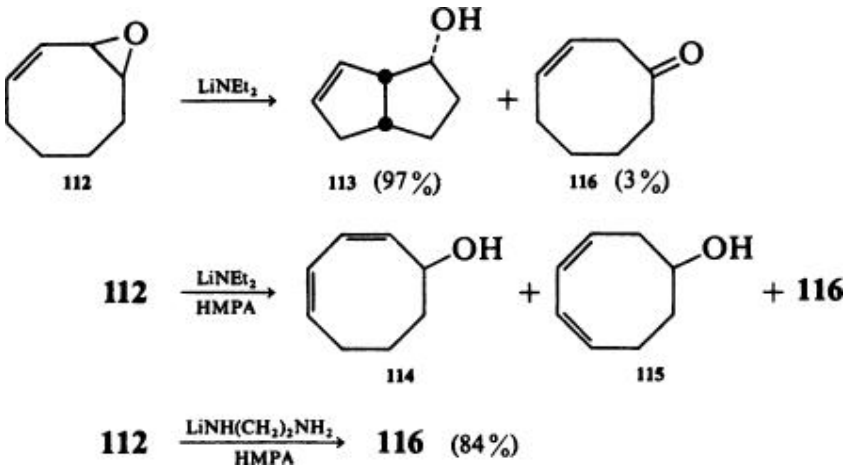


The monoepoxide from cyclooctatetraene **111** is transformed rapidly and in good yield to cyclooctatrienone. (95) This unusually efficient formation of a ketone probably benefits from allylic stabilization in the metalation event.

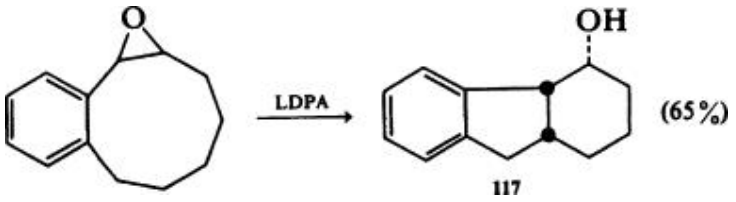


Unsaturated epoxides also partake in transannular insertions similar to those found with medium-ring epoxycycloalkanes. An example of this behavior is the

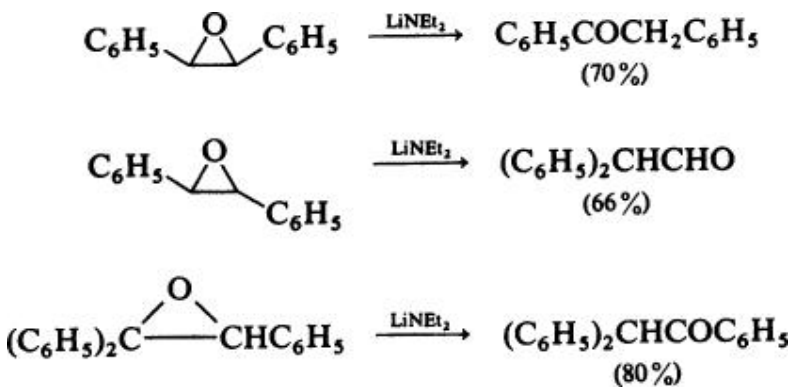
conversion of 3,4-epoxycyclooctene (**112**) to the bicyclic alcohol **113**. (26, 96) This implies that metalation is directed exclusively to the allylic position of **112** and that the intermediate species interacts very efficiently with a proximate C — H bond. This process can, however, be completely circumvented by the use of hexamethylphosphoramide. (26, 27) In this reaction 1,4 elimination gives dienol **114** that is rapidly equilibrated with isomeric dienol **115**. Prolonged base treatment ultimately converts this mixture to 3-cyclooctenone (**116**). Alternatively, a clean, one-step transformation to **116** is effected by the lithium derivative of ethylenediamine. (26)



Medium-ring 3,4-epoxybenzocycloalkenes also show typical carbenoid reactivity. (41) The isomerization of the seven-ring compound to 3,4-benzocycloheptenone is considered in the context of the mechanism of ketone formation (p. 358). The nine-membered ring compound gives mainly bicyclic alcohol **117**. Metalation is again directed by the aryl group and the C — H insertion process is highly selective for the center that is conformationally more accessible to the reactive site.



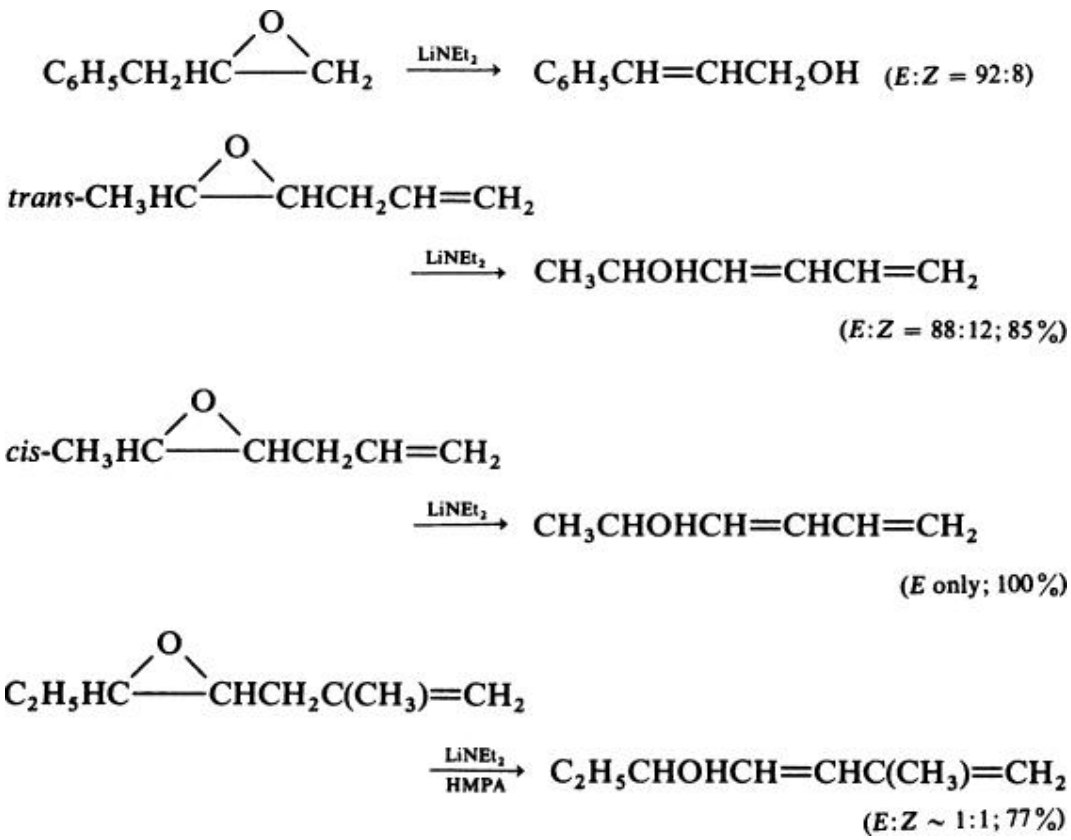
Finally, the dichotomy in the isomerizations of the stilbene oxides is noteworthy. (47) Whereas the *cis* isomer rearranges by migration of a hydrogen, a more



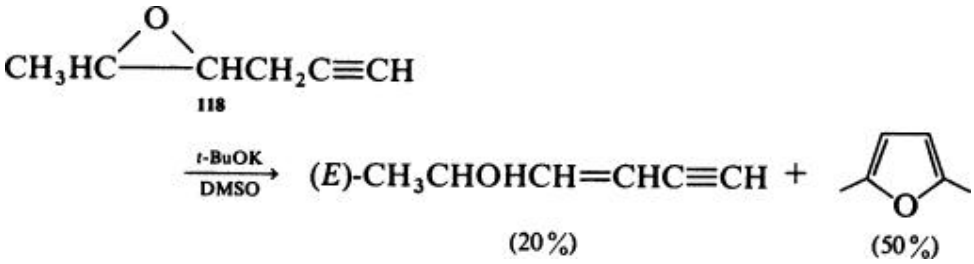
profound change is involved in the transformation of the *trans* isomer to diphenylacetaldehyde. This implies that an efficient phenyl migration to the metalated epoxide center takes place when this group is *cis* to the lithium, but not when it is *trans*. Minor products derived from a similar alkyl group migration are observed with saturated epoxides with the *trans* geometry. (9, 15) Interestingly, triphenylethylene oxide apparently isomerizes without phenyl migration. (47)

3.2.1.2. β Unsaturation

The situation with epoxides that have an adjacent allylic, benzylic, or propargylic substituent is more straightforward. Normally, removal of a proton from the activated center leads to a highly regioselective β elimination, yielding the corresponding conjugated system in a fast, clean transformation. (43, 44, 94) Interestingly, *trans*-disubstituted epoxides of this type do not exhibit the very high degree of stereoselectivity for the *trans* allylic alcohols that the less reactive saturated analogs display. The more congested *cis* isomers still give exclusively the *trans* product. The use of hexamethylphosphoramide in benzene as the solvent for isomerizations of epoxides of this type results in a nonstereoselective elimination producing roughly equivalent amounts of the isomeric alcohols. (97)

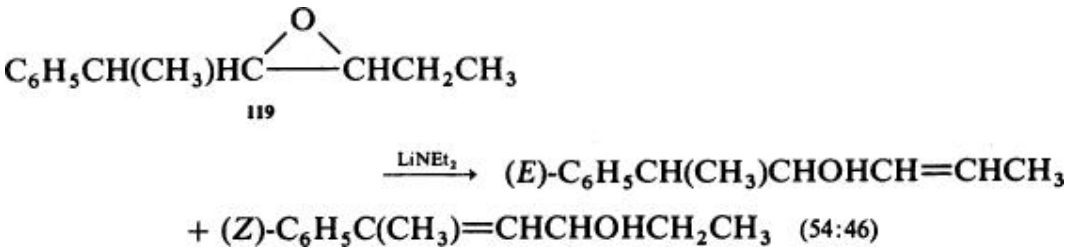


The facility of these β eliminations generally allows for clean conversions without complications from competing or subsequent transformations. However, the treatment of propargylic epoxides with potassium *tert*-butoxide in dimethyl sulfoxide can result in a secondary isomerization to furans as observed with **118**. (94)

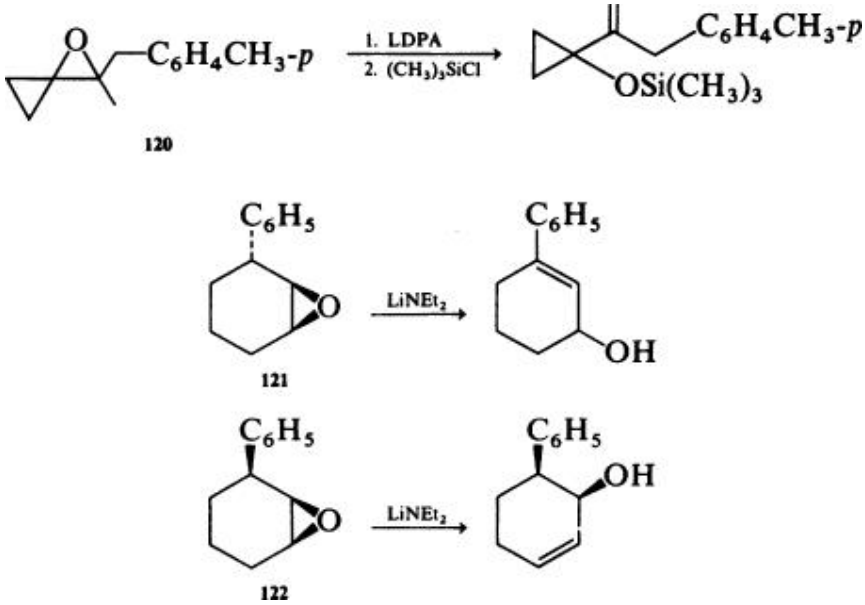


The activating effect of a substituent can be negated by other features of a substrate. Thus additional substitution at an activated position can overcome the influence of an activating group. This is demonstrated with epoxide **119**,

which shows a competition between the two possible β -elimination modes. (43)



The spiroepoxide **120** prefers proton abstraction from a CH_3 over a benzylic CH_2, especially with the bulky lithium diisopropylamide. (98) In this case the steric congestion on the side of the ring bearing the benzylic substituent favors complex formation on the other face and probably also twists the aryl group away from its most effective geometry.

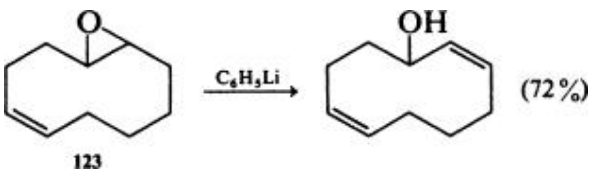


Finally, stereochemical features are clearly important as shown with the isomeric 3-phenylcyclohexene oxides. (43) The *trans* isomer **121** undergoes β elimination by proton abstraction at the benzylic position as anticipated. However, the *cis* isomer **122** slowly yields alcohol by removal of an unactivated proton. These results clearly indicate that *syn* elimination is preferred even with these activated epoxides.

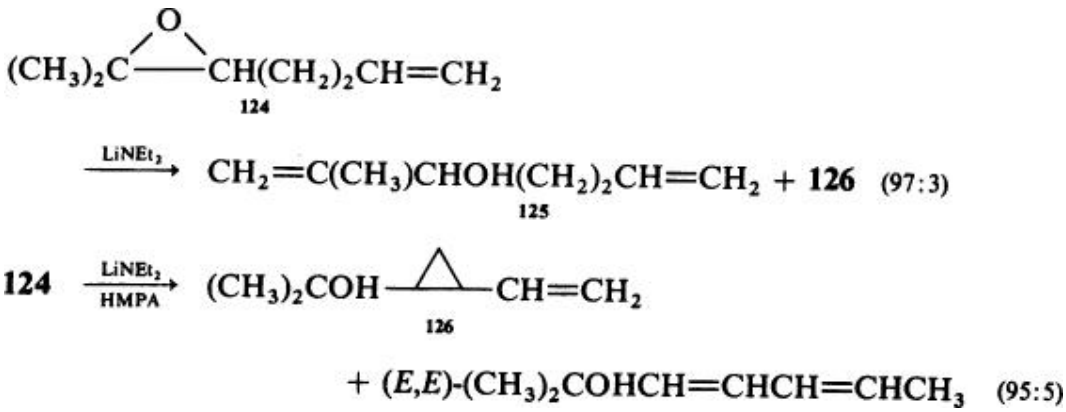
3.2.1.3. γ Unsaturation

The isomerizations of epoxides in this category depend significantly on the reaction conditions. In nonpolar solvents the rearrangements proceed in a manner analogous to those observed with saturated epoxides. However, the presence of hexamethylphosphoramide drastically affects the reactions in a fashion that is quite different from its effect on the isomerizations of saturated epoxides. This is attributed to the remarkable ability of hexamethylphosphoramide to promote metalation adjacent to sites of unsaturation.

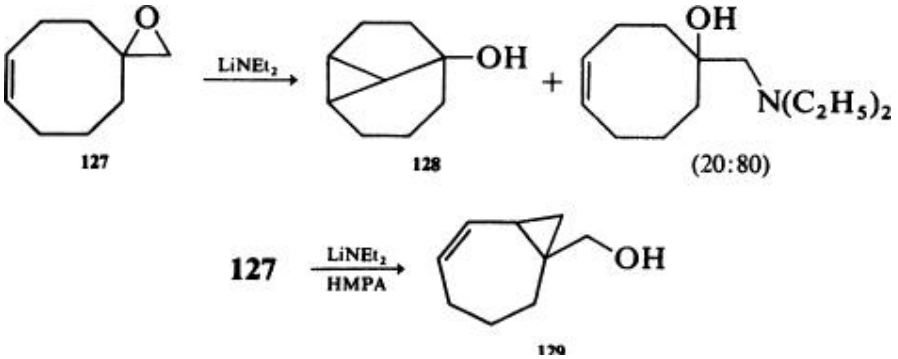
The reaction of medium-ring epoxide **123** with phenyllithium under non-polar conditions is interesting in that β elimination is the dominant process. (99) Transannular carbenoid reactions are not important with **123**, unlike the situation with medium-ring epoxycycloalkanes. The regioselectivity and stereochemistry of this β elimination are also notable. This unexpected selectivity seems to be derived from conformational features of the substrate.



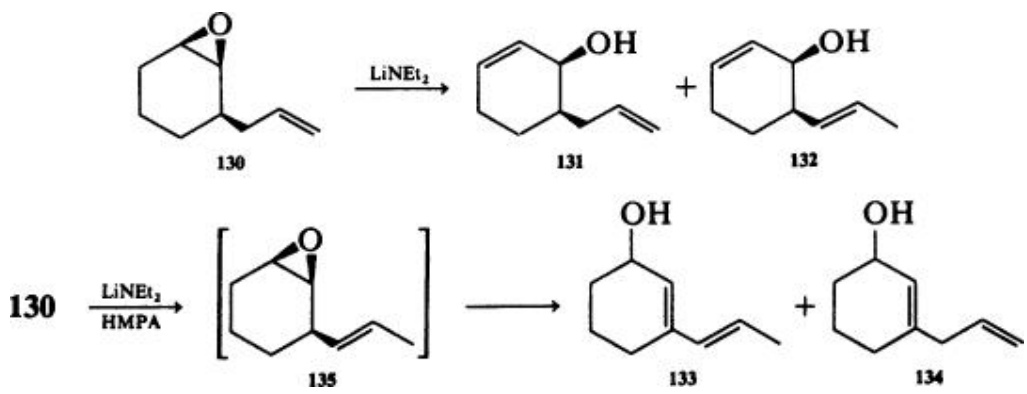
The isomerization of epoxide **124** with lithium diethylamide in ether–hexane gives the anticipated allylic alcohol **125** as the major product. (11) In hexamethylphosphoramide, on the other hand, the epimeric cyclopropylcarbinols **126** are the predominant products (*cis*:*trans* = 5:95).



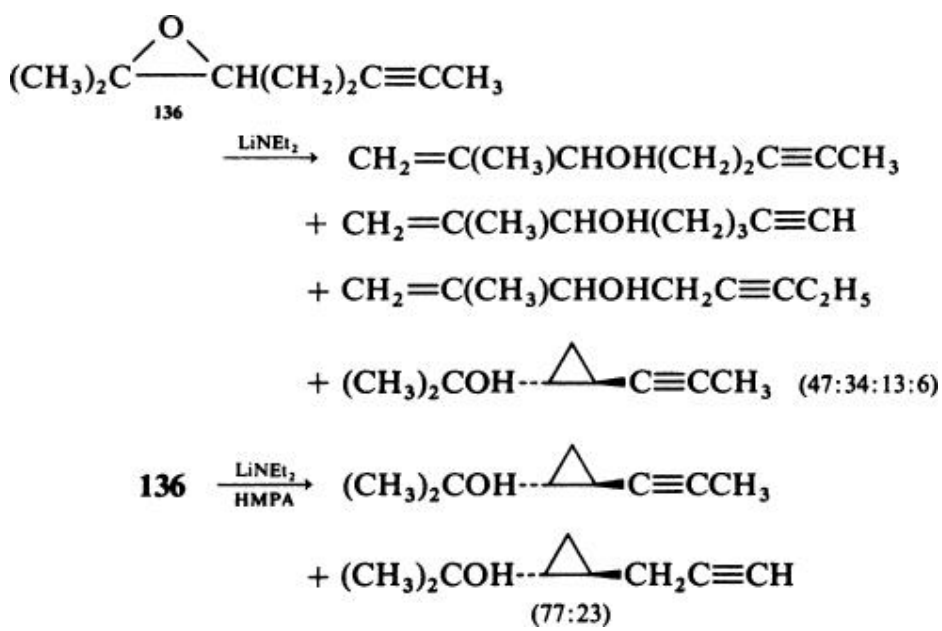
The unsaturated spiroepoxide **127** is an interesting substrate. Under non-polar conditions some of the tricyclic alcohol **128** is formed along with the nucleophilic adduct. (11) This reaction is a rare example of an intramolecular capture of a carbenoid center by a double bond. In hexamethylphosphoramide a clean conversion to bicyclic alcohol **129** is observed.



Double-bond isomerizations can take place under the strongly basic conditions of these reactions. This is illustrated with *cis* epoxide **130**, which reacts slowly in ether–hexane to yield a mixture of alcohols **131** and **132**. (11) The *syn* mechanism accounts for the regioselectivity of this β elimination. Alcohol **132** is derived from **131** by base isomerization, presumably after epoxide rearrangement. A much faster reaction occurs in the presence of hexamethylphosphoramide, leading predominantly to alcohols **133** and **134**. It appears likely that double-bond migration precedes epoxide opening in this instance. The isomeric epoxide **135** thus formed as a transient intermediate is activated for elimination in the direction observed. Interestingly, β elimination in the case of **135** probably takes place with *anti* stereochemistry. Cyclopropane formation by intramolecular alkylation of the intermediate allylic anion from **130** is precluded by its stereochemistry, unlike the isomeric *trans* epoxide **34**, which yields the cyclopropyl compound **35** cleanly (p. 360).

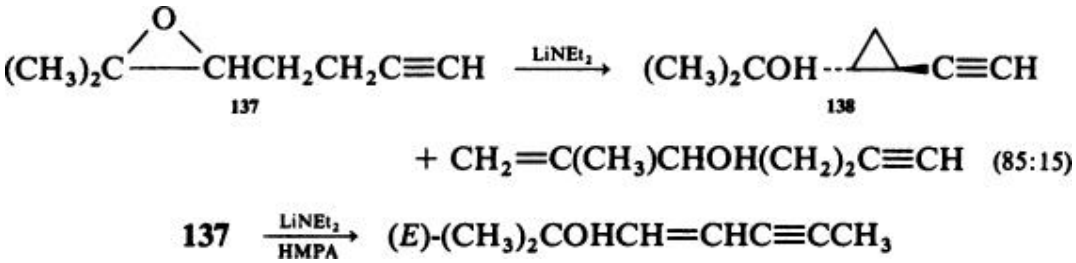


Phenyl activation for cyclopropane formation in hexamethylphosphoramide-mediated reactions also works well, as illustrated earlier. (11) However, the ease of metalation of acetylenic compounds leads to complications with epoxides of this type. Thus treatment of epoxide **136** with lithium diethylamide in ether–hexane results in dominant β elimination toward a CH_3 group. (100) Nonetheless, a mixture of products is obtained as a result of concomitant migration of the triple bond. The isomerization of **136** in hexamethylphosphoramide results in cyclopropane formation, although triple-bond migration is a problem.



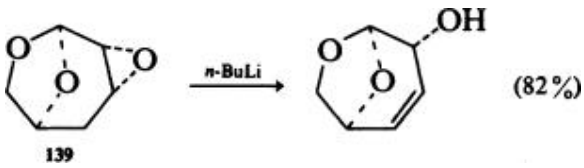
A somewhat different situation is found with the terminal acetylene **137**, which requires two equivalents of base since removal of the acetylenic hydrogen

consumes the first equivalent. In this case intramolecular alkylation to give the cyclopropane **138** is the major conversion in ether–hexane. (100) On the other hand, added hexamethylphosphoramide results in the clean production of the vinylacetylene shown in the accompanying formula. (101) Under these conditions rapid isomerization of the triple bond is probably responsible for this conversion. Thus the usual effect of hexamethylphosphoramide is reversed with this particular epoxide.

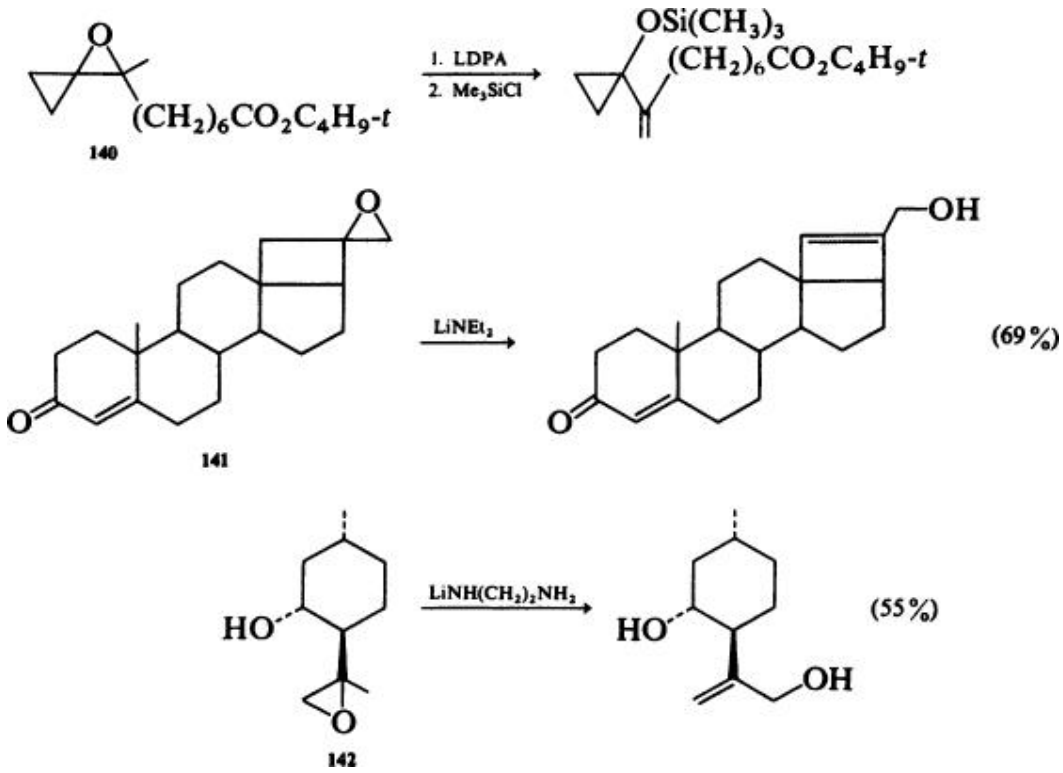


3.3. Functional Epoxides

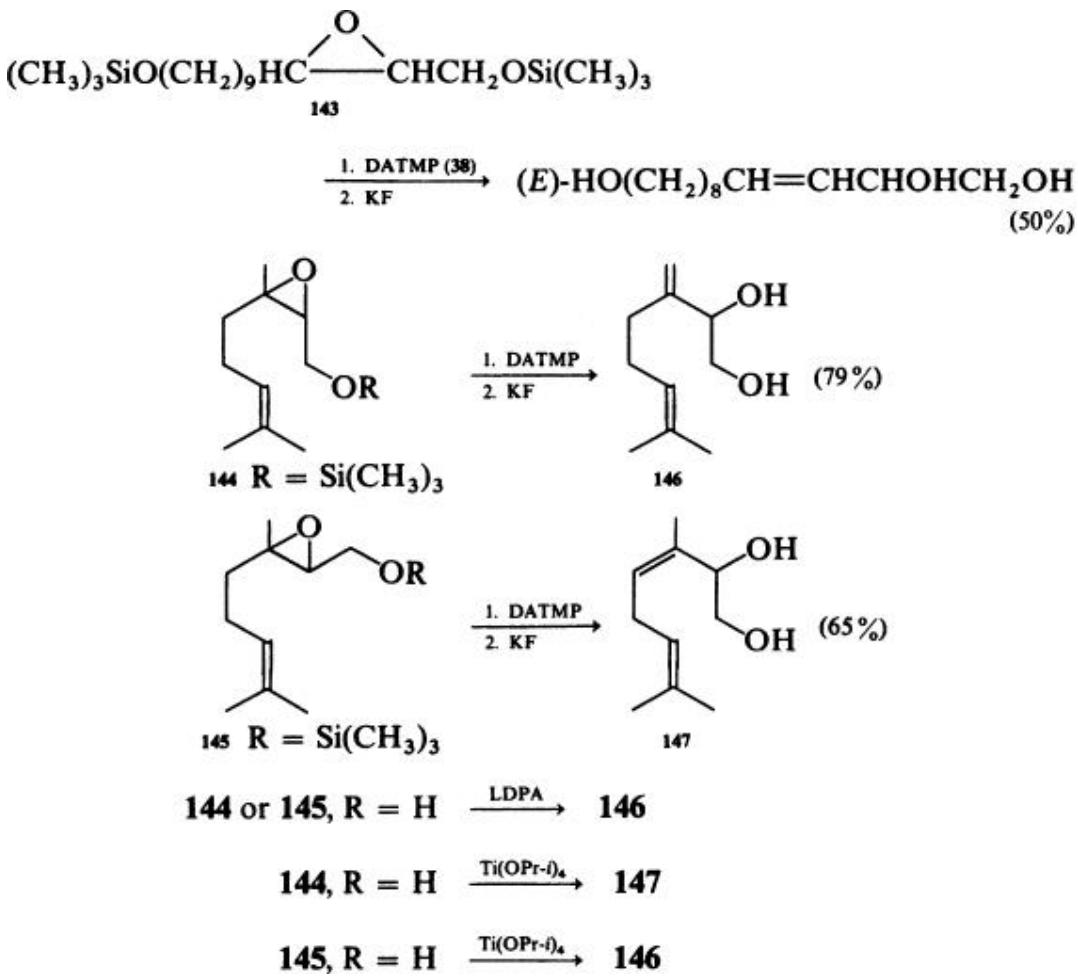
Relatively little work is recorded concerning the strong-base isomerizations of epoxides bearing important additional functionality. This is largely attributable to the anticipated reactivity of many functional groups under the reaction conditions normally utilized. However, epoxides possessing remote functionality in protected form behave in the normal fashion. Several examples of compounds with ether and ketal groups are discussed along with saturated epoxides. A further illustration is provided by the smooth isomerization of the sugar derivative **139** by *n*-butyllithium. (102)



In fact, significant functionality remote from the epoxide group can be tolerated as indicated by the conversions of the carbonyl compounds **140** and **141**. (98, 103) Alcohol **142** is also transformed to the indicated diol by the lithium salt of ethylenediamine. (104)



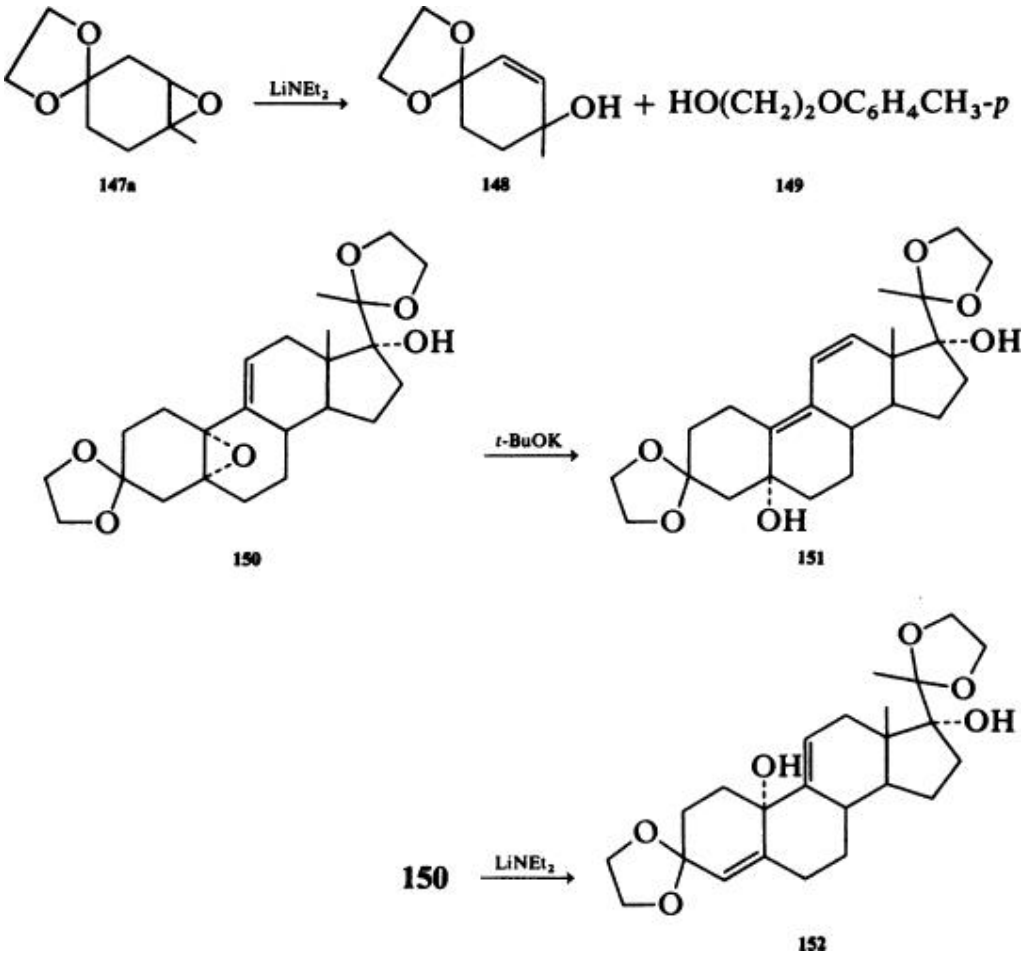
The trimethylsilyl ethers of a number of epoxides of allylic alcohols are isomerized by diethylaluminum 2,2,6,6-tetramethylpiperidide (**38**). (105) These substrates lead to the production of vicinal diols after removal of the protecting group. Thus elimination always involves removal of a proton away from the protected alcohol, even where the possible modes of elimination involve two equivalently situated CH_2 groups, as with epoxide **143**. The stereochemical features of these reactions are identical to those of simple trisubstituted epoxides with diethylaluminum 2,2,6,6-tetramethylpiperidide. This is illustrated for the isomeric epoxides **144** and **145** that yield products derived from the more stable complex. Interestingly, these substrates in their unprotected alcohol forms both react with lithium diisopropylamide to give diol **146** as the predominant product. (106)



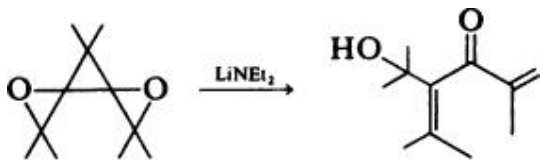
The above conversions contrast with those of the free alcohols with titanium tetraisopropoxide. (106) This reagent, like diethylaluminum 2,2,6,6-tetramethylpiperidide, results in stereospecific isomerizations, but just the opposite stereochemistry is observed, specifically, **144** →**147** and **145** → **146**. A free hydroxyl group is necessary for the titanium reagent to be effective, implicating a *syn* elimination from an intermediate titanium alkoxide of the substrate. The generality of these results is not entirely clear since complex cationic reactions occur with other substrates. Nonetheless, the concept of using a second functional group to control the site of proton removal is worthy of further exploration.

The isomerization of epoxide **147a** yields allylic alcohol **148** in addition to large amounts of the secondary product **149**. (107) The regiochemistry of this reaction is unexpected and may result from the involvement of the ketal function as an alternative site for base coordination. This complexation could direct proton removal from the adjacent CH_2 group. A second example in

which a ketal group is suspected of directing elimination is the steroid epoxide **150**. (108) This compound gives the 1,4-elimination product **151** with potassium *tert*-butoxide, whereas lithium amides promote a 1,2 elimination toward the ketal to yield **152**. However, different stereochemical requirements for the two elimination reagents cannot be discounted with this conformationally rigid molecule.



Neighboring reactive functions can be more intimately involved in the isomerizations. The diepoxides **153** and **154** demonstrate that rather complicated structural changes occur in some instances. (100, 109) The chloroepoxide **155** is a further example of such complex behavior. (110)



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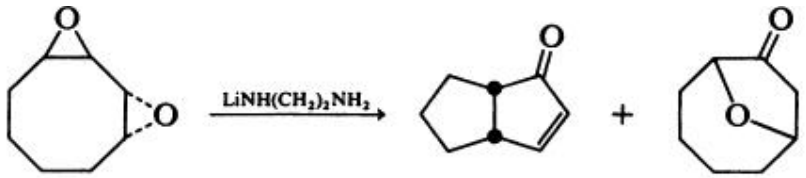
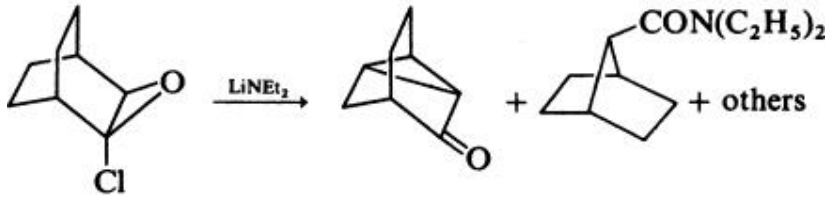
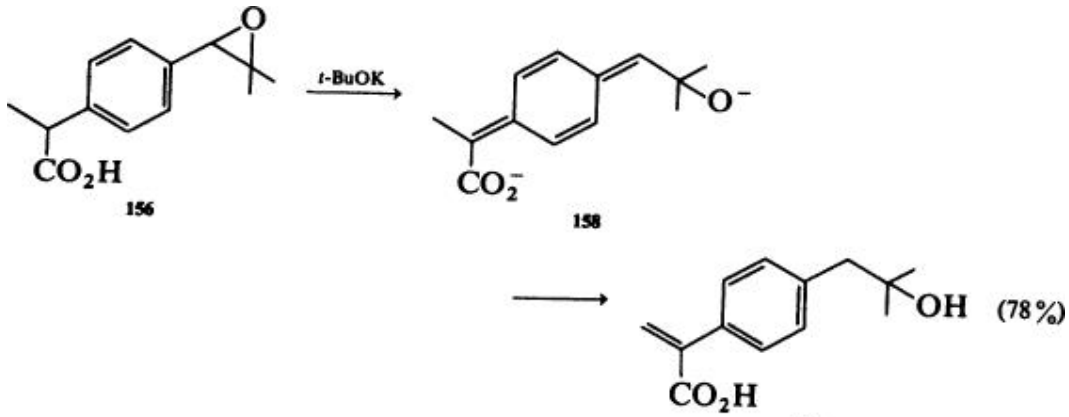


154 (9:92;80%)



155

A final illustration demonstrating a rather long-range interaction involves the potassium *tert*-butoxide-promoted isomerization of epoxide **156** to conjugate acid **157**. (111) This intriguing conversion is rationalized in terms of a 1,6 elimination to give intermediate **158**, which subsequently tautomerizes to the observed product **157**.



156 158 157

It is clear from the examples discussed above that many functionalized epoxides undergo complex transformations involving interplay of the two functions. In some of these cases, useful synthetic conversions take place that can be understood and perhaps anticipated. In other instances the usual reactions occur with or without modification by the second functional group. Surprisingly, reactive functionality (*e.g.*, carbonyl groups) remote from the epoxide site is not detrimental to isomerizations in several cases. These results suggest that much profitable work remains to be done with functionalized epoxides.

Specifically excluded from this survey are the isomerizations of epoxides with neighboring carbonyl groups and other anion-stabilizing substituents that dominate the reactions of such substrates with their own typical chemistry. Nonetheless, some leading references to these rearrangements, eliminations, and intramolecular alkylation reactions are supplied here for completeness. (1, 4, 5)

4. Experimental Conditions

The choice of an appropriate base for effecting a desired transformation of a specific epoxide is discussed in detail in the section entitled “Scope and Limitations.” The present section is concerned with the experimental aspects of performing an epoxide isomerization in the laboratory, focusing on the other parameters that can exert a significant influence on the outcome of an isomerization.

4.1. Lithium Amide Reactions

The lithium amides are the most commonly used bases, especially the diethyl and diisopropyl derivatives. These are usually prepared by the addition of a standardized solution of *n*-butyllithium in hexane to a solution of the amine in ether. No particular precautions are required in this preparation other than the use of a dry apparatus, anhydrous solvents, an inert atmosphere, and syringe techniques for the transfer of alkyllithium solutions. The quantity of the lithium amide is estimated by assuming complete conversion of the alkyllithium. Methyllithium in ether is also occasionally used to prepare amides. Alternatively, the lithium amides can be prepared directly from the amines and metallic lithium under appropriate conditions. (97, 112-114) This approach is not used frequently but provides a more economical source of amides for large-scale preparations. *N*-Lithioethylenediamine is readily prepared in this fashion and is recommended as a base worthy of more widespread application for epoxide isomerizations. (26, 115) It should be noted, however, that direct preparations of lithium amides utilizing hexamethylphosphoramide give a reagent that may behave differently from the lithium amides obtained in the usual fashion because of the special effect of hexamethylphosphoramide on some epoxide rearrangements. Of course, hexamethylphosphoramide can be added to the usual preparations of lithium amides when it is needed to produce a desired effect. Likewise, excess lithium salts, sometimes present in solutions of organolithium reagents prepared in ether, also have a significant effect on the course of certain isomerizations. (58)

Typical reaction conditions for performing an epoxide isomerization call for treatment of the substrate with an excess of the lithium amide, often 2–5 eqs, in an ether–hexane solvent mixture. This is convenient, especially with small-scale reactions, in dealing with impurities that consume base. Furthermore, base decomposition of the ether solvent also occurs. (53) However, a large excess of amide is not, in general, necessary. (6, 15, 27, 33, 116) In fact, excess base can be detrimental when subsequent transformations of the primary products are facile (p. 373). Moreover, in the well-studied isomerization of cyclohexene oxide, a decrease in the ratio of base to epoxide results in lowering of the amount of both nucleophilic adduct and cyclohexanone relative to 2-cyclohexenol. (53)

The ether–hexane solvent system is most often used for lithium amide isomerizations, partly as a consequence of the usual method of preparation of this base and partly because this solvent mixture usually results in homogeneous reaction mixtures, which is seldom the case with less polar solvents. Although the ratio of the solvent components is usually rather arbitrarily determined, it is recommended that the amount of ether be limited to that required to obtain homogeneous solutions. Isomerizations are significantly slower in pure ether solvent, undoubtedly as a result of complexation of the lithium amide with ether. This competition between the substrate and the solvent for the reagent results in lowering of the concentration of the epoxide–base complex. This situation may also affect the selectivity of certain epoxide isomerizations that are controlled by complex formation, but information regarding this point is lacking.

Most isomerizations by lithium amides are run between 0° and reflux temperature of the ether–hexane solvent mixture, usually the latter. Some epoxides react very slowly under these conditions. In this situation benzene can be employed to facilitate reaction by allowing higher reaction temperatures. However, side reactions are also more likely at higher temperatures. Alternatively, tetrahydrofuran is used in some instances, although it should be noted that this polar solvent can significantly affect the product ratios in cases where competing processes are possible.

In general, it is strongly recommended that the course of the reaction be followed closely by a rapid assay technique such as gas chromatography or thinlayer chromatography. This allows the reaction to be stopped when the starting epoxide is consumed or when the desired product is maximized.

The significant influence of hexamethylphosphoramide on epoxide rearrangements is very useful synthetically in a number of instances. Although many of these reactions have been performed in hexamethylphosphoramide as the solvent, its effect appears to be achieved with as little as 2–4 eqs of hexamethylphosphoramide per equivalent of lithium amide. (11, 26, 27, 100) This is recommended in view of the cost and biohazards associated with hexamethylphosphoramide.

Caution! Hexamethylphosphoramide is an animal carcinogen. Appropriate handling and disposal procedures should be followed.

4.2. Organolithium Reactions

Organolithium reagents are only infrequently used as the functioning base in epoxide isomerizations. Nonetheless, these reagents are of central importance because they serve as the source of amide bases in most rearrangement procedures. A recent *Organic Reactions* chapter details the use of

organolithium reagents. (117) Solutions of *n*-butyllithium in hexane are generally available from commercial sources, as are methyllithium solutions in ether, *tert*-butyllithium solutions in hydrocarbon solvents, and other organolithium reagents. When these are not available, organolithium reagents can be obtained by literature preparations. (118-120) The quality of fresh commercial solutions is generally good, and the indicated assay is usually sufficiently accurate for most synthetic applications. In reactions where the exact amount of base is critical or when the concentration of the reagent is uncertain (as with aged commercial reagents or those prepared in the laboratory), several methods of analysis are available. (117, 121-123) The direct titration with *sec*-butyl alcohol by use of 2,2-biquinoline as an indicator is a simple and reliable method for the assay of most organolithium reagents. (124) The commonly used hexane solutions of *n*-butyllithium can normally be stored for several months in bottles capped with serum stoppers, provided transfers are carefully performed by using dry syringes. The deposit of large amounts of solid material from the clear yellow commercial solutions is usually an indication of reagent deterioration.

Isomerizations using organolithium reagents as the effective base are generally performed with an excess of the reagent in hydrocarbon solvents at temperatures ranging from –78° to reflux temperatures of the solvents employed. Because of possible decomposition of the reagent at higher temperatures, the lowest convenient temperatures consistent with reasonable reaction times are recommended. Ether is sometimes used as a solvent or cosolvent in isomerizations in which organolithium reagents are used as bases, but these reactions appear to give more complicated product mixtures than do those run in hydrocarbon solvents.

4.3. Aluminum Amide Reactions

These reagents deserve more widespread application to the isomerization of suitable epoxides. The efficiency of these conversions appears to increase with increasing steric bulk of the substituents on nitrogen. The diethylaluminum derivative of 2,2,6,6-tetramethylpiperidine is most commonly used, although the species derived from diisopropylamine, *N*-methylaniline, and other more readily available amines also effect the reaction, albeit more slowly. (32)

Reactions are normally performed with four equivalents of the reagent at 0° in benzene solution. Hexane is also suitable as a reaction medium, but ether and especially tetrahydrofuran inhibit the reaction. Diethylaluminum *N*-methylanilide is a superior reagent for the analogous isomerization of several oxetanes, which require prolonged reaction times in refluxing benzene. (125) Use of this reagent with certain epoxides may also be advantageous.

The aluminum amides are prepared *in situ* in the desired solvent prior to the addition of the epoxide. The reaction of the appropriate lithium amide,

prepared in the usual manner, with diethylaluminum chloride at 0° in benzene for 30 minutes is a convenient procedure. (32) Alternatively, diisobutylaluminum hydride reacts with secondary amines in benzene at slightly higher temperatures with the evolution of hydrogen to give related aluminum amides. (32) Secondary amines also react with trimethylaluminum to give dimethylaluminum amides and methane. (126)

The various organoaluminum reagents required for preparation of the aluminum amides are available commercially in lecture bottles as the pure materials or as standardized solutions in hydrocarbon solvents. (127) The pure materials are highly *pyrophoric* and require special handling. (128) It is much more convenient to use the commercial solutions, and this is recommended whenever possible. These solutions react with air and moisture, but they can be transferred by dry syringe techniques from solutions stored in bottles sealed with rubber septa. Reactions should be run under anhydrous conditions under an inert atmosphere of dry nitrogen or argon.

5. Experimental Procedures

The following procedures have been chosen to illustrate typical reaction conditions for effecting various types of isomerization with different bases. Reactions are normally performed in an apparatus consisting of a three-necked, round-bottomed flask equipped with a reflux condenser to which a gas inlet tube is attached, with a pressure-regulating dropping funnel and a rubber septum. A stream of dry nitrogen is passed through the assembly while it is flame-dried with a Bunsen burner and subsequently charged with the reactants. At this point the system is closed so as to maintain a slight positive pressure of nitrogen. A magnetic stirrer is usually adequate for agitation. The course of the reaction is followed by withdrawing aliquots by syringe through the rubber septum. These are hydrolyzed and assayed for the disappearance of starting material by gas chromatography or thin-layer chromatography (TLC).

5.1. 2-*p*-Tolyl-2-propen-1-ol (Isomerization of a Terminal Epoxide to an Allylic Alcohol by Using Lithium Diisopropylamide in Ether) (92)

To a solution of 3 g (0.03 mol) of diisopropylamine in 25 mL of ether was added 15 mL (0.03 mol) of 2.1 *M* *n*-butyllithium in ether. After 30 minutes a solution of 3 g (0.02 mol) of 1,2-epoxy-2-*p*-tolylpropane in 40 mL of ether was added slowly. The reaction mixture was stirred overnight at room temperature, heated to reflux for 4 hours, and, after cooling, partitioned between ether and water. The organic layer was washed successively with water and brine and dried. Solvent evaporation followed by chromatography on neutral alumina afforded 2.6 g (85%) of 2-*p*-tolyl-2-propen-1-ol; bp 105–107° (5–7 torr); IR(neat) 3380, 3070, 1650, 1050, 890, and 820 cm^{-1}. This product showed a single spot by TLC analysis.

5.2. *trans*-Pinocarveol [2(10)-Pinen-3 α -ol] (Isomerization of a 1-Methylepoxycycloalkane to an Allylic Alcohol with Lithium Diethylamide in Ether–Hexane) (6)

The isomerization of α -pinene oxide to *trans*-pinocarveol in 90–95% yield is described in *Organic Syntheses*. (6)

5.3. 12-Methoxy-19-norpodocarpa-4(18),8,11,13-tetraen-3 α -ol (Isomerization of a 1-Methylepoxycycloalkane with Lithium Diethylamide in Ether) (78)

To 12.1 mL (0.02 mol) of a 1.6 *M* solution of methyllithium in ether at 0° was added 3 mL of dry diethylamine in 5 mL of ether. After 10 minutes the evolution of methane had ceased. A solution of 1.0 g (0.004 mol) of 3 α ,4 α -epoxy-12-methoxy-18-norpodocarpa-8,11,13-triene in 18 mL of ether was added slowly, and the mixture was heated to reflux for 36 hours. The cooled reaction mixture was poured into ice water and extracted with ether. The ether

extract was washed with 2 *N* hydrochloric acid, water, and brine. After drying, the solvent was removed to give 1.0 g (100%) of 12-methoxy-19-norpodocarpa-4(18),8,11,13-tetraen-3 α -ol, which crystallized from light petroleum as needles: mp 93–95°, $[\alpha]_D$ + 163° (c, 0.45), IR ($CHCl_3$) 3600, 1660, 1040, and 910 cm^{-1}, NMR δ 1.00 (s, 3), 1.62 (s, 1, exchanged with D_2O), 3.88 (s, 3), 4.35 (m, 1), 4.74 (br s, 1), 5.07 (br s, 1), and 6.7–7.0 (m, 3).

5.4. 2,4,7-Cyclononatrien-1-ol (Isomerization of an Unsaturated Epoxide to an Allylic Alcohol by *n*-Butyllithium in Ether–Hexane) (129)

To a stirred solution of 40.0 g (0.30 mol) of 1,4,7-cyclononatriene oxide in 650 mL of ether at 0° was added 320 mL (0.51 mol) of a 1.6 *M* solution of *n*-butyllithium in hexane over a period of 1 hour. After an additional 4.5 hours, 200 mL of a saturated ammonium chloride solution was added slowly, with stirring and cooling, over a period of approximately 1 hour. The organic layer was separated, washed with 200 mL of water and dried over anhydrous potassium carbonate. The solvent was removed to give a yellow oil that was distilled under reduced pressure to give 6 g of volatile material followed by 26.3 g (66%) of 2,4,7-cyclononatrien-1-ol of bp 80° (0.1 torr) that crystallized on standing, mp 40–42°. The IR spectrum of this material was identical with that of an authentic sample.

5.5. *endo,cis*-Bicyclo[3.3.0]octan-2-ol (Isomerization of an Epoxycycloalkane to a Bicyclic Alcohol by Lithium Diisopropylamide in Ether–Hexane) (58)

To a solution consisting of 90 mL (0.22 mol) of 2.4 *M n*-butyllithium in hexane and 90 mL of ether in an ice bath was added 35 mL (0.25 mol) of diisopropylamine over a period of 5 minutes. After 30 minutes 12.6 g (0.1 mol) of *cis*-cyclooctene oxide in 20 mL of ether was added and the reaction mixture was heated to reflux for 2 days. The cooled solution was washed with 100 mL of water, dried, and concentrated under reduced pressure. The residue was distilled under vacuum to afford 10.1 g (80%) of *endo,cis*-bicyclo[3.3.0]octan-2-ol, bp 103–105° (25 torr). This product contained less than 2% of 2-cyclooctenol as determined by gas chromatographic analysis on a Carbowax 20 M column.

5.6. *exo*-Tetracyclo[5.2.1.0.^{3,7}0^{3,8}]decan-9-ol (Transannular Insertion of a Polycyclic Epoxide by Lithium Diethylamide in Benzene–Hexane) (130)

To a solution of 0.45 g (0.006 mol) of dry diethylamine in 2.8 mL of dry benzene at 0° was added 2.8 mL (0.0045 mol) of 1.6 *M n*-butyllithium in hexane. After stirring for 20 minutes, a solution of 0.40 g (0.0027 mol) of *exo*-8,9-epoxytricyclo[5.2.1.0^{3,7}]decane in 2.8 mL of benzene was added, and the mixture was heated to reflux for 48 hours. The cooled reaction mixture was poured into ice water and extracted with ether. The extract was washed with saturated aqueous ammonium chloride solution and water, dried, and concentrated. Distillation at reduced pressure gave 0.34 g (86%) of tetracyclic

alcohol: bp 50–60° (0.4 torr), mp 56–70°, near IR (CCl_4) 1.676 μ*M* (ε 0.38), NMR (CCl_4) δ 1.0–2.1 (m, 14), 3.86 (s, 1), and 4.45 (s, 1).

5.7. 1,2-Benzocyclohepten-4-one (Isomerization of an Epoxide to a Ketone with Lithium Diisopropylamide) (41)

To a solution of 0.77 mL (0.0055 mol) of diisopropylamine in 15 mL of anhydrous ether at –78° was slowly added 2.4 mL (0.0055 mol) of 2.3 *M* *n*-butyllithium. After 15 minutes the mixture was allowed to warm to room temperature, and a solution of 0.35 g (0.0022 mol) of 3,4-epoxy-1,2-benzocycloheptene in 5 mL of anhydrous ether was added slowly. After stirring for 1 hour, the reaction was quenched by the addition of 5 mL of water. The aqueous layer was separated and extracted twice with 10 mL of ether. The combined organic layers were washed with 10% aqueous hydrochloric acid, dried, and concentrated. Vacuum transfer gave 0.22 g (63%) of 1,2-benzocyclohepten-4-one: NMR ($CDCl_3$) δ 1.6–2.0 (m, 2), 2.3–2.8 (m, 2), 2.8–3.0 (m, 2), 3.7 (s, 2), and 7.2 (s, 4).

5.8. *endo*-Bicyclo[5.1.0]oct-5-en-2-ol (Isomerization of an Unsaturated Epoxide to a Cyclopropylcarbinol by *N*-Lithioethylenediamine in Benzene–Hexamethylphosphoramide (11)

5.8.1.1. Preparation of N-Lithioethylenediamine in Benzene (115)

Lithium (5 g of a 40% dispersion in mineral oil) was added to the reaction vessel under an inert atmosphere and washed several times with small quantities of pentane, which was removed by syringe. Anhydrous benzene (200 mL) was added, followed by 18 g (0.3 mol) of dry ethylenediamine over a period of 30 minutes. The reaction mixture was heated to reflux; the liberation of gas was followed by attachment of a gas bubbler. After about 3 hours, gas evolution ceased and a white powder formed in the reaction flask.

5.8.1.2. Isomerization of 5,6-Epoxycyclooctene

The base mixture was cooled to room temperature and 200 mL of hexamethylphosphoramide was added, followed by 10.0 g (0.08 mol) of epoxide. The epoxide disappeared within 15 minutes to give a product containing the desired alcohol and a small amount of 3,5-cyclooctadienol. The mixture was heated to 60° until the latter was completely converted to 3-cyclooctenone. The cooled reaction mixture was poured into a large amount of water and extracted with ether. The extract was washed with saturated ammonium chloride solution, dried, and concentrated. Distillation of the residue under reduced pressure gave, after a small forerun of 3-cyclooctenone, 8.0 g (80%) of *endo*-bicyclo[5.1.0]oct-5-en-2-ol: bp 90° (9 torr); IR 3350, 3080, 3008, 1660, 695 cm^{-1}; NMR (CCl_4) δ 0.3–2.1 (m, 8), 3.5 (s, 1), 3.95–4.35 (m, 1), and 5.1–5.9 (m, 2). (84)

5.9. (2-Phenylcyclopropyl)methanol (Formation of a Cyclopropylcarbinol by Lithium Diethylamide Prepared in Benzene–Hexamethylphosphoramide (11)

5.9.1.1. Base Preparation (114)

A mixture of 0.7 g (0.1 mol) of hammered lithium wire, 7.3 g (0.1 mol) of diethylamine, 20 mL of hexamethylphosphoramide and 20 mL of benzene was stirred at temperatures below 25° under an argon atmosphere for several hours until the lithium disappeared, giving a dark red homogeneous solution.

5.9.1.2. Isomerization of 4-Phenyl-1,2-epoxybutane

To 0.05 mol of the lithium diethylamide solution in benzene–hexamethylphosphoramide was added 2.0 g (0.013 mol) of epoxide. After 30 minutes the reaction mixture was poured into a large quantity of water and extracted with ether. The extract was washed with saturated ammonium chloride solution, dried, and concentrated. The residue was distilled at reduced pressure to give 1.7 g (86%) of *trans*-(2-phenylcyclopropyl)methanol: bp 137° (12 torr); IR 3340, 1605, 1595, 740, 695 cm^{-1}; NMR (250 MHz) δ0.68–0.85 (m, 2), 1.16–1.40 (m, 1), 1.60–1.78 (m, 1), 3.30–3.54 (m, 2), 3.98 (s, 1), and 6.70–7.40 (m, 5). A small doublet at δ 3.8 indicated the presence of 6% of the *cis* isomer.

5.10. (*E*)-2-Cyclododecenol (Isomerization of an Epoxide to an Allylic Alcohol by Diethylaluminum 2,2,6,6-Tetramethylpiperidide) (32)

5.10.1.1. Preparation of Diethylaluminum 2,2,6,6-Tetramethylpiperidide

A benzene solution of 1 eq of diethylaluminum chloride was added dropwise at 0° to a solution of 1 eq of lithium 2,2,6,6-tetramethylpiperidide prepared in the usual fashion in benzene. (131) The resulting slurry was stirred for 30 minutes and used immediately.

5.10.1.2. Isomerization of trans-Epoxycyclododecane

To a stirred mixture of 0.004 mol of diethylaluminum 2,2,6,6-tetramethylpiperidide in 10 mL of benzene at 0° was added dropwise over 5 minutes a solution of 0.18 g (0.001 mol) of epoxide in 3 mL of benzene. The mixture was stirred at 0° until analysis indicated the absence of starting material. The reaction was quenched by the addition of ice-cold 1 *N* hydrochloric acid. The organic layer was separated, and the aqueous layer was extracted with ether. The organic layers were combined, washed with brine, dried, and concentrated. The residue was purified by preparative TLC (R_f 0.22 in 1:2 ether–hexane) to give 99% of (*E*)-2-cyclododecenol: IR (neat) 3330–3370, 1465, 1450, 970 cm^{-1}; NMR (CCl_4) δ 3.73–4.20 (1, m), 4.97–5.82 (2, m); mass spectrum (*m/z*) 182 (16), 164 (13), 139 (32), 125 (46), and 98 (100).

6. Tabular Survey

Examples of base-promoted isomerizations of unactivated epoxides falling within the limitations described in the text are summarized in the following tables. An attempt has been made to include all reports of such reactions appearing in the literature through late 1982. The tables are organized to parallel the discussion in the section entitled “Scope and Limitations.” Table I lists the saturated epoxides that have been exposed to base isomerization. This table is further divided into acyclic, spiro, and cyclic epoxides. Table II gives epoxides that have unsaturation present in the molecule as olefinic, acetylenic, or aromatic functions and is subdivided according to the type of unsaturation present. Table III groups those epoxides that have additional functionality in the molecule. Within each subdivision of these tables the epoxides utilized as substrates are listed in order of increasing number of carbon atoms and then increasing number of hydrogen atoms in the molecular formula. A dash in the yield or reaction conditions column indicates that the appropriate information was not reported. In many instances products that are not isomeric with the starting epoxide are given in order to help define the limitations on the title reaction.

The following abbreviations are used in the tables:

DATMP	Diethylaluminum 2,2,6,6-tetramethylpiperidide
Diglyme	Diethylene glycol dimethyl ether
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
Ether	Diethyl ether
HMPA	Hexamethylphosphoramide
LDPA	Lithium diisopropylamide
THF	Tetrahydrofuran
THP	Tetrahydropyranyl ether

Table I. Saturated Epoxides

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Table II. Unsaturated Epoxides

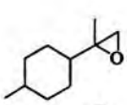
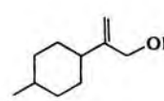
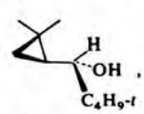
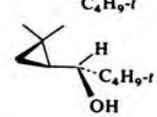
View PDF

Table III. Functional Epoxides

View PDF

TABLE I. Saturated Epoxides

A. Acyclic Epoxides

	Epoxide	Base	Reaction Conditions	Products and Yields (%)	Refs.
C_5	$CH_3HC(O)CHC_2H_5$ *cis:trans* (44:56)	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux	$CH_2{=}CHCHOHC_2H_5$ (68)	21
	$CH_3HC(O)C(CH_3)_2$	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux	$CH_2{=}CHCOH(CH_3)_2$ (I), $CH_3CHOHC(CH_3){=}CH_2$ (II) 41:59 (—)	21
		t-BuOK, 1 eq	DMSO, 45°, 2 weeks	I (80) + II (15)	46
C_6	$(CH_3)_2C(O)C(CH_3)_2$	*t*-BuOK, 1 eq	DMSO, 45°, 2 weeks	$CH_2{=}C(CH_3)COH(CH_3)_2$ (98)	46
	$t\text{-}C_4H_9HC(O)CH_2$	*t*-BuOK, 1 eq	DMSO, room temp, 2 weeks	No reaction	46
C_8	$n\text{-}C_3H_7HC(O)CHC_3H_7\text{-}n$ *cis*	$LiNEt_2$, 1.2 eq	Ether, room temp, 3 days	(*E*)-$n\text{-}C_3H_7CHOHCH{=}CHC_2H_5$ (55), *threo*-$n\text{-}C_3H_7CHOHCH(C_3H_7\text{-}n)N(C_2H_5)_2$ (14)	15
	$n\text{-}C_3H_7HC(O)CHC_3H_7\text{-}n$ *trans*	$LiNEt_2$, 1.2 eq	Ether, room temp, 3 days	(*E*)-$n\text{-}C_3H_7CHOHCH{=}CHC_2H_5$ (79), $(n\text{-}C_3H_7)_2CHCHO$ (3)	15
	$i\text{-}C_3H_7HC(O)CHC_3H_7\text{-}n$ *cis:trans* (88:12)	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux	(*E*)-$i\text{-}C_3H_7CHOHCH{=}CHC_2H_5$ (—)	21
	$i\text{-}C_3H_7HC(O)CHC_3H_7\text{-}i$	$LiNEt_2$	Ether–hexane, reflux, 2 days	No reaction	29
	$t\text{-}C_4H_9HC(O)C(CH_3)_2$	$LiNEt_2$, 2.5 eq *t*-BuLi, 3 eq	Ether–hexane, reflux Pentane, reflux, 1 day	$t\text{-}C_4H_9CHOHC(CH_3){=}CH_2$ (87) " (74)	52 50
C_{10}		LDPA, 2.2 eq	Ether, room temp, 6 hr	 (64)	49
	$t\text{-}C_4H_9HC(O)CHC_4H_9\text{-}t$ *trans*	*t*-BuLi, 3 eq	Pentane, reflux	$t\text{-}C_4H_9COCH_2C_4H_9\text{-}t$,  ,  28:56:16 (—)	39
	$t\text{-}C_4H_9HC(O)CHC_4H_9\text{-}t$ *cis*	*t*-BuLi, 3 eq	Pentane, reflux	$t\text{-}C_4H_9COCH_2C_4H_9\text{-}t$, $(t\text{-}C_4H_9)_2COHCH_2C_4H_9\text{-}t$ 73:27 (—)	62
C_{12}	(*Z*)-$n\text{-}C_4H_9HC(O)C(CH_3)C_5H_{11}\text{-}n$	DATMP, 4 eq	C_6H_6, 0°, 2 hr	$n\text{-}C_4H_9CHOHC({=}CH_2)C_5H_{11}\text{-}n$ (90)	31, 32
	(*E*)-$n\text{-}C_4H_9HC(O)C(CH_3)C_5H_{11}\text{-}n$	DATMP, 4 eq	C_6H_6, 0°, 2 hr	$n\text{-}C_4H_9CHOHC({=}CH_2)C_5H_{11}\text{-}n$ (12), (*E*)-$n\text{-}C_4H_9CHOHC(CH_3){=}CHC_4H_9\text{-}n$ (78)	31, 32

B. Spiro Epoxides

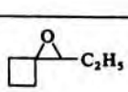
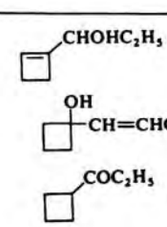
C_7		$LiNEt_2$, 2.5 eq	Ether–hexane, reflux, 6 hr	 (51) + (10) + (3)	29

TABLE I. SATURATED EPOXIDES (*Continued*)

B. Spiro Epoxides (Continued)

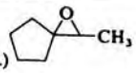
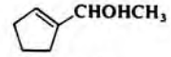
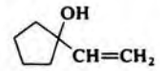
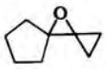
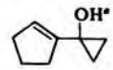
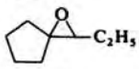
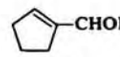
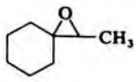
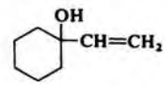
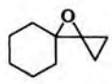
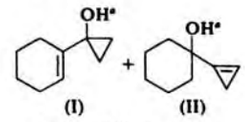
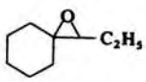
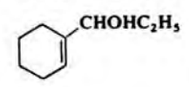
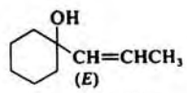
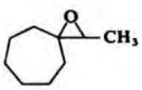
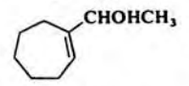
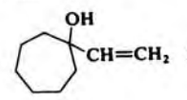
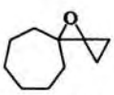
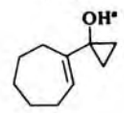
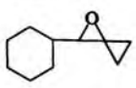
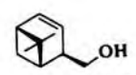
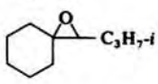
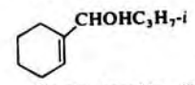
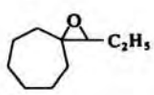
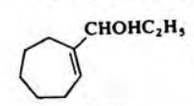
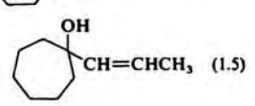
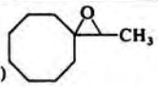
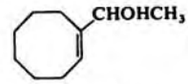
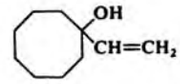
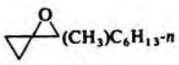
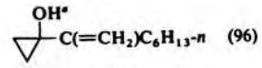
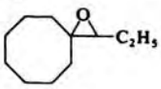
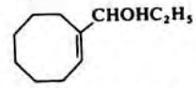
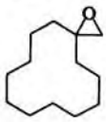
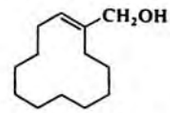
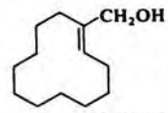
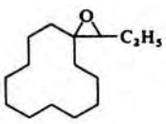
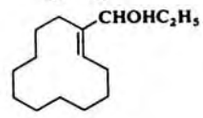
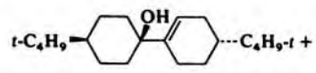
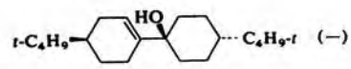
Epoxide	Base	Reaction Conditions	Products and Yields (%)	Refs.
C_7 (*Contd.*) 	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux, 1.5 hr	 (57) +  (25)	29
C_8 	$LiNEt_2$, 2 eq	Hexane, room temp	 (94)	79
	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux, 1 hr	 (84)	29
	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux, 2 hr	 (66)	29
C_9 	$LiNEt_2$, 1.1 eq	Ether, room temp, 2 hr	 (I) + (II) 60:40 (–)	79
	$LiNMe_2$, 1.1 eq	Ether, room temp, 2 hr	I + II 14:86 (–)	79
	$LiNEt_2$, 1.1 eq	Pentane, room temp, 2 hr	I + II 90:10 (–)	79
	LDPA, 1.1 eq	Ether, room temp, 2 hr	I + II 12:88 (–)	79
	n-BuLi, 1.1 eq	Pentane, room temp, 2 hr	I + II 78:22 (–)	79
	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux, 49 hr	 (3.5) +  (66)	29
	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux, 2.5 hr	 (28) +  (46)	29
C_{10} 	$LiNEt_2$, 2 eq	Hexane, room temp	 (91)	79
	$LiNEt_2$	—	No reaction	79
	$LiNEt_2$, 2.5 eq	Ether, reflux, 2 days	 (81)	48
	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux, 72 hr	 (–) + Starting epoxide (76)	29
	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux, 5 hr	 (74.5) +  (1.5)	29

TABLE I. SATURATED EPOXIDES (*Continued*)

B. Spiro Epoxides (Continued)

Epoxide	Base	Reaction Conditions	Products and Yields (%)	Refs.
C_{10} (*Contd.*) 	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux, 2 hr	 (48) +  (25)	29
C_{11} 	$LiNEt_2$, 2 eq	Hexane, room temp	 (96)	79
	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux, 2 hr	 (74)	29
C_{13} 	DATMP, 4 eq	C_6H_6, 0°, 2 hr	 (63) +  (29)	31, 32
C_{15} 	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux, 22 hr	 (55)	29
C_{20}	*n*-BuLi	Ether	 +  (—)	133

C. Alicyclic Epoxides

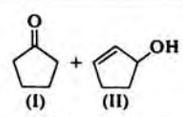
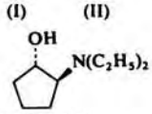
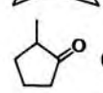
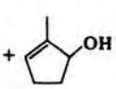
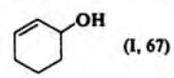
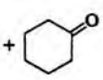
C_5	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux, 2 days	 (I) (II) (I + II, 12) +  (36)	52
	LDPA	Ether–hexane, reflux, 7 hr	I + II (50)	52
	DATMP, 4 eq	C_6H_6, 0°, 2 hr	No reaction	32
C_6	$LiNEt_2$, 3 eq	C_6H_6–hexane, room temp, 65 hr	(46)	10
	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux, 5 hr	 (7.5) +  (61)	67
	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux, 2 days	 (I, 67)	52, 53
	LDPA, 2.5 eq	Ether–hexane, HMPA (5 eq), room temp, 1.5 hr	I (—)	26
	n-BuLi, 3 eq	Ether–hexane, −78°, 3 hr; 25°, 15 hr	I +  34:66 (—)	42

TABLE I. SATURATED EPOXIDES (*Continued*)

C. Alicyclic Expoxides (Continued)

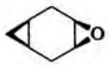
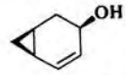
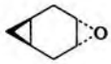
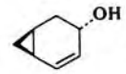
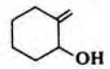
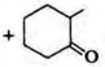
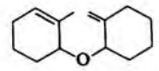
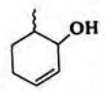
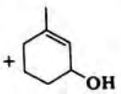
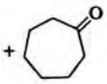
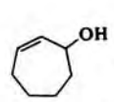
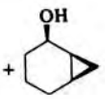
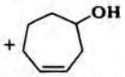
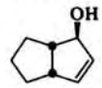
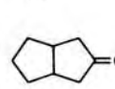
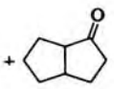
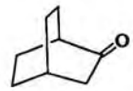
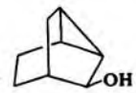
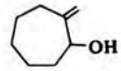
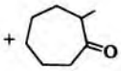
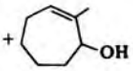
Epoxide	Base	Reaction Conditions	Products and Yields (%)	Refs.
C_6 (*Contd.*)	*t*-BuOK, 2.8 eq	Pyridine, reflux, 1 hr	I (—)	134
	DATMP	C_6H_6, 0°, 3 hr	No reaction	32
C_7 	$LiNEt_2$, 4.7 eq	Ether–hexane, room temp, 48 hr	 (40)	55
	$LiNEt_2$, 4.7 eq	Ether–hexane, room temp, 48 hr	 (—)	55
	$LiNEt_2$, 2.3 eq	C_6H_6, reflux, 2 days	(55)	60
	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux, 1 day	 (46) +  (6) +  (6)	67
cis:*trans* *ca.* 50:50	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux	 (66) +  (2) *cis*:*trans* *ca.* 50:50	21
	$LiNEt_2$, 2.5 eq	C_6H_6, reflux, 2 days	(13) +  (I, 16) +  (II, 10) +  (III, 18)	26, 39
	$LiNEt_2$, 2.5 eq	HMPA, 30°, 20 min	II +  82:18 (—)	26
	n-BuLi, 3 eq	Ether–hexane, −78°, 3 hr; 25°, 15 hr	I + III 87:13 (—)	42
	DATMP	C_6H_6, 0°, 3 hr	No reaction	32
C_8	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux, 48 hr	 (55) + (I)  (7) +  (10)	18
	$LiNEt_2$, 2.5 eq	HMPA, 45°, 3 hr	I (70)	26
	$LiNEt_2$, 2.5 eq	C_6H_6	(—)	18
	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux, 20 hr	 (90) +  (5)	18
	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux, 1 day	 (I, quant)	67
	$LiNEt_2$, 2.5 eq	C_6H_6, reflux, 2 days	I (24) +  (II, 34) +  (10)	67

TABLE I. SATURATED EPOXIDES (*Continued*)

C. Alicyclic Expoxides (Continued)

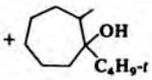
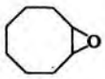
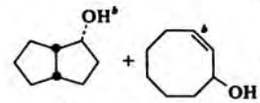
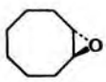
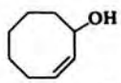
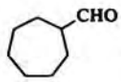
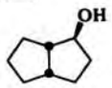
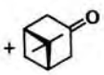
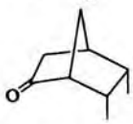
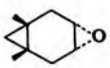
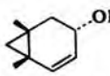
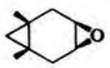
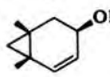
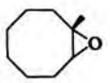
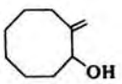
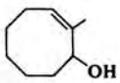
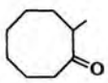
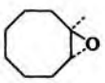
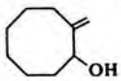
Epoxide	Base	Reaction Conditions	Products and Yields (%)	Refs.
C_8 (*Contd.*)	*t*-BuLi, 3 eq	Pentane, reflux 2 days	I (52) + II (6) +  (9)	67
	$LiNEt_2$	Ether–hexane, (1:1), reflux, 2 days	 (I) (II) 8:92 (≥80)	42
	$LiNEt_2$	Ether–hexane	I + II 20:80 (—)	58
	$LiNEt_2$	Ether–hexane, LiBr	I + II 80:20 (—)	58
	$LiNEt_2$	Ether–LiBr, reflux, 2 days	I (70) + II (16)	9
	$LiNEt_2$	Ether, reflux, 2 days	I + II 65:35 (≥80)	42
	$LiNEt_2$	Ether–HMPA, room temp	I[b] + II[b] 4:96 (≥80)	42
	$LiNEt_2$	THF, reflux, 2 days	I[b] + II[b] 7:93 (≥80)	42
	$LiNEt_2$	THF, HMPA, 1 eq	I[b] + II[b] 9:91 (≥80)	42
	LDPA, 2.2 eq	Ether–hexane, reflux, 2 days	I + II 98:2 (80)	26, 58
	LDPA, 2.5 eq	HMPA, room temp, 72 hr	II (70)	26
	n-BuLi, 3 eq	Ether–hexane, −78°, 3 hr; 25°, 15 hr	I (Good)	42
	C_6H_5Li, 1.8 eq	C_6H_6, LiBr, reflux, 18 hr	I (50) + II (27)	9
	t-BuOK, 1 eq	DMSO, 80°, 22 hr	II (40)	59
	$LiNEt_2$, 2.4 eq	C_6H_6, reflux, 72 hr	 (10) +  (27) +  (47)	9
C_9	$LiNEt_2$, 2.5 eq	C_6H_6, reflux, 2 days	(17) +  (40) + (20)	52
	$LiNEt_2$, 2.5 eq	Ether–hexane	 (86)	18
	$LiNEt_2$, 4.7 eq	Ether–hexane, room temp, 48 hr	 (—)	55
	$LiNEt_2$, 4.7 eq	Ether–hexane, room temp, 48 hr	 (—)	55
	$LiNEt_2$, 2.5 eq	Ether–hexane, room temp, 1 day	 (I, 88) +  (II, 6)	67
	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux, 1 day	I (37) + II (41) +  (III, 9)	67
	$LiNEt_2$, 2.5 eq	C_6H_6, reflux, 2 days	I (5) + II (68) + III (22)	67
	$LiN(C_6H_{11})Pr\text{-}i$, 2 eq	10 min	 (56)	135
C_{10}	$LiNEt_2$, 1.7 eq	C_6H_6, reflux, 2 days	(86)	130

TABLE I. SATURATED EPOXIDES (*Continued*)

C. Alicyclic Expoxides (Continued)

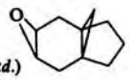
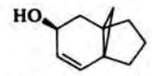
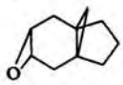
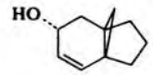
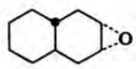
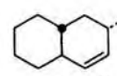
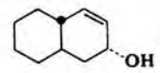
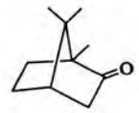
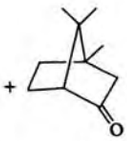
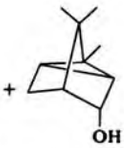
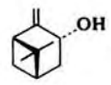
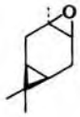
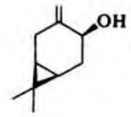
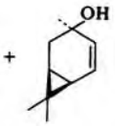
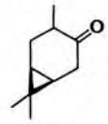
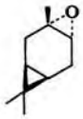
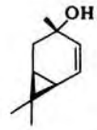
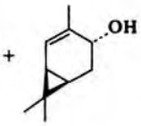
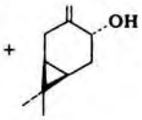
Epoxide	Base	Reaction Conditions	Products and Yields (%)	Refs.
C_{10} (*Contd.*) 	$LiNEt_2$, 4.7 eq	Ether–hexane, room temp, 2 days	 (–)	55
	$LiNEt_2$, 4.7 eq	Ether–hexane, room temp, 2 days	 (–)	55
	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux	 +  2:98 (–)	21
	$LiNEt_2$, 2.5 eq	C_6H_6, reflux, 12 hr	 (I, 32) +  (II, 26) + (III, 9) +  (IV, 11)	18
	$LiNEt_2$, 2.5 eq	C_6H_6, room temp, 12 hr	I + II + III + IV 35:26:24:15 (–)	18
	$LiNEt_2$, 1 eq	Ether–hexane, reflux, 6 hr	 (I, 90–95)	6, 52
	n-BuLi	Ether, reflux, 6 hr	I (51)	132
	t-BuOK, 4.5 eq	*t*-BuOH, reflux, 3 hr	No reaction	86
	t-BuOK, 4.4 eq	DMF, 115°, 1 hr	I + (II) 71:29 (–)	85
	t-BuOK, 4.5 eq	Pyridine, reflux, 4.5 hr	I (91)	86
	t-BuOK, 1.1 eq	DMSO, 90°, 48 hr	I + II 62:38 (–)	85
	*n*-PrLi, 5 eq	Ether, room temp, 24 hr; reflux, 16 hr	 (26) +  (27) +  (23)	80
	*n*-PrLi, 5 eq	Ether, room temp, 24 hr; reflux, 3 hr	 (46) +  (I, 26) +  (6)	80
	t-BuOK, 4.4 eq	Pyridine, reflux 2.5 hr	I (75)	134

TABLE I. SATURATED EPOXIDES (*Continued*)

C. *Alicyclic Epoxides* (*Continued*)

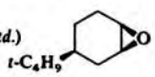
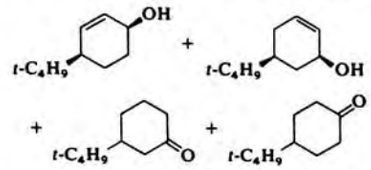
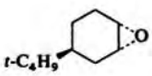
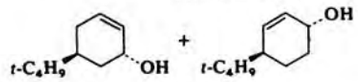
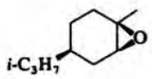
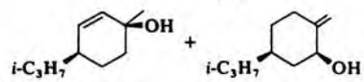
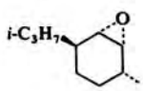
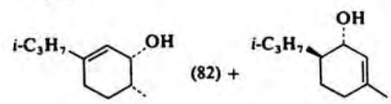
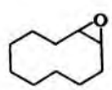
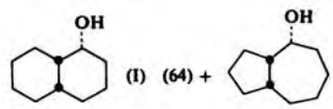
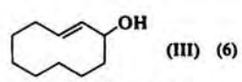
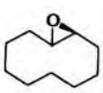
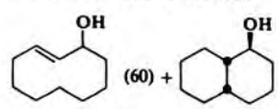
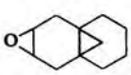
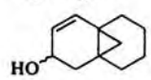
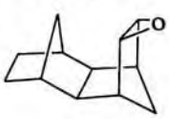
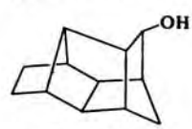
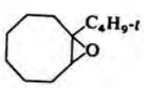
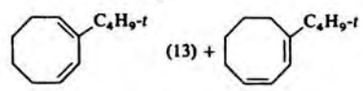
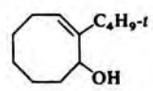
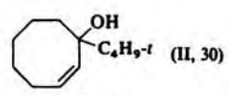
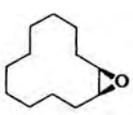
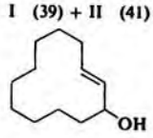
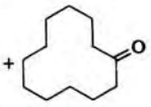
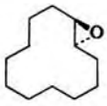
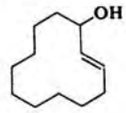
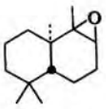
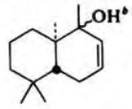
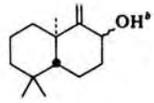
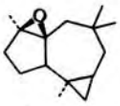
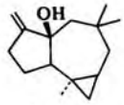
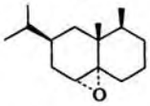
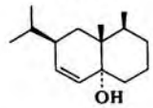
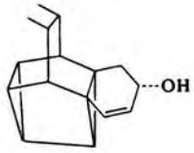
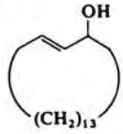
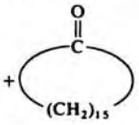
Epoxide	Base	Reaction Conditions	Products and Yields (%)	Refs.
C_{10} (*Contd.*) 	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux	 50:24:22:4 (—)	21
	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux	 97:3 (—)	21
	*n*-PrLi, 6 eq	Ether, reflux, 30 hr	 (I, 58) (II, 31)	138
	t-BuOK, 3 eq	Pyridine, reflux, 3 hr	II (—)	134
	t-BuOK, 3 eq	DMF, 120°, 1 hr	II (—)	134
	t-BuOK, 3 eq	DMSO, 115°, 3 hr	II (—)	134
	*n*-PrLi, 5 eq	Ether, room temp, 24 hr; reflux, 6 hr	 (82) + (13)	138
	$LiNEt_2$, 1 eq	C_6H_6, reflux, 72 hr	 (I) (64) + (II) (7) +	33
	n-BuLi	Ether–hexane, −78°, 3 hr; 25°, 15 hr	 (III) (6) I + II + III 98:1:1 (Good)	42
	$LiNEt_2$, 3.3 eq	C_6H_6, reflux, 42 hr	 (60) + (33)	33
C_{11} 	$LiNEt_2$, 2.5 eq	Ether, reflux, 24 hr	 (67)	56
C_{12} 	$LiNEt_2$, 2.5 eq	Ether, reflux, 48 hr	 (82)	61
	$LiNEt_2$, 2.5 eq	C_6H_6, reflux, 3 days	 (13) + (4) +  (I, 42) +  (II, 30)	67
	t-BuLi, 3 eq	Pentane, reflux, 3 days	I (39) + II (41)	67
	*n*-BuLi, 1.6 eq	Ether, −40°, 30 min; room temp, 15 hr; reflux, 1 hr	 (I, 62)	30

TABLE I. SATURATED EPOXIDES (*Continued*)

C. Alicyclic Epoxides (Continued)

Epoxide	Base	Reaction Conditions	Products and Yields (%)	Refs.
C_{12} (*Contd.*)	*n*-BuLi, 3 eq	Ether–hexane, −78°, 3 hr; 25°, 15 hr	I +  89:11 (Good)	42
	DATMP, 4 eq	C_6H_6, 0°, 3 hr	I (20)	31
	n-BuLi, 1.6 eq	Ether, reflux	 (I, 72–81)	30
		C_6H_6, 0°, 1 hr	I (<5)	31
	Et_2NAlEt_2	C_6H_6, 0°, 1 hr	I (<5)	32
	$(i\text{-}Pr)_2NAlEt_2$	C_6H_6, 0°, 1 hr	I (45)	31
	$(C_6H_{11})_2NAlEt_2$	C_6H_6, 0°, 1 hr	I (36)	32
	DATMP, 4 eq	C_6H_6, 0°, 3 hr	I (90)	31
C_{14}  *α*, *β* epoxides (ca. 50:50)	LDPA, 3 eq	THF, reflux, 6 hr	 (22) +  (47)	73
C_{15} 	$LiNEt_2$	—	 (68)	139
	LDPA	THF	 (—)	77
C_{16}	$LiNEt_2$, 11 eq	Ether–hexane	 (42)	140
cis-trans mixture	$LiNEt_2$, 2.4 eq	Ether–hexane, reflux, 51 hr	 (I) + 93:7 (—)	51
	n-BuLi, 1.1 eq	Hexane, 0°, 30 min; 65°, 3 hr	I (19) +  (54)	51

[a] The product was isolated as the trimethylsilyl ether.
[b] The product was analyzed after oxidation to the corresponding ketone with CrO_3.

TABLE II. Unsaturated Epoxides

A. Olefinic Epoxides

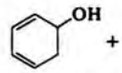
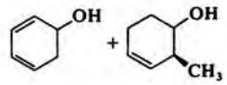
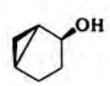
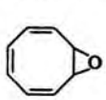
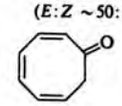
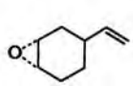
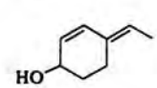
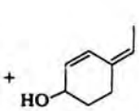
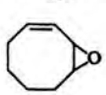
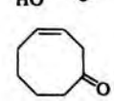
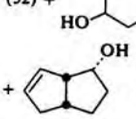
	Epoxide	Base	Reaction Conditions	Products and Yields (%)	Refs.
C_5	H_2C—O—$C(CH_3)CH{=}CH_2$	LDPA, 1.3 eq	Ether	$HOCH_2C({=}CH_2)CH{=}CH_2$ (76)	91
C_6		$LiNEt_2$, 2.5 eq	Ether–hexane, room temp	Benzene (Quant)	44
		CH_3Li		 + benzene 75:25 (—)	93
		$CH_2{=}CHCH_2Li$	Ether–THF, HMPA	" 65:35 (—)	84
		$LiNEt_2$, 2.5 eq	Ether–hexane, room temp	Benzene (Quant)	44
		CH_3Li	—	 63:37 (—)	93
	CH_3HC—O—$CHCH_2CH{=}CH_2$ *cis*	$LiNEt_2$, 2.5 eq	Ether–hexane, several minutes	(*E*)-$CH_3CHOHCH{=}CHCH{=}CH_2$ (Quant)	44
	CH_3HC—O—$CHCH_2CH{=}CH_2$ *trans*	$LiNEt_2$, 2.5 eq	Ether–hexane, 4 min	$CH_3CHOHCH{=}CHCH{=}CH_2$ (85) (*E*:*Z* = 88:12)	44
	H_2C—O—$CH(CH_2)_2CH{=}CH_2$	$LiNEt_2$, 2.5 eq	Ether–HMPA, room temp, 15 min	$HOCH_2$— —$CH{=}CH_2$ (37) + $HOCH_2$— ···$CH{=}CH_2$ (63)	11
		$LiNH(CH_2)_2NH_2$	Ether–hexane, reflux, 72 hr	$H_2N(CH_2)_2NHCH_2CHOH(CH_2)_2CH{=}CH_2$ (—) +  (I, —)	11
		t-BuLi	Hydrocarbon	*t*-$C_4H_9CH{=}CH(CH_2)_2CH{=}CH_2$ (34) + (*E*, *Z* mixture) *t*-$C_4H_9CH_2CHOH(CH_2)_2CH{=}CH_2$ (11) + I (9)	39, 50
	CH_3HC—O—$CHCH{=}CHCH_3$ *cis, cis*	$LiNEt_2$, 2.5 eq	Ether–hexane, 20 min	(*E*)-$CH_3CHOHCH{=}CHCH{=}CH_2$ (I, 65) + (*E*)-$CH_3COCH{=}CHC_2H_5$ (II, 1)	44
		LDPA, 2.5 eq	Ether–hexane, 6 hr	I (18) + II (7) + (*Z*)-$CH_3COCH_2CH{=}CHCH_3$ (45)	44
	CH_3HC—O—$CHCH{=}CHCH_3$ *trans, trans*	$LiNEt_2$, 2.5 eq	Ether–hexane, 1 hr	(*E*)-$CH_3CHOHCH{=}CHCH{=}CH_2$ (I, 11) + (*E*)-$CH_2{=}CHCHOHCH{=}CHCH_3$ (II, 5) + aminoalcohols (54)	44
		LDPA, 2.5 eq	Ether–hexane, 6 hr	I (38) + II (22) + (*E*)-$CH_3COCH_2CH{=}CHCH_3$ (12) + (*E*)-$CH_3COCH{=}CHC_2H_5$ (3)	44
C_7		$LiNEt_2$, 2.5 eq	Ether–hexane, room temp	Toluene (Quant)	44
	C_2H_5HC—O—$CHCH_2CH{=}CH_2$	$LiNEt_2$, 1 eq	C_6H_6–HMPA, room temp, 1 hr	$C_2H_5CHOHCH{=}CHCH{=}CH_2$ (52) (*E*:*Z* ~50:50)	97
C_8		$LiNEt_2$, 2 eq	Ether, −10°, 15 min	 (71)	95
		$(CH_3)_3C_6H_2Li$	Ether, room temp, 40 hr	" (39)	95
		$LiNEt_2$	HMPA, room temp, 30 min	 (52) +  (28)	11
		$LiNEt_2$, 2.5 eq	Ether–hexane, reflux, 22 hr	 (I, 6) +  (II, 65)	96
		$LiNEt_2$, 2.5 eq	C_6H_6, 50°, 1 hr	" (3) + " (97)	26

TABLE II. UNSATURATED EPOXIDES (*Continued*)

A. Olefinic Epoxides (Continued)

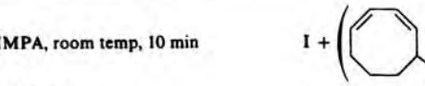
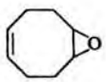
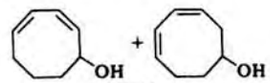
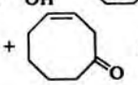
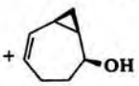
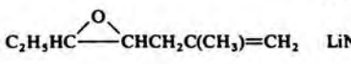
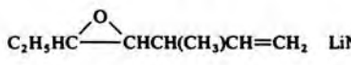
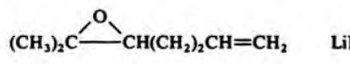
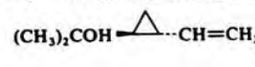
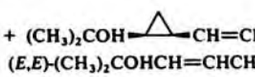
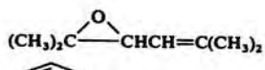
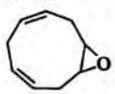
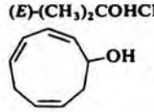
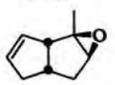
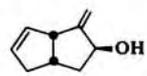
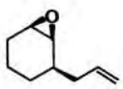
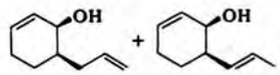
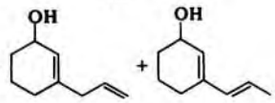
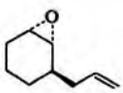
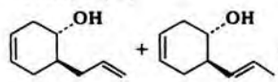
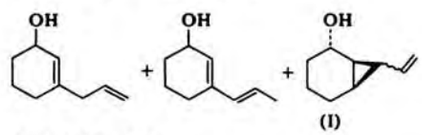
Epoxide	Base	Reaction Conditions	Products and Yields (%)	Refs.
C_8 (*Contd.*)	$LiNEt_2$, 2.5 eq	HMPA, room temp, 10 min	I + ( 20:80 (—)	26
	$LiNH(CH_2)_2NH_2$	HMPA, 60°	I (84)	26
	$LiNEt_2$, 2.5 eq	Ether–hexane, room temp, 7 hr	 (I, 32)	96
	$LiNEt_2$, 2.5 eq	Ether–hexane, room temp, 2 days	I (15) +  (30) + (22)	96
	$LiNEt_2$, 2.5 eq	HMPA, 35°, 15 min	I (8) +  (II, 92)	11
	LDPA, 2.5 eq	HMPA	I + II 21:79 (—)	11
	$LiNHC_6H_{11}$, 2.5 eq	HMPA	I + II 8:92 (—)	11
	$LiNH(CH_2)_2NH_2$, 3.7 eq	C_6H_6–HMPA, room temp, 15 min	I (4) + II (76)	11
	$LiNEt_2$, 1 eq	C_6H_6–HMPA, room temp, 1 hr	$C_2H_5CHOHCH{=}CHC(CH_3){=}CH_2$ (77) (E:Z ~50:50)	97
	$LiNEt_2$, 1 eq	C_6H_6–HMPA, room temp, 1 hr	$C_2H_5CHOHCH{=}C(CH_3)CH{=}CH_2$ (79) (E:Z ~50:50)	97
	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux, 2 hr	$CH_2{=}C(CH_3)CHOH(CH_2)_2CH{=}CH_2$ +  (I) 97:3 (—)	11
	$LiNEt_2$, 2.5 eq	HMPA, room temp, 1 hr	I +  + (E,E)-$(CH_3)_2COHCH{=}CHCH{=}CHCH_3$ 90:5:5 (—)	11
	$LiNEt_2$, 2.5 eq	Ether–hexane, 26 min	(E)-$(CH_3)_2COHCH{=}CHC(CH_3){=}CH_2$ (Quant)	44
C_9 	n-BuLi, 2.3 eq	Ether–hexane, 0°, 5.5 hr	 (66)	129, 141
	$LiNEt_2$, 2.6 eq	Ether–hexane, reflux, 1.3 hr	 (73)	68
	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux, 2 days	 (I) (II) *ca.* 50:50 (25)	11
	$LiNEt_2$, 2.5 eq	Ether–HMPA, 35°, 40 min	(I + II) +  9:10:81 (—)	11
	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux, 1 day	 +  (I) 40:52:2:3:3 (—)	11
	$LiNEt_2$, 2.5 eq	Ether–HMPA, 35°, 40 min	I (—)	11

TABLE II. UNSATURATED EPOXIDES (*Continued*)

A. Olefinic Epoxides (Continued)

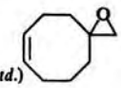
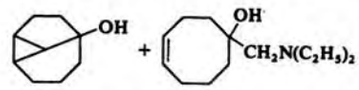
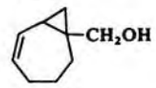
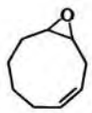
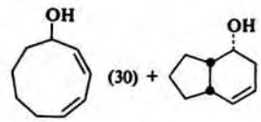
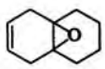
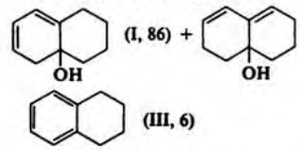
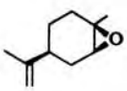
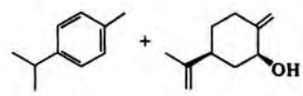
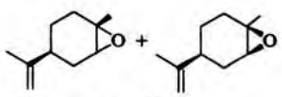
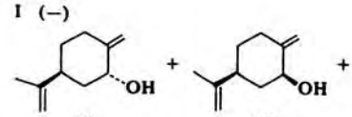
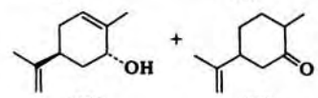
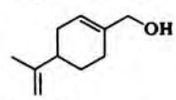
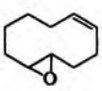
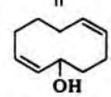
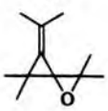
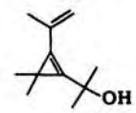
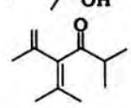
Epoxide	Base	Reaction Conditions	Products and Yields (%)	Refs.
C_9 (*Contd.*) 	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux, 4 days	 20:80 (–)	11
	$LiNEt_2$, 2.5 eq	HMPA, room temp, 3 hr	 (–)	11
	LDPA, 1.1 eq	Ether–hexane, 0°, 6 hr	 (30) + (20)	136
$(CH_3)_2C$—O—$C(CH_3)CH{=}C(CH_3)_2$	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux, 2 hr	$(CH_3)_2COHC(=CH_2)CH{=}C(CH_3)_2$ (53) + (*E*)-$(CH_3)_2COHC(CH_3){=}CHC(CH_3){=}CH_2$ (10) + $CH_2{=}C(CH_3)C(CH_3)OHCH{=}C(CH_3)_2$ (7)	44
C_{10} 	$LiNEt_2$, 2.5 eq	Ether–hexane, 1 min	 (I, 86) + (II, 8) + (III, 6)	44
	$LiNEt_2$, 2.5 eq	Ether–hexane, 45 min	I + II + III 13:45:42 (–)	44
	*t*-BuOK, 3 eq	Pyridine, reflux, 3.5 hr	 (I) 10:77 (–)	134
	t-BuOK, 2.4 eq	DMF, 120°, 5 hr	I (–)	134
	t-BuOK, 2.2 eq	DMSO, 120°, 5 hr	I (–)	134
 $\alpha:\beta = 55:45$	$LiNEt_2$, 2.5 eq	Ether, reflux, 6 hr	 (I) (II)	70
			 (III) (IV) 18:17:17:10 (–)	
	$LiNEt_2$	THF, 50°, 1 hr	I + II + III + IV 32:43:22:3 (–)	70
	LDPA	Hexane, 37°, 3 hr	I + II + III + IV +  32:35:18:10:1 (–)	70
	C_6H_5Li, 1.3 eq	Ether, reflux, 8–12 hr	 (72)	99
C_{11} 	$LiNEt_2$, 1.6 eq	Ether–hexane	 (I, 25) +  (II, 50)	142
	t-BuOK, 3 eq	C_6H_6, reflux, 6 hr	I (76) + II (9)	142

TABLE II. UNSATURATED EPOXIDES (*Continued*)

A. Olefinic Epoxides (Continued)

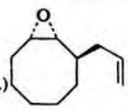
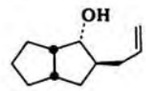
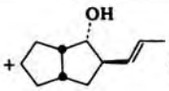
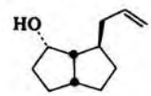
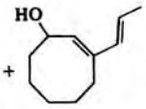
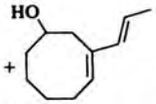
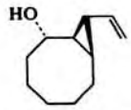
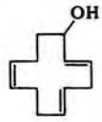
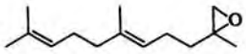
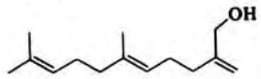
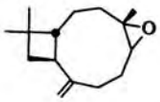
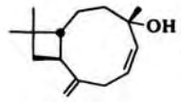
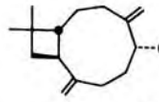
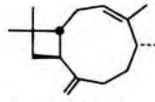
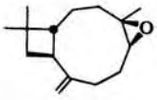
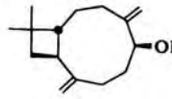
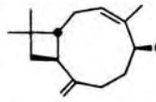
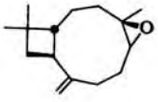
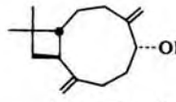
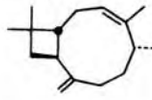
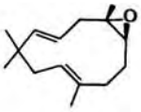
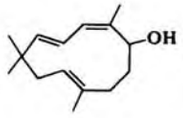
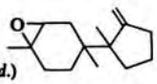
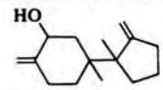
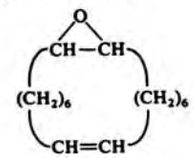
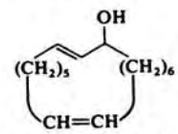
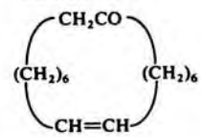
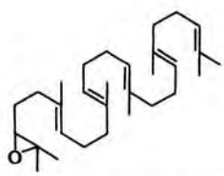
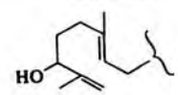
Epoxide	Base	Reaction Conditions	Products and Yields (%)	Refs.
C_{11} (*Contd.*) 	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux, 3 hr	 (65) +  (3) +  (19) +  (I, 2)	27
	$LiNEt_2$, 2.5 eq	Ether–hexane, 5 eq HMPA, room temp, several hours	I +  +  (II) 37:24:39 (–)	27
	$LiNEt_2$, 2.5 eq	Ether–hexane, 10 eq, HMPA, room temp, several hours	I + II 25:75 (–)	27
C_{12}	*n*-BuLi, 2.7 eq	Ether	 (66)	143
C_{14} 	, 2 eq	THF–hexane, room temp, 12 hr	 (54)	144
C_{15} 	*n*-BuLi, 1.4 eq	Ether–C_6H_6, 35°, 3 hr	 +  +  9:84:7 (–)	71
	*n*-BuLi, 1.4 eq	Ether–C_6H_6, 35°, 3 hr	 (43) +  (34)	71
	*n*-BuLi, 1.4 eq	Ether–C_6H_6, 35°, 3 hr	 (58) +  (8)	71
	LDPA, 3 eq	THF, room temp, 2 hr	 (70)	145

TABLE II. Unsaturated Epoxides (*Continued*)

A. Olefinic Epoxides (Continued)

Epoxide	Base	Reaction Conditions	Products and Yields (%)	Refs.
C_{15} (*Contd.*) 	$LiNEt_2$	C_6H_6, Reflux	 (—)	146
C_{16}  (Mixture of four isomers)	*n*-BuLi, 1.3 eq	Hexane, 65°, 3 hr	 (51) + (Mixture of *E,E* and *E,Z* isomers)	51
			 (—)	
C_{30} 	DATMP, 4 eq	C_6H_6, 0°, 2 hr	 (84)	31, 32

B. Acetylenic Epoxides

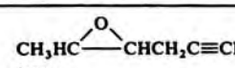
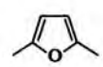
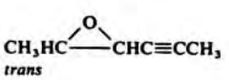
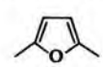
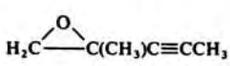
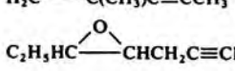
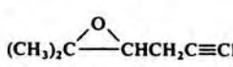
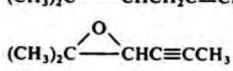
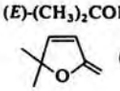
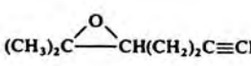
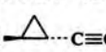
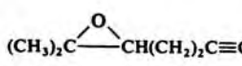
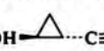
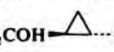
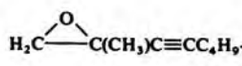
C_6  *trans*	*t*-BuOK, 1.1 eq	DMSO, 25–35°, 45 min	(*E*)-$CH_3CHOHCH{=}CHC{\equiv}CH$ (20) +  (50)	94
 *trans*	*t*-BuOK, 1.1 eq	DMSO, 25–35°, 45 min	(*E*)-$CH_3CHOHCH{=}CHC{\equiv}CH$ (9) +  (40)	94
	LDPA, 2.2 eq	Hexane, 0°, 2 hr: room temp, 1 hr	$HOCH_2C(CH_3){=}CHC{\equiv}CH$ (40)	147
C_7 	$LiNEt_2$, 2 eq	C_6H_6–HMPA, room temp, 1 hr	$C_2H_5CHOHCH{=}CHC{\equiv}CH$ (58) *E*:*Z* = *ca.* 50:50	97
	*t*-BuOK, 1.1 eq	DMSO, 25–35°, 45 min	(*E*)-$(CH_3)_2COHCH{=}CHC{\equiv}CH$ (70)	94
	*t*-BuOK, 1.1 eq	DMSO, 25–35°, 45 min	(*E*)-$(CH_3)_2COHCH{=}CHC{\equiv}CH$ (50) +  (7)	94
C_8 	$LiNEt_2$, 2 eq	Ether–HMPA, 45°, 2.3 hr	(*E*)-$(CH_3)_2COHCH{=}CHC{\equiv}CCH_3$ (—)	100, 101
	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux, 1 hr	$(CH_3)_2COH$–  ···$C{\equiv}CH$ + $CH_2{=}C(CH_3)CHOH(CH_2)_2C{\equiv}CH$ 85:15 (—)	100, 101
C_9 	$LiNEt_2$, 2.5 eq	Ether–hexane, reflux, 2 hr	$CH_2{=}C(CH_3)CHOHCH_2CH_2C{\equiv}CCH_3$ + $CH_2{=}C(CH_3)CHOHCH_2C{\equiv}CC_2H_5$ + $CH_2{=}C(CH_3)CHOH(CH_2)_3C{\equiv}CH$ + $(CH_3)_2COH$–  ···$C{\equiv}CCH_3$ (I) 47:13:34:6 (—)	100
	$LiNEt_2$, 2 eq	HMPA, 30°, 1 hr	I + $(CH_3)_2COH$–  ···$CH_2C{\equiv}CH$ 77:23 (—)	100
	LDPA, 2.2 eq	Hexane, reflux, 1 hr	$HOCH_2C({=}CH_2)C{\equiv}CC_4H_9$-*t* (15)	147

TABLE II. UNSATURATED EPOXIDES (*Continued*)

C. Aryl Epoxides

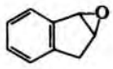
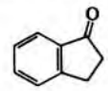
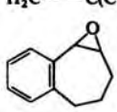
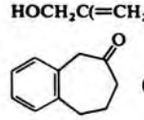
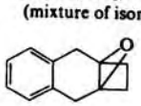
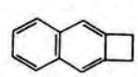
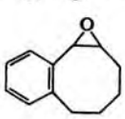
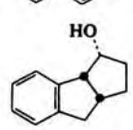
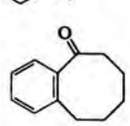
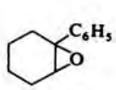
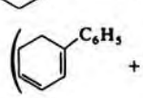
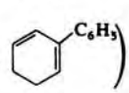
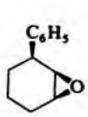
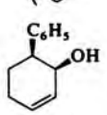
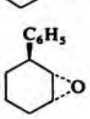
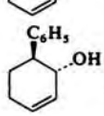
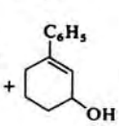
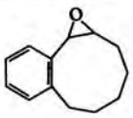
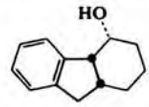
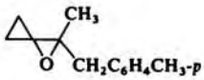
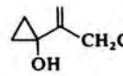
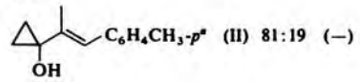
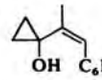
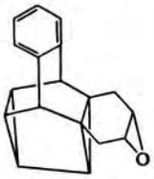
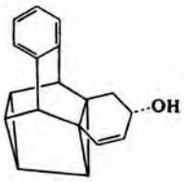
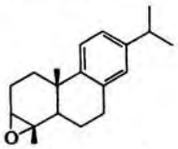
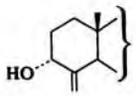
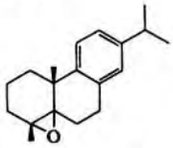
	Epoxide	Base	Reaction Conditions	Products and Yields (%)	Refs.
C_9		$LiNEt_2$	Ether–hexane, 1 min	 (10)	43
	$C_6H_5CH_2HC$—O—CH_2	$LiNEt_2$	Ether–hexane, 7 min	$C_6H_5CH{=}CHCH_2OH$ (High) (E:Z = 92:8)	43
	C_6H_5HC—O—$CHCH_3$ *cis*	$LiNEt_2$	Ether–hexane, 5 hr	$C_6H_5COC_2H_5$ + $C_6H_5CH_2COCH_3$ + $C_6H_5CHOHCH{=}CH_2$ 91:2:7 (—)	43
	C_6H_5HC—O—$CHCH_3$ *trans*:*cis* 94:6	$LiNEt_2$	Ether–hexane, reflux, 2 hr	$C_6H_5COC_2H_5$ + $C_6H_5CH_2COCH_3$ + $C_6H_5CHOHCH{=}CH_2$ + $C_6H_5COCH_3$ 33:13:35:19 (—)	43
C_{10}	$C_6H_5CH_2CH_2HC$—O—CH_2	$LiNEt_2$	HMPA, room temp, 30 min	C_6H_5—△···CH_2OH (81) + C_6H_5—△—CH_2OH (5)	11
	$C_6H_5CH_2HC$—O—$CHCH_3$ *cis*	$LiNEt_2$	Ether–hexane, 9 min	(E)-$C_6H_5CH{=}CHCHOHCH_3$ (Quant)	43
	$C_6H_5CH_2HC$—O—$CHCH_3$ *trans*	$LiNEt_2$	Ether–hexane, 5 min	$C_6H_5CH{=}CHCHOHCH_3$ (High) (E:Z = 95:5)	43
	H_2C—O—$C(CH_3)C_6H_4CH_3$-p	LDPA, 1.5 eq	Ether, reflux, 4 hr	$HOCH_2C({=}CH_2)C_6H_4CH_3$-$p$ (85)	92
C_{11}		LDPA, 2.5 eq	Ether, room temp, 1 hr	 (64)	41
	$C_6H_5CH(CH_3)HC$—O—$CHCH_3$ (mixture of isomers)	$LiNEt_2$	Ether–hexane, 7 hr	$C_6H_5CH(CH_3)CHOHCH{=}CH_2$ + $C_6H_5C(CH_3){=}CHCHOHCH_3$ 93:7 (High)	43
C_{12}		$LiNEt_2$, 2 eq	Ether–hexane, room temp, 2 hr	 (—)	148
		LDPA, 2.5 eq	Ether, room temp, 1 hr	 (54) +  (11)	41
		$LiNEt_2$	Ether–hexane, 7 hr	+ $C_6H_5C_6H_5$ + ( + ) 14:68:18 (—)	43
		$LiNEt_2$	Ether–hexane, 12 hr	 (High)	43
	 *trans*:*cis* 74:26	$LiNEt_2$	Ether–hexane, 55 min	 +  4:96 (—)	43
	$C_6H_5CH(CH_3)HC$—O—CHC_2H_5 (Mixture of isomers)	$LiNEt_2$	Ether–hexane, 23 hr	(E)-$C_6H_5CH(CH_3)CHOHCH{=}CHCH_3$ + (Z)-$C_6H_5C(CH_3){=}CHCHOHC_2H_5$ 54:46 (—)	43

TABLE II. UNSATURATED EPOXIDES (*Continued*)

C. Aryl Epoxides (Continued)

	Epoxide	Base	Reaction Conditions	Products and Yields (%)	Refs.
C_{13}		LDPA, 2.5 eq	Ether, room temp, 1 hr	 (65)	41
		$LiNEt_2$	Hexane, −78°, 5 min; room temp, 30 min	 $CH_2C_6H_4CH_3$-*p*[a] (I) +  $C_6H_4CH_3$-*p*[a] (II) 81:19 (—)	98
		LDPA	Hexane, −78°, 5 min ; room temp, 30 min	I + II 99:1 (—)	98
			Hexane, −78°, 5 min ; room temp, 15 min	I + II +  $C_6H_4CH_3$-*p*[a] (III) 34:56:10 (—)	98
			Hexane, −78°, 5 min ; room temp, 120 min	II + III 98:2 (—)	98
			Ether, −78°, 5 min ; room temp, 30 min	II + III 52:48 (—)	98
C_{14}	$(C_6H_5)_2C$—O—CH_2	$LiNEt_2$	Ether, reflux	$(C_6H_5)_2COHCH_2N(C_2H_5)_2$ (26)	47
	C_6H_5HC—O—CHC_6H_5 *cis*	$LiNEt_2$, 2 eq	Ether, reflux, 1 hr	$C_6H_5COCH_2C_6H_5$ (70)	47
	C_6H_5HC—O—CHC_6H_5 *trans*	$LiNEt_2$, 2 eq	Ether, reflux, 1 hr	$(C_6H_5)_2CHCHO$[b] (66)	47
C_{18}		$LiNEt_2$, 7.5 eq	Ether–hexane, room temp, 72 hr	 (98)	140
C_{19}		$LiNEt_2$, 4 eq	Ether, reflux, 36 hr	 (100)	81
		$LiNEt_2$, 2.5 eq	Ether, reflux, 2 days	(60)	78
C_{20}	$(C_6H_5)_2C$—O—CHC_6H_5	$LiNEt_2$	C_6H_6, 63°, 5 hr	$(C_6H_5)_2CHCOC_6H_5$ (80)	47
C_{21}	$(C_6H_5)_2C$—O—$CHC_6H_4CH_3$-*p*	$LiNEt_2$	C_6H_6, reflux, 18 hr	$(C_6H_5)_2CHCOC_6H_4CH_3$-*p* (31) + $(C_6H_5)_2CHCHOHC_6H_4CH_3$-*p* (18)	47
C_{26}	$(C_6H_5)_2C$—O—$C(C_6H_5)_2$	$LiNEt_2$	C_6H_6, reflux	No reaction	47

[a] Isolated as the trimethylsilyl ether.
[b] Isolated as the dimedone derivative.

TABLE III. FUNCTIONAL EPOXIDES

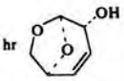
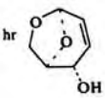
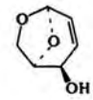
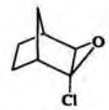
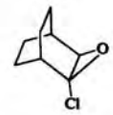
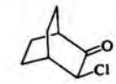
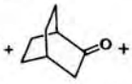
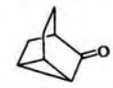
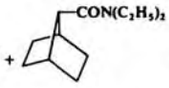
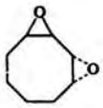
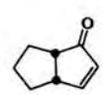
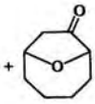
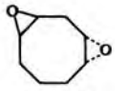
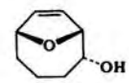
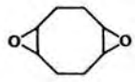
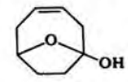
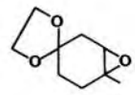
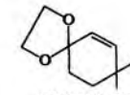
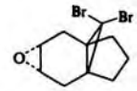
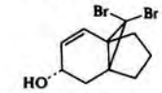
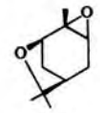
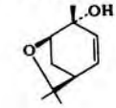
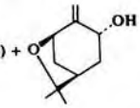
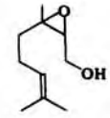
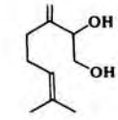
	Epoxide	Base	Reaction Conditions	Products and Yields (%)	Refs.
C_3	$ClCH_2HC$ CH_2	*n*-BuLi	THF, −80°	(*E*)-ClCH=CHCH$_2$OH (I, 40–60)	149
		n-BuLi	THF, room temp	I + (*Z*)-ClCH=CHCH$_2$OH (II) 70:30 (—)	149
		n-BuLi	Ether–heptane, −50°, 1 hr; warm	I (15) + II (60) + HC≡CCH$_2$OH (15)	150
C_6		*n*-BuLi, 2 eq	Ether–hexane, room temp, 12 hr	 (82)	102
		n-BuLi, 2 eq	Ether–hexane, room temp, 12 hr	 (65)	151
		$LiNEt_2$, 3 eq	C_6H_6–hexane, room temp, 18 hr; reflux, 1 hr	(20)	151
		$LiNEt_2$, 3 eq	C_6H_6–hexane, room temp, 18 hr; reflux, 1 hr	 (50)	151
C_7		$LiNEt_2$, 1.7 eq	C_6H_6–ether, reflux, 50 hr	(59) + (6)	110
		$LiNEt_2$, 2.1 eq	Ether, −15°, 8 min, 0°, 1 hr	" (44) + " (20)	110
C_8		$LiNEt_2$, 1.5 eq	C_6H_6–ether, reflux, 4 days	 +  +  +  10:1:62:27 (—)	110
		$LiNH(CH_2)_2NH_2$	C_6H_6, 35°, 1 hr	 (7) +  (I, 73)	100
		$LiNH(CH_2)_2NH_2$	HMPA, 30°, 1 hr	I (—)	100
		$LiNH(CH_2)_2NH_2$	HMPA, 50°, 12 hr	 (90)	100
		$LiNH(CH_2)_2NH_2$, 4.5 eq	C_6H_6, 50°, 30 min	 (85)	100
		$LiNH(CH_2)_2NH_2$, 4.5 eq	HMPA, 50°, 30 min	" (—)	100
C_9		$LiNEt_2$	Ether	 + $HO(CH_2)_2OC_6H_4CH_3$-*p* (—)	107
C_{10}		$LiNEt_2$, 1.5 eq	THF–hexane, 0°, 5 min	 (61)	54
		$LiNEt_2$, 2.5 eq	Ether, reflux, 12 hr	 (88) +  (12)	72
		LDPA, 2.2 eq	THF, 0°, 4 hr	 (65)	106

TABLE III. FUNCTIONAL EPOXIDES (*Continued*)

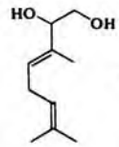
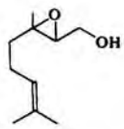
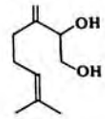
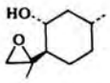
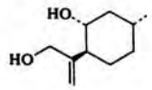
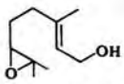
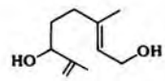
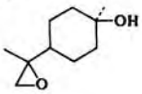
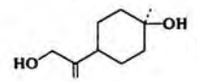
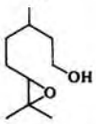
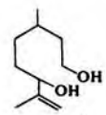
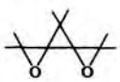
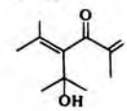
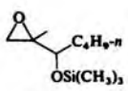
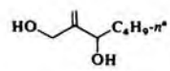
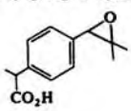
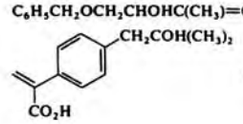
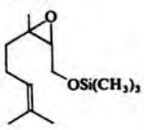
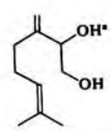
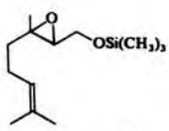
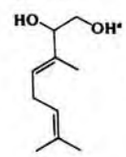
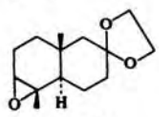
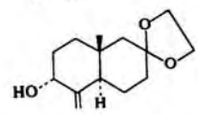
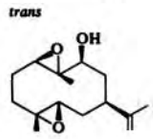
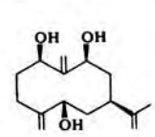
Epoxide	Base	Reaction Conditions	Products and Yields (%)	Refs.
C_{10} (*Contd.*)	$Ti(OPr\text{-}i)_4$, 1.2 eq	CH_2Cl_2, room temp, 12 hr	 (70)	106
	LDPA, 2.2 eq	THF, 0°, 4 hr	 (65)	106
	$Ti(OPr\text{-}i)_4$, 1.2 eq	CH_2Cl_2, room temp, 12 hr	" (70)	106
	$LiNH(CH_2)_2NH_2$	$H_2N(CH_2)_2NH_2$, 110°, 30 min	 (55)	104
	DATMP, 4 eq	C_6H_6, 0°, 30 min	 (88)	31, 32
	$Al(OPr\text{-}i)_3$	No solvent, 120°	 (–)	87
	$Al(OPr\text{-}i)_3$	No solvent, 120°	 (–)	87
C_{11} 	$LiNEt_2$, 3.5 eq	Ether–hexane, reflux, 12 hr	 (76)	109
	DATMP	C_6H_6, 0°, 2 hr	 (75)	105
C_{12} $C_6H_5CH_2OCH_2HC$ $C(CH_3)_2$	$Al(OPr\text{-}i)_3$, 1 eq	Toluene, reflux	$C_6H_5CH_2OCH_2CHOHC(CH_3)=CH_2$ (99)	89
C_{13} 	*t*-BuOK, 3 eq	THF, 15°	 (78)	111
	DATMP	C_6H_6, 0°, 2 hr	 (79)	105
	DATMP	C_6H_6, 0°, 2 hr	 (65)	105
C_{14} 	LDPA, 2.5 eq	Ether, room temp, 24 hr	 (82)	152
$C_6H_5CH(OSi(CH_3)_3)HC$$CHC_2H_5$ *trans*	DATMP	C_6H_6, 0°, 2 hr	(*E*)-$C_6H_5CHOHCHOHCH=CHCH_3$ (60)	105
C_{15} 	$LiNEt_2$, 5 eq	C_6H_6, reflux, 2 hr	 (25)	153

TABLE III. FUNCTIONAL EPOXIDES (*Continued*)

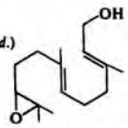
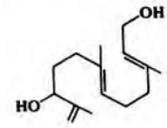
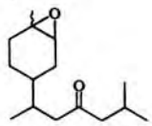
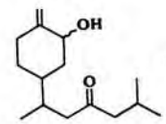
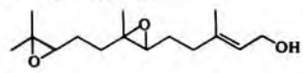
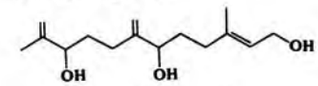
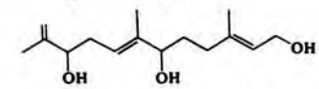
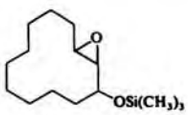
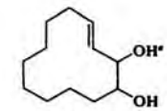
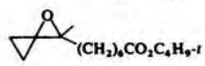
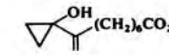
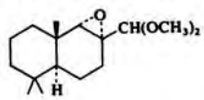
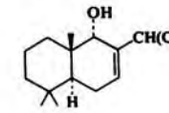
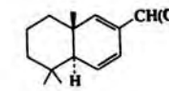
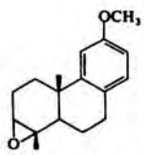
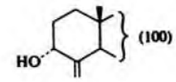
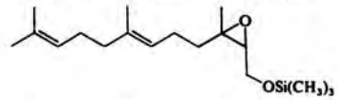
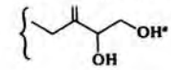
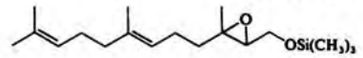
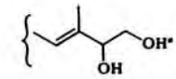
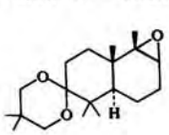
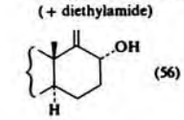
Epoxide	Base	Reaction Conditions	Products and Yields (%)	Refs.
C_{15} (*Contd.*) 	DATMP, 5 eq	C_6H_6, 0°, 30 min	 (90)	31
	$LiNEt_2$, 4 eq	THF–hexane, reflux, 3 hr	 (95)	76
	$LiNEt_2$, 5 eq	C_6H_6, reflux, 1 hr	 (>50)	65
	DATMP, 10 eq	C_6H_6, 0°, 3 hr	 (41)	32
$(CH_3)_2C$—O—$CH(CH_2)_2CH(CH_3)(CH_2)_2OTHP$	LDPA, 1.8 eq	Ether, reflux	$CH_2{=}C(CH_3)CHOH(CH_2)_2CH(CH_3)(CH_2)_2OTHP$ + (major) (*E*)-$(CH_3)_2COHCH{=}CHCH_2CH(CH_3)(CH_2)_2OTHP$ (minor) (60, total)	64
	DATMP	C_6H_6, 0°, 2 hr	 (63)	105
C_{16} 	LDPA	Hexane	 (High)	98
	$MgBrN(Pr\text{-}i)C_6H_{11}$, 27 eq	THF, 45°, 30 hr	 (62) +	137
			 (10)	
C_{17} 	$LiNEt_2$, 5 eq	Ether, reflux, 36 hr	 (100)	78
$(CH_3)_2C$—O—$CH(CH_2)_2C(CH_3){=}CHCH_2OCH_2C_6H_5$	$Al(OPr\text{-}i)_3$, 1 eq	Toluene, reflux	$CH_2{=}C(CH_3)CHOH$—} (93)	89
$(CH_3)_2C$—O—$CH(CH_2)_2C(CH_3){=}CHCH_2SO_2C_6H_4CH_3\text{-}p$	$Al(OPr\text{-}i)_3$, 1 eq	Toluene, reflux	$CH_2{=}C(CH_3)CHOH$—} (94)	89
C_{18} 	DATMP	C_6H_6, 0°, 2 hr	 (71)	105
	DATMP	C_6H_6, 0°, 2 hr	 (70)	105
$(CH_3)_3SiO(CH_2)_9HC$—O—$CHCH_2OSi(CH_3)_3$ *trans*	DATMP	C_6H_6, 0°, 2 hr	(*E*)-$HO(CH_2)_9CH{=}CHCHOHCH_2OH$* (50)	105
C_{19} $n\text{-}C_5H_{11}C{\equiv}CCH_2HC$—O—$CH(CH_2)_7CO_2CH_3$ *cis*	$LiNEt_2$	Ether	(*E*)-$n\text{-}C_5H_{11}C{\equiv}CCH{=}CHCHOH(CH_2)_7CO_2CH_3$ (50) (+ diethylamide)	154
$n\text{-}C_5H_{11}HC$—O—$CHCH_2CH{=}CH(CH_2)_7CO_2CH_3$	$LiNEt_2$	Ether, 0°, 1 hr	$n\text{-}C_5H_{11}CHOHCH{=}CHCH{=}CH(CH_2)_7CO_2CH_3$ (~60) (+ diethylamide)	154
	$LiN(Pr\text{-}n)_2$, 1.5 eq	THF–hexane, reflux, 2 hr	 (56) + (38)	69

TABLE III. FUNCTIONAL EPOXIDES (*Continued*)

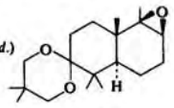
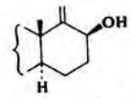
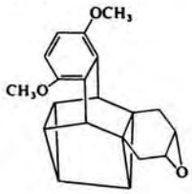
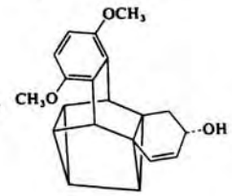
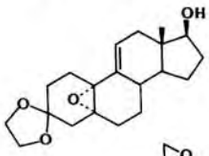
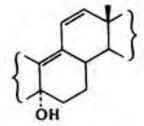
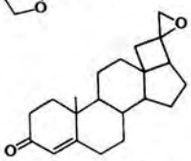
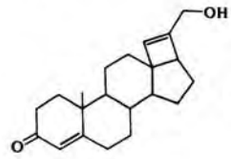
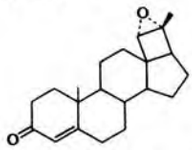
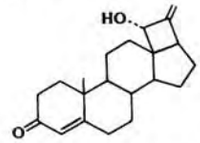
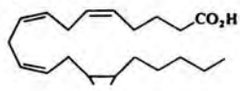
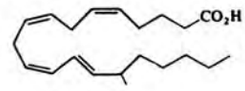
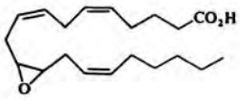
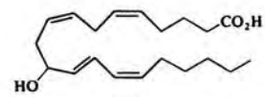
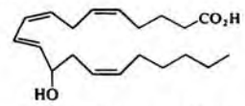
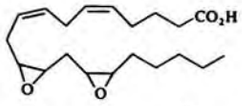
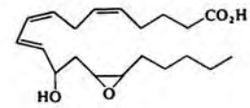
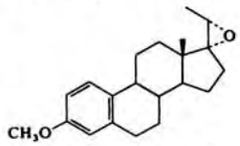
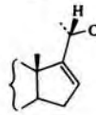
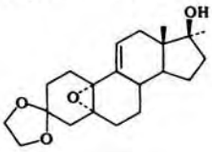
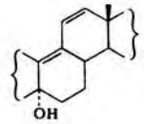
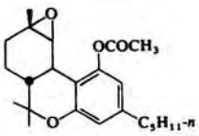
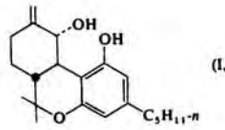
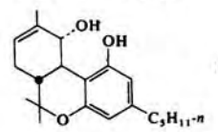
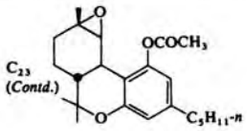
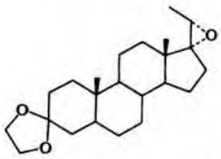
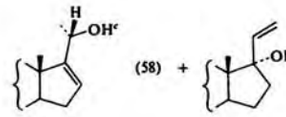
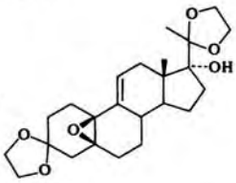
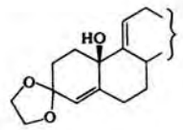
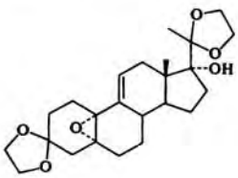
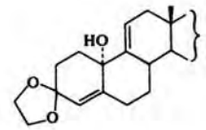
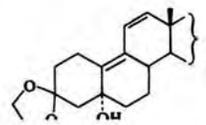
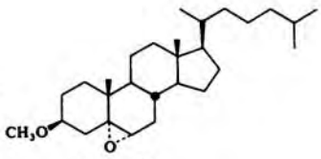
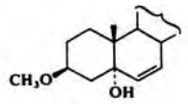
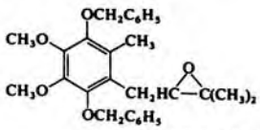
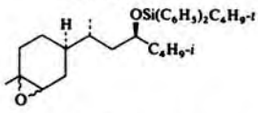
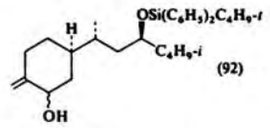
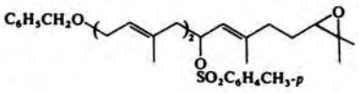
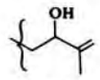
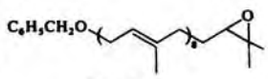
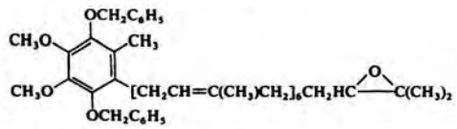
	Epoxide	Base	Reaction Conditions	Products and Yields (%)	Refs.
C_{19} (*Contd.*)		$LiN(Pr\text{-}n)_2$, 1.5 eq	THF–hexane, reflux, 6 hr	 (89)	69
C_{20}		$LiNEt_2$, 8 eq	Ether–hexane, room temp, 60 hr	 (44)	140
		*t*-BuOK	THF, reflux	 (>80)	108
		$LiNEt_2$, 8 eq	THF–hexane, 25°, 2 hr	 (69)	103
		$LiNEt_2$, 8 eq	THF–hexane, 25°, 2 hr	 (–)	103
		$MgBrN(Pr\text{-}i)C_6H_{11}$, 5 eq	THF, 0°–23°, 2 hr; 23°, 3.5 hr	 (70)	90
		$MgBrN(Pr\text{-}i)C_6H_{11}$, 5 eq	THF, 0°, 0.5 hr; 23°, 3.5 hr	 (28) +  (42)	90
		$MgBrN(Pr\text{-}i)C_6H_{11}$		 (–)	90
C_{21}		$LiNEt_2$, 5 eq	Hexane, HMPA, (2 eq), room temp, 10 hr	 (74)	66
		*t*-BuOK	THF, reflux	 (15)	108
C_{23}		$LiN(Bu\text{-}t)Si(CH_3)_3$, 4.5 eq	Ether–hexane, reflux, 4 days	 (I, 71) +  (II, 18)	74

TABLE III. FUNCTIONAL EPOXIDES (*Continued*)

Epoxide	Base	Reaction Conditions	Products and Yields (%)	Refs.
C_{23} (*Contd.*) 	$LiNEt_2$ or $LiN(Pr\text{-}i)C_6H_5$	Ether–hexane	I + II 17:83 (–)	74
	LDPA, $LiN[Si(CH_3)_3]_2$, or	Ether–hexane	I + II 50:50 (–)	74
	$LiNEt_2$, 6 eq	Hexane, room temp, 24 hr	 (58) + (18)	66
C_{24} 	$LiNEt_2$ or LDPA	Room temp, 10 min	 (–)	108
	t-BuOK	THF, reflux	" (–)	108
	$LiNEt_2$ or LDPA	Room temp, 10 min	 (–)	108
	t-BuOK	THF, reflux	 (>80)	108
	$NaNH_2$	$H_2N(CH_2)_2NH_2$	" (–)	108
C_{28} 	*n*-BuLi, 15 eq, H_2O (1 eq)	Diglyme–hexane, 200°, 18 hr	 (51)	155
	$Al(OPr\text{-}i)_3$	Toluene, reflux, 7 hr	$\{-CH_2CHOHC(CH_3)=CH_2$ (91)	156
C_{31} 	DATMP	C_6H_6, 0°, 3 hr	 (92)	75
C_{34} 	$Al(OPr\text{-}i)_3$, 1 eq	Toluene, reflux	 (97)	89
C_{52} 	$Al(OPr\text{-}i)_3$, 1 eq	Toluene, reflux	(74)	89
C_{58} 	LDPA, 5 eq	THF, 5°, 10 hr	$\{-[CH_2CH=C(CH_3)CH_2]_6CH_2CHOHC(CH_3)=CH_2$ (86)	62

[a] The product was obtained after removal of the trimethylsilyl group with potassium fluoride in methanol. The indicated yield is for the overall process starting with the allylic alcohol, which was epoxidized with $V(acac)_3$/*t*-BuOOH and silylated prior to treatment with base.

[b] The product was isolated as the trimethylsilyl ether.

[c] The product was isolated as the acetate.

7. Acknowledgment

We gratefully thank Mr. T. C. Johns for help with the literature search.

End Throughout the text, LDPA is used to denote lithium diisopropylamide.

Notes

References

1. A. Rosowsky, in *Heterocyclic Compounds with Three- and Four-Membered Rings*, Part I, A. Weissberger, Ed., Wiley-Interscience, New York, 1964, p. 1.
2. G. Berti, in *Topics in Stereochemistry*, Vol. **7**, N. L. Allinger and E. L. Eliel, Eds., Wiley-Interscience, New York, 1973, p. 93.
3. J. G. Buchanan and H. Z. Sable, in *Selective Organic Transformations*, Vol. **2**, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, 1972, p. 1.
4. V. N. Yandovskii and B. A. Ershov, Russ. Chem. Rev., **41**, 403 (1972).
5. C. J. M. Stirling, Chem. Rev., **78**, 517 (1978).
6. J. K. Crandall and L. C. Crawley, Org. Synth., **53**, 17 (1973).
7. R. L. Letsinger, J. G. Traynham, and E. Bobko, J. Am. Chem. Soc., **74**, 399 (1952).
8. L. J. Haynes, I. Heilbron, E. H. R. Jones, and F. Sondheimer, J. Chem. Soc., 1583 (1947).
9. A. C. Cope, H. H. Lee, and H. E. Petree, J. Am. Chem. Soc., **80**, 2849 (1958).
10. F. T. Bond and C. Y. Ho, J. Org. Chem., **41**, 1421 (1976).
11. M. Apparu and M. Barrelle, Tetrahedron, **34**, 1691 (1978).
12. H. Yamamoto and H. Nozaki, Angew. Chem., Int. Ed. Engl., **17**, 169 (1978).
13. M. F. Lappert, P. P. Power, A. R. Sanger, and R. C. Srivastave, *Metal and Metalloid Amides*, Wiley, New York, 1980, Chapter "2".
14. T. L. Brown, Adv. Organomet. Chem., **3**, 365 (1965).
15. A. C. Cope and J. K. Heeren, J. Am. Chem. Soc., **87**, 3125 (1965).
16. A. C. Cope, G. A. Berchtold, P. E. Peterson, and S. H. Sharman, J. Am. Chem. Soc., **82**, 6370 (1960).
17. R. P. Thummel and B. Rickborn, J. Am. Chem. Soc., **92**, 2064 (1970).
18. J. K. Crandall, L. C. Crawley, D. B. Banks, and L. C. Lin, J. Org. Chem., **36**, 510 (1971).
19. J. J. Eisch and J. E. Galle, J. Organomet. Chem., **121**, C10 (1976).
20. J. J. Eisch and J. E. Galle, J. Am. Chem. Soc., **98**, 4646 (1976).
21. B. Rickborn and R. P. Thummel, J. Org. Chem., **34**, 3583 (1969).
22. M. Hassan, A. R. O. Abdel Nour, and A. M. Satti, Revue Roumaine de Chimie, **23**, 747 (1978).
23. J. Poláková, M. Palecek, and M. Procházka, Collect. Czech. Chem. Commun., **44**, 3705 (1979).
24. W. H. Saunders and A. F. Cockerill, *Mechanisms of Elimination Reactions*, Wiley-Interscience, New York, 1973.

25. R. A. Bartsch and J. Závada, Chem. Rev., **80**, 453 (1980).
26. M. Apparu and M. Barrelle, Tetrahedron, **34**, 1541 (1978).
27. M. Apparu and M. Barrelle, Tetrahedron, **34**, 1817 (1978).
28. J. Smid, Angew. Chem., Int. Ed., Engl., **11**, 112 (1972).
29. R. P. Thummel and B. Rickborn, J. Org. Chem., **36**, 1365 (1971).
30. H. Nozaki, T. Mori, and R. Noyori, Tetrahedron, **22**, 1207 (1966).
31. A. Yasuda, S. Tanaka, K. Oshima, H. Yamamoto, and H. Nozaki, J. Am. Chem. Soc., **96**, 6513 (1974).
32. A. Yasuda, H. Yamamoto, and H. Nozaki, Bull. Chem. Soc. Jpn., **52**, 1705 (1979).
33. A. C. Cope, M. Brown, and H. H. Lee, J. Am. Chem. Soc., **80**, 2855 (1958).
34. J. Sicher, Angew. Chem., Int. Ed. Engl., **11**, 200 (1972).
35. A. Nickon and N. H. Werstiuk, J. Am. Chem. Soc., **89**, 3914 (1967).
36. W. Kirmse, *Carbene Chemistry*, 2nd Ed., Academic Press, New York, 1971, Chapter "7".
37. G. Köbrich, Angew. Chem., Int. Ed. Engl., **6**, 41 (1967).
38. R. A. Moss, in *Carbenes*, Vol. **1**, M. Jones and R. A. Moss, Eds., Wiley-Interscience, New York, 1973, Chapter "2".
39. J. K. Crandall and L. H. C. Lin, J. Am. Chem. Soc., **89**, 4526 (1967).
40. J. K. Crandall and L. H. C. Lin, J. Am. Chem. Soc., **89**, 4527 (1967).
41. R. W. Thies and R. H. Chiarello, J. Org. Chem., **44**, 1342 (1979).
42. R. K. Boeckman, Jr., Tetrahedron Lett., **1977**, 4281.
43. R. P. Thummel and B. Rickborn, J. Org. Chem., **37**, 3919 (1972).
44. R. P. Thummel and B. Rickborn, J. Org. Chem., **37**, 4250 (1972).
45. J. K. Crandall, R. D. Huntington, and G. L. Brunner, J. Org. Chem., **37**, 2911 (1972).
46. C. C. Price and D. D. Carmelite, J. Am. Chem. Soc., **88**, 4039 (1966).
47. A. C. Cope, P. A. Trumbull, and E. R. Trumbull, J. Am. Chem. Soc., **80**, 2844 (1958).
48. R. K. Hill, J. W. Morgan, R. V. Shetty, and M. E. Synerholm, J. Am. Chem. Soc., **96**, 4201 (1974).
49. T. J. Brocksom and J. T. B. Ferreira, Synth. Commun., **11**, 105 (1981).
50. L. C. Lin, Ph.D. Thesis, Indiana University, 1967 [Diss. Abstr. B, **28**, 3650 (1968)].
51. B. D. Mookherjee, R. W. Trenkle, and R. R. Patel, J. Org. Chem., **36**, 3266 (1971).
52. J. K. Crandall and L. H. Chang, J. Org. Chem., **32**, 435 (1967).
53. C. Kissel and B. Rickborn, J. Org. Chem., **37**, 2060 (1972).

54. P. Warner, W. Boulanger, T. Schleis, S. L. Lu, Z. Le, and S. C. Chang, J. Org. Chem., **43**, 4388 (1978).
55. L. A. Paquette, W. E. Fristad, C. A. Schuman, M. A. Beno, and G. G. Christoph, J. Am. Chem. Soc., **101**, 4645 (1979).
56. J. A. Marshall and R. A. Ruden, J. Org. Chem., **37**, 659 (1972).
57. J. K. Whitesell and S. W. Felman, J. Org. Chem., **45**, 755 (1980).
58. J. K. Whitesell and P. D. White, Synthesis, **1975**, 602.
59. M. N. Sheng, Synthesis, **1972**, 194.
60. J. K. Crandall, J. Org. Chem., **29**, 2830 (1964).
61. J. R. Neff and J. E. Nordlander, Tetrahedron Lett., **1977**, 499.
62. L. C. Crawley, M. S. Thesis, Indiana University, 1969.
63. S. Terao, K. Kato, M. Shiraishi, and H. Morimoto, J. Chem. Soc., Perkin Trans. 1, **1978**, 1101.
64. O. P. Vig, S. D. Sharma, R. Vig, and S. D. Kumar, Indian J. Chem., **18B**, 31 (1979).
65. E. E. van Tamelen and J. P. McCormick, J. Am. Chem. Soc., **92**, 737 (1970).
66. B. M. Trost and T. R. Verhoeven, J. Am. Chem. Soc., **100**, 3435 (1978).
67. J. K. Crandall and L. H. C. Lin, J. Org. Chem., **33**, 2375 (1968).
68. J. K. Whitesell, R. S. Matthews, and P. K. S. Wang, Synth. Commun., **7**, 355 (1977).
69. J. S. Dutcher, J. G. Macmillan, and C. H. Heathcock, J. Org. Chem., **41**, 2663 (1976).
70. Y. Bessière and R. Derguini-Bouméchal, J. Chem. Res. (M), **1977**, 3519.
71. K. H. Schulte-Elte and G. Ohloff, Helv. Chim. Acta, **51**, 494 (1968).
72. D. Mrozinska, A. Siemieniuk, K. Piatkowski, and H. Kuczynski, Pol. J. Chem., **53**, 2213 (1979).
73. S. C. Welch and A. S. C. Prakasa Rao, J. Org. Chem., **43**, 1957 (1978).
74. C. G. Pitt, M. S. Fowler, S. Sathe, S. C. Srivastava, and D. L. Williams, J. Am. Chem. Soc., **97**, 3798 (1975).
75. D. R. Williams and J. G. Phillips, J. Org. Chem., **46**, 5452 (1981).
76. B. A. Pawson, H. C. Cheung, S. Gurbaxani, and G. Saucy, J. Am. Chem. Soc., **92**, 336 (1970).
77. J. E. McMurry, J. H. Musser, M. S. Ahmad, and L. C. Blaszczak, J. Org. Chem., **40**, 1829 (1975).
78. R. C. Cambie, R. A. Franich, and T. J. Fullerton, Aust. J. Chem., **24**, 593 (1971).
79. B. M. Trost and M. J. Bogdanowicz, J. Am. Chem. Soc., **95**, 5311 (1973).
80. H. Kuczynski and K. Marks, Rocz. Chem., **43**, 943 (1969) [C. A., **71**,

61558 (1970)].
81. R. C. Cambie and R. A. Franich, Aust. J. Chem., **23**, 93 (1970).
82. A. R. Lepley, W. G. Khan, A. B. Giumanini, and A. G. Giumanini, J. Org. Chem., **31**, 2047 (1966).
83. L. E. Overman and L. A. Flippin, Tetrahedron Lett., **22**, 195 (1981).
84. M. Apparu and M. Barrelle, Bull. Soc. Chim. Fr., **1977**, 947.
85. S. G. Traynor, B. J. Kane, J. B. Coleman, and C. G. Cardenas, J. Org. Chem., **45**, 900 (1980).
86. Z. Rykowski, K. Burak, and Z. Chabudzinski, Rocz. Chem., **48**, 1619 (1974) [C. A., **82**, 98160 (1975)].
87. E. H. Eschinasi, Isr. J. Chem., **6**, 713 (1968).
88. E. H. Eschinasi, J. Org. Chem., **35**, 1598 (1970).
89. S. Terao, M. Shiraishi, and K. Kato, Synthesis, **1979**, 467.
90. E. J. Corey, A. Marfat, J. R. Falck, and J. O. Albright, J. Am. Chem. Soc., **102**, 1433 (1980).
91. R. G. Riley, R. M. Silverstein, J. A. Katzenellenbogen, and R. S. Lenox, J. Org. Chem., **39**, 1957 (1974).
92. O. P. Vig, S. S. Bari, S. D. Sharma, and S. S. Rana, Indian J. Chem., **15B**, 1076 (1977).
93. J. Staroscik and B. Rickborn, J. Am. Chem. Soc., **93**, 3046 (1971).
94. P. H. M. Schreurs, A. J. de Jong, and L. Brandsma, Recl. Trav. Chim. Pays-Bas, **95**, 75 (1976).
95. A. C. Cope and B. D. Tiffany, J. Am. Chem. Soc., **73**, 4158 (1951).
96. J. K. Crandall and L. H. Chang, J. Org. Chem., **32**, 532 (1967).
97. P. Miginiac and G. Zamlouty, Bull. Soc. Chim. Fr., **1975**, 1740.
98. B. M. Trost and S. Kurozumi, Tetrahedron Lett., **1974**, 1929.
99. S. K. Taylor and C. B. Rose, J. Org. Chem., **42**, 2175 (1977).
100. M. Apparu, Thesis, Université Scientifique et Médicale de Grenoble, Grenoble, France, 1977.
101. M. Apparu and M. Barrelle, Tetrahedron Lett., **1976**, 2837.
102. U. P. Singh and R. K. Brown, Can. J. Chem., **49**, 3342 (1971).
103. M. Miyano, J. Org. Chem., **46**, 1846 (1981).
104. K. H. Schulte-Elte and G. Ohloff, Helv. Chim. Acta, **50**, 153 (1967).
105. S. Tanaka, A. Yasuda, H. Yamamoto, and H. Nozaki, J. Am. Chem. Soc., **97**, 3252 (1975).
106. D. J. Morgans, K. B. Sharpless, and S. G. Traynor, J. Am. Chem. Soc., **103**, 462 (1981).
107. W. C. Still, A. J. Lewis, and D. Goldsmith, Tetrahedron Lett., **1971**, 1421.
108. G. Teutsch and R. Bucourt, J. Chem. Soc., Chem. Commun., **1974**, 763.

109. J. K. Crandall and D. R. Paulson, J. Org. Chem., **33**, 3291 (1968).
110. R. N. McDonald, R. N. Steppel, and R. C. Cousins, J. Org. Chem., **40**, 1694 (1975).
111. R. R. Kurtz and D. J. Houser, J. Org. Chem., **46**, 202 (1981).
112. M. T. Reetz and W. F. Maier, Justus Liebigs Ann. Chem., **1980**, 1471.
113. H. Normant, T. Cuvigny, and D. Reisdorf, C. R. Acad. Sci. Paris, Ser. C, **268**, 521 (1969).
114. P. Hullot and T. Cuvigny, Bull. Soc. Chim. Fr., **1973**, 2985.
115. O. F. Beumel and R. F. Harris, J. Org. Chem., **28**, 2775 (1963).
116. J. J. Eisch and J. E. Galle, J. Org. Chem., **44**, 3277 (1979).
117. H. W. Gschwend and H. R. Rodriguez, Org. React., **26**, 93 (1979).
118. H. Gilman and J. W. Morton, Org. React., **8**, 258 (1954).
119. J. M. Mallan and R. L. Bebb, Chem. Rev., **69**, 693 (1969).
120. B. J. Wakefield, *The Chemistry of Organolithium Compounds*, Pergamon Press, New York, 1974.
121. M. F. Lipton, C. M. Sorensen, A. C. Sadler, and R. H. Shapiro, J. Organomet. Chem., **186**, 155 (1980).
122. D. E. Bergbreiter and E. Pendergrass, J. Org. Chem., **46**, 219 (1981).
123. M. R. Winkle, J. M. Lansinger, and R. C. Ronald, J. Chem. Soc., Chem. Commun., **1980**, 87.
124. S. C. Watson and J. F. Eastham, J. Organomet. Chem., **9**, 165 (1967).
125. Y. Kitagawa, A. Itoh, S. Hashimoto, H. Yamamoto, and H. Nozaki, J. Am. Chem. Soc., **99**, 3864 (1977).
126. A. Basha, M. Lipton, and S. M. Weinreb, Tetrahedron Lett., **1977**, 4171.
127. W. Nagata and M. Yoshioka, Org. React., **25**, 354 (1977).
128. W. Nagata and M. Yoshioka, Org. Synth., **52**, 90 (1972).
129. R. W. Thies, M. Gasic, D. Whalen, J. B. Grutzner, M. Sakai, B. Johnson, and S. Winstein, J. Am. Chem. Soc., **94**, 2262 (1972).
130. E. J. Corey and R. S. Glass, J. Am. Chem. Soc., **89**, 2600 (1967).
131. R. A. Olofson and C. M. Dougherty, J. Am. Chem. Soc., **95**, 581, 582 (1973).
132. J. P. Monthéard and Y. Chrétien-Bessière, Bull. Soc. Chim. Fr., **1968**, 336.
133. R. M. Kellogg and J. K. Kaiser, J. Org. Chem., **40**, 2575 (1975).
134. Z. Rykowski and K. Burak, Rocz. Chem., **50**, 1709 (1976) [C. A., **86**, 140258r (1977)].
135. A. J. Bridges and G. H. Whitham, J. Chem. Soc., Perkin Trans. 1, **1975**, 2264.
136. L. A. Paquette, G. D. Crouse, and A. K. Sharma, J. Am. Chem. Soc., **104**,

4411 (1982).

137. P. A. Wender and S. L. Eck, Tetrahedron Lett., **23**, 1871 (1982).
138. H. Kuczynski and K. Marks, Rocz. Chem., **42**, 647 (1968) [C. A., **71**, 39190 (1970)].
139. H. Shirahama, K. Hayano, Y. Kanemoto, S. Misumi, T. Ohtsuka, N. Hashiba, A. Furusaki, S. Murata, R. Noyori, and T. Matsumoto, Tetrahedron Lett., **21**, 4835 (1980).
140. L. A. Paquette and G. Kretschmer, J. Am. Chem. Soc., **101**, 4655 (1979).
141. M. Gasic, D. Whalen, B. Johnson, and S. Winstein, J. Am. Chem. Soc., **89**, 6382 (1967).
142. J. K. Crandall and D. R. Paulson, J. Org. Chem., **36**, 1184 (1971).
143. L. I. Zakharkin, Bull. Acad. Sci. USSR, Engl. Transl., **1961**, 2103.
144. A. Ogiso, E. Kitazawa, M. Kurabayashi, A. Sato, S. Takahashi, H. Noguchi, H. Kuwano, S. Kobayashi, and H. Mishima, Chem. Pharm. Bull., **26**, 3117 (1978).
145. H. Shirahama, B. R. Chhabra, and T. Matsumoto, Chem. Lett., **1981**, 717.
146. Y. Machida and S. Nozoe, Tetrahedron Lett., **1972**, 1969.
147. F. Y. Perveev and L. N. Gonoboblev, J. Org. Chem. USSR, **5**, 987 (1969).
148. R. P. Thummel, W. E. Cravey, and W. Nutakul, J. Org. Chem., **43**, 2473 (1978).
149. D. F. Hoeg, J. E. Forrette, and D. I. Lusk, Tetrahedron Lett., **1964**, 2059.
150. H. J. Fabris, J. Org. Chem., **32**, 2031 (1967).
151. K. Ranganayakulu, U. P. Singh, T. P. Murray, and R. K. Brown, Can. J. Chem., **52**, 988 (1974).
152. R. B. Miller and E. S. Behare, J. Am. Chem. Soc., **96**, 8102 (1974).
153. F. Bellesia, U. M. Pagnoni, and R. Trave, Tetrahedron Lett., **1974**, 1245.
154. H. B. S. Conacher and F. D. Gunstone, J. Chem. Soc., Chem. Commun., **1968**, 281.
155. C. E. Slemon and P. Yates, Can. J. Chem., **57**, 304 (1979).
156. S. Terao, K. Kato, M. Shiraishi, and H. Morimoto, J. Org. Chem., **44**, 868 (1979).

Reductive Dehalogenation of Polyhalo Ketones with Low-Valent Metals and Related Reducing Agents

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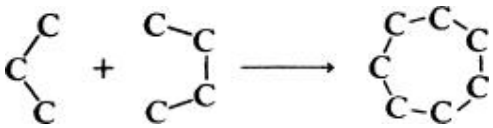
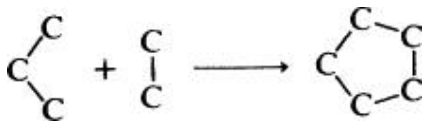
1. Introduction

α-Halo ketones play a significant role in organic synthesis because of their ready availability and the diversity of their chemical reactions, which reflect the various functionalities in the molecule, *viz.*, a reactive halogen－carbon bond, acidic hydrogen atoms, and a carbonyl moiety. An important reaction of halo ketones is removal of the halogen atom(s) by low-valent transition metals and related reducing agents to generate reactive species that are capable of undergoing carbon-carbon bond-forming reactions. The cyclocoupling reactions of α, α′ -dihalo or more highly halogenated ketones across 1,3-dienic or olefinic substrates to give seven-or five-membered ketones, respectively, are especially noteworthy from the synthetic viewpoint.

The direct preparation of odd-membered carbocycles has remained a persistent problem, and until recently only a few methods of synthesis were available. The existing methods for obtaining seven-membered carbocycles have been limited to expansion of six-membered rings and certain cyclization reactions. (1) The construction of five-membered carbocyclic systems has generally been accomplished only by intramolecular condensation of open-chain dicarbonyl compounds or dicarboxylic acid derivatives, (2, 3) ring contraction of six-membered cyclic ketones, (4, 5) or ring expansion of four-membered cyclic ketones. (6) These methods, however, are not always useful because of the limited availability of the starting materials in certain reactions. In principle the most direct method for construction of seven-membered carbocycles is the cyclocondensation between three-carbon and four-carbon units, *viz.*, 1,3-dienes, as shown in Eq. 1; for preparation of five-membered carbocycles, the combination



(1)



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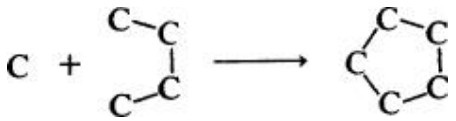


(3)

of three-carbon and two-carbon units, *viz.*, olefinic substances, or one-carbon and four-carbon units, as illustrated in Eqs. 2 and 3, respectively, can be considered. However, these reactions are not achieved easily because of the difficulty of generating reactive three-carbon and one-carbon units that are capable of undergoing cycloaddition across the unsaturated substrates. Reactions of low-valent metals and α, α′ -dihalo or more highly halogenated ketones generate such bifunctional three-carbon species that can enter into both types of cycloaddition reactions (Eqs. 1 and 2). Moreover, these reactive species also undergo [3 + 2] cycloadditions across certain unsaturated bonds containing heteroatoms, thereby giving rise to five-membered heterocycles. Thus these [3 + 4]and[3 + 2] annulations have allowed easy access to a wide range of organic frameworks that are of theoretical or practical importance. The scope and limitations of these cyclocoupling reactions and their synthetic applications (7, 8) are the main concern of this chapter, which briefly describes other examples of dehalogenation of α-mono- and α, α′ -polyhalo ketones using low-valent transition metals and related reducing agents. Also described are the mechanistic aspects of the reductions and several representative experimental procedures.

2. Mechanism

2.1. Reduction of α -Monohalo Ketones

For the initial step in the reduction of organic halides by metals or their complexes, three pathways have been proposed and classified by the mode of electron changes, which, in turn, depend on the nature of the reducing agent. (9)

Atom-transfer process:

$$R\text{–}X + M^{n} \longrightarrow R\cdot + M^{(n+1)}X$$

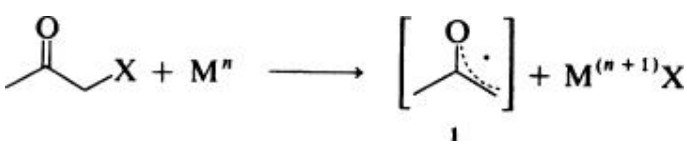
Electron-transfer process[*]:

$$R\text{–}X + M^{n} \longrightarrow R\text{–}X^{\cdot-} + M^{(n+1)}$$

Oxidative-addition process:

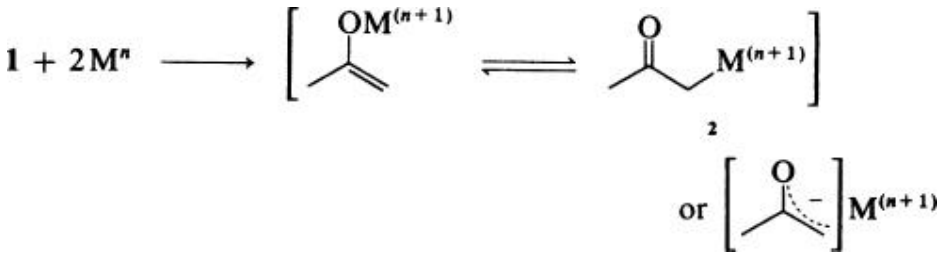
$$R\text{–}X + M^{n} \longrightarrow R\text{–}M^{(n+2)}X$$

The reduction of α -halo ketones appears to proceed similarly. The atom-transfer or electron-transfer process generating the radical species **1** (Eq. 4) is



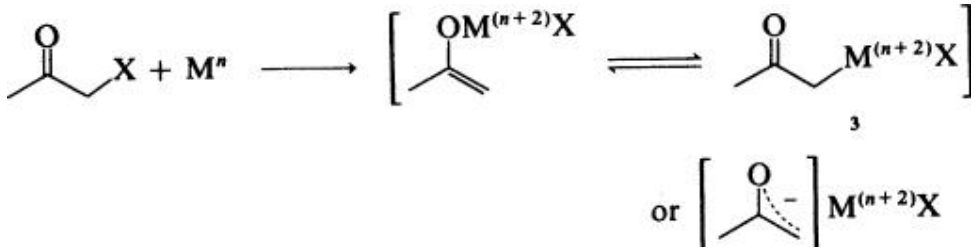
(4)

considered for reactions using one-equivalent reductants such as alkali metals or certain low-valent transition metal complexes containing, e.g., chromium(II), (10) iron(II), (11) cobalt(II), (11) and molybdenum(0), (12) which tend to release one electron to attain a higher oxidation state. Though not general, use of two or more equivalents of such reagents drives reduction via enolate intermediate **2**, which is generated by two successive one-electron changes (Eq. 5).



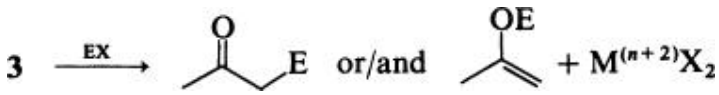
(5)

Reduction takes place via the oxidative addition mechanism, directly forming the metal enolate intermediate **3** (Eq. 6), when it is carried out with two-equivalent reductants, e.g., iodide salts or low-valent transition metals capable



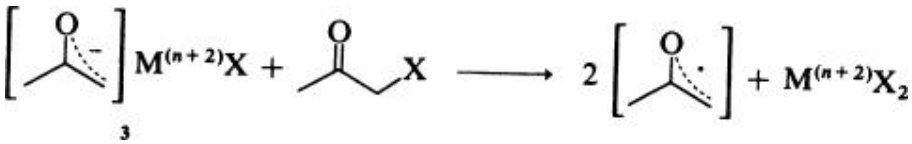
(6)

of changing the oxidation state either by concerted two-equivalent transformations or by successions of one-electron transfers. A related mechanism has been proposed also for electrochemical reductions of α -halo ketones. (13) A reactive enolate metal complex has been isolated from a reduction promoted by an iron carbonyl in an aprotic solvent. (14) In most reactions, however, the intervention of a metal enolate species is supported chemically by a subsequent nucleophilic reaction, as depicted in Eq. 7. Zinc enolates sometimes undergo



(7)

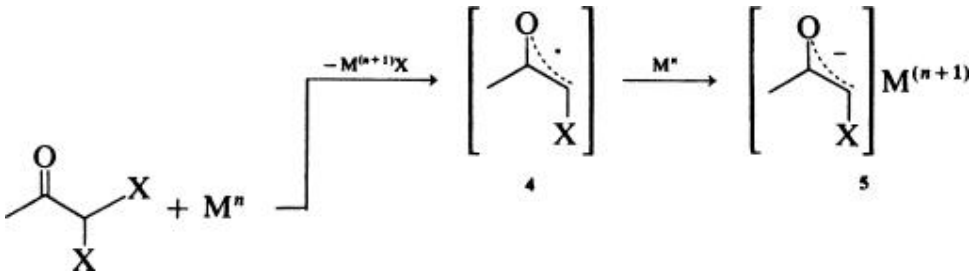
disproportionation with the starting halo ketones to form two equivalents of radical species (Eq. 8), which have actually been detected by chemical and spectroscopic techniques. (15)



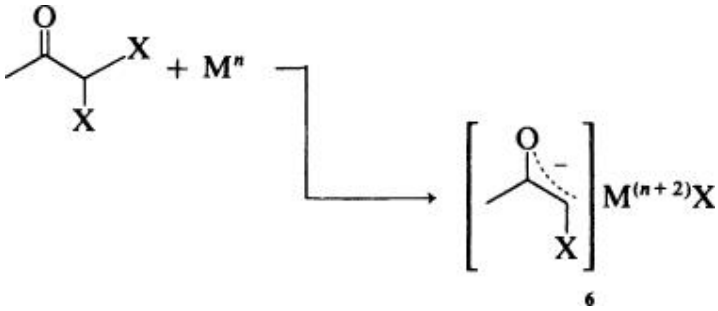
(8)

2.2. Reduction of α , α -Dihalo Ketones

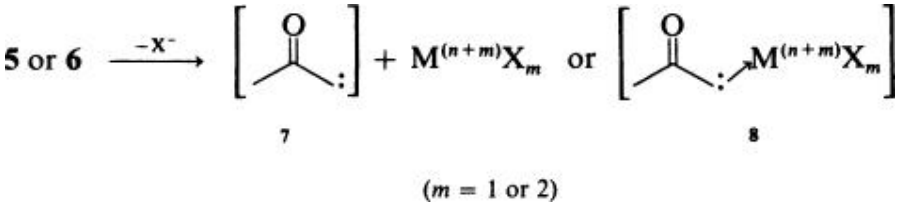
The reduction of geminal dihalo ketones begins in the same manner as that of α-monohalo ketones to form the radical species **4** (Eq. 9) or enolate intermediate **5** or **6** (Eqs. 9 and 10), as indicated by their chemical behavior. Enolate intermediate **5** or **6** further eliminates the remaining halogen atom, giving rise



(9)



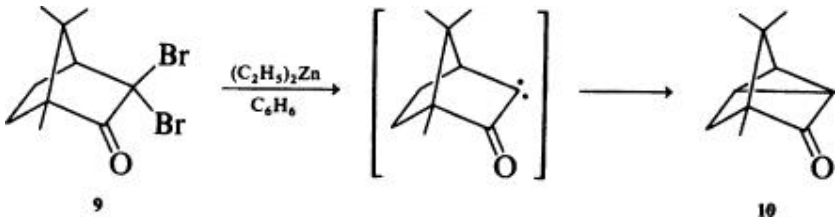
(10)



(11)

$(m = 1 \text{ or } 2)$

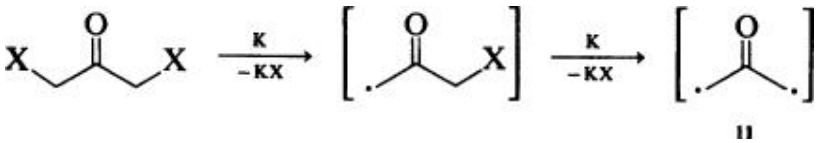
to ketocarbene **7** or its metal complex **8** (Eq. 11). Intervention of such species is convincingly argued for the reduction of **9**, which leads to tricyclic ketone **10** as the result of carbenoid γ C — H bond insertion. (16)



2.3. Reduction of α , α′-Dihalo and Polyhalogenated Ketones

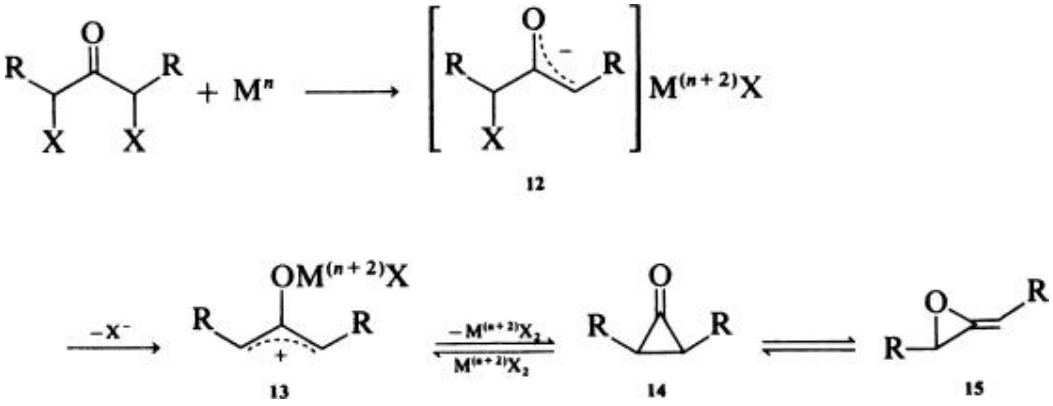
2.3.1.1. Vapor-Phase Reduction

Vapor-phase reduction of α , α′-dihalo ketones with potassium occurs by the successive atom-transfer mechanism to generate intermediary 2-oxo-1, 3-alkadiyl diradical species of type **11**, which decompose to carbon monoxide and olefins through cyclopropanones. (17)



2.3.1.2. Reduction in Solution

Reductions of α , α′-dihalo ketones and more highly halogenated ketones in organic solvents have been performed with two-equivalent reducing agents or electrochemically. The reaction is initiated by two-equivalent reduction of the polyhalo ketone to give metal enolate **12**, as ascertained by quenching in protic media to afford the protonated products. Enolate **12** suffers subsequent S_N 1-type or Lewis-acid-assisted elimination of the



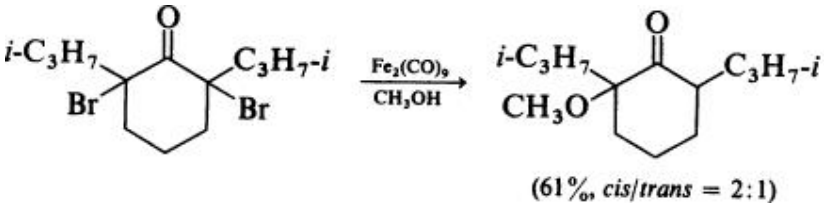
(12)

allylic bromine atom to produce 2-oxyallyl-metal complex **13** or its structural isomers, viz., cyclopropanone **14** and allene oxide **15** (Eq. 12). The relative stabilities of these species are influenced by a variety of factors. Theoretical treatments suggest that the parent 2-oxyallyl dipolar ion in a free form is very labile, isomerizing immediately to **14** and/or **15**. (18, 19) The oxyallyl species **13** receives greatest stabilization from electron-releasing substituents present at the C-1 and C-3 termini and from an increase in the covalent character of the M —O bond. Actually, α , α ′-dibromoacetone cannot be used as a starting C_3 substance since it leads to the extremely labile oxyallyl intermediate **13**(R = H), which bears no carbocation-stabilizing substituents. On the other hand, α , α, α′, α′-tetrabromoacetone or secondary and tertiary bis(bromoalkyl)ketones are utilized because the added substituent R (Br or alkyl) increases the stability of the resulting oxyallyl species **13** by mesomeric and inductive effects, respectively. The existence of the 2-oxyallyl species is possible only in the metal-complexed or protonated form (**13**, M = metal or H). The stability of **13** depends strongly on the nature of the M — O bond, which is influenced greatly by the nature of M and the solvents used. The more covalent the character of the metal–oxygen bond, the more the equilibrium lies in the direction of 2-oxyallyl cation formation. When the M — O bond is rather ionic, the equilibrium tends to shift toward the formation of the ring-closed isomers **14** or **15**. The polarity and metal-coordinating tendency of the solvent also affect the nature of the M —O linkage.

Many lines of evidence suggest the intermediacy of oxyallyl species through nucleophilic trapping (20-29) (Eqs. 13–15) and a variety of cationic rearrangements.

$$\underset{\mathbf{16}}{(CH_3)_2CBrCOCBr(CH_3)_2} \xrightarrow[CH_3CO_2D]{Hg} \underset{(60\%)}{(CH_3)_2C(OCOCH_3)COCD(CH_3)_2} \quad (13)$$

(Eq. 13)[23]



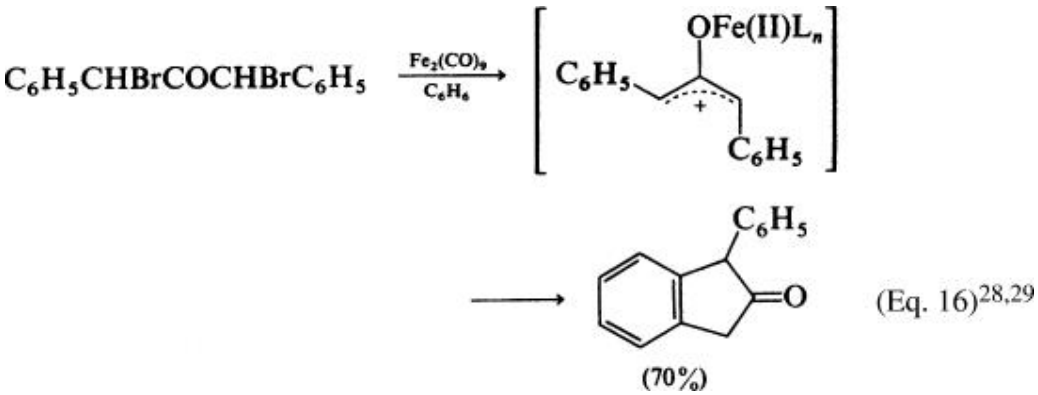
(Eq. 14)[28] (14)

$(CH_3)_2CBrCOCHBrC_4H_9\text{-}t$

$$\xrightarrow[t\text{-}C_4H_9CO_2H/DMF]{2e^-,\ t\text{-}C_4H_9CO_2Na} (CH_3)_2C(OCOC_4H_9\text{-}t)COCH_2C_4H_9\text{-}t \quad \text{(Eq. 15)}^{27} \quad (15)$$

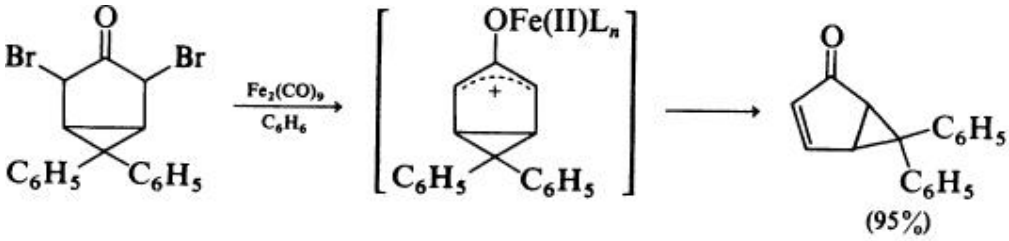
(67%)

The skeletal changes include electrocyclization of the 2-oxypentadienyl-type cation (Eq. 16), (28, 29) and [1_a,4_s] sigmatropic (Eq. 17), (28-31) neopentyl (Eq. 18), (28, 29) *tert*-butylallyl-cyclopropylcarbinyl (Eq. 19), (28, 29) and cationic



(16)

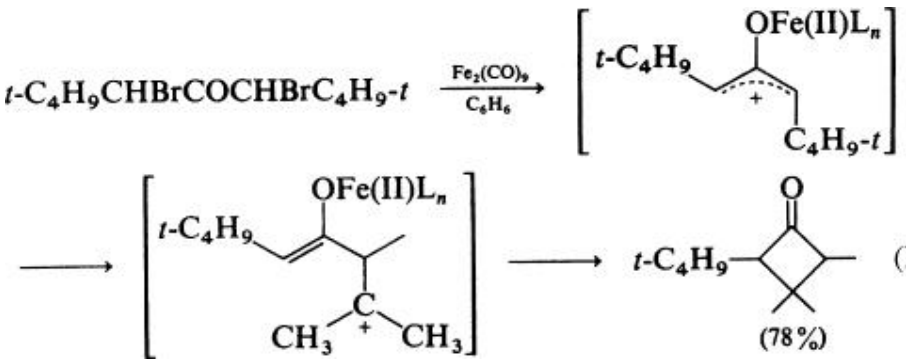
(Eq. 16)[28,29]



(17)

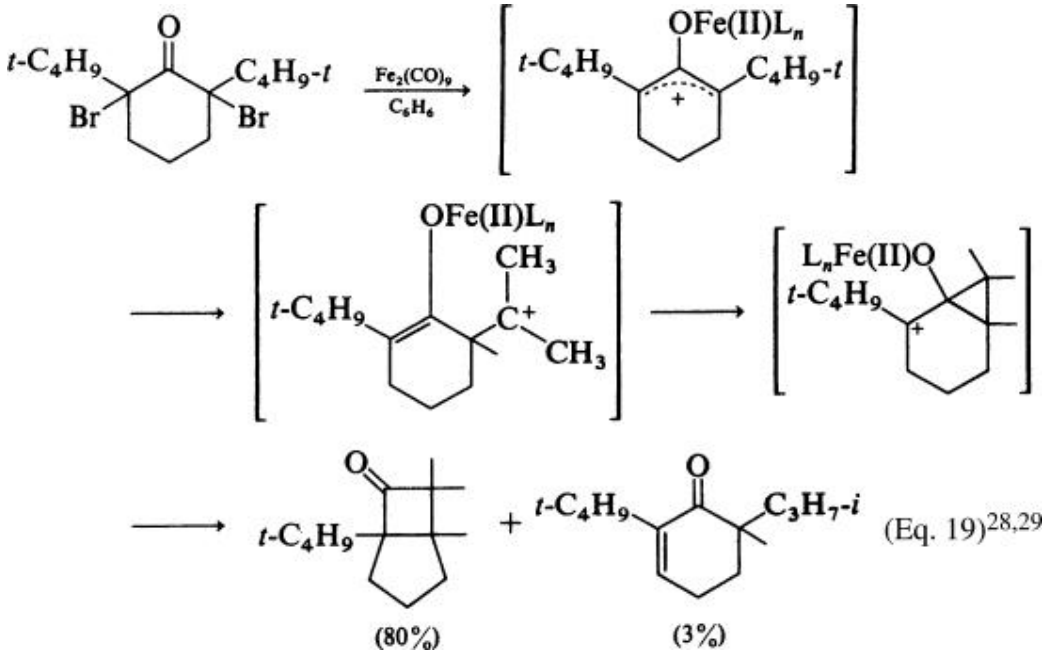
(Eq. 17)[28,29]

[3, 4] sigmatropic (Eq. 20) (32) rearrangements. Ene reactions between 2-oxyallyl cations and olefins are also reported (Eq. 21). (33) In some reactions reduction in



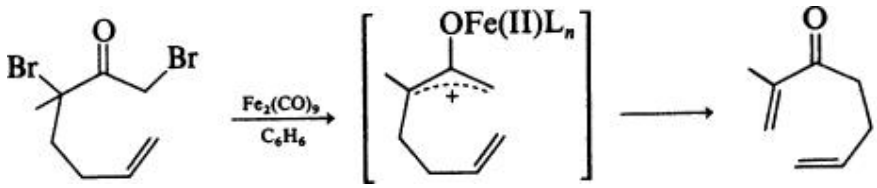
(18)

(Eq. 18)[28,29]

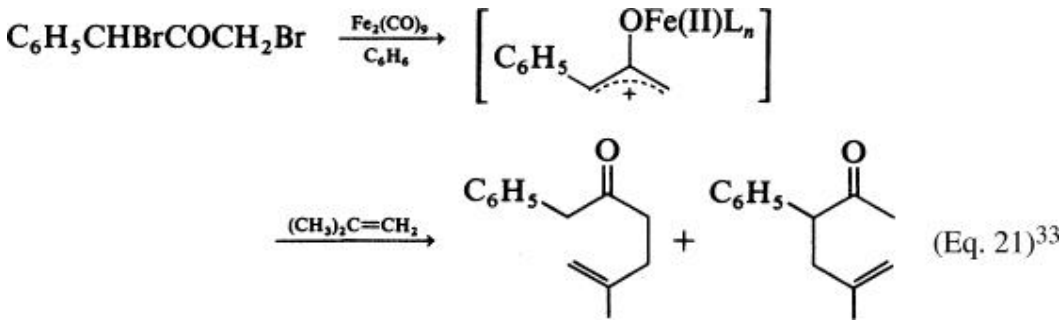


(19)

(Eq. 19)[28,29]



(Eq. 20)[32] (20)



(21)

(Eq. 21)[33]

basic media such as tetrahydrofuran (THF) or *N,N*-dimethylformamide (DMF) yields α , β -unsaturated ketones resulting from prototropy of the 2-oxyallyl intermediate. (20, 28, 29, 34, 35) Furthermore, the intervention of an allyl

$$\underset{16}{(CH_3)_2CBrCOCBr(CH_3)_2} \xrightarrow[DMF]{Fe_2(CO)_9} \underset{17\ (80\%)}{CH_2{=}C(CH_3)COC_3H_7\text{-}i} \quad \text{(Eq. 22)}^{34,35} \tag{22}$$

cationic species is in accord with the reductive [3 + 4] or [3 + 2] cyclocoupling reactions between polyhalo ketones and 1,3-dienes or certain olefins, respectively. (33, 36) Cyclopropanones as transient intermediates are detected by IR analysis of certain electrochemical reductions in dimethylformamide. (37) Some products derivable in principle from cyclopropanones are isolated from electrolysis (37, 38) or zinc/copper couple reduction (39) in protic solvents. Formation of allene oxides as product-determining intermediates has not yet been substantiated.

3. Scope and Limitations

3.1. Reduction of α -Monohalo Ketones

3.1.1.1. Formation of the Parent Ketones

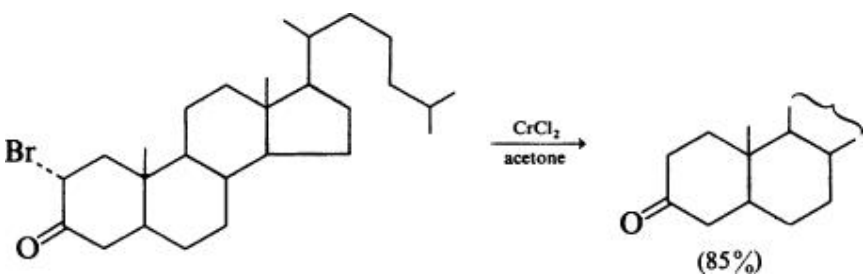
When α -monohalo ketones are treated with either one- or two-equivalent reductants in protic or aprotic media, the parent ketones are produced; the latter reaction usually, though not always, requires aqueous workup. Electroreduction proceeds analogously.

Lithium metal, a one-electron reductant, in ethereal solvents is adequate for the reduction of halo ketones lacking active α -hydrogen atoms. (40) Use of

$$C_2H_5C(CH_3)_2COCBr(CH_3)C_2H_5 \xrightarrow[\text{ether}]{\text{Li}} C_2H_5C(CH_3)_2COCH(CH_3)C_2H_5 \quad (97\%)$$

molybdenum hexacarbonyl-alumina (12) and chromium(II), (41) iron(II), (11, 42) and cobalt(II) (42) species also leads to satisfactory reduction; tungsten hexacarbonyl is rather less effective. (43) Usually such reductions require the stoichiometric use

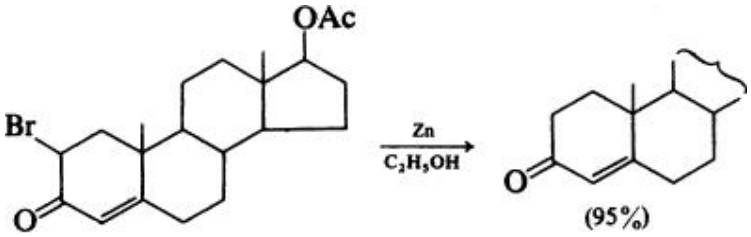
$$\underset{\mathbf{18}}{p\text{-}C_6H_5C_6H_4COCH_2Br} \xrightarrow[\text{THF}]{Mo(CO)_6,\ Al_2O_3} \underset{\mathbf{19}\ (73\%)}{p\text{-}C_6H_5C_6H_4COCH_3}$$



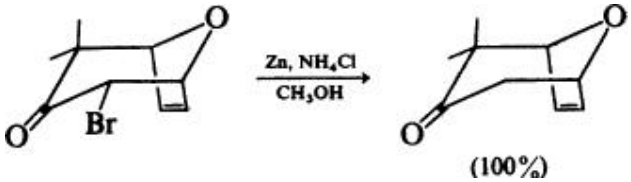
of reducing agents. Reduction can be achieved by the use of either catalytic or stoichiometric amounts of iron(II) salts in the presence of thiophenol; the stoichiometric conditions generally provide better yields. (11, 42)

$$\mathbf{18} \xrightarrow[H_2O\text{-}CH_3OH]{\text{0.1 eq. Fe(II)-polyphthalocyanine complex, } C_6H_5SH} \underset{(67\%)}{\mathbf{19}}$$

Equations 23 and 24 show examples of reductions that are assisted by two-equivalent reducing agents. Zinc metal and zinc/copper couple are the most conventional reagents; the addition of acidic substances accelerates the reduction to some extent. (44-49) Iron pentacarbonyl [$Fe(CO)_5$] and diiron enneacarbonyl [$Fe_2(CO)_9$] may be employed stoichiometrically; (28, 29) the former reagent

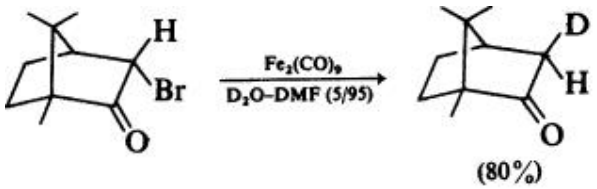


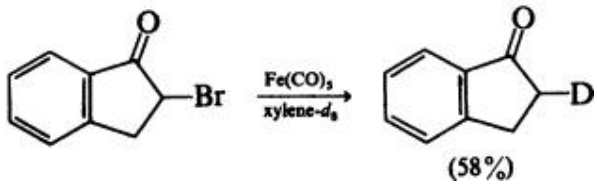
(23)



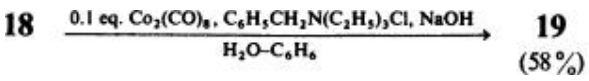
(24)

reduces the bromo ketone in an aprotic solvent to give the parent ketone without any aqueous workup. (50) Catalytic reduction using dicobalt octacarbonyl [$Co_2(CO)_8$] is a practical and useful process; a phase-transfer catalyst

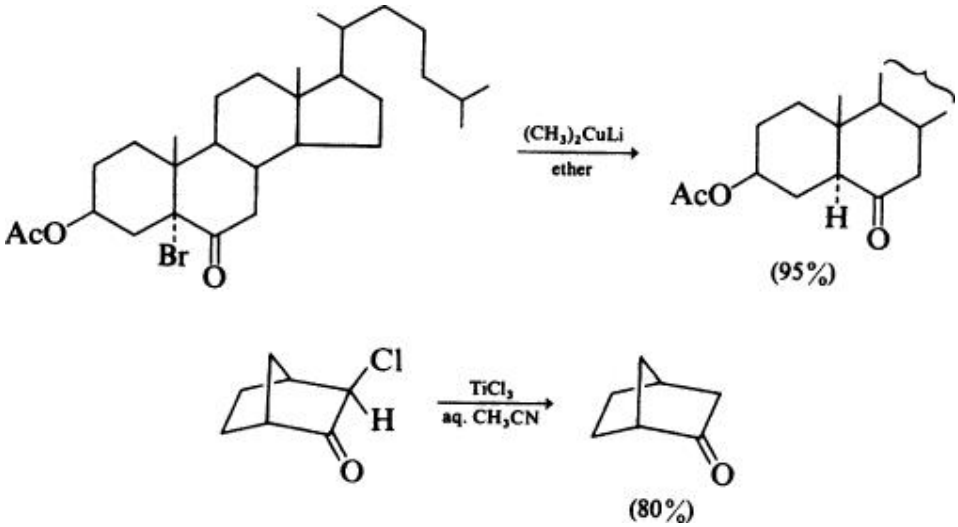




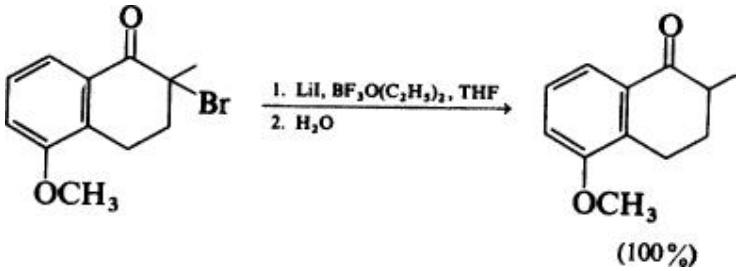
and sodium hydroxide are required to generate the actual reducing agent, $[Co(CO)_4]^-$. (51)



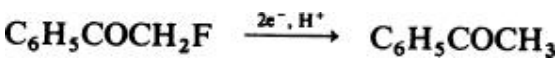
Lithium dialkylcuprates perform the reduction under very mild conditions, (52) but undesired alkylations often occur. (53) Use of aqueous titanium(III) (54) or vanadium(II) (55) chlorides is convenient. Reductive dehalogenation with an



excess of lithium iodide is promoted to a considerable extent by the combined use of boron trifluoride etherate (56) or hydriodic acid. (31)



A clean reduction, even of fluoro ketones, is effected by electrochemical treatment. (13)



In general, the two-equivalent reduction of bromo ketones, excluding tertiary ones, (7) is strongly accelerated by the addition of sodium iodide, (15) because iodide ion converts the bromo ketones to the more reactive iodo ketones via S_N2 displacement.

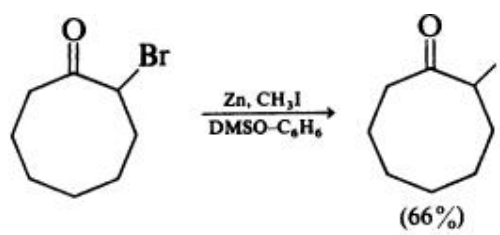
1,4-Diketones resulting from reductive dimerization of the starting halo ketones are typical side products in the reaction, particularly of alkyl halomethyl ketones in aprotic media.

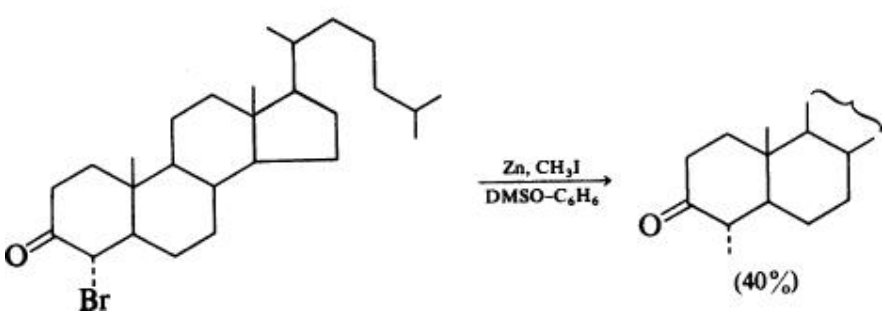
3.1.1.2. Formation of α -Alkyl Ketones

The reduction of α -monobromo ketones in the presence of electrophilic alkylating agents gives rise to α-alkyl ketones. However, only methyl iodide and certain activated alkyl halides appear to be of synthetic value here; ordinary higher alkyl iodides are not sufficiently reactive. For instance, the lithium-promoted reaction of **20** and methyl iodide in ether affords the methylation product **21** (R = CH_3) in 93% yield, while the reaction

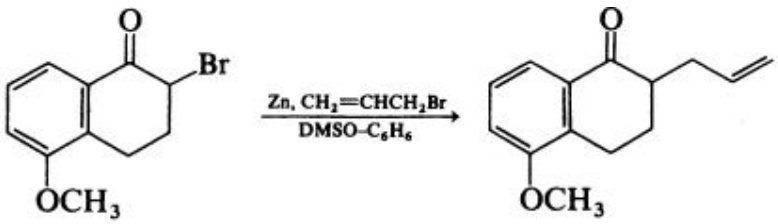
$$\underset{\mathbf{20}}{t\text{-}C_4H_9COCBr(CH_3)_2} \xrightarrow[R = CH_3,\ C_2H_5]{Li,\ RI,\ (HMPA)} \underset{\mathbf{21}\ (15\text{–}93\%)}{t\text{-}C_4H_9COCR(CH_3)_2} \qquad \text{(Eq. 25)}^{40} \qquad (25)$$

with ethyl iodide fails to yield the ethylated product (see Eq. 25); the use of hexamethylphosphoramide (HMPA) as a solvent facilitates the ethylation to some extent to give **21** (R = C_2H_5) in 15% yield. (40) Similar reactivity is observed in alkylations promoted by zinc dust in dimethyl sulfoxide (DMSO)-benzene. (57) Ethylation is achieved very slowly but in moderate to high yields





in hexamethylphosphoramide-benzene. (58) Efficient alkylations have been reported using activated alkyl halides such as allyl bromide (57) and α -chloro thioethers. (59) Reductive methylations of unsymmetrically substituted bromo ketones take place specifically at the carbon originally attached to bromine, producing single positional isomers. (57) A typical side reaction is the formation



(75%)

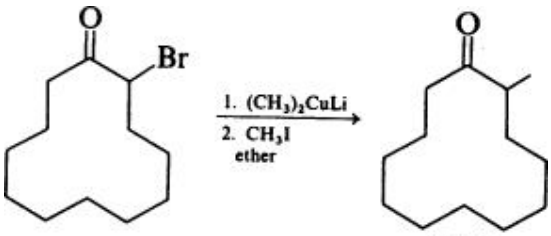
n-$C_3H_7COCHBrC_2H_5$

$$\xrightarrow[CH_3CO_2C_2H_5]{Zn,\ CH_3CH(SC_2H_5)Cl} n\text{-}C_3H_7COCH(C_2H_5)CH(SC_2H_5)CH_3$$

(82%)

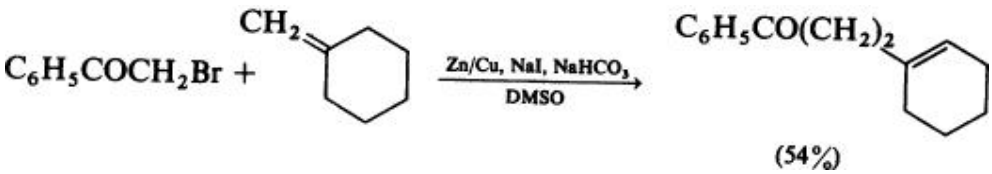
of furans arising via aldol condensation of an intermediary zinc enolate and an α -bromo ketone, which can be suppressed by lowering the concentration of starting bromide.

The reduction of bromo ketones with lithium dimethylcuprate followed by treatment with methyl iodide affords methylation products. (60)



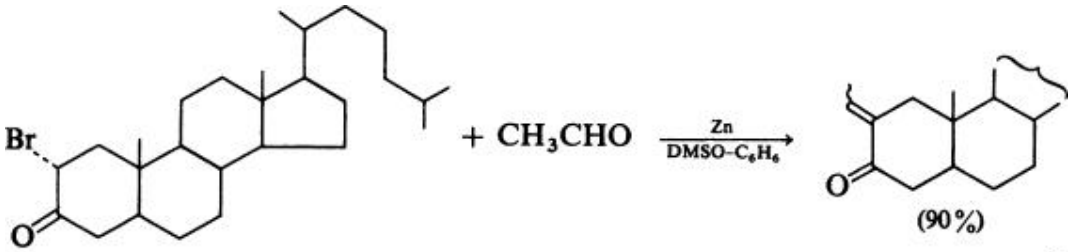
(67%)

The reduction of α -bromo ketones with zinc dust or zinc/copper couple in dimethyl sulfoxide containing sodium iodide and sodium hydrogen carbonate produces a radical species via the mechanism illustrated in Eq. 8 (see p. 168). (15) This intermediate can be trapped by aryl-substituted olefins or methylenecycloalkanes to give substitutive addition products possessing predominantly an endocyclic double bond. (15) Conjugated dienes and enynes undergo similar alkylations. (61)



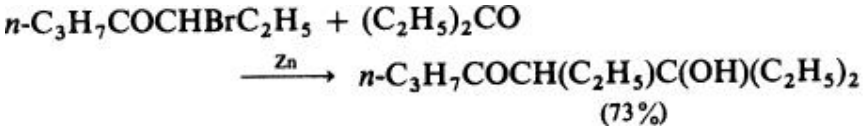
3.1.1.3. Formation of Aldols

A reductive aldol reaction between α -monobromo ketones and aldehydes or ketones can be achieved with zinc dust either alone (57, 62) or in combination with diethylaluminum chloride and a catalytic amount of copper(I) bromide. (63) Regiospecific aldol formation is observed in the reaction of the bromide derived from an unsymmetrical ketone. (63)

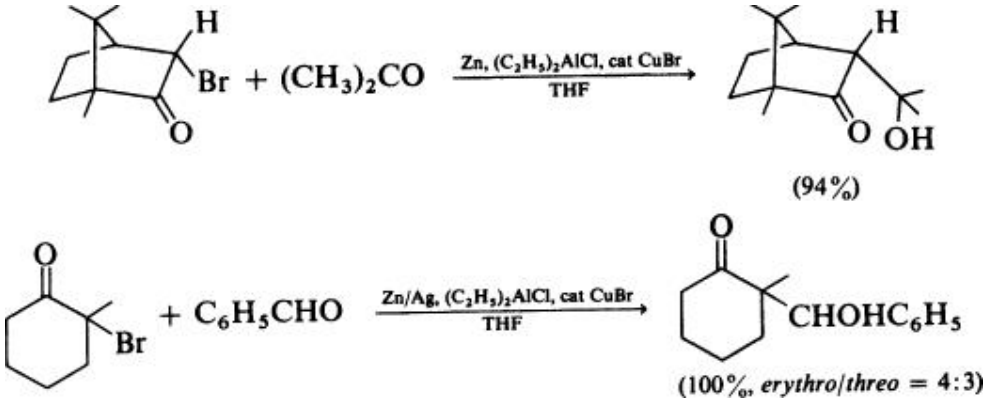


(26)

(Eq. 26)[57]



(Eq. 27)[62] (27)



3.1.1.4. Formation of 1, 3-Diketones and Enol Carboxylates

Acyl chlorides undergo effective C- and O-acylation reactions with the intermediary enolates generated by reduction of halo ketones, yielding 1, 3-diketones or enol carboxylates, respectively. Diketones are formed by reduction with zinc dust in ethyl acetate (64) or lithium dimethylcuprate in ether, (65) whereas enol carboxylates result from use of disodium tetracarbonylferrate [$Na_2Fe(CO)_4$] in tetrahydrofuran containing pyridine (Py). (66)

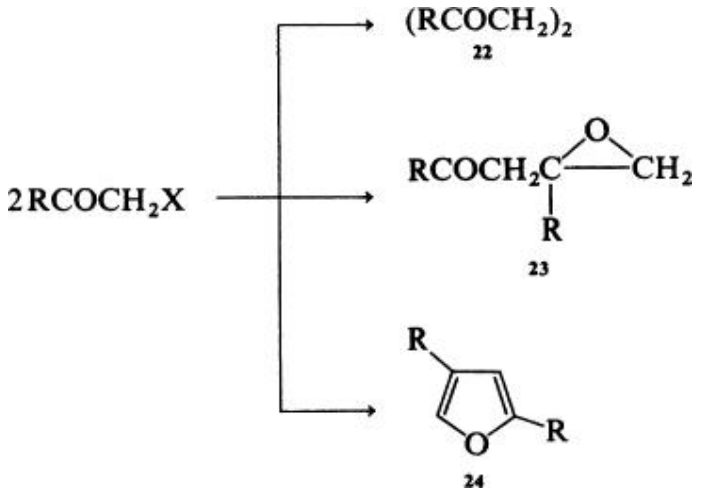
$$n\text{-}C_4H_9COCHBrC_3H_7\text{-}n + CH_3COCl \xrightarrow[CH_3CO_2C_2H_5]{Zn} n\text{-}C_4H_9COCH(COCH_3)C_3H_7\text{-}n \quad (56\%)$$

$$CH_3COCH_2Cl + (CH_3)_2CHCH_2COCl \xrightarrow[THF]{Na_2Fe(CO)_4,\ Py} CH_3C[OCOCH_2CH(CH_3)_2]{=}CH_2 \quad (97\%)$$

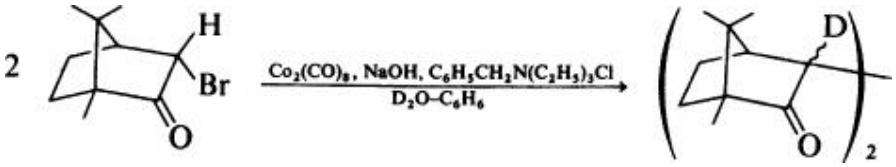
3.1.1.5. Reductive Dimerization to 1,4-Diketones, β -Epoxy Ketones, and Furans

The following three types of reductive dimerizations are reported (Scheme I): (1) formation of 1,4-diketone **22** through coupling at α carbons, (2) formation of β -epoxy ketone **23** by aldol reaction of an enolate intermediate with another α -halo ketone molecule followed by intramolecular S_N2 displacement of the resulting aldolate anion, and (3) production of unsymmetrically substituted furan **24**, probably arising from thermal rearrangement of the β -epoxy ketone accompanied by dehydration. (67)

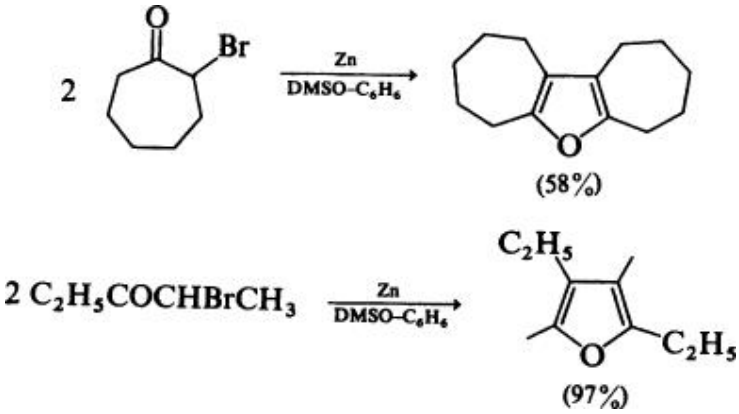
Scheme I.



These self-coupling reactions are usually nonselective, resulting in complex mixtures. However, a clean reaction producing 1,4-diarylbutane-1, 4-diones is achieved by use of $Fe(CO)_5$ in 1, 2-dimethoxyethane (DME). (14) The water–benzene two-phase reaction using $Co_2(CO)_8$ in the presence of sodium hydroxide and a phase-transfer catalyst is usually efficient for the self-coupling of sterically crowded bromo ketones to give 1, 4-diketones. (51)

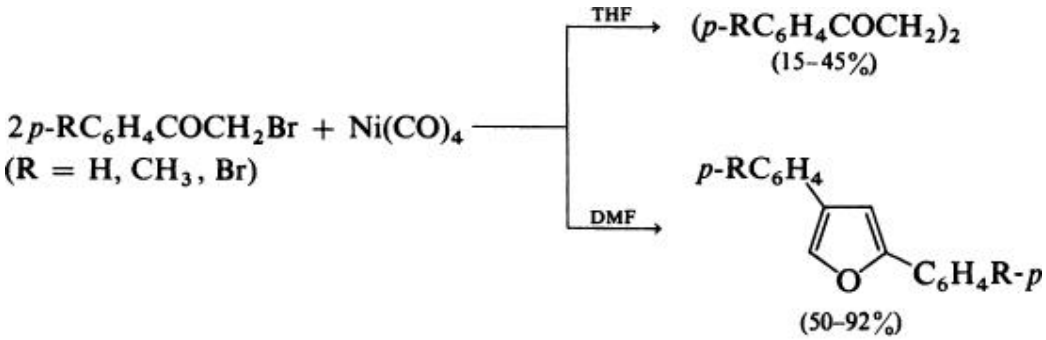


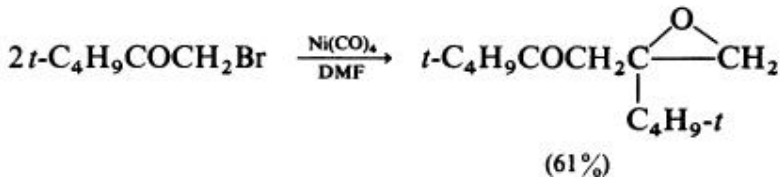
A high-concentration reduction with zinc dust in dimethylsulfoxide–benzene produces furans. (57) Noteworthy is the use of nickel tetracarbonyl [$Ni(CO)_4$]



for the reaction of aryl bromomethyl ketones, which leads exclusively to 1, 4-diketones in tetrahydrofuran or to 2,4-diarylfurans in dimethylformamide,

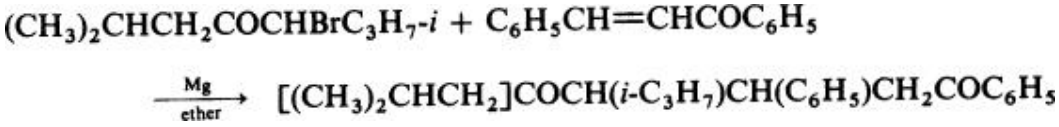
respectively. (68) β -Epoxy ketones are obtained from alkyl (but not aryl) bromoalkyl ketones in dimethylformamide. (67)





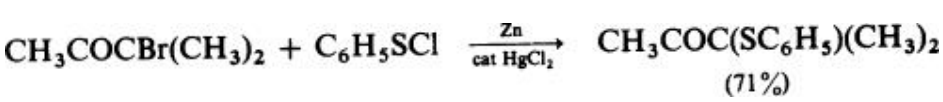
3.1.1.6. Formation of 1, 5-Dicarbonyl Compounds

α-Chloro or α -bromo ketones can undergo reductive Michael addition to α , β -unsaturated ketones or esters, giving rise to 1, 5-dicarbonyl products. Reactions with magnesium metal (69) or an organo cuprate (65) in ether are examples.



3.1.1.7. Formation of α -Arenesulfenyl Ketones

When α -bromo ketones are reduced with zinc dust in ether in the presence of arenesulfenyl chlorides and a catalytic amount of mercury (II) chloride, α -arenesulfenyl ketones are produced in high yields. (70)

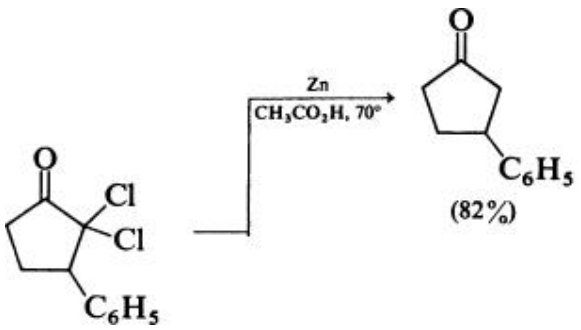


3.2. Reduction of α , α -Dihalo Ketones

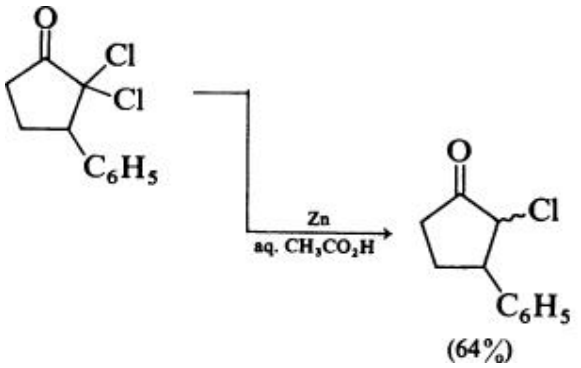
3.2.1.1. Formation of α -Monohalo Ketones and Parent Ketones

α, α-Dihalo ketones are reduced stepwise to form initially the corresponding α -monohalo ketones and subsequently the parent ketones.

Zinc dust in protic solvents is frequently used for this purpose. Glacial acetic acid is recommended as a solvent to obtain a high yield of completely dehalogenated ketone (Eq. 28a), (71) whereas milder reaction in aqueous acetic acid tends to afford monohalo ketones predominantly (Eq. 27b). (72)

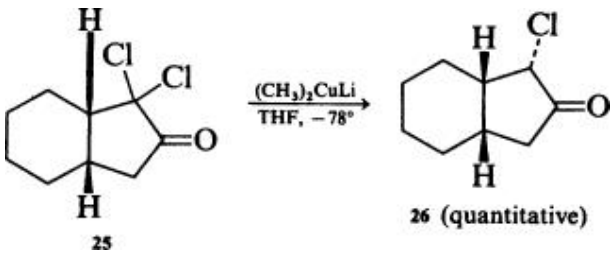


(Eq. 28a)[71] (28a)



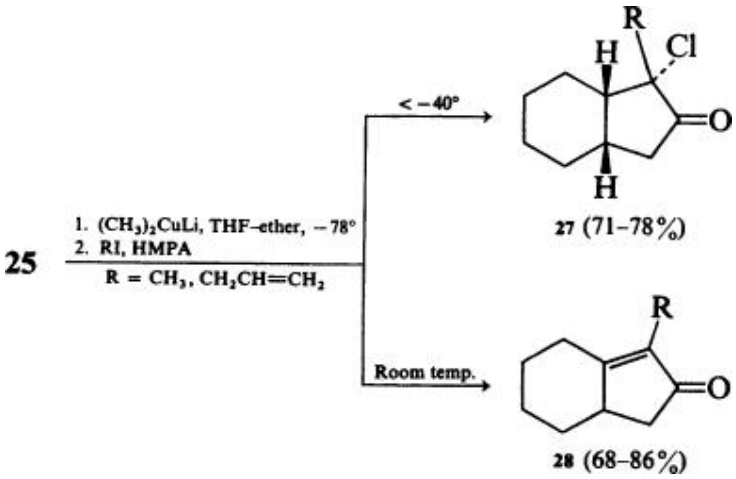
(Eq. 28b)[72] (27b)

Reduction of α , α -dichloro ketone **25** with lithium dimethylcuprate in tetrahydrofuran at –78° affords α -monochloro ketone **26** exclusively after aqueous workup; (73) this procedure is substantially easier and higher yielding than the zinc reduction. Diethylzinc in benzene is another excellent reducing agent for the preparation of monohalo ketones. (16)



3.2.1.2. Formation of α -Alkyl α -Monohalo Ketones and α-Alkyl α , β -Unsaturated Ketones

Quenching of the reaction mixture of **25** and lithium dimethylcuprate in tetrahydrofuran–ether with alkyl iodides and hexamethylphosphoramide below –40° gives rise to α -alkyl α -chloro ketone **27**; (73) workup at

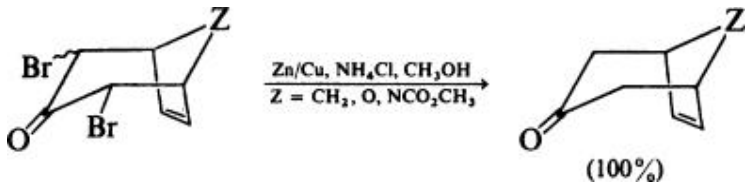


ambient temperature results in dehydrochlorination of **27** and formation of enone **28**. (73)

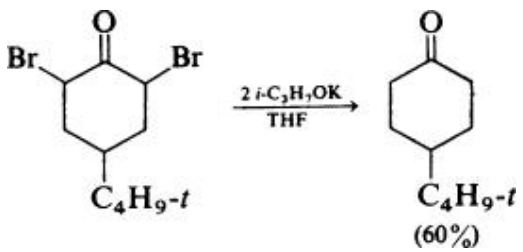
3.3. Reduction of α , α′-Dihalo and Polyhalogenated Ketones in Solution

3.3.1.1. Formation of α -Monohalo Ketones and Parent Ketones

When α , α ′-dibromoketones are treated with two-equivalent reductants in protic media, stepwise debromination occurs to afford ultimately the parent ketones; the selective preparation of intermediary monobromo ketones is difficult. (28) Zinc dust and zinc/copper couple in methanol are the most commonly employed reductants. Formation of α -methoxy ketones is a serious side reaction, but can be prevented by using methanol containing ammonium chloride as solvent. (74, 75) Hydriodic

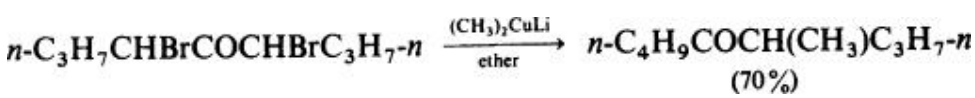


acid also can effect the reduction. (32) Use of two molar equivalents of primary or secondary alkoxides in tetrahydrofuran or alcoholic tetrahydrofuran reduces certain dibromides to the parent ketones in fair to good yields. (76, 77)

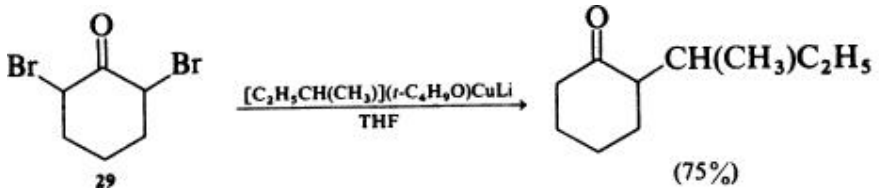


3.3.1.2. Formation of α -Monoalkyl Ketones

Reduction of open-chain and cyclic dibromo ketones with organo cuprate reagents such as lithium dialkylcuprates and lithium alkyl(alkoxy)- or alkyl(phenylthio)cuprates gives α -monoalkyl ketones after aqueous workup. (60, 78) Primary, secondary, and tertiary alkylations can be achieved with the appropriate quantity of cuprate, the structure of

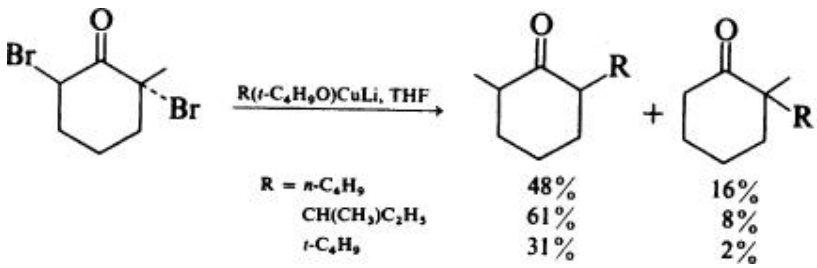


which has an important influence on the yield of product. Alkyl heterocuprates generally work better than the corresponding dialkyl reagents for α -secondary and α -tertiary alkylations. For example, the *sec*-butylation of 2, 6-dibromocyclo-hexanone (**29**) is achieved in 75% yield using $[C_2H_5CH(CH_3)]$ $(t\text{-}C_4H_9O)CuLi$ in tetrahydrofuran, but only in 38% yield with $[C_2H_5CH(CH_3)]_2CuLi$ in ether. (60, 78) Introduction of primary alkyl groups is performed in comparable yield using dialkyl cuprates or alkyl heterocuprates. (60, 78)

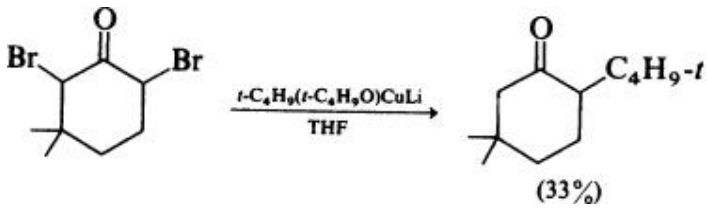


Grignard reagents are adequately effective only for the preparation of α -methylated ketones; other higher-alkylated derivatives cannot be prepared in this manner. (78) The major side product obtained in these alkylation reactions is the parent ketone; no dialkylated products are formed.

Alkylation of unsymmetrical α , α ′-dibromo ketones usually affords a mixture of two possible positional isomers, with the less substituted one predominating. The degree of regioselectivity decreases in the order tertiary alkylation > secondary alkylation > primary alkylation (cf. Eq. 29). (78) β-Substituents also affect the regioselectivity (Eq. 30). (78)



(Eq. 29)[78] (29)



(Eq. 30)[78] (30)

Another type of reductive α-alkylation of dibromo ketone **30** is achieved with propargyl alcohol or its ethers using copper powder in acetonitrile containing sodium iodide. α -Allenyl ketones are produced. (79)

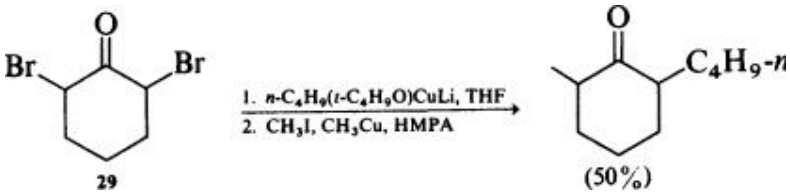
$$\underset{\mathbf{30}}{CH_3CHBrCOCHBrCH_3} + HC{\equiv}CCH_2OR \xrightarrow[R = H,\ CH_3]{Cu,\ NaI,\ CH_3CN} \underset{(25\text{–}35\%)}{C_2H_5COC(CH_3){=}C{=}CHCH_2OR}$$

3.3.1.3. Formation of α , α′-Dialkyl Ketones

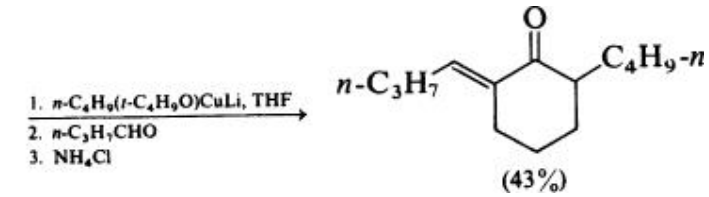
Reaction of α , α ′-dibromo ketones with organo cuprates followed by treatment with alkyl iodides affords α , α ′-dialkyl ketones. (78, 80, 81) Use of alkyl bromides or alkyl tosylates results in relatively little alkylation. (81) Addition of *N*,*N*,*N′*,*N′*-tetramethylethylenediamine (TMED)

$$t\text{-}C_4H_9CHBrCOCHBrC_4H_9\text{-}t \xrightarrow[2.\ CH_3I]{1.\ (CH_3)_2CuLi,\ ether} \underset{(80\%)}{t\text{-}C_4H_9CH(CH_3)COCH(CH_3)C_4H_9\text{-}t}$$

or hexamethylphosphoramide to the reaction mixture facilitates the second alkylation. (81) The formation of α -monoalkyl (80) or α , α-dialkyl ketones is a serious side reaction.

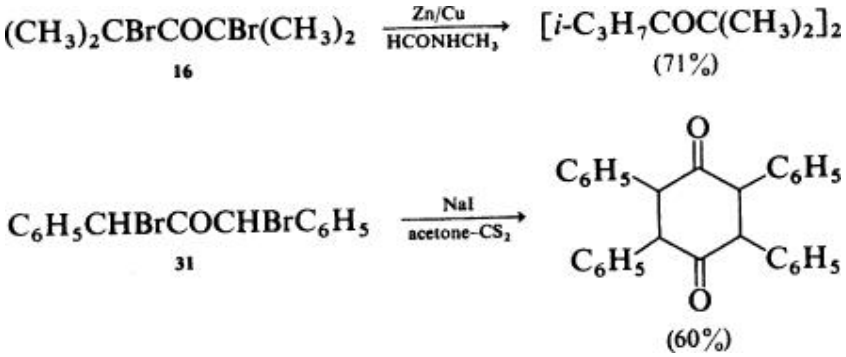


Quenching of cuprate-generated enolates with aldehydes followed by treatment with ammonium chloride yields α -alkyl α ′-(*E*)-alkylidene ketones. (81)



3.3.1.4. Reductive Dimerization to Form 1, 4-Diketones

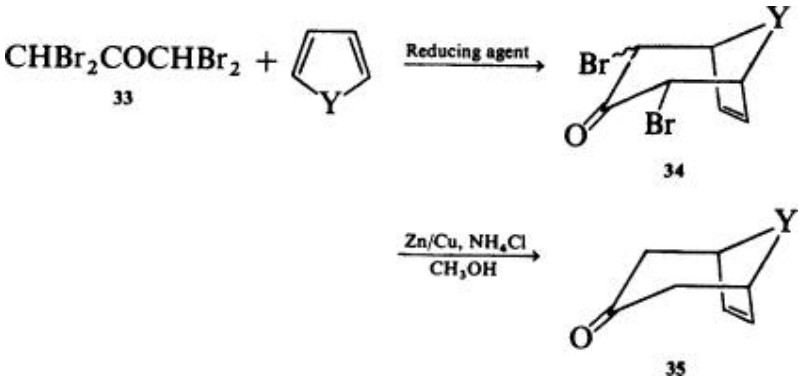
α, α ′-Dibromo ketones undergo two types of reductive dimerizations, giving the corresponding open-chain and cyclic 1, 4-diketones. Open-chain diones are obtained by reduction with zinc/copper couple in *N*-methylformamide (82) or $Fe_2(CO)_9$ in tetrahydrofuran, (83) whereas cyclic diones result from sodium iodide reduction in acetone or acetone-carbon disulfide. (84, 85) Reactions of unsymmetrical dibromides are nonregioselective. (82)



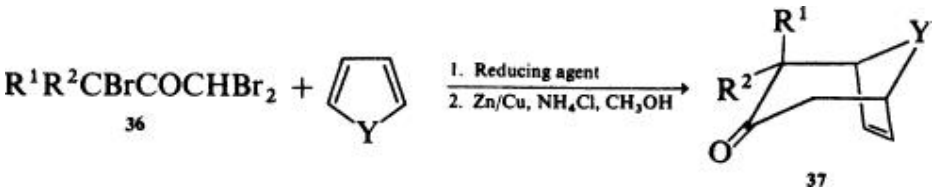
3.4. Formation of Seven-Membered Ketones by Intermolecular [3 + 4] Cyclocoupling

3.4.1.1. General Aspects

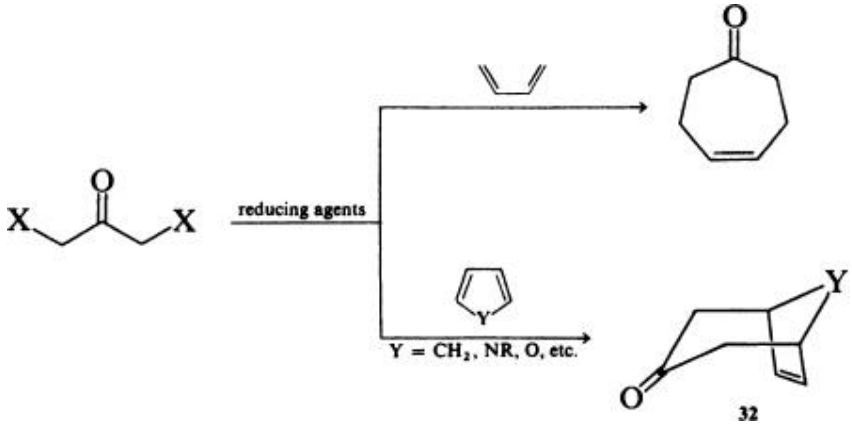
Before the scope and limitations of the reductive [3 + 4] cyclocouplings outlined in Scheme II are discussed, it may be useful to consider some of the general aspects of the reaction. The yields of 4-cycloheptenones appear to depend on the efficiency of the generation of 2-oxyallyl or related species and the ease of the trapping by 1,3-dienes. As mentioned in the MECHANISM section, secondary and tertiary dibromides can generate the three-carbon reactive intermediates, while dibromoacetone and other methyl alkyl ketone dibromides are unable to produce such intermediates effectively. However, α , α, α′,α′-tetrabromoacetone (**33**) reacts with cyclic dienes to give **34**, which on brief treatment with zinc/copper couple in methanol is converted to ketone **35**. (74) The overall process is regarded formally as a cyclocoupling reaction



between dibromoacetone and the diene. The modified procedure is widely applicable; **37** is obtained using methyl alkyl ketone tribromides such as **36**. (41)



Scheme II.



(Eq. 31)

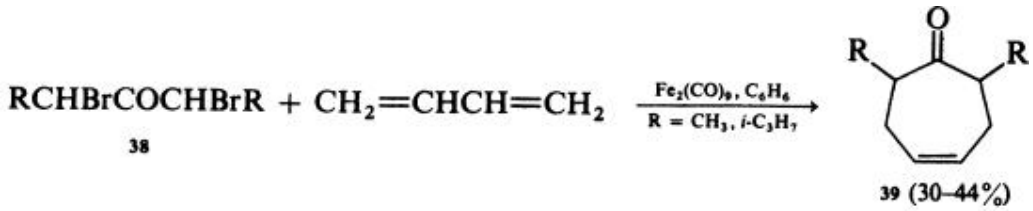
(Eq. 32)

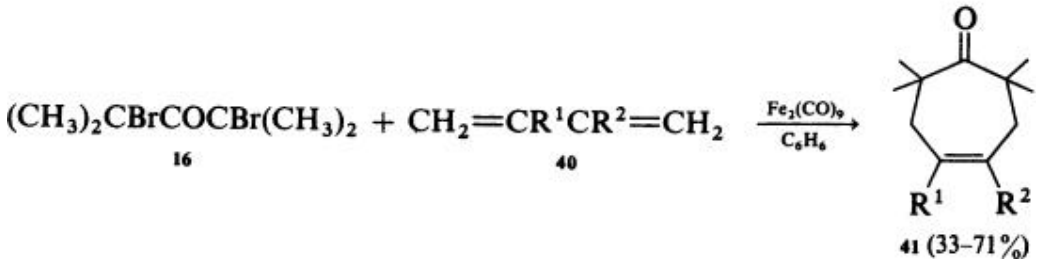
The [3 + 4] reaction is a cycloaddition of the intermediary 2-oxyallyl species or a cyclopropanone, depending on the reaction conditions, across the diene. (36) Therefore, as in the Diels-Alder reaction, dienes with a high equilibrium concentration of the *s-cis* conformer serve as efficient four-carbon receptors. Thus in general cyclic dienes undergo the cycloaddition reaction better than conformationally flexible open-chain derivatives. (8)

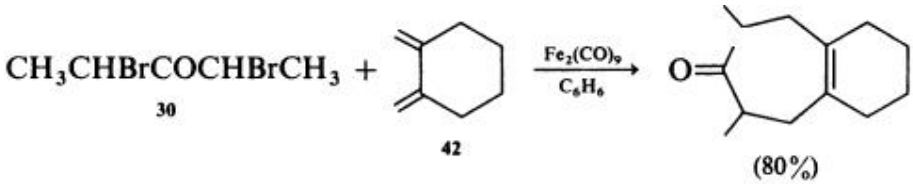
Discussed below are the scope and limitations of the [3 + 4] cyclocoupling reaction classified according to the structure of the diene component.

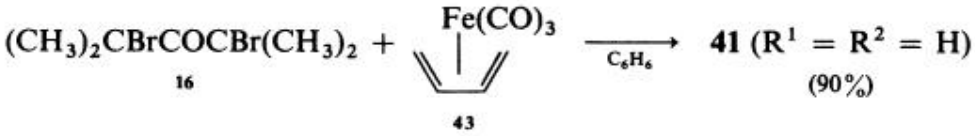
3.4.1.2. Formation of 4-Cycloheptenones and Related Compounds

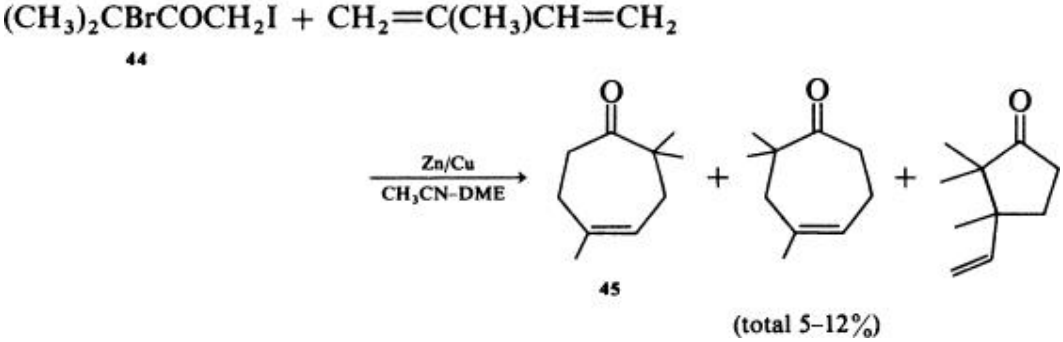
Whenα, α′-dihaloketones are reduced with iron carbonyls or zinc/copper couple in the presence of open-chain 1,3-dienes, 4-cycloheptenones are obtained. Of the various kinds of dienes, 2,3-dialkylbutadienes usually give the best yields of cycloadducts, because of their high equilibrium concentration of *s-cis* conformer. For instance, the $Fe_2(CO)_9$-promoted cyclocoupling of **16** and 2,3-dimethylbutadiene (**40**, $R^1 = R^2 = CH_3$) proceeds in a higher yield (71%) than reactions using butadiene (33%) or isoprene (**40**, $R^1 = H$, $R^2 = CH_3$, 47%). (74) The 1,2-bismethylenecycloalkane **42**, in which the *s-cis* conformation is frozen by inclusion of the C-2 and C-3 positions of the diene in the cycloalkane system, is among the most reactive four-carbon units. (74) Diiron enneacarbonyl is conventionally employed as the reducing agent. When dieneiron tricarbonyl complexes of type **43** are used in place of the free dienes and $Fe_2(CO)_9$, forcing reaction conditions are required, but the result is still a remarkable increase in yields of cycloheptenones. For example, the reaction of **16** and butadiene with $Fe_2(CO)_9$ at 60° for 38 hours produces **41** ($R^1 = R^2 = H$) in only 33% yield, while use of **43** at 80° for 4 hours gives the same adduct in 90% yield. (74) Iron pentacarbonyl gives a lower yield. (74, 86) Zinc/copper couple as the reducing agent affords in addition to 4-cycloheptenones many undesirable side products such as five-membered ketones and 1,4-diketones. (87, 88)







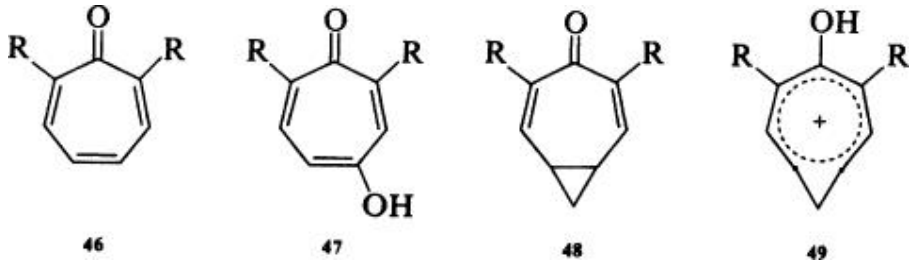




3.4.1.2.1. Synthetic Applications

2,7-Dialkylated 4-cycloheptenones such as **39** are utilized as key intermediates in the preparation of various kinds of troponoid compounds including the 2,7-dialkylated tropone **46**, (86, 89) γ -tropolone **47**, (86, 89) and 4,5-homotropone **48**, which exists as the hydrohomotropylium ion **49** in

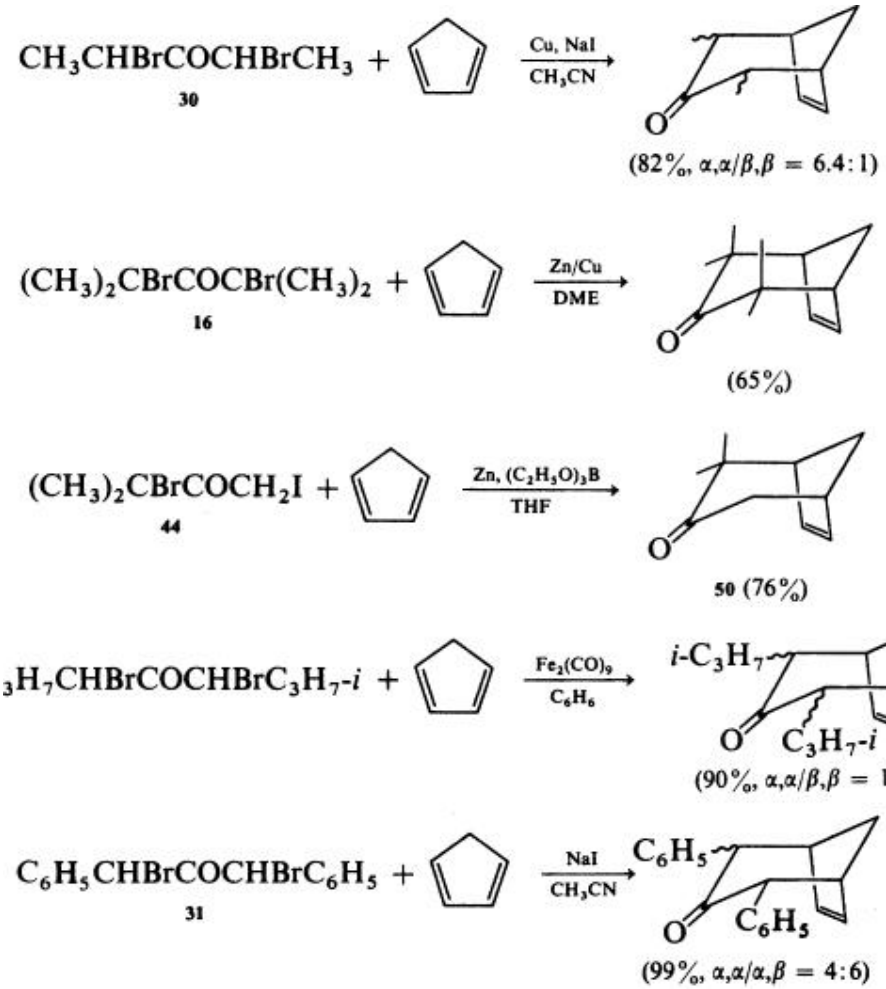
concentrated sulfuric acid. (89, 90) A single-step synthesis of karahanaenone (**45**),



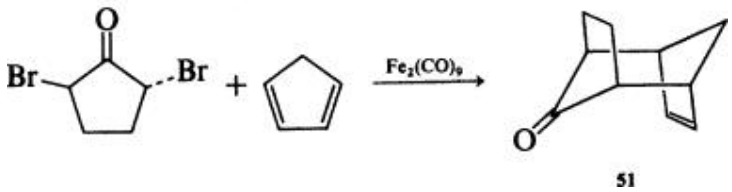
a monoterpene, was achieved by the reaction between **44** and isoprene with zinc/copper couple or $Fe_2(CO)_9$, though in very poor yield. (87)

3.4.1.3. Formation of Bicyclo [3.2.n]alkenones and Related Compounds

Reductive cyclocoupling of dibromo ketones across cyclopentadiene gives rise to bicyclo [3.2.1]oct-6-en-3-ones in generally high yields. Copper-sodium iodide in acetonitrile, (91, 92) zinc dust-triethyl borate in tetrahydrofuran, (47) zinc/copper couple in 1,2-dimethoxyethane or acetone, (93) $Fe_2(CO)_9$ in benzene, (74, 87) and sodium iodide in acetone or acetonitrile (84, 94) are reducing agents and solvents of choice. The combination of zinc powder and a trialkyl borate effects reduction of the dihalo derivatives of methyl alkyl ketone **44**. (47) The 2,4-disubstituted

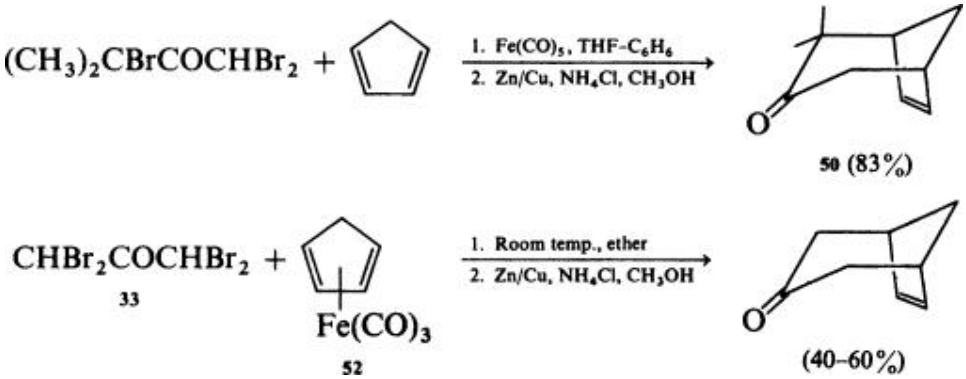


product obtained is usually a mixture of two *cis* isomers (74, 91) except for the diphenyl adduct. (94) The reaction of 2,5-dibromocyclopentanone yields tricyclic ketone **51**. (95)



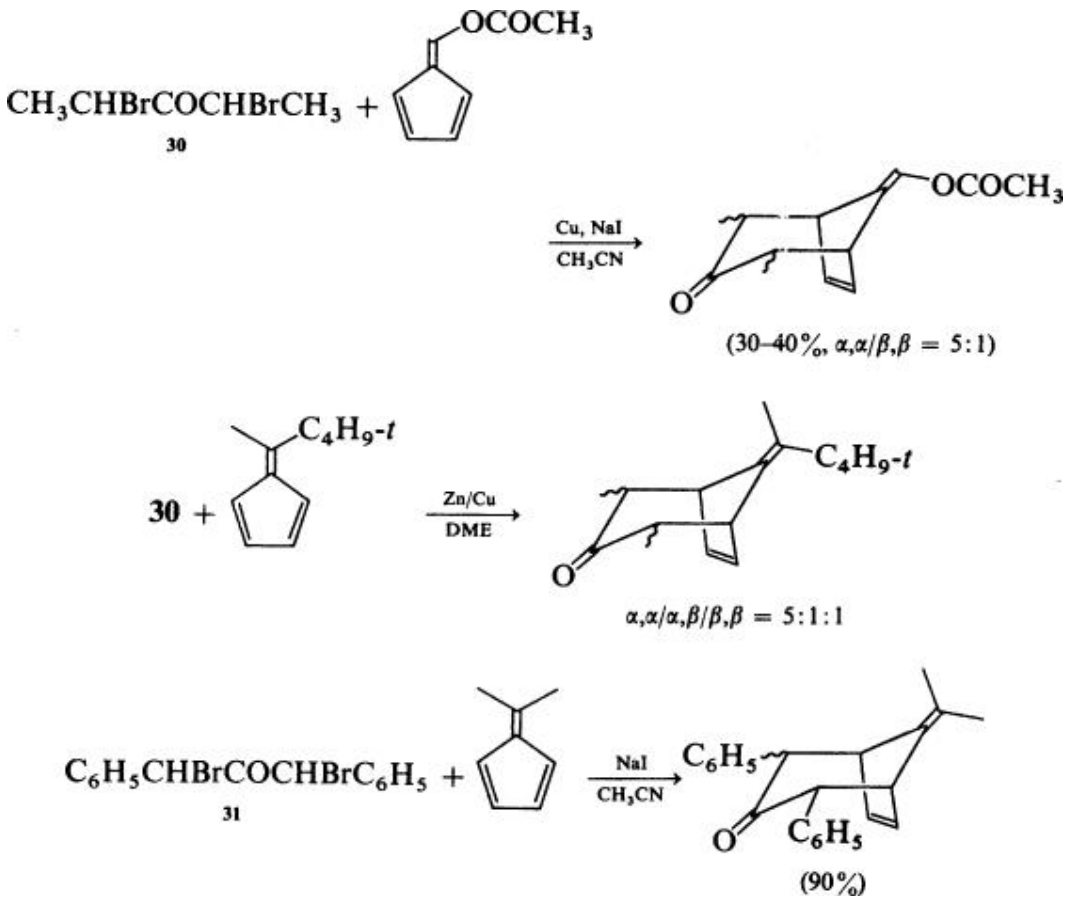
Tri- and tetrabromo ketones also react with cyclopentadiene with the assistance of $Fe(CO)_5$ in benzene (96) or tetrahydrofuran-benzene, (48, 74) alternatively, cyclopentadieneiron tricarbonyl (**52**) is a good reducing agent. (97) The extra bromine atoms in the resulting cycloadducts are quantitatively removed by treatment with zinc/copper couple in ammonium

chloride-saturated methanol. (48, 74) Poor results are obtained with $Fe_2(CO)_9$ (48) or zinc/copper

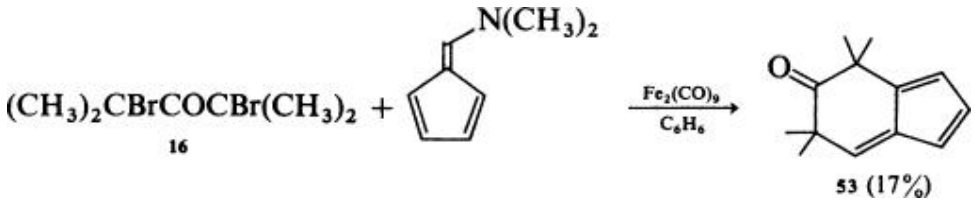


couple-triethyl borate. (47) 5,5-Dimethylcyclopentadiene fails to give a cycloadduct. (92)

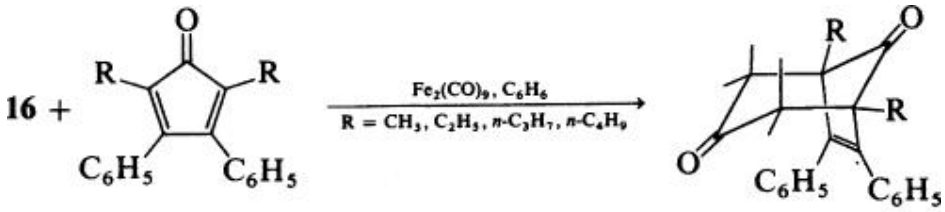
Fulvenes also enter into cyclocoupling with dibromo ketones, aided by copper-sodium iodide in acetonitrile, (92) zinc/copper couple in 1,2-dimethoxyethane, (92, 98) or sodium iodide in acetonitrile, (98) giving 8-alkylidenebicyclo-[3.2.1]oct-6-en-3-ones. The reactions with 6,6-dialkylfulvenes generally give



good results; hetero substituents at the C-6 position depress the yields. 6-(Dimethylamino)fulvene acts as a 6 π -electron component, giving a different type of cyclic adduct, **53**, in the reaction with $Fe_2(CO)_9$. (99)

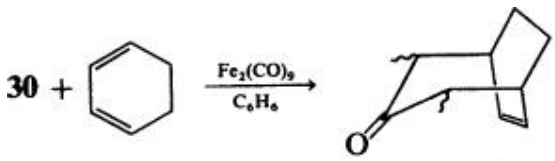


Cyclopentadienones are fair to good C_4 substrates, giving bicyclo[3.2.1]oct-6-ene-3,8-dione **54** by reaction of **16** with $Fe_2(CO)_9$ in benzene. (99) Diiron



54 (22–35%)

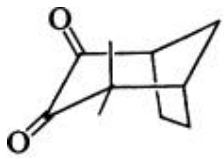
enneacarbonyl assists the cyclocoupling of **30** and 1,3-cyclohexadiene to form bicyclo[3.2.2]non-6-en-3-one **55**. (100)



55 (50%, α,α/β,β = 1.5:1)

3.4.1.3.1. Synthetic Applications

Carbocamphenilone (**56**), a terpenic α-diketone, and its oxidized product, camphenic acid (**57**), are prepared via the cycloadduct **50** as a key intermediate. (48)



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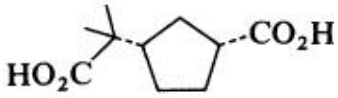

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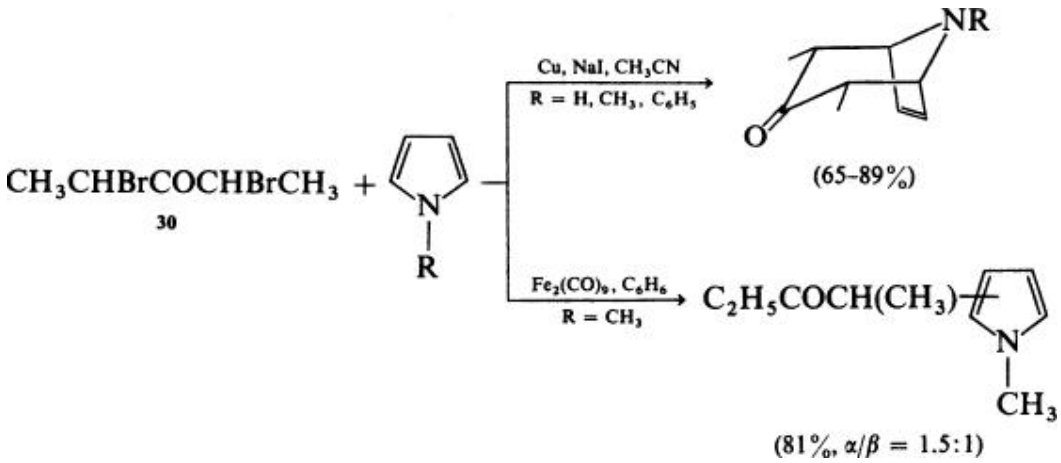
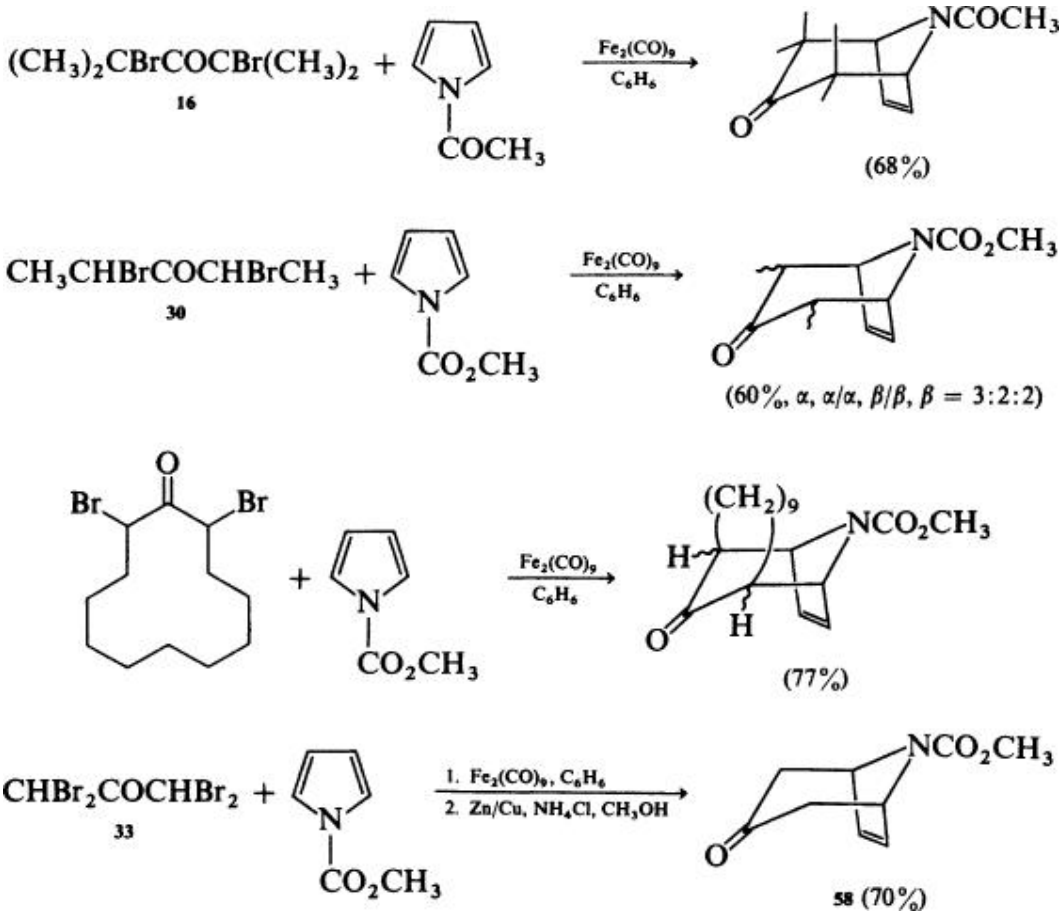
3.4.1.4. Formation of 8-Azabicyclo[3.2.1]oct-6-en-3-ones and Related Compounds

Pyrrole and its *N*-alkyl derivatives can be employed as diene substrates for the copper-sodium iodide-promoted [3 + 4] cyclocoupling reaction of open-chain dibromo ketones. (92, 101, 102) Reaction with cyclic dibromo ketones such as 2,6-dibromocyclohexanone affords only substitution products. Treatment of both open-chain and cyclic dibromides with zinc or iron carbonyls results only in substitution. (74, 102, 103)



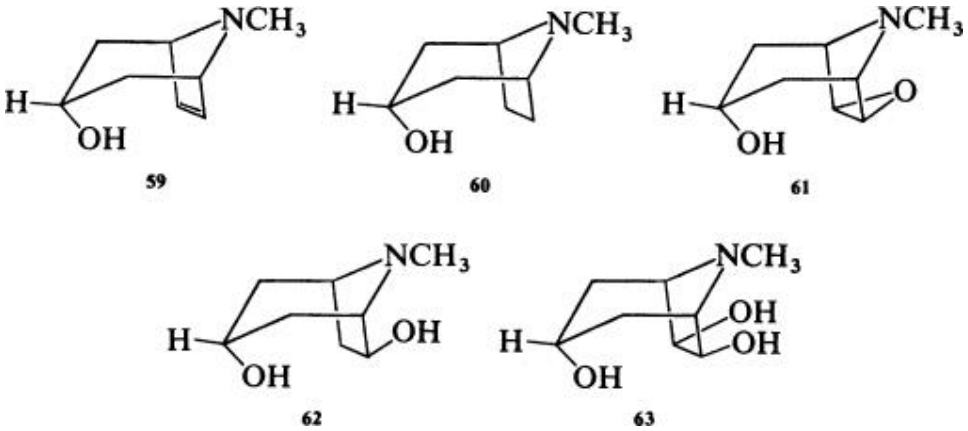
Pyrrole derivatives bearing an electron-withdrawing substituent such as acetyl or methoxycarbonyl on the nitrogen undergo the cyclocoupling reaction with dibromo (74) or more highly brominated ketones. (75) The reducing agent of



choice is $Fe_2(CO)_9$ in benzene. Use of $Fe(CO)_5$ or zinc/copper couple gives less satisfactory results. Attempts to use copper-sodium iodide have not succeeded.

3.4.1.4.1. Synthetic Applications

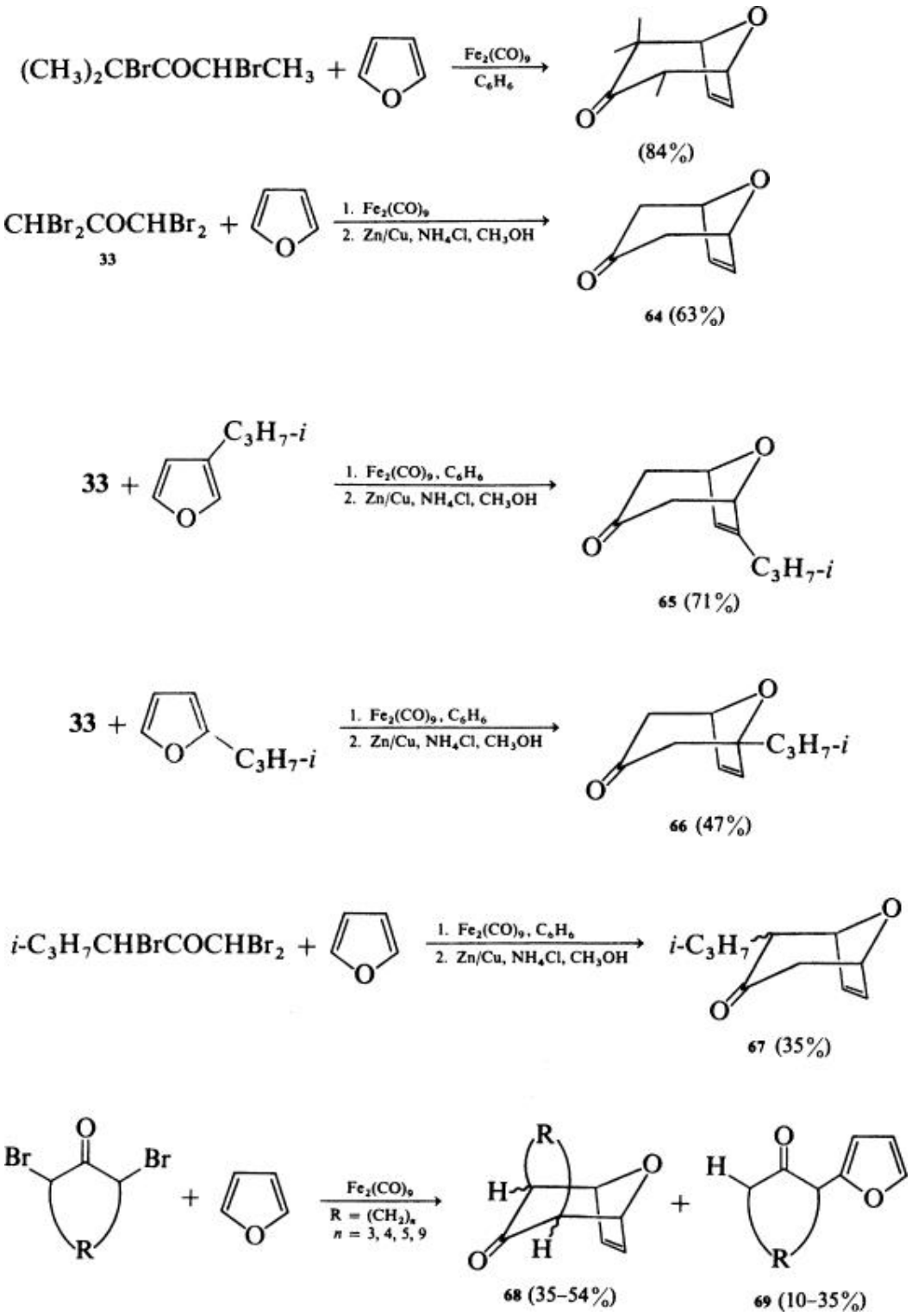
The synthesis of a variety of tropane alkaloids has been achieved via 6,7-dehydrotropine (**59**), derived from **58** by diisobutyl-aluminum hydride reduction in tetrahydrofuran; subsequent appropriate modification of the double bond leads to several naturally occurring products, including tropine (**60**), scopine (**61**), tropanediol (**62**), and teloidine (**63**). (75, 104) Unnatural analogs can also be prepared. (101-103)



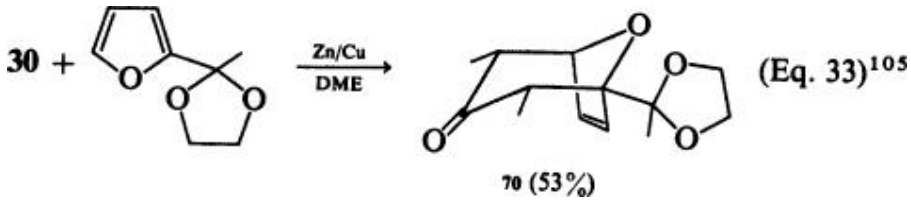
3.4.1.5. Formation of 8-Oxabicyclo[3.2.1]oct-6-en-3-ones and Related Compounds

8-Oxabicyclo[3.2.1]oct-6-en-3-ones can be prepared by reductive cyclocoupling of dibromo or polybromo ketones with furan or its alkyl, alkoxy-carbonyl, or halo derivatives; the ester group and halogen atom attached to the sp^2-carbon atom are left intact.

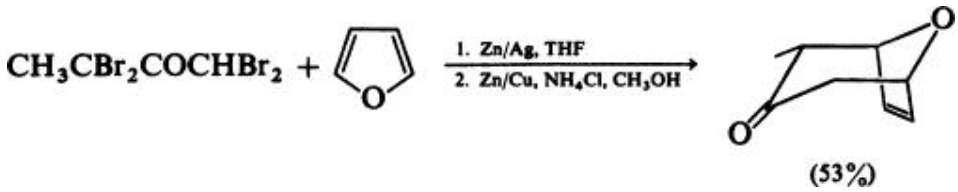
Iron carbonyls, especially $Fe_2(CO)_9$, are the most widely used reducing agents for the cyclocoupling of open-chain dibromo or polybromo ketones and cyclic dibromo ketones to afford the corresponding adducts, generally in fair to high yields; (74, 89) cyclic dibromides undergo somewhat erratic transformations accompanied by α -substitution reactions to give **69**. (74) Reactions involving methyl alkyl ketone dibromides are reasonably efficient. (36)



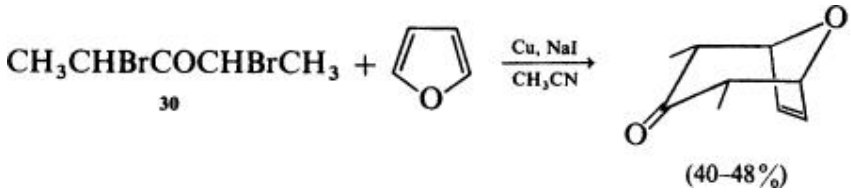
Zinc/copper (92, 93, 102, 105, 106) or zinc/silver couple (45) also effects the reactions. In addition, Grignard reagents, (78) the copper-sodium iodide reagent, (92, 102, 107)



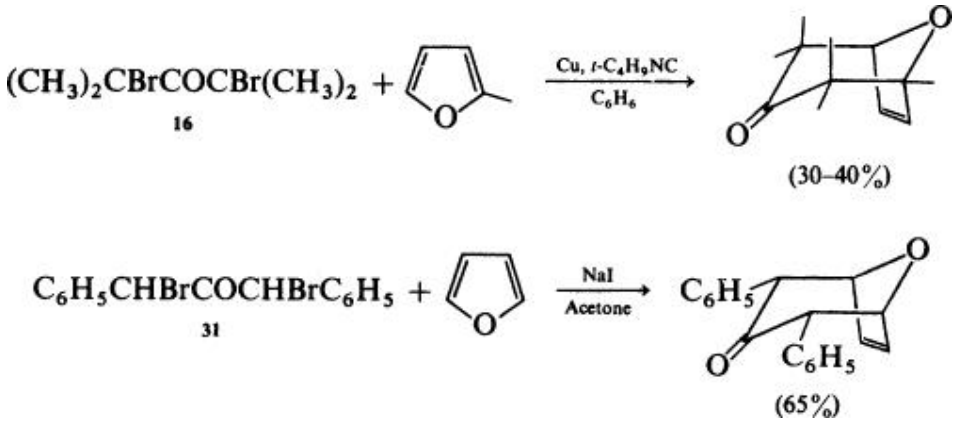
(Eq. 33)[105] (33)



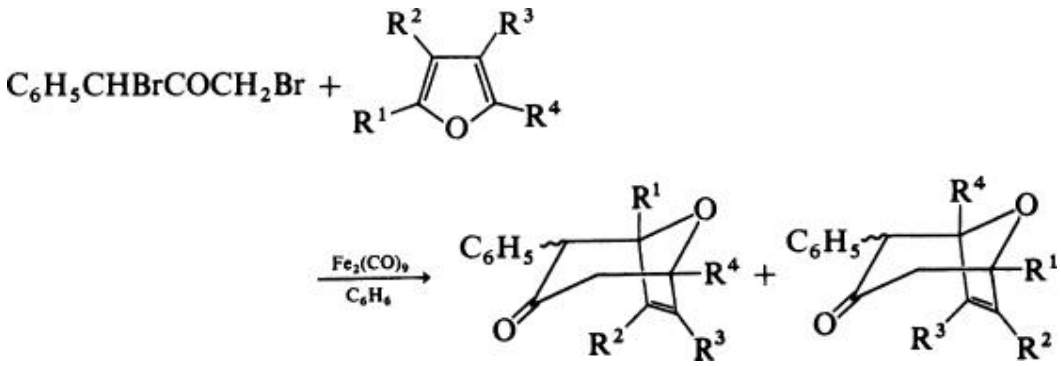
organo cuprates, (78) a copper/isonitrile complex, (108) and sodium iodide (84, 94) are capable of effecting the reaction with open-chain dibromides.



(Eq. 34)[107] (34)

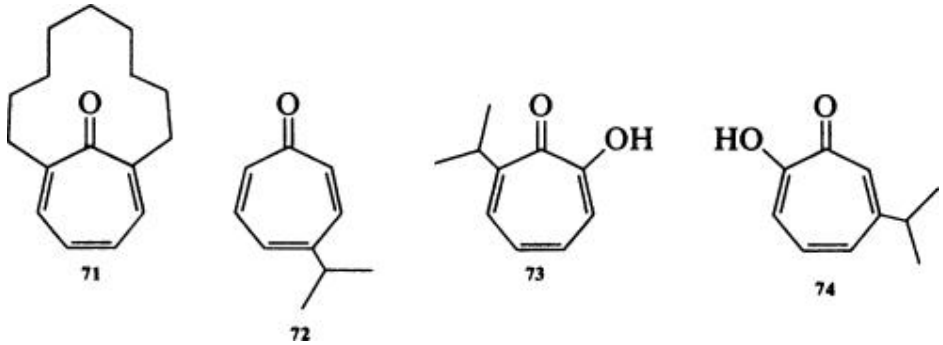


When the $Fe_2(CO)_9$- and zinc/copper-couple-promoted cyclocoupling reactions are performed using 1, 3-dibromo-1-phenylpropan-2-one and substituted furans, a regioisomeric mixture of [3 + 4] adducts is obtained. (36) The regioselectivity, which is usually moderately good, is controlled by the frontier molecular orbitals of the intermediary oxyallyl species (LUMOs) and furan (HOMOs).

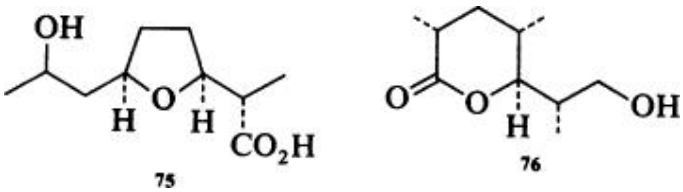


3.4.1.5.1. Synthetic Applications

The resulting oxabicyclic ketones are readily transformed in a few steps to the tropone **46** or γ -tropolone **47**. (89) The tricyclic adduct **68** [R = $(CH_2)_9$] can be converted to the troponophane **71**. (89, 109) Success in the use of tetrabromoacetone and tribromo derivatives of methyl alkyl ketones in these reactions opens a new route to various naturally occurring troponoid compounds, viz., nezukone (**72**) from **65**, (89, 110) α-thujaplicin (**73**) from **67**, (89, 111) and hinokitiol (β-thujaplicin, **74**) from **66**, (89, 111) respectively. The reaction in

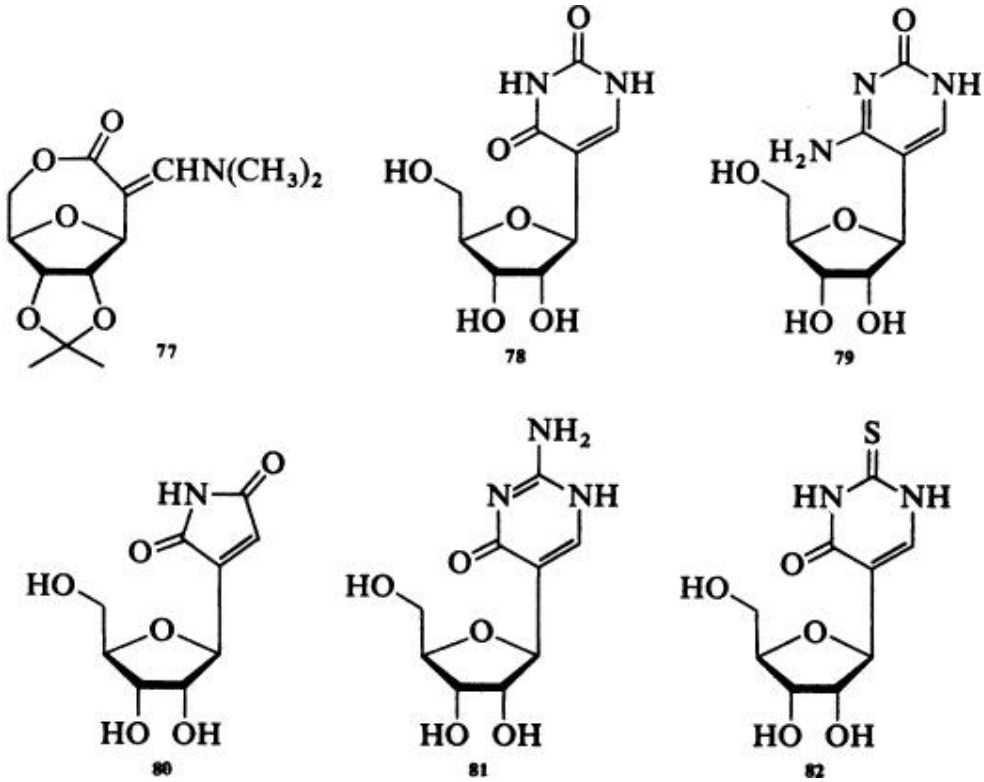


Eq. 33 giving **70** has been utilized for the synthesis of nonactic acid (**75**). (106) The Prelog-Djerassi lactone (**76**), a pivotal intermediate in Masamune's methymycin synthesis, (112) has been prepared through the key reaction shown in

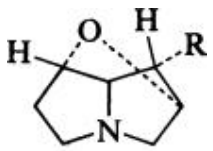


Eq. 34. (105) The readily available oxabicyclic ketone **64** is converted to **77**, which provides an efficient entry into the *C*-nucleoside family. Thus there is

accomplished the stereocontrolled synthesis of natural products such as pseudouridine (**78**), pseudocytidine (**79**), and showdomycin (**80**), as well as a number of unnatural analogs such as pseudoisocytidine (**81**) and 2-thiopseudouridine

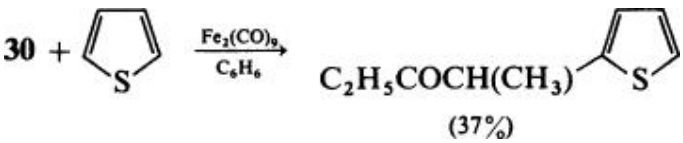


(**82**). (113, 114) Construction of the basic skeleton of lolium alkaloids **83** has also been achieved by way of **64**. (115)



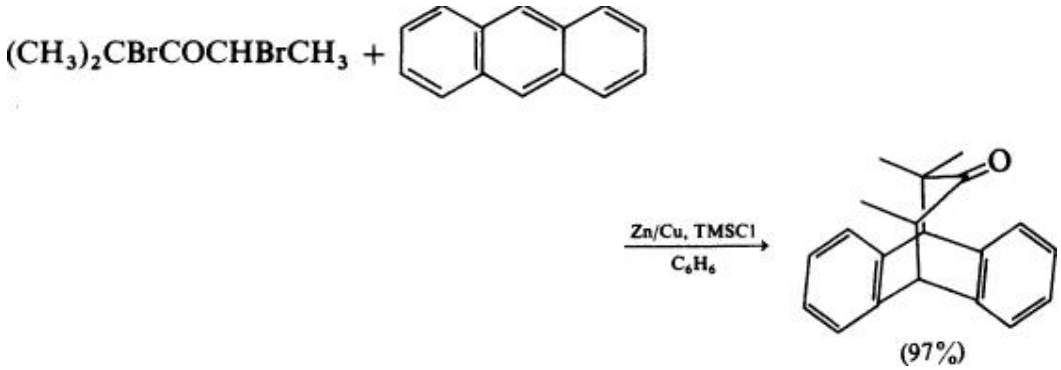
3.4.1.6. Attempted Cyclocoupling between Dibromo Ketones and Thiophene

Several cyclocoupling reactions between dibromo ketones and thiophene have been tried with copper-sodium iodide (102) or $Fe_2(CO)_9$ (74) without success, resulting only in theα-substitution product.



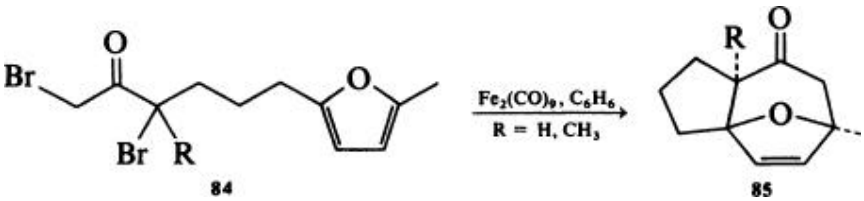
3.4.1.7. Formation of 6,7;8,9-Dibenzobicyclo[3.2.2]nonan-3-ones

Reduction ofα, α′-dibromo ketones with zinc/copper couple in dioxane containing anthracene affords the 6,7;8,9-dibenzobicyclo[3.2.2]nonan-3-one [3 + 4] cyclocoupling products in 3–25% yields. (116) Addition of chlorotrimethylsilane (TMSCl) to the system and changing the solvent to benzene result in substantially increased yields of products (71–97%). (116)



3.5. Intramolecular [3 + 4] Cyclocoupling Leading to 11-Oxatricyclo[5.3.0.1 ^{1,4}]undec-2-en-6-ones (Oxidoperhydroazulenes)

The $Fe_2(CO)_9$ reduction of dibromide **84** in benzene permits the direct construction of oxatricyclic ketone **85**, whose oxidoperhydroazulene structure is the basic skeleton of naturally occurring daucon, ambrosic acid, and germacrol. (117)



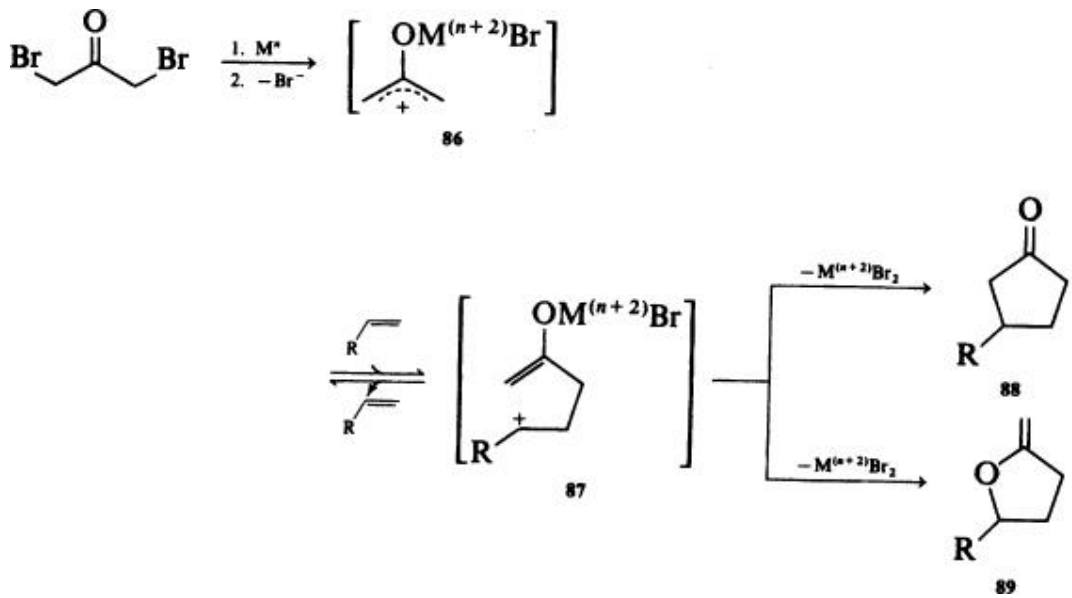
3.6. Formation of Five-Membered Ketones and Heterocycles by Intermolecular [3 + 2] Cyclocoupling

3.6.1.1. General Aspects

When α , α ′-dibromo ketones are reduced in the presence of certain olefins or carbonyl compounds, the [3 + 2] cyclocoupling reactions proceed to give five-membered ketones or oxacycles, respectively; the reaction course depends on the nature of the reducing agents and the structures of the dibromo ketones or olefins employed.

Scheme III outlines the general reaction pathways. Actually the C_3 units must be the dibromides derived from alkyl or aryl ketones rather than acetone, and the C_2 components must be the substances which, through addition of **86**, form the intermediate **87** stable enough to shift the equilibrium to the right, thereby completing the cyclocoupling reaction. Therefore the choice of cationstabilizing R group in the C_2 units is crucial for the success of the reaction. Only a few examples have been reported using polybromo ketones or cyclic dibromo ketones.

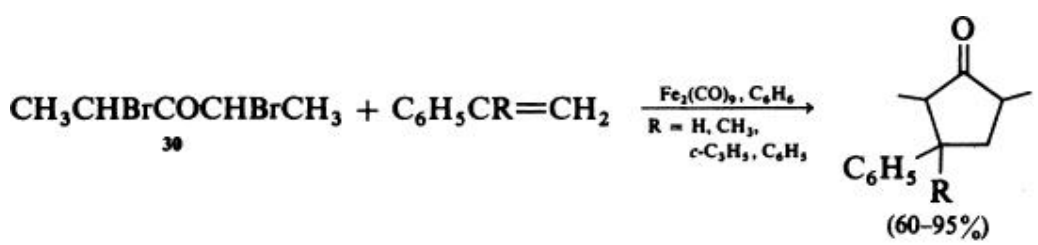
Scheme III.



Below are described the scope and limitations of the [3 + 2] cyclocoupling reaction classified by the kinds of receptors and reducing agents.

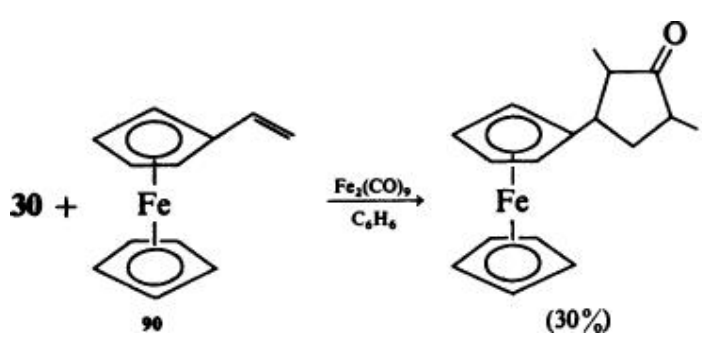
3.6.1.2. Formation of 3-Arylcyclopentanones

The [3 + 2] cyclocoupling reaction with aryl-substituted olefins gives 3-arylcyclopentanone adducts. The products are mixtures of diastereomers, where possible (see Eqs. 35 and 36). (118, 119)



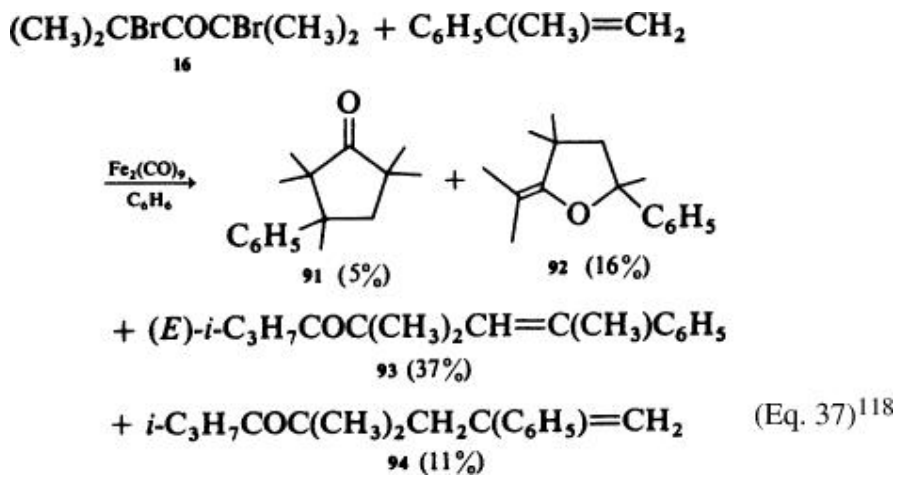
(35)

(Eq. 35)[118]



(Eq. 36)[118]

(36)



(37)

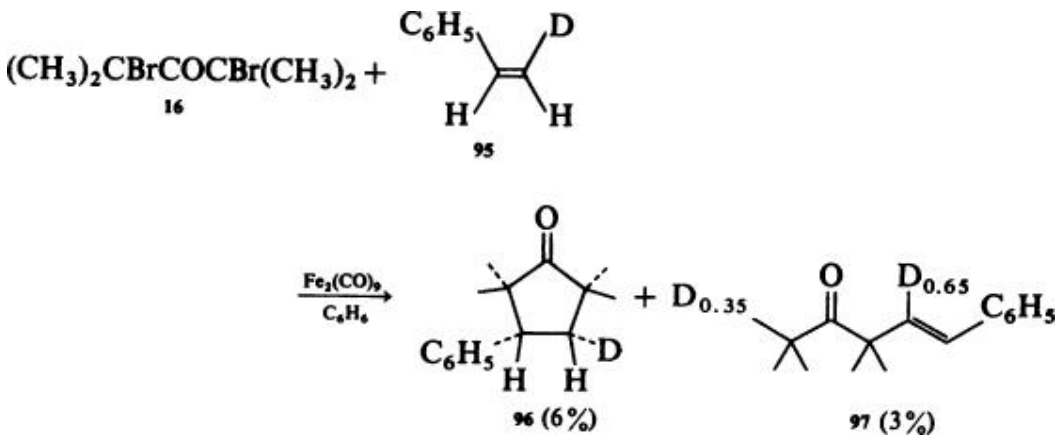
(Eq. 37)[118]

Most phenylated olefins, even ferrocenylethylene (**90**), undergo the reaction. Placement of a carbocation-stabilizing group, particularly cyclopropyl, phenyl, or methoxyl, at the arylated olefin carbon or in the aromatic ring, results in a smooth reaction.

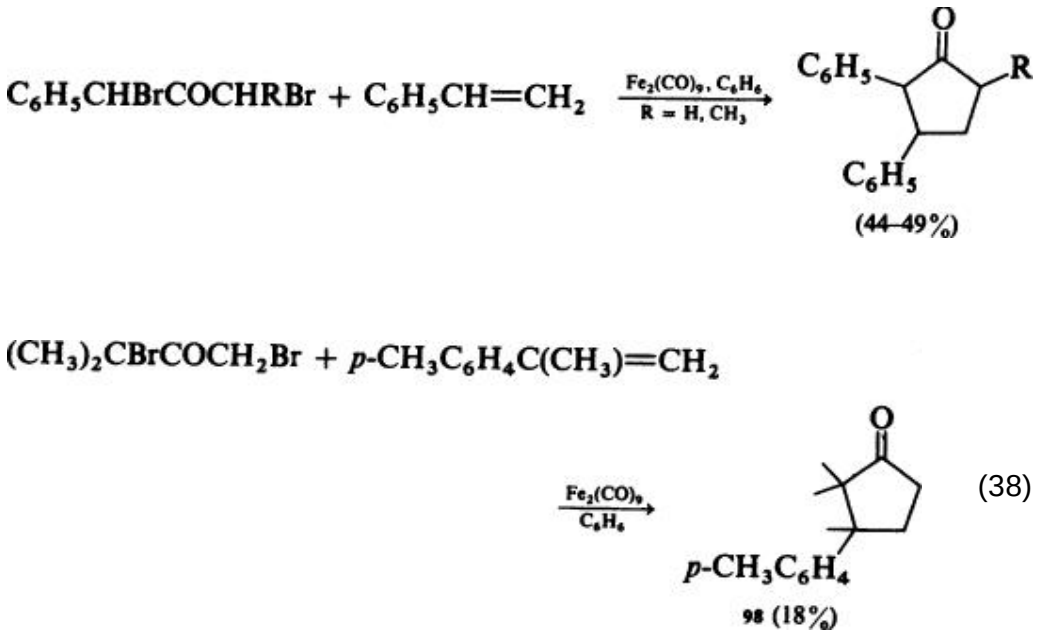
As for the reducing agent, $Fe_2(CO)_9$ gives a satisfactory result; $Fe(CO)_5$ is less effective. Use of aromatic olefin– $Fe(CO)_4$ complexes does not improve the yield. (118) Reaction using zinc/copper couple in benzene or 1,2-dimethoxyethane gives rise to no cyclopentanones. (118)

In general, reaction of tertiary dibromides and aromatic olefins proceeds rather sluggishly, probably because of steric factors, and tends to afford various kinds of byproducts, including substitution products like **93** and **94**, and 2-alkylidenetetrahydrofurans like **92** (see Eq. 37). (118)

An experiment using the α , α′-dibromo ketone **16** and (*Z*)- β -deuteriostyrene (**95**) demonstrates that the cyclocoupling reaction giving **96** proceeds stereo-specifically, whereas the olefinic substitution giving **97** occurs in a nonstereo-specific fashion. (118-120)



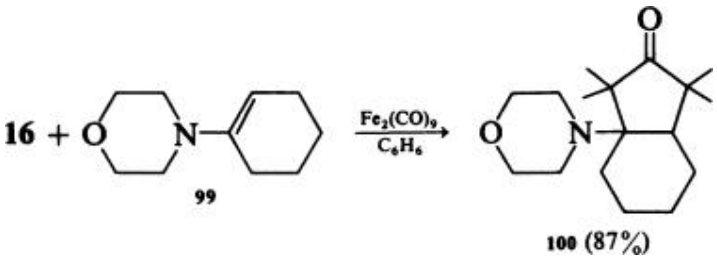
A high degree of regioselectivity is observed in the reaction using styrene as the C_2 component, which is best interpreted in terms of relative stabilities of the possible zwitterionic intermediates of type **87** in Scheme III. (36) The regio-selective, single-step synthesis of α -cuparenone (**98**), a sesquiterpenic ketone, has been performed according to Eq. 38. (121)



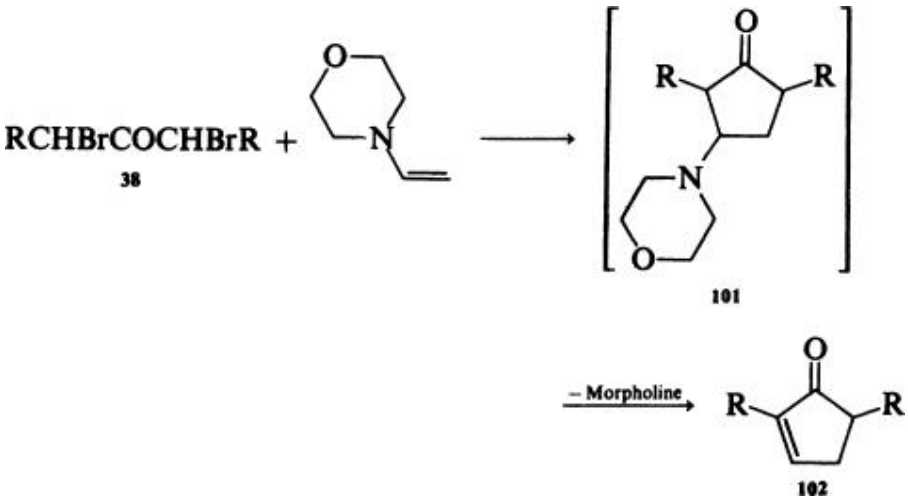
(38)

3.6.1.3. Formation of 2-Cyclopentenones and Related Compounds

Enamines are two-carbon substrates capable of entering into the reductive [3 + 2] reaction. The $Fe_2(CO)_9$ reduction of tertiary dibromo ketone **16** in the presence of enamine **99** produces the β -morpholinocyclopentanone derivative **100**. (122, 123)

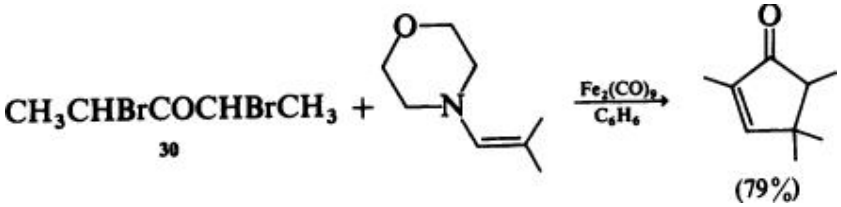


In the reaction of secondary dibromide **38**, the initially formed labile morpholino adduct **101** suffers elimination of morpholine on brief treatment with silica gel (124) or dilute ethanolic sodium hydroxide, or even spontaneously in certain cases, to give the 2-cyclopentenone **102**, as depicted in Eq. 39. Thus the

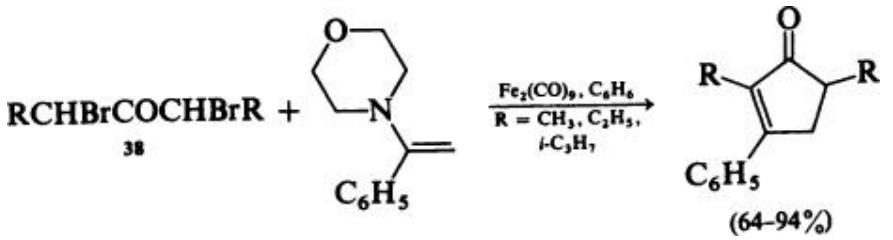


(39)

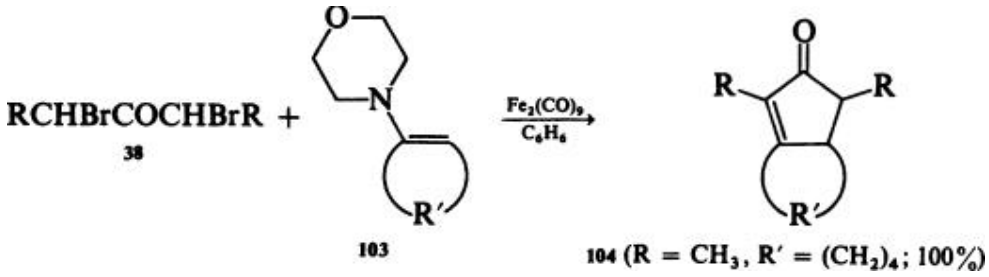
overall transformation provides a single-pot procedure for the preparation of substituted cyclopentenones. Several representative reactions are shown in Eqs. 40–43. (122)



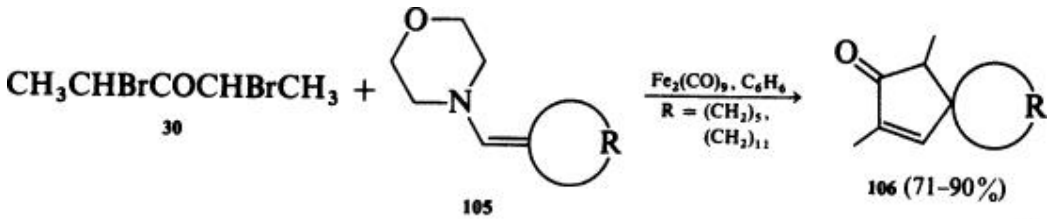
(40)



(41)



(42)

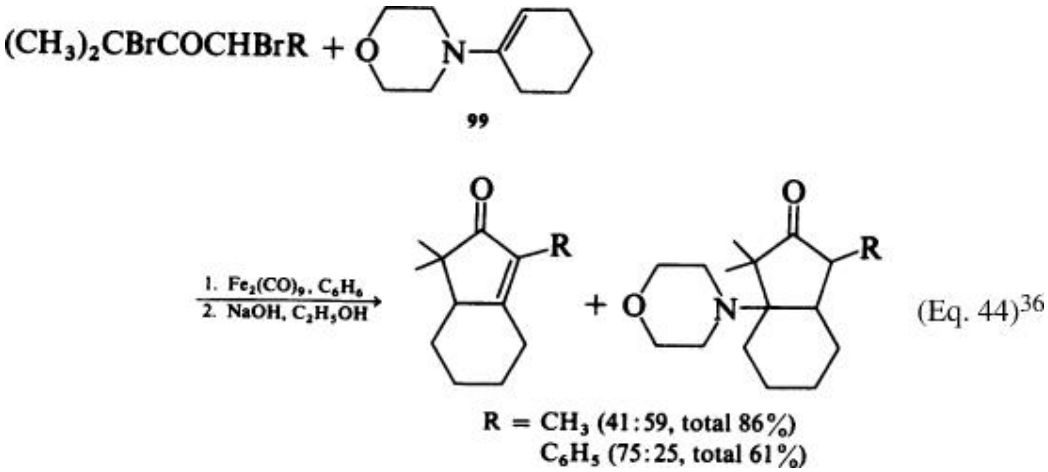


(43)

(Eq. 43)[122]

This cyclocoupling reaction is achieved using enamine derivatives of either open-chain or cyclic ketones, and of aldehydes. Diiron enneacarbonyl is the best reducing agent; $Fe(CO)_5$ gives less satisfactory results. Benzene is recommended as the solvent; tetrahydrofuran or dimethylformamide gives little or no cyclocoupling products. The reduction with zinc/copper couple in 1,2-dimethoxyethane drastically diminishes the yield of adduct, and sodium iodide is not usable.

Equation 44 illustrates some reactions of unsymmetrically substituted C_2 and C_3 components, giving mixtures of regioisomeric [3 + 2] adducts. The regiochemistry is controlled primarily by the stability of zwitterionic intermediates of type **87** (see p. 197). (36)



(44)

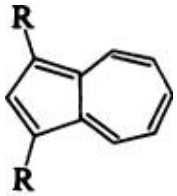
(Eq. 44)[36]

Some enol ethers and ketene diphenyl acetal undergo a similar reaction, but much less effectively. (83)

3.6.1.3.1. Synthetic Utility and Applications

This cyclocoupling reaction using secondary dibromo ketones opens a new route to α , α′-dialkylcyclopentenones. The attractive features include the ready availability of starting materials, operational simplicity, and wide generality. The advantages may be offset to some extent by the incapability of preparing α -unsubstituted cyclopentenones. This feature, however, can be a virtue of this method in view of the difficulty of introducing alkyl groups, particularly bulky ones such as isopropyl, into α positions of five-membered ketones. (125)

The reaction with cycloalkanone enamine **103** and secondary dibromo ketones leads efficiently to the bicyclic cyclopentenone **104**, where the second ring size can be changed *ad libitum*. The 5/7-fused derivatives [**104**, R¢ = $(CH_2)_5$] are potential intermediates for the synthesis of 1, 3-dialkylazulenes of type **107**.



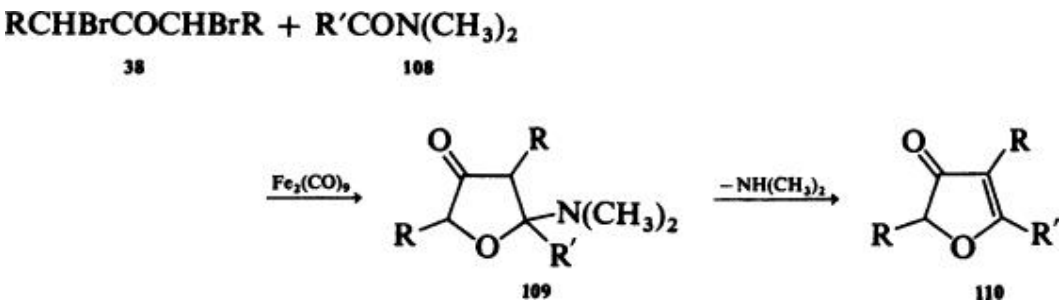
107

Another utility is the convenient formation of the spiro[*n*,4]alkenone system **106**, accomplished by reaction between secondary dibromo ketones and enamines of cycloalkanecarboxaldehydes (**105**) (Eq. 43). This spiroannelation finds wider generality in comparison with existing methods (126) because one

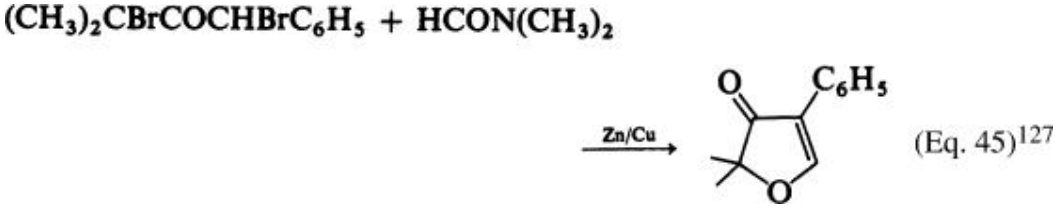
can prepare derivatives bearing optional alkyl substituents at the α and α′ positions to the carbonyl group or a desired second ring size by suitable choice of starting materials.

3.6.1.4. Formation of 3(2H)-Furanones and Dihydro Derivatives

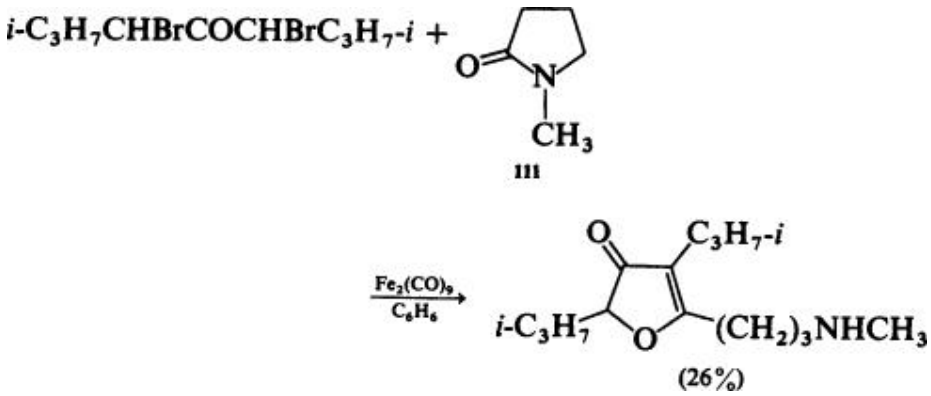
N,N-Dimethyl-carboxamides undergo the hetero [3 + 2] cyclocoupling reaction with dibromo ketones, providing a tool for the preparation of the title five-membered hetero-cyclic ketones. The $Fe_2(CO)_9$-assisted reaction of **38** and **108** first leads to the labile dimethylamino cycloadduct **109**, which in turn suffers facile elimination of dimethylamine to product **110** in moderate to good yield. (34, 35) The overall



conversion can be viewed as the construction of a carbon-oxygen bridge between the α and α ′ positions of the parent dialkyl ketones. Other examples are shown in Eqs. 45–48. The reaction of dibromides with bulky alkyl substituents like isopropyl and *tert*-butyl gives amino ketones of type **109** in isolable form; the complete deamination requires brief heating at elevated temperature. The di-*tert*-butyl derivative **112** (Eq. 47) is quite stable on heating. (34) Use of tertiary dibromo ketones of type **16** generally affords little of the cyclocoupling product; instead, enones of type **17** predominate (Eq. 48, see also Eq. 22, p. 173). (28, 34)



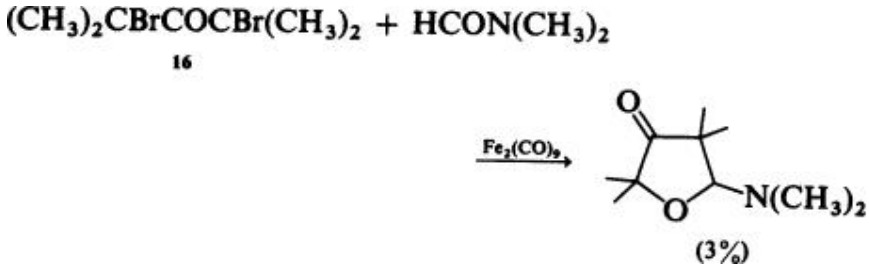
(Eq. 45)[127] (45)



(46)

(Eq. 47)[34]

(47)



(Eq. 48)[28,34]

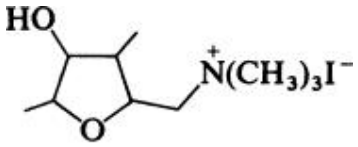
(48)

This operationally simple cyclocoupling procedure has wide applicability. The employable nucleophilic substrates include dimethylformamide, *N,N*-dimethylacetamide, and lactam **111**. (34)

The reaction with $Fe_2(CO)_9$ occurs most successfully. (34, 35) Use of $Fe(CO)_5$ requires irradiation by visible light to achieve reaction. (34) Zinc/copper couple can be used only in limited cases such as the reaction shown in Eq. 45; (127) usually another type of 1:1 cyclocoupling product with a 1,3-dioxolane structure is formed (see p. 205). (128)

3.6.1.4.1. Synthetic Applications

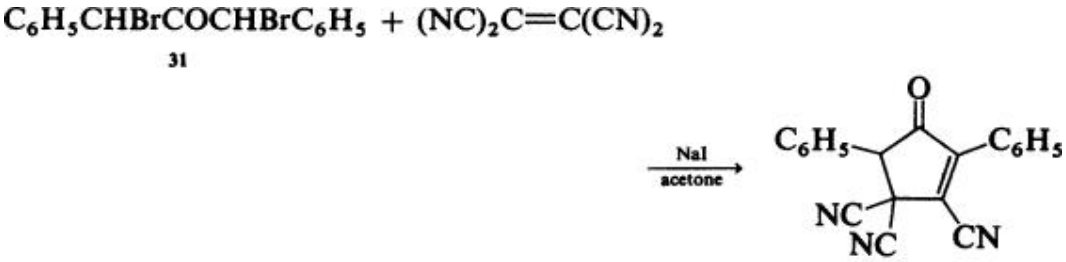
3(2*H*)-Furanones obtained by this reaction are structurally related to muscarine alkaloids, (129) and the synthesis of 4-methyl-muscarine iodide (**113**) has been achieved via **110** (R = CH_3, R¢ = H). (35)



113

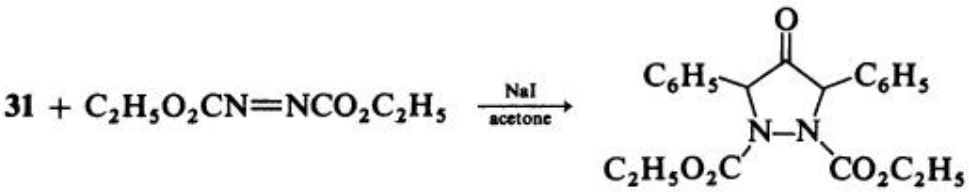
3.6.1.5. Formation of Other Ketonic Five-Membered Compounds

The reduction of **31** with sodium iodide in acetone or acetonitrile containing certain dipolarophiles such as tetracyanoethylene or diethyl azodicarboxylate forms five-membered ketone **114** (85) and pyrazolidone **115**, (85) respectively.



31

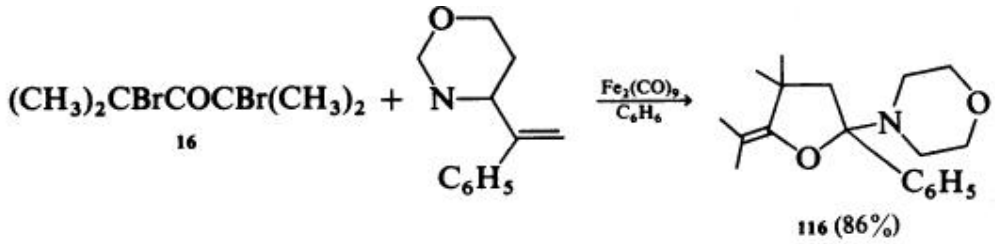
114 (35%)

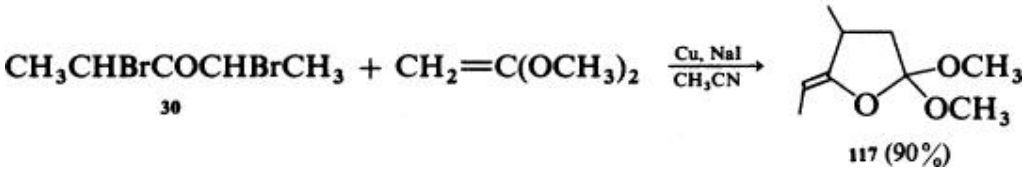


115 (15%)

3.6.1.6. Formation of Alkylidenetetrahydrofurans

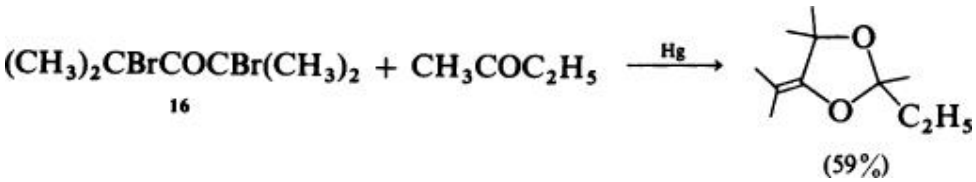
Diiron enneacarbonyl promotes the hetero cyclocoupling reaction of tertiary dibromo ketone **16** and α -morpho-linostyrene in benzene, yielding the alkylidenetetrahydrofuran **116**. (118). A similar product **117** is obtained in the reaction of **30** and 1, 1-dimethoxyethene with copper-sodium iodide in acetonitrile. (79)



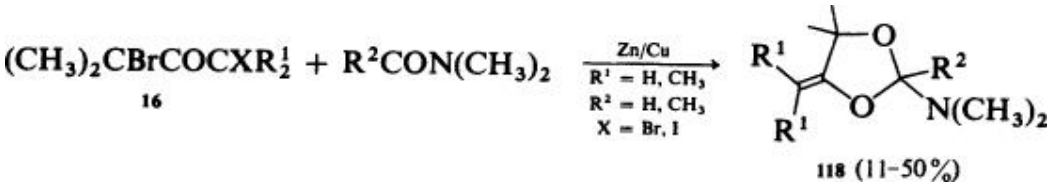


3.6.1.7. Formation of 1,3-Dioxolanes

Reaction of **16** and ultrasonically dispersed mercury in ketonic solvents (but not aldehydes) allows a simple preparation of the 4-isopropylidene-5, 5-dimethyl-1, 3-dioxolane ring system. (130) Zinc-copper



couple reduction of dibromo or bromo iodo ketones in dimethylformamide or *N, N*-dimethylacetamide also affords the 1, 3-dioxolane **118**, (128) which is readily converted to the above-mentioned 3(*2 H*)-furanone by acid treatment. Of

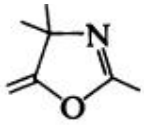


greater importance, these products react with cyclopentadiene or furan under acid catalysis to give bicyclic ketones of type **32** (Y = CH_2 or O, respectively, see Eq. 32, p. 185) on elimination of dimethylformamide. (93)

3.6.1.8. Formation of 5-Alkylidene-2-oxazolines

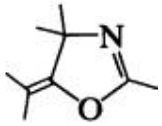
When dibromo or bromo iodo ketones are reduced with zinc/copper couple (87) or $Fe_2(CO)_9$ (83) in acetonitrile, 5-alkylidene-2-oxazolines are produced in generally low yields.

$$(CH_3)_2CBrCOCH_2Br + CH_3CN \xrightarrow[\text{DME}]{\text{Zn/Cu}}$$



$$(CH_3)_2CBrCOCBr(CH_3)_2 + CH_3CN \xrightarrow{Fe_2(CO)_9}$$

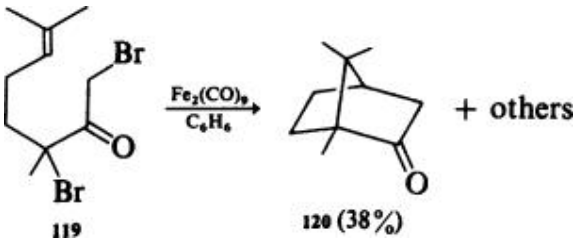
16



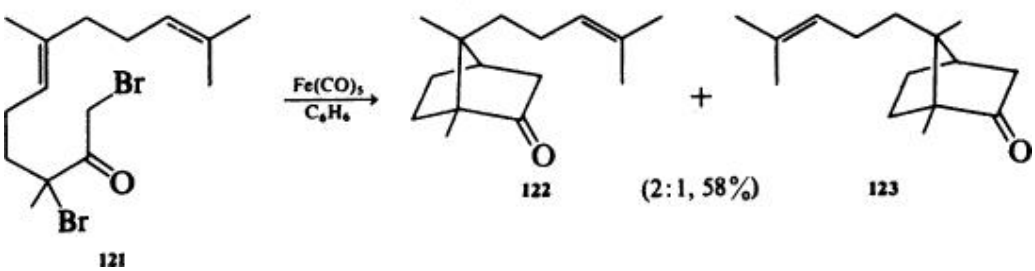
(50%)

3.7. Intramolecular [3 + 2] Cyclocoupling to Form Bicyclo[2.2.1]heptan-2-ones

Simple olefins such as isobutylene do not smoothly undergo the intermolecular [3 + 2] cyclocoupling reaction, (33) rather, the intramolecular version occurs to give bicyclic products. Thus reduction of dibromide **119** with $Fe_2(CO)_9$ in benzene affords a mixture of C_{10} products with camphor (**120**) as the major



component. (117) In a similar fashion reaction of dibromo ketone (*E*)-**121** and $Fe(CO)_5$ in benzene affords a 2:1 mixture of campherenone (**122**) and epicampherenone (**123**). (117) The reaction using the stereoisomer, (*Z*)-**121**, produces a 1:2 mixture of **122** and **123**. (117) The ease with which intramolecular [3 + 2]



reactions take place is affected profoundly by the substitution pattern around the olefinic bond as well as the length of the methylene chain that links the double bond and the dibromo ketone moiety. Attempted reactions of **124–126** fail to afford the desired bicyclic ketones.

$R^1R^2C{=}CH(R^3)(CH_2)_nCBr(R^4)COCH_2Br$

124, $R^1 = R^2 = R^3 = H; R^4 = CH_3; n = 2$

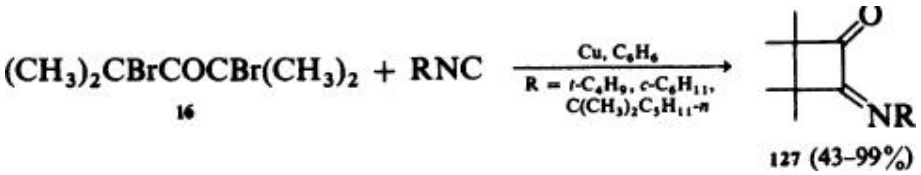
125, $R^1 = R^2 = R^4 = CH_3; R^3 = H; n = 3$

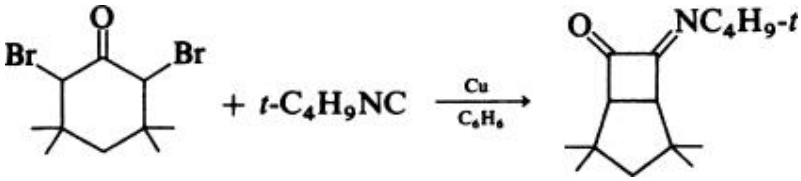
126, $R^1 = R^2 = R^4 = H; R^3 = CH_3; n = 3$

3.8. Miscellaneous Reactions

3.8.1.1. Formation of 2-(N-Alkylimino)cyclobutanones

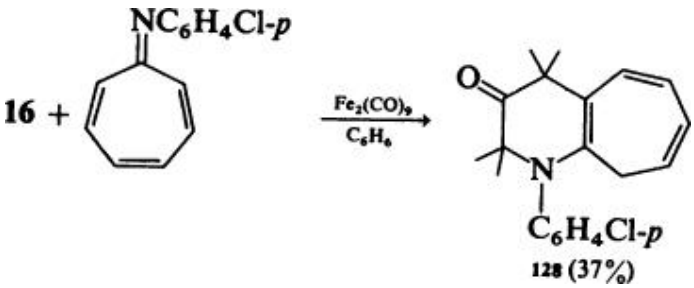
Treatment of a mixture of **16** and an isonitrile with copper in benzene or zinc in pyridine-benzene gives the 2-(*N*-alkylimino)cyclobutanone **127**. (108) Certain cyclic dibromides undergo an unusual annelation with ring contraction. (108)



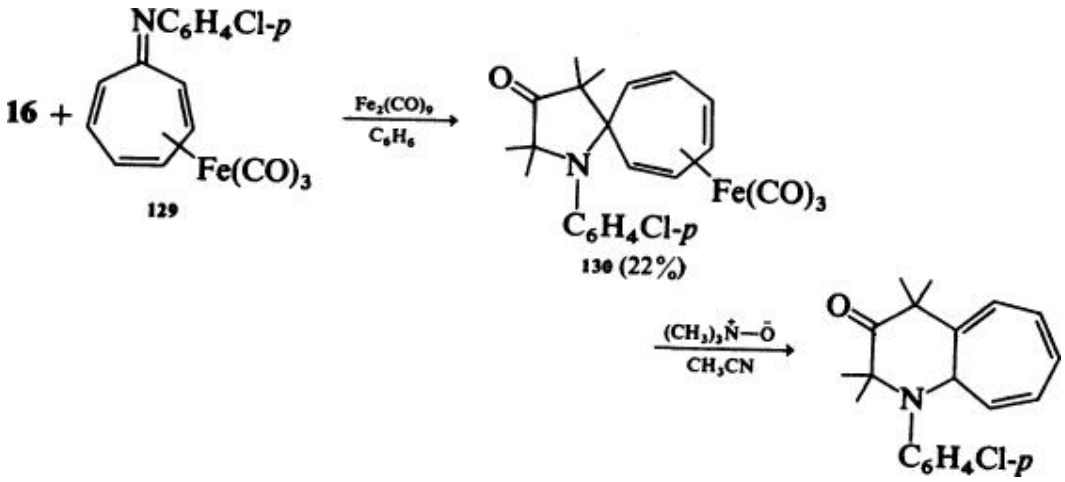


3.8.1.2. Formation of 8-Azabicyclo[5.4.0]undecatrienones

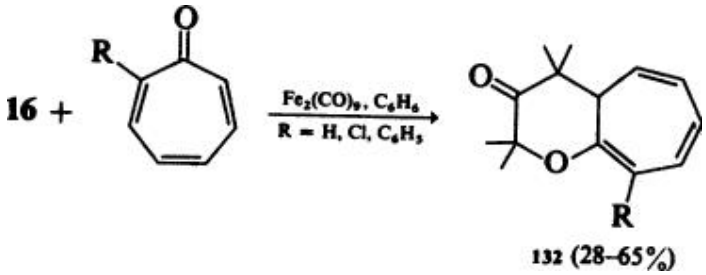
8-(4-Chlorophenyl)-8-azaheptafulvene serves as an 8 π -electron receptor and undergoes $Fe_2(CO)_9$-promoted cyclocoupling with **16** to produce azabicyclic ketone **128**. 131a In



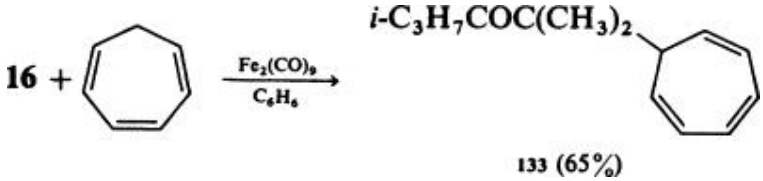
contrast, its tricarbonyliron complex **129** serves as a 2 π -electron receptor and, on reaction with **16**, gives rise to spiro adduct **130**, which is converted to **131** on treatment with trimethylamine *N*-oxide. 131a



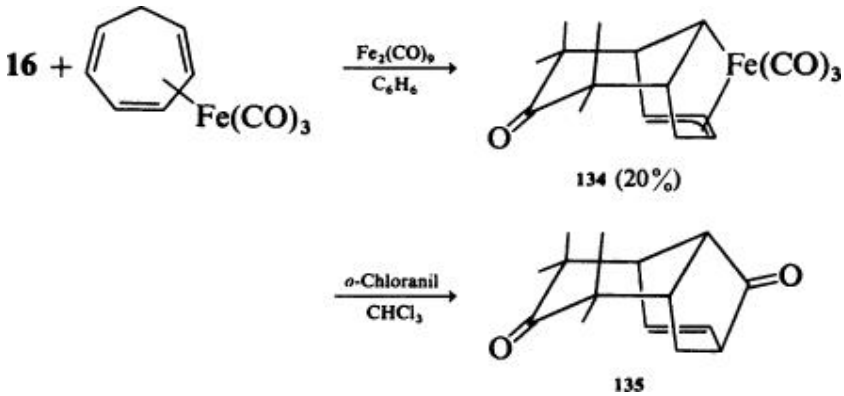
3.8.1.3. Formation of 8-Oxabicyclo[5.4.0]undeca-2,4,6-trien-10-ones
Tropone derivatives undergo $Fe_2(CO)_9$-aided cyclocoupling with **16**, yielding the oxabicyclic ketone **132**. (99)



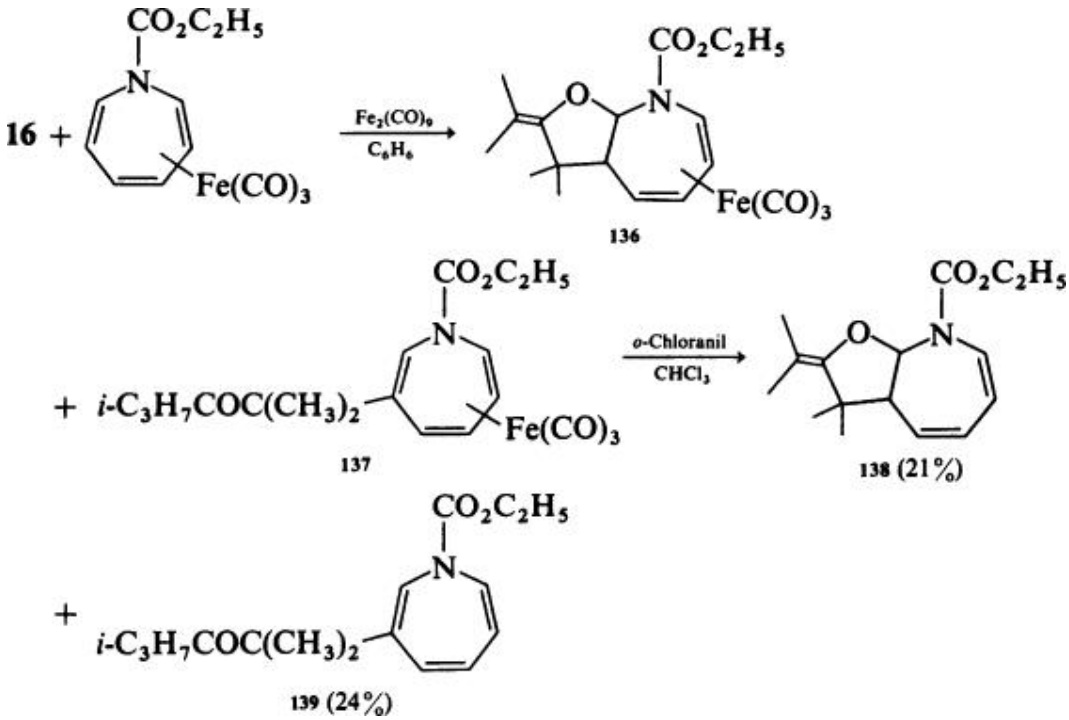
3.8.1.4. Reaction with Seven-Membered Cyclic Trienes
1,3,5-Cycloheptatriene reacts with **16** in the presence of $Fe_2(CO)_9$ to give **133** as the sole product. 131b By contrast, reaction with tricarbonyl(cycloheptatriene)iron gives the isolable



tricarbonyl complex **134**, whose oxidative degradation with *o*-chloranil affords the tricyclic dione **135**. 131a When tricarbonyl(*N*-ethoxycarbonylazepine)iron

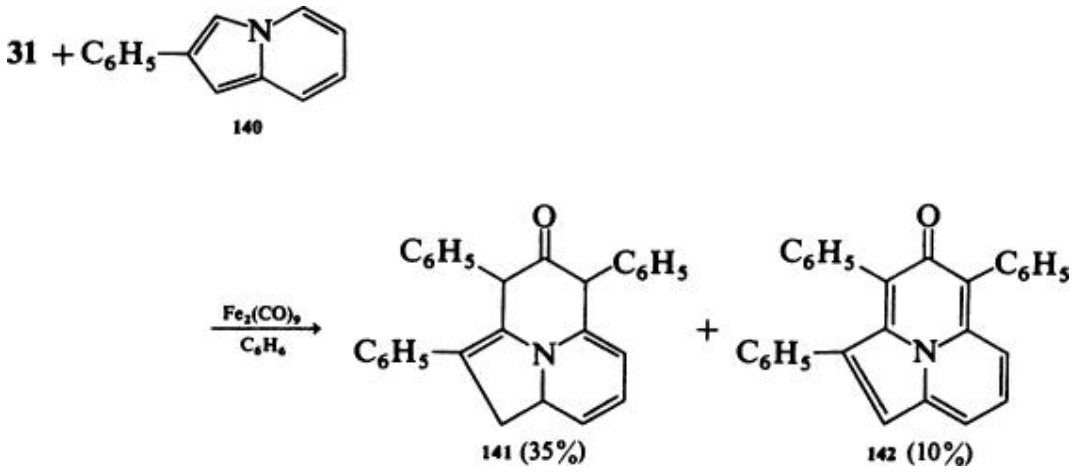


is used as a cyclic triene, a mixture of adducts **136** and **137** is obtained. 131a Successive oxidative treatment of the mixture with *o*-chloranil affords a mixture of **138** and **139**.



3.8.1.5. Formation of Cyclo[3.3.2]azine Derivatives

When dibromide **31** is reduced with $Fe_2(CO)_9$ or copper-sodium iodide in the presence of 2-phenylindoline (**140**), which is an alternative 8 π -electron reactant, the tricyclic polyenic ketone **141** is prepared, accompanied by a minor amount of **142**. (132)


31 + C6H5
N
140
Fe2(CO)9
C6H4
O
C6H5
C6H5
C6H5
N
141 (35%)
+
O
C6H5
C6H5
C6H5
N
142 (10%)

4. Experimental Factors

4.1. Preparation and Properties of Bromo Ketones

α -Bromo ketones are prepared according to the methods found in the literature. (133) Care should be taken to prevent the bromo derivatives from coming into contact with the skin, since allergic reactions and lachrymatory properties have been observed in several cases. Although certain bromo ketones are obtained as mixtures of diastereomers, no efforts to separate them are usually needed. All substances should be stored under an inert gas in a refrigerator. It is recommended that liquid materials be used immediately after distillation or, if more convenient, after passage of stored material through a short alumina column.

4.2. Preparation and Handling of Reducing Agents

Most commercially available reducing agents can be employed directly or after ordinary purification. Reagents that require preparation in the laboratory are: zinc/copper (134) or zinc/silver (135) couple made from zinc metal and copper(II) acetate or silver(I) acetate, respectively; 1,3-diene- $Fe(CO)_3$ (136) complexes from the dienes and $Fe(CO)_5$ by irradiation with visible light; organo cuprates from alkyllithiums and copper(I) salts. (55, 78)

Caution: Reactions with metal carbonyls and the subsequent workup should be carried out in a well-ventilated hood because the carbonyl complexes are extremely toxic and carbon monoxide gas is evolved during the reaction .

5. Experimental Procedures

The following examples of reactions have been chosen to illustrate useful and general experimental procedures. They are organized into the following six categories: (1) reactions ofα-monobromo ketones, (2) alkylations of α , α′-dibromo ketones, (3) [3 + 4] cyclocoupling reactions ofα, α′-dibromo ketones and 1,3-dienes, (4) [3 + 4] cyclocoupling reactions of tri- or tetra-bromo ketones, (5) [3 + 2] cyclocoupling reactions ofα, α′-dibromo ketones and olefinic substrates, and (6) miscellaneous reactions.

5.1. Reactions ofα-Monobromo Ketones

5.1.1.1. p -Bromo-(+)-camphor (Reduction of anα-Monobromo Ketone to the Parent Ketone) (49)

To 155 g(0.50 mol) ofα, π -dibromocamphor dissolved in 600 mL of dichloromethane was added 104 g (1.59 g-atoms) of zinc powder. A gentle stream of hydrogen bromide was passed into the mixture with stirring for 2.5–4 hours. Occasionally it was necessary to moderate the reaction by cooling with a water bath. The mixture was filtered, and the dichloromethane solution was washed with water and dried over magnesium sulfate. Removal of dichloromethane by distillation on a steam bath yielded 109 g of crude product, which was recrystallized from hexane. There was obtained 74 g (64%) of π -bromo-(+)-camphor, mp 93–95°, $[\alpha]_D^{26} + 115°$($CHCl_3$): IR (CCl_4)cm^{-1}: 1750 (C = O);UV(C_2H_5OH), nm max (ε): 289 (58.7). Concentration of the mother liquor yielded an additional 12.7 g (11%) of product, mp 80–90°, $[\alpha]_D^{26} + 115°$. The total yield of ketone was 75%.

5.1.1.2. 1,5-Diphenyl-3-hydroxypent-4-en-1-one (Aldol Reaction of an α-Bromo Ketone with an Aldehyde) (63)

To a stirred slurry of 196 mg (3.0 mg-atoms) of zinc dust and 14 mg (0.1 mmol) of copper(I) bromide in 6 mL of anhydrous tetrahydrofuran at 25° under an argon atmosphere was added via syringe 2.2 mL (2.2 mmol) of a 1 *M* solution of diethylaluminum chloride in hexane. The resulting mixture was stirred at 25° for 10 minutes and cooled to –20° with a carbon tetrachloride-dry ice bath. A solution of 398 mg (2.0 mmol) of α-bromo-acetophenone and 290 mg (2.2 mmol) of *trans*-cinnamaldehyde in 10 mL of anhydrous tetrahydrofuran was added dropwise at –20° over a period of 40 minutes. Stirring was continued for an additional 15 minutes at –20°, and then the reaction mixture was quenched by the addition of 0.6 mL of pyridine at –20°. After removal of the cooling bath, the reaction mixture was poured into 20 mL of iced 6% hydrochloric acid and extracted with ether. The ether extract was washed with brine, dried over magnesium sulfate, concentrated *in vacuo*, and purified by preparative TLC on silica gel with 1:5 ether-benzene as eluent to give 464 mg

(92%) of the title compound as a yellow oil that was crystallized from ether-pentane, mp 51–53°; IR (neat) cm^{-1}: 3740 (OH), 1675 (C = O); ^{1}HNMR($CDCl_3$) δ: 2.84–3.61 (broad singlet, 1 *H*, OH), 3.22 (d, *J* = 6 Hz, 2*H*, CH_2C = O), 4.91 (q, *J* = 6 Hz, 1*H*, C*H*OH), 6.24 (dd, *J* = 16 and 6 Hz, 1*H*, C*H* = CHC_6H_5), 6.70 (d, *J* = 16 Hz, 1*H*, CH = C*H*C_6H_5), 6.94–8.31 (m, 10*H*, aromatic protons); mass spectrum *m/e*: 234 (M – 18).

5.2. Alkylations of α, α′-Dibromo Ketones

5.2.1.1. 2-Methylcyclododecanone (Monoalkylation of an α, α′-Dibromo Ketone) (78)

A flame-dried, three-necked, round-bottomed flask equipped with serum stoppers and a nitrogen-filled balloon was charged with 7.76 g (40.8 mmol) of copper(I) iodide and 14 mL of anhydrous ether, and to this at 0° was added 46.5 mL of 1.72*M* (80 mmol) methyllithium in ether via syringe. To the resulting clear solution at –78° was added 3.44 g (10.0 mmol) of solid *cis*-2, 12-dibromocyclododecanone through a side arm. After 15 minutes 10 mL of methanol was added to the yellow suspension. The reaction mixture was allowed to warm to room temperature and poured into 200 mL of saturated, aqueous ammonium chloride, and the yellow precipitate thus formed was removed by suction filtration. The aqueous layer was extracted with three 100-mL portions of ether, and the combined ethereal extracts were washed twice with 50 mL of 1*N* sodium hydroxide and dried over magnesium sulfate. Solvent was removed *in vacuo* to leave 1.88 g (99%) of a yellow oil. Analytical GC (FFAP on Chromosorb W, 60–80 mesh, 304 × 0.6 cm,200°) indicated two peaks: **A**, 7 minutes; **B**, 8 minutes. **A**, identified as cyclododecanone by comparing its retention time with that of authentic material, accounted for *ca*. 1% of the mixture. **B** corresponded to 2-methylcyclododecanone. Distillation at a bath temperature of ca. 100° (0.2 mm) gave a clear colorless oil, semicarbazone mp 211–213°: IR (CCl_4) cm^{-1}: 1710 (C = O);^{1}H NMR(CCl_4) δ: 1.02 (d, *J* = 7.0 Hz, 3*H*, CH_3), 1.3 (m, 18*H*, 9 CH_2), 2.5 (broad multiplet, 3*H*, methylene and methine protonsαto carbonyl group); mass spectrum (70 eV) *m/e*: 196 (M).

5.2.1.2. 2,12-Dimethylcyclododecanone (Dialkylation of an α,α′-Dibromo Ketone) (78)

To 10.0 mmol of lithium dimethylcuprate prepared according to the same procedure as above was added at –78° through a side arm 680 mg (2.0 mmol) of solid *cis*-2, 12-dibromocyclododecanone. After 30 minutes 3.6 mL (50 mmol) of neat methyl iodide was added, and the reaction mixture was allowed to stir at ambient temperature overnight. Workup as in the preceding example was followed by solvent removal, leaving 420 mg of a yellow oil. Analytical GC (5% Silicone SE-30 on Chromosorb G, 100–120 mesh, 213 × 0.3 cm,180°) indicated three products: **A**, 6 minutes; **B**, 7 minutes; **C**, 8 minutes. Product **A** was identified as 2-methylcyclododecanone by comparing its retention time with that of authentic material. Preparative GC (20% Silicone SE-30 on

Chromosorb W, 45–60 mesh, 610 × 0.3 cm,215°) was used to isolate **B** (30 minutes) and **C** (34 minutes). **B** was 2, 12-dimethylcyclododecanone (285 mg, 68%) recrystallized from methanol, mp 43–44°: IR (CCl_4)cm^{-1}: 1710 (C = O); ^{1}H NMR(CCl_4) δ : 1.00 (d, *J* = 7 Hz, 6*H*, 2 CH_3), 1.31 (m, 18*H*, 9 CH_2), 2.72 (broad multiplet, 2*H*, 2 CH); mass spectrum (70 eV) *m/e*: 210 (M). **C** was an isomeric 2,12-dimethylcyclododecanone (122 mg, 29%): IR (CCl_4)cm^{-1}: 1700 (C = O):^{1}H NMR(CCl_4) δ : 1.04 (d, *J* = 7 Hz, 6*H*, 2 CH_3), 1.33 (m, 18*H* 9 CH_2), 2.72 (broad multiplet, 2*H*, 2 CH); mass spectrum (70 ev) *m/e*: 210 (M). The isomeric nature of **B** and **C** was confirmed by combining them for micro-analysis. They are apparently *cis*- and *trans*-2, 12-dimethylcyclododecanones. The total yield of the product was 97%.

5.3. [3 + 4] Cyclocoupling ofα, α′-Dibromo Ketones and 1,3-Dienes

5.3.1.1. 3,5-Dimethylbicyclo[5.4.0]undec-1(7)-en-4-one ([3 + 4] Cyclocoupling Reaction between an α, α′-Dibromo Ketone and an Open-Chain 1,3-Diene with Diiron Enneacarbonyl) (74)

In a 30-mL, two-necked flask equipped with a serum cap and a three-way stopcock carrying a nitrogen-filled rubber balloon was placed 906 mg (2.49 mmol) of diiron enneacarbonyl. The system was flushed with nitrogen, and to this was added a solution of 108 mg (1.00 mmol) of 1,2-bismethylenecyclohexane in 2.5 mL of dry benzene followed by 608 mg (2.49 mmol) of 2,4-dibromopentan-3-one. The mixture was stirred magnetically at 62–64° for 46 hours, then cooled to room temperature, and poured into 15 mL of saturated sodium hydrogen carbonate solution. To this was added 60 mL of ethyl acetate, and the solid material was removed by filtration through a pad of Celite 545. The organic layer was separated, and the aqueous layer was extracted with two 10-mL portions of ethyl acetate. The combined extracts were dried over sodium sulfate, and the solvent was evaporated to give 261 mg of a dark brown oil. Purification by silica gel chromatography using 1:1 benzene-hexane as eluent yielded 153 mg (80%) of the title adduct as a colorless oil that was homogeneous on gas chromatography analysis (10% Silicone SE-30 on Chromosorb W AW, 80–100 mesh, 100 × 0.3 cm,110°): IR (CCl_4)cm^{-1}: 1705 (C = O), 1660 (C = C);^{1}H NMR(CCl_4) δ : 1.03 (d, *J* = 6.5 Hz, 6*H*, 2 CH_3), 1.4–1.6 (m, 4*H*, 2 CH_2), 1.7–2.3(m, 8*H*, 4 = CCH_2), 2.6–3.0 (m, 2*H*, 2 C*H*CH_3); mass spectrum (70 eV) *m/e*: 192 (M).

5.3.1.2. 2,2,4,5,7,7-Hexamethyl-4-cycloheptenone (41, $R^1 = R^2 = CH_3$, p. 186) ([3 + 4] Cyclocoupling Reaction of anα, α′-Dibromo Ketone and a 1,3-Dieneiron Tricarbonyl Complex) (74)

In a 300-mL pressure bottle was placed 3.92 g (20.0 mmol) of iron pentacarbonyl. The system was evacuated and flushed with nitrogen. Then a mixture of 4.93 g (60.0 mmol) of 2,3-dimethyl-1,3-butadiene and 20 mL of dry benzene was introduced with a syringe. The mixture was irradiated at 55° for 6.5 hours with a 200-W high-pressure mercury lamp. The bottle was opened, and an aliquot of the mixture was analyzed by ^{1}H NMR using dioxane as an

internal standard to confirm the quantitative formation of the dieneiron tricarbonyl complex. To this was added a solution of 4.08 g (15.0 mmol) of 2,4-dibromo-2,4-dimethylpentan-3-one in a small amount of benzene. The mixture was again covered with nitrogen and heated at 80° for 12 hours. The reaction mixture was filtered through a pad of 2 g of Celite 545, and the filtrate was concentrated on a rotary evaporator to give a pale yellow oil. This oil was dissolved in 20 mL of acetone, mixed with 1.70 g (10 mmol) of copper(II) chloride dihydrate, and stirred at room temperature for 15 minutes to decompose the remaining dieneiron tricarbonyl complex. The slurry was then passed through a short column packed with Celite 545, and the filtrate was concentrated under reduced pressure. The residue was dissolved in 40–50 mL of dichloromethane and washed with four 20-mL portions of a 5% aqueous solution of ethylenediaminetetraacetic acid disodium salt (Na_2H_2EDTA). The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated on a rotary evaporator to give 6.20 g of a yellow oil, distillation of which under reduced pressure with a Kugelrohr apparatus yielded 2.90 g (100%) of the title adduct as a colorless oil; bp 120–130° (0.02 mm). An analytical sample was obtained by preparative GC (33% Apiezon grease L on Neopak 1 A, 60–80 mesh, 213 × 1 cm,165°); retention time (t_R), 20 minutes: IR (CCl_4)cm^{-1}: 1685 (C = O);^{1}H NMR(CCl_4) δ : 1.07 (s, 12*H*, 4 CH_3), 1.79 (s, 6*H*, 2 = CCH_3), 2.25 (s, 4*H*, 2 = CCH_2); mass spectrum (70 eV) *m/e*: 194 (M), 123 (M – 71, base peak), 110 (M – 84), 109 (M – 85).

*5.3.1.3. 2,4-Diphenylbicyclo[3.2.1]oct-6-en-3-one ([3 + 4] Cyclocoupling of an*α*, α′-Dibromo Ketone and Cyclopentadiene with Sodium Iodide) (94)*

A mixture of 5.0 g (14 mmol) of 1,3-dibromo-1,3-diphenylpropan-2-one, 25 g (167 mmol) of sodium iodide, 50 mL (40 g, 606 mmol) of cyclopentadiene, and 150 mL of acetonitrile was boiled for 15 minutes. Chloroform was added, and the mixture was washed, first with sodium thiosulfate solution, then water, and dried over sodium sulfate. Concentration gave the crude material, which was chromatographed on a long column of silica gel to afford 7.4 g (99%) of a mixture of 2α,4α- and 2α,4 β -diphenylbicyclo[3.2.1]oct-6-en-3-ones in a 40:60 ratio as judged by the IR spectrum. Crystallization from ethanol yielded mainly the *cis* isomer as the first crop of crystals, and crystallization of the material in the mother liquor from acetone gave mainly the *trans* isomer. The *cis* adduct melted at 149.5–151.5° (from ethanol): IR (Nujol) cm^{-1}: 1700, 755, 740, 705. The *trans* adduct melted at 134–136° (from acetone); IR (Nujol) cm^{-1}: 1700, 1665, 750, 740, 700.

*5.3.1.4. 2*α*,4 β ,8-Trimethyl-8-azabicyclo[3.2.1]oct-6-en-3-one ([3 + 4] Cyclocoupling Reaction of an*α*, α′-Dibromo Ketone and N-Methylpyrrole with Copper-Sodium Iodide)* * *(102)*

A solution of 0.97 g (12 mmol) of *N*-methylpyrrole and 2.4 g (10 mmol) of 2,4-dibromopentan-3-one was added during a 30-minute period to a solution of 6.0 g (40 mmol) of sodium iodide in 50 mL of acetonitrile containing 1.9 g

(30 mg-atoms) of copper powder reduced by hydrogen, as supplied commercially. The mixture was stirred magnetically and maintained under an atmosphere of nitrogen throughout the preparation. After 8 hours, 25 mL of water and 50 mL of dichloromethane were added, and the mixture was stirred vigorously for 10 minutes to precipitate copper(II) iodide and filtered. The filtrate was washed successively with dilute ammonium hydroxide solution and brine. The organic layer was separated and extracted with cold 2*N* hydrochloric acid. After neutralization the aqueous layer was extracted again with dichloromethane, and the extract was dried over magnesium sulfate. Removal of solvent gave a crude oil, which was purified by fast filtration through silica gel with ether as eluent, giving 0.8–1.0 g (50–60%) of rather unstable title product. A sample of at least 95% purity, obtained by preparative TLC, had the following spectral characteristics: IR (neat) cm^{-1}: 3055, 1705, 707; ^1H NMR ($CDCl_3$) δ : 1.0 (d, *J* = 7 Hz, 6*H*, 2 CH_3), 2.3 (s, 3*H*, NCH_3), 2.7 (m, 2*H*, 2 COCH), 3.5 (d, *J* = 4 Hz, 2*H*, 2 NCH), 6.1 (d, *J* = 0.5 Hz, 2*H*, 2 = CH); mass spectrum *m/e* (relative intensity): 165 (M, 25), 108 (M – 57, 100), 94 (M – 71, 50).

5.3.1.5. 8-Acetyl-2,2,4,4-tetramethyl-8-azabicyclo[3.2.1]oct-6-en-3-one ([3 + 4] Cyclocoupling of an α*,* α*′-Dibromo Ketone and N-Acetylpyrrole with Diiron Enneacarbonyl) (74)*

Into a 50-mL, two-necked flask equipped with a serum cap and a nitrogen balloon was placed 1.10 g (3.02 mmol) of diiron enneacarbonyl. After the system was flushed with nitrogen, 10 mL of dry benzene, 1.62 g (5.96 mmol) of 2,4-dibromo-2,4-dimethylpentan-3-one, and 218 mg (2.00 mmol) of *N*-acetylpyrrole freshly distilled from sodium hydride were successively added through the rubber septum by a syringe. The mixture was stirred at 40–50° for 18.5 hours. The reaction mixture was diluted with 15 mL of ethyl acetate, washed with three 10-mL portions of saturated sodium hydrogen carbonate solution followed by 5 mL of brine, and dried over sodium sulfate. Concentration of the organic layer gave 1.2 g of an orange oil, which was subjected to column chromatography (25 g of silica gel). Elution with 1:3 ethyl acetate-*n*-hexane followed by evaporation of the solvents gave some unreacted starting dibromo ketone. The fractions eluted with ethyl acetate afforded 302 mg (68%) of the title compound as pale yellow crystals. Recrystallization from hexane gave an analytical sample: IR (CCl_4)cm^{-1}: 1720 (C = O), 1660 ($NCOCH_3$);^1H NMR(CCl_4) δ : 1.02 (s, 6*H*, 2 CH_3), 1.23 (s, 3*H*, CH_3), 1.30 (s, 3*H*, CH_3), 2.08 (s, 3*H*, $COCH_3$), 4.32 (broad singlet, 1*H*, NCH), 4.92 (broad singlet, 1*H*, NCH), 6.42 (broad singlet, 2*H*, 2 = CH); mass spectrum (70 eV) *m/e*: 221 (M), 206 (M – 15), 178 (M – 43), 164 (M – 57), 151 (M – 70), 150 (M – 71), 109 (M – 112), 108 (M – 113).

*5.3.1.6. 2*α*,4*α*-Dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one ([3 + 4] Cyclocoupling of an* α*,* α*′-Dibromo Ketone and Furan with the Aid of Zinc/Silver Couple) (45)*

A mixture of 19.6 g (0.30 g-atom) of zinc/silver couple, 140 mL (2.00 mol) of furan, and 300 mL of tetrahydrofuran was stirred at –10°, and a solution of 48.8 g (0.20 mol) of 2,4-dibromopentan-3-one in 150 mL of tetrahydrofuran was added dropwise over a period of 1 hour. The mixture was allowed to warm to room temperature and stirred for an additional 12 hours. The insoluble precipitate was removed by filtration, and the filtrate was concentrated. Chromatography of the residue on a column using 500 g of silica gel with 1:20 to 1:5 ethyl acetate-*n*-hexane as eluent afforded 24.2 g (80%) of the title compound as a colorless liquid: IR (CCl_4)cm^{-1}: 1715 (C ═ O);^{1}H NMR(CCl_4) δ : 0.90 (d, *J* = 7 Hz, 6*H*, 2 CH_3), 2.67 (d of q, *J* = 5 and 7 Hz, 2*H*, 2 COCH), 4.72 (d, *J* = 5 Hz, 2*H*, 2 OCH), 6.38 (broad singlet, 2*H*, 2 ═ CH); mass spectrum *m/e* (relative intensity): 152 (M, 23), 137 (M – 15, 14), 109 (M – 43, 10), 97 (M – 55, 9), 96 (M – 56, 54), 95 (M – 57, 40), 91 (M – 61, 9), 81 (M – 71, 100), 68 (M – 84, 9), 67 (M – 85, 16), 65 (M – 87, 7), 57 (M – 95, 7), 56 (M – 96, 14), 55 (M – 97, 15), 53 (M – 99, 15), 44 (M – 108, 10), 43 (M – 109, 13), 41 (M – 111, 20), 39 (M – 113, 27).

5.3.1.7. 2,2,4,4-Tetramethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one ([3 + 4] Cyclocoupling of anα, α′-Dibromo Ketone and Furan with Diiron Enneacarbonyl) (74)

In a nitrogen-flushed, 100-mL two-necked flask equipped with a serum cap was placed 3.64 g (10.0 mmol) of diiron enneacarbonyl. To this were added 2.18 g (8.00 mmol) of 2,4-dibromo-2,4-dimethylpentan-3-one, 5.44 g (80.0 mmol) of furan, and 20 mL of benzene. The mixture was stirred at 40° for 38 hours. The resulting precipitate was removed by filtration through a Celite 545 pad. The filtrate was washed with 5% aqueous Na_2H_2 EDTA solution. The organic layer was dried over sodium sulfate and evaporated to give a yellow-green oil, which was subjected to silica gel column chromatography with 1:10 ether-hexane as eluent to afford 12.8 g (89%) of the title adduct: IR (CCl_4)cm^{-1}: 1710 (C ═O); ^{1}H NMR(CCl_4) δ : 0.86 (s, 6*H*, 2 CH_3), 1.29 (s, 6*H*, 2 CH_3), 4.23 (s, 2*H*, 2 OCH), 6.19 (s, 2*H*, 2 ═ CH); mass spectrum (75 eV) *m/e* (relative intensity): 180 (M, 23), 110 (M – 70, 85), 95 (M – 85, 100) (major peaks only).

5.4. [3 + 4] Cyclocoupling Reactions of Tri- or Tetrabromo Ketones

5.4.1.1. 2,2-Dimethylbicyclo[3.2.1]oct-6-en-3-one (Iron Pentacarbonyl-Assisted [3 + 4] Cyclocoupling Reaction of a Tribromo Ketone and Cyclopentadiene) (48)

To a stirred, hot (80°) mixture of 1.0 mL of freshly distilled cyclopentadiene, 0.78 mL (1.17 g, 5.98 mmol) of iron pentacarbonyl (Strem), 1.0 mL of tetrahydrofuran, and 10.0 mL of dry benzene was added dropwise, under argon, a solution of 1.62 g (5.00 mmol) of 1, 1, 3-tribromo-3-methylbutan-2-one in 7.5 mL of 1:1 cyclopentadiene-benzene over 25 minutes. The resulting mixture was stirred for an additional 45-minute period at the same temperature, cooled, quenched by addition of 12.0 mL of

methanol saturated with ammonium chloride, and shaken vigorously with 3.80 g (57.8 mg-atoms) of zinc/copper couple for 20 minutes. The reaction mixture was diluted with 200 mL of dichloromethane and 100 mL of saturated aqueous Na_2H_2 EDTA solution. The insoluble materials were removed by filtration, and the filtrate was extracted twice with 50- and 30-mL portions of dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated to give 2.16 g of an oily residue, whose GC analysis showed the yield of the title bicyclic adduct (t_R 8 minutes) to be 83%. The oil was dissolved in 20 mL of dichloromethane and added dropwise to 200 mL of vigorously stirred hexane. The resulting precipitate was removed by passage through a Celite 545 pad. The filtrate was evaporated to leave 1.10 g of an oil, which was chromatographed on 15.0 g of Merck Kieselgel 60 (70–230 mesh). Elution with 110 mL of 1:1 benzene-*n*-hexane and 50 mL of 1:10 ethyl acetate-*n*-hexane in 10-mL fractions gave 520 mg (66%) of the title product (95% pure based on PMR analysis) in fractions 9–15. Bulb-to-bulb distillation of this oil produced 375 mg of an analytical sample, bp (bath temperature of 70°) 120° (2 mm), as colorless crystals, mp 45–48°: IR (CCl_4)cm^{-1}: 1714 (C = O); ^{1}H NMR(CCl_4) δ : 1.00 (s, 3*H*, CH_3), 1.17 (s, 3*H*, CH_3), 1.75–2.97 (m, 6*H*, 2 CH_2,2 = CHC*H*), 5.95–6.25 (multiplet appearing to be an AB quartet centered at δ6.1 with J_{AB} approximately 6 Hz and △ v $_{AB}$ ~ 4.5 Hz, 2*H*, 2 = CH); mass spectrum (75 eV) *m/e* (relative intensity): 150 (M, 94), 93 (M – 57, 100), 84 (M – 66, 90.8), 79 (M – 71, 87.8) (major peaks only).

5.4.1.2. N-Methoxycarbonyl-2, 4-dibromo-8-azabicyclo[3.2.1]oct-6-en-3-ones and N-Methoxycarbonyl-8-azabicyclo[3.2.1]oct-6-en-3-one (Diiron Enneacarbonyl-Promoted [3 + 4] Cyclocoupling of α*,* α*,* α′α′*-Tetrabromoacetone and N-Methoxycarbonylpyrrole) (75)*

Into a 30-mL, two-necked flask charged with 1.09 g (3.00 mmol) of diiron enneacarbonyl was poured a solution of 1.13 g (3.00 mmol) ofα, α, α′,α′-tetrabromoacetone in 7.5 mL of benzene. The mixture was heated at 50° with stirring for 5 minutes. *N*-Methoxycarbonylpyrrole (125 mg, 1.00 mmol) was added, and the mixture was stirred at 50° for 72 hours. The dark brown reaction mixture was diluted with 15 mL of ethyl acetate, and the insoluble material was removed by filtration through a Celite 545 pad. The filtrate was evaporated under reduced pressure, leaving a black, tarry oil. ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as internal standard showed that the desired 1:1 adducts, *N*-methoxycarbonyl-2α,4α-dibromo-8-azabicyclo[3.2.1]oct-6-en-3-one and *N*-methoxycarbonyl-2α,4 β -dibromo-8-azabicyclo[3.2.1]oct-6-en-3-one, were formed in 70% yield in a 2:1 ratio. Preparative TLC of the tar with 1:3 ethyl acetate-hexane afforded 145 mg (52%) of a mixture of the bicyclic adducts (R_f 0.6–0.7). Fractional recrystallization from ethyl acetate-*n*-hexane afforded an analytical sample of the *cis* isomer as colorless crystals, mp 155–157°: IR ($CHCl_3$)cm^{-1}: 1748 (C = O), 1710 (NCO_2CH_3); ^{1}H NMR($CDCl_3$) δ : 3.82 (s, 3*H*, OCH_3), 4.80 (d, *J* = 4.0 Hz, 2*H*, 2 CHBr), 5.11 (dd, *J* = 1.0 and 4.0 Hz, 2

NCH), 6.53 (tripletlike multiplet, *J* = 1.0 Hz, 2*H*, 2 ═ CH); mass spectrum (70 eV) *m/e*: 341, 339, 337 (1:2:1 ratio, M), 310, 308, 306 (1:2:1 ratio, M – OCH_3), 282, 280, 278 (1:2:1 ratio, M – CO_2CH_3), 260, 258 (1:1 ratio, M – OCH_3), 282, 280, 278 (1:2:1 ratio, M – CO_2CH_3), 260, 258 (1:1 ratio, M – Br). The mother liquor was concentrated and subjected to further TLC using 1:3 ethyl acetate-*n*-hexane as eluent, yielding the pure *trans* dibromide (R_f0.60), mp 112–114° from ethyl acetate-hexane: IR ($CHCl_3$)cm^{-1}: 1740 (C ═O), 1710 (NCO_2CH_3); ^1H NMR($CDCl_3$) δ : 3.82 (s, 3*H*, OCH_3), 4.27 (d, *J* = 2.0 Hz, 1*H*, an equatorial methine proton at C-4), 5.11 (d, *J* = 3.5 Hz, 1*H*, an axial methine proton at C-2), 5.0–5.3 (m, 2*H*, 2 NCH), 6.36 (dd, *J* = 2.0 and 6.0 Hz, 1*H*, ═ CH), 6.61 (dd, *J* = 2.0 and 6.0 Hz, 1*H*, ═CH); mass spectrum (70 eV) *m/e*: 341, 339, 337 (1:2:1 ratio, M), 310, 308, 306 (1:2:1 ratio, M – OCH_3), 282, 280, 278 (1:2:1 ratio, M – CO_2CH_3), 260, 258 (1:1 ratio, M – Br).

A 300-mg (0.87 mmol) mixture of the dibromo ketones and 750 mg (11.5 mg-atoms) of zinc/copper couple in 15 mL of methanol saturated with ammonium chloride was stirred at room temperature for 10 minutes. To this mixture was added 30 mL of ethyl acetate, and the insoluble material was removed by filtration. The filtrate was concentrated to afford an oil containing some solid, to which was added 20 mL of 1:1 ethyl acetate-*n*-hexane. The precipitate was removed by decantation and rinsed with 1:1 ethyl acetate-*n*-hexane. The organic layers were combined, washed with a small amount of water, dried, and evaporated to give 160 mg (100%) of *N*-methoxycarbonyl-8-azabicyclo[3.2.1]oct-6-en-3-one as colorless crystals. Recrystallizations from hexane produced an analytical specimen, mp 69–70°: IR ($CHCl_3$)cm^{-1}: 3005 (═ C ─ H), 1700–1710 (C ═ O and NCO_2CH_3), 1600 (C ═ C); ^1H NMR($CDCl_3$) δ : 2.40 (dd, *J* = 16.5 and 1.5 Hz, 2*H*, equatorial protons at C-2 and C-4), 2.80 (dd, *J* = 16.5 and 4.5 Hz, 2*H*, axial protons at C-2 and C-4), 3.84 (s, 3*H*, OCH_3), 4.90 (broad doublet, *J* = 4.5 Hz, 2*H*, 2 NCH), 6.27 (tripletlike multiplet, *J* = 1.0 Hz, 2*H*, 2 ═ CH); mass spectrum (70 eV) *m/e*: 181 (M), 138 (M – 43).

5.4.1.3. 8-Oxabicyclo[3.2.1]oct-6-en-3-one ([3 + 4] Cyclocoupling of α*,* α*,* α′*,*α′*-Tetrabromoacetone and Furan with Zinc/Silver Couple) (45)*

A mixture of 29.3 g (0.45 g-atom) of zinc/silver couple and 210 mL (3.00 mol) of furan in 450 mL of dry tetrahydrofuran was placed in a 2-L, three-necked flask and cooled to –10°. A solution of 112 g (0.30 mol) ofα, α, α′,α′-tetrabromoacetone in 200 mL of dry tetrahydrofuran was added dropwise over a period of 2 hours with stirring, and the resulting mixture was allowed to warm to room temperature and stirred for 12 hours. The insoluble materials were removed by filtration, and the filtrate was concentrated. The tarry brown residue was chromatographed on a column packed with 700 g of Merck Kieselgel 60 (70–230 mesh) using 1:20 to 1:5 ethyl acetate-*n*-hexane as eluent to give 55 g of crude 2α,4α-dibromo-8-oxabicyclo[3.2.1]oct-6-en-3-one as yellow crystals. Recrystallization from hexane gave a pure sample melting

at 126.5–127°. The dibromo adduct was dissolved in 1.3 L of saturated ammonium chloride solution in methanol, and to this was added portionwise 120 g (1.85 g-atoms) of zinc/copper couple over 10 minutes at room temperature. The suspension was stirred for an additional hour and filtered. The filtrate was divided into four portions, and each portion was diluted with 200 mL of water and 300 mL of saturated Na_2H_2EDTA solution. Extraction was performed with 300 mL and then two 200-mL portions of dichloromethane successively. The combined extracts were dried, and the organic solvent was removed by distillation at atmospheric pressure through a 40-cm Vigreux column. Finally the residue was subjected to light suction by an aspirator at room temperature to leave 20.4 g of the title bicyclic compound, contaminated with a small amount of dichloromethane (95% pure by ^{1}H NMR analysis). Overall yield based on tetrabromoacetone was 55%. A pure crystalline sample of the desired product, mp 37–39°, was obtained by bulb-to-bulb distillation at a bath temperature of 50–80° (0.01 mm): IR (CCl_4)cm^{-1}: 1720 (C = O); ^{1}H NMR(CCl_4) δ : 2.19 (dd, *J* = 17 and ~1.5 Hz, 2*H*, equatorial methylene protons at C-2 and C-4), 2.61 (dd, *J* = 5 and 17 Hz, 2*H*, axial methylene protons at C-2 and C-4), 4.91 (broad doublet, *J* = 5 Hz, 2*H*, 2 OCH), 6.19 (broad singlet, 2*H*, 2 = CH); mass spectrum (70 eV) *m/e* (relative intensity): 124 (M, 16), 95 (M – 29, 8), 83 (M – 41, 4), 82 (M – 42, 60), 81 (M – 43, 100), 68 (M – 56, 14), 67 (M – 57, 14), 66 (M – 58, 4), 65 (M – 59, 4).

5.5. [3 + 2] Cyclocoupling ofα, α′-Dibromo Ketones and Olefinic Substrates

5.5.1.1. 3-Cyclopropyl-2,5-dimethyl-3-phenylcyclopentanone ([3 + 2] Cyclocoupling of anα, α′-Dibromo Ketone and an Aryl-Substituted Olefin) (118)

In a two-necked flask equipped with a magnetic stirrer, a rubber septum, and a three-way stopcock fitted with an argon-filled balloon was placed 437 mg (1.20 mmol) of diiron enneacarbonyl; the flask was evacuated and flushed with argon. To the flask were added successively 9.0 mL of benzene, 288 mg (2.00 mmol) ofα-cyclopropylstyrene, and 244 mg (1.00 mmol) of 2,4-dibromopentan-3-one through the rubber septum via syringe. The resulting mixture was magnetically stirred at 65° for 24 hours, diluted with 30 mL of ethyl acetate, washed with saturated sodium hydrogen carbonate solution and potassium nitrate solution, dried over sodium sulfate, and concentrated on a rotary evaporator under reduced pressure (60–90 mm) at 25–50° to leave an oil that consisted mainly of 3-cyclopropyl-*cis*-2,5-dimethyl-3-phenylcyclopentanone and 3-cyclopropyl-*trans*-2,5-dimethyl-3-phenylcyclopentanone (ca. 3:1 ratio based on ^{1}H NMR analysis). The *cis* isomer: IR (CCl_4)cm^{-1}: 1736 (C = O); ^{1}H NMR(CCl_4) δ : 0.0–0.5 (m, 4*H*, methylene protons of cyclopropyl group), 0.75 (d, *J* = 7.5 Hz, 3*H*, CH_3), 1.17 (d, *J* = 6.5 Hz, 3*H*, CH_3), 1.5–3.0 (m, 5*H*, methylene and methine protons of five-membered ring and a methine proton of cyclopropyl group), 7.15 (m, 5*H*, aromatic protons); mass spectrum (70 eV)

m/e: 228 (M). The *trans* isomer: IR (CCl_4)cm^{-1}: 1736 (C ═ O); ^1H NMR(CCl_4) δ : 0.0–1.0 (m, 4*H*, methylene protons of cyclopropyl group), 1.14 (d, *J* = 6.5 Hz, 3*H*, CH_3), 1.35 (d, *J* = 6.5 Hz, 3*H*, CH_3), 1.5–2.9 (m, 5*H*, methylene and methine protons of five-membered ring and a methine proton of cyclopropyl group), 7.11 (m, 5*H*, aromatic protons); mass spectrum (70 eV) *m/e*: 228 (M). After long standing, the mixture gave 215 mg (95%) of the crystalline *trans* ketone as a single epimer. Recrystallization from hexane afforded colorless prisms: mp 92–94°.

5.5.1.2. 2,5-Dimethyl-3-phenylpent-2-enone ([3 + 2] Cyclocoupling of anα, α ′-Dibromo Ketone and an Enamine with Diiron Enneacarbonyl) * *(122)*

A mixture of 4.00 g (11.0 mmol) of diiron enneacarbonyl, 2.44 g (10.0 mmol) of 2,4-dibromopentan-3-one, and 3.78 g (20.0 mmol) of α-*N*-morpholinostyrene in 25 mL of benzene was maintained at 30° for 20 hours with efficient stirring. The reaction mixture was diluted with 15–50 mL of ethyl acetate and then washed with 30 mL of saturated sodium hydrogen carbonate solution and 30 mL of brine. The organic layer was dried over sodium sulfate and concentrated under reduced pressure (50–90 mm), giving 3.0 g of an orange liquid. The oil was subjected to column chromatography on 150 g of Merck Kieselgel 60 (70–230 mesh). Elution with 1:10 ethyl acetate-*n*-hexane yielded 1.68 g (91%) of the title cyclopentenone as a semisolid, which was recrystallized from hexane, giving rise to a pure sample, mp 57–59°: IR (neat) cm^{-1}: 1696 (C ═ O), 1626 (conjugated C ═C); UV (C_2H_5OH), nm max (ε): 220 (5220), 279 (11200); ^1H NMR(CCl_4) δ : 1.22 (d, *J* = 7.0 Hz, 3*H*, $CHCH_3$), 1.91 (t, *J* = 2.0 Hz, 3*H*, vinyl CH_3), 2.1–2.7 (m, 2*H*, $CHCH_3$ and a methylene proton *cis* to CH_3 group), 3.14 (dd of quartet, *J* = 18, 7.5, and 2.0 Hz, 1*H*, a methylene proton *trans* to CH_3 group), 7.38 (m, 5*H*, aromatic protons); mass spectrum (70 eV) *m/e*: 186 (M), 171 (M – 15), 158 (M – 28).

5.6. Miscellaneous Reactions

5.6.1.1. 2,4-Diisopropyl-5-methyl-3(2H)-furanone (Diiron Enneacarbonyl-Promoted [3 + 2] Cyclocoupling of anα, α′-Dibromo Ketone and an N,N-Dimethylcarboxamide) (34)

To a mixture of 874 mg (2.40 mmol) of diiron enneacarbonyl and 2.03 g (6.00 mmol) of Na_2H_2EDTA was added a solution of 600 mg (2.00 mmol) of 3,5-dibromo-2,6-dimethylheptan-4-one and 26.4 mg (0.20 mmol) of tetralin in 7.0 mL of *N,N*-dimethylacetamide. The resulting mixture was stirred at room temperature for 12 hours. The reaction mixture was poured into 20 mL of saturated sodium hydrogen carbonate-potassium nitrate solution and extracted with five 8-mL portions of ethyl acetate. The combined organic extracts were washed with three 8-mL portions of water and dried over sodium sulfate. After evaporation of the solvent an oil was obtained. The ^1H NMR spectrum of this residue indicated two doublets at δ 3.95(*J* = 3.8 Hz) and 3.38 (*J* = 4.5 Hz) due to the C-2 methine protons of the title 3(2*H*)-furanone and 5-(dimethylamino)-2, 4-diisopropyl-5-methyltetrahydro-3-furanone,

respectively. The intensity of signals, as compared with that of a singlet due to the aromatic protons of tetralin added as an internal standard, showed that the 3(2*H*)-furanone and aminotetrahydro-3-furanone were produced in 49% and 39% yields, respectively. When the crude oil was heated at 110° for 15 minutes under nitrogen, 316 mg (87%) of the 3(2*H*)-furanone was obtained as an oily product. Distillation at a bath temperature of 90° (3 mm), followed by preparative GC (10% LAC on Chromosorb W AW, 80–100 mesh, 400 × 0.4 cm,108°), afforded an analytical sample: IR (neat) cm^{-1}: 1691 (C = O), 1631 (C= C); UV (C_2H_5OH), nm max (ε): 273 (9550); ^1H NMR(CCl_4) δ : 0.79 [d, *J* = 6.5 Hz, 3*H*, CHCH(CH_3)$_2$], 1.05 [d, *J* = 6.5 Hz, 3*H*, CHCH(CH_3)$_2$], 1.15 [d, *J* = 7.0 Hz, 6*H*, = CCH(CH_3)$_2$], 2.15 (s, 3*H*, = CCH_3), 2.0–2.8 [m, 2*H*, 2 C*H*(CH_3)$_2$], 3.95 (d, *J* = 3.8 Hz, 1*H*, OCH); mass spectrum (70 eV) *m/e*: 1 82.1295 (M).

5.6.1.2. 2-(N-Cyclohexylimino)-3,3,4,4-tetramethylcyclobutanone (Reaction of anα, α′-Dibromo Ketone and a Copper-Isocyanide Complex) (108)

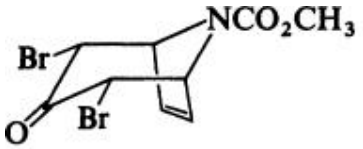
A solution of 2.72 g (10 mmol) of 2,4-dibromo-2, 4-dimethylpentan-3-one in 4 mL of benzene was added to a mixture of 1.27 g (20 mg-atoms) of metallic copper and 8.7 g (80 mmol) of cyclohexyl isocyanide in 20 mL of benzene at room temperature. The mixture was stirred at room temperature for 12 hours and treated with *ca.* 25 mL of ether to precipitate the resulting copper(I) cyclohexyl isocyanide complex. The ether solution was filtered and concentrated, and the residue was distilled to give 1.9 g (86%) of 2-(*N*-cyclohexylimino)-3,3,4,4-tetramethylcyclo-butanone, bp 98–100° (2 mm): IR (neat) cm^{-1}: 1765 (C = O), 1669 (C = N), 890; ^1H NMR($CDCl_3$) δ : 1.04 (s, 6*H*, 2 CH_3), 1.10 (s, 6*H*, 2 CH_3), 0.9–2.5 (broad envelope, 10*H*, 5 CH_2), 3.9–4.2 (broad multiplet, 1*H*, = NCH); mass spectrum *m/e*: 221 (M).

6. Tabular Survey

An attempt has been made to include in Tables I–X synthetic applications of reductive dehalogenation of halo ketones using low-valent transition metals and related reducing agents reported through December 1980, but lack of a systematic method of searching the literature for the reaction makes it likely that some examples were overlooked.

The tables are arranged, in general, according to the presentation in the discussion. Table I summarizes the reductions of α , α′-dihalo ketones that form intramolecular skeletal-changed compounds, α, β -unsaturated ketones, etc. Table II gives examples of the reduction ofα, α′-dihalo ketones in the presence of oxy or amino nucleophiles producing the parent ketones, α-oxy-substituted ketones, etc. Table III covers the reductive dehalogenation ofα-monohalo ketones to the parent ketones. Table IV is concerned with reductive alkylation of monohalo ketones, including examples of reductive aldol reaction, acylation, self-dimerization, etc. Table V comprises reactions ofα, α-dihalo ketones consisting of simple dehalogenation and reductive alkylation. Table VI, which lists reductive alkylations ofα, α′-dihalo ketones, is divided into three sections: (1) formation ofα-monoalkylated ketones, (2) production ofα, α′-dialkyl ketones, and (3) reductive dimerization. Table VII, which includes the [3 + 4] cyclocoupling ofα, α′-dihalo and more highly halogenated ketones, consists of the following six sections according to the structures of the C_4 receptors: (1) open-chain 1,3-dienes; (2) carbocycles such as cyclopentadiene, fulvenes, cyclohexadiene, etc.; (3) pyrrole derivatives; (4) furan derivatives; (5) thiophene; and (6) anthracene. Table VIII, consisting of five sections, is concerned with the [3 + 2] cyclocoupling ofα, α′-dibromo ketones with: (1) simple olefins, (2) aryl-substituted olefins, (3) enamines, (4) carboxamides and a lactam, and (5) other C_2 substrates. Table IX lists other cyclocoupling reactions ofα, α′-dibromo ketones. Table X covers miscellaneous reactions.

Within each table the substrates are arranged in order of increasing number of carbon atoms. Derivatives of alcohols, amines, ketones, and carboxylic acids are listed by the number of carbon atoms in the parent skeletons, respectively. For instance, the bromo ketones **143** and **144** are dealt with as C_7 and C_8 compounds, respectively. Substrates with the same number of carbon atoms are listed in order of increasing complexity of the structures, e.g., primary before secondary alkyl, alkyl before alkenyl, aliphatic before aromatic, five-membered



143

p-$CH_3OC_6H_4COCH_2Br$

144

before six-membered cyclic, monocyclic before bicyclic, hydrocarbon before heteroatom-containing, chloro before bromo compounds.

When there is more than one reference, the experimental data are taken from the first reference, and the remaining references are arranged in numerical order.

In all the tables the numbers in parentheses shown after the reactants indicate the stoichiometric ratio of reactants to the halides; no number means that an excess of reagents is used or that the stoichiometric relation is not critical for the reaction. The symbol e^- signifies electrochemical treatment with a mercury cathode. Yields are based on the reactant present in the lowest concentration. Unless otherwise noted, yields were either estimated by GC or obtained by product isolation; when both yields are given in the experiments, the chromatographically obtained ones are shown first, followed by the isolated ones. A dash (—) the reaction conditions or yield column indicates that no information is given in the reference. In addition to the usual chemical symbols, the following abbreviations are used in the tables:

Ac	Acetyl
acac	Acetylacetonate
bbn	9-Bicyclo[3.3.1]nonyl
DME	1, 2-Dimethoxyethane
DMF	*N, N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
Ether	Diethyl ether
HMPA	Hexamethylphosphoramide
MVK	Methyl vinyl ketone
Na_2H_2EDTA	Ethylenediaminetetraacetic acid disodium salt
PC	Phthalocyanine
Py	Pyridine
THP	Tetrahydropyranyl
TMEDA	*N*,*N*,*N*′,*N*′-Tetramethylethylenediamine
TMS	Trimethylsilyl
Ts	Tosyl, p-$CH_3C_6H_4SO_2$

Table I. Intramolecular Reactions

View PDF

Table II. Reduction of α, α′-Dihalo Ketones in the Presence of Oxy or Amino Nucleophiles

View PDF

Table III. Reductive Dehalogenation of α-Monohalo Ketones to the Parent Ketones

View PDF

Table IV. Reductive Alkylation of α-Monohalo Ketones

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Table V. Reactions of α, α-Dihalo Ketones

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Table VI. Reductive Alkylation ofα, α′-Dihalo Ketones

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Table VII. [3 + 4] Cyclocoupling ofα, α′-Dihalo and Polyhalogenated Ketones

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Table VIII. [3 + 2] Cyclocoupling ofα, α′-Dibromo Ketones

View PDF

Table IX. Miscellaneous Cyclocouplings ofα, α′-Dibromo Ketones

View PDF

Table X. Miscellaneous Reactions ofα, α′-Dibromo Ketones

View PDF

TABLE I. INTRAMOLECULAR REACTIONS

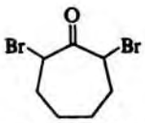
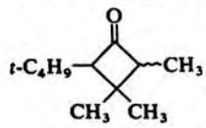
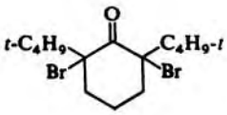
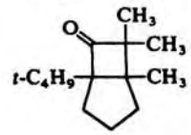
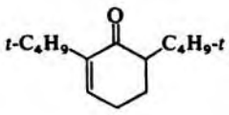
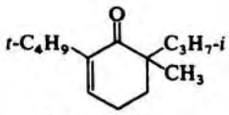
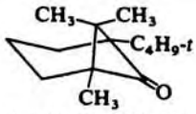
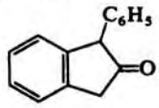
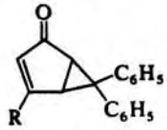
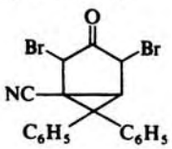
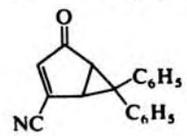
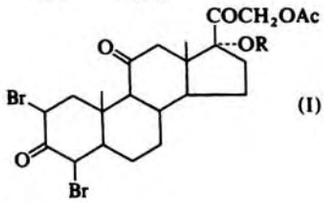
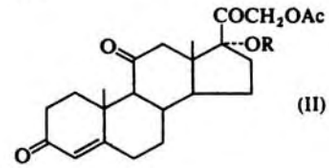
	Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_3	$(CH_2Cl)_2CO$	K[a] (2)	295–303°	$CH_2{=}CH_2$ (33.3)	17
		"	272–281°	" (16.2)	17
		"	257–265°	" (11.9)	17
C_5	$(CH_3CHBr)_2CO$	"	224–257°	$CH_3CH{=}CHCH_3$ (*Z*) (11.5); (*E*) (15.1)	17
	$(CH_3)_2CBrCOCH_2Br$	"	217–232°	$(CH_3)_2C{=}CH_2$ (22.9)	17
C_7	$[(CH_3)_2CBr]_2CO$	"	277–297°	$i\text{-}C_3H_7C(CH_3){=}CH_2$, $(CH_3)_2C{=}C(CH_3)_2$ (total 11.6)	17
		$Fe_2(CO)_9$	DMF, 25°, 18 hr	$CH_2{=}C(CH_3)COC_3H_7\text{-}i$ (80), $(i\text{-}C_3H_7)_2CO$ (9)	28
		K[a] (2)	255–265°	(22)	17
C_8	$CH_2{=}CH(CH_2)_2CBr(CH_3)COCH_2Br$	$Fe_2(CO)_9$	C_6H_6, reflux	$CH_2{=}CH(CH_2)_2COC(CH_3){=}CH_2$ (—)	32
C_{11}	$(t\text{-}C_4H_9CHBr)_2CO$	"	C_6H_6, 80°, 6 hr	 *cis/trans* (5 : 1) (78)	28, 29
C_{14}				 (I),  (II),  (III),  (IV)	
		Zn/Cu	C_6H_6, reflux, 48 hr	I (11), II (28), IV (40)	28
		$Fe_2(CO)_9$	C_6H_6, 25°, 23 hr	I (80), II (15), III (3)	28, 29
		$Ni(CO)_4$	C_6H_6, 24 hr	I (5), II (64)	28
C_{15}	$(C_6H_5CHBr)_2CO$	$Fe_2(CO)_9$	C_6H_6, 25°, 24 hr	 (70)	28, 29
C_{18}	(I) I, R = H			 (II)	
		Na/Hg	C_6H_6, 3 min	II, R = H (13.6)	31
		Ca	THF, −70°, 23 min	II, R = H (26)	31
		Zn	Dioxane, 60°, 125 min	II, R = H (74)	31
		"	Dioxane, reflux, 25 min	II, R = H (70)	31

TABLE I. INTRAMOLECULAR REACTIONS (*Continued*)

	Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_{18} (*Contd.*)	I, R = H	$Fe_2(CO)_9$	C_6H_6	II, R = H (—)	28
		"	DMF, 25°, 24 hr	II, R = H (95)	28, 29
		Aq HI	Acetone, 10 min	II, R = H (89)	31
	I, R = OCH_3	$Fe_2(CO)_9$	C_6H_6, 3.5 hr	II, R = OCH_3 (72)	30b
C_{19}		"	C_6H_6, 20 hr	 (80)	30a
C_{21}	 (I)			 (II)	
	I, R = H	NaI	Acetone, reflux, 15 min	II, R = H (—)	137
	I, R = Ac	"	Acetone, reflux, 4.5 hr	II, R = Ac (—)	"

[a] Potassium vapor was used.

TABLE II. REDUCTION OF α,α′-DIHALO KETONES IN THE PRESENCE OF OXY OR AMINO NUCLEOPHILES

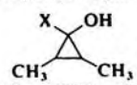
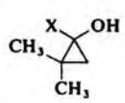
	Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_3	$ClCH_2COCH_2Cl$	t-C_4H_9OK (1–2), $(C_2H_5)_3B$	THF, 20°, 3 hr	CH_3COCH_3 (55)	76
	$ClCH_2COCH_2Br$	t-C_4H_9OK (1), $(C_2H_5)_3B$	"	CH_3COCH_3 (50)	76
	$BrCH_2COCH_2Br$	t-C_4H_9OK (1–2), $(C_2H_5)_3B$	"	CH_3COCH_3 (41)	76
		2,6-(t-C_4H_9)$_2C_6H_3OK$ (2), $(C_2H_5)_3B$	"	CH_3COCH_3 (42)	76
		$2e^-$, $C_6H_5CO_2Na$	$C_6H_5CO_2H$/DMF, 14°	$C_6H_5CO_2CH_2OCH_3$ (—)	20
	ICH_2COCH_2I	Zn/Cu	CH_3OH, −5 to 0°, 75 min	CH_3COCH_3 (100)	21
C_4	$CH_3CHBrCOCH_2Br$	Zn/Cu	CH_3OH, −35 to 0°, 75 min	$C_2H_5COCH_3$ (100)	21
C_5	$(CH_3CHBr)_2CO$	"	CH_3OH, −5 to 0° 75 min	$(C_2H_5)_2CO$ (38), $CH_3CH(OCH_3)COC_2H_5$ (62)	21
		$2e^-$	CH_3OH, −10°	$CH_3CH(OCH_3)COC_2H_5$ (62),  (I) X = OCH_3 (30)	38
		$2e^-$, CH_3OH (2)	CH_3CN, −10°	I, X = OCH_3 (50)	38
	$(CH_3)_2CBrCOCH_2Br$	$2e^-$, $(CH_3)_2NH$ (2)	CH_3CN, −20°	I, X = $N(CH_3)_2$ (70) $(CH_3)_2C(OR)COCH_3$ (I), i-$C_3H_7COCH_2OR$ (II), i-$C_3H_7COCH_3$ (III)	38
		Zn/Cu	CH_3OH, −35 to 5°, 75 min	R = CH_3 I/III (14 : 86) (—)	21
		Hg	AcOH, 14 ± 2°, 72 hr	R = Ac I/II (72 : 28) (26)	27
		Hg, AcONa	AcOH/DMF, 14 ± 2°	R = Ac I/II (20 : 80) (53)	27
		Hg	t-$C_4H_9CO_2H$, 14 ± 2°	R = COC_4H_9-t I/II (87 : 13) (74)	27
		$2e^-$, AcONa	AcOH/DMF, 14 ± 2°	R = Ac I/II (11 : 89) (43)	27
		$2e^-$, t-$C_4H_9CO_2Na$	t-$C_4H_9CO_2H$/DMF, 14 ± 2°	II, R = COC_4H_9-t (65)	27
		$2e^-$, CH_3OH (2)	CH_3CN, −10°	 (I) X = OCH_3 (50)	38

TABLE II. REDUCTION OF α,α′-DIHALO KETONES IN THE PRESENCE OF OXY OR AMINO NUCLEOPHILES (*Continued*)

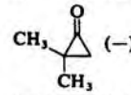
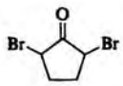
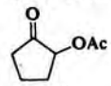
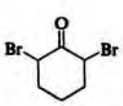
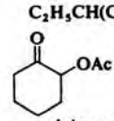
	Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_5 (*Contd.*)	$(CH_3)_2CBrCOCH_2Br$	$2e^-$, $(CH_3)_2NH$ (20)	CH_3CN, −20°	I, X = $N(CH_3)_2$ (30)	38
		$2e^-$, $(CH_3)_2NH$ (2)	"	I, X = $N(CH_3)_2$ (70)	38
		$2e^-$, $(C_2H_5)_4NBr$	DMF	 (−)	37
	$(CH_3)_2CBrCOCH_2I$	Zn/Cu	CH_3OH, −35 to −5°, 75 min	$(CH_3)_2C(OCH_3)COCH_3$ (I), i-$C_3H_7COCH_3$ (II) I/II (5–33 : 67–95) (−)	21
		Hg	AcOH	 (I) (36)	26
		"	AcOH/THF (1 : 9)	I (16)	26
		"	AcOH/C_6H_6 (1 : 9)	I (19)	26
C_6	$(CH_3)_2CBrCOCHBrCH_3$			$(CH_3)_2C(OR)COC_2H_5$ (I), i-$C_3H_7COCH(OR)CH_3$ (II), i-$C_3H_7COC_2H_5$ (III)	
		Zn/Cu	CH_3OH, 0°, 75 min	R = CH_3 I/III (76 : 24) (−)	21
		Hg	AcOH, 14 ± 2°, 72 hr	R = Ac I/II (80 : 20) (84)	27
		Hg[a]	AcOH, 25°, 1–4 days	R = Ac I/II (55 : 45) (68)	23
		Hg, AcONa	AcOH/DMF, 25°, 1–4 days	R = Ac I/II (77 : 23) (61)	27
		Hg	t-$C_4H_9CO_2H$, 25°, 1–4 days	R = COC_4H_9-t I/II (98 : 2) (64)	27
		$Fe_2(CO)_9$	CH_3OH, 25°, 38 hr	R = CH_3 I/II (9 : 1) (45), III (<3)	28
		$Fe_2(CO)_9$, AcONa	DMF, 25°, 16 hr	R = Ac I/II (69 : 31) (46), III (3)	28
		$2e^-$, AcONa	AcOH, 25°, 1–4 days	R = Ac I/II (87 : 13) (28), III (1)	27
		"	AcOH/DMF, 25°, 1–4 days	R = Ac I/II (33 : 67) (73)	27
		$2e^-$, t-$C_4H_9CO_2Na$	t-$C_4H_9CO_2H$/DME, 1–4 days	R = COC_4H_9-t I/II (40 : 60) (71)	27
	$C_2H_5CBr(CH_3)COCH_2Br$	Hg[a]	AcOH	$C_2H_5C(OAc)(CH_3)COCH_3$ (I), $C_2H_5CH(CH_3)COCH_2OAc$ (II) I/II (70 : 30) (31), $C_2H_5CH(CH_3)COCH_3$ (4)	23
		Hg	"	 (46), cyclohexanone (11)	26
C_7	$(C_2H_5CHBr)_2CO$	$2e^-$, NaOAc	AcOH, 25 ± 1°	$(n$-$C_3H_7)_2CO$ (90)	22
	$(CH_3)_2CBrCOCHBrC_2H_5$			$(CH_3)_2C(OR)COC_3H_7$-n (I), i-$C_3H_7COCH(OR)C_2H_5$ (II), i-$C_3H_7COC_3H_7$-n (III)	
		Hg	AcOH, 14 ± 2°, 72 hr	R = Ac I/II (85 : 15) (90), III (4)	27
		Hg, AcONa	AcOH/DMF, 14 ± 2°, 72 hr	R = Ac I/II (85 : 15) (82), III (2)	27
		Hg	t-$C_4H_9CO_2H$, 14 ± 2°, 72 hr	R = COC_4H_9-t I/II (99 : 1) (72), III (2)	27
		$2e^-$, AcONa	AcOH, 14 ± 2°, 72 hr	R = Ac I/II (86 : 14) (72), III (23)	27
		"	AcOH/DMF, 14 ± 2°, 72 hr	R = Ac I/II (50 : 50) (74), III (8)	27
		$2e^-$, t-$C_4H_9CO_2Na$	t-$C_4H_9CO_2H$/DMF, 14 ± 2°, 72 hr	R = COC_4H_9-t I/II (30 : 70) (66), III (4)	27
	$[(CH_3)_2CBr]_2CO$			i-$C_3H_7COC(OR)(CH_3)_2$ (I), $(i$-$C_3H_7)_2CO$ (II)	
		Zn/Cu	CH_3OH, −5 to 0°, 75 min	I, R = CH_3 (72), II (28)	21
		Hg[a]	CH_3OH, 25°, 1–4 days	I, R = CH_3 (71)	23
		Hg	AcOH, 14 ± 2°, 72 hr	I, R = Ac (73), II (1)	27
		Hg[a]	AcOH, 25°, 1–4 days	I, R = Ac (71)	23
		"	AcOD, 25°, 1–4 days	$(CH_3)_2CDCOC(OAc)(CH_3)_2$ (60)	23
		"	$C_2H_5CO_2H$, 25°, 1–4 days	I, R = C_2H_5 (80)	23
		Hg	t-$C_4H_9CO_2H$, 14 ± 2°, 72 hr	I, R = COC_4H_9-t (62), II (1)	27
		Hg[a]	t-$C_4H_9CO_2H$, 25°, 1–4 days	I, R = COC_4H_9-t (75)	23
		$Fe_2(CO)_9$	H_2O/DMF (5 : 95), 24 hr	II (25), $(CH_3)_2CBrCOC_3H_7$-i (15)	28

TABLE II. REDUCTION OF α,α′-DIHALO KETONES IN THE PRESENCE OF OXY OR AMINO NUCLEOPHILES (*Continued*)

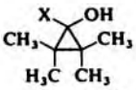
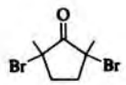
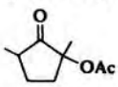
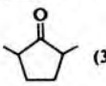
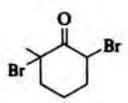
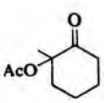
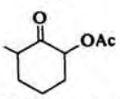
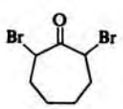
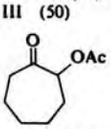
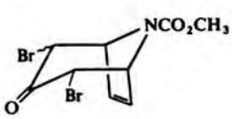
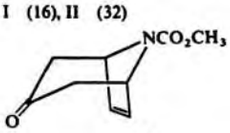
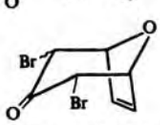
Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_7 $[(CH_3)_2CBr]_2CO$ (*Contd.*)	$Fe_2(CO)_9$, AcONa	DMF, 30°, 19 hr	I, R = Ac (60), II (20)	28, 29
	$2e^-$, LiCl (1)	H_2O/DMF (5:95), −8 to 40°	I, R = H (−)[b]	20
	$2e^-$, $(n\text{-}C_4H_9)_4NBF_4$ (0.2)	C_2H_5OH/CH_3CN (1:99), 14°	I, R = H (−)[b]	20
	$2e^-$, $(n\text{-}C_4H_9)_4NBF_4$ (0.2), AcONa,[c] AcOH[c]	DMF, −32°	R = Ac I/II (17:1) (−)[b]	20
	$2e^-$, AcONa	AcOH/DMF, 14 ± 2°, 72 hr	I, R = Ac (61), II (2)	27, 20
	"	AcOH, 25 ± 1°	R = Ac I/II (91.9:1.2) (75)[d]	22
	$2e^-$[e]	"	R = Ac I/II (94:1) (81)[d]	22
	$2e^-$, $t\text{-}C_4H_9CO_2Na$	$t\text{-}C_4H_9CO_2H$/DMF, 14 ± 2°, 72 hr	I, R = Ac (57)	27
	$2e^-$	CH_3OH	 (I) X = OCH_3 (90), $i\text{-}C_3H_7C(CH_3)_2CO_2CH_3$ (4), $i\text{-}C_3H_7COC(OCH_3)(CH_3)_2$ (6)	37
	"	CH_3OH, <0°	I, X = OCH_3 (100)	37, 38
	$2e^-$, CH_3OH (2)	CH_3CN, −5°	I, X = OCH_3 (85)	38
	$2e^-$, $(CH_3)_2NH$ (2)	"	I, X = $N(CH_3)_2$ (80)	38
	$2e^-$, CH_3NH_2 (2)	CH_3CN, −20°	I, X = $NHCH_3$ (60)	38
	$2e^-$, $C_6H_5NH_2$ (2)	CH_3CN, −5°	I, X = NHC_6H_5 (80)	38
	$2e^-$, AcONa	AcOH, 25 ± 1°	 (2.1),  (32)	22
	Hg[a]	AcOH, 25°, 1–4 days	 (I),  (II), I/*cis*-II/*trans*-II (44:32:24) (66), 2-methylcyclohexanone (III) (1)	23
	$t\text{-}C_4H_9OK$ (2), $(C_2H_5)_3B$	THF	III (50)	76
			 (I), cycloheptanone (II)	
	Hg	$AcOH/C_6H_6$ (1:9)	I (14), II (35)	26
	"	AcOH/THF	I (13), II (28)	26
	"	AcOH	I (16), II (32)	26
	Zn/Cu, NH_4Cl	CH_3OH, 15 min	 (100)	75, 104
	"	"	(100)	74, 45, 110
C_8 $(CH_3)_2CBrCOCHBrC_3H_7\text{-}n$	Hg[a]	AcOH, 25°, 1–4 days	$(CH_3)_2C(OR)COC_4H_9\text{-}n$ (I), $i\text{-}C_3H_7COCH(OAc)C_3H_7\text{-}n$ (II)	
	"		R = Ac I/II (70:30) (75)	23
	"	$t\text{-}C_4H_9CO_2H$, 25°, 1–4 days	R = $COC_4H_9\text{-}t$ I/II (96:4) (74)	23
$(CH_3)_2CBrCOCHBrC_3H_7\text{-}i$			$(CH_3)_2C(OR)COCH_2C_3H_7\text{-}i$ (I), $i\text{-}C_3H_7COCH(OR)C_3H_7\text{-}i$ (II), $i\text{-}C_3H_7COCH_2C_3H_7\text{-}i$ (III)	

TABLE II. REDUCTION OF α,α′-DIHALO KETONES IN THE PRESENCE OF OXY OR AMINO NUCLEOPHILES (*Continued*)

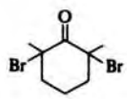
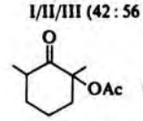
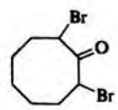
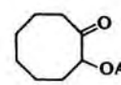
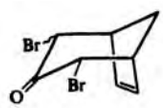
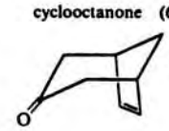
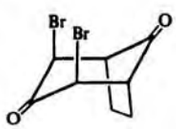
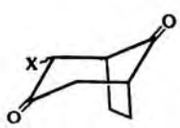
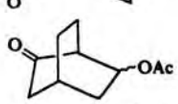
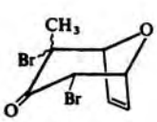
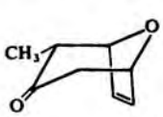
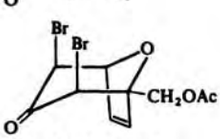
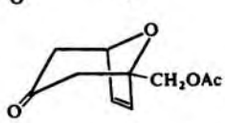
	Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_8 (*Contd.*)	$(CH_3)_2CBrCOCHBrC_3H_7$-*i*	Hg	AcOH, 14 ± 2°, 72 hr	R = Ac I/II (91 : 9) (89), III (2)	27
		Hg[a]	AcOH, 25°, 1–4 days	R = Ac I/II (93 : 7) (60)	23
		Hg	*t*-$C_4H_9CO_2H$, 14 ± 2°, 72 hr	R = COC_4H_9-*t* I/II (99 : 1) (68), III (1)	27
		Hg[a]	$(C_2H_5)_3CCO_2H$, 25°, 1–4 days	I, R = $COC(C_2H_5)_3$ (76)	23
		2e⁻, AcONa	AcOH, 25 ± 1°	R = Ac I/II/III (65 : 12 : 15) (73)	22
		"	AcOH/DMF, 14 ± 2° 72 hr	R = Ac I/II (98 : 2) (74), III (12)	27
		2e⁻, *t*-$C_4H_9CO_2Na$	*t*-$C_4H_9CO_2H$/DMF, 14 ± 2°, 72 hr	R = COC_4H_9-*t* I/II (99 : 1) (50), III (6)	27
	$(CH_3)_2CBrCOCBr(CH_3)C_2H_5$[f]	2e⁻, AcONa	AcOH	$(CH_3)_2C(OAc)COCH(CH_3)C_2H_5$ (I), *i*-$C_3H_7COC(OAc)(CH_3)C_2H_5$ (II), *i*-$C_3H_7COCH(CH_3)C_2H_5$ (III) I/II/III (42 : 56 : 1) (85)[d,f]	22
		"	AcOH, 25 ± 1°	 (I), 2,6-dimethylcyclohexanone (II) I/II (59 : 2) (68)	22
		Hg	AcOH	 (2), cyclooctanone (61)	26
		Zn/Cu, NH_4Cl	CH_3OH/ether, 18 hr	 (100)	97, 74, 96
				 (I),  (II)	
		Hg	AcOH	I, X = β-OAc (43), I, X = α-Br (25), I, X = β-Br (20), II (4)	25
		2e⁻, AcONa	AcOH/DMF (1 : 9)	I, X = β-OAc (73), I, X = α-Br (9), I, X = β-Br (7), II (6)	25
		Zn/Cu, NH_4Cl	CH_3OH, 1 hr	 (—)	45
		"	CH_3OH, 20°, 1 hr	 (89)	83
C_9	$(n\text{-}C_3H_7CHBr)_2CO$	Hg[a]	AcOH, 25 ± 1°, 1–4 days	*n*-$C_4H_9COCH(OAc)C_3H_7$-*n* (35), $(n\text{-}C_4H_9)_2CO$ (10), *n*-$C_4H_9COCHBrC_3H_7$-*n* (5)	23
	$(CH_3)_2CBrCOCBr(CH_3)C_3H_7$-*n*	2e⁻, AcONa	"	$(CH_3)_2C(OAc)COCH(CH_3)C_3H_7$-*n* (I), *i*-$C_3H_7COC(OAc)(CH_3)C_3H_7$-*n* (II), *i*-$C_3H_7COCH(CH_3)C_3H_7$-*n* (III), I/II/III (56 : 34 : 1) (85)[d]	22
	$[C_2H_5CBr(CH_3)]_2CO$	"	"	$C_2H_5CH(CH_3)COC(OAc)(CH_3)C_2H_5$ (I), $[C_2H_5CH(CH_3)]_2CO$ (II), I/II (90 : 4) (82)[d]	22
	$(CH_3)_2CBrCOCHBrC_4H_9$-*t*			$(CH_3)_2C(OR)COCH_2C_4H_9$-*t* (I), *i*-$C_3H_7COCH(OR)C_4H_9$-*t* (II), *i*-$C_3H_7COCH_2C_4H_9$-*t* (III)	

TABLE II. REDUCTION OF α,α′-DIHALO KETONES IN THE PRESENCE OF OXY OR AMINO NUCLEOPHILES (*Continued*)

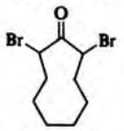
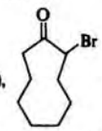
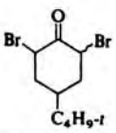
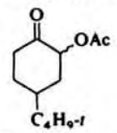
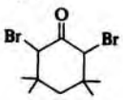
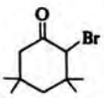
Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_9 $(CH_3)_2CBrCOCHBrC_4H_9$-*t* (*Contd.*)	Hg	AcOH, 14 ± 2°, 72 hr	R = Ac I/II (95 : 5) (58), III (1)	27
	"	*t*-$C_4H_9CO_2H$, 14 ± 2°, 72 hr	R = COC_4H_9-*t* I/II (99 : 1) (50), III (2)	27
	2e⁻, AcONa	AcOH/DMF, 14 ± 2°, 72 hr	I, R = Ac (48), III (5)	27
	2e⁻, *t*-$C_4H_9CO_2Na$	*t*-$C_4H_9CO_2H$/DMF, 14°, 72 hr	I, R = COC_4H_9-*t* (67), III (7)	27
$C_6H_5CHBrCOCH_2Br$	2e⁻, AcONa	AcOH, 25°	$C_6H_5CH_2COCH_3$ (100, 85)	24, 22
	Hg	AcOH	Cyclononanone (44),  (22)	26
C_{10} $(CH_3)_2CBrCOCHBrCH_2C_4H_9$-*t*			$(CH_3)_2C(OR)CO(CH_2)_2C_4H_9$-*t* (I), *i*-$C_3H_7COCH(OR)CH_2C_4H_9$-*t* (II), *i*-$C_3H_7CO(CH_2)_2C_4H_9$-*t* (III)	
	Hg	AcOH, 14 ± 2°, 72 hr	R = Ac I/II (95 : 5) (85)	27
	"	*t*-$C_4H_9CO_2H$, 14 ± 2°, 72 hr	R = COC_4H_9-*t* I/II (99 : 1) (85)	27
	2e⁻, AcONa	AcOH, 14 ± 2°, 72 hr	R = Ac I/II (84 : 6) (37), III (13)	27
	2e⁻, *t*-$C_4H_9CO_2Na$	*t*-$C_4H_9CO_2H$, 14 ± 2°, 72 hr	R = COC_4H_9-*t* I/II (40 : 60) (61), III (20)	27
$C_2H_5CBr(CH_3)COCBr(CH_3)C_3H_7$-*n*	2e⁻, AcONa	AcOH	$C_2H_5C(OAc)(CH_3)COCH(CH_3)C_3H_7$-*n* (I), $C_2H_5CH(CH_3)COC(OAc)(CH_3)C_3H_7$-*n* (II), $C_2H_5CH(CH_3)COCH(CH_3)C_3H_7$-*n* (III) I/II/III (56 : 39 : 0.2) (86)[d]	22
$C_6H_5CHBrCOCHBrCH_3$			$C_6H_5CH(OR)COC_2H_5$ (I), $C_6H_5CH_2COCH(OR)CH_3$ (II), $C_6H_5CH_2COC_2H_5$ (III)	
	Zn/Cu	CH_3OH, −5 to 0°, 75 min	R = CH_3 II/III (28 : 72) (—)	21
	Hg	AcOH, 25°	R = Ac I (7), II (59), III (16)	24
	Hg, AcONa	"	R = Ac I (12), II (66), III (16)	24
	2e⁻, AcONa	"	R = Ac I (8), II (21), III (66)	24
 (I)			4-*t*-Butylcyclohexanone (II),  (III)	
I (α- and β-Br)	Hg	AcOH	II (65), III (24)	25
	2e⁻, AcONa	AcOH, 25 ± 1°	II/III (1 : 99) (90)	25
I (β-Br)	CH_3OK (2), $(n\text{-}C_4H_9)_3B$	THF, 20°	II (20)	76
	i-C_3H_7ONa (2), $(n\text{-}C_4H_9)_3B$	"	II (52)	76
	i-C_3H_7OK (2), $(n\text{-}C_4H_9)_3B$	"	II (60)	76
	t-C_4H_9OK (1), $(n\text{-}C_4H_9)_3B$	"	II (20)	76
	$(C_2H_5)_3COK$ (2) C_2H_5B-bbn	THF	II (70)	76
	2,4,6-$(t\text{-}C_4H_9)_3C_6H_2OK$ (2), $(n\text{-}C_4H_9)_3B$	THF, 20°	II (40)	76
	2e⁻, AcONa	AcOH, 25 ± 1°	II/III (1 : 99) (90)	22
I (α-Br)	*t*-C_4H_9OK (2), $(C_2H_5)_3B$	THF	II (10)	76
			(I),  (II)	
	Hg[a]	AcOH	I (76), II (5)	25
	2e⁻, AcONa	AcOH/DMF (1 : 9)	I (80), II (1)	25

TABLE II. REDUCTION OF α,α′-DIHALO KETONES IN THE PRESENCE OF OXY OR AMINO NUCLEOPHILES (*Continued*)

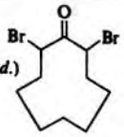
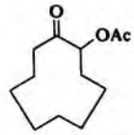
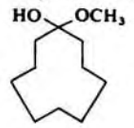
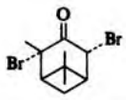
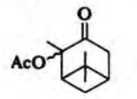
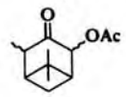
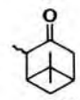
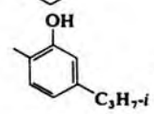
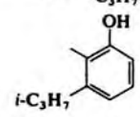
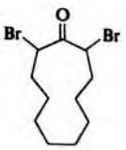
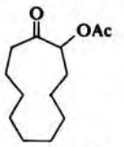
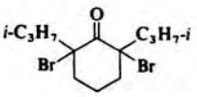
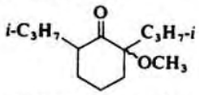
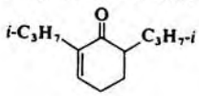
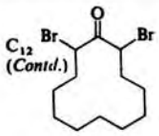
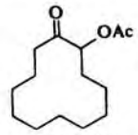
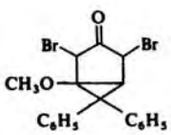
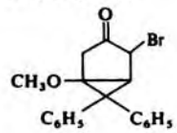
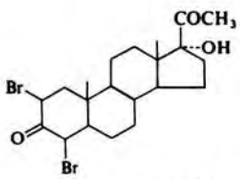
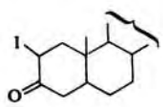
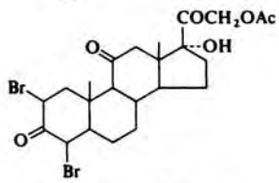
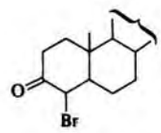
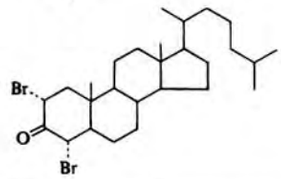
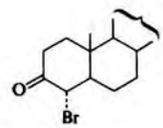
Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_{10} (*Contd.*) 	Hg	AcOH	 (15), cyclodecanone (58)	26
	2e⁻, CH_3OH (2)	CH_3CN, −10°	 (40)	38
			 (I),  (II),  (III),  (IV),  (V)	
C_{11} $C_6H_5CBr(C_2H_5)COCH_2Br$	Hg	AcOH	I (5), II (24), III (14), IV (25), V (14)	25
	2e⁻, AcONa	AcOH/DMF (1 : 9)	I (7.5), II (37), III (22), IV (17), V (11.5)	25
			$C_6H_5C(OAc)(C_2H_5)COCH_3$ (I), $C_6H_5CH(C_2H_5)COCH_2OAc$ (II), $C_6H_5CH(C_2H_5)COCH_3$ (III)	
$C_6H_5CHBrCOCBr(CH_3)_2$	Hg, AcONa	AcOH, 25°	I (29), II (8), III (20)	24
	2e⁻, AcONa	"	I (43), II (11), III (38)	24
			$C_6H_5CH(OR)COC_3H_7$-*i* (I), $C_6H_5CH_2COC(OR)(CH_3)_2$ (II), $C_6H_5CH_2COC_3H_7$-*i* (III)	
	Zn/Cu	CH_3OH, −5°, 75 min	R = CH_3, II/III (84 : 16) (−)	21
$C_6H_5CBr(CH_3)COCHBrCH_3$	Hg, AcONa	AcOH, 25°	R = Ac I (6), II (88)	24
	2e⁻, AcONa	"	R = Ac I (3), II (88), III (8)	24
			$C_6H_5C(OAc)(CH_3)COC_2H_5$ (I), $C_6H_5CH(CH_3)COCH(OAc)CH_3$ (II), $C_6H_5CH(CH_3)COC_2H_5$ (III)	
	Hg, AcONa	"	I (62), II (17), III (12)	24
	2e⁻, AcONa	"	I (64), II (15), III (14)	24
	Hg	AcOH/THF (1 : 9)	 (I) (21), cycloundecanone (II) (9)	26
	"	$AcOH/C_6H_6$ (1 : 9)	I (28), II (7)	26
C_{12} 	$Fe_2(CO)_9$	CH_3OH, 25°, 24 hr	 (I), *cis*-I/*trans*-I (2 : 1) (61),  (21)	28

TABLE II. REDUCTION OF α,α′-DIHALO KETONES IN THE PRESENCE OF OXY OR AMINO NUCLEOPHILES (*Continued*)

Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_{12} (*Contd.*) 	Hg	AcOH/THF (1 : 9)	 (I) (9), cyclododecanone (II) (8)	26
	"	AcOH/C_6H_6 (1 : 9)	I (8), II (6)	26
236 C_{15} $(C_6H_5CHBr)_2CO$			$C_6H_5CH(OR)COCH_2C_6H_5$ (I)	
	Zn/Cu	CH_3OH, −5 to 0°, 75 min	I, R = CH_3 (−)	21
	Hg, AcONa	AcOH, 25°	I, R = Ac (100)	24
	NaI	CH_3OH, reflux, 1 hr	I, R = CH_3 (57)	138
		Aq acetone, reflux, 50 min	I, R = H (93)	138
$(C_6H_5)_2CBrCOCH_2Br$			$(C_6H_5)_2C(OCH_3)COCH_3$ (I), $(C_6H_5)_2CHCH_2CO_2CH_3$ (II)	
	Zn/Cu	CH_3OH, −40 to −35°, 210 min	I (16), II (42)	39
	"	CH_3OH, 0°, 210 min	I (35), II (65)	39
	"	CH_3OH, 25°, 210 min	I (30), II (45)	39
C_{18} 	Aq HI	1 min	 (73)	30b
C_{21} 	NaI	Acetone, reflux, 2 hr	 (86)	139
	$CrCl_2$, HCl	CH_3OH/acetone, −45°, 8 min	 (21)	137
237 C_{27} 	$Cr(OAc)_2$	$AcOH/CHCl_3$, 30 min	 (20)	137, 140

[a] Ultrasonically dispersed mercury was used.
[b] An α,β-unsaturated ketone was formed as a byproduct.
[c] Sodium acetate in acetic acid was added after the electrolysis.
[d] A 1,4-diketone was also formed.
[e] Constant-current electrolysis was used.
[f] The starting material was a 55 : 45 mixture of the dibromide and the corresponding monobromide; the yields were 55% of the acetoxy ketone and 45% of the parent ketone.

TABLE III. REDUCTIVE DEHALOGENATION OF α-MONOHALO KETONES TO THE PARENT KETONES

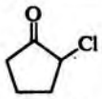
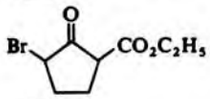
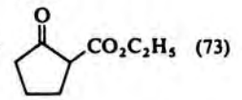
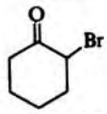
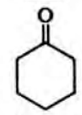
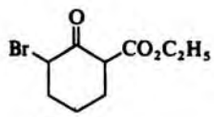
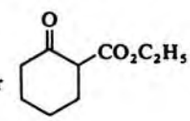
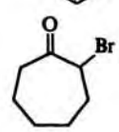
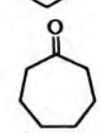
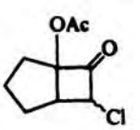
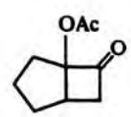
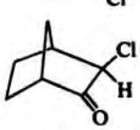
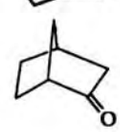
	Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_5		LiI, $BF_3O(C_2H_5)_2$	—	(100, 97)	56
C_6		$Fe(CO)_5$ (1.7)	Xylene, reflux, 6 hr	 (73)	50
		LiI, $BF_3O(C_2H_5)_2$	—	 (100)	56
C_7	n-$C_3H_7COCHBrC_2H_5$	VCl_2	Aq THF, reflux, 2–3 min	$(n\text{-}C_3H_7)_2CO$ (88)	55
	i-$C_3H_7COCBr(CH_3)_2$	$2e^-$, LiCl	Aq DMF, −5 to 25°	$(i\text{-}C_3H_7)_2CO$ (—)	20
		$Fe(CO)_5$ (2)	Xylene, reflux, 6 hr	 (68)	50
		$TiCl_3$	Aq CH_3CN, reflux, 18 hr	 (I) (86)	54
		VCl_2	Aq THF, reflux, 2–3 min	I (96)	55
		$CrCl_2$	Acetone, 15 min	 (>80)	141
		$TiCl_3$	Aq CH_3CN, reflux, 18 hr	 (80)	54
C_8	t-$C_4H_9COCBr(CH_3)_2$	$(t\text{-}C_4H_9)_2CuLi$	1. Ether, −78° 2. H_2O	t-$C_4H_9COC_3H_7$-i (51)	142
	$C_6H_5COCH_2F$	$2e^-$	C_2H_5OH, 10 min	$C_6H_5COCH_3$ (—)	13
	$C_6H_5COCH_2Cl$	LiI, $BF_3O(C_2H_5)_2$	—	$C_6H_5COCH_3$ (100)	56
	$RCOCH_2Br$ (I)			$RCOCH_3$ (II)	
	I, R = C_6H_5	Fe(II)–polyPC (1), C_6H_5SH	C_6H_6, 80°, 24 hr	II, R = C_6H_5 (16)	11, 42
		Zn/Cu, NaI, collidine	DMSO, 90°, 30 min	II, R = C_6H_5 (22)[a]	15
		$Fe(CO)_5$ (2)	Xylene, reflux, 4 hr	II, R = C_6H_5 (57)	50
		$Co_2(CO)_8$ (0.1), $C_6H_5CH_2N(C_2H_5)_3Cl$ (0.5), NaOH	H_2O/C_6H_6, 2 hr	II, R = C_6H_5 (23)[a]	51
		$CuC{\equiv}CC_6H_5$	$(CH_2OH)_2$, 140°, 16 hr	II, R = C_6H_5 (47)	143
		$TiCl_3$	Aq CH_3CN, reflux, 18 hr	II, R = C_6H_5 (100)	54
		VCl_2	Aq THF	II, R = C_6H_5 (92)	55
	I, R = p-ClC_6H_4	$Mo(CO)_6$, Al_2O_3	THF, 18 hr	II, R = p-ClC_6H_4 (83)	12
	I, R = p-BrC_6H_4	$Mo(CO)_6$	DME, 85 to 90°, 48 hr	II, R = p-BrC_6H_4 (25)[b]	43
		$Mo(CO)_6$, Al_2O_3	THF, 18 hr	II, R = p-BrC_6H_4 (71)	12
		Zn/Cu, NaI, collidine	DMSO, 70°, 30 min	II, R = p-BrC_6H_4 (22)[a]	15

TABLE III. REDUCTIVE DEHALOGENATION OF α-MONOHALO KETONES TO THE PARENT KETONES (*Continued*)

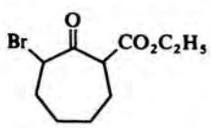
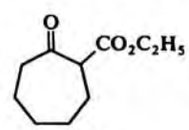
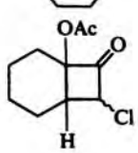
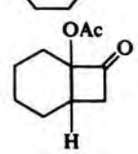
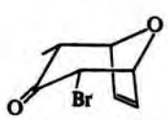
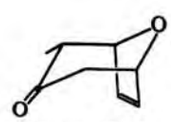
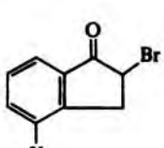
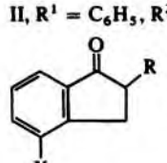
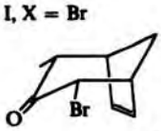
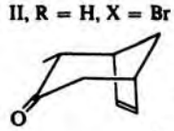
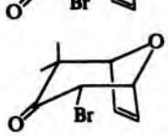
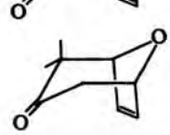
	Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_8 (*Contd.*)	I, R = p-BrC_6H_4	$Co_2(CO)_8$ (0.1), $C_6H_5CH_2N(C_2H_5)_3Cl$ (0.5), NaOH	H_2O/C_6H_6, 2 hr	II, R = p-BrC_6H_4 (69)[a]	51
		$TiCl_3$	Aq CH_3CN, reflux, 18 hr	II, R = p-BrC_6H_4 (98)	54
		VCl_2	Aq THF, 2–3 min	II, R = p-BrC_6H_4 (98)	55
		LiI, $BF_3O(C_2H_5)_2$	—	II, R = p-BrC_6H_4 (100)	56
	I, R = p-$CH_3OC_6H_4$	$Mo(CO)_6$	DME, 85 to 90°, 48 hr	II, R = p-$CH_3OC_6H_4$ (46)[b]	43
		$Mo(CO)_6$, Al_2O_3	—	II, R = p-$CH_3OC_6H_4$ (60)	12
		Zn/Cu, NaI, collidine	DMSO, 170°, 60 min	II, R = p-$CH_3OC_6H_4$ (31)[a]	15
		$Co_2(CO)_8$ (0.1), $C_6H_5CH_2N(C_2H_5)_3Cl$ (0.5), NaOH	H_2O/C_6H_6	II, R = p-$CH_3OC_6H_4$ (25)[a]	51
	I, R = p-$O_2NC_6H_4$	$Mo(CO)_6$	DME, 85 to 90°, 48 hr	II, R = p-$O_2NC_6H_4$ (20)[a]	43
		$Fe(CO)_5$ (1.9)	Xylene, reflux, 6 hr	 (54)	50
		$CrCl_2$	Acetone	 (>72)	141
		Zn/Cu, NH_4Cl	CH_3OH, 15 min	 (100)	45, 74
C_9	$R^1COCBr(R^2)CH_3$ (I)			$R^1COCH(R^2)CH_3$ (II)	
	I, R^1 = t-C_4H_9, R^2 = C_2H_5	$(t\text{-}C_4H_9)_2CuLi$	1. Ether, −78° 2. H_2O	II, R^1 = t-C_4H_9, R^2 = C_2H_5 (75)	142
	I, R^1 = $C(CH_3)_2C_2H_5$, R^2 = CH_3	"	1. Ether, −78° 2. H_2O	II, R^1 = $C(CH_3)_2C_2H_5$, R^2 = CH_3 (56)	142
	I, R^1 = C_6H_5, R^2 = H	Fe(II)–polyPC (1), C_6H_5SH	Aq CH_3OH, 80°, 30 min	II, R^1 = C_6H_5, R^2 = H (58)	11
		"	C_6H_6, 80°, 96 hr	II, R^1 = C_6H_5, R^2 = H (56)	11
	 (I)			 (II)	
	I, X = H	$Fe(CO)_5$ (2)	Xylene, reflux, 4 hr	II, R = X = H (55)	50
		1. $Fe(CO)_5$ (2) 2. D_2O	"	II, R = X = H (—)	50
		$Fe(CO)_5$ (2)	Xylene-d_8, reflux, 5 hr	II, R = D, X = H (57)	50
	I, X = Br	"	Xylene, reflux, 4 hr	II, R = H, X = Br (45)	50
		Zn, NH_4Cl	CH_3OH	 (—)	47
		Zn/Cu, NH_4Cl	CH_3OH, 1 hr	 (>90)	45, 74

TABLE III. REDUCTIVE DEHALOGENATION OF α-MONOHALO KETONES TO THE PARENT KETONES (*Continued*)

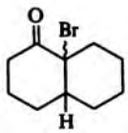
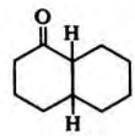
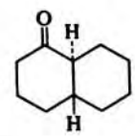
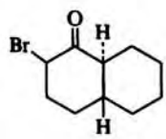
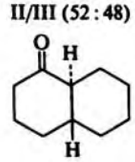
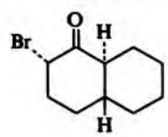
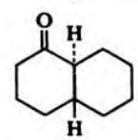
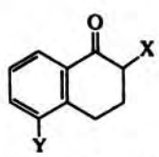
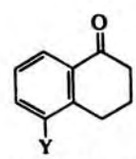
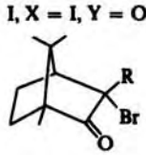
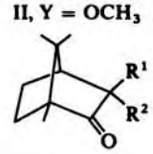
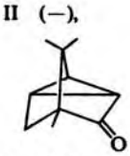
	Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_{10}	t-$C_4H_9COCBr(C_2H_5)_2$	$(t\text{-}C_4H_9)_2CuLi$	Ether, −78°	t-$C_4H_9COCH(C_2H_5)_2$ (78)	142
	$C_2H_5C(CH_3)_2COCBr(CH_3)C_2H_5$	Li	1. Ether 2. H_2O	$C_2H_5C(CH_3)_2COCH(CH_3)C_2H_5$ (97)	40
		"	1. Ether 2. D_2O	$C_2H_5C(CH_3)_2COCD(CH_3)C_2H_5$ (50)	40
	 (I)			 (II),  (III)	
	cis-I	Zn	AcOH, 4.5 hr	II/III (37 : 63) (—)	46
		Zn, collidine·HCl	Collidine, 23 hr	II/III (77 : 23) (—)	46
	trans-I	Zn	AcOH, 5.5 hr	II/III (39 : 61) (—)	46
		Zn, collidine·HCl	Collidine, 39 hr	II/III (74 : 26) (—)	46
		"	CH_3OH, 19 hr	II/III (59 : 41) (—)	46
		"	CH_3CN, 8 hr	II/III (52 : 48) (—)	46
		Zn	AcOH, 4 hr	 (—)	46
		"	AcOH, 3.5 hr	 (—)	46
	 (I)			 (II)	
	I, X = Br, Y = H	$Fe(CO)_5$ (2)	Xylene, reflux, 4 hr	II, Y = H (56)	50
	I, X = Br, Y = OCH_3	LiI, $BF_3O(C_2H_5)_2$	Ether	II, Y = OCH_3 (100, 98)	56
	I, X = I, Y = OCH_3	"	"	II, Y = OCH_3 (100)	56
	 (I)			 (II) $R^1 = R^2 = H$, (III) $R^1 = H$, $R^2 = D$, (IV) $R^1 = D$, $R^2 = H$, (V) $R^1 = R^2 = D$	
	I, R = H	Zn	AcOD, 90°, 14.5 hr	II/IV (12 : 88) (75)	144
		$Fe_2(CO)_9$	D_2O/DMF (5:95), 60°, 20 min	II/IV (13:87) (80)	28, 29
		$TiCl_3$	Aq CH_3CN, reflux, 18 hr	II (84)	54
		$(C_2H_5)_2Zn$	C_6H_6, reflux, 48 hr	II (—),  (—)	22
		LiI, $BF_3O(C_2H_5)_2$	—	II (95)	56
	I, R = D	Zn	AcOH, 90°, 14.5 hr	II/III/V (8 : 91 : 0.5) (89)	144

TABLE III. REDUCTIVE DEHALOGENATION OF α-MONOHALO KETONES TO THE PARENT KETONES (*Continued*)

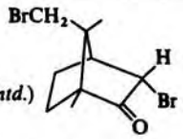
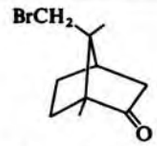
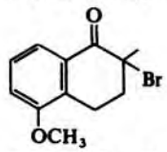
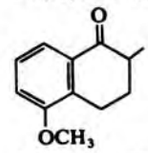
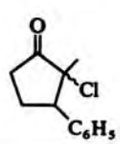
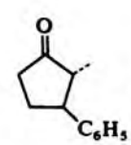
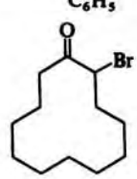
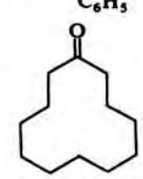
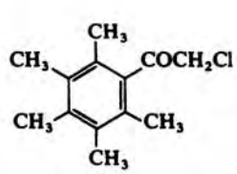
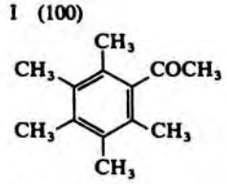
Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_{10} (*Contd.*) 	Zn, HBr(g)	CH_2Cl_2, 2.5–4 hr	 (75)	49
C_{11} t-$C_4H_9C(CH_3)_2COCBr(CH_3)_2$	$(t\text{-}C_4H_9)_2CuLi$	Ether, −78°	t-$C_4H_9C(CH_3)_2COC_3H_7$-i (61)	142
	LiI, $BF_3O(C_2H_5)_2$	—	 (100)	56
C_{12} $RCOCH_2Br$ (I)			$RCOCH_3$ (II)	
I, R = 1-adamantyl	$Mo(CO)_6$	DME, 85 to 90°, 48 hr	II, R = 1-adamantyl (14)[b]	43, 12
	$Mo(CO)_6$, Al_2O_3	—	II, R = 1-adamantyl (88)	12
	$Co_2(CO)_8$ (0.1), $C_6H_5CH_2N(C_2H_5)_3Cl$ (0.5), NaOH	H_2O/C_6H_6, 2 hr	II, R = 1-adamantyl (60)	51
I, R = 2-naphthyl	$Mo(CO)_6$, Al_2O_3	—	II, R = 2-naphthyl (80)	12
	$CO_2(CO)_8$ (0.1), $C_6H_5CH_2N(C_2H_5)_3Cl$ (0.5), NaOH	H_2O/C_6H_6	II, R = 2-naphthyl (64)	51
	$Co_2(CO)_8$ (1), $C_6H_5CH_2N(C_2H_5)_3Cl$ (0.5), NaOH	H_2O/C_6H_6	II, R = 2-naphthyl (97)	51
	Zn	AcOH	 (—)	73
	$TiCl_3$	Aq CH_3CN, reflux, 18 hr	 (I) (90)	54
	$(CH_3)_2CuLi$	1. Ether 2. H^+	I (95)	60
	"	1. Ether 2. D_2O	I-d^c (88)	60
	LiI, $BF_3O(C_2H_5)_2$	—	I (100)	56
C_{13} 	$Mo(CO)_6$	DME, 85–90°, 48 hr	 (I) (51)	43
	$(C_6H_5)_3PMo(CO)_5$	"	I (76)	43
	$W(CO)_6$	DME, 85–90°, 8 days	I (12)	43
C_{14} p-$C_6H_5C_6H_4COCH_2X$ (I)			p-$C_6H_5C_6H_4COCH_3$ (II)	
I, X = Cl	Fe(II)–PC (1), C_6H_5SH	C_6H_6, 80°, 48 hr	II (83)	42
	Fe(II)–polyPC (0.1), C_6H_5SH	Aq CH_3OH, 80°, 2 hr	II (67)	42
	Fe(II)–polyPC (1), C_6H_5SH	Aq CH_3OH, 80°, 30 min	II (92)	42
	"	C_6H_6, 80°, 48 hr	II (75)	42

TABLE III. REDUCTIVE DEHALOGENATION OF α-MONOHALO KETONES TO THE PARENT KETONES (*Continued*)

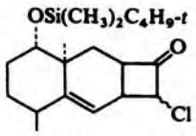
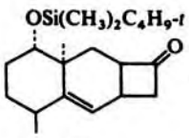
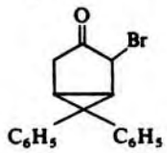
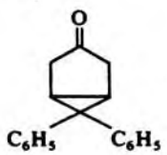
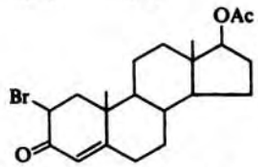
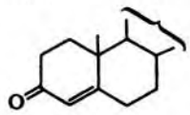
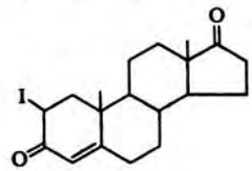
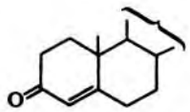
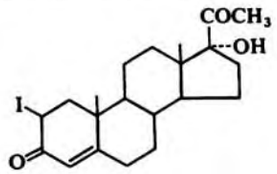
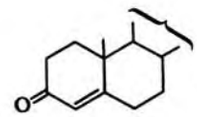
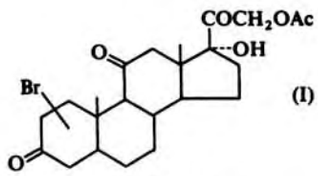
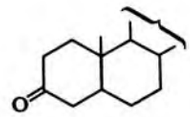
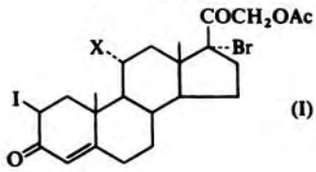
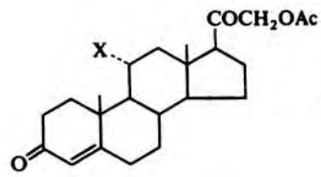
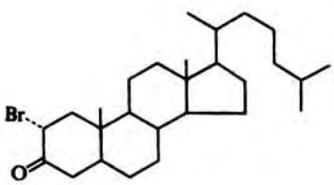
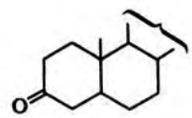
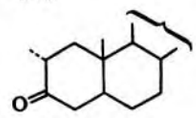
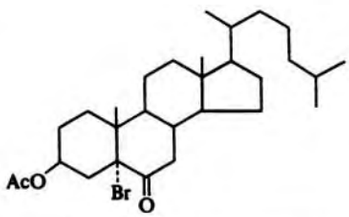
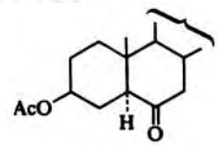
Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_{14} I, X = Cl (*Contd.*)	$Fe(acac)_3$ (1), C_6H_5SH	C_6H_6, 80°, 48 hr	II (72)	42
	$Fe(OAc)_3$ (1), C_6H_5SH	"	II (31)	42
	$FeCl_3$ (1), C_6H_5SH	"	II (11)	42
	$FeCl_3$ (1), py(2), C_6H_5SH	"	II (36)	42
	Co(III)–PC (1), C_6H_5SH	"	II (64)	42
I, X = Br	Fe(II)–PC (1), C_6H_5SH	Aq CH_3OH, 25°, 5 min	II (31)	11
	Fe(II)–PC (1), C_6H_5SH	Aq CH_3OH, 80°, 5 min	II (59)	11
	$Mo(CO)_6$	DME, 85–90°, 48 hr	II (51)[b]	43
	$Mo(CO)_6$, Al_2O_3	THF, 18 hr	II (73)	12
	$Co_2(CO)_8$ (0.1), $C_6H_5CH_2N(C_2H_5)_3Cl$ (0.5), NaOH	H_2O/C_6H_6, 2 hr	II (58)	51
	$Co_2(CO)_8$ (1), $C_6H_5CH_2N(C_2H_5)_3Cl$ (0.5), NaOH	"	II (64)	51
	VCl_2	Aq THF, reflux, 2–3 min	II (96)	55
	Fe(II)–PC (1), C_6H_5SH	C_6H_6, 80°, 24 hr	II (37)	11
	Fe(II)–polyPC (0.1), C_6H_5SH	Aq CH_3OH, 25°, 2 hr	II (67)	11
	Fe(II)–polyPC (1), C_6H_6SH	Aq CH_3OH, 25°, 30 min	II (47)	11
	"	Aq CH_3OH, 80°, 5 min	II (87)	11
	Fe(II)–polyPC (0.1), C_6H_5SH	C_6H_6, 80°, 120 hr	II (34)	11
	Fe(II)–polyPC (1), C_6H_5SH	C_6H_6, 80°, 12 hr	II (67)	11
	1. $Fe(CO)_5$ 2. D_2O	DME	p-$C_6H_5C_6H_4COCH_2D$ (–)	14
C_{18} 	Zn	AcOH	 (–)	145
	HI	Aq acetone, 10 min	 (81)	31
C_{19} 	Zn	C_2H_5OH, 3 hr	 (99)	44
	$CrCl_2$	Acetone, 10–30 min	 (I) (63)	146
	Zn	C_2H_5OH/dioxane, reflux, 7 hr	I (56)	146

TABLE III. REDUCTIVE DEHALOGENATION OF α-MONOHALO KETONES TO THE PARENT KETONES (*Continued*)

Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_{21} 	$CrCl_2$	Acetone, 5 min	 (83)	139
 (I)	NaI	Acetone, reflux, 1 hr	 (—)	137
2- and 4-Br-I				
 (I)			 (II)	
I, X = H	$CrCl_2$	Acetone, 10 min	II, X = H (ca. 15)	147
I, X = OAc	"	"	II, X = OAc (ca. 60)	147
C_{27} 	"	Acetone, 30 min	 (I) (85)	41
	Zn	AcOH, reflux, 10 hr	I (66)	41
	$(CH_3)_2CuLi$ (2)	Ether, 0°	I (80),  (12)	52
	LiI, $BF_3O(C_2H_5)_2$	Ether/C_6H_6	I (100)	56
	$(CH_3)_2CuLi$ (2)	Ether, 0°, 2 min	 (95)	48

[a] A moderate amount of $(RCOCH_2)_2$ was also obtained.
[b] The ketone $RCOCH{=}C(R)CH_3$ was also obtained.
[c] The product was 2-monodeuteriocyclododecanone.

TABLE IV. Reductive Alkylation of α-Monohalo Ketones

A. With Alkyl Halides, Alkyl Sulfonates, etc.

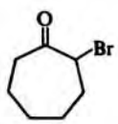
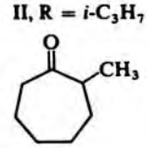
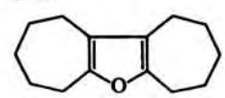
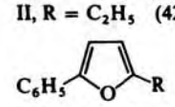
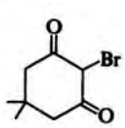
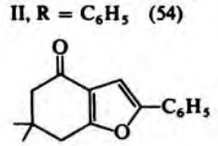
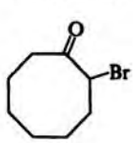
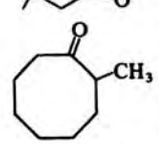
	Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_5	$CH_3COCBr(CH_3)_2$	Zn, $R^1CH(SR^2)Cl$ (I)		$CH_3COC(CH_3)_2CHR^1(SR^2)$ (II)	
		I, $R^1 = H$, $R^2 = n\text{-}C_3H_7$	$AcOC_2H_5$, 1 hr	II, $R^1 = H$, $R^2 = n\text{-}C_3H_7$ (73)	59
		I, $R^1 = CH_3$, $R^2 = CH_2CH{=}CH_2$	"	II, $R^1 = CH_3$, $R^2 = CH_2CH{=}CH_2$ (51)	59
C_7	$n\text{-}C_3H_7COCHBrC_2H_5$	Zn, $R^1CH(SR^2)Cl$ (I)		$n\text{-}C_3H_7COCH(C_2H_5)CHR^1(SR^2)$ (II)	
		I, $R^1 = H$, $R^2 = n\text{-}C_4H_9$	"	II, $R^1 = H$, $R^2 = n\text{-}C_4H_9$ (77)	59
250		I, $R^1 = H$, $R^2 = n\text{-}C_3H_7$	"	II, $R^1 = H$, $R^2 = n\text{-}C_3H_7$ (67)	59
		I, $R^1 = CH_3$, $R^2 = C_2H_5$	"	II, $R^1 = CH_3$, $R^2 = C_2H_5$ (82)	59
		I, $R^1 = CH_3$, $R^2 = CH_2CH{=}CH_2$	"	II, $R^1 = CH_3$, $R^2 = CH_2CH{=}CH_2$ (62)	59
		I, $R^1 = CH_3$, $R^2 = n\text{-}C_4H_9$	"	II, $R^1 = CH_3$, $R^2 = n\text{-}C_4H_9$ (61)	59
	$i\text{-}C_3H_7COCBr(CH_3)_2$	Li, RI (I)		$i\text{-}C_3H_7COCR(CH_3)_2$ (II)	
		I, $R = CH_3$	Ether	II, $R = CH_3$ (94)	40
		I, $R = C_2H_5$	HMPA	II, $R = C_2H_5$ (50)	40
		I, $R = i\text{-}C_3H_7$	"	II, $R = i\text{-}C_3H_7$ (20)	40
	 (I)			 (II),  (III)	
	I (0.016*M*)	Zn, CH_3I	$DMSO/C_6H_6$ (1 : 10), 8 hr	II (43), III (2)	57
	I (0.060*M*)	"	"	II (23), III (—)	57
	I (0.28*M*)	"	"	II (6), III (58), cycloheptanone (8)	57
C_8	$t\text{-}C_4H_9COCBr(CH_3)_2$	Li, RI (I)		$t\text{-}C_4H_9COCR(CH_3)_2$ (II)	40
		I, $R = CH_3$	Ether	II, $R = CH_3$ (93)	
		I, $R = C_2H_5$	HMPA	II, $R = C_2H_5$ (15)	40
		1. $(t\text{-}C_4H_9)_2CuLi$ 2. RI (I)		$t\text{-}C_4H_9COCR(CH_3)_2$ (II)	
		I, $R = CH_3$	Ether, −78°	II, $R = CH_3$ (51)	142
		I, $R = C_2H_5$	"	II, $R = C_2H_5$ (42)	142
	$C_6H_5COCH_2Br$	$CuC{\equiv}CR$ (I)		 (II)	
		I, $R = n\text{-}C_3H_7$	Neat, 140°, 5 min	II, $R = n\text{-}C_3H_7$ (29)	143
251		I, $R = C_6H_5$	$C_6H_5NO_2$, 240°, 5 min	II, $R = C_6H_5$ (54)	143
		$CuC{\equiv}CC_6H_5$	—	 (43)	143
		Zn, CH_3I	$DMSO/C_6H_6$ (1 : 10), 8 hr	 (66), cyclooctanone (7)	57
C_9	$n\text{-}C_4H_9COCHBrC_3H_7\text{-}n$	Zn, $R^1CH(SR^2)Cl$ (I)		$n\text{-}C_4H_9COCH(C_3H_7\text{-}n)CHR^1(SR^2)$ (II)	
		I, $R^1 = H$, $R^2 = n\text{-}C_3H_7$	$AcOC_2H_5$, 1 hr	II, $R^1 = H$, $R^2 = n\text{-}C_3H_7$ (58)	59
		I, $R^1 = H$, $R^2 = n\text{-}C_4H_9$	"	II, $R^1 = H$, $R^2 = n\text{-}C_4H_9$ (59)	59
		I, $R^1 = CH_3$, $R^2 = C_2H_5$	"	II, $R^1 = CH_3$, $R^2 = C_2H_5$ (55)	59

TABLE IV. REDUCTIVE ALKYLATION OF α-MONOHALO KETONES (*Continued*)

A. With Alkyl Halides, Alkyl Sulfonates, etc. (*Continued*)

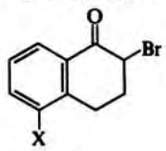
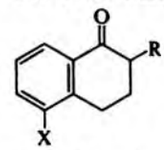
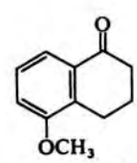
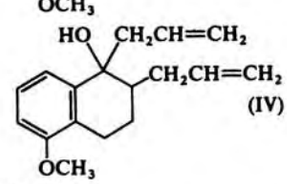
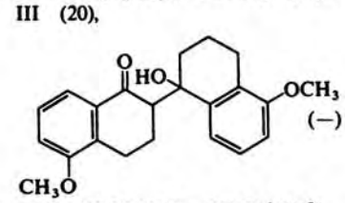
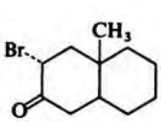
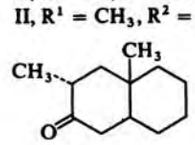
Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_9 n-$C_4H_9COCHBrC_3H_7$-n (*Contd.*)	I, $R^1 = CH_3$, $R^2 = CH_2CH{=}CH_2$	$AcOC_2H_5$, 1 hr	II, $R^1 = CH_3$, $R^2 = CH_2CH{=}CH_2$ (56)	59
	I, $R^1 = CH_3$, $R^2 = n$-C_4H_9	"	II, $R^1 = CH_3$, $R^2 = n$-C_4H_9 (53)	59
	I, $R^1 = CH_3$, $R^2 = C_6H_5$	"	II, $R^1 = CH_3$, $R^2 = C_6H_5$ (51)	59
$C_2H_5C(CH_3)_2COCBr(CH_3)_2$	1. $(t\text{-}C_4H_9)_2CuLi$ 2. CH_3I	Ether, −78°	$C_2H_5C(CH_3)_2COC_4H_9$-t (51)	142
C_{10} $C_2H_5C(CH_3)_2COCBr(CH_3)C_2H_5$	Li, CH_3I	Ether	$[C_2H_5C(CH_3)_2]_2CO$ (45)	40
 (I)			 (II)	
I, X = H	Zn, CH_3I (2)	$DMSO/C_6H_6$ (1 : 10), 8 hr	II, R = CH_3, X = H (85)	57, 58
I, X = OCH_3	Zn, CH_3I (2)	$DMSO/C_6H_6$ (1 : 10)	II, R = CH_3, X = OCH_3 (75)	58
	Zn, C_2H_5I	DMSO	II, R = C_2H_5, X = OCH_3 (15)	58
	"	$DMSO/C_6H_6$ (1 : 10)	II, R = C_2H_5, X = OCH_3 (<5)	58
	"	$HMPA/C_6H_6$ (2 : 3)	II, R = C_2H_5, X = OCH_3 (55)	58
	Zn, $CH_2{=}CHCH_2Br$ (1)	$DMSO/C_6H_6$	II, R = $CH_2CH{=}CH_2$, X = OCH_3 (75)	57
	"	"	II, R = $CH_2CH{=}CH_2$, X = OCH_3 (60),  (III) (20),  (IV) (20)	58
	Zn, $CH_2{=}CHCH_2Br$ (2)	"	IV (—)	57, 58
	Zn, $C_6H_5CH_2Br$	"	II, R = $CH_2C_6H_5$, X = OCH_3 (20), III (20),  (—)	58
C_{11} n-$C_5H_{11}COCHBrC_4H_9$-n	Zn, $R^1CH(SR^2)Cl$ (I)		n-$C_5H_{11}COCH(C_4H_9$-$n)CHR^1(SR^2)$ (II)	
	I, $R^1 = H$, $R^2 = n$-C_4H_9	$AcOC_2H_5$, 1 hr	II, $R^1 = H$, $R^2 = n$-C_4H_9 (57)	59
	I, $R^1 = CH_3$, $R^2 = C_2H_5$	"	II, $R^1 = CH_3$, $R^2 = n$-C_4H_9 (51)	59
	Zn, CH_3I	$DMSO/C_6H_6$, 5 hr	 (25)	58

TABLE IV. REDUCTIVE ALKYLATION OF α-MONOHALO KETONES (*Continued*)

A. With Alkyl Halides, Alkyl Sulfonates, etc. (*Continued*)

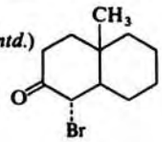
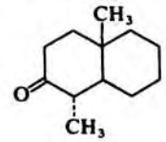
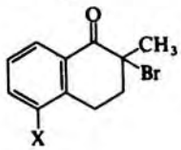
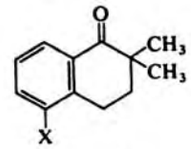
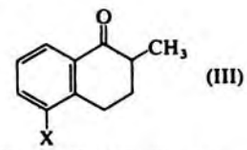
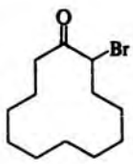
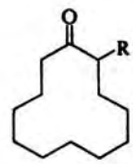
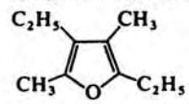
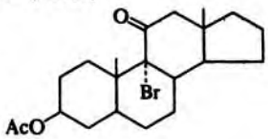
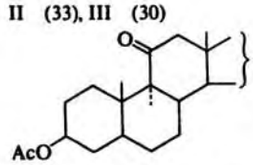
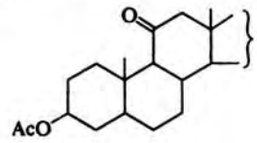
Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_{11} (*Contd.*) 	Zn, CH_3I	DMSO/C_6H_6, 5 hr	 (20)	58
 (I)			 (II),  (III)	
I, X = H	"	DMSO/C_6H_6 (1 : 10), 8 hr	X = H, II (57), III (43)	57
I, X = OCH_3	"	—	X = OCH_3, II (60), III (20)	58
C_{12} $(C_2H_5)_3CCOCBr(CH_3)C_2H_5$	Li, C_2H_5I	HMPA	$(C_2H_5)_3CCOC(C_2H_5)_2CH_3$ (14)	40
	Zn, CH_3I	DMSO/C_6H_6 (1 : 10), 8 hr	 (I)	57
			R = CH_3 (99)	
	Zn, C_2H_5OTs	14 days	I, R = C_2H_5 (13)	57
	Zn, C_2H_5I	HMPA/C_6H_6 (1 : 10)	I, R = C_2H_5 (35)	58
	$(CH_3)_2CuLi$, CH_3I	Ether	I, R = CH_3 (67)	60
C_{13} n-$C_6H_{13}COCHBrC_5H_{11}$-n (I)			n-$C_6H_{13}COCH(CH_3)C_5H_{11}$-$n$ (II),  (III)	
I (0.013*M*)	Zn, CH_2I	DMSO/C_6H_6 (1 : 10), 8 hr	II (67), III (<2)	57
I (0.051*M*)	"	"	II (61), III (2)	57
I (0.18*M*)	"	"	II (33), III (30)	57
C_{19} 	1. CH_3MgI 2. CH_3I 3. H_2SO_4 4. Ac_2O	1. THF, 20°, 15 min 2. Reflux, 45 min THF, reflux, 18 hr CH_3OH, reflux Py	 (45),  (50)	148

TABLE IV. REDUCTIVE ALKYLATION OF α-MONOHALO KETONES (*Continued*)

A. With Alkyl Halides, Alkyl Sulfonates, etc. (*Continued*)

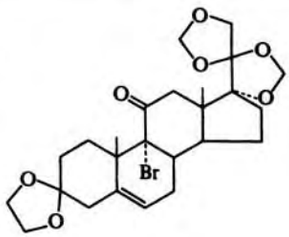
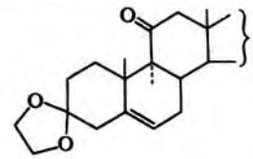
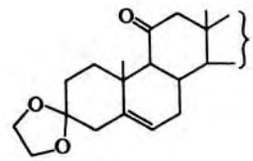
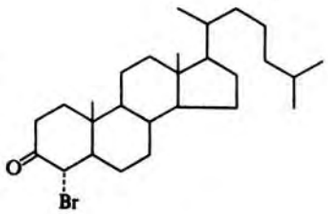
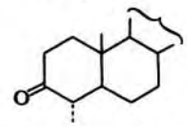
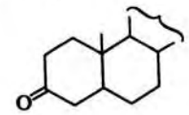
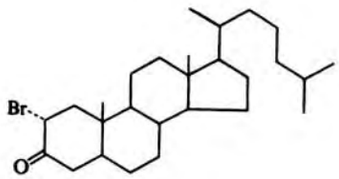
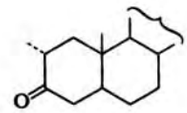
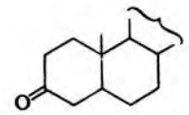
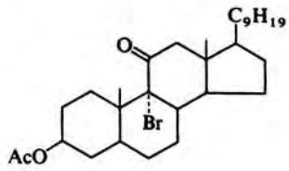
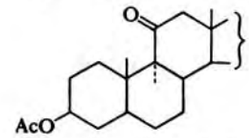
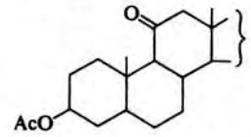
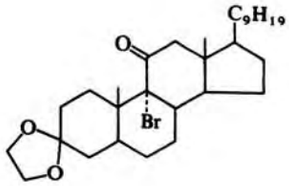
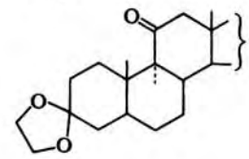
Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_{21} 	1. CH_3MgI 2. CH_3I	Ether 1. THF/ether, 15 min 2. Reflux, 1 hr	 (30),	149
			 (—)	
C_{27} 	Zn, CH_3I	DMSO/C_6H_6 (1 : 10), 8 hr	 (40),	57
			 (40)	
	$(CH_3)_2CuLi$ (2)	Ether, 0°	 (12),	52
			 (80)	
C_{28} 	1. CH_3MgI 2. CH_3I 3. H_2SO_4 4. Ac_2O	THF " CH_3OH Py	 (45),	148
			 (50)	
	1. CH_3MgI 2. CH_3I	Ether 1. THF, 20°, 30 min 2. Reflux, 1 hr	 (20)	148

TABLE IV. REDUCTIVE ALKYLATION OF α-MONOHALO KETONES (*Continued*)

B. With Olefins or Acetylenes

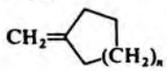
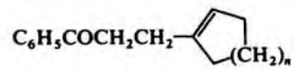
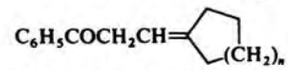
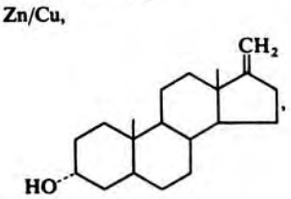
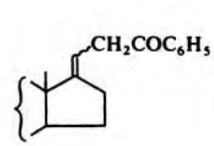
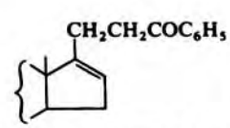
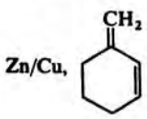
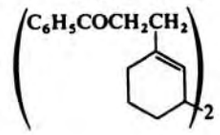
	Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_8	$C_6H_5COCH_2Br$	Zn/Cu,  (I) (0.2), NaI, $NaHCO_3$		 (II),  (III)	
		I, $n = 1$	DMSO, 60°, 1 hr	$n = 1$ II (43), III (5)	15
		I, $n = 2$	DMSO, 80°, 1 hr	II, $n = 2$ (54)	15
		I, $n = 3$	DMSO, 60°, 1 hr	$n = 3$ II (50), III (6)	15
		Zn/Cu, $C_6H_5CH{=}CH_2$ (0.5–3), NaI, collidine	DMSO, 90°, 30 min	$(C_6H_5COCH_2CH_2CHC_6H_5)_2$ (10), $(C_6H_5COCH_2)_2$ (7)	15
		Zn/Cu, $(C_6H_5)_2C{=}CH_2$, NaI, $NaHCO_3$	DMSO, 140°, 1 hr	$C_6H_5CO(CH_2)_2CH(C_6H_5)_2$ (56)	15
		Zn/Cu, $(p\text{-}CH_3OC_6H_4)_2C{=}CH_2$, NaI, $NaHCO_3$	"	$C_6H_5CO(CH_2)_2CH(C_6H_4OCH_3\text{-}p)_2$ (54)	15
		Zn/Cu, 	DMSO, 60°, 1 hr	 (23),	15
		NaI, $NaHCO_3$		 (23)	
		Zn/Cu,	—	$(C_6H_5COCH_2CH_2CR{=}CRCH_2)_2$ (II), $C_6H_5CO(CH_2)_2CR(CR{=}CH_2)CH_2$ | $C_6H_5CO(CH_2)_2CR{=}CR$ (III)	
		$CH_2{=}CRCR{=}CH_2$ (I) (0.2)	—		
		I, R = CH_3	DMSO, 60°	*cis,cis*-II/*cis,trans*-II/*trans,trans*-II (15 : 47 : 27) (55), III (7)	61
		I, R = C_6H_5	"	*cis,cis*-II/*cis,trans*-II/*trans,trans*-II (28 : 60 : 12) (73)	61
		Zn/Cu,	—	$[C_6H_5COCH_2CH_2C(CH_3){=}C{=}CR]_2$ (II), $C_6H_5CO(CH_2)_2C(CH_3)(C{\equiv}CR)CR$ ‖ $C_6H_5(CH_2)_2C(CH_3)C{=}C$ (III), $[C_6H_5COCH_2CH_2C(CH_3)C{\equiv}CR]_2$ (IV)	
		$CH_2{=}C(CH_3)C{\equiv}CR$ (I) (0.2)			
		I, R = C_2H_5	DMSO	R = C_2H_5 II/III/IV (total 78)	61
		I, R = C_6H_5	"	R = C_6H_5 II/III/IV (total 91)	61
		Zn/Cu, 	"	 (62)	61

TABLE IV. REDUCTIVE ALKYLATION OF α-MONOHALO KETONES (*Continued*)

C. With Aldehydes

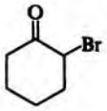
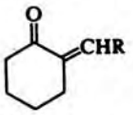
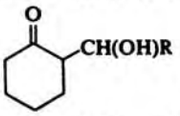
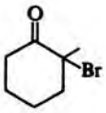
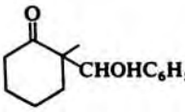
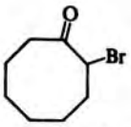
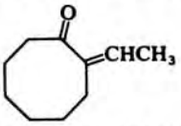
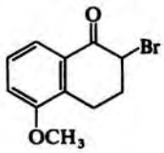
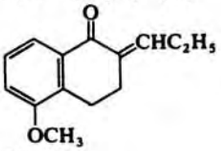
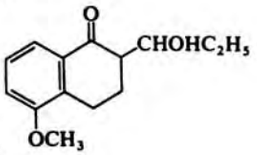
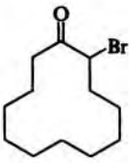
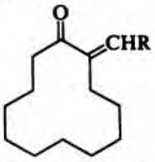
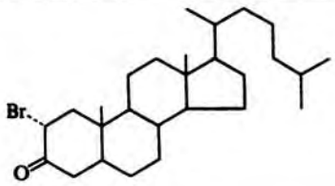
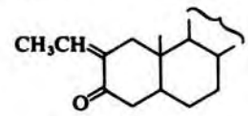
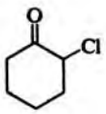
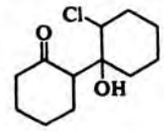
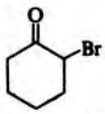
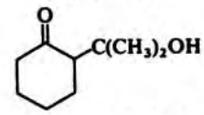
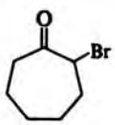
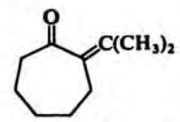
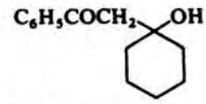
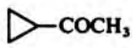
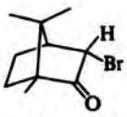
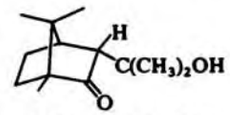
Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_6 	Zn, RCHO (I)		 (II)	
	I, R = CH_3	DMSO/C_6H_6 (1 : 10), 24 hr	II, R = CH_3 (57)[a]	57
	I, R = C_2H_5	DMSO/C_6H_6 (1 : 10)	II, R = C_2H_5 (67)[a]	57
	Zn (1.5), RCHO (I) (1.1), $(C_2H_5)_2AlCl$ (1.1), CuBr (0.05)		 (II)	
	I, R = *i*-C_3H_7	THF/hexane, −20°	II, R = *i*-C_3H_7 (93)[b]	63
	I, R = C_6H_5	"	II, R = C_6H_5 (97)[c]	63
C_7 *n*-$C_3H_7COCHBrC_2H_5$	Zn, *n*-C_3H_7CHO	—	*n*-$C_3H_7COCH(C_2H_5)CHOHC_3H_7$-*n* (49)	62
	Zn/Ag (1.5), C_6H_5CHO (1.1), $(C_2H_5)_2AlCl$ (1.1), CuBr (0.05)	THF/hexane, −20°, 55 min	 (100)[d]	63
C_8 $C_6H_5COCH_2Br$	Zn (1.5), RCHO (I) (1.1), $(C_2H_5)_2AlCl$ (1.1), CuBr (0.05)		$C_6H_5COCH_2CHOHR$ (II)	
	I, R = *i*-C_3H_7	THF/hexane, −20°	II, R = *i*-C_3H_7 (92)	63
	I, R = C_6H_5	"	II, R = C_6H_5 (95)	63
	I, R = $CH{=}CHC_6H_5$	"	II, R = $CH{=}CHC_6H_5$ (92)	63
	Zn, CH_3CHO	DMSO/C_6H_6 (1 : 10), 24 hr	 (57)[a]	57
C_9 *n*-$C_4H_9COCHBrC_3H_7$-*n*	Zn, RCHO (I)		*n*-$C_4H_9COCH(C_3H_7$-*n*$)CHOHR$ (II)	
	I, R = CH_3		II, R = CH_3 (63)	62
	I, R = *n*-C_3H_7		II, R = *n*-C_3H_7 (58)	62
C_{10} 	Zn, RCHO (I)		 (II)	
	I, R = C_2H_5	DMSO/C_6H_6 (1 : 10)	II (95)[a]	57
	"	DME, 3 hr	II +  (total 95)	58
	"	DME, 18 hr	II (70)[a]	58
C_{12} 	Zn, RCHO (I)		 (II)	
	I, R = CH_3	DMSO/C_6H_6 (1 : 10)	II, R = CH_3 (70)[a]	57
	I, R = C_2H_5	"	II, R = C_2H_5 (85)[a]	57

TABLE IV. REDUCTIVE ALKYLATION OF α-MONOHALO KETONES (*Continued*)

C. With Aldehydes (Continued)

	Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_{27}		Zn, CH_3CHO	$DMSO/C_6H_6$ (1 : 10)	 (97)	57, 58

D. With Ketones

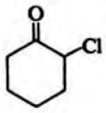
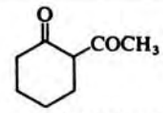
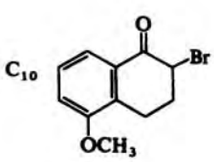
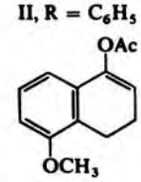
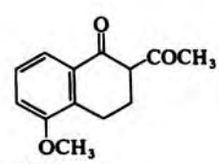
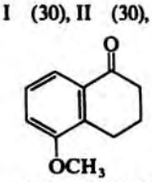
C_6		$(CH_3)_2CuLi$	Ether, −40°	 (I) (37), cyclohexanone (II) (38)	65
			Ether, −10°	I (10), II (65)	65
		Zn/Ag, $(CH_3)_2CO$, $(C_2H_5)_2AlCl$, CuBr (0.05)	THF/hexane, −20°	 (75)	63
C_7	n-$C_3H_7COCHBrC_2H_5$	Zn, R_2CO (I)		n-$C_3H_7COCH(C_2H_5)COHR_2$ (II)	
		I, R = C_2H_5		II, R = C_2H_5 (73)	62
		I, R_2 = $(CH_2)_5$		II, R_2 = $(CH_2)_5$ (57)	62
		Zn, $(CH_3)_2CO$	$DMSO/C_6H_6$ (1 : 10)	 (16)[a]	57
C_8	$C_6H_5COCH_2Br$	Zn (1.5), cyclohexanone (1.1), $(C_2H_5)_2AlCl$ (1.1), CuBr (0.05)	THF/hexane, −20°	 (83)	63
C_9	n-$C_4H_9COCHBrC_3H_7$-n	Zn, 	—	n-$C_4H_9COCH(C_3H_7$-$n)COHCH_3$ (70)	62
C_{10}		Zn (1.5), $(CH_3)_2CO$ (1.1), $(C_2H_5)_2AlCl$ (1.1), CuBr (0.05)	THF/hexane	 (79)	63
C_{11}	n-$C_5H_{11}COCHBrC_4H_9$-n	Zn, $C_6H_5COCH_3$		n-$C_5H_{11}COCH(C_4H_9$-$n)C(OH)$-$(CH_3)C_6H_5$ (53)	62

E. With Acyl Chlorides or Acid Anhydrides

C_3	CH_3COCH_2Cl	$Na_2Fe(CO)_4$, RCOCl (I) (1), Py		$CH_3C(OCOR)=CH_2$ (II)	
		I, R = $CH_2CH(CH_3)_2$	THF, 25°, 10 min	II, R = $CH_2CH(CH_3)_2$ (97)	66
		I, R = p-$CH_3OC_6H_4$	"	II, R = p-$CH_3OC_6H_4$ (71)	66
C_5	$C_2H_5COCHBrCH_3$	Zn, RCOCl (I) (1.5)		$C_2H_5COCH(COR)CH_3$ (II)	
		I, R = CH_3	$AcOC_2H_5$	II, R = CH_3 (46)	64
		I, R = n-C_3H_7	"	II, R = n-C_3H_7 (49)	64
		I, R = C_6H_5	"	II, R = C_6H_5 (51)	64

TABLE IV. REDUCTIVE ALKYLATION OF α-MONOHALO KETONES (*Continued*)

E. With Acyl Chlorides or Acid Anhydrides (*Continued*)

	Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_6		$(CH_3)_2CuLi$, CH_3COCl	Ether, −10°	 (50), cyclohexanone (50)	65
264 C_8	$C_6H_5COCH_2Cl$	$Na_2Fe(CO)_4$, RCOCl (I) (1), Py		$C_6H_5C(OCOR)=CH_2$ (II)	
		I, R = CH_3	THF, 25°, 10 min	II, R = CH_3 (88)	66
		I, R = i-C_3H_7	"	II, R = i-C_3H_7 (79)	66
		I, R = n-C_4H_9	"	II, R = n-C_4H_9 (74)	66
		I, R = t-C_4H_9	"	II, R = t-C_4H_9 (87)	66
		I, R = C_6H_5	"	II, R = C_6H_5 (78)	66
C_9	n-$C_4H_9COCHBrC_3H_7$-n	Zn, RCOCl (I) (1.5)		n-$C_4H_9COCH(COR)C_3H_7$-n (II)	
		I, R = CH_3	$AcOC_2H_5$	II, R = CH_3 (56)	64
		I, R = n-C_3H_7	"	II, R = n-C_3H_7 (53)	64
		I, R = n-C_4H_9	"	II, R = n-C_4H_9 (48)	64
		I, R = C_6H_5	"	II, R = C_6H_5 (55)	64
C_{10}				 (I),	
				 (II)	
		Zn, CH_3COCl	DME	I (60)	58
		Zn, Ac_2O	"	I (30), II (30),	58
				 (40)	58
C_{11}	n-$C_5H_{11}COCHBrC_4H_9$-n	Zn, RCOCl (I) (1.5)		n-$C_5H_{11}COCH(COR)C_4H_9$-n (II)	
265		I, R = CH_3	$AcOC_2H_5$	II, R = CH_3 (52)	64
		I, R = n-C_3H_7	"	II, R = n-C_3H_7 (50)	64
		I, R = n-C_4H_9	"	II, R = n-C_4H_9 (45)	64
		I, R = C_6H_5	"	II, R = C_6H_5 (47)	64

F. With α-Bromo Ketones (*Dimerization*)

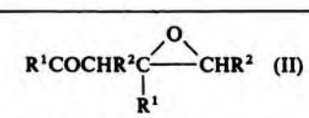
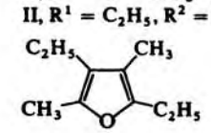
C_4	$R^1COCHBrR^2$ (I)			 (II)	
	I, $R^1 = R^2 = CH_3$	$Ni(CO)_4$ (0.6)	DMF, 30°, 5 hr	II, $R^1 = R^2 = CH_3$ (70)	67
	I, $R^1 = C_2H_5$, R^2 = H	"	"	II, $R^1 = C_2H_5$, R^2 = H (52)	67
C_5	$C_2H_5COCHBrCH_3$	Mg	Ether	 (I) (−)	150

TABLE IV. REDUCTIVE ALKYLATION OF α-MONOHALO KETONES (*Continued*)

F. With α-Bromo Ketones (Dimerization) (Continued)

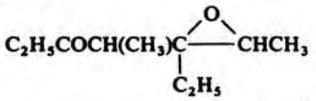
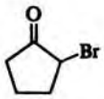
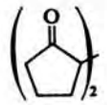
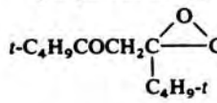
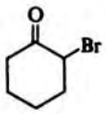
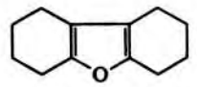
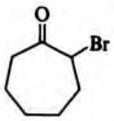
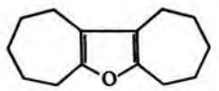
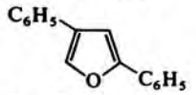
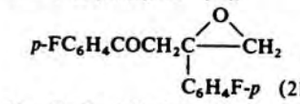
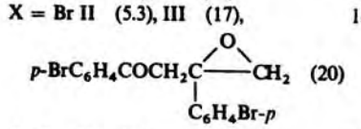
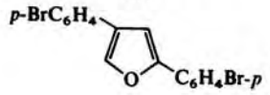
Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_5 $C_2H_5COCHBrCH_3$ (*Contd.*)	Zn	—	I (47), $(C_2H_5)_2CO$ (1)	58
	"	—	I (98)	57
	$Ni(CO)_4$ (0.6)	DMF, 30°, 5 hr	 (84)	67
	Zn	DMSO/C_6H_6 (1 : 10)	 (18), cyclopentanone (3)	58
C_6 t-$C_4H_9COCH_2Br$	$Ni(CO)_4$ (0.6)	DMF, 30°, 5 hr	 (61)	67
	Zn	DMSO/C_6H_6 (1 : 10), 8 hr	 (62), cyclohexanone (6)	57
C_7 	"	"	 (58), cycloheptanone (8)	57
C_8 p-$XC_6H_4COCH_2Br$ (I)			$(p\text{-}XC_6H_4COCH_2)_2$ (II), p-$XC_6H_4COCH_3$ (III)	
I, X = H	Zn/Cu or Zn, NaI, collidine	DMSO, 90°, 30 min	X = H II (32), III (22)	15
	Zn/Cu, NaI, collidine, styrene (0.5–3)	"	II, X = H (7), $[C_6H_5COCH_2CH_2CH(C_6H_5)]_2$ (10)	15
	$Fe(CO)_5$ (0.57)	DME, reflux	X = H II (35), III (25)	14
	$Ni(CO)_4$ (1.2)	THF, 50°, 10 hr	II, X = H (28)	68
	"	DMF, 10 hr	 (40)	68
I, X = F	$Fe(CO)_5$ (0.57)	1. DME, reflux 2. 140°, 5 min	X = F II (trace), III (34),  (21)	14
I, X = Br	Zn	DMSO/C_6H_6 (1/10)	X = Br II (30), III (15)	58
	Zn/Cu, NaI, collidine	DMSO, 70°, 30 min	X = Br II (32), III (22)	15
	$Fe(CO)_5$ (0.57)	1. DME, reflux 2. 140°, 15 min	X = Br II (5.3), III (17),  (20)	14
	$Ni(CO)_4$ (1.2)	THF, 50°, 10 hr	II, X = Br (45)	68
	"	DMF, 10 hr	 (92)	68

TABLE IV. REDUCTIVE ALKYLATION OF α-MONOHALO KETONES (*Continued*)

F. With α-Bromo Ketones (Dimerization) (Continued)

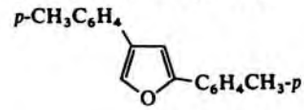
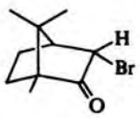
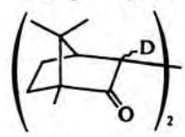
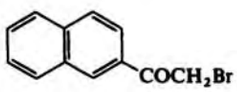
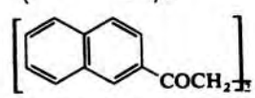
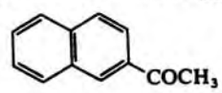
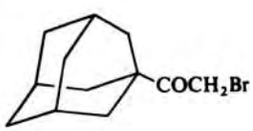
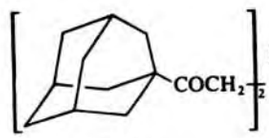
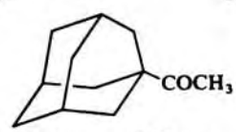
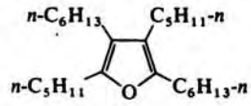
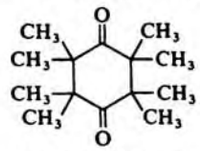
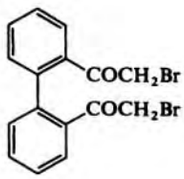
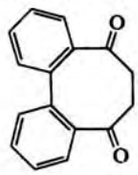
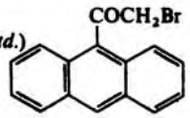
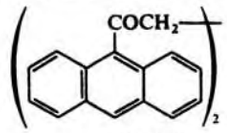
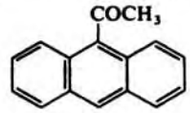
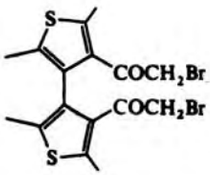
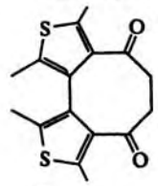
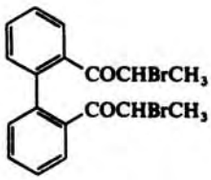
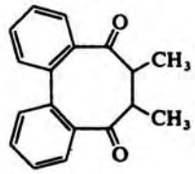
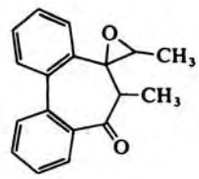
	Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_8 (*Contd.*)	I, X = OCH_3	Zn/Cu, NaI, collidine	DMSO, 170°, 60 min	X = OCH_3 II (25), III (31)	15
		$Fe(CO)_5$ (0.57)	1. DME, reflux 2. 140°, 5 min	X = OCH_3 II (51), III (25)	14
C_9	p-$CH_3C_6H_4COCH_2Br$	$Ni(CO)_4$ (1.2)	THF, 50°, 10 hr	$(p\text{-}CH_3C_6H_4COCH_2)_2$ (15)	68
		"	DMF, 10 hr	 (50)	68
	$C_6H_5COCHBrCH_3$	$Fe(CO)_5$ (0.57)	1. DME, reflux 2. 140°, 5 min	$(C_6H_5COCHCH_3)_2$ (46), $C_6H_5COC_2H_5$ (31)	14
C_{10}	$C_6H_5COCBr(CH_3)_2$	"	—	$[C_6H_5COC(CH_3)_2]_2$ (47), $C_6H_5COC_3H_7$-i (14)	14
		$Co_2(CO)_8$ (0.05), $C_6H_5CH_2N(C_2H_5)_3Cl$, $NaOD/D_2O$	—	 (—)	51
C_{12}		$Fe(CO)_5$ (0.57)	1. DME, reflux 2. 140°, 5 min	 (6),  (24)	14
		"	"	 (4.6),  (13)	14
C_{13}	n-$C_6H_{13}COCHBrC_5H_{11}$-n (0.18M)	Zn	DMSO/C_6H_6 (1/10), 8 hr	 (30)	57
C_{14}	$[(CH_3)_2CCOCBr(CH_3)_2]_2$	Zn/Cu, $LiBF_4$	DME, 24 hr	 (3.6)	151
	p-$C_6H_5C_6H_4COCH_2Br$			$(p\text{-}C_6H_5C_6H_4COCH_2)_2$ (I), p-$C_6H_5C_6H_4COCH_3$ (II)	
		$Fe(CO)_5$ (0.57)	1. DME, reflux 2. 140°, 5 min	I (63), II (30)	14
		"	$CH_3CON(CH_3)_2$	I (—), II (—)	14
		"	$[(CH_3)_2N]_2CO$	I (—), II (—)	14
C_{16}		Zn/Cu, NaI, $NaHCO_3$ (2)	DMSO, 60°, 30 min	 (48)	152

TABLE IV. REDUCTIVE ALKYLATION OF α-MONOHALO KETONES (*Continued*)

F. With α-Bromo Ketones (Dimerization) (Continued)

Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_{16} (*Contd.*) 	$Fe(CO)_5$ (0.57)	1. DME, reflux 2. 140°, 5 min	 (15),  (13)	14
	Zn/Cu, NaI, $NaHCO_3$ (2)	DMSO, 70°, 30 min	 (56)	152
C_{18} 	"	"	 (64),  (17)	152

G. With α,β-Unsaturated Ketones

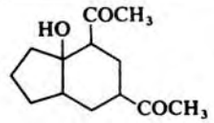
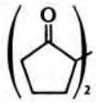
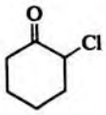
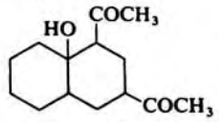
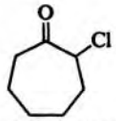
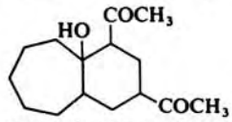
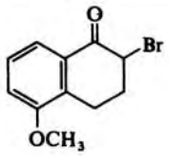
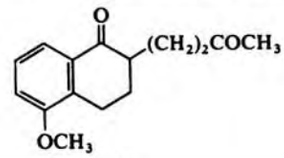
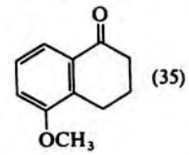
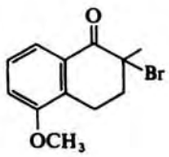
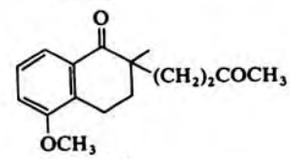
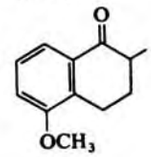
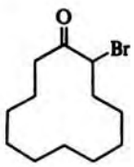
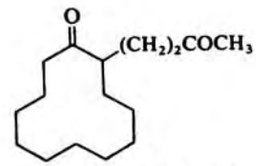
C_5	$(CH_3)_2CuLi$, MVK	Ether	 (—),  (—)	65
C_6 	"	"	 (50)	65
C_7 	"	"	 (—)	65
C_9 $(CH_3)_2CHCH_2COCHBrC_3H_7$-*i*	Mg, $C_6H_5COCH{=}CHC_6H_5$	"	$(CH_3)_2CHCH_2COCHC_3H_7$-*i* | $C_6H_5COCH_2CHC_6H_5$ (—)	69

TABLE IV. REDUCTIVE ALKYLATION OF α-MONOHALO KETONES (*Continued*)

G. With α,β-Unsaturated Ketones (Continued)

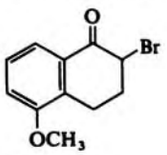
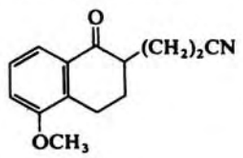
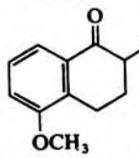
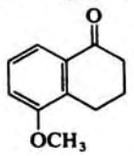
	Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_{10}		Zn, MVK	DME	 (17),  (35)	58
C_{11}		"	"	 (25),	58
		"	"	 (10)	
C_{12}		"	"	 (20), cyclododecanone (45)	58

H. With Arenesulfenyl Chlorides

C_5	$CH_3COCBr(CH_3)_2$	Zn, ArSCl (I), $HgCl_2$ (cat)		$CH_3COC(SAr)(CH_3)_2$ (II)	
		I, Ar = C_6H_5	Ether, reflux	II, Ar = C_6H_5 (71)	70
		I, Ar = p-ClC_6H_4	"	II, Ar = p-ClC_6H_4 (68)	70
		I, Ar = p-n-$C_4H_9C_6H_4$	"	II, Ar = p-n-$C_4H_9C_6H_4$ (77)	70
	$C_2H_5COCHBrCH_3$	Zn, C_6H_5SCl, $HgCl_2$ (cat)	"	$C_2H_5COCH(SC_6H_5)CH_3$ (70)	70
C_9	n-$C_4H_9COCHBrC_3H_7$-i	"	"	n-$C_4H_9COCH(SC_6H_5)C_3H_7$-$i$ (69)	70
	$C_6H_5COCHBrCH_3$	Zn, ArSCl (I), $HgCl_2$ (cat)		$C_6H_5COCH(SAr)CH_3$ (II)	
		I, Ar = C_6H_5	"	II, Ar = C_6H_5 (73)	70
		I, Ar = p-ClC_6H_4	"	II, Ar = p-ClC_6H_4 (72)	70
C_{10}	$C_6H_5COCHBrC_2H_5$	Zn, C_6H_5SCl, $HgCl_2$ (cat)	"	$C_6H_5COCH(SC_6H_5)C_2H_5$ (75)	70
	$C_6H_5COCBr(CH_3)_2$	Zn, ArSCl (I), $HgCl_2$ (cat)		$C_6H_5COC(SAr)(CH_3)_2$ (II)	
		I, Ar = C_6H_5	"	II, Ar = C_6H_5 (71)	70
		I, Ar = p-ClC_6H_4	"	II, Ar = p-ClC_6H_4 (73)	70
C_{11}	$C_6H_5COCHBrC_3H_7$-n	Zn, ArSCl (I), $HgCl_2$ (cat)		$C_6H_5COCH(SAr)C_3H_7$-n (II)	
		I, Ar = C_6H_5	"	II, Ar = C_6H_5 (68)	70
		I, Ar = p-ClC_6H_4	"	II, Ar = p-ClC_6H_4 (71)	70

TABLE IV. REDUCTIVE ALKYLATION OF α-MONOHALO KETONES (*Continued*)

1. With Miscellaneous Substrates

Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_{10} 	Zn, $CH_2{=}CHCN$	DME	 (4)	58
	Zn, CO_2	1. DMSO/C_6H_6 (1 : 10) 2. CH_3OH, H^+	 (I) R = CH_3 (—)	58
	Zn, $(CH_3O)_2CO$	DMSO/C_6H_6 (1 : 10)	I, R = CH_3 (5)	58
	Zn, $(C_2H_5O)_2POCO_2C_2H_5$	1. DME 2. C_2H_5OH, H_2SO_4	I, R = C_2H_5 (50),  (40)	58

[a] Product was obtained by treatment of the crude aldol with *p*-toluenesulfonic acid in benzene.
[b] Ratio of *erythro* to *threo* isomer was not determined.
[c] A 1 : 1 mixture of *erythro* and *threo* isomers was obtained.
[d] A 4 : 1 mixture of *erythro* and *threo* isomers was obtained.

TABLE V. REACTIONS OF α,α-DIHALO KETONES

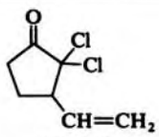
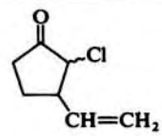
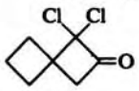
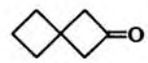
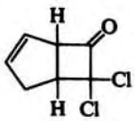
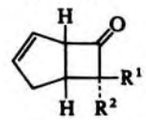
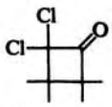
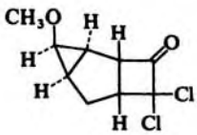
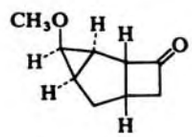
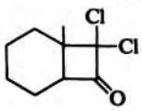
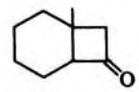
	Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_7		$(CH_3)_2CuLi$	THF or ether, −78°	 (—)	73
		Zn, NH_4Cl	CH_3OH	 (poor)	153
		Zn	—	 (I)	154
		"	AcOH	$R^1 = H, R^2 = Cl$ (—) I, $R^1 = R^2 = H$ (56)	154
C_8		"	AcOH, reflux, 17 hr	(66)	155
		"	AcOH, 40°, 1 hr	 (78)	156
C_9		"	AcOH, reflux	 (I),	155

TABLE V. REACTIONS OF α,α-DIHALO KETONES (*Continued*)

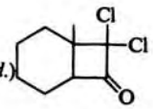
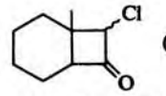
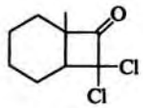
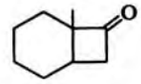
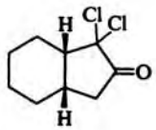
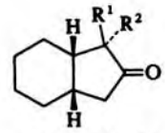
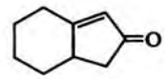
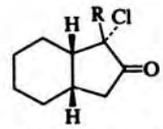
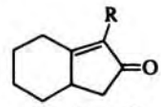
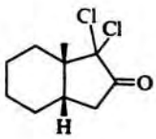
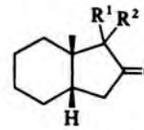
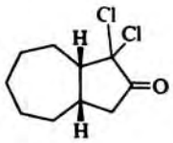
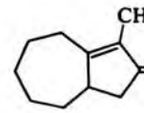
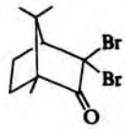
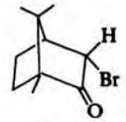
Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_9 (*Contd.*) 	Zn	AcOH, reflux	 (II) I/II (70:9) (90)	
	"	"	 (90)	155
	"	AcOH, 70°	 (I) $R^1 = R^2 = H$ (90)	73
	$(CH_3)_2CuLi$ (1-2)	1. THF, −78° 2. AcOH or H_2O	I, $R^1 = H$, $R^2 = Cl$ (ca. 100)	73
	1. $(CH_3)_2CuLi$ (1-2) 2. $LiI \cdot 2H_2O$	THF or ether, −78° HMPA, −78° to room temp.	 (60)	73
	1. $(CH_3)_2CuLi$ (1-2) 2. CH_3I	THF, −78° HMPA, −78 to −40°	 (I) $R = CH_3$ (78)	73
	1. $(CH_3)_2CuLi$ (1-2) 2. $CH_2{=}CHCH_2Br$	THF, −78 to −40° HMPA, −78 to −40°	I, $R = CH_2CH{=}CH_2$ (71)	73
	1. $(CH_3)_2CuLi$ (1-2) 2. CH_3I	THF, −78° HMPA, −78° to room temp.	 (I) $R = CH_3$ (78)	73
	1. $(CH_3)_2CuLi$ (1-2) 2. $CH_2{=}CHCH_2I$	THF, −78° HMPA, −78° to room temp.	I, $R = CH_2CH{=}CH_2$ (68)	73
C_{10} 	Zn	Aq AcOH	 (I) $R^1 = H$, $R^2 = Cl$ (67)	71
	1. $(CH_3)_2CuLi$ (1-2) 2. CH_3I	THF, −78° HMPA, −78 to −40°	I, $R^1 = CH_3$, $R^2 = Cl$ (70)	73
	1. $(CH_3)_2CuLi$ (1-2) 2. CH_3I	THF, −78° HMPA, −78° to room temp.	 (65)	73
 (I)			 (II), (III)	

TABLE V. REACTIONS OF α,α-DIHALO KETONES (*Continued*)

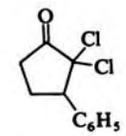
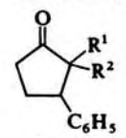
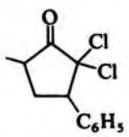
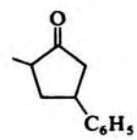
Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_{10} (*Contd.*)	$(C_2H_5)_2Zn$	C_6H_6	II (100)	16
	"	C_6H_6, reflux, 22 hr	II (10), III (80)	16
	$(C_2H_5)_2Zn$ (0.5)	"	I (5), II (11), III (60)	16
	Zn	DMF	III (ca. 75)	16
	Zn/Cu	"	III (ca. 35)	16
C_{11} 	Zn	Aq AcOH	 (I) $R^1 = H, R^2 = Cl$ (>64)	71, 72
	"	AcOH, 70°, 15 hr	I, $R^1 = R^2 = H$ (82)	71
	$(CH_3)_2CuLi$ (1-2)	THF or ether, −78°	I, $R^1 = H, R^2 = Cl$ (—)	73
	1. $(CH_3)_2CuLi$ (1-2) 2. CH_3I	" HMPA, −78 to −40°	I, $R^1 = CH_3, R^2 = H$ (>49)	73
C_{12} 	Zn	AcOH, 70°	 (74)	73

TABLE VI. REDUCTIVE ALKYLATION OF α,α′-DIHALO KETONES

A. α-Monoalkylation

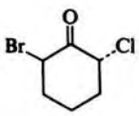
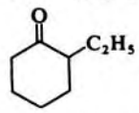
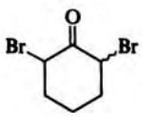
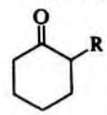
	Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_5	$(CH_3CHBr)_2CO$	$(CH_3)_2CuLi$	Pentane, −50°, 30 min	$C_2H_5COC_3H_7$-*i* (54)	60, 78
	$(CH_3)_2CBrCOCH_2Br$	$R(t\text{-}C_4H_9)CuLi$ (I)		$i\text{-}C_3H_7COCH_2R$ (II), $(CH_3)_2CRCOCH_3$ (III)	
		I, R = $n\text{-}C_4H_9$	THF, −78°, 30 min	R = $n\text{-}C_4H_9$ II (55), III (25)	60, 78
		I, R = $CH(CH_3)C_2H_5$	"	R = $CH(CH_3)C_2H_5$ II (42), III (8)	60, 78
		I, R = $t\text{-}C_4H_9$	THF, −78°,	R = $t\text{-}C_4H_9$ II (56), III (10)	60, 78
C_6		$t\text{-}C_4H_9OK$ (2), $(C_2H_5)_3B$	THF, 20°, 2 hr	 (31), cyclohexanone (37)	76
	 (I)	R^1R^2CuLi (II)		 (III)	
	cis- and *trans*-I	II, $R^1 = n\text{-}C_4H_9$, $R^2 = n\text{-}C_4H_9$	Ether, −78°, 30 min	III, R = $n\text{-}C_4H_9$ (81)	78, 60
		II, $R^1 = n\text{-}C_4H_9$, $R^2 = t\text{-}C_4H_9O$	THF, −78°, 30 min	III, R = $n\text{-}C_4H_9$ (77), cyclohexanone (—)	78, 60
		II, $R^1 = CH(CH_3)C_2H_5$ $R^2 = CH(CH_3)C_2H_5$	Ether, −78°, 30 min	III, R = $CH(CH_3)C_2H_5$ (38)	78, 60
		II, $R^1 = CH(CH_3)C_2H_5$ $R^2 = t\text{-}C_4H_9O$	THF, −78°, 30 min	III, R = $CH(CH_3)C_2H_5$ (75), cyclohexanone (—)	78, 60
		II, $R^1 = t\text{-}C_4H_9$ $R^2 = CH_3$	Ether, −78°, 30 min	III, R = $t\text{-}C_4H_9$ (20)	78, 60

TABLE VI. REDUCTIVE ALKYLATION OF α,α′-DIHALO KETONES (*Continued*)

A. α-Monoalkylation (Continued)

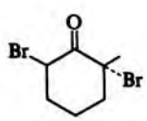
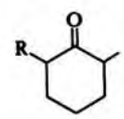
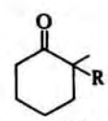
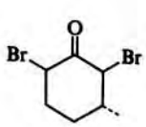
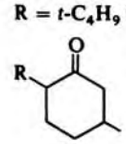
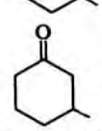
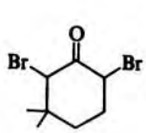
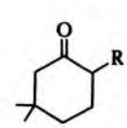
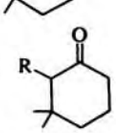
	Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_6 (*Contd.*)		II, $R^1 = t\text{-}C_4H_9$, $R^2 = t\text{-}C_4H_9$	Ether, −78°, 30 min	III, R = $t\text{-}C_4H_9$ (18)	78, 60
		II, $R^1 = t\text{-}C_4H_9$, $R^2 = t\text{-}C_4H_9O$	THF, −78°, 30 min	III, R = $t\text{-}C_4H_9$ (65), cyclohexanone (—)	78, 60
		II, $R^1 = t\text{-}C_4H_9$, $R^2 = C_6H_5S$	"	III, R = $t\text{-}C_4H_9$ (63)	78, 60
	cis-I	CH_3MgI (2)	Ether, 25°, 30 min	III, R = CH_3 (<10)	78
		II, $R^1 = R^2 = CH_3$	Ether, −78°, 30 min	III, R = CH_3 (70)	60
		"	1. Ether, −78°, 5 min 2. 25°, 1 hr	III, R = CH_3 (95)	78, 60
		$t\text{-}C_4H_9OK$ (2), $(C_2H_5)_3B$	THF, 20°, 2 hr	III, R = C_2H_5 (76), cyclohexanone (12)	76, 77
	trans-I	CH_3MgI	Ether, −78°, 30 min	III, R = CH_3 (<1)	60
		$(CH_3)_2CuLi$	"	III, R = CH_3 (98)	78, 60
C_7	$n\text{-}C_4H_9CHBrCOCH_2Br$	$R(t\text{-}C_4H_9O)CuLi$ (I)		$n\text{-}C_5H_{11}COCH_2R$ (II), $n\text{-}C_4H_9CHRCOCH_3$ (III)	
		I, R = $n\text{-}C_4H_9$	THF, −78°, 30 min	R = $n\text{-}C_4H_9$ II (37), III (11)	78, 60
		I, R = $CH(CH_3)C_2H_5$	"	R = $CH(CH_3)C_2H_5$ II (49), III (8)	78, 60
		I, R = $t\text{-}C_4H_9$	THF, −78°	R = $t\text{-}C_4H_9$ II (53), III (6)	78, 60
	$[(CH_3)_2CBr]_2CO$	CH_3MgI (2)	Ether, 25°, 30 min	$i\text{-}C_3H_7COC_4H_9\text{-}t$ (I) (70)	78
		$(CH_3)_2CuLi$ (2)	Pentane, −50°, 30 min	I (54)	78, 60
		1. $(CH_3)_2CuLi$ 2. D_2O	Ether, 0°	$(CH_3)_2CDCOC_4H_9\text{-}t$ (87)	80
		$R(t\text{-}C_4H_9O)CuLi$ (I)		 (II),  (III)	
		I, R = $n\text{-}C_4H_9$	THF, −78°, 30 min	R = $n\text{-}C_4H_9$ II (48), III (16)	78, 60
		I, R = $CH(CH_3)C_2H_5$	"	R = $CH(CH_3)C_2H_5$ II (61), III (8)	78, 60
		I, R = $t\text{-}C_4H_9$	"	R = $t\text{-}C_4H_9$ II (31), III (2)	78, 60
		R_3COK (I) (2), R_3B (II)		 (III),  (IV)	
		I, R = CH_3, II, R = C_2H_5	THF, 20°	III, R = C_2H_5 (35), IV (52)	76
		I, R = C_2H_5, II, R = C_2H_5	"	III, R = C_2H_5 (61), IV (12)	76
		I, R = CH_3, II, R = $n\text{-}C_4H_9$	"	III, R = $n\text{-}C_4H_9$ (65), IV (10)	76, 77
C_8		$R(t\text{-}C_4H_9O)CuLi$ (I)		 (II),  (III)	
		I, R = $n\text{-}C_4H_9$	THF, −78°, 30 min	R = $n\text{-}C_4H_9$ II (31), III (5)	78, 60
		I, R = $t\text{-}C_4H_9$	"	R = $t\text{-}C_4H_9$ II (33), III (10)	78, 60

TABLE VI. REDUCTIVE ALKYLATION OF α,α′-DIHALO KETONES (*Continued*)

A. α-Monoalkylation (Continued)

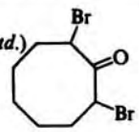
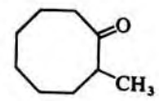
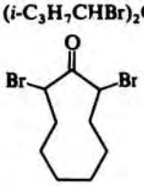
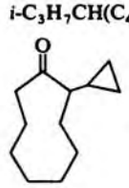
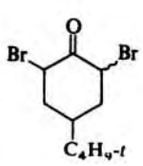
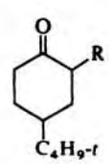
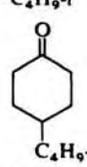
Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_8 (*Contd.*) 	CH_3MgI (2)	Ether, 25°, 30 min	 (I) (65)	78
	$(CH_3)_2CuLi$ (2)	1. Ether, −78°, 5 min 2. 25°, 1 hr	I (80)	78, 60
C_9 $(n\text{-}C_3H_7CHBr)_2CO$	CH_3MgI (2) R^1R^2CuLi (I)	Ether, 25°, 30 min	$n\text{-}C_4H_9COCH(CH_3)C_3H_7\text{-}n$ (17) $n\text{-}C_4H_9COCHRC_3H_7\text{-}n$ (II)	78
	I, $R^1 = R^2 = CH_3$	Ether, −78°, 30 min	II, R = CH_3 (70)	78, 60
	I, $R^1 = n\text{-}C_4H_9$, $R^2 = t\text{-}C_4H_9O$	THF, −78°, 30 min	II, R = $n\text{-}C_4H_9$ (75)	78, 60
	I, $R^1 = CH(CH_3)C_2H_5$, $R^2 = t\text{-}C_4H_9O$	"	II, R = $CH(CH_3)C_2H_5$ (67)	78, 60
	I, $R^1 = t\text{-}C_4H_9$, $R^2 = t\text{-}C_4H_9O$	"	II, R = $t\text{-}C_4H_9$ (60)	78, 60
$(i\text{-}C_3H_7CHBr)_2CO$	$(t\text{-}C_4H_9)_2CuLi$	Pentane, −78°	$i\text{-}C_3H_7CH(C_4H_9\text{-}t)COCH_2CH(CH_3)_2$ (60)	80
		—	 (—)	157
C_{10}  (I)	RONa (II) (2), R_3B (III)		 (IV),  (V)	
cis-I	II, R = $C(CH_3)_2C_2H_5$ III, R = $n\text{-}C_4H_9$	THF, 20°	IV, R = $n\text{-}C_4H_9$ (75), V (4)	76
	II, R = $C(C_2H_5)_3$ III, R = $n\text{-}C_4H_9$	"	"	76
	$t\text{-}C_4H_9OK$ (1.5), $(n\text{-}C_4H_9)_3B$	"	IV, R = $n\text{-}C_4H_9$ (67), V (8)	76
	ROK (II) (2), R_3B (III)			
	II, R = $t\text{-}C_4H_9$ III, R = C_2H_5	"	IV, R = C_2H_5 (85), V (10)	76, 77
	II, R = $t\text{-}C_4H_9$ III, R = $n\text{-}C_3H_7$	"	IV, R = $n\text{-}C_3H_7$ (83), V (10)	76
	II, R = $t\text{-}C_4H_9$ III, R = $n\text{-}C_4H_9$	THF, 0°, 0.2 hr	IV, R = $n\text{-}C_4H_9$ (4), V (—)	76
	"	THF, 0°, 1 hr	IV, R = $n\text{-}C_4H_9$ (15), V (—)	76
	"	THF, 0°, 1.5 hr	IV, R = $n\text{-}C_4H_9$ (25), V (—)	76
	"	THF, 0°, 4 hr	IV, R = $n\text{-}C_4H_9$ (63)	76
	"	THF, 20°, 0.1 hr	R = $n\text{-}C_4H_9$ *cis*-IV (25), *trans*-IV (6), V (6)	
	"	THF, 20°, 0.5 hr	R = $n\text{-}C_4H_9$ *cis*-IV (50), *trans*-IV (12), V (9)	76
	"	THF, 20°, 1–24 hr	R = $n\text{-}C_4H_9$ *cis*-IV (70), *trans*-IV (15), V (10)	
	"	THF, 65°, 0.2–4 hr	IV, R = $n\text{-}C_4H_9$ (40), V (—)	76
	"	THF, 70°	IV, R = $n\text{-}C_4H_9$ (51), V (—)	76

TABLE VI. REDUCTIVE ALKYLATION OF α,α′-DIHALO KETONES (*Continued*)

A. α-Monoalkylation (Continued)

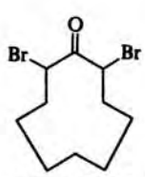
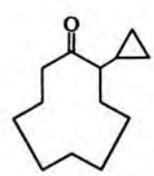
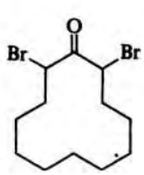
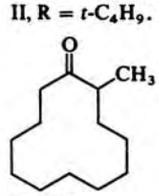
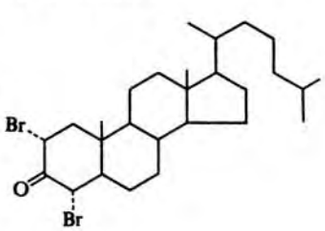
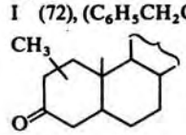
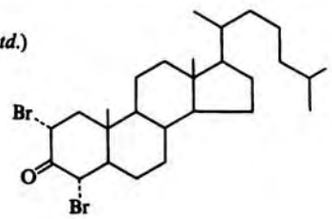
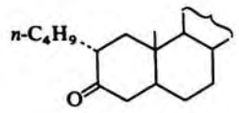
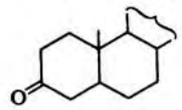
Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_{10} (*Contd.*)	II, R = $C(CH_3)_2C_2H_5$ III, R = n-C_4H_9	THF, 20°	IV, R = n-C_4H_9 (95), V (5)	76
	II, R = $C(C_2H_5)_3$ III, R = n-C_4H_9	"	IV, R = n-C_4H_9 (100)	76, 77
	II, R = t-C_4H_9 III, R = n-C_4H_9 t-C_4H_9OH (0.5)	"	IV, R = n-C_4H_9 (80), V (20)	76
	II, R = t-C_4H_9 III, R = n-C_4H_9 t-C_4H_9OH (2)	"	IV, R = n-C_4H_9 (20), V (26)	76
	II, R = t-C_4H_9 III, R = n-C_4H_9	DME, 20°	IV, R = n-C_4H_9 (trace)	76
	"	C_6H_6, 20°	"	76
	II, R = t-C_4H_9 III, R = $CH_2CH(CH_3)_2$	THF, 20°	IV, R = $CH_2CH(CH_3)_2$ (trace)	76
	II, R = $C(C_2H_5)_3$ III, R = $CH_2CH(CH_3)_2$	"	IV, R = $CH_2CH(CH_3)_2$ (5)	76
	II, R = $C(C_2H_5)_3$ III, R = $CH(CH_3)C_2H_5$	"	IV, R = $CH(CH_3)C_2H_5$ (8), V (1)	76
	II, R = $C(C_2H_5)_3$, $[CH(CH_3)C_2H_5]$B-bbn	"	IV, R = $CH(CH_3)C_2H_5$ (6), V (27)	76
	II, R = $C(C_2H_5)_3$, (c-C_6H_{11})B-bbn	"	IV, R = c-C_6H_{11} (7)	76
trans-I	II, R = t-C_4H_9 III, R = C_2H_5	"	V (10)	76
	$_2$CuLi	—	 (—)	157
C_{11} $(t\text{-}C_4H_9CHBr)_2CO$	1. R_2CuLi (I) 2. D_2O		t-$C_4H_9CHRCOCHDC_4H_9$-t (II)	
	I, R = CH_3	Ether, 0°	II, R = CH_3 (85)	80
	I, R = t-C_4H_9	Pentane, −78°	II, R = t-C_4H_9. (50)	80
C_{12} 	CH_3MgI (2)	Ether, 25°, 30 min	 (I) (86)	78
	$(CH_3)_2CuLi$ (2.5)	1. Ether, −78°, 30 min 2. H_2O	I (97)	78, 60
	"	1. Ether, −78°, 30 min 2. D_2O	I-d^a (91)	78, 60
C_{15} $(C_6H_5CHBr)_2CO$	CH_3MgI	Ether, 25°, 30 min	$C_6H_5CH_2COCH(CH_3)C_6H_5$ (I) (<20)	78, 60
	$(CH_3)_2CuLi$	Ether, −78°, 30 min	I (72), $(C_6H_5CH_2COCHC_6H_5)_2$ (18)	78, 60
C_{27} 	"	"	 (99)[b]	78, 60

TABLE VI. REDUCTIVE ALKYLATION OF α,α′-DIHALO KETONES (*Continued*)

A. α-Monoalkylation (Continued)

Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_{27} (*Contd.*) 	t-C_4H_9OK (2), $(n$-$C_4H_9)_3B$	THF, 20°	 (15),  (20)	76

B. α,α′-Dialkylation

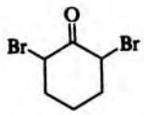
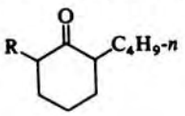
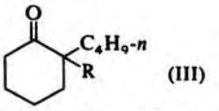
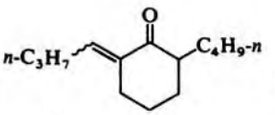
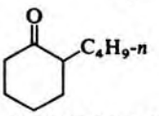
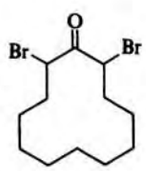
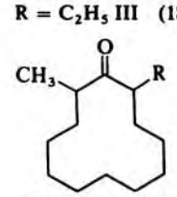
Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_5 $(CH_3CHBr)_2CO$	1. R_2CuLi (I) 2. RX (II)		$(CH_3CHR)_2CO$ (III), $C_2H_5COCHRCH_3$ (IV)	
	R = CH_3 I, II	Ether, 0°	R = CH_3 III (48), IV (22)	80, 55
	R = C_2H_5 I, II	"	R = C_2H_5 III (60), IV (25)	80
	R = i-C_3H_7 I, II	Pentane, −78°	R = i-C_3H_7 III (8), IV (86)	80, 55
C_6 	$(n$-$C_4H_9)RCuLi$ (I)		 (II),  (III)	
	1. I, R = n-C_4H_9 2. HMPA 3. CH_3I	THF, −78°, 30 min −78°, 30 min 25°, 30 min	R = CH_3 cis-II (40), *trans*-II (10)[c]	81
	1. I, R = t-C_4H_9O 2. CH_3I 3. NH_4Cl	THF, −78°, 30 min 0°, 1 hr H_2O/ether, 1 hr	R = CH_3 *cis*-II (18), *trans*-II (18), III (1)	81
	1. I, R = n-C_4H_9 2. n-C_4H_9I, HMPA	THF, −78°, 30 min 25°, 2 hr	R = n-C_4H_9 II/III (total 31)	81
	1. I, R = t-C_4H_9O 2. n-C_4H_9I, HMPA 3. NH_4Cl	THF, −78°, 30 min 25°, 2 hr H_2O/ether, 1 hr	R = n-C_4H_9 II (28), III (17)[d]	81
	1. R = t-C_4H_9O 2. n-C_3H_7CHO 3. NH_4Cl	THF, −78°, 30 min THF, −78°, 5 min H_2O/ether, 1 hr	 (43),  (4)	81
C_7 $(C_2H_5CHBr)_2CO$	1. R_2CuLi (I) 2. CH_3I		$C_2H_5CHR^1COCHR^2C_2H_5$ (II)	
	I, R = CH_3	Ether, 0°	II, $R^1 = R^2 = CH_3$ (87)	80
	I, R = C_2H_5	"	II, $R^1 = CH_3$, $R^2 = C_2H_5$ (74)	80
$[(CH_3)_2CBr]_2CO$	1. R_2CuLi (I) 2. RX (II)		$(CH_3)_2CRCOCR(CH_3)_2$ (III)	
	R = CH_3I, II	Ether, 0°	III, R = CH_3 (33)	55
	R = i-C_3H_7I, II	"	III, R = i-C_3H_7 (11), $(CH_3)_2C(i$-$C_3H_7)COC_3H_7$-i (29)	80

TABLE VI. REDUCTIVE ALKYLATION OF α,α′-DIHALO KETONES (*Continued*)

B. α,α′-Dialkylation (Continued)

	Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_9	$(n\text{-}C_3H_7CHBr)_2CO$			$n\text{-}C_3H_7CHR^1COCHR^2C_3H_7\text{-}n$ (I)	
		1. $(CH_3)_2CuLi$ 2. CH_3I	Ether, −78°, 5 min 25°, 12 hr	I, $R^1 = R^2 = CH_3$ (62)	78, 60
		1. $(CH_3)_2CuLi$ 2. $C_6H_5CH_2Br$	— —	I, $R^1 = CH_3$, $R^2 = CH_2C_6H_5$ (—)	78, 60
	$(i\text{-}C_3H_7CHBr)_2CO$	1. R_2CuLi (I) 2. RX (II)		$(i\text{-}C_3H_7CHR)_2CO$ (III), $i\text{-}C_3H_7CHRCOCH_2C_3H_7\text{-}i$ (IV)	
		R = CH_3I, II	Ether, 0°	R = CH_3 III (16), IV (76)	80
		R = $i\text{-}C_3H_7$ I, II	Pentane, −78°	R = $i\text{-}C_3H_7$ III (12), IV (78)	80, 55
C_{11}	$(t\text{-}C_4H_9CHBr)_2CO$	1. R_2CuLi (I) 2. RX (II)		$(t\text{-}C_4H_9CHR)_2CO$ (III), $t\text{-}C_4H_9CHRCOCH_2C_4H_9\text{-}t$ (IV)	
		R = CH_3 I, II	Ether, 0°	III, R = CH_3 (80)	80
		R = C_2H_5 I, II	"	R = C_2H_5 III (18), IV (42)	80
C_{12}				 (I)	
		1. $(CH_3)_2CuLi$ 2. CH_3I	THF, −78°, 30 min 25°, 12 hr	I, R = CH_3 (97)	78, 60
		1. $(CH_3)_2CuLi$ 2. $C_6H_5CH_2Br$	— —	I, R = $CH_2C_6H_5$ (—)	78, 60

C. Reductive Dimerization

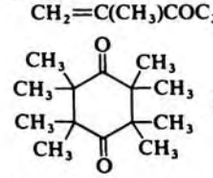
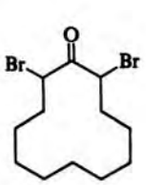
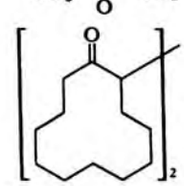
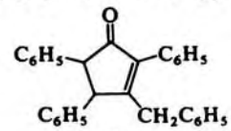
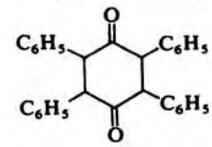
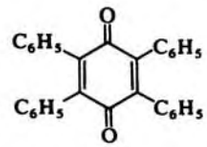
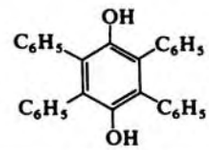
C_5	$(CH_3CHBr)_2CO$	Zn/Cu	$HCONHCH_3$, 25°,	$(C_2H_5COCHCH_3)_2$ (55)	82
	$(CH_3)_2CBrCOCH_2Br$	"	$HCONHCH_3$, 25°, 24 hr	$i\text{-}C_3H_7COCH_2C(CH_3)_2COCH_3$ (I), $(i\text{-}C_3H_7COCH_2)_2$ (II), $[CH_3COC(CH_3)_2]_2$ (III) I/II/III (39 : 38 : 23) (36)	82
C_6	$(CH_3)_2CBrCOCHBrCH_3$	"	$HCONHCH_3$, −5°, 2 hr	$i\text{-}C_3H_7COCH(CH_3)C(CH_3)_2COC_2H_5$ (I), $[C_2H_5COC(CH_3)_2]_2$ (II), $[i\text{-}C_3H_7COCHCH_3]_2$ (III) I/II/III (56 : 25 : 18) (65)	82
C_7	$[(CH_3)_2CBr]_2CO$	"	"	$[i\text{-}C_3H_7COC(CH_3)_2]_2$ (71), $CH_2{=}C(CH_3)COC_3H_7\text{-}i$ (10)	82
		Zn/Cu, $LiClO_4$	DME, overnight	 (2.5)	151
C_{12}		Zn/Cu	$HCONHCH_3$, 50°, 24 hr	 (25)	82

TABLE VI. REDUCTIVE ALKYLATION OF α,α′-DIHALO KETONES (*Continued*)

C. Reductive Dimerization (*Continued*)

Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_{15} $(C_6H_5CHBr)_2CO$			$(C_6H_5CH_2COCHC_6H_5)_2$ (I),  (II),  (III)	
	Zn	CH_3CN, reflux	I (60)	84
	Zn	$CH_2{=}CHCN$, reflux	I (—), II (—)	84
	Zn/Cu	$HCONHCH_3$, 25°, 12 hr	I (43)	82
	"	$CH_2{=}CHCN$, reflux, 6 hr	I (22)	85
	"	CH_3CN, reflux, 1 week	II (60)	85
	$(CH_3)_2CuLi$	Ether, −78°, 30 min	III (18), $C_6H_5CH_2COCH(CH_3)C_6H_5$ (72)	78, 60
	NaI	Acetone, 1 week	III (41)	85
	"	CS_2/acetone, reflux, 0.5 hr	III (60),  (—),  (—)	85

[a] The product contained 95% deuterium at C-12.
[b] The product was a mixture of 2α- and 4α-methyl-5α-cholestan-3-one.
[c] 2-Methylcyclohexanone (3%) was also formed.
[d] 2,2,6-Tri-*n*-butylcyclohexanone was also formed in 13% yield.

TABLE VII. [3 + 4] Cyclocoupling of α,α′-Dihalo and Polyhalogenated Ketones

A. With Open-Chain 1,3-Dienes

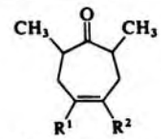
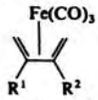
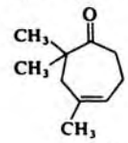
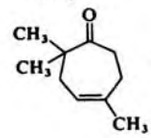
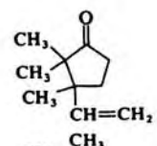
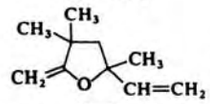
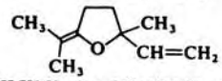
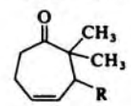
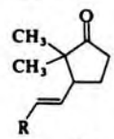
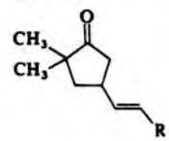
Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_5 $(CH_3CHBr)_2CO$	$Fe_2(CO)_9$, $CH_2{=}CR^1CR^2{=}CH_2$ (I)		 (II)	
	I, $R^1 = R^2 = H$	C_6H_6, 80°, 16 hr	II, $R^1 = R^2 = H$ (30)	74, 86
	I, $R^1 = H$, $R^2 = CH_3$	C_6H_6, 25°, 36 hr, *hν*[a]	II, $R^1 = H$, $R^2 = CH_3$ (36)	74, 86
	I, $R^1 = R^2 = CH_3$	C_6H_6, 60°, 34 hr	II, $R^1 = R^2 = CH_3$ (46)	74, 86
	I, $R^1{-}R^2 = (CH_2)_4$ (1)	C_6H_6, 63°, 46 hr	II, $R^1{-}R^2 = (CH_2)_4$ (80)	74
	 (I)[b]			
	I, $R^1 = R^2 = H$	C_6H_6, 80°, 9 hr	II, $R^1 = R^2 = H$ (40)	74, 86
	I, $R^1 = H$, $R^2 = CH_3$	C_6H_6, 120°, 12 hr	II, $R^1 = H$, $R^2 = CH_3$ (51)	74
	I, $R^1 = R^2 = CH_3$	C_6H_6, 120°, 4 hr	II, $R^1 = R^2 = CH_3$ (33)	74
$(CH_3)_2CBrCOCH_2X$ (I)	$CH_2{=}C(CH_3)CH{=}CH_2$ (II)		 (III),  (IV),  (V),  (VI),  (VII)	
I, X = Br	Cu, II, LiI	CH_3CN, <30°, 9 hr	III/IV/V (total 2), VI/VII (19:7) (−)[c]	158
	Cu, II, NaI	"	III/IV/V (total 2), VI/VII (35:8) (−)[c]	158
	"	DME, <30°, 9 hr	III/IV/V (total 2), VI/VII (25:8) (−)[c]	158
	Cu, II, $(n\text{-}C_4H_9)_4NI$	CH_3CN, <30°, 9 hr	III/IV/V (total 2), VI/VII (11:5) (−)[c]	158
	Zn/Cu, $RCH{=}CHCH{=}CH_2$ (II)		 (III),  (IV),  (V)	

TABLE VII. [3 + 4] CYCLOCOUPLING OF α,α′-DIHALO AND POLYHALOGENATED KETONES (*Continued*)

A. With Open-Chain 1,3-*Dienes* (*Continued*)

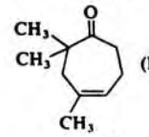
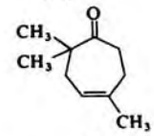
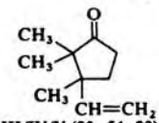
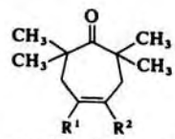
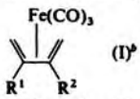
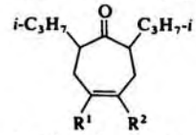
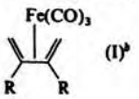
Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_5 I, X = Br (*Contd.*)	II, R = H	CH_3CN/DME	R = H III/IV (93 : 7) (1)	87
	II, R = CH_3	1. CH_3CN/DME, 10°, 1.5 hr 2. 25°, 24 hr	R = CH_3 III/IV (62 : 38) (8)	87
I, X = I	"	Isopentane	R = CH_3 III/IV/V (26 : 65 : 9) (20)	87
	$CH_2{=}C(CH_3)CH{=}CH_2$ (II)		 (III),  (IV),  (V)	
	Zn/Cu, II	C_6H_6/isopentane or DME	III/IV/V (23 : 54 : 23) (12)	88, 87
	"	CH_3CN/DME, 10°, 24 hr	III/IV/V (48 : 43 : 9) (5)	88
	Hg, II, NaI	CH_3CN	III/IV/V (total 2)	86
	$Fe_2(CO)_9$, II	C_6H_6, 57°, 10 hr	III/IV/V (24 : 46 : 30) (—)	88
	"	C_6H_6, 57°, 20 hr	III/IV/V (22 : 43 : 30) (—)	88
	"	C_6H_6, 60 to 80°, 12 hr	III/IV/V (11 : 28 : 61) (—)	88
	"[d]	C_6H_6, reflux, 4.5 hr	III/IV/V (— : 1 : 3.6) (—)	88
C_7 $[(CH_3)_2CBr]_2CO$	$Fe_2(CO)_9$, $CH_2{=}CR^1CR^2{=}CH_2$ (I)		 (II)	
	I, $R^1 = R^2 = H$	C_6H_6, 60°, 38 hr	II, $R^1 = R^2 = H$ (33)	74, 86
	I, $R^1 = H$, $R^2 = CH_3$	C_6H_6, 65°, 38 hr	II, $R^1 = H$, $R^2 = CH_3$ (47)	74, 86
	I, $R^1 = R^2 = CH_3$	C_6H_6, 60°, 38 hr	II, $R^1 = R^2 = CH_3$ (71)	74, 86
	 (I)[b]			
	I, $R^1 = R^2 = H$	C_6H_6, 80°, 4 hr	II, $R^1 = R^2 = H$ (90)	74, 86
	I, $R^1 = H$, $R^2 = CH_3$	C_6H_6, 87°, 12 hr	II, $R^1 = H$, $R^2 = CH_3$ (70)	74, 86
	I, $R^1 = R^2 = CH_3$	C_6H_6, 80°, 12 hr	II, $R^1 = R^2 = CH_3$ (100)	74
C_9 $(i\text{-}C_3H_7CHBr)_2CO$	$Fe_2(CO)_9$, $CH_2{=}CR^1CR^2{=}CH_2$ (I)		 (II)	
	I, $R^1 = R^2 = H$	C_6H_6, 90°, 12 hr	II, $R^1 = R^2 = H$ (44)	74, 86
	I, $R^1 = H$, $R^2 = CH_3$	C_6H_6, 25°, 36 hr, *hν*[a]	II, $R^1 = H$, $R^2 = CH_3$ (31)	74, 86
	I, $R^1 = R^2 = CH_3$	C_6H_6, 60°, 38 hr	II, $R^1 = R^2 = CH_3$ (36)	74
	 (I)[b]			
	I, R = H	C_6H_6, 70°, 40 hr	II, $R^1 = R^2 = H$ (77)	74, 86
	I, R = CH_3	C_6H_6, 120°, 20 hr	II, $R^1 = R^2 = CH_3$ (55)	74, 86

TABLE VII. [3 + 4] CYCLOCOUPLING OF α,α′-DIHALO AND POLYHALOGENATED KETONES (*Continued*)

B. With Carbocyclic Dienes

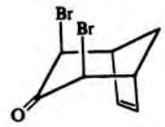
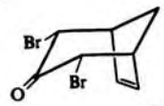
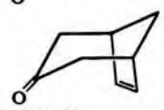
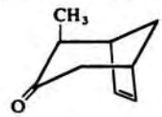
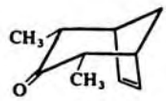
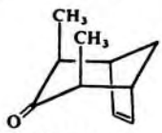
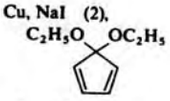
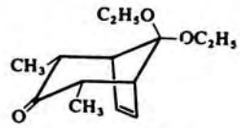
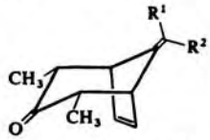
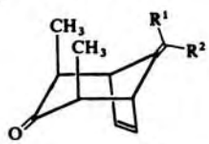
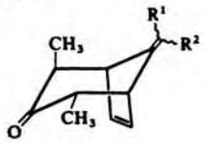
	Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_3	$(CHBr_2)_2CO$	Zn, cyclopentadiene, $(C_2H_5O)_3B$	THF, overnight	 (12),  (25),  (I) (8)	47
		1. $Fe(CO)_5$, cyclopentadiene 2. Zn/Cu, NH_4Cl	THF/C_6H_6 (1/5), 80°, 30–40 min CH_3OH, 15 min	I (60, 47)	74, 96, 111
		1. $Fe(CO)_3$ 2. Zn/Cu, NH_4Cl	Ether, 14 hr CH_3OH, 18 hr	I (56)	97
C_4	$CH_3CHBrCOCH_2Br$	Zn, cyclopentadiene, $(C_2H_5O)_3B$	THF, overnight	(8),  (6)	47
C_5	$(CH_3CHBr)_2CO$	Cyclopentadiene (I)		 (II),  (III)	
		Cu, I, NaI (2) " Zn/Cu, I $Fe_2(CO)_9$, I	CH_3CN, 4.5 hr CH_3CN, 50°, 2 hr DME, −10° C_6H_6, 60°, 25 hr	II/III (6.4 : 1) (91) II/III (6.4 : 1) (82) II/III (1.67 : 1) (—) II/III (47 : 53) (86)	92 91 93 74, 86
		Cu, NaI (2), 	CH_3CN, 20°, 18 hr	 (11)	92
		(I)		 (II),  (III),  (IV)	

TABLE VII. [3 + 4] CYCLOCOUPLING OF α,α'-DIHALO AND POLYHALOGENATED KETONES (*Continued*)

B. With Carbocyclic Dienes (Continued)

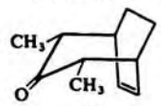
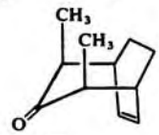
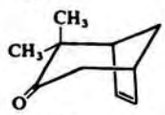
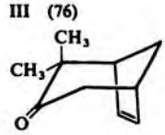
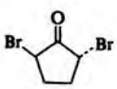
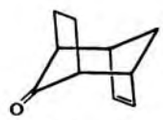
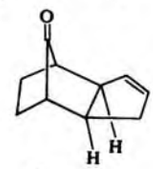
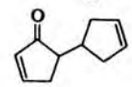
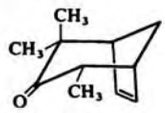
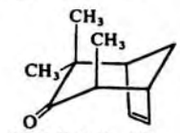
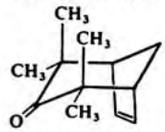
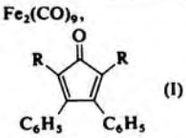
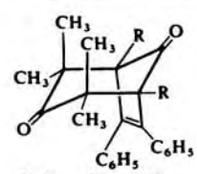
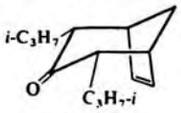
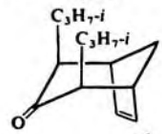
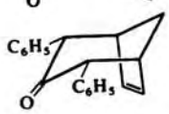
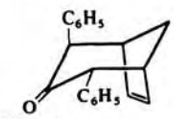
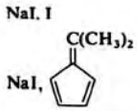
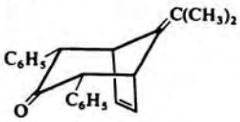
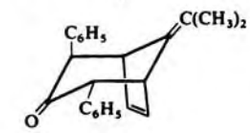
	Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_5 (*Contd.*)	$(CH_3CHBr)_2CO$	Cu, NaI (2), I, $R^1 = R^2 = CH_3$	CH_3CN, 20°, 24.5 hr	$R^1 = R^2 = CH_3$ II/III (4.6 : 1) (80)	92
		Cu, NaI (2), I, $R^1 = H$, $R^2 = OAc$	CH_3CN, 20°, 18 hr	$R^1 = H$, $R^2 = OAc$ II/IV (5.2 : 1) (70,[e] 33[f])	92
		Zn/Cu, I, $R^1 = R^2 = CH_3$	DME, −15°, 2 hr	$R^1 = R^2 = CH_3$ II/III/IV (12.2 : 10 : 1) (—)	92
		"	—	$R^1 = R^2 = CH_3$ II/III (ca. 5 : 1) (60)	98
		Zn/Cu, I, $R^1 = CH_3$, $R^2 = t\text{-}C_4H_9$	—	$R^1 = CH_3$, $R^2 = t\text{-}C_4H_9$, II/III/IV (ca. 20 : 1 : 1) (60)	98
		Zn/Cu, I, $R^1 = CH_3$, $R^2 = C_6H_5$	—	$R^1 = CH_3$, $R^2 = C_6H_5$ II/III/IV (ca. 5 : 1 : trace) (60)	98
		$Fe_2(CO)_9$, 1,3-cyclohexadiene	C_6H_6, 30°, 24 hr	 (52),	100
				 (34)	
	$(CH_3)_2CBrCOCH_2X$ (I)	Cyclopentadiene (II)		 (III)	
	I, X = Br	Zn, II, $(C_2H_5O)_3B$	THF, overnight	III (55)	47
		Zn/Cu, II	—	III (30)	93
	I, X = I	Zn, II, $(C_2H_5O)_3B$	THF, overnight	III (76)	47
	$(CH_3)_2CBrCOCHBr_2$	1. $Fe(CO)_5$, cyclopentadiene	THF/C_6H_6 (1 : 10), 80°, 70 min	 (83, 66)	48, 74
		2. Zn/Cu, NH_4Cl	CH_3OH, 20 min		
		$Fe_2(CO)_9$, cyclopentadiene	—	 (—),	95
				 (—),	
				 (—)	
C_6	$(CH_3)_2CBrCOCHBrCH_3$	Cyclopentadiene (I)		 (II),	
				 (III)	
		Zn, I, $(C_2H_5O)_3B$	THF, overnight	II/III (2.2 : 1) (78)	47
		Zn/Cu, I	DME, −5 to 0°	II/III (3.8 : 1) (60)	93
C_7	$[(CH_3)_2CBr]_2CO$	Zn/Cu, cyclopentadiene (I)	DME, −5° to room temp.	 (II) (65)	93
		$Fe_2(CO)_9$, I	C_6H_6, 60°, 38 hr	II (82, 71)	74, 86

TABLE VII. [3 + 4] CYCLOCOUPLING OF α,α′-DIHALO AND POLYHALOGENATED KETONES (*Continued*)

B. With Carbocyclic Dienes (Continued)

Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_7 $[(CH_3)_2CBr]_2CO$ (*Contd.*)	$Fe_2(CO)_9$,  (I)		 (II)	
	I, R = CH_3	C_6H_6, 50°, 35 hr	II, R = CH_3 (35)	99
	I, R = C_2H_5	C_6H_6, 60°, 16 hr	II, R = C_2H_5 (29)	99
	I, R = n-C_3H_7	C_6H_6, 50°, 34 hr	II, R = n-C_3H_7 (26)	99
	I, R = n-C_4H_9	C_6H_6, 60°, 32 hr	II, R = n-C_4H_9 (22)	99
	I, R = C_6H_5	—	II, R = C_6H_5 (0)	99
C_9 (i-$C_3H_7CHBr)_2CO$	$Fe_2(CO)_9$, cyclopentadiene	C_6H_6, 90°, 12 hr	 (47),	74, 86
			 (43)	
C_{15} $(C_6H_5CHBr)_2CO$	NaI, cyclopentadiene (I)	CH_3CN, reflux, 15 min	 (II) (40),	94
			 (60)	
	NaI, I	Acetone	II (—)	84
	NaI, 	Acetone	 +  (total 90)	98

C. With Pyrrole Derivatives

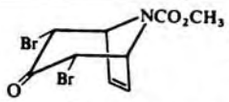
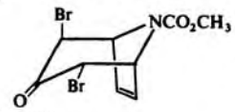
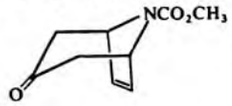
C_3 $(CHBr_2)_2CO$	*N*-Methoxycarbonylpyrrole (I)		 (II),  (III)	
	Zn/Cu, I	DME, −5°, 2.5 hr	II (30)	75
	$Fe_2(CO)_9$, I	C_6H_6, 50°, 72 hr	II/III (2 : 1) (70, 52)	75, 104
	1. Zn/Cu, I 2. Zn/Cu, NH_4Cl	1. DME, −5 to 0°, 1 hr 2. 25°, 2 hr CH_3OH, 5 min	 (II) (25)	75

TABLE VII. [3 + 4] CYCLOCOUPLING OF α,α′-DIHALO AND POLYHALOGENATED KETONES (*Continued*)

C. With Pyrrole Derivatives (Continued)

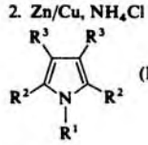
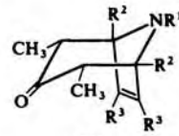
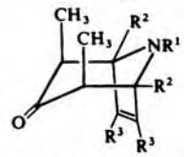
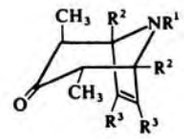
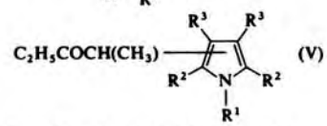
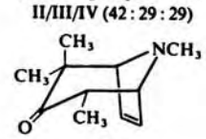
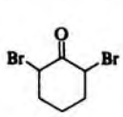
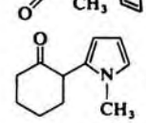
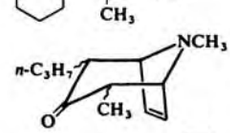
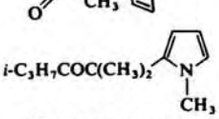
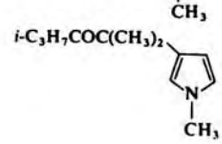
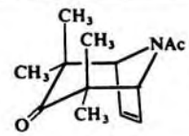
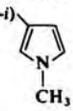
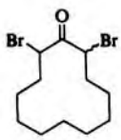
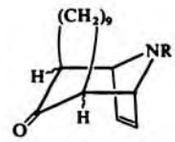
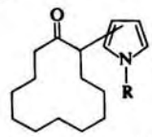
	Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
		1. $Fe_2(CO)_9$, I 2. Zn/Cu, NH_4Cl	C_6H_6, 50°, 72 hr CH_3OH, 3 hr	II (57)	75
C_5	$(CH_3CHBr)_2CO$	 (I)		 (II),	
				 (III),	
				 (IV),	
				 (V)	
		Cu, NaI (2), I, $R^1 = R^2 = R^3 = H$	CH_3CN, 3–4 hr	$R^1 = R^2 = R^3 = H$ II/III (6 : 1) (65)	101
		Cu, NaI (2), I, $R^1 = CH_3$, $R^2 = R^3 = H$	CH_3CN, 3–4 hr	II, $R^1 = CH_3$, $R^2 = R^3 = H$ (89)	101
		Cu, NaI (2), I, $R^1 = CH_3$, $R^2 = R^3 = H$	CH_3CN, 8 hr	III, $R^1 = CH_3$, $R^2 = R^3 = H$ (52)	102
		Cu, NaI (2), I, $R^1 = C_6H_5$, $R^2 = R^3 = H$	CH_3CN, 20°, 4.25 hr	II, $R^1 = C_6H_5$, $R^2 = R^3 = H$ (—)	92
		Cu, NaI (2), I, $R^1 = R^3 = H$, $R^2 = CH_3$	CH_3CN, 3–4 hr	II, $R^1 = R^3 = H$, $R^2 = CH_3$ (66)	101
		Cu, NaI (2), I, $R^1 = H$, $R^2 = R^3 = CH_3$	"	II, $R^1 = H$, $R^2 = R^3 = CH_3$ (50)	101
		Cu, NaI (2), I, $R^1 = R^2 = CH_3$, $R^3 = H$	"	II, $R^1 = R^2 = CH_3$, $R^3 = H$ (74)	101
		Zn/Cu, I, $R^1 = CH_3$, $R^2 = R^3 = H$	—	α-V, $R^1 = CH_3$, $R^2 = R^3 = H$ (60)	102
		$Fe_2(CO)_9$, I, $R^1 = CH_3$, $R^2 = R^3 = H$	C_6H_6, 40°, 70 hr	$R^1 = CH_3$, $R^2 = R^3 = H$, α-V (48), β-V (33)	74, 103, 159
		$Fe_2(CO)_9$, I, $R^1 = CO_2CH_3$, $R^2 = R^3 = H$	C_6H_6, 10 hr, $h\nu$[a]	$R^1 = CO_2CH_3$, $R^2 = R^3 = H$, II/III/IV (42 : 29 : 29) (60)[b]	74
C_6	$(CH_3)_2CBrCOCHBrCH_3$	Cu, NaI (2), *N*-methylpyrrole	CH_3CN, 3–4 hr	 (70)	101
		"	—	 (40)	102
C_7	n-$C_3H_7CHBrCOCHBrCH_3$	"	—	 (57)	102
	$[(CH_3)_2CBr]_2CO$	$Fe_2(CO)_9$, *N*-methylpyrrole	C_6H_6, 40°, 18 hr	 (31),	74, 159
				 (51)	

TABLE VII. [3 + 4] CYCLOCOUPLING OF α,α′-DIHALO AND POLYHALOGENATED KETONES (*Continued*)

C. With Pyrrole Derivatives (Continued)

Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_7 $[(CH_3)_2CBr]_2CO$ (*Contd.*)	$Fe_2(CO)_9$, *N*-acetylpyrrole	C_6H_6, 40 to 50°, 18.5 hr	 (68)	74, 103
C_9 $(i\text{-}C_3H_7CHBr)_2CO$	$Fe_2(CO)_9$, *N*-methylpyrrole	C_6H_6, 40°, 60 hr	$(CH_3)_2CHCH_2COCH(C_3H_7\text{-}i)$ (62), $(CH_3)_2CHCH_2COCH(C_3H_7\text{-}i)$  (15)	74, 159
C_{12}  (I)	(II)		 (III),  (IV)	
cis-I	Cu, NaI (2), II, R = CH_3	CH_3CN/C_6H_6, 50°, 48 hr	α-IV, R = CH_3 (34)	83
	Cu, NaI (2), II, R = TMS	CH_3CN/C_6H_6, 24 hr	α-IV, R = H (—), β-IV, R = H (—), R = TMS (—)	83
	$Fe_2(CO)_9$, II, R = CO_2CH_3	C_6H_6, 50°, 48 hr	III, R = CO_2CH_3 (77)	83
	$Fe_2(CO)_9$, II, R = $CO_2CH_2CCl_3$	C_6H_6, 64°, 2 hr	R = $CO_2CH_2CCl_3$ III (58), α-IV (19)	83
	$Fe_2(CO)_9$, II, R = $CO_2C_4H_9\text{-}t$	C_6H_6, 50°, 21 hr	III, R = $CO_2C_4H_9\text{-}t$ (5), α-IV, R = H (2), R = $CO_2C_4H_9\text{-}t$ (25)	83
	$Fe_2(CO)_9$, II, R = $CO_2CH_2C_6H_5$	C_6H_6, 91°, 2 hr	R = $CO_2CH_2C_6H_5$ III (58), α-IV (14)	83
trans-I	Cu, NaI (2), II, R = CH_3	CH_3CN/C_6H_6, 50°, 45 hr	α-IV, R = CH_3 (5)	83
C_{15} $(C_6H_5CHBr)_2CO$	Cu, NaI (2), *N*-methylpyrrole	80°	$C_6H_5CH_2COCH(C_6H_5)$ (50)	102

D. With Furan Derivatives

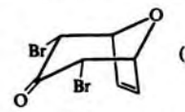
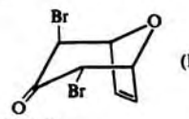
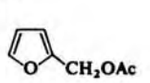
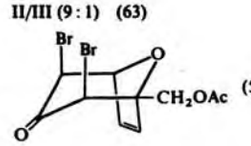
C_3 $(CHBr_2)_2CO$	Furan (I)		 (II),  (III)	
	Zn, I, $(C_2H_5O)_2B$	THF, overnight	II (30)[i]	47, 102
	Zn/Ag, I	1. THF, −10°, 2 hr 2. 25°, 12 hr	II (65)	45
	$Fe_2(CO)_9$, I	Reflux, 48 hr	II/III (9 : 1) (63)	74, 111
	Zn/Ag, 	1. THF, −10°, 10 min 2. 20°, 12 hr	 (52)	83

TABLE VII. [3 + 4] CYCLOCOUPLING OF α,α′-DIHALO AND POLYHALOGENATED KETONES (*Continued*)

D. With Furan Derivatives (*Continued*)

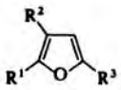
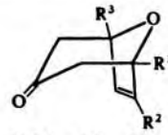
Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_3 $(CHBr_2)_2CO$ (*Contd.*)	 (I)		 (II)	
	1. Zn/Ag, I, $R^1 = R^2 = R^3 = H$	1. THF, −10°, 2 hr 2. 25°, 12 hr	II, $R^1 = R^2 = R^3 = H$ (55)	45
	2. Zn/Cu, NH_4Cl	CH_3OH, 15 min		
	1. Zn/Ag, I, $R^1 = R^3 = H$, $R^2 = OCH_2C_6H_5$	1. THF, 0°, 1 hr 2. 20°, 48 hr	II, $R^1 = R^3 = H$, $R^2 = OCH_2C_6H_5$ (14)	160
	2. Zn/Cu, NH_4Cl	CH_3OH, 25°, 1 hr		
	1. Zn/Ag, I, $R^1 = R^3 = H$, $R^2 = OTHP$	1. THF, 0°, 1 hr 2. 20°, 60 hr	II, $R^1 = R^3 = H$, $R^2 = OTHP$ (31)	83, 114l
	2. Zn/Cu, NH_4Cl	CH_3OH, 20°, 2 hr		
	1. Zn/Ag, I, $R^1 = R^2 = H$ $R^3 = OCH_2C_6H_5$	1. THF, −10°, 1 hr 2. 30°, 49 hr	II, $R^1 = R^2 = H$, $R^3 = OCH_2C_6H_5$ (35)	83
	2. Zn/Cu, NH_4Cl	1. CH_3OH, 0°, 2 hr 2. 25°, 1 hr		
	1. Zn/Ag, I, $R^1 = R^2 = H$, $R^3 = OAc$	THF, 20°, 12 hr	II, $R^1 = R^2 = H$, $R^3 = OAc$ (46)	114k
	2. Zn/Cu, NH_4Cl	CH_3OH, 20°, 1 hr		
	1. Zn/Ag, I, $R^1 = R^3 = H$, $R^2 = CH_3$	THF, 20°	II, $R^1 = R^3 = H$, $R^2 = CH_3$ (60)	161
	2. Zn/Cu, NH_4Cl	CH_3OH, 20°		
	1. Zn/Ag, I, $R^1 = R^2 = H$, $R^3 = CH_3$	THF, 20°, 14 hr	II, $R^1 = R^2 = H$, $R^3 = CH_3$ (86)	114i
	2. Zn/Cu, NH_4Cl	CH_3OH, 20°, 1 hr		
	1. Zn/Ag, I, $R^1 = R^3 = CH_3$, $R^2 = H$	THF, 20°, 12 hr	II, $R^1 = R^3 = CH_3$, $R^2 = H$ (66)	114j
	2. Zn/Cu, NH_4Cl	1. CH_3OH, 0°, 2 hr 2. 20°, 1 hr		
	1. Zn/Ag, I, $R^1 = R^3 = H$, $R^2 = C_4H_9$-*t*	1. THF, 0° 2. 20°, 60 hr	II, $R^1 = R^3 = H$, $R^2 = C_4H_9$-*t* (23)	83, 160
	2. Zn/Cu, NH_4Cl	CH_3OH, 20°, 1 hr		
	1. Zn/Ag, I, $R^1 = R^3 = H$, $R^2 = C_5H_{11}$-*n*	1. THF, 0°, 1 hr 2. 30°, 48 hr	II, $R^1 = R^3 = H$, $R^2 = C_5H_{11}$-*n* (20)	83, 160
	2. Zn/Cu, NH_4Cl	CH_3OH, 15°, 2 hr		
	1. Zn/Ag, I, $R^1 = R^2 = H$, $R^3 = C_5H_{11}$-*n*	1. THF, −10°, 1 hr 2. 25°, 12 hr	II, $R^1 = R^2 = H$, $R^3 = C_5H_{11}$-*n* (50)	83
	2. Zn/Cu, NH_4Cl	CH_3OH, 1 hr		
	1. Zn/Ag, I, $R^1 = R^2 = H$, $R^3 = C_6H_5$	1. THF, −10 to 25°, 1 hr 2. 25°, 40 hr	II, $R^1 = R^2 = H$, $R^3 = C_6H_5$ (62)	83
	2. Zn/Cu, NH_4Cl	CH_3OH, 2 hr		
	1. Zn/Ag, I, $R^1 = R^3 = H$, $R^2 = C_6H_5$	1. THF, 0° 2. 19°, 48 hr	II, $R^1 = R^3 = H$, $R^2 = C_6H_5$ (22)	83
	2. Zn/Cu, NH_4Cl	CH_3OH, 2 hr		
	1. Zn/Ag, I, $R^1 = R^3 = CH_3$, $R^2 = H$	1. THF, −10°, 30 min 2. 20°, 12 hr	II, $R^1 = R^3 = CH_3$, $R^2 = H$ (66)	83
	2. Zn/Cu, NH_4Cl	CH_3OH, 20°, 1 hr		
	1. Zn/Ag, I, $R^1 = R^3 = C_5H_{11}$-*n*, $R^2 = H$	1. THF, −10°, 1 hr 2. 20°, 24 hr	II, $R^1 = R^3 = C_5H_{11}$-*n*, $R^2 = H$ (41)	83, 114j
	2. Zn/Cu, NH_4Cl	CH_3OH, 0°, 4 hr		
	1. Zn/Ag, I, $R^1 = R^3 = C_6H_5$, $R^2 = H$	1. THF, −10°, 10 min 2. 20°, 12 hr	II, $R^1 = R^3 = C_6H_5$, $R^2 = H$ (53)	83
	2. Zn/Cu, NH_4Cl	CH_3OH, 20°, 1 hr		
	1. $Fe_2(CO)_9$, I, $R^1 = R^2 = R^3 = H$	Reflux, 48 hr	II, $R^1 = R^2 = R^3 = H$ (63)	74, 111
	2. Zn/Cu, NH_4Cl	CH_3OH, 15 min		
	1. $Fe_2(CO)_9$, I, $R^1 = R^2 = H$, $R^3 = Br$	C_6H_6, 60°, 3 hr	II, $R^1 = R^2 = H$, $R^3 = Br$ (44)	83
	2. Zn/Cu, NH_4Cl	CH_3OH, 15 min		
	1. $Fe_2(CO)_9$, I, $R^1 = R^2 = H$, $R^3 = CH_3$	C_6H_6, 60°, 5 hr	II, $R^1 = R^2 = H$, $R^3 = CH_3$ (70)	161
	2. Zn/Cu, NH_4Cl	CH_3OH, 25°, 1 hr		
	1. $Fe_2(CO)_9$, I, $R^1 = R^2 = H$, $R^3 = i$-C_3H_7	C_6H_6, 60°, 2 hr	II, $R^1 = R^2 = H$, $R^3 = i$-C_3H_7 (47)	89, 111
	2. Zn/Cu, NH_4Cl	CH_3OH, 30 hr		

TABLE VII. [3 + 4] CYCLOCOUPLING OF α,α′-DIHALO AND POLYHALOGENATED KETONES (*Continued*)

D. With Furan Derivatives (Continued)

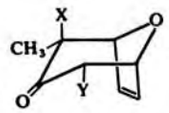
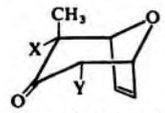
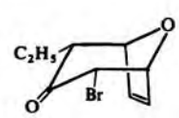
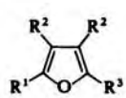
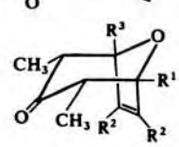
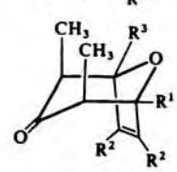
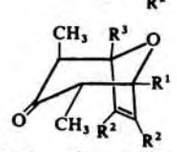
Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_3 $(CHBr_2)_2CO$ (*Contd.*)	1. $Fe_2(CO)_9$, I, $R^1 = R^3 = H$, $R^2 = i\text{-}C_3H_7$	C_6H_6, 60°, 2.5 hr	II, $R^1 = R^3 = H$, $R^2 = i\text{-}C_3H_7$ (71)	89, 110
	2. Zn/Cu, NH_4Cl	CH_3OH, 20 min		
	1. $Fe_2(CO)_9$, I, $R^1 = R^2 = H$, $R^3 = C_5H_{11}\text{-}n$	C_6H_6, 60°, 5 hr	II, $R^1 = R^2 = H$, $R^3 = C_5H_{11}\text{-}n$ (67)	83, 161
	2. Zn/Cu, NH_4Cl	CH_3OH, 25°, 1 hr		
	1. $Fe_2(CO)_9$, I, $R^1 = R^2 = H$, $R^3 = C_6H_5$	C_6H_6, 60°, 5 hr	II, $R^1 = R^2 = H$, $R^3 = C_6H_5$ (63)	114h
	2. Zn/Cu, NH_4Cl	CH_3OH, 25°, 1 hr		
C_4 $CH_3CXBrCOCHYBr$ (I)	Furan (II)		 (III),  (IV)	
I, X = Y = H	Zn, II, $(C_2H_5O)_3B$	THF, overnight	X = Y = H III/IV (total 10)	47
I, X, Y = H, Br[j]	"	"	X = Y = H III/IV (total 9), III, X = H, Y = Br (23), III and/or IV, X = Br, Y = H (14)	47
I, X = Y = Br	Zn/Ag, II	1. THF, −10°, 2.5 hr 2. 25°, 17 hr	III and/or IV, X = Y = Br (61)	45, 114a,b
	1. Zn/Ag, II	1. THF, −10°, 2.5 hr 2. 25°, 17 hr	III, X = Y = H (53)	45
	2. Zn/Cu, NH_4Cl	CH_3OH, 1 hr		
	1. $Fe_2(CO)_9$, II	24 hr	X = Y = H III/IV (55 : 45) (63)	74
	2. Zn/Cu, NH_4Cl	CH_3OH, 15 min		
C_5 $C_2H_5CHBrCOCHBr_2$	Zn/Cu, furan	—	 (30)	102
$(CH_3CHBr)_2CO$	 (I)		 (II),  (III),  (IV)	
	Cu, I, $R^1 = R^2 = R^3 = H$, NaI (2)	CH_3CN, 45 to 60°, 4 hr	II, $R^1 = R^2 = R^3 = H$ (48)	107, 102
	"	CH_3CN	$R^1 = R^2 = R^3 = H$ II/III/IV (91 : 3 : 6) (—)	92
	Zn/Cu, I, $R^1 = R^2 = R^3 = H$	—	$R^1 = R^2 = R^3 = H$ II/III/IV (total 70)	102
	"	DME, −10°, 1.5 hr	$R^1 = R^2 = R^3 = H$ II/III/IV (81 : 10 : 9) (85)	93, 105
	"	DME	$R^1 = R^2 = R^3 = H$ II/III/IV (74 : 9 : 7) (—)	92
	"	CH_3CN	$R^1 = R^2 = R^3 = H$ II/III/IV (75 : 10 : 15) (—)	92
	Zn/Cu, I, $R^1 = R^2 = R^3 = H$, $(n\text{-}C_4H_9)_4NClO_4$	DME	$R^1 = R^2 = R^3 = H$ II/III/IV (79 : 8 : 13) (—)	92

TABLE VII. [3 + 4] CYCLOCOUPLING OF α,α′-DIHALO AND POLYHALOGENATED KETONES (*Continued*)

D. With Furan Derivatives (Continued)

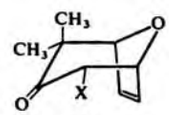
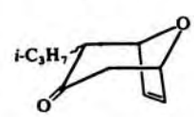
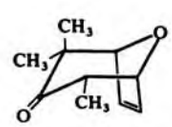
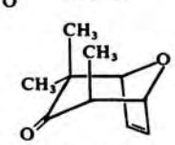
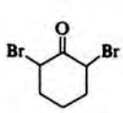
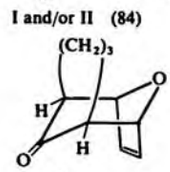
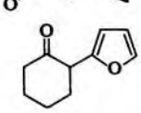
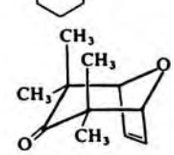
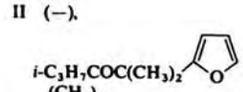
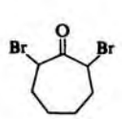
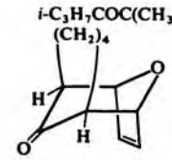
Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_5 $(CH_3CHBr)_2CO$ (*Contd.*)	Zn/Cu, I, $R^1 = R^2 = R^3 = H$, $LiClO_4$	"	$R^1 = R^2 = R^3 = H$ II/III/IV (92 : 4 : 4) (—)	92
	Zn/Cu, I, $R^1 = R^2 = H$, $R^3 = \overline{C(CH_3)O(CH_2)_2O}$	DME, 0 to 25°, 16 hr	II, $R^1 = R^2 = H$, $R^3 = \overline{C(CH_3)O(CH_2)_2O}$ (53)	105
	Zn/Cu, I, $R^1 = R^3 = H$, $R^2 = CH_3$	DME	$R^1 = R^3 = H$, $R^2 = CH_3$ II/III/IV (45 : 34 : 21) (—)	92
	Zn/Ag, I, $R^1 = R^2 = R^3 = H$	1. THF, −10°, 1 hr 2. 25°, 12 hr	II, $R^1 = R^2 = R^3 = H$ (80)	45
	$Fe_2(CO)_9$, I, $R^1 = R^2 = R^3 = H$	C_6H_6, 40°, 53 hr	$R^1 = R^2 = R^3 = H$ II/IV (44 : 56) (90)	74
	$Fe_2(CO)_9$, I, $R^1 = R^3 = CH_3$, $R^2 = H$	C_6H_6, 80°, 16 hr	II, $R^1 = R^3 = CH_3$, $R^2 = H$ (78)	74
$(CH_3)_2CBrCOCHXBr$ (I)	Furan (II)		 (III)	
I, X = H	Zn/Cu, II	Acetone	III, X = H (20)	93
I, X = Br	Zn/Ag, II	1. THF, −10°, 1.5 hr 2. 25°, 16 hr	III, X = Br (55)	45, 114a,b
	1. Zn/Ag, II 2. Zn/Cu, NH_4Cl	1. THF, −10°, 1.5 hr 2. 25°, 19 hr CH_3OH, 1 hr	III, X = H (50)	45
	1. $Fe_2(CO)_9$, II 2. Zn/Cu, NH_4Cl	Reflux, 40 hr CH_3OH, 15 min	III, X = H (93)	74
C_6 $i\text{-}C_3H_7CHBrCOCHBr_2$	1. $Fe_2(CO)_9$, furan 2. Zn/Cu, NH_4Cl	Reflux, 16 hr CH_3OH, 1.5 hr	 (35)	89, 111
$(CH_3)_2CBrCOCHBrCH_3$	Zn/Cu, furan	Acetone, −5° to room temp.	 (I) (35),  (II) (<5)	93
	$Fe_2(CO)_9$, furan	40°, 45 hr	I and/or II (84)	74
	"	Reflux, 30 hr	 (35),  (35)	74, 159
C_7 $[(CH_3)_2CBr]_2CO$	Furan (I)		 (II)	
	Zn/Cu, I	Acetone, −5° to room temp.	II (43)	93
	$Fe_2(CO)_9$, I	40°, 38 hr	II (96)	74
	"	C_6H_6, 40°, 38 hr	II (89)	74
	$2e^-$, I, $(n\text{-}C_4H_9)_4NBF_4$	CH_3CN, 14°	II (—),  (—)	20
	$Fe_2(CO)_9$, furan	Reflux, 62 hr	 (54),	74, 159

TABLE VII. [3 + 4] CYCLOCOUPLING OF α,α′-DIHALO AND POLYHALOGENATED KETONES (*Continued*)

D. With Furan Derivatives (Continued)

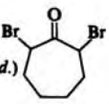
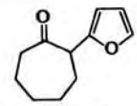
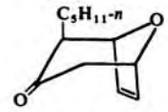
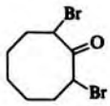
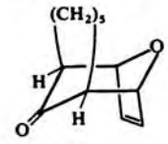
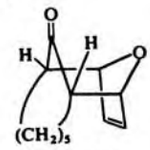
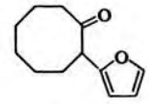
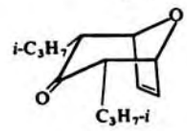
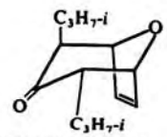
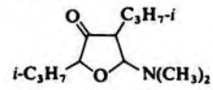
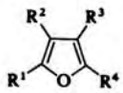
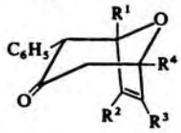
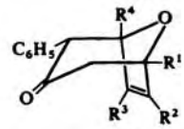
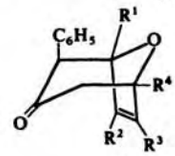
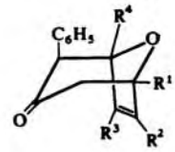
Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_7 (*Contd.*) 	$Fe_2(CO)_9$, furan	Reflux, 62 hr	 (21)	
C_8 n-$C_5H_{11}CBr_2COCHBr_2$	1. Zn/Ag, furan 2. Zn/Cu, NH_4Cl	1. THF, −10°, 2 hr 2. 25°, 39 hr CH_3OH	 (47)	83, 114a,b
	$Fe_2(CO)_9$, furan	Reflux, 48 hr	 (27),	74, 159
			 (10),	
			 (10)	
C_9 $(i\text{-}C_3H_7CHBr)_2CO$	$Fe_2(CO)_9$, furan (I)		 (II),	
			 (III)	
	I	40°, 80 hr	II/III (77 : 23) (96)	74
	"	C_6H_6, 40°, 80 hr	II/III (75 : 25) (89)	74
	"	DMF, 22 hr	II (20),	34
			 (49)	
$C_6H_5CHBrCOCH_2Br$	 (I)		 (II),	
			 (III),	
			 (IV),	
			 (V)	

TABLE VII. [3 + 4] CYCLOCOUPLING OF α,α′-DIHALO AND POLYHALOGENATED KETONES (*Continued*)

D. With Furan Derivatives (Continued)

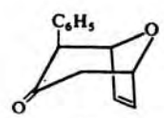
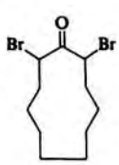
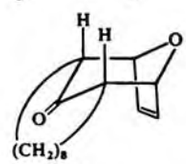
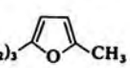
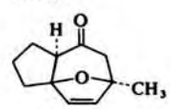
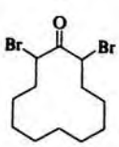
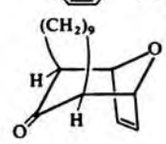
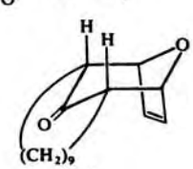
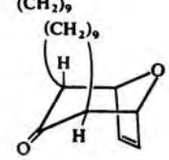
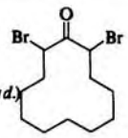
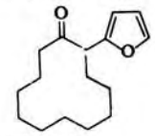
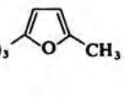
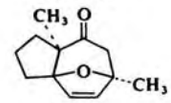
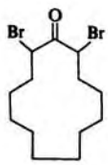
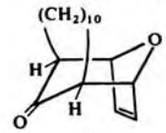
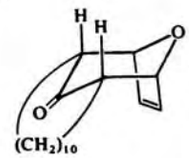
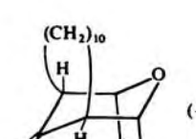
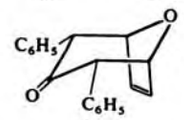
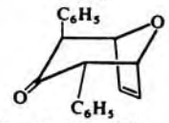
	Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_9 (*Contd.*)	$C_6H_5CHBrCOCH_2Br$	Zn/Cu, I, $R^1 = R^3 = R^4 = H$, $R^2 = CH_3$	DME, −10°	$R^1 = R^3 = R^4 = H$, $R^2 = CH_3$ II/III (65:35) (36), IV/V (64:36) (18)	83
		Zn/Cu, I, $R^1 = R^3 = R^4 = H$, $R^2 = CO_2C_2H_5$	"	$R^1 = R^3 = R^4 = H$, $R^2 = CO_2C_2H_5$ II/III (67:33) (41)	83
		Zn/Cu, I, $R^1 = CO_2C_2H_5$, $R^2 = R^3 = R^4 = H$	"	$R^1 = CO_2C_2H_5$, $R^2 = R^3 = R^4 = H$ II/III (88:12) (40)	83
		Zn/Cu, I, $R^1 = CO_2CH_3$, $R^2 = CH_3$, $R^3 = R^4 = H$	"	$R^1 = CO_2CH_3$, $R^2 = CH_3$, $R^3 = R^4 = H$ II/III (95:5) (20)	83
		Zn/Cu, I, $R^1 = CO_2CH_3$, $R^2 = R^3 = H$, $R^4 = CH_3$	"	$R^1 = CO_2CH_3$, $R^2 = R^3 = H$, $R^4 = CH_3$ II/III (79:21) (23)	83
		Zn/Cu, I, $R^1 = CO_2CH_3$, $R^2 = R^4 = H$, $R^3 = CH_3$	"	$R^1 = CO_2CH_3$, $R^2 = R^4 = H$, $R^3 = CH_3$ II/III (80:20) (20)	83
		Zn/Ag, I, $R^1 = R^2 = R^3 = R^4 = H$	1. THF, −10°, 1.5 hr 2. 25°, 19 hr	II, $R^1 = R^2 = R^3 = R^4 = H$ (77)	83
		$Fe_2(CO)_9$, I, $R^1 = R^3 = R^4 = H$, $R^2 = Br$	C_6H_6, 30°	$R^1 = R^3 = R^4 = H$, $R^2 = Br$ II/III (65:35) (44), IV/V (66:34) (29)	36
		$Fe_2(CO)_9$, I, $R^1 = R^3 = R^4 = H$, $R^2 = CH_3$	C_6H_6, 30°	$R^1 = R^3 = R^4 = H$, $R^2 = CH_3$ II/III (56:44) (29), IV/V (56:44) (19)	36
		$Fe_2(CO)_9$, I, $R^1 = R^3 = R^4 = H$, $R^2 = CO_2C_2H_5$	"	$R^1 = R^3 = R^4 = H$, $R^2 = CO_2C_2H_5$ II/III (55:45) (52)	36
		$Fe_2(CO)_9$, I, $R^1 = CO_2C_2H_5$, $R^2 = R^3 = R^4 = H$	"	$R^1 = CO_2C_2H_5$, $R^2 = R^3 = R^4 = H$ II/III (90:10) (56)	36
		$Fe_2(CO)_9$, I, $R^1 = CO_2CH_3$, $R^2 = CH_3$, $R^3 = R^4 = H$	"	$R^1 = CO_2CH_3$, $R^2 = CH_3$, $R^3 = R^4 = H$ II/III (92:8) (63)	36
		$Fe_2(CO)_9$, I, $R^1 = CO_2CH_3$, $R^2 = R^3 = H$, $R^4 = CH_3$	"	$R^1 = CO_2CH_3$, $R^2 = R^3 = H$, $R^4 = CH_3$ II/III (65:35) (65)	36
		$Fe_2(CO)_9$, I, $R^1 = CO_2CH_3$, $R^2 = R^4 = H$, $R^3 = CH_3$	"	$R^1 = CO_2CH_3$, $R^2 = R^4 = H$, $R^3 = CH_3$ II/III (76:24) (68)	36
	$C_6H_5CBr_2COCHBr_2$	1. Zn/Ag, furan 2. Zn/Cu, NH_4Cl	1. THF, −10°, 2 hr 2. 25°, 12 hr CH_3OH, 1 hr	 (48)	83, 114a,b
C_{11}		Zn/Cu, furan	—	 (−)	162
	$BrCH_2COCHBr(CH_2)_3$  CH_3	$Fe_2(CO)_9$	C_6H_6, 80°, 3 hr	 (41)	117
C_{12}		Zn/Cu, furan (I)	—	 (II) (−),  (−),  (III) (−)	162

TABLE VII. [3 + 4] CYCLOCOUPLING OF α,α′-DIHALO AND POLYHALOGENATED KETONES (*Continued*)

D. With Furan Derivatives (Continued)

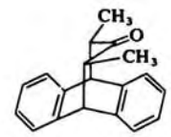
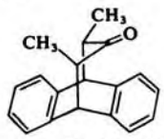
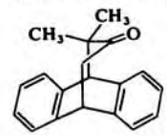
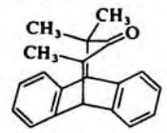
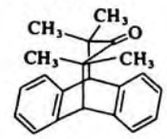
Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_{12} (*Contd.*) 	$Fe_2(CO)_9$, I	Reflux, 40 hr	II (7), III (45),  (34)	74, 159
$BrCH_2COCBr(CH_3)(CH_2)_3$ 	$Fe_2(CO)_9$	C_6H_6, 80°, 3 hr	 (38)	117
C_{13} 	Zn/Cu, furan	—	 (−),  (−),  (−)	162
C_{15} $(C_6H_5CHBr)_2CO$	Furan (I)		 (II),  (III)	
	Cu, I, NaI (2)	CH_3CN, 80°	II and/or III (80)	102
	Zn/Cu, I	CH_3CN, reflux, 2 days	II (29), $(C_6H_5CH_2COCHC_6H_5)_2$ (49)	94
	Hg, I	—	II (35)	94
	$Fe_2(CO)_9$, I	25°, 6 hr	II (45), III (45)	74
	"	C_6H_6, 25°, 12 hr	II/III (1 : 1) (90)	29, 28
	$(CH_3)_2CuLi$, I	−78°	II and/or III (20)	78
	NaI, I	—	II (65)	84
	"	CH_3CN, reflux,	II (30), III (10), $C_6H_5CH_2COCH(C_6H_5)$ (45)	94

E. With Thiophene

C_5 $(CH_3CHBr)_2CO$	$Fe_2(CO)_9$, thiophene	C_6H_6, 35 hr, $h\nu$[a]	$C_2H_5COCH(CH_3)$ (37)	74

TABLE VII. [3 + 4] CYCLOCOUPLING OF α,α′-DIHALO AND POLYHALOGENATED KETONES (*Continued*)

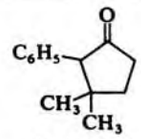
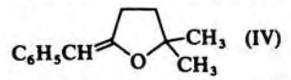
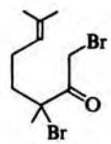
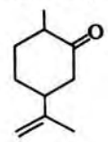
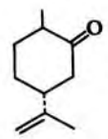
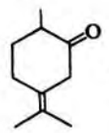
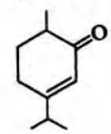
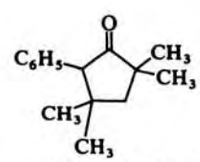
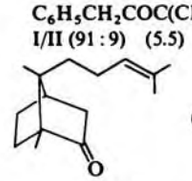
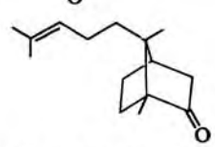
F. With Anthracene

	Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_5	$(CH_3CHBr)_2CO$	Anthracene (I)		 (II),  (III)	
		Zn, I, CuCl (0.4)	Dioxane, 80 to 85°, 5 hr	II/III (ca. 90 : 10) (22)	116
		Zn, I, CuCl (0.4), TMSCl (2.1)	C_6H_6	II/III (ca. 1 : 1) (93)	116
	$(CH_3)_2CBrCOCH_2Br$	Zn, anthracene (I), CuCl (0.4)	Dioxane, 80 to 85°, 5 hr	 (II) (12)	116
		Zn, I, CuCl (0.4), TMSCl (2.1)	C_6H_6	II (76)	116
C_6	$(CH_3)_2CBrCOCHBrCH_3$	Zn, anthracene (I), CuCl (0.4)	Dioxane, 80 to 85°, 5 hr	 (II) (25)	116
		Zn, I, CuCl (0.4), TMSCl (2.1)	C_6H_6	II (97)	116
C_7	$[(CH_3)_2CBr]_2CO$	Zn, anthracene (I), CuCl (0.4)	Dioxane, 80 to 85°, 5 hr	 (II) (3)	116
		Zn, I, CuCl (0.4), TMSCl (2.1)	C_6H_6	II (71)	116

[a] The mixture of dibromide, diene, and $Fe_2(CO)_9$ was irradiated with visible light.
[b] The complex was prepared *in situ* by irradiation of a mixture of the diene and $Fe(CO)_5$.
[c] A major product was 3-bromo-3-methylbutan-2-one.
[d] The iron carbonyl was added batchwise to the refluxing reaction mixture.
[e] The yield represents crude product.
[f] The products were hydrolyzed under workup conditions to give small amounts of *syn*- (6.3%) and *anti*-8-aldehydes (3.2%).
[g] The reaction mixture was irradiated with visible light.
[h] The yield was determined by ^1H NMR.
[i] 8-Oxabicyclo[3.2.1]oct-6-en-3-one (2%) and the 2,2,4-tribromo derivative (2%) were also formed.
[j] A mixture of the two tribromides was used.

TABLE VIII. [3 + 2] CYCLOCOUPLING OF α,α′-DIBROMO KETONES (*Continued*)

A. With Simple Olefins

	Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs
C_9	$C_6H_5CHBrCOCH_2Br$	$Fe_2(CO)_9$, $(CH_3)_2C{=}CH_2$	C_6H_6, 55°	 (I), $C_6H_5CH_2CO(CH_2)_2C(CH_3){=}CH_2$ (II), $CH_3COCH(C_6H_5)CH_2C(CH_3){=}CH_2$ (III),  (IV) I/II/III/IV (14 : 52 : 5 : 29) (35)	33
C_{10}		$Fe_2(CO)_9$	C_6H_6, 100 to 115°, 1.5 hr	(I),  (II),  (III),  (IV),  (V) I/II/III/IV/V (54 : 6 : 14 : 4 : 10) (70)	117
C_{11}	$C_6H_5CHBrCOCBr(CH_3)_2$	$Fe_2(CO)_9$, $(CH_3)_2C{=}CH_2$	C_6H_6, 55°	 (I), $C_6H_5CH_2COC(CH_3)_2CH_2C(CH_3){=}CH_2$ (II) I/II (91 : 9) (5.5)	33
C_{15}	(I)			 (II),  (III)	
	(*E*)-I	$Fe_2(CO)_9$	C_6H_6, 100°	II/III (2:1) (58)	117
	(*Z*)-I	"	"	II/III (1:2) (—)	117

B. With Aryl-Substituted Olefins

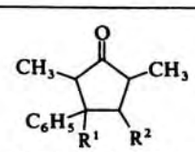
C_5	$(CH_3CHBr)_2CO$	$Fe_2(CO)_9$, $C_6H_5CR^1{=}CHR^2$ (I)		 (II)	
		I, $R^1 = R^2 = H$	C_6H_6, 50°, 14 hr	II, $R^1 = R^2 = H$ (65)[a]	118, 119
		I, $R^1 = H$, $R^2 = CH_3$	C_6H_6, 55°, 14 hr	II, $R^1 = H$, $R^2 = CH_3$ (20)[b]	118, 119
		I, $R^1 = CH_3$, $R^2 = H$	C_6H_6, 60°, 12 hr	II, $R^1 = CH_3$, $R^2 = H$ (70)[a]	118, 119
		I, R^1 = cyclopropyl, $R^2 = H$	C_6H_6, 65°, 24 hr	II, R^1 = cyclopropyl, $R^2 = H$ (95)[b]	118, 119

TABLE VIII. [3 + 2] CYCLOCOUPLING OF α,α′-DIBROMO KETONES (*Continued*)

B. With Aryl-Substituted Olefins (*Continued*)

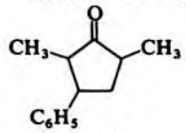
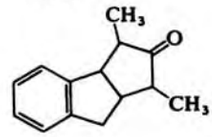
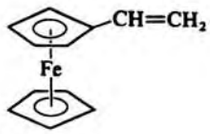
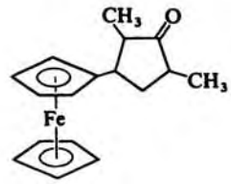
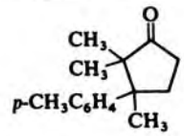
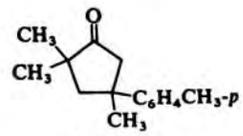
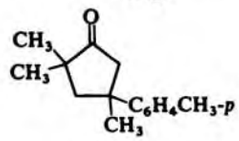
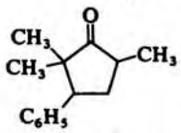
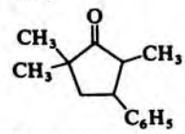
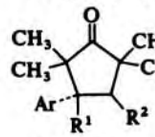
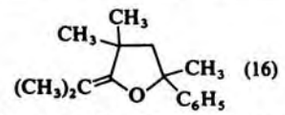
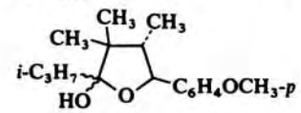
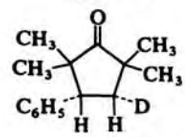
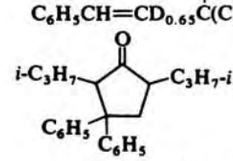
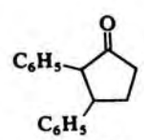
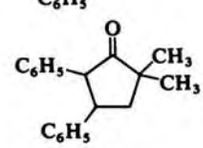
	Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_5 (*Contd.*)	$(CH_3CHBr)_2CO$	I, $R^1 = H$, $R^2 = C_6H_5$	C_6H_6, 50°, 14 hr	II, $R^1 = H$, $R^2 = C_6H_5$ (30)[a]	118, 119
		I, $R^1 = C_6H_5$, $R^2 = H$	C_6H_6, 60°, 14 hr	II, $R^1 = C_6H_5$, $R^2 = H$ (70),[a] $C_2H_5COCH(CH_3)CH{=}C(C_6H_5)_2$ (7)	118, 119
		$C_6H_5CH{=}CH_2$[c] $Fe(CO)_4$	C_6H_6, 50°, 19 hr	 (16)[a]	118, 119
		$Fe_2(CO)_9$, indene	C_6H_6, 50°, 14 hr	 (45)[b]	118, 119
		$Fe_2(CO)_9$, 	C_6H_6, 65°, 14 hr	 (30)[b]	118, 119
	$(CH_3)_2CBrCOCH_2Br$	$Fe_2(CO)_9$, $p\text{-}CH_3C_6H_4C(CH_3){=}CH_2$	C_6H_6, 55°, 17 hr	 (18),	121
				 (1.2)	
	$(CH_3)_2CBrCOCHBr_2$	1. $Fe_2(CO)_9$, $p\text{-}CH_3C_6H_4C(CH_3){=}CH_2$ 2. Zn/Cu, NH_4Cl	C_6H_6 CH_3OH	 (35)	121
C_6	$(CH_3)_2CBrCOCHBrCH_3$	$Fe_2(CO)_9$, $C_6H_5CH{=}CH_2$	C_6H_6, 55°	 (I),	36
				 (II) I/II (94 : 6) (31)	
C_7	$[(CH_3)_2CBr]_2CO$	$Fe_2(CO)_9$, $ArCR^1{=}CHR^2$ (I)		 (II), $(E)\text{-}i\text{-}C_3H_7COC(CH_3)_2CR^2{=}CR^1Ar$ (III)	
		I, $Ar = C_6H_5$, $R^1 = R^2 = H$	C_6H_6, 55°, 12 hr	$Ar = C_6H_5$, $R^1 = R^2 = H$ II (23), III (23)	118, 119
		I, $Ar = C_6H_5$, $R^1 = CH_3$, $R^2 = H$	C_6H_6	$Ar = C_6H_5$, $R^1 = CH_3$, $R^2 = H$ II (5), III (37), $i\text{-}C_3H_7COC(CH_3)_2CH_2C(C_6H_5){=}CH_2$ (11),	118, 119

TABLE VIII. [3 + 2] CYCLOCOUPLING OF α,α′-DIBROMO KETONES (*Continued*)

B. With Aryl-Substituted Olefins (Continued)

Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_7 $[(CH_3)_2CBr]_2CO$ (*Contd.*)	I, Ar = C_6H_5, R^1 = CH_3, R^2 = H	C_6H_6	 (16)	
	(*E*)-I, Ar = *p*-$CH_3OC_6H_4$, R^1 = H, R^2 = CH_3	C_6H_6, 55°, 12 hr	II, Ar = *p*-$CH_3OC_6H_4$, R^1 = H, R^2 = CH_3 (55), III (3),  (30)	118, 119
	1. $Fe_2(CO)_9$ 2. (*Z*)-$C_6H_5CH{=}CHD$	C_6H_6, 50°, 15 min 50°, 1 hr	 (6), (*E*)-$(CH_3)_2CD_{0.35}CO$ | $C_6H_5CH{=}CD_{0.65}C(CH_3)_2$ (3)	118, 119 120
C_9 $(i\text{-}C_3H_7CHBr)_2CO$	$Fe_2(CO)_9$, $(C_6H_5)_2C{=}CH_2$	C_6H_6, 50°, 18 hr	 (44),[a] *i*-$C_3H_7CH_2CO$ | $(C_6H_5)_2C{=}CHCHC_3H_7$-*i* (11)	118, 119
$C_6H_5CHBrCOCH_2Br$	$Fe_2(CO)_9$, $C_6H_5CH{=}CH_2$	C_6H_6, 55°	 (44)	36
C_{11} $C_6H_5CHBrCOCBr(CH_3)_2$	"	"	 (49)	36

C. With Enamines[d]

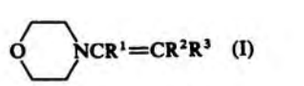
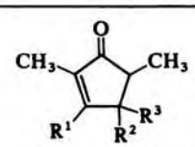
C_5 $(CH_3CHBr)_2CO$	 (I)		 (II)[e]	
	Zn/Cu, I, $R^1{-}R^2$ = $(CH_2)_4$, R^3 = H	1. DME, −5°, 30 min 2. 25°, 16 hr	II, $R^1{-}R^2$ = $(CH_2)_4$, R^3 = H (39)	122
	$Fe_2(CO)_9$, I, R^1 = H, R^2 = R^3 = CH_3	1. C_6H_6, 60°, 20 min 2. 25°, 12 hr	II, R^1 = H, R^2 = R^3 = CH_3 (79)	122, 123
	$Fe_2(CO)_9$, I, R^1 = C_2H_5, R^2 = H, R^3 = CH_3	C_6H_6, 45°, 18 hr	II, R^1 = C_2H_5, R^2 = H, R^3 = CH_3 (73)	122
	$Fe_2(CO)_9$, I, R^1 = C_6H_5, R^2 = R^3 = H	C_6H_6, 32°, 20 hr	II, R^1 = C_6H_5, R^2 = R^3 = H (84,[e] 91[f])	124, 122
	$Fe_2(CO)_9$, I, $R^1{-}R^2$ = $(CH_2)_3$, R^3 = H	C_6H_6, 25°, 12 hr	II, $R^1{-}R^2$ = $(CH_2)_3$, R^3 = H (74)	122, 123
	$Fe_2(CO)_9$, I, $R^1{-}R^2$ = $(CH_2)_4$, R^3 = H	C_6H_6, 25°, 24 hr	II, $R^1{-}R^2$ = $(CH_2)_4$, R^3 = H (100)	122, 123
	$Fe_2(CO)_9$, I, $R^1{-}R^2$ = $(CH_2)_4$, R^3 = H, furan	25°, 24 hr	II, $R^1{-}R^2$ = $(CH_2)_4$, R^3 = H (4),	122

TABLE VIII. [3 + 2] CYCLOCOUPLING OF α,α′-DIBROMO KETONES (*Continued*)

C. With Enamines[d] (*Continued*)

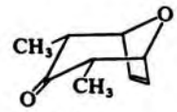
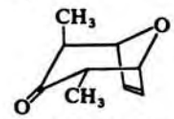
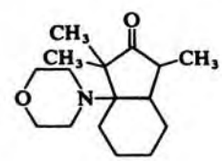
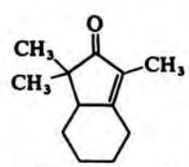
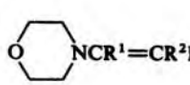
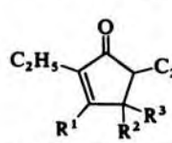
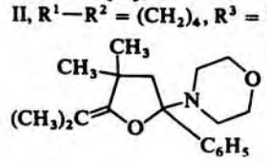
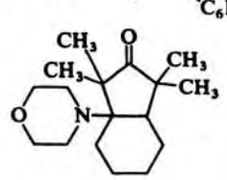
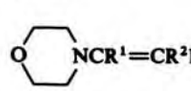
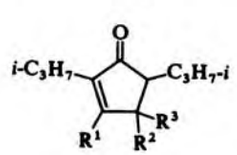
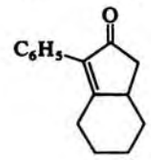
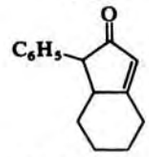
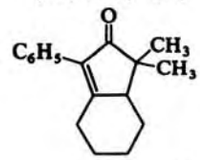
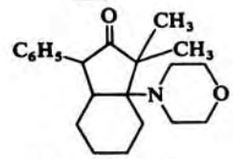
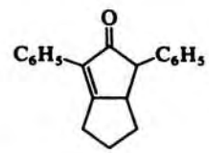
Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_5 $(CH_3CHBr)_2CO$ (*Contd.*)			 (III),  (IV) III/IV (2 : 1) (35)	
	$Fe_2(CO)_9$, I, $R^1—R^2 = (CH_2)_4$, $R^3 = H$, furan	40°, 24 hr	II, $R^1—R^2 = (CH_2)_4$, $R^3 = H$ (10), III/IV (Total 90)	122
	$Fe_2(CO)_9$, I, $R^1 = H$, $R^2—R^3 = (CH_2)_5$	C_6H_6, 42°, 18 hr	II, $R^1 = H$, $R^2—R^3 = (CH_2)_5$ (71)	122, 123
	$Fe_2(CO)_9$, I, $R^1—R^2 = (CH_2)_5$, $R^3 = H$	C_6H_6, 25°, 14 hr	II, $R^1—R^2 = (CH_2)_5$, $R^3 = H$ (100)	122, 123
	$Fe_2(CO)_9$, $R^1—R^2 = (CH_2)_{10}$, $R^3 = H$	C_6H_6, 45°, 19 hr	II, $R^1—R^2 = (CH_2)_{10}$, $R^3 = H$ (90)	122, 123
	$Fe_2(CO)_9$, I, $R^1 = H$, $R^2—R^3 = (CH_2)_{11}$	C_6H_6, 25°, 12 hr	II, $R^1 = H$, $R^2—R^3 = (CH_2)_{11}$ (65)	122 123
C_6 $(CH_3)_2CBrCOCHBrCH_3$	$Fe_2(CO)_9$, 1-morpholinocyclohexene	C_6H_6, 30°	 (I),[a]  (II) I/II (59 : 41) (86)	36
C_7 $(C_2H_5CHBr)_2CO$	$Fe_2(CO)_9$,  (I)		 (II)[a]	
	I, $R^1 = C_2H_5$, $R^2 = H$, $R^3 = CH_3$	C_6H_6, 46°, 16 hr	II, $R^1 = C_2H_5$, $R^2 = H$, $R^3 = CH_3$ (70)	122, 123
	I, $R^1 = C_6H_5$, $R^2 = R^3 = H$	C_6H_6, 25°, 14 hr	II, $R^1 = C_6H_5$, $R^2 = R^3 = H$ (64)	122
	I, $R^1—R^2 = (CH_2)_4$, $R^3 = H$	C_6H_6, 25°, 12 hr, *hν*[g]	II, $R^1—R^2 = (CH_2)_4$, $R^3 = H$ (89)	122
$[(CH_3)_2CBr]_2CO$	$Fe_2(CO)_9$, α-morpholinostyrene	C_6H_6, 40°, 22 hr	 (>86)	118
	$Fe_2(CO)_9$, 1-morpholinocyclohexene	1. C_6H_6, 60°, 10 hr, *hν*[g] 2. 25°, 12 hr, *hν*[g]	 (87)	122, 123
C_9 $(i\text{-}C_3H_7CHBr)_2CO$	$Fe_2(CO)_9$,  (I)		 (II)	

TABLE VIII. [3 + 2] CYCLOCOUPLING OF α,α′-DIBROMO KETONES (*Continued*)

C. With Enamines[d] (*Continued*)

Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_9 $(i\text{-}C_3H_7CHBr)_2CO$ (*Contd.*)	I, $R^1 = C_6H_5$, $R^2 = R^3 = H$	C_6H_6, 30°, 15 hr	II, $R^1 = C_6H_5$, $R^2 = R^3 = H$ (72)	122, 123
	I, $R^1—R^2 = (CH_2)_4$, $R_3 = H$	C_6H_6, 32°, 12 hr	I, $R^1—R^2 = (CH_2)_4$, $R^3 = H$ (73)[h]	122, 123
$C_6H_5CHBrCOCH_2Br$	$Fe_2(CO)_9$, 1-morpholinocyclohexene	C_6H_6, 30°	 (I),  (II) I/II (76 : 24) (22)	36
C_{11} $C_6H_5CHBrCOCHBr(CH_3)_2$	"	"	 (I),  (II) I/II (75:25) (61)	36
C_{15} $(C_6H_5CHBr)_2CO$	$Fe_2(CO)_9$, 1-morpholinocyclopentene	C_6H_6, 30°, 22 hr	 (66)[h]	122

D. With Carboxamides and Lactams

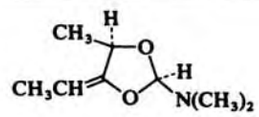
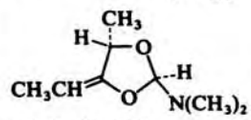
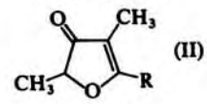
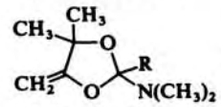
C_5 $(CH_3CHBr)_2CO$	Zn/Cu, DMF	−35°, 10 min	 (I),  (II) I/II (5 : 3) (15)	128
	$Fe_2(CO)_9$, $RCON(CH_3)_2$ (I)		 (II)	
	I, R = H	12 hr	II, R = H (53)	34, 35
	I, R = CH_3	14 hr	II, R = CH_3 (21)	34, 35
	I, R = C_6H_5	C_6H_6, 19 hr	II, R = C_6H_5 (25)	34, 35
$(CH_3)_2CBrCOCH_2X$ (I)	Zn/Cu, $RCONC(CH_3)_2$ (II)		 (III)	
I, X = Br	II, R = H	−35°, 10 min	III, R = H (5.2)	128
	II, R = CH_3	−15°, 55 min	III, R = CH_3 (—)	128
I, X = I	II, R = H	−35°, 10 min	III, R = H (11)	128

TABLE VIII. [3 + 2] CYCLOCOUPLING OF α,α′-DIBROMO KETONES (*Continued*)

D. With Carboxamides and Lactams (Continued)

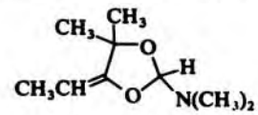
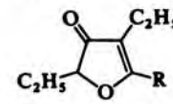
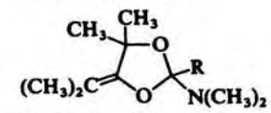
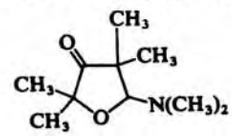
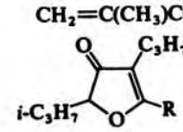
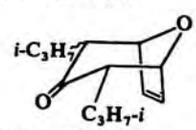
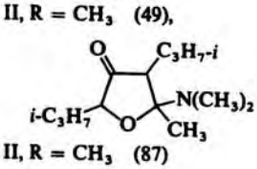
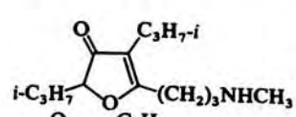
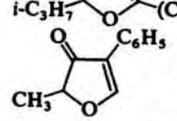
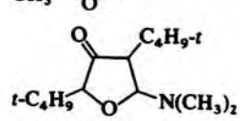
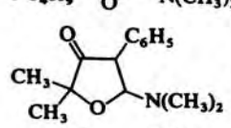
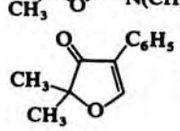
	Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_6	$(CH_3)_2CBrCOCHBrCH_3$	Zn/Cu, DMF	−35°, 10 min	 (50)	128
C_7	$(C_2H_5CHBr)_2CO$	$Fe_2(CO)_9$, $RCON(CH_3)_2$ (I)		 (II)	
		I, R = H	12 hr	II, R = H (92, 64)	34, 35
		I, R = CH_3	19 hr	II, R = CH_3 (51)	34, 35
		I, R = CH_3	24 hr, *hv*[i]	II, R = CH_3 (41)	34, 35
		I, R = C_6H_5	C_6H_6, 14 hr	II, R = C_6H_5 (42)	34, 35
	$[(CH_3)_2CBr]_2CO$	Zn/Cu, $RCON(CH_3)_2$ (I)		 (II)	
		I, R = H	−35°, 10 min	II, R = H (—)	128, 164
		I, R = CH_3	−15°, 55 min	II, R = CH_3 (30), $[i\text{-}C_3H_7COC(CH_3)_2]_2$ (3)	128
		$Fe_2(CO)_9$, DMF	18 hr	 (3), $CH_2{=}C(CH_3)COC_3H_7\text{-}i$ (80)	34, 28, 35
C_9	$(i\text{-}C_3H_7CHBr)_2CO$	$Fe_2(CO)_9$, $RCON(CH_3)_2$ (I)		 (II)	
		I, R = H	1. 25°, 12 hr 2. 140°, 15 min	II, R = H (89)	34, 35
		I, R = H, furan	1. 25°, 12 hr 2. 140°	II, R = H (49),  (20)[j]	34, 35
		I, R = CH_3	12 hr	II, R = CH_3 (49),  (39)	34, 35
		I, R = CH_3	1. 25°, 12 hr 2. 110°, 15 min	II, R = CH_3 (87)	34, 35
		$Fe_2(CO)_9$, *N*-methylpyrrolidone	48 hr	 (26)	34, 35
C_{10}	$CH_3CHBrCOCHBrC_6H_5$	Zn/Cu, DMF	1. −35°, 2 hr 2. 25°, overnight	 (—)	127
C_{11}	$(t\text{-}C_4H_9CHBr)_2CO$	$Fe_2(CO)_9$, DMF	17 hr	 (98)	34
	$(CH_3)_2CBrCOCHBrC_6H_5$	Zn/Cu, DMF	1. −35°, 2 hr 2. 25°, overnight	 (—),  (—)	127

TABLE VIII. [3 + 2] CYCLOCOUPLING OF α,α′-DIBROMO KETONES (*Continued*)

E. With Other C_2 Substrates

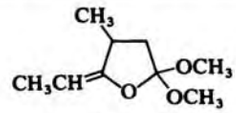
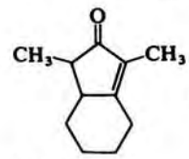
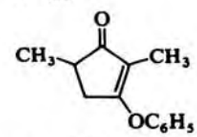
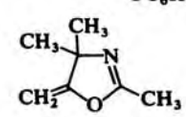
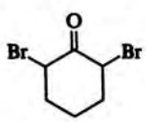
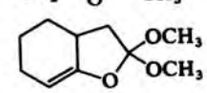
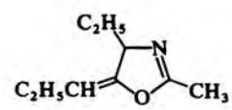
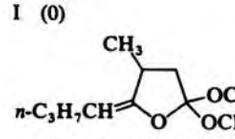
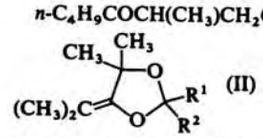
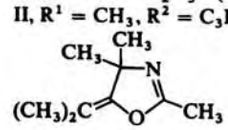
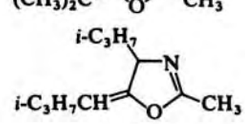
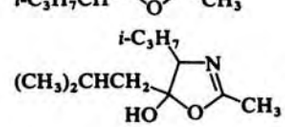
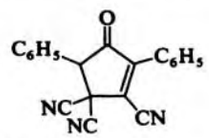
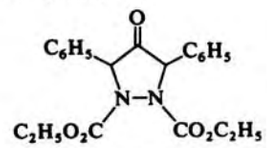
	Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_5	$(CH_3CHBr)_2CO$	Cu, NaI (4), $CH_2{=}C(OCH_3)_2$ (1)	CH_3CN, 8–10 hr	 (90)	79
		$Fe_2(CO)_9$, 1-methoxycyclohexene	C_6H_6, 15.5 hr	 (I) (12)	83
		$Fe_2(CO)_9$, 1-ethoxycyclohexene	C_6H_6, 7.5 hr	I (10)	83
		1. $Fe_2(CO)_9$ 2. $CH_2{=}C(OC_6H_5)_2$	C_6H_6, 1.5 hr 21 hr	 (8)	83
	$(CH_3)_2CBrCOCH_2Br$	Zn/Cu, CH_3CN	DME	 (—)	87
C_6		Cu, $CH_2{=}C(OCH_3)_2$ (1), NaI (4)	CH_3CN, 8–10 hr	 (—)	79
C_7	$(C_2H_5CBr)_2CO$	$Fe_2(CO)_9$, CH_3CN	40°, 20 hr	 (I) (27)	83
		$Fe_2(CO)_9$, CH_3CN (100)	C_6H_6, 40°, 13 hr	I (44)	83
		$Fe_2(CO)_9$, CH_3CN (10)	C_6H_6, 40°, 20 hr	I (31)	83
		$Fe_2(CO)_9$, CH_3CN (1.2)	C_6H_6, 40°, 20 hr	I (0)	83
	$CH_3CHBrCOCHBrC_3H_7$-*n*	Cu, $CH_2{=}C(OCH_3)_2$ (1), NaI (4)	CH_3CN, 8–10 hr	 (—), n-$C_4H_9COCH(CH_3)CH_2CO_2CH_3$ (—)	79
	$[(CH_3)_2CBr]_2CO$	Hg,[k] R^1COR^2 (I)		 (II)	
		I, $R^1 = R^2 = CH_3$	25°, 1–2 days	II, $R^1 = R^2 = CH_3$ (49)	130
		I, $R^1 = CH_3$, $R^2 = C_2H_5$	"	II, $R^1 = CH_3$, $R^2 = C_2H_5$ (59)	130
		I, $R^1 = R^2 = C_2H_5$	"	II, $R^1 = R^2 = C_2H_5$ (25)	130
		I, $R^1 = CH_3$, $R^2 = C_3H_7$-*n*	"	II, $R^1 = CH_3$, $R^2 = C_3H_7$-*n* (47)	130
		$Fe_2(CO)_9$, CH_3CN	14 hr	 (50)	83
C_9	$(i$-$C_3H_7CHBr)_2CO$	"	30°, 40 hr	 (64)	83
		"	CH_3CONH_2, 22 hr	 (90, 76)	83

TABLE VIII. [3 + 2] CYCLOCOUPLING OF α,α′-DIBROMO KETONES (*Continued*)

E. With Other C_2 Substrates (Continued)

Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_{15} $(C_6H_5CHBr)_2CO$	NaI, $(NC)_2C{=}C(CN)_2$ (I)	Acetone, reflux, 1 hr	 (II) (36)	84, 85
	NaI, I	CH_3CN, reflux, 1 hr	II (trace)	85
	NaI, $C_2H_5O_2CN{=}NCO_2C_2H_5$	1. CH_3CN, 1 day 2. Reflux, 1 hr	 (15)	85

[a] The product was a mixture of diastereoisomers.
[b] The product was a mixture of diastereoisomers, from which a single epimer was obtained by thin-layer chromatography on silica gel or by distillation.
[c] Prepared according to reference 163.
[d] Generally, treatment of the initial products with silica gel or 3% ethanolic sodium hydroxide was required to obtain the cyclopentenones.
[e] This yield was obtained on a 100-mmol scale.
[f] This yield was obtained on a 10-mmol scale.
[g] The reaction mixture was irradiated with visible light through 10% aqueous copper sulfate.
[h] A single *trans* isomer was obtained.
[i] The reaction mixture was irradiated with visible light (>350 nm).
[j] A 1 : 1 mixture of *cis* and *trans* isomers.
[k] Ultrasonically dispersed mercury was used.

TABLE IX. MISCELLANEOUS CYCLOCOUPLINGS OF α,α′-DIBROMO KETONES

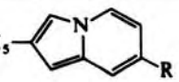
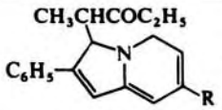
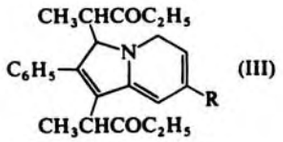
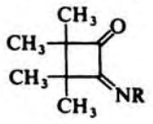
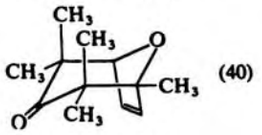
	Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_5	$(CH_3CHBr)_2CO$	Cu,  (I)		 (II),  (III)	
		I, R = H	CH_3CN	R = H II (—), III (—)	132
		I, R = CH_3	CH_3CN	R = CH_3 II (—), III (—)	132
C_7	$[(CH_3)_2CBr]_2CO$	Cu, RNC (I)		 (II)	
		I, R = C_4H_9-*t*	C_6H_6, 12 hr	II, R = C_4H_9-*t* (65)	108
		I, R = cyclohexyl	C_6H_6, 12 hr	II, R = cyclohexyl (99, 86)	108
		I, R = $C(CH_3)_2C_5H_{11}$-*n*	—	II, R = $C(CH_3)_2C_5H_{11}$-*n* (60)	108
		I, R = C_4H_9-*t*, 2-methylfuran	C_6H_6, 10 hr	II, R = C_4H_9-*t* (—),  (40)	108
		Zn, I, R = C_4H_9-*t*	Py/C_6H_6, 3 hr	II, R = C_4H_9-*t* (43)	108

TABLE IX. MISCELLANEOUS CYCLOCOUPLINGS OF α,α′-DIBROMO KETONES (*Continued*)

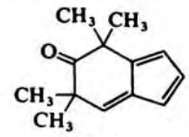
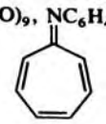
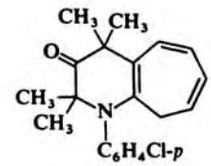
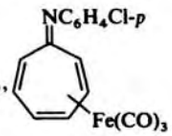
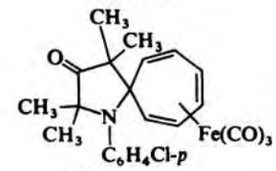
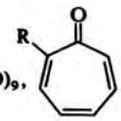
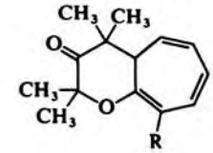
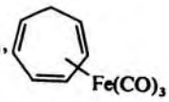
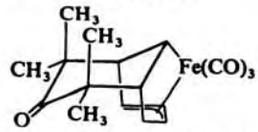
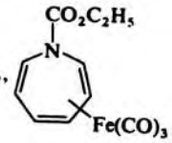
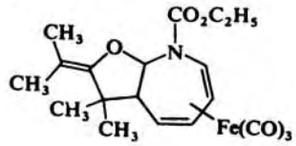
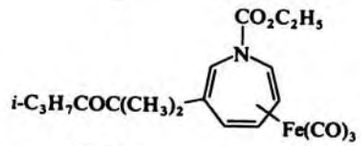
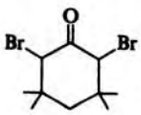
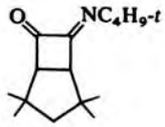
Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_7 (*Contd.*) $[(CH_3)_2CBr]_2CO$	$Fe_2(CO)_9$, 6-dimethylaminofulvene	C_6H_6, 45°, 6 hr	 (17)	99
	$Fe_2(CO)_9$, 	C_6H_6, 50°, 8 hr	 (37)	131a
	 $Fe_2(CO)_9$,	C_6H_6, 45°, 8 hr	 (22)	131a
	 $Fe_2(CO)_9$, (I)		 (II)	
	I, R = H	C_6H_6, 50°, 30 hr	II, R = H (50)	99
	I, R = Cl	C_6H_6, 40°, 70 hr	II, R = Cl (28)	99
	I, R = C_6H_5	C_6H_6, 45°, 30 hr	II, R = C_6H_5 (65)	99
	$Fe_2(CO)_9$, 	C_6H_6, 50°, 8 hr	 (20)	131a
	 $Fe_2(CO)_9$,	C_6H_6, 60°, 8 hr	 (−),	131a
			 (−)	
C_{10} 	Cu, t-C_4H_9NC	C_6H_6, 12 hr	 (70)	108

TABLE IX. MISCELLANEOUS CYCLOCOUPLINGS OF α,α'-DIBROMO KETONES (*Continued*)

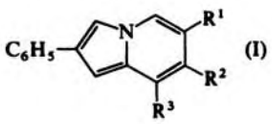
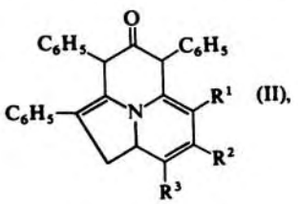
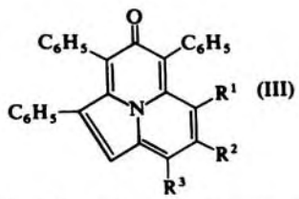
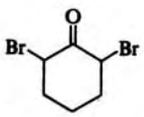
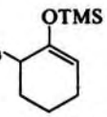
	Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_{15}	$(C_6H_5CHBr)_2CO$	 (I)		 (II),  (III)	
		Cu, I, $R^1 = R^2 = R^3 = H$, NaI	—	$R^1 = R^2 = R^3 = H$ II (—), III (—)	132
		Cu, I, $R^1 = R^2 = H$, $R^3 = CH_3$, NaI	—	II, $R^1 = R^2 = H$, $R^3 = CH_3$ (—)	132
		Cu, I, $R^1 = R^3 = H$, $R^2 = CH_3$, NaI	—	II, $R^1 = R^3 = H$, $R^2 = CH_3$ (—)	132
		Cu, I, $R^1 = CH_3$, $R^2 = R^3 = H$, NaI	—	$R^1 = CH_3$, $R^2 = R^3 = H$ II (—), III (—)	132
		$Fe_2(CO)_9$, I, $R^1 = R^2 = R^3 = H$	C_6H_6, 60°	$R^1 = R^2 = R^3 = H$ II (35), III (10)	132

TABLE X. MISCELLANEOUS REACTIONS OF α,α′-DIBROMO KETONES

	Halo Ketone	Reactants (equiv.)	Conditions	Products and Yields (%)	Refs.
C_5	$(CH_3CHBr)_2CO$	$HC{\equiv}CR$ (I)		$RCH{=}C{=}C(CH_3)COC_2H_5$ (II)	
		Cu, I, R = CH_2OH, NaI	CH_3CN, 8–10 hr	II, R = CH_2OH (25)	79
		Cu, I, R = $CH(OC_2H_5)_2$, NaI	"	II, R = $CH(OC_2H_5)_2$ (30)	79
		Cu, I, R = CH_2OCH_3, NaI	"	II, R = CH_2OCH_3 (35)	79
		$Fe_2(CO)_9$, 2,3-dihydropyrane	C_6H_6,	$C_2H_5COCH(CH_3)$- (10)	83
C_6		1. $(CH_3)_2CuLi$ 2. TMSCl, $(C_2H_5)_3N$	Ether, −78°, 0.5 hr 1 hr	CH_3-  (46)	81
C_7	$[(CH_3)_2CBr]_2CO$	$Fe_2(CO)_9$, 1,3,5-cycloheptatriene	C_6H_6, 70°, 6 hr	i-$C_3H_7COC(CH_3)_2$- (65)	131b
C_9	$(i$-$C_3H_7CHBr)_2CO$	$Fe_2(CO)_9$, 2,3-dihydropyrane	C_6H_6	i-$C_3H_7CH_2COCH(C_3H_7$-$i)$- (3)	83

7. Acknowledgment

The assistance of Mr. Thomas C. Johns of Wilmington, Delaware in searching the literature is gratefully acknowledged.

End Notes

The initially generated anion radical $R-X^{\cdot-}$, suffers subsequent elimination of X^-, giving rise to radical $R^{\cdot}$. Thus in practice this process is difficult to distinguish experimentally from the atom-transfer process, since they differ mainly in the timing of the bond-making and bond-breaking sequence.

*

* See also reference (101), which indicates that the reaction gave the 2 α ,4 α ,8-trimethyl-8-aza-bicyclo[3.2.1]oct-6-en-3-one, but not the 2 α ,4 β ,8-trimethyl isomer, in 89% yield.

* A different procedure on a large scale is cited in *Organic Syntheses*. (124)

References

1. (a) C. D. Gutsche and D. Redmore, *Carbocyclic Ring Expansion Reactions*, Academic Press, New York, 1968, "Chap. 4"; (b) C. D. Gutsche, Org. React., **8**, 364 (1954).
2. (a) A. T. Nielsen and W. J. Houlihan, Org. React., **16**, 1 (1968); (b) R. A. Raphael, *Chemistry of Carbon Compounds*, E. H. Rodd, Ed., Vol. **IIA**, Elsevier, Amsterdam, 1953, "Chap. 4"; (c) M. Green, G. R. Knox, and P. L. Pauson, *Rodd's Chemistry of Carbon Compounds*, S. Coffey, Ed., Vol. **IIA**, Elsevier, Amsterdam, 1967, "Chap. 4"; (d) R. A. Ellison, Synthesis, **1973**, 397; (e) B. M. Trost and M. J. Bogdanowicz, J. Am. Chem. Soc., **95**, 5311 (1973).
3. (a) B. M. Trost, Acc. Chem. Res., **7**, 85 (1974); (b) P. T. Lansbury, *ibid.*, **5**, 311 (1972).
4. B. G. McFarland, *Steroid Reactions*, C. Djerassi, Ed., Holden-Day, San Francisco, 1963, p. 427.
5. (a) R. Jacquier, Bull. Soc. Chim. Fr., **1950**, 35; (b) A. S. Kende, Org. React., **11**, 261 (1969); (c) D. Redmore and C. D. Gutsche, Adv. Alicycl. Chem., **3**, 1 (1971).
6. D. F + rcasiu and P. v. R. Schleyer, J. Org. Chem., **38**, 3455 (1973).
7. R. Noyori, Acc. Chem. Res., **12**, 61 (1979).
8. H. M. R. Hoffmann, Angew. Chem., Int. Ed. Engl., **12**, 819 (1973).
9. J. K. Kochi, *Organometallic Mechanisms and Catalysis*, Academic Press, New York, 1978, "Chap. 7".
10. J. R. Hanson and E. Premuzic, Angew. Chem., Int. Ed. Engl., **7**, 247 (1968).
11. H. Inoue, T. Nagata, H. Hata, and E. Imoto, Bull. Chem. Soc. Jpn., **52**, 469 (1979).
12. H. Alper and L. Pattee, J. Org. Chem., **44**, 2568 (1979).
13. P. J. Elving and J. T. Leone, J. Am. Chem. Soc., **79**, 1546 (1957).
14. H. Alper and E. C. H. Keung, J. Org. Chem., **37**, 2566 (1972).
15. E. Ghera, D. H. Perry, and S. Shoua, J. Chem. Soc., Chem. Commun., **1973**, 858.
16. L. T. Scott and W. D. Cotton, J. Am. Chem. Soc., **95**, 2708 (1973).
17. R. G. Doerr and P. S. Skell, J. Am. Chem. Soc., **89**, 4684 (1967).
18. R. Hoffmann, J. Am. Chem. Soc., **90**, 1475 (1968).
19. R. C. Bingham, M. J. S. Dewar, and D. H. Lo, J. Am. Chem. Soc., **97**, 1302 (1975).
20. J. P. Dirlam, L. Eberson, and J. Casanova, J. Am. Chem. Soc., **94**, 240 (1972).

21. H. M. R. Hoffmann, T. A. Nour, and R. H. Smithers, J. Chem. Soc., Chem. Commun., **1972**, 963.
22. A. J. Fry and J. J. O'Dea, J. Org. Chem., **40**, 3625 (1975).
23. A. J. Fry and D. Herr, Tetrahedron Lett., **1978**, 1721.
24. A. J. Fry and J. P. Bujanauskas, J. Org. Chem., **43**, 3157 (1978).
25. A. J. Fry and G. S. Ginsburg, J. Am. Chem. Soc., **101**, 3927 (1979).
26. A. J. Fry, W. A. Donaldson, and G. S. Ginsburg, J. Org. Chem., **44**, 349 (1979).
27. A. J. Fry and A. T. Lefor, J. Org. Chem., **44**, 1270 (1979).
28. R. Noyori, Y. Hayakawa, H. Takaya, S. Murai, R. Kobayashi, and N. Sonoda, J. Am. Chem. Soc., **100**, 1759 (1978).
29. R. Noyori, Y. Hayakawa, M. Funakura, H. Takaya, S. Murai, R. Kobayashi, and S. Tsutsumi, J. Am. Chem. Soc., **94**, 7202 (1972).
30. (a) H. E. Zimmerman and R. J. Pasteris, J. Org. Chem., **45**, 4864 (1980); (b) *ibid.*, **45**, 4876 (1980).
31. H. E. Zimmerman, D. S. Crumrine, D. Döpp, and P. S. Huyffer, J. Am. Chem. Soc., **91**, 434 (1969).
32. M. Nishizawa and R. Noyori, Bull. Chem. Soc. Jpn., **54**, 2233 (1981).
33. R. Noyori, F. Shimizu, and Y. Hayakawa, Tetrahedron Lett., **1978**, 2091.
34. Y. Hayakawa, H. Takaya, S. Makino, N. Hayakawa, and R. Noyori, Bull. Chem. Soc. Jpn., **50**, 1990 (1977).
35. R. Noyori, Y. Hayakawa, S. Makino, N. Hayakawa, and H. Takaya, J. Am. Chem. Soc., **95**, 4103 (1973).
36. (a) R. Noyori, F. Shimizu, K. Fukuta, H. Takaya, and Y. Hayakawa, J. Am. Chem. Soc., **99**, 5196 (1977); (b) R. Noyori, Ann. N. Y. Acad. Sci., **295**, 225 (1977).
37. A. J. Fry and R. Scoggins, Tetrahedron Lett., **1972**, 4079.
38. W. J. M. van Tilborg, R. Plomp, R. de Ruiter, and C. J. Smit, Recl. Trav. Chim. Pays-Bas, **99**, 206 (1980).
39. H. M. R. Hoffmann and T. A. Nour, J. Chem. Soc., Chem. Commun., **1975**, 37.
40. J.-E. Dubois, P. Fournier, and C. Lion, C. R. Acad. Sci., Ser. C, **279**, 965 (1974).
41. J. J. Beereboom, C. Djerassi, D. Ginsburg, and L. F. Fieser, J. Am. Chem. Soc., **75**, 3500 (1953).
42. H. Inoue, H. Hata, and E. Imoto, Chem. Lett., **1975**, 1241.
43. H. Alper and D. D. Roches, J. Org. Chem., **41**, 806 (1976).
44. H. H. Inhoffen and G. Zühlsdorff, Ber., **76**, 233 (1943).
45. T. Sato and R. Noyori, Bull. Chem. Soc. Jpn., **51**, 2745 (1978).

46. H. E. Zimmerman and A. Mais, J. Am. Chem. Soc., **81**, 3644 (1959).
47. H. M. R. Hoffmann and M. N. Iqbal, Tetrahedron Lett., **1975**, 4487.
48. R. Noyori, T. Souchi, and Y. Hayakawa, J. Org. Chem., **40**, 2681 (1975).
49. E. J. Corey, S. W. Chow, and R. A. Scherrer, J. Am. Chem. Soc., **79**, 5773 (1957).
50. T.-Y. Luh, C. H. Lai, K. L. Lei, and S. W. Tam, J. Org. Chem., **44**, 641 (1979).
51. H. Alper, K. D. Logbo, and H. des Abbayes, Tetrahedron Lett., **1977**, 2861.
52. J. R. Bull and A. Tuinman, Tetrahedron Lett., **1973**, 4349.
53. J.-E. Dubois, C. Lion, and C. Moulineau, Tetrahedron Lett., **1971**, 177.
54. T.-L. Ho and C. M. Wong, Synth. Commun., **3**, 237 (1973).
55. T.-L. Ho and G. A. Olah, Synthesis, **1976**, 807.
56. J. M. Townsend and T. A. Spencer, Tetrahedron Lett., **1971**, 137.
57. T. A. Spencer, R. W. Britton, and D. S. Watt, J. Am. Chem. Soc., **89**, 5727 (1967).
58. J. M. Townsend, Ph.D. Dissertation, Dartmouth College, Hanover, N.H., 1971, [Diss. Abstr. Int. B, **32**, 5118 (1972)].
59. F. G. Saitkulova, G. G. Abashev, and I. I. Lapkin, Zh. Org. Khim., **9**, 1405 (1973) [C. A., **79**, 91529z (1973)].
60. G. H. Posner and J. J. Sterling, J. Am. Chem. Soc., **95**, 3076 (1973).
61. E. Ghera and S. Shoua, Tetrahedron Lett., **1974**, 3843.
62. F. G. Saitkulova, G. G. Abashev, I. I. Lapkin, Izv. Vyssh., Ucheb. Zaved., Khim. Khim. Tekhnol., **16**, 1458 (1973) [C. A., **80**, 36667p (1973)].
63. K. Maruoka, S. Hashimoto, Y. Kitagawa, H. Yamamoto, and H. Nozaki, J. Am. Chem. Soc., **99**, 7705 (1977).
64. I. I. Lapkin and F. G. Saitkulova, Zh. Org. Khim., **7**, 2488 (1971) [C. A., **76**, 71955v (1971)].
65. C. Wakselman and M. Mondon, Tetrahedron Lett., **1973**, 4285.
66. T. Mitsudo, Y. Watanabe, T. Sasaki, H. Nakanishi, M. Yamashita, and Y. Takegami, Tetrahedron Lett., **1975**, 3163.
67. E. Yoshisato and S. Tsutsumi, J. Am. Chem. Soc., **90**, 4488 (1968).
68. E. Yoshisato and S. Tsutsumi, J. Chem. Soc., Chem. Commun., **1968**, 33.
69. L. Gorrichon-Guigon, Y. Maroni-Barnaud, and P. Maroni, Bull. Soc. Chim. Fr., **1975**, 291.
70. I. I. Lapkin, G. G. Abashev, and F. G. Saitkulova, Zh. Org. Khim., **12**, 967 (1976) [C. A., **85**, 46149p (1976)].
71. A. E. Greene and J.-P. Deprés, J. Am. Chem. Soc., **101**, 4003 (1979).

72. C. Djerassi, *Steroid Reactions*, Holden-Day, San Francisco, 1963, "Chap. 4", and references cited therein.
73. J.-P. Deprés and A. E. Greene, J. Org. Chem., **45**, 2036 (1980).
74. H. Takaya, S. Makino, Y. Hayakawa, and R. Noyori, J. Am. Chem. Soc., **100**, 1765 (1978).
75. Y. Hayakawa, Y. Baba, S. Makino, and R. Noyori, J. Am. Chem. Soc., **100**, 1786 (1978).
76. (a) R. H. Prager and J. M. Tippett, Aust. J. Chem., **27**, 1457 (1974); (b) *ibid.*, **27**, 1467 (1974).
77. R. H. Prager and J. M. Tippett, Tetrahedron Lett., **1973**, 5199.
78. G. H. Posner, C. E. Whitten, and J. J. Sterling, J. Am. Chem. Soc., **95**, 7788 (1973).
79. A. P. Cowling and J. Mann, J. Chem. Soc., Chem. Commun., **1978**, 1006.
80. C. Lion and J.-E. Dubois, Tetrahedron, **31**, 1223 (1975).
81. G. H. Posner, J. J. Sterling, C. E. Whitten, C. M. Lentz, and D. J. Brunelle, J. Am. Chem. Soc., **97**, 107 (1975).
82. C. Chassin, E. A. Schmidt, and H. M. R. Hoffmann, J. Am. Chem. Soc., **96**, 606 (1974).
83. Y. Hayakawa and R. Noyori, Nagoya University, Nagoya, Japan, unpublished results.
84. R. C. Cookson and M. J. Nye, Proc. Chem. Soc., London, **1963**, 129.
85. R. C. Cookson and M. J. Nye, J. Chem. Soc., **1965**, 2009.
86. R. Noyori, S. Makino, and H. Takaya, J. Am. Chem. Soc., **93**, 1272 (1971).
87. H. M. R. Hoffmann and R. Chidgey, Tetrahedron Lett., **1978**, 85.
88. R. Chidgey and H. M. R. Hoffmann, Tetrahedron Lett., **1977**, 2633.
89. H. Takaya, Y. Hayakawa, S. Makino, and R. Noyori, J. Am. Chem. Soc., **100**, 1778 (1978).
90. R. Noyori, Y. Hayakawa, S. Makino, and H. Takaya, Chem. Lett., **1973**, 3.
91. A. Busch and H. M. R. Hoffmann, Tetrahedron Lett., **1976**, 2379.
92. D. I. Rawson, B. K. Carpenter, and H. M. R. Hoffmann, J. Am. Chem. Soc., **101**, 1786 (1979).
93. H. M. R. Hoffmann, K. E. Clemens, and R. H. Smithers, J. Am. Chem. Soc., **94**, 3940 (1972).
94. R. C. Cookson, M. J. Nye, and G. Subrahmanyam, J. Chem. Soc. C, **1967**, 473.
95. R. K. Siemionko and J. A. Berson, J. Am. Chem. Soc., **102**, 3870 (1980).
96. W. Wierenga, B. R. Evans, and J. A. Woltersom, J. Am. Chem. Soc., **101**, 1334 (1979).

97. S. A. Monti and J. M. Harless, J. Am. Chem. Soc., **99**, 2690 (1977).
98. K. Kashman and A. Rudi, Tetrahedron, **30**, 109 (1974).
99. T. Ishizu, M. Mori, and K. Kanematsu, J. Org. Chem., **46**, 526 (1981).
100. A. S. Narula, Tetrahedron Lett., **1979**, 1921.
101. G. Fierz, R. Chidgey, and H. M. R. Hoffmann, Angew. Chem., Int. Ed. Engl., **13**, 410 (1974).
102. (a) A. P. Cowling and J. Mann, J. Chem. Soc., Perkin Trans. 1, **1978**, 1564; (b) A. P. Cowling, J. Mann, and A. A. Usmani, *ibid.*, **1981**, 2116.
103. R. Noyori, S. Makino, Y. Baba, and Y. Hayakawa, Tetrahedron Lett., **1974**, 1049.
104. R. Noyori, Y. Baba, and Y. Hayakawa, J. Am. Chem. Soc., **96**, 3336 (1974).
105. J. D. White and Y. Fukuyama, J. Am. Chem. Soc., **101**, 226 (1979).
106. M. J. Arco, M. H. Trammell, and J. D. White, J. Org. Chem., **41**, 2075 (1976).
107. M. R. Ashcroft and H. M. R. Hoffmann, Org. Synth., **58**, 17 (1978).
108. Y. Ito, M. Asada, K. Yonezawa, and T. Saegusa, Synth. Commun., **4**, 87 (1974).
109. R. Noyori, S. Makino, and H. Takaya, Tetrahedron Lett., **1973**, 1745.
110. Y. Hayakawa, M. Sakai, and R. Noyori, Chem. Lett., **1975**, 509.
111. R. Noyori, S. Makino, T. Okita, and Y. Hayakawa, J. Org. Chem., **40**, 806 (1975).
112. (a) S. Masamune, C. U. Kim, K. E. Wilson, G. O. Spessard, P. E. Georghiou, and G. S. Bates, J. Am. Chem. Soc., **97**, 3512 (1975); (b) S. Masamune, H. Yamamoto, S. Kamata, and A. Fukuzawa, *ibid.*, **97**, 3513 (1975).
113. (a) R. Noyori, T. Sato, and Y. Hayakawa, J. Am. Chem. Soc., **100**, 2561 (1978); (b) T. Sato, R. Ito, Y. Hayakawa, and R. Noyori, Tetrahedron Lett., **1978**, 1829.
114. (a) T. Sato, M. Watanabe, and R. Noyori, Tetrahedron Lett., **1978**, 4403; (b) T. Sato, M. Watanabe, and R. Noyori, Chem. Lett., **1978**, 1297; (c) T. Sato, M. Watanabe, and R. Noyori, Tetrahedron Lett., **1979**, 2897; (d) T. Sato, K. Marunouchi, and R. Noyori, *ibid.*, **1979**, 3669; (e) T. Sato and R. Noyori, *Nucleic Acids Research*, Symposium Series No. 6, 19 (1979); (f) T. Sato and R. Noyori, Heterocycles, **13**, 141 (1979); (g) T. Sato and R. Noyori, Bull. Chem. Soc. Jpn., **53**, 1195 (1980); (h) T. Sato, M. Watanabe, and R. Noyori, Heterocycles, **14**, 761 (1980); (i) T. Sato, H. Kobayashi, and R. Noyori, Tetrahedron Lett., **21**, 1971 (1980); (j) T. Sato, M. Watanabe, and R. Noyori, Chem. Lett., **1980**, 679; (k) T. Sato and R. Noyori, Tetrahedron Lett., **21**, 2535 (1980); (l) T. Sato, H. Kobayashi, and R. Noyori, Heterocycles, **15**, 321 (1981).

115. (a) R. S. Glass, D. R. Deardorff, and L. H. Gains, Tetrahedron Lett., **1978**, 2965; (b) S. R. Wilson and R. A. Sawicki, *ibid.*, **1978**, 2969.
116. (a) R. J. Giguere, D. I. Rawson, and H. M. R. Hoffmann, Synthesis, **1978**, 902; (b) R. J. Giguere, H. M. R. Hoffmann, M. B. Hursthouse, and J. Trotter, J. Org. Chem., **46**, 2868 (1981).
117. R. Noyori, M. Nishizawa, F. Shimizu, Y. Hayakawa, K. Maruoka, S. Hashimoto, H. Yamamoto, and H. Nozaki, J. Am. Chem. Soc., **101**, 220 (1979).
118. Y. Hayakawa, K. Yokoyama, and R. Noyori, J. Am. Chem. Soc., **100**, 1791 (1978).
119. R. Noyori, K. Yokoyama, and Y. Hayakawa, J. Am. Chem. Soc., **95**, 2722 (1973).
120. Y. Hayakawa, K. Yokoyama, and R. Noyori, Tetrahedron Lett., **1976**, 4347.
121. Y. Hayakawa, F. Shimizu, and R. Noyori, Tetrahedron Lett., **1978**, 993.
122. Y. Hayakawa, K. Yokoyama, and R. Noyori, J. Am. Chem. Soc., **100**, 1799 (1978).
123. R. Noyori, K. Yokoyama, S. Makino, and Y. Hayakawa, J. Am. Chem. Soc., **94**, 1772 (1972).
124. R. Noyori, K. Yokoyama, and Y. Hayakawa, Org. Synth., **58**, 56 (1978).
125. (a) R. M. Coates and R. L. Sowerby, J. Am. Chem. Soc., **93**, 1027 (1971); (b) G. Stork and J. Benaim, *ibid.*, **93**, 5938 (1971).
126. (a) R. A. Raphael, *Chemistry of Carbon Compounds*, E. H. Rodd, Ed., Vol. **IIA**, Elsevier, Amsterdam, 1953, pp. 298–307; (b) N. A. J. Rogers, *Rodd's Chemistry of Carbon Compounds*, S. Coffey, Ed., Vol. **IIC**, 2nd ed., Elsevier, Amsterdam, 1969, pp. 20–31; (c) A. P. Krapcho, Synthesis, **1974**, 383.
127. M.-A. Barrow, A. C. Richards, R. H. Smithers, and H. M. R. Hoffmann, Tetrahedron Lett., **1972**, 3101.
128. H. M. R. Hoffmann, K. E. Clemens, and E. A. Schmidt, J. Am. Chem. Soc., **94**, 3201 (1972).
129. (a) C. H. Eugster, Adv. Org. Chem., **2**, 427 (1960); (b) S. Wilkinson, Quart. Rev., Chem. Soc., **15**, 153 (1961).
130. A. J. Fry, G. S. Ginsburg, and R. A. Parente, J. Chem. Soc., Chem. Commun., **1978**, 1040.
131. (a) T. Ishizu, K. Harano, M. Yasuda, and K. Kanematsu, J. Org. Chem., **46**, 3630 (1981); (b) T. Ishizu, K. Harano, M. Yasuda, and K. Kanematsu, Tetrahedron Lett., **22**, 1601 (1981).
132. T. Nakao, K. Kurita, H. Awaya, Y. Tominaga, Y. Matsuda, and G. Kobayashi, *"Abstracts of Papers," 11th Symposium on Nonbenzenoid Aromatic Compounds, Osaka, Oct. 1978*, Chemical Society of Japan,

Tokyo, 1978.
133. C. Rappe, Acta Chem. Scand., **16**, 2467 (1962).
134. E. LeGoff, J. Org. Chem., **29**, 2048 (1964).
135. (a) R. D. Clark and C. H. Heathcock, J. Org. Chem., **41**, 636 (1976); (b) J. M. Denis, C. Girard, and J. M. Conia, Synthesis, **1972**, 549.
136. R. B. King, Organometal. Synth., **1**, 128 (1965).
137. R. M. Evans, J. C. Hamlet, J. S. Hunt, P. G. Jones, A. G. Long, J. F. Oughton, L. Stephenson, T. Walker, and B. M. Wilson, J. Chem. Soc., **1956**, 4356.
138. A. W. Fort, J. Am. Chem. Soc., **84**, 2620 (1962).
139. G. Rosenkranz, J. Pataki, St. Kaufmann, J. Berlin, and C. Djerassi, J. Am. Chem. Soc., **72**, 4081 (1950).
140. K. L. Williamson and W. S. Johnson, J. Org. Chem., **26**, 4563 (1961).
141. K. E. Harding, J. W. Trotter, and L. May, Synth. Commun., **2**, 231 (1972).
142. J.-E. Dubois, P. Fournier, and C. Lion, Tetrahedron Lett., **1975**, 4263.
143. K. Gump, S. W. Moje, and C. E. Castro, J. Am. Chem. Soc., **89**, 6770 (1967).
144. R. R. Sauers and C. K. Hu, J. Org. Chem., **36**, 1153 (1971).
145. P. A. Grieco, T. Oguri, and S. Gilman, J. Am. Chem. Soc., **102**, 5886 (1980).
146. G. Rosenkranz, O. Mancera, J. Gatica, and C. Djerassi, J. Am. Chem. Soc., **72**, 4077 (1950).
147. F. Sondheimer, G. Rosenkranz, O. Mancera, and C. Djerassi, J. Am. Chem. Soc., **75**, 2601 (1953).
148. S. Binns, J. S. G. Cox, E. R. H. Jones, and B. G. Ketcheson, J. Chem. Soc., **1964**, 1161.
149. R. E. Beyler, F. Hoffman, L. H. Sarett, and M. Tishler, J. Org. Chem., **26**, 2426 (1961).
150. J.-E. Dubois and J. Itzkowitch, Tetrahedron Lett., **1965**, 2839.
151. B. K. Carpenter, D. I. Rawson, and H. M. R. Hoffmann, Chem. Ind. (London), **1975**, 886.
152. E. Ghera, Y. Gaoni, and S. Shoua, J. Am. Chem. Soc., **98**, 3627 (1976).
153. P. R. Brook and J. G. Griffiths, J. Chem. Soc. D, Chem. Commun., **1970**, 1344.
154. M. Rey, U. A. Huber, and A. S. Dreiding, Tetrahedron Lett., **1968**, 3583.
155. D. A. Bak and W. T. Brady, J. Org. Chem., **44**, 107 (1979).
156. E. J. Corey, Z. Arnold, and J. Hutton, Tetrahedron Lett., **1970**, 307.
157. R. G. Carlson and W. S. Mardis, J. Org. Chem., **40**, 817 (1975).

158. R. Chidgey and H. M. R. Hoffmann, Tetrahedron Lett., **1978**, 1001.
159. R. Noyori, Y. Baba, S. Makino, and H. Takaya, Tetrahedron Lett., **1973**, 1741.
160. R. Noyori, H. Kobayashi, and T. Sato, Tetrahedron Lett., **21**, 2573 (1980).
161. R. Noyori, T. Sato, and H. Kobayashi, Tetrahedron Lett., **21**, 2569 (1980).
162. J. G. Vinter and H. M. R. Hoffmann, J. Am. Chem. Soc., **95**, 3051 (1973).
163. H. E. Hennis and W. B. Trapp, J. Org. Chem., **26**, 4678 (1961).
164. H. M. R. Hoffmann and R. H. Smithers, Angew. Chem., **82**, 43 (1970).

Replacement of Alcoholic Hydroxyl Groups by Halogens and Other Nucleophiles via Oxyphosphonium Intermediates

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1. Introduction

The Michaelis–Arbuzov reaction involves the formation of dialkyl alkylphosphonates by heating alkyl halides with trialkyl phosphites, via an intermediate phosphonium salt **1**. (1, 2)

$$(RO)_3P + R'X \longrightarrow \underset{\mathbf{1}}{(RO)_3P^+R', X^-} \xrightarrow{\text{Heat}} (RO)_2P(O)R' + RX \quad (1)$$

In recent years it has been found that phosphonium salts analogous to **1** can be formed by reaction of a variety of trivalent phosphorus compounds with oxidizing electrophiles, and that the resulting phosphonium intermediates can be trapped with an alcohol to form alkoxyphosphonium cations. These cations can then undergo nucleophilic displacements, either with their own counterions or with added nucleophiles (Eqs. 2 and 3).

$$Y_3P + XE \longrightarrow Y_3P^+E, X^- \xrightarrow{\text{ROH}} Y_3P^+OR \quad (2)$$

$$Y_3P^+OR \begin{cases} \xrightarrow{\text{(a) } E^-} Y_3PO + RE \\ \xrightarrow{\text{(b) } X^-} Y_3PO + RX \\ \xrightarrow[\text{(c)}]{A^-} Y_3PO + RA \end{cases} \quad (3)$$

In Eq. 2, XE is the oxidizing electrophile. The path followed in Eq. 3 depends on the reagents and the reaction conditions.

Although the electrophilic phosphorus species Y_3P^+E, X^- in Eq. 2 are formally equivalents of phosphorus pentachloride, this review is limited to species formed *in situ* from trivalent phosphorus compounds and various oxidants. The most commonly used trivalent phosphorus compounds are triphenyl phosphite, triphenylphosphine, and tris(dimethylamino)phosphine. The most commonly used oxidants are molecular halogens, alkyl halides, carbon tetrahalides,

N-haloamides, N-haloamines, and diethyl azodicarboxylate (DEAD). Other oxidants that have been used include mercuric salts, peroxides, dithioesters, and sulfenamides. The more common combinations of phosphorus(III) compounds and oxidants are summarized in Table 1.

Table 1. Combinations of Phosphorus(III) Compounds and Oxidants for Replacement of Hydroxyl Groups by Halogens (X) or Other Nucleophiles (O, N, S, C)

	PY_3		
Oxidant	**$P(OC_6H_5)_3$**	**$P(C_6H_5)_3$**	**$P[N(CH_3)_2]_3$**
X_2	X	X	
RX	X		
CX_4		X, N	X, N, S, O, C
R_2NX		X	X, N, S, O, C
DEAD		O, N, C, X	

The replacement of hydroxyl groups by halogen, the most common use of oxyphosphonium intermediates, is the principal subject of this chapter. However, the replacement of hydroxyl groups by oxygen, nitrogen, sulfur, and carbon nucleophiles is also discussed. This review is restricted to alcoholic hydroxyl groups, and does not include a discussion of carboxylic hydroxyl groups.

The principal combinations covered are triphenylphosphine–diethyl azodicarboxylate, triphenyl phosphite-methiodide, triphenylphosphine-halogen, triphenylphosphine–tetrahalomethane, triphenylphosphine–N-haloimide, and tris(dimethylamino)phosphine–tetrahalomethane. Some of these combinations have been discussed in recent reviews. (3-7)

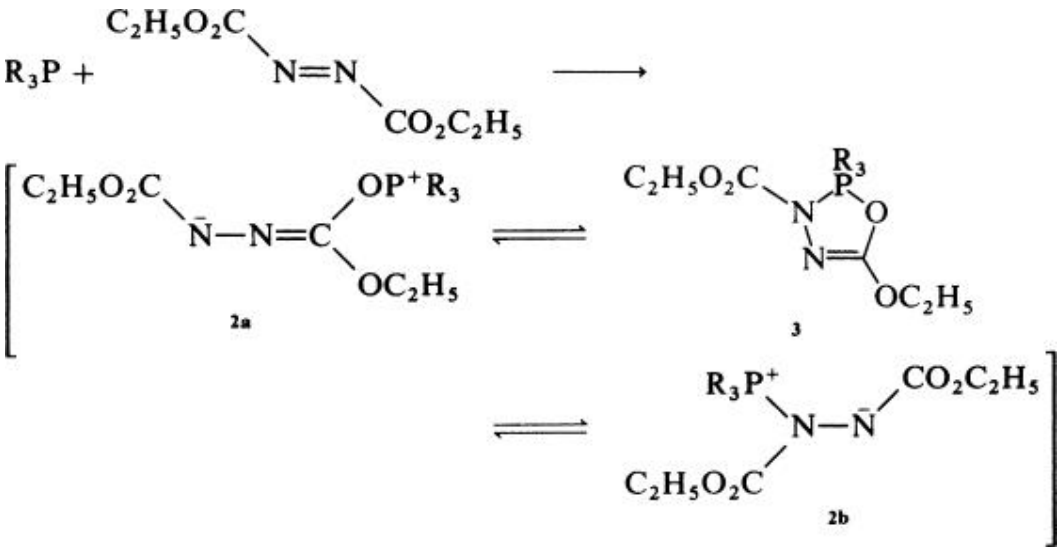
2. Mechanism

The general course of the replacement of alcoholic hydroxyl groups via oxyphosphonium intermediates is shown in Eqs. 2 and 3. Some insight into the details of the mechanism has been obtained from studies of the triphenylphosphine–diethyl azodicarboxylate, triphenylphosphine–carbon tetrachloride, and tris(dimethylamino)phosphine–carbon tetrachloride systems.

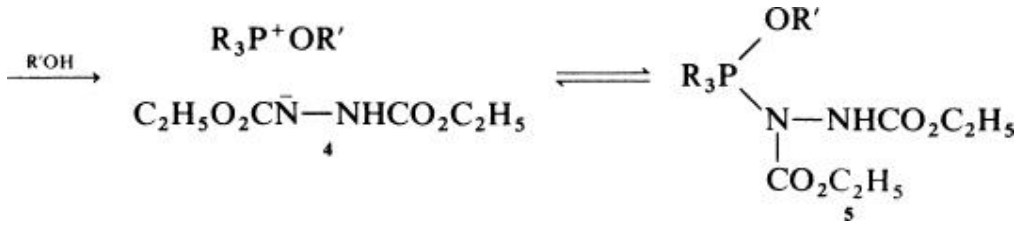
2.1. Triphenylphosphine–Diethyl Azodicarboxylate

The structure of the initial reaction product of a trivalent phosphorus compound with DEAD depends on the nature of the groups attached to phosphorus. With triphenylphosphine, both of the betaine intermediates **2a** (8) and **2b** (9, 10) have been postulated, and evidence in support of a betaine intermediate is found in the ^{31}P NMR spectrum of the adduct, in which the phosphorus chemical shift is 43 ppm downfield from phosphoric acid. On the other hand ^{31}P NMR spectra indicate that a pentacovalent phosphorane **3** is the intermediate when RO or R_2N groups are attached to phosphorus. (11, 12) These intermediates may be in dynamic equilibrium, as shown in Eq. 4.

In the presence of an alcohol R′OH the R′O group of the alcohol attaches to phosphorus to form an alkoxyphosphonium intermediate **4** or a phosphorane intermediate **5** (Eq. 5); the former appears more probable. In the absence of another nucleophile a displacement occurs to form a substituted hydrazino ester **6** (Eq. 6). However, in the presence of another nucleophile nucleophilic substitution takes place at the R¢ group of the alcohol (Eq. 7).



(4)



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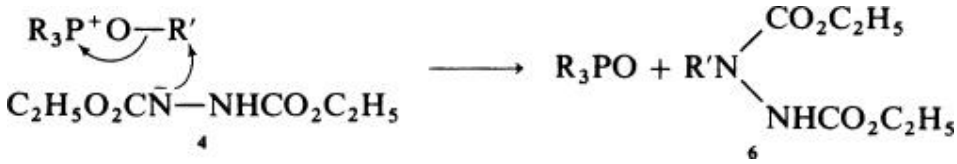
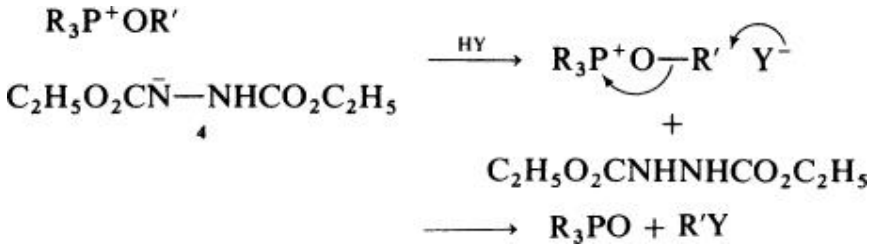


(6)



(7)

The nucleophilic substitution shown in Eq. 7 generally proceeds by an S_N2 mechanism with inversion of configuration, even with allylic substrates (13-15) and with substrates that can undergo neighboring group participation. (16) This characteristic inversion of configuration is one of the useful features of this reaction. On the other hand mixtures of products are usually found in substitutions at the anomeric position of sugars, and in reactions of cholesterol, (17) where an S_N1 mechanism appears to be involved.

2.2. Triphenylphosphine–Carbon Tetrachloride

Pure triphenylphosphine and pure carbon tetrachloride react only very slowly, even at reflux temperature. (18, 19) A small amount of a polar substance such as water, an alcohol, a ketone, or a solvent such as methylene chloride or acetonitrile is necessary to initiate the reaction. Furthermore, the polarity of the solvent plays an important role in determining the reaction rate, which is 10^4 and 10^6 times higher in methylene chloride and acetonitrile, respectively, than it is in carbon tetrachloride alone.

It has been shown that in the absence of an alcohol the reaction proceeds as shown in Eqs. 8–11. (20, 21)

$$R_3P + CCl_4 \longrightarrow \underset{7}{R_3P^+CCl_3, Cl^-} \quad (8)$$

$$R_3P^+CCl_3, Cl^- + R_3P \longrightarrow R_3P{=}CCl_2 + R_3PCl_2 \quad (9)$$

$$R_3P{=}CCl_2 + R_3PCl_2 \longrightarrow R_3P^+CCl_2P^+R_3, 2Cl^- \quad (10)$$

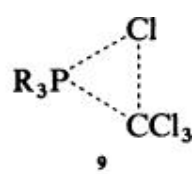
$$R_3P^+CCl_2P^+R_3, 2Cl^- + R_3P \longrightarrow R_3P^+CCl{=}PR_3, Cl^- + R_3PCl_2 \quad (11)$$

There is no accumulation of any of the intermediates in these four steps, and the reaction appears to proceed directly as shown in Eq. 12.

$$3R_3P + CCl_4 \longrightarrow R_3P^+CCl{=}PR_3, Cl^- + R_3PCl_2 \quad (12)$$

The intermediates shown in Eqs. 8–11 have been isolated and characterized. However, since the first step of the reaction does not occur spontaneously but must be catalyzed by a substrate or a solvent, charge-transfer species such as **8** and **9** appear to be involved.

$$R_3P + CCl_4 \rightleftharpoons \underset{8}{R_3P^{\delta+}\text{---}Cl\text{---}^{\delta-}CCl_3} \rightleftharpoons$$

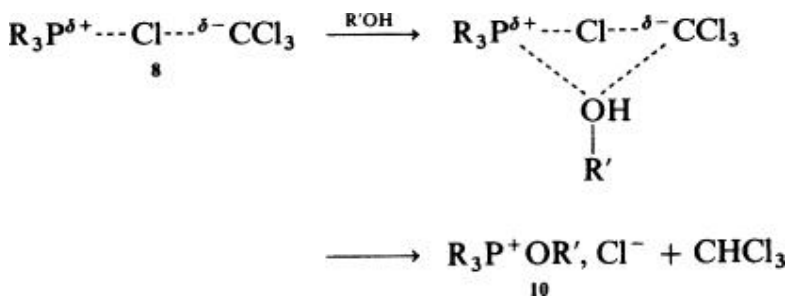


9

$$\longrightarrow \underset{7}{R_3P^+CCl_3, Cl^-}$$

When the reaction is carried out in the presence of an alcohol, oxyphosphonium intermediates (**10**) can be formed by two different routes:

1. In the *chloroform route* (Eq. 13) the alcohol reacts directly with the charge-transfer species, liberating chloroform.



(13)

2. In the *ylid route* (Eq. 14) the reaction of the phosphine and the halide proceeds by way of Eqs. 8 and 9, and the oxyphosphonium ion **10** is formed by trapping the basic ylid and the chloromethylphosphonium chloride **11**.

$$R_3P{=}CCl_2 + R_3PCl_2 + R'OH \longrightarrow \underset{11}{R_3P^+CHCl_2, Cl^-} + \underset{10}{R_3P^+OR', Cl^-} \qquad (14)$$

When the reaction proceeds by way of Eq. 14, the intermediate phosphonium salt **11** is dehalogenated by triphenylphosphine to give an ylid **12** and a triphenylphosphine–chlorine complex **13** that can be trapped by another molecule of alcohol (Eq. 15).

$$\underset{11}{R_3P^+CHCl_2, Cl^-} + R_3P \longrightarrow \underset{12}{R_3P{=}CHCl} + \underset{13}{R_3PCl_2}$$

$$\xrightarrow{R'OH} R_3P^+CH_2Cl, Cl^- + \underset{10}{R_3P^+OR', Cl^-} \qquad (15)$$

Reactions that proceed by the ylid route (Eqs. 14 and 15) are characterized by the facts that (1) little or no chloroform is evolved, and (2) more triphenylphosphine is required to complete the reaction. The latter point is important to the achievement of high yields.

The polarity of the reaction solvent appears to influence which of the two routes is followed. When the reaction is carried out with benzyl alcohol in the moderately polar methylene chloride, 46% of the theoretical amount of

chloroform is evolved, and the balance of the reaction proceeds by the ylid route. (20) On the other hand, when the reaction is carried out with cyclohexanol in the less polar carbon tetrachloride, less than 5% of the theoretical amount of chloroform is evolved, and the chloromethylphosphonium chloride **11** is isolated in 95% yield. (22)

The oxyphosphonium intermediate **10** is generally written in the ionic form first postulated by Downie and co-workers. (23)

$$\underset{\mathbf{10}}{(C_6H_5)_3P^+OR,\ Cl^-}$$

However, later investigators favor a molecular pentacovalent intermediate, and such intermediates have been isolated from reactions of hindered alcohols such as neopentyl alcohol, (24, 25) isocholesterol, (26) norbornanols, (24) and benzobicyclooctadienols. (27)

Formation of intermediate salt **10** is generally fast and largely independent of steric hindrance. (25) On the other hand the rates of decay of the intermediate salts **10** to the products are much more sensitive to steric hindrance: primary intermediates give halides very quickly at room temperature, whereas secondary and neopentylic intermediates require prolonged heating.

This feature often allows selective reaction of primary and secondary alcoholic hydroxyl groups; even if both hydroxyls are activated in the first step of the reaction, careful optimization of reaction time and temperature can allow decay of the primary intermediate and hydrolysis of the secondary one during workup.

The intermediate salt **10** usually exhibits a strong tendency to undergo an S_N2 displacement with inversion of configuration, and neopentylic rearrangement does not take place.

$$(S)\text{-}t\text{-}C_4H_9CHDOH \xrightarrow{(C_6H_5)_3P/CBr_4} \underset{\mathbf{14}}{(R)\text{-}t\text{-}C_4H_9CHDBr}$$

The optical rotation of the deuteriobromide **14** is 3.5 times higher than that of **14** obtained by displacement of the corresponding alcohol tosylate with lithium bromide. (28)

Alcohols that have a tendency to undergo S_N1 reactions generally give rearrangement products if the reaction cannot be performed at low temperature; such rearrangements are often observed with allylic substrates. (29, 30) Reactions at the anomeric position of sugars generally proceed by an S_N1 mechanism. (31) Skeletal rearrangements are usually observed with hindered structures bearing groups that can participate in the reaction. (24, 27)

2.3. Tris(dimethylamino)phosphine–Carbon Tetrachloride

This reaction appears to proceed by the mechanism shown in Eq. 16.

$$[(CH_3)_2N]_3P + ClCCl_3 \xrightarrow{\text{Fast}} \underset{15}{[(CH_3)_2N]_3P^+Cl, CCl_3^-} \xrightarrow{\text{ROH}}$$

$$\underset{16}{HCCl_3 + [(CH_3)_2N]_3P^+OR, Cl^-} \begin{cases} \xrightarrow{\text{Slow}} [(CH_3)_2N]_3PO + RCl \\ \xrightarrow[H_2O]{NH_4PF_6} [(CH_3)_2N]_3P^+OR, PF_6^- \end{cases} \quad (16)$$

The high nucleophilicity of the aminophosphine allows complete charge transfer to the trichloromethyl anion, whose existence has been demonstrated by trapping experiments with aldehydes, ketones, and acid anhydrides. (32-34) The existence of the oxyphosphonium salt **16** is established by running the reaction at low temperatures, since the salt does not break down to the alkyl chloride at temperatures below 0°. The formation of salt **16** is very rapid with primary alcohols. However, with bulky or secondary alcohols the aminophosphine must be added to the carbon tetrachloride solution of the alcohol slowly to obtain high yields; too rapid an addition is signaled by a darkening of the solution. This effect can be explained by the equilibrium shown in Eq. 17. When the formation of the intermediate **17** is slow because of the bulk of the **R** group, the alternative reactions shown in Eqs. 18 and 19 become prominent.

$$\underset{15}{[(CH_3)_2N]_3P^+Cl, CCl_3^-} + ROH \rightleftharpoons CHCl_3 + \underset{17}{[(CH_3)_2N]_3P^+Cl, RO^-}$$

$$\longrightarrow \underset{16}{[(CH_3)_2N]_3P^+OR, Cl^-} \quad (17)$$

$$\underset{15}{[(CH_3)_2N]_3P^+Cl, CCl_3^-} \longrightarrow CCl_2 + [(CH_3)_2N]_3P^+Cl, Cl^- \quad (18)$$

$$\underset{15}{[(CH_3)_2N]_3P^+Cl, CCl_3^-} \longrightarrow [(CH_3)_2N]_3P^+CCl_3, Cl^- \quad (19)$$

Replacement of carbon tetrachloride with N-chlorodiisopropylamine gives a more stable conjugate base than the trichloromethide ion, allowing the preparation of oxyphosphonium salts in high yields from secondary alcohols. (35)

The reaction is faster in nonpolar solvents, where the ionic partners form a tight ion pair, than in polar solvents, where the ions are dissociated. (36) The hexamethylaminophosphoryl group appears to be a poorer leaving group than triphenylphosphoryl in the triphenylphosphine–carbon tetrachloride system, and there is less tendency for an S_N1 displacement in the former case. Hexafluorophosphate salts derived from anomeric hydroxyl groups of carbohydrates (37-40) and from substituted allylic alcohols (41) are not easily isolated at room temperature because they are hydrolyzed to the starting alcohols. They are detectable at low temperatures by their characteristic ^{31}P NMR signal, which is 35 ppm downfield from phosphoric acid.

3. Scope and Limitations

Each of the phosphorus(III) systems covered in this review has its own characteristics and area of utility; accordingly, the scope and limitations of each are discussed separately in this section.

3.1. Triphenylphosphine–Diethyl Azodicarboxylate and Related Systems

The first studies of the reactions of azodicarboxylic esters with trivalent phosphites and phosphines appeared from 1958 to 1960. (42, 43) It was later shown that the triphenylphosphine–diethyl azodicarboxylate combination can activate the alcoholic hydroxyl group, leading to formation of substituted hydrazino esters containing the R group of the alcohol. (8) Addition of various nucleophiles to this combination has provided routes for conversion of alcohols to a variety of carbon–nitrogen compounds, esters, ethers, and alcohol dehydration products. This system has become the most versatile and synthetically useful of all the phosphorus(III) systems for replacement of alcoholic hydroxyl groups.

3.1.1.1. Formation of Carbon — Nitrogen Bonds *

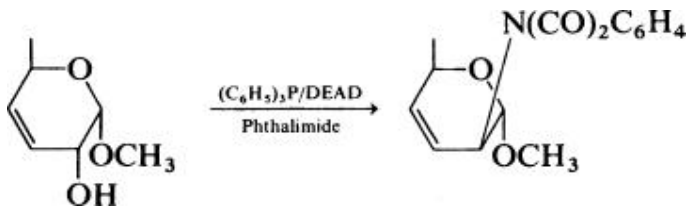
The reaction of an alcohol, DEAD, and triphenylphosphine generally proceeds in less than 1 hour at room temperature to give an N-alkyl-N,N -dicarbethoxyhydrazine (**6**, Eqs. 4-6). (8, 44-46) A tricarbethoxy compound $RN(CO_2C_2H_5)N(CO_2C_2H_5)_2$ is often obtained as a by-product; the reason for its formation is not clear. (44) Another side reaction is the formation of an ethyl alkyl carbonate, particularly when tris(dimethylamino)phosphine is used in place of triphenylphosphine. (47) Reaction at the anomeric position of sugars gives glycosylhydrazines. (45)

In four-component systems, where the alcohol is used with another nucleophile, the triphenylphosphine–diethyl azodicarboxylate combination has the role of a water acceptor.

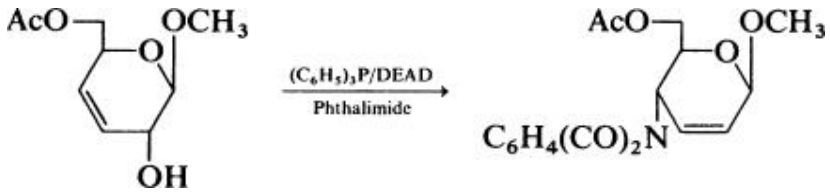
Condensations with imides, particularly phthalimides, can be used to form N-alkylphthalimides, which are useful precursors of alkylamines; this reaction is a modification of the Gabriel reaction. (48-52) Phthalimidation of secondary alcohols proceeds with inversion of configuration.

$$(S)\text{-}(+)\text{-}C_6H_{13}CHOHCH_3 + HN(CO)_2C_6H_4 \longrightarrow (R)\text{-}(-)\text{-}C_6H_{13}CH(CH_3)N(CO)_2C_6H_4$$

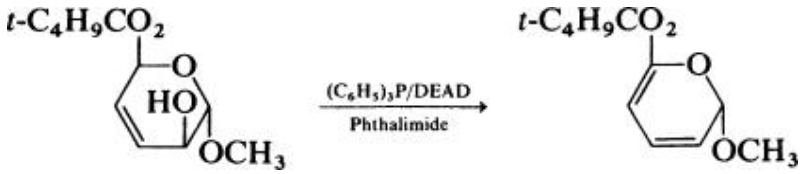
Reaction of allylic alcohols in the unsaturated sugar series can proceed by S_N2 (inversion, Eq. 20), S_N2' (retention, Eq. 21), or with elimination (Eq. 22), depending on the structure of the substrate.



(20)



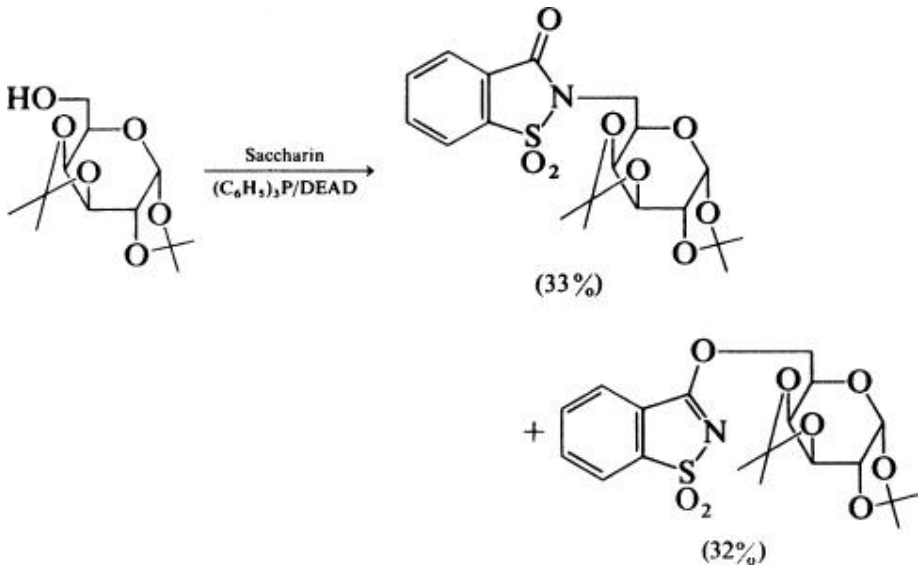
(21)



(22)

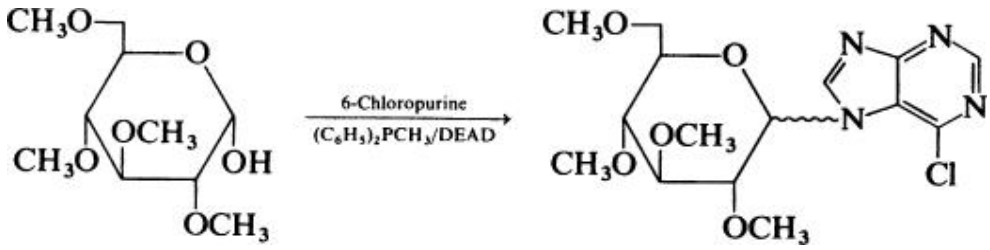
Phthalimidation of the anomeric position of sugars usually gives a mixture of α and β anomers.

Other imides, such as benzyloxycarbonyl benzamide (53-55) and saccharin, (56) can be used. Mixtures of N- and O-alkylation products are generally obtained (Eq. 23).



(23)

Nucleosides have been made by reacting sugars with 6-chloropurine in the presence of methyldiphenylphosphine and diethyl azodicarboxylate. The anomeric selectivity has been poor, apparently because the substrates have no participating or orienting groups. (57)



Use of hydrazoic acid as the nucleophile provides a very useful method for converting alcoholic hydroxyl groups into azides, (11, 58-64) and can lead to formation of a carbon — nitrogen bond in reactions in which phthalimide simply dehydrates the alcohol.

$$C_2H_5O_2CCHOHCH_2CO_2C_2H_5 \xrightarrow[\text{DEAD}]{(C_6H_5)_3P} \begin{cases} \xrightarrow{\text{Phthalimide}} C_2H_5O_2CCH{=}CHCO_2C_2H_5 \ (trans)\ (80\%) \\ \xrightarrow{HN_3} C_2H_5O_2CCH(N_3)CH_2CO_2C_2H_5 \ (75\%) \end{cases}$$

Diphenylphosphoryl azide has been used as a source of azide ion. (65)

$$3\text{-}\beta\text{-Cholestanol} \xrightarrow[(C_6H_5O)_2P(O)N_3]{(C_6H_5)_3P/\text{DEAD}} 3\text{-}\alpha\text{-Azidocholestane}$$

3.1.1.2. Formation of Esters

Esters of lower alcohols can be prepared by reaction of alkyl phosphites with acids in the presence of diethyl azodicarboxylate. (10, 66)

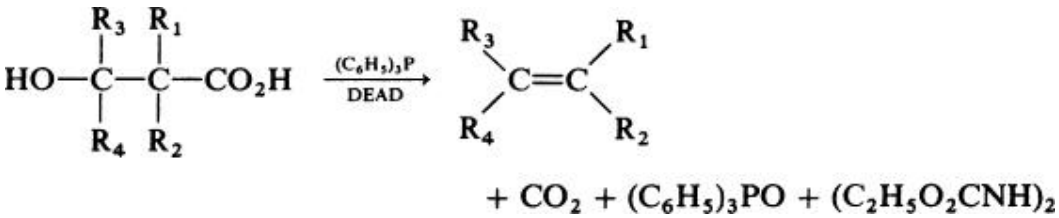
$$(C_2H_5O)_2POCH_2CH{=}CH_2 + n\text{-}C_4H_9CO_2H \xrightarrow{\text{DEAD}} n\text{-}C_4H_9CO_2CH_2CH{=}CH_2$$

Inversion of configuration is observed with phosphites of secondary alcohols.

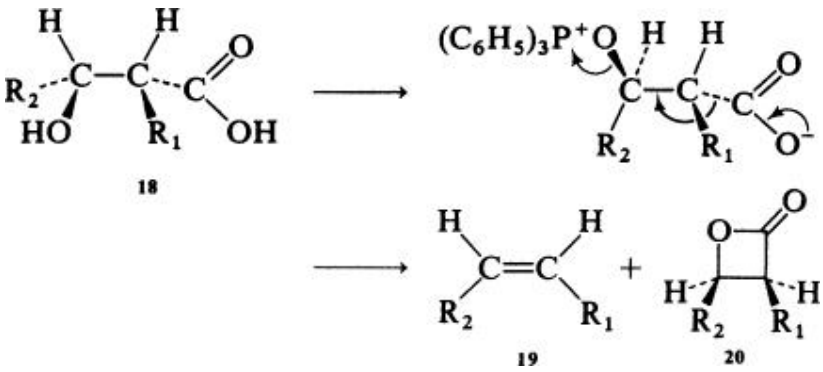
The trivalent phosphorus system most widely used for forming esters is triphenylphosphine–diethyl azodicarboxylate plus the alcohol and acid. Yields are generally excellent. Secondary alcohols undergo inversion of configuration. (11, 13, 15-17, 58, 66-69)

When highly hindered alcohols are used, only low yields of esters are obtained, and with retention of configuration. (70) Here it appears that the intermediate is an acyloxyphosphonium ion rather than an alkoxyphosphonium ion, and that ester formation results from reaction of this intermediate with the free alcohol. (71)

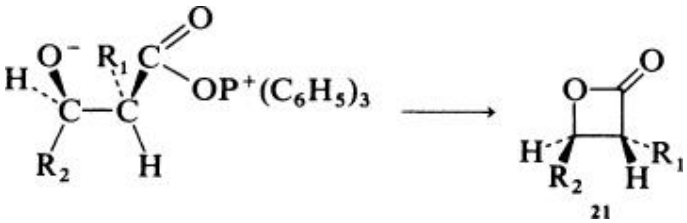
Treatment of β-hydroxy acids with this reagent brings about a decarboxylative dehydration to form an olefin. (72)



This reaction can be used for stereoselective preparation of (*Z*) and (*E*) alkenes. (73, 74) For example, the *threo*- β -hydroxy acid **18** is converted into the (*Z*) alkene **19**, with a small amount of the *cis*- β -lactone **20** as a by-product.

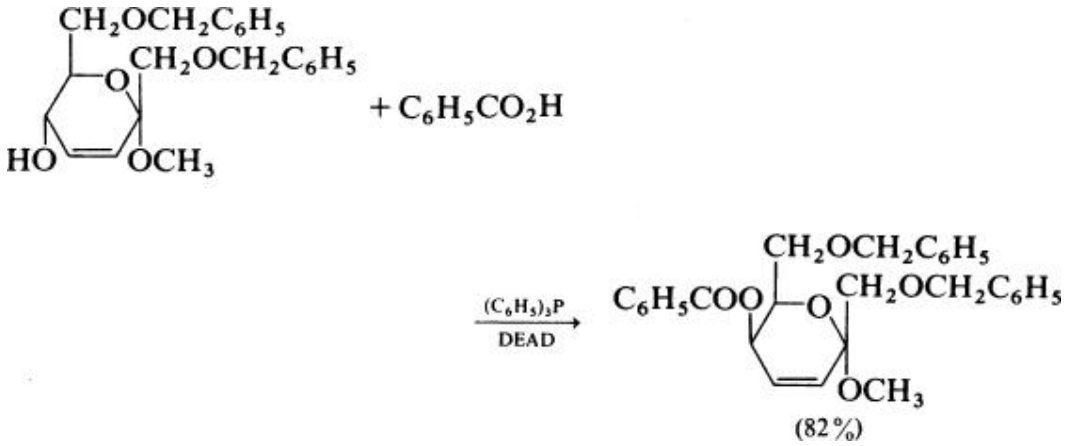


However, if $\mathbf{R}^1$ and $\mathbf{R}^2$ are bulky, an abnormal carboxyl activation occurs, resulting in exclusive formation of a *trans*- β-lactone (**21**).

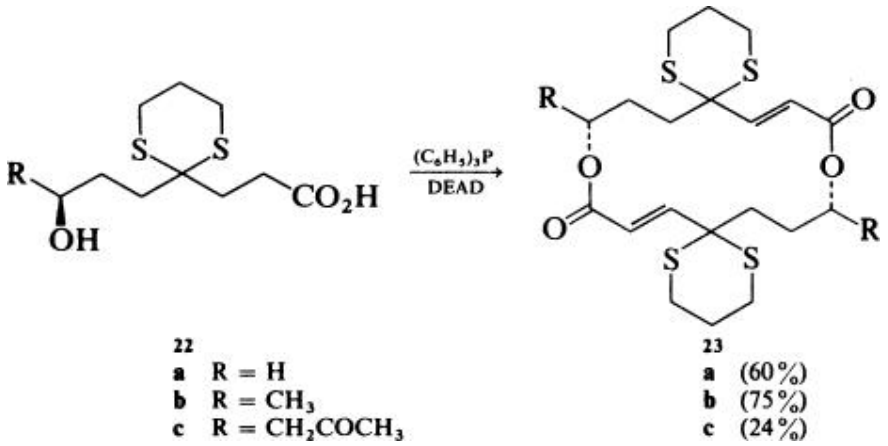


This reaction reflects the fact that hindered hydroxyl groups react more sluggishly with the triphenylphosphine–diethyl azodicarboxylate betaine intermediate, allowing time for activation of the carboxyl group. The effect seems closely related to the retention of configuration observed in the esterification of diacetone glucose. (70, 71)

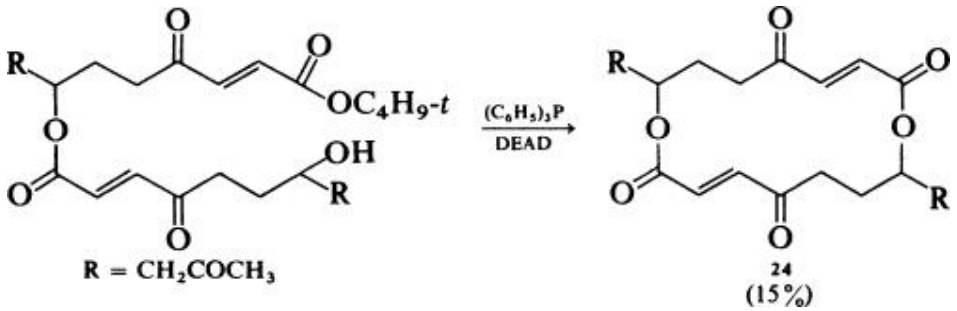
Substitution of allylic sugar alcohols leads to inverted, nontransposed products. (14)



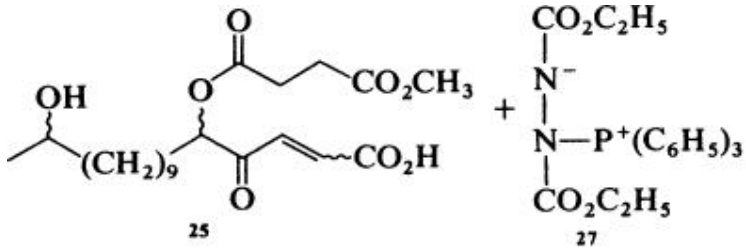
Long-chain ω -hydroxy acids can be converted into macrocyclic diolide lactones. (75) This type of cyclization has proven useful in syntheses of natural products. Thus double lactonizations of **22a** and **22b** to the carbonyl-protected derivatives of the diolides norpyrenophorin and pyrenophorin (**23a** and **23b**) have been accomplished in 60–75% yields (Eq. 24). (76) A significantly lower yield (24%) was obtained in converting **22c** to the vermiculine derivative **23c**. The deleterious effect of an unprotected carbonyl group in reactions with this reagent is manifested by the low yield (15%) in an earlier synthesis of vermiculine (**24**), which involved only a single lactonization (Eq. 25). (77) Another example of a low yield in the lactonization of a compound containing an open carbonyl group is the synthesis of the antibiotic **26** (designated A26771B). (78) Treatment of **25** with triphenylphosphine and diethyl azodicarboxylate gave a 1% yield of **26**; when the betaine **27**, preformed from triphenylphosphine and diethyl azodicarboxylate, was used as the reagent, the yield of **26** was 8% (Eq. 26).


R
OH
S
S
CO2H
(C6H5)3P
DEAD
O
R
22
a R = H
b R = CH3
c R = CH2COCH3
23
a (60%)
b (75%)
c (24%)

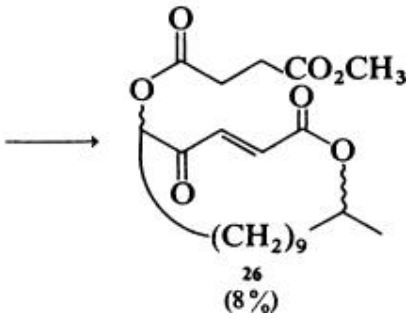
(24)


R
O
OC4H9-t
OH
R = CH2COCH3
(C6H5)3P
DEAD
24
(15%)

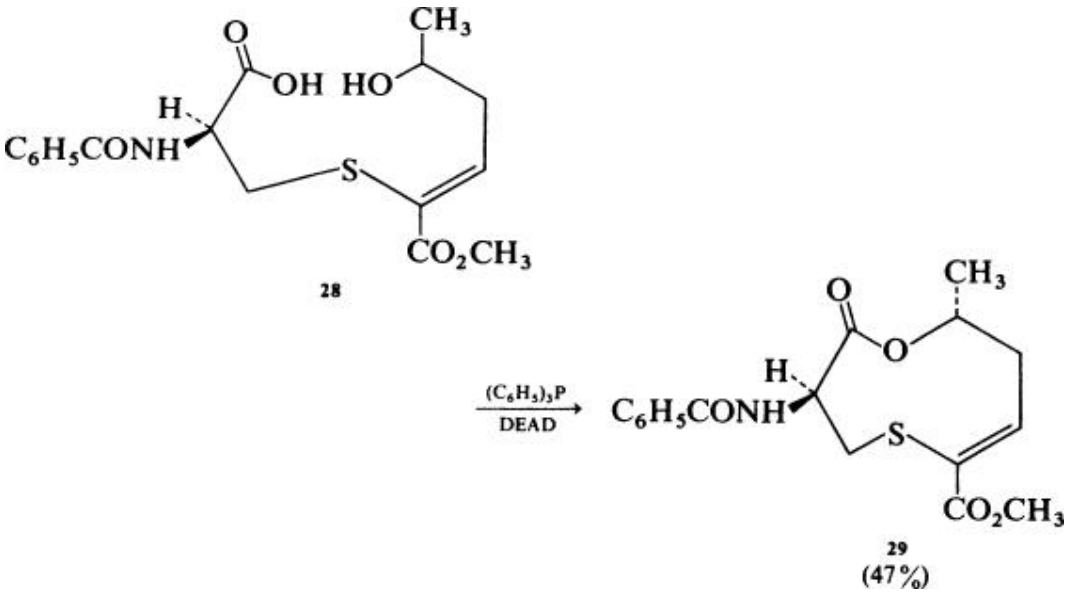
(25)


OH
O
CO2CH3
(CH2)9
CO2H
25
+
CO2C2H5
N−
N—P+(C6H5)3
CO2C2H5
27

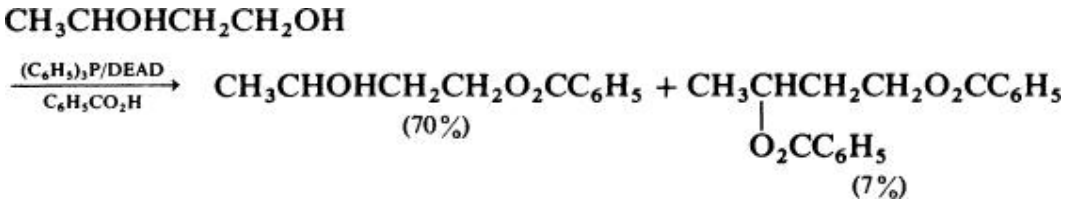
(26)


O
CO2CH3
(CH2)9
26
(8%)

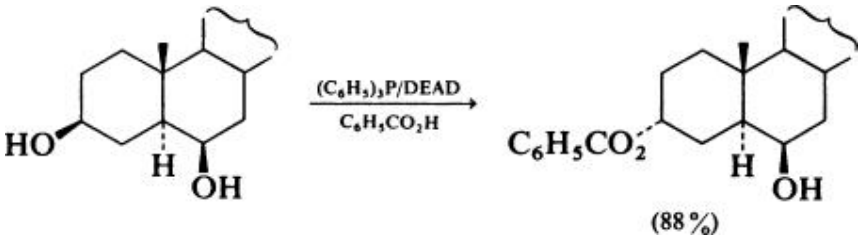
Stereospecific synthesis of the nine-membered lactone ring of griseoviridine (**29**) has been reported; (79) the chiral center in the hydroxy acid **28** controls the stereochemistry at the methyl group of lactone **29** during ring closure.



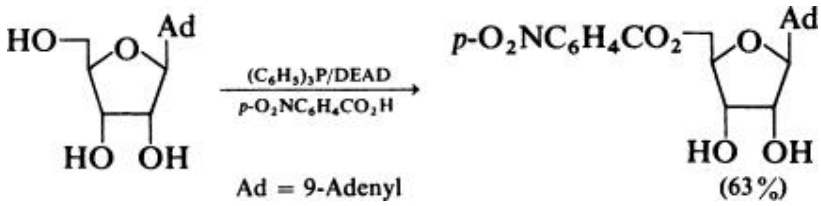
Benzoylation of aliphatic glycols generally gives mixtures of mono- and disubstituted esters, even where primary or secondary glycols are involved.



Selective esterification of the less hindered of two secondary hydroxyl groups in a steroid has been observed (Eq. 27). (69) The primary hydroxyl group of sugars is esterified selectively (Eq. 28). (13, 68, 80)

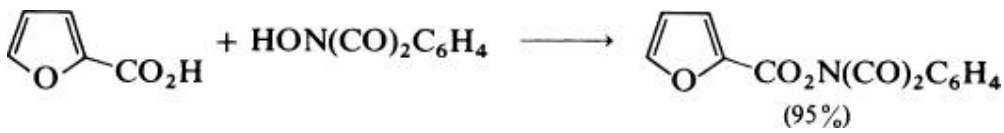


(27)

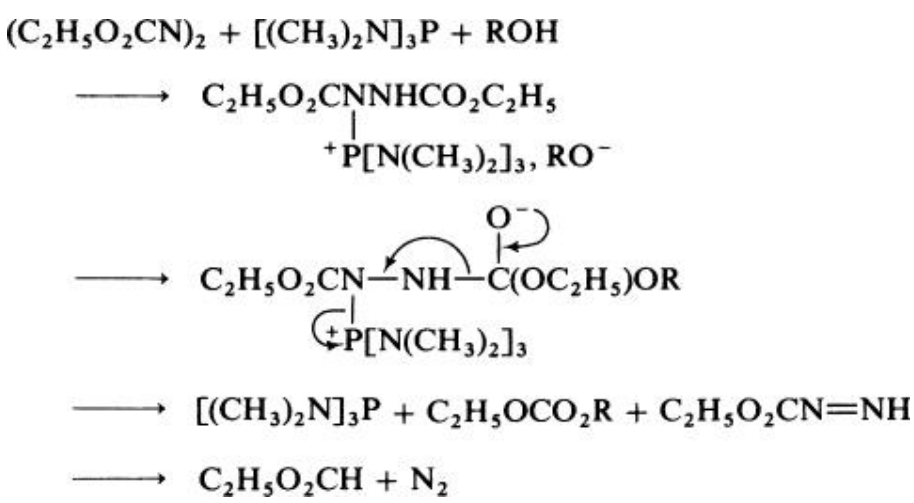


(28)

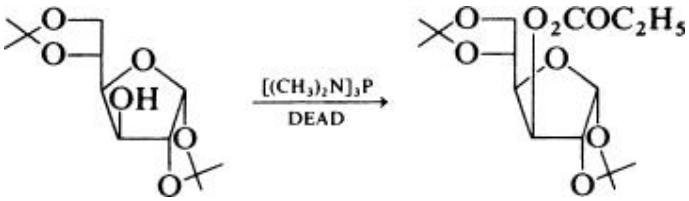
Esters of N-hydroxysuccinimide and N-hydroxyphthalimide can be prepared with this reagent. (81) The reaction appears to involve formation of an oxyphosphonium derivative of the N-hydroxyimide, which is attacked by the acid to give a transient acyloxyphosphonium cation that breaks down to the ester. (82)



The formation of carbonates, which is sometimes a side reaction in the use of the triphenylphosphine–diethyl azodicarboxylate reagent, (45) becomes the principal reaction when tris(dimethylamino)phosphine is used in place of triphenylphosphine. (47, 83) In this reaction transfer of the alkoxycarbonyl group from the azo ester is catalyzed by tris(dimethylamino)phosphine, and nitrogen is evolved. Yields are often good.



The reaction can be used to form carbonates of sugar secondary alcohols without inversion.

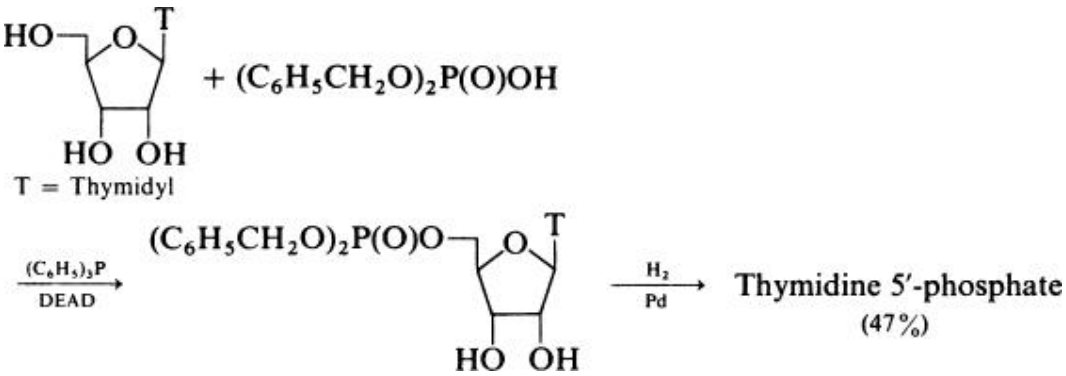


Sulfinic esters can be prepared by reaction of *p*-toluenesulfinic or *n*-dodecylsulfinic acid with alcohols in the presence of triphenylphosphine–diethyl azodicarboxylate. (84)

The triphenylphosphine–diethyl azodicarboxylate reagent can be used to prepare trisubstituted phosphates from disubstituted phosphates. (10, 53, 66, 85)

$$(C_6H_5CH_2O)_2P(O)OH + ROH \xrightarrow[\text{DEAD}]{(C_6H_5)_3P} (C_6H_5CH_2O)_2P(O)OR$$

Such esterification of di-*t*-butyl phosphate gives excellent yields of triesters that can be readily converted to monoalkyl phosphates by cleavage with trifluoroacetic acid. (86) This reaction can be used for selective phosphorylation of the 5 position of nucleosides. (85)

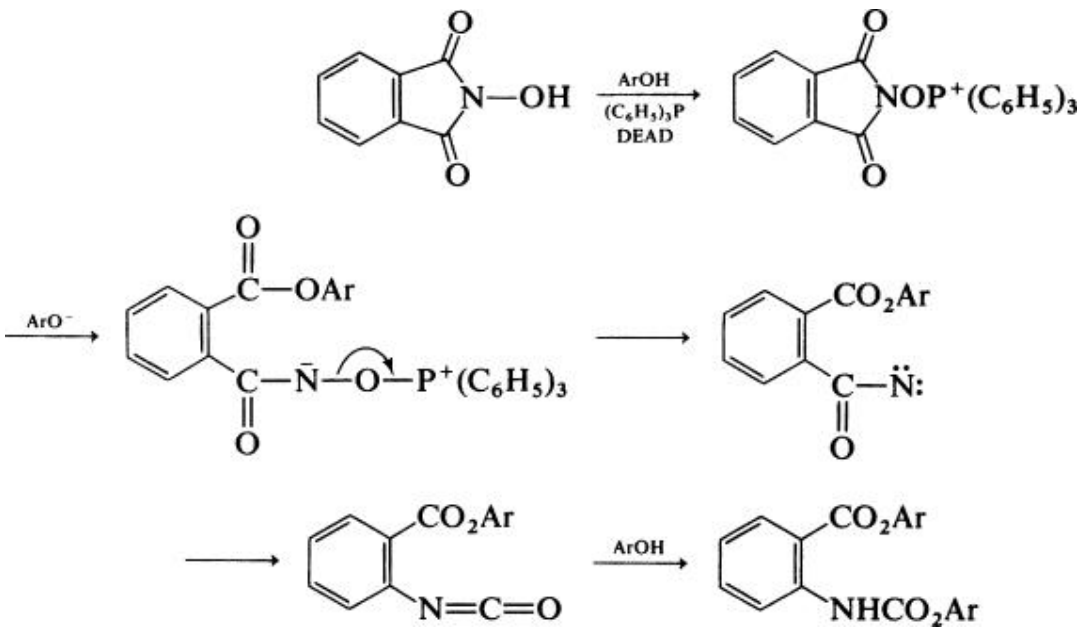


3.1.1.3. Formation of Ethers

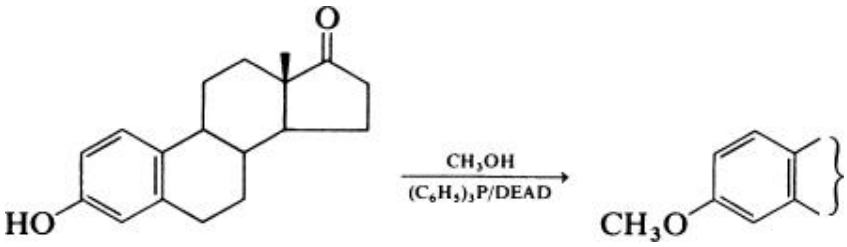
N-Hydroxyimides can be reacted with alcohols to give N-alkoxyimides; (87-89) the latter can be converted to O-alkylhydroxylamines by cleavage with hydrazine.

$$C_6H_5CH_2OH + HON(CO)_2C_6H_4 \xrightarrow[\text{DEAD}]{(C_6H_5)_3P} C_6H_5CH_2ON(CO)_2C_6H_4$$

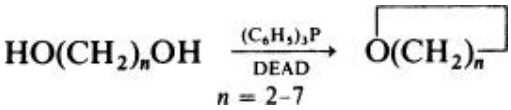
A similar reaction has been described with N-hydroxybenzotriazole. (90) Reaction of N-hydroxyphthalimide with phenols produces aryl N-aryloxycarbonyl-anthranilates. (91)



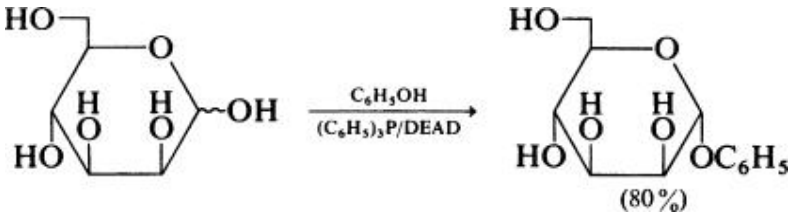
The triphenylphosphine–diethyl azodicarboxylate reagent is useful for alkylation of phenolic hydroxyl groups. (92, 93) These two references differ as to whether nitrophenols and tertiary alcohols can be used in this reaction.



α , ω -Glycols can be cyclized into ethers containing 3–8 members in the ring. (94)

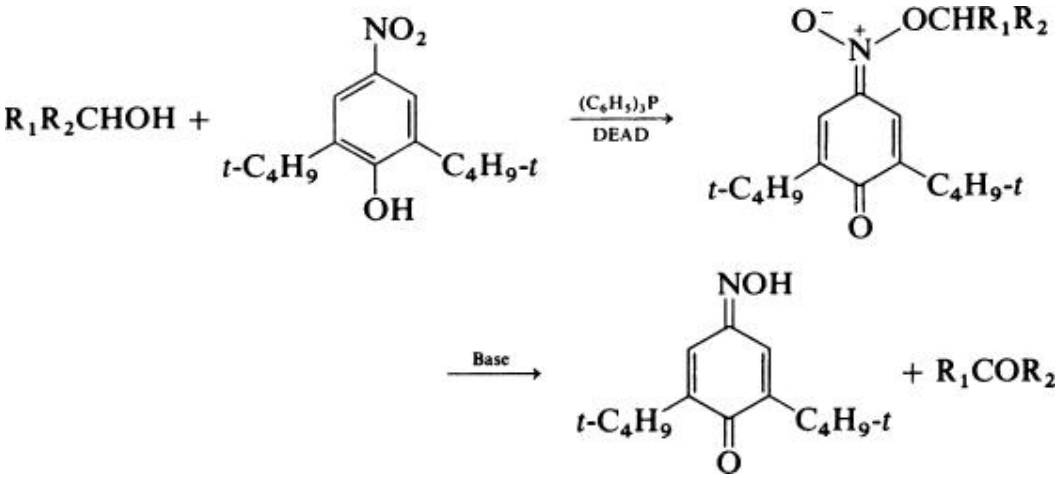


Free sugars can be converted into aryl glycosides in good yields. (95, 96)



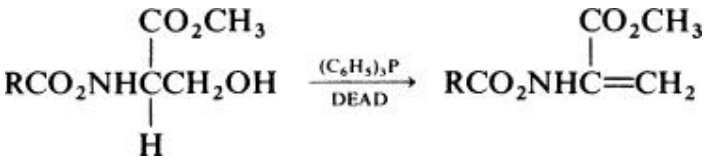
Glycosides of aliphatic alcohols can be made if mercuric chloride is added to the reaction mixture; it is likely that the reaction proceeds through formation of the glycosyl chloride. Anomeric mixtures are generally formed. (97, 98)

Reaction of alcohols with 2,6-di-*t*-butyl-4-nitrophenol produces *aci*-nitro ethers, which can be converted by treatment with base into the aldehyde or ketone derived from the alcohol. The primary hydroxyl group of primary-secondary diols reacts preferentially. (99)

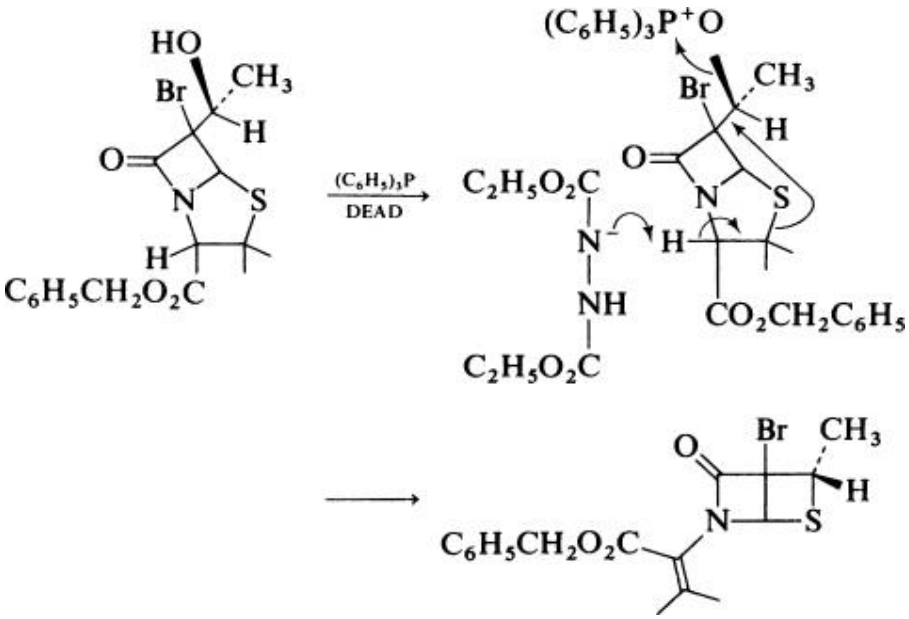


3.1.1.4. Alcohol Dehydration

Dehydration of alcohols to alkenes is often observed as a side reaction in substitutions. (58) Acyl derivatives of serine and threonine can be converted to the corresponding vinyl amino acids by a simple β -elimination. (100)



An unusual dehydration with formation of a thioether bond has been accomplished in the cyclization of a penam to a β -lactam. (101)



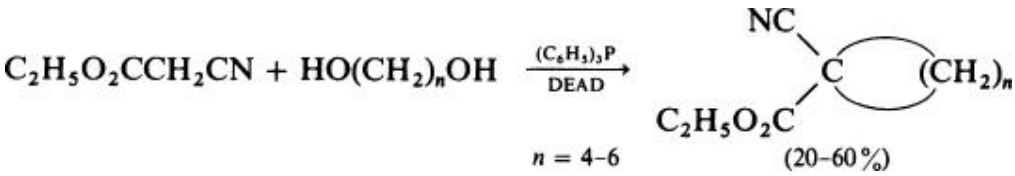
3.1.1.5. Other Applications

Alcoholic hydroxyl groups can be converted into halides by using alkyl halides as the source of halide ion. (11) Treatment of diacetone glucose with triphenylphosphine–diethyl azodicarboxylate in the presence of methyl iodide gives an oxyphosphonium iodide that decomposes in boiling toluene to the inverted iodide. (102) The same replacement, also with inversion, can be achieved with triphenylphosphine, iodine, and imidazole or with triphenylphosphine and 2,4,5-triiodoimidazole. (103) In contrast, treatment of diacetone glucose with triphenylphosphine–carbon tetrachloride, triphenyl phosphite methiodide, or triphenyl phosphite dibromide effects rearrangement of the 5,6-isopropylidene acetal to the 3,5 positions and halogenation at C_6. (104, 105)

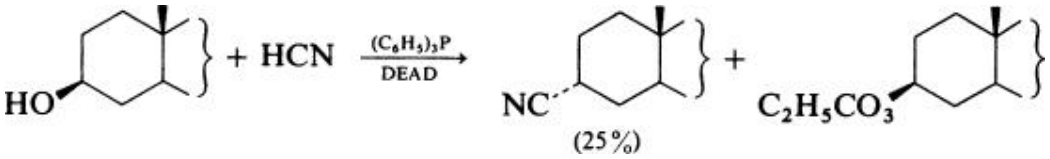
There are a few reports of the use of triphenylphosphine–diethyl azodicarboxylate to form carbon －carbon bonds. Thus ethyl cyanoacetate

can be alkylated with alcohols (Eqs. 29 and 30). (54, 75) The alcoholic hydroxyl group in a steroid has been replaced with a cyano group by carrying out the reaction in the presence of hydrogen cyanide (Eq. 31). (11)

$$C_2H_5O_2CCH_2CN + n\text{-}C_3H_7OH \xrightarrow[\text{DEAD}]{(C_6H_5)_3P} \underset{(52\%)}{C_2H_5O_2CCH(CN)C_3H_7\text{-}n} \quad (29)$$



(30)

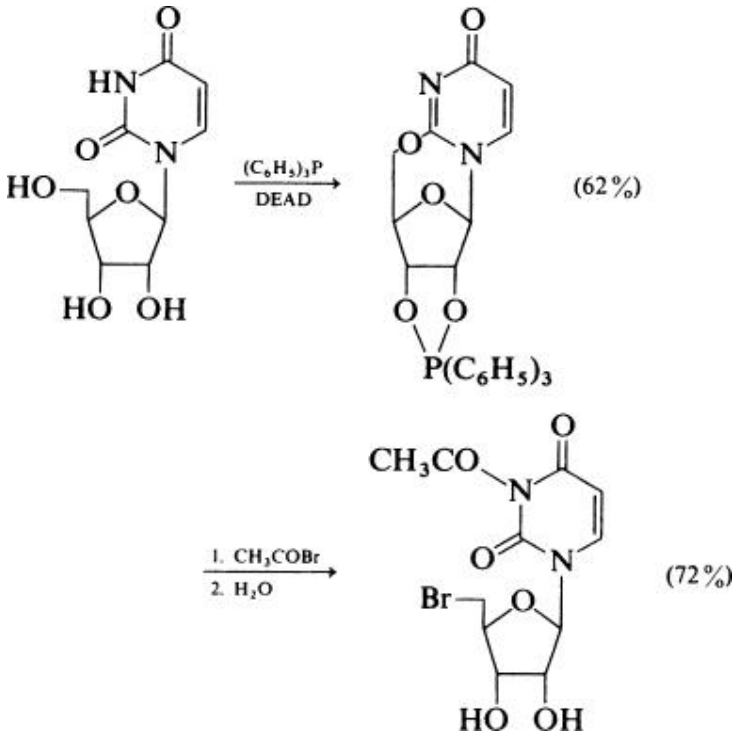


(31)

Thiols cannot be used in place of alcohols with this reagent because they are oxidized to disulfides. (106)

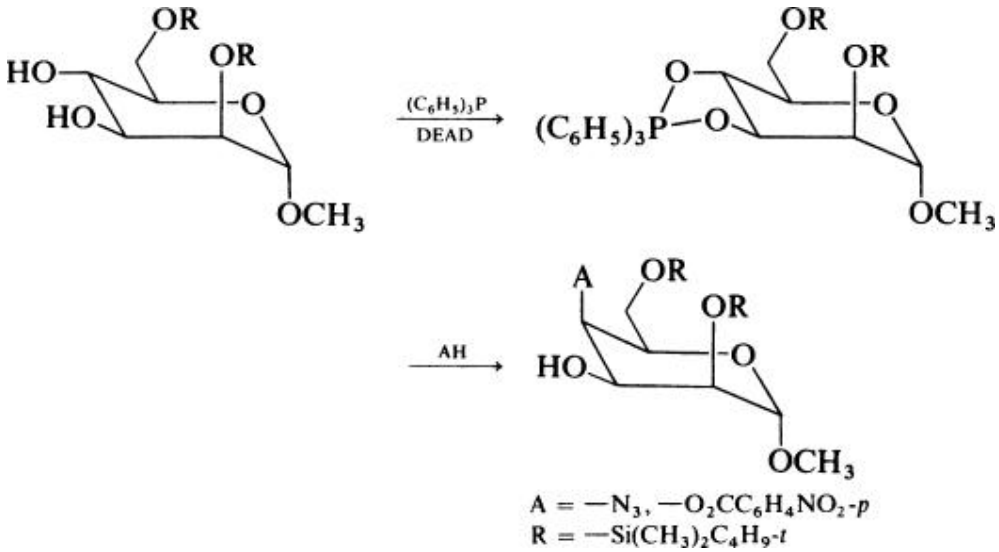
3.1.1.6. Formation of Pentacoordinated Phosphoranes

Reaction of triphenylphosphine–DEAD with *cis*-1,2-diols and with 1,3-diols gives pentacoordinated



phosphoranes, (107, 108) analogous to the reaction of diols with triphenylphosphine–hexamethylphosphoramide. (35, 109) Phosphorane formation occurs only with *cis*-1,2-diols; the *trans* diols form epoxides. (11, 58, 107, 108) The phosphorane group can be used for temporary protection of *cis*-1,2-diols. (110-112)

Regiospecific splitting of such phosphoranes can be accomplished with hydrazoic acid or *p*-nitrobenzoic acid. (63)



Gluco derivatives that bear free hydroxyl groups at positions 2 and 3 can be similarly substituted selectively at position 3.

3.2. The Triphenyl Phosphite–Methiodide Reagent

The adduct of triphenyl phosphite and methyl iodide was first described in 1898. (1) The oxyphosphonium salt **30** formed in this reaction is stable in the absence of moisture, in contrast to the intermediates **1** (Eq. 1) in the Michaelis–Arbuzov reaction, which undergo nucleophilic displacement with their own counterions unless very bulky substituents are involved. (113) The stability of the salt **30** results from the inability of the phenyl group to under go nucleophilic substitution.

$$(C_6H_5O)_3P + CH_3I \longrightarrow \underset{\mathbf{30}}{(C_6H_5O)_3P^+CH_3, I^-}$$

In 1951 it was reported that Michaelis' salt **30** reacted with alcohols to form alkyl iodides with the liberation of phenol and methyl diphenylphosphonate. (114)

$$HOCH_2C(CH_3)_2CH_2OH \xrightarrow{(C_6H_5O)_3P^+CH_3, I^-} ICH_2C(CH_3)_2CH_2I$$

The reaction was used to prepare 1,3-diiodo-2,2-dimethylpropane, a key intermediate for the synthesis of caryophyllenic acid. The reaction appears to involve initial displacement of a phenoxy group by the hydroxyl group of the alcohol, followed by nucleophilic displacement to form the iodide. (115)

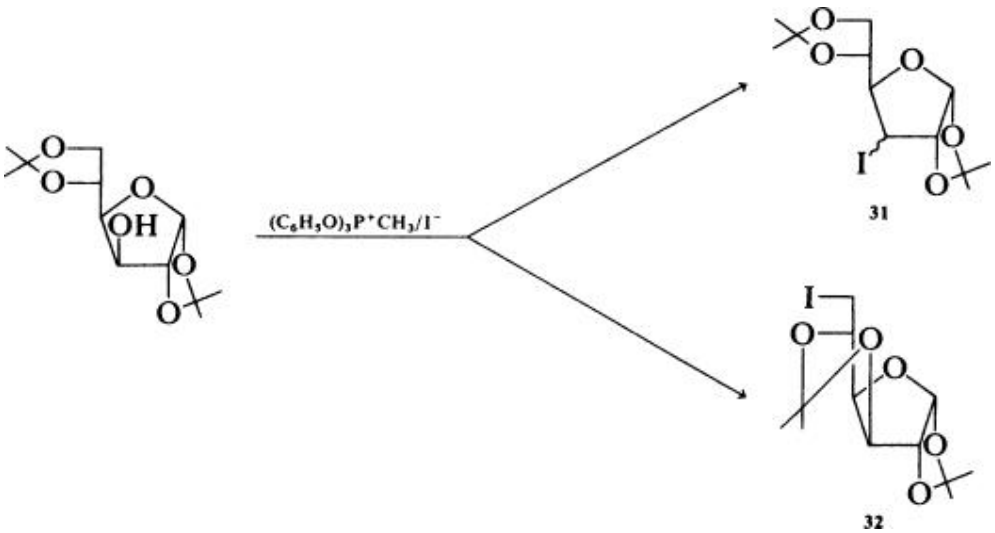
$$\begin{aligned}(C_6H_5O)_3P^+CH_3, I^- + ROH \\ &\longrightarrow C_6H_5OH + (C_6H_5O)_2(RO)P^+CH_3, I^- \\ &\longrightarrow RI + (C_6H_5O)_2P(O)CH_3\end{aligned}$$

The ionic tetracovalent nature of phosphorus in salt **30** was confirmed by ^{31}P NMR studies. (116)

The triphenyl phosphite–methiodide reagent can be used to convert alcoholic hydroxyl groups into iodides in aliphatic compounds, (116) carbohydrates, (117, 105-119) and nucleosides. (120-126) Some carbon skeleton rearrangement is observed with highly hindered compounds: *t*-amyliodide (6%) is formed in the preparation of neopentyl iodide from neopentyl alcohol. (127)

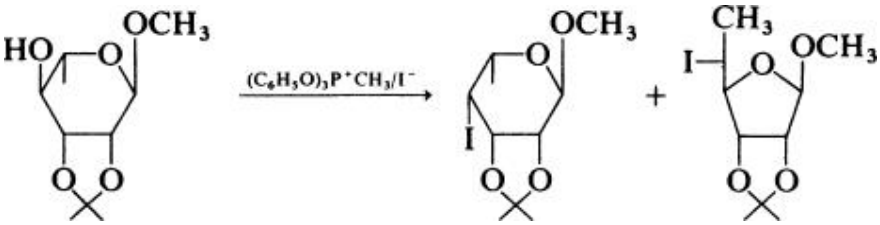
It has been reported that a nonrearranged 3-deoxy-3-iodohexose (**31**) was

obtained from the treatment of diacetone glucose with the triphenyl phosphite–methiodide reagent, (128) but the report was later questioned, and structure **32** was proposed for the product (Eq. 32). (105) However, neither of these references gives experimental conditions, and it now seems likely that structure **31** is correct in light of a recent report of the preparation of 1,2:5,6-di-O-isopropylidene-3-iodoallose. (103)



(32)

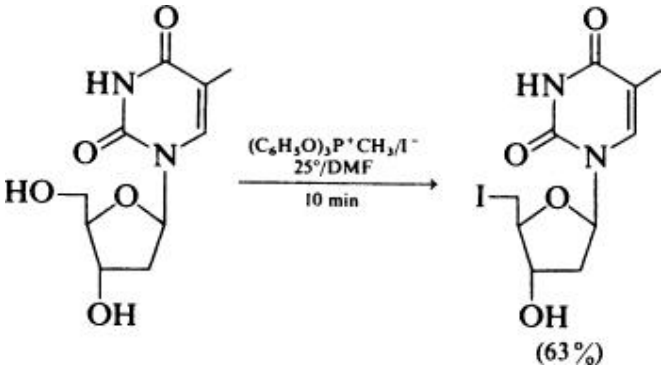
A structural rearrangement also occurs to some extent with a 2,3-isopropylidene rhamnoside. (119, 129)



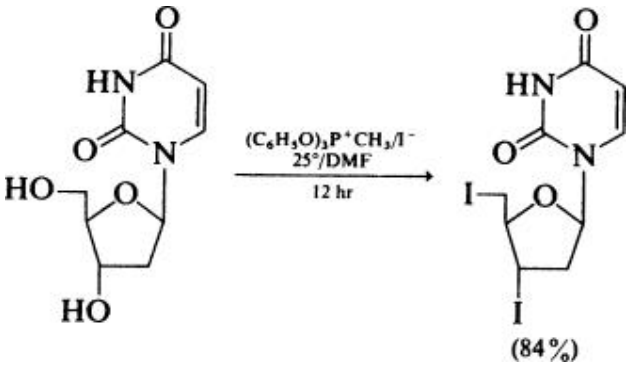
Steroidal neopentylic alcohols undergo rearrangement followed by an elimination reaction. (130) Allylic and propargylic alcohols give products that result from S_N2' reactions, but products that arise from secondary rearrangements may also occur. (116)

$$HC{\equiv}CCHOHR \longrightarrow ICH{=}C{=}CHR$$

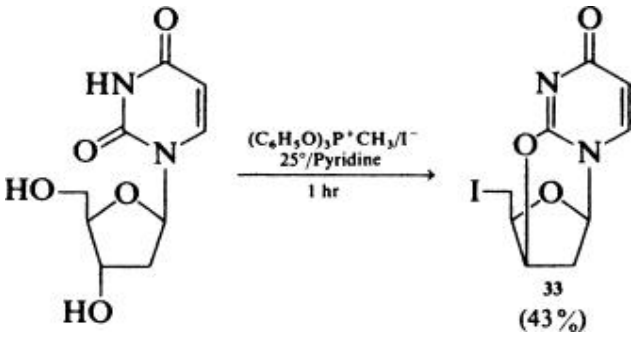
The 5′-hydroxyl group of nucleosides is substituted in high yield, and the reaction can exhibit primary/secondary selectivity. (120)



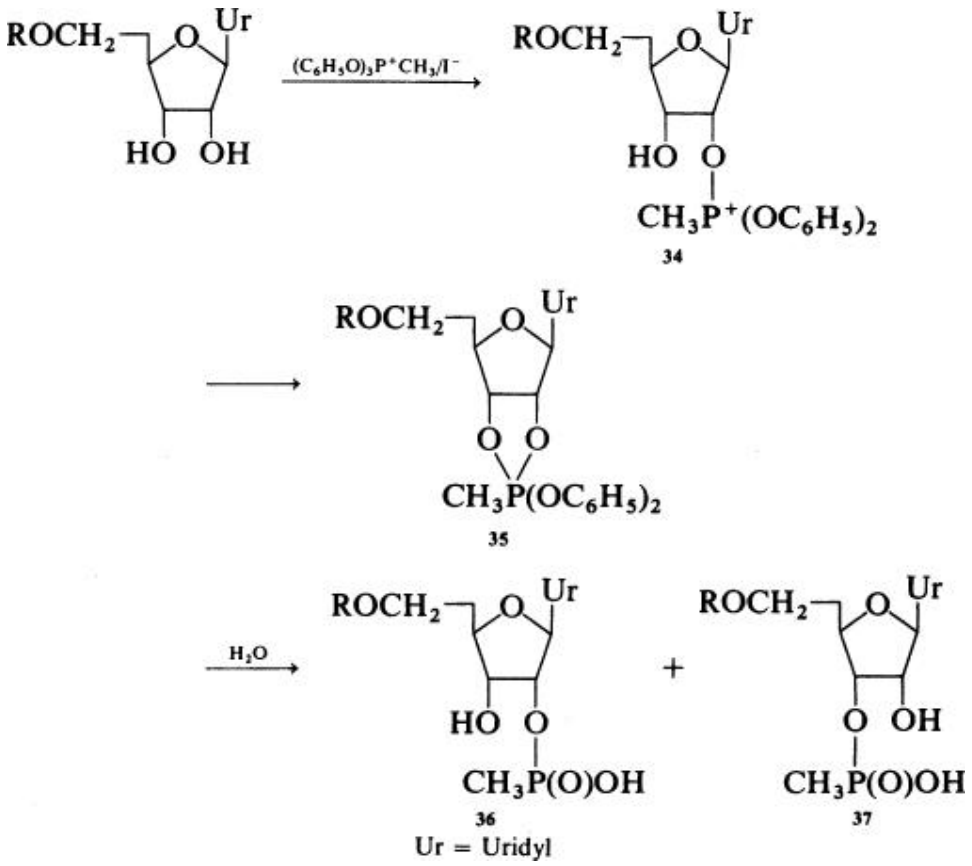
Substitution of 2′- or 3′-hydroxyl groups proceeds with retention of configuration because of participation by the heterocyclic nucleus. (120)



The participating intermediate (**33**) can be isolated in some reactions.



Reactions with vicinal glycols form phosphorane intermediates (**34, 35**) that yield a mixture of phosphonates (**36, 37**). (121)



Whereas primary alcohols undergo replacement by iodide with triphenyl phosphite–methiodide, secondary alcohols are selectively dehydrated by this reagent in hexamethylphosphortriamide at 75°. (131) Tertiary alcohols are unaffected under these conditions.

A modification of the triphenyl phosphite–methiodide reagent involves the use of methyl trifluoromethanesulfonate (triflate) in place of methyl iodide, thus producing a nonnucleophilic anion instead of iodide. (132)

$$(C_6H_5O)_3P + CF_3SO_3CH_3 \longrightarrow (C_6H_5O)_3P^+CH_3, CF_3SO_3^-$$

Reaction of this reagent with aliphatic alcohols gives symmetrical dialkyl ethers, whereas with sodium alcoholates, alkyl phenyl ethers are formed.

Reaction of benzyl chloride with triphenyl phosphite gives a reagent that can be used to form chlorides from alcohols. (115, 133)

3.3. Reagents Formed from Halogens and Triphenylphosphine or Triphenyl Phosphite

Only a few studies report the use of the triphenyl phosphite–halogen reagent for the preparation of halides. (134-136) The reagent has two disadvantages: it gives phenol as a by-product and usually produces mixtures of phosphorus species. (137, 138)

Triphenylphosphine–halogen adducts have the advantage of containing only two replaceable groups, (139) and are useful and versatile reagents for converting alcohols into halides. (140) Their reaction with alcohols involves the rapid and irreversible formation of an alkoxyphosphonium salt that decomposes by a slow S_N2 reaction to form an alkyl halide. (141, 142)

$$(C_6H_5)_3P^+X, X^- + ROH \xrightarrow{\text{Fast}} HX + (C_6H_5)_3P^+OR, X^-$$

$$\xrightarrow{\text{Slow}} (C_6H_5)_3PO + RX$$

Although acetonitrile or dimethylformamide is recommended as the solvent, the latter can react with the reagent to form halomethylene-N,N-dimethyliminium halides **38**. (124, 143) These intermediates can react with alcohols to give

$$(C_6H_5)_3P^+X, X^- + OCHN(CH_3)_2$$

$$\longrightarrow (C_6H_5)_3P^+OCH{=}N^+(CH_3)_2, 2X^-$$

$$\longrightarrow (C_6H_5)_3PO + \underset{\mathbf{38}}{XCH{=}N^+(CH_3)_2, X^-}$$

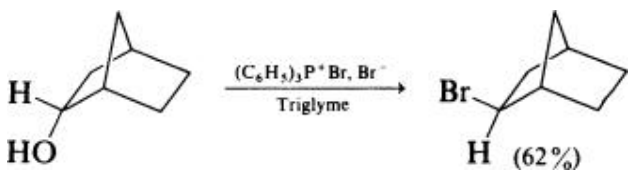
alkoxymethylene-N,N-dimethyliminium halides (**39**), which can then undergo either S_N2 replacement by halide ion (Eq. 33), especially with primary alcohols, or hydrolysis during workup to give a formate or to reform the starting material (Eq. 34).

$$\underset{\mathbf{38}}{XCH{=}N^+(CH_3)_2, X^-} + ROH \longrightarrow HX + \underset{\mathbf{39}}{ROCH{=}N^+(CH_3)_2, X^-}$$

$$\underset{\mathbf{39}}{ROCH{=}N^+(CH_3)_2, X^-} \xrightarrow{\text{Heat}} RX + OHCN(CH_3)_2 \qquad (33)$$

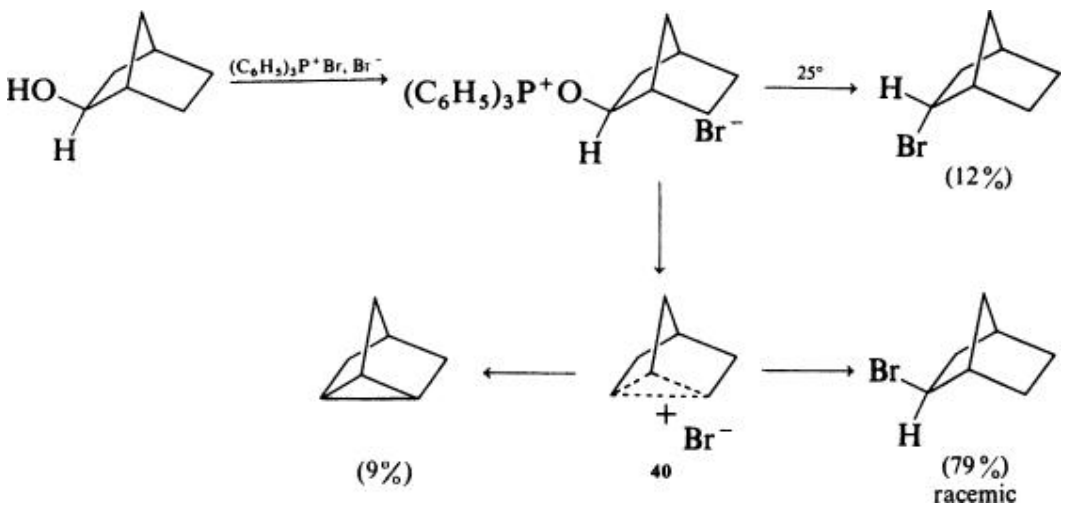
$$\underset{39}{ROCH{=}N^{+}(CH_3)_2,\ X^{-}} \xrightarrow{H_2O} ROCHO + H_2N^{+}(CH_3)_2,\ X^{-} \qquad (34)$$

The replacement of alcoholic hydroxyl groups by halogen with the triphenylphosphine–halogen reagent generally involves inversion of configuration. No skeletal rearrangement is observed in the preparation of neopentyl halides from neopentyl alcohol (139) or in the S_N2 reactions of *endo*-norbornanol (Eq. 35) and 7-norbornanol.



(35)

However, a similar reaction of *exo*-norbornanol appears to involve the non-classical Winstein intermediate (**40**).



Likewise, little rearrangement is observed in the halogenation of 3-methyl-2-butanol. (144)

$$(CH_3)_2CHCHOHCH_3 \xrightarrow{(C_6H_5)_3P^{+}Br,\ Br^{-}} \underset{(43.8\%)}{(CH_3)_2CHCHBrCH_3} + \underset{(1.4\%)}{(CH_3)_2CBrCH_2CH_3}$$

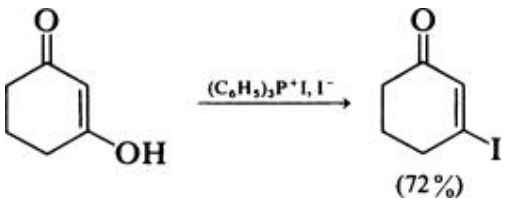
Greater amounts of rearranged product are found in the same reaction with other reagents: $(C_6H_5)_3P^+CN$, Br^-(3%), $(C_6H_5O)_3P^+Br$, Br^-(55.6%), and $(C_6H_5)_3P^+CBr_3$, Br^-(6–10%).

The triphenylphosphine–halogen reagent has been used less than other phosphorus reagents for the halogenation of nucleosides. (124, 145)

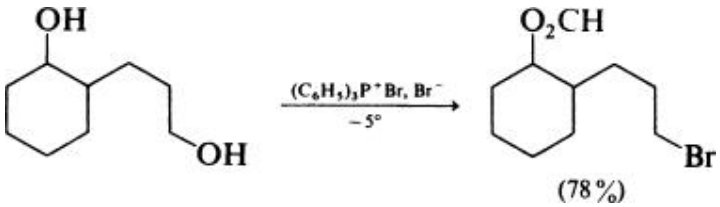
The triphenylphosphine–iodine reagent is less active than triphenyl phosphite–methiodide for the conversion of 5¢-O-*p*-nitrobenzoylthymidine to 3′-desoxy-3′-iodo-5′-O-*p*-nitrobenzoylthymidine. (122)

Aryl halides are formed at temperatures up to 300°. (135, 146)

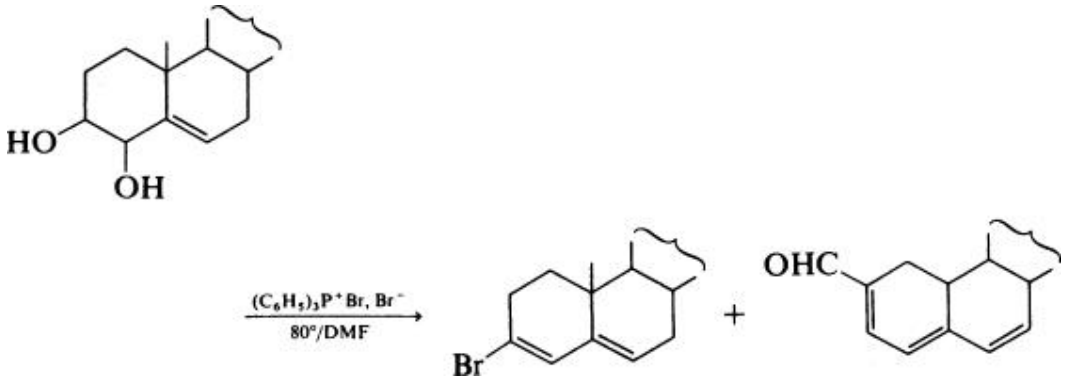
β -Diketones react as β -hydroxy enones to give β -halo- α , β -enones. (147)



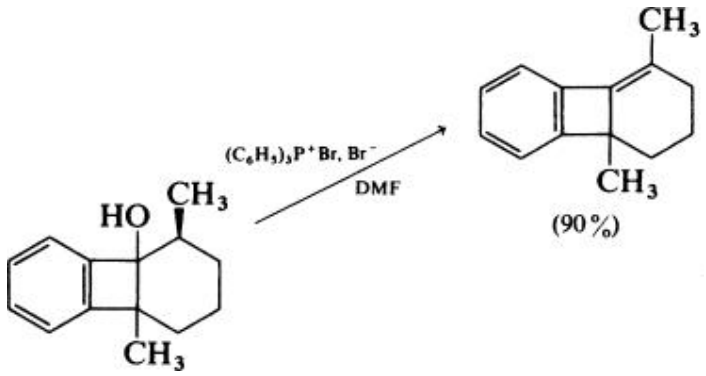
The selective halogenation of unsymmetrical diols can be achieved by conducting the reaction in dimethylformamide. (148) At temperatures below 0° the primary hydroxyl is converted to the halide, whereas the secondary hydroxyl is protected as the formate.



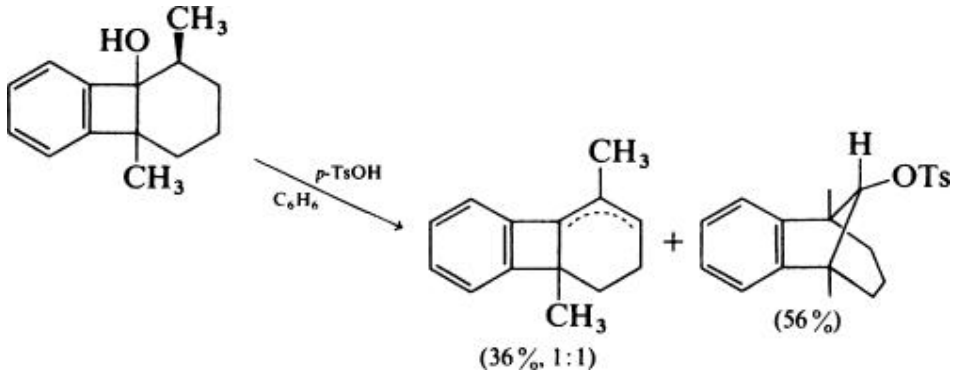
Replacement of hydroxyl by bromine in a steroidal glycol is accompanied by Vilsmeier-type formylation of the dehydrated intermediate. (149)



Dehydration of tertiary benzocyclobutanols proceeds with higher selectivity (Eq. 36) than the dehydration with *p*-toluenesulfonic acid (Eq. 37). (150)



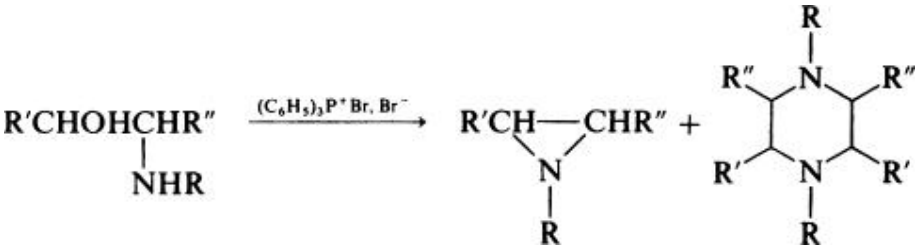
(36)



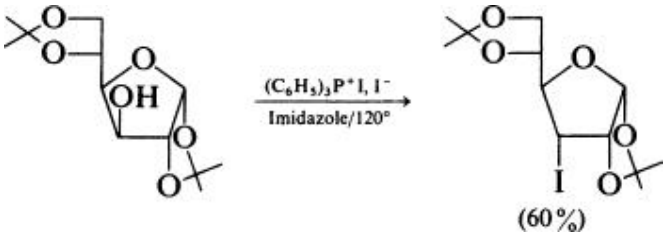
(37)

2-N-Alkylaminoalcohols are converted to N-alkylaziridines in good yield, with

minor amounts of N,N-dialkylpiperazines as by-products. (151) Only piperazines are formed when R is hydrogen.



It has been shown recently that addition of imidazole to triphenylphosphine–iodine gives improved results in the conversion of alcohols to iodides, particularly with highly hindered secondary alcohols. (103) For example, substitution without isopropylidene rearrangement (120, 121) occurs with the hydroxyl group of diacetone glucose. The use of triiodoimidazole and triphenylphosphine appears even more advantageous. The reason for the beneficial effect of an imidazole in this reaction has not been established.



An immobilized form of the triphenylphosphine–chlorine reagent has been prepared by treatment of cross-linked, chloromethylated or brominated polystyrene beads with lithium diphenyl phosphide, oxidation with peracetic acid, and reaction with phosgene. (152) This reagent converts benzyl alcohol into benzyl chloride in 88% yield, and can be regenerated after use by retreatment with phosgene.

3.4. The Triphenylphosphine–Carbon Tetrachloride and Related Reagents

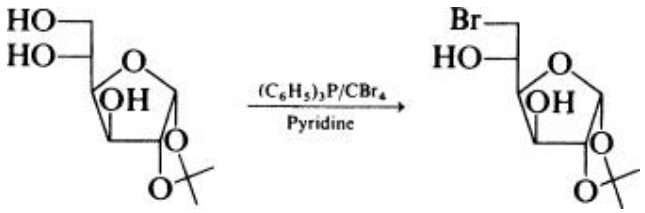
The triphenylphosphine–carbon tetrachloride system has been used extensively for the transformation of alcohols into chlorides. Variations in the final stage of the reaction to substitute other nucleophiles have not been common, and in this respect the system appears less versatile than the triphenylphosphine–diethyl azodicarboxylate or the tris(dimethylamino)phosphine–carbon tetrachloride systems.

3.4.1.1. Synthesis of Halides

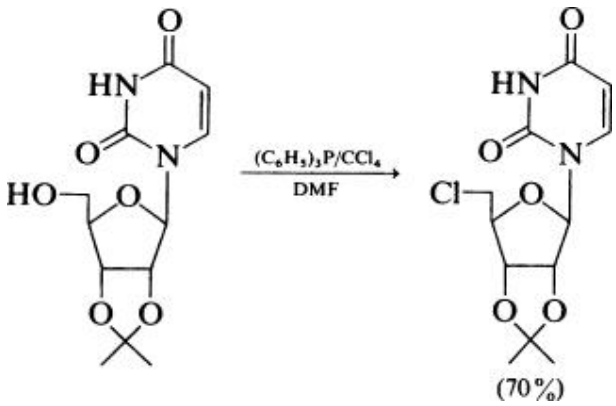
Halides have been synthesized from a wide variety of primary and secondary alcohols. With secondary or hindered alcohols inversion of configuration is often predominant or total. (153) However, the course of the reaction is dependent on the nature of both the substrate and the halide ion, and the reaction can produce partially racemized or rearranged products.

Carbon tetrachloride has been used most frequently as the solvent, but it is often not the most effective solvent for achieving a rapid, high-yield, selective reaction. Acetonitrile is an effective solvent, usually leading to rapid formation of the phosphonium salt intermediate. (27, 154, 155)

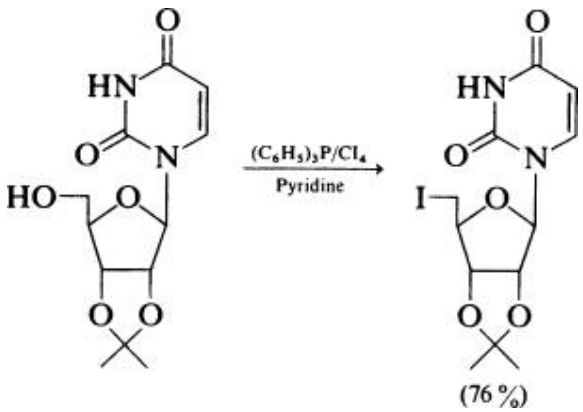
Use of pyridine as the solvent has provided high yields and selectivity in the preparation of halodeoxy sugars. (156) Twice the normal quantity of triphenylphosphine must be used to obtain high yields, indicating that the reaction proceeds by the ylid route (Eqs. 14 and 15). Primary hydroxyl groups are replaced selectively, and there is no undesirable formation of phosphoranes or epoxides from vicinal diols.



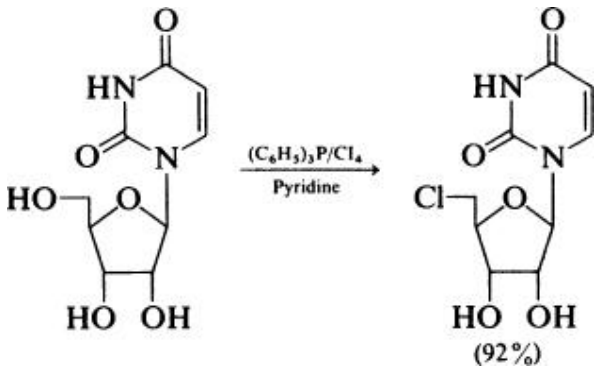
Dimethylformamide has been used as the solvent for most reactions of nucleosides. (124)



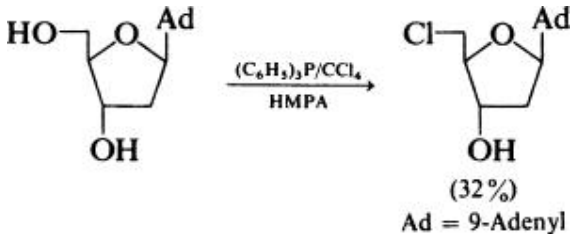
It is necessary to use pyridine as the solvent when triphenylphosphine–carbon tetraiodide is the reagent. (143)



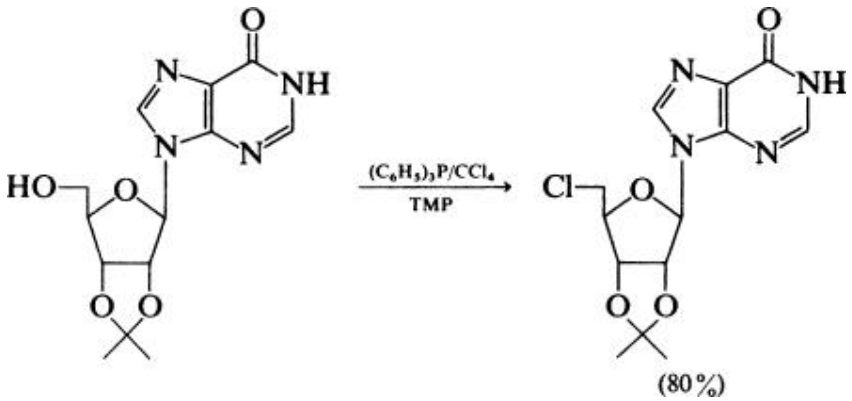
Selective replacement of primary hydroxyl groups is observed in pyridine. (156)



Somewhat lower yields are obtained with hexamethylphosphortriamide (HMPA) as the solvent. (157)

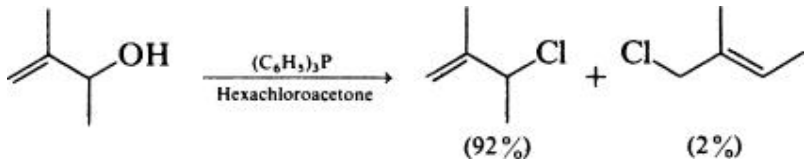


Trimethyl phosphate (TMP) can also be used as the solvent. (145, 158)



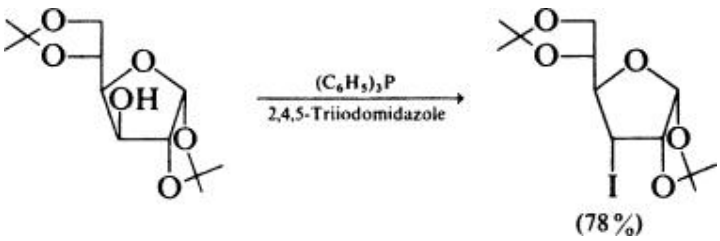
Polystyryl–diphenylphosphine can be used as a polymer-supported replacement for triphenylphosphine. (159, 160) This reagent avoids the sometimes tedious separation of the reaction product from triphenylphosphine oxide and other phosphorus-containing by-products, and gives higher reaction rates than those obtained with triphenylphosphine. (161)

Hexachloroacetone can be used instead of carbon tetrachloride to avoid contamination of lighter allylic chlorides with chloroform and carbon tetrachloride. (30, 162) The reaction products can be removed by distillation as they are formed, thereby avoiding the isomerization that can occur if they remain in the reaction mixture.

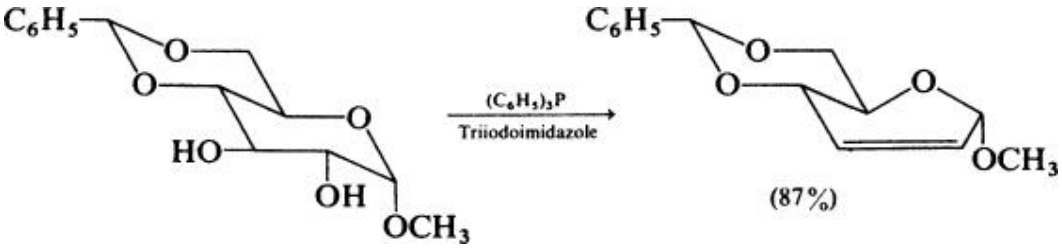


The reaction products are nevertheless contaminated with a minute quantity of chloroform, formed by an unknown mechanism.

Carbon tetraiodide can be replaced by 2,4,5-triiodoimidazole, with a slight improvement in yield. (103) Use of this reagent in substituting the 3-hydroxyl group of diacetone glucose gives inversion without skeletal rearrangement.

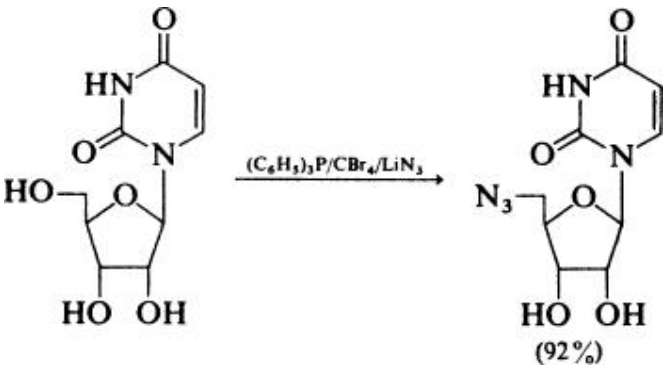


Use of this reagent with vicinal diols gives eliminative deoxygenation, (163) in contrast with the substitution observed with triphenylphosphine–carbon tetrabromide. (156)



3.4.1.2. Formation of Carbon — Nitrogen Bonds

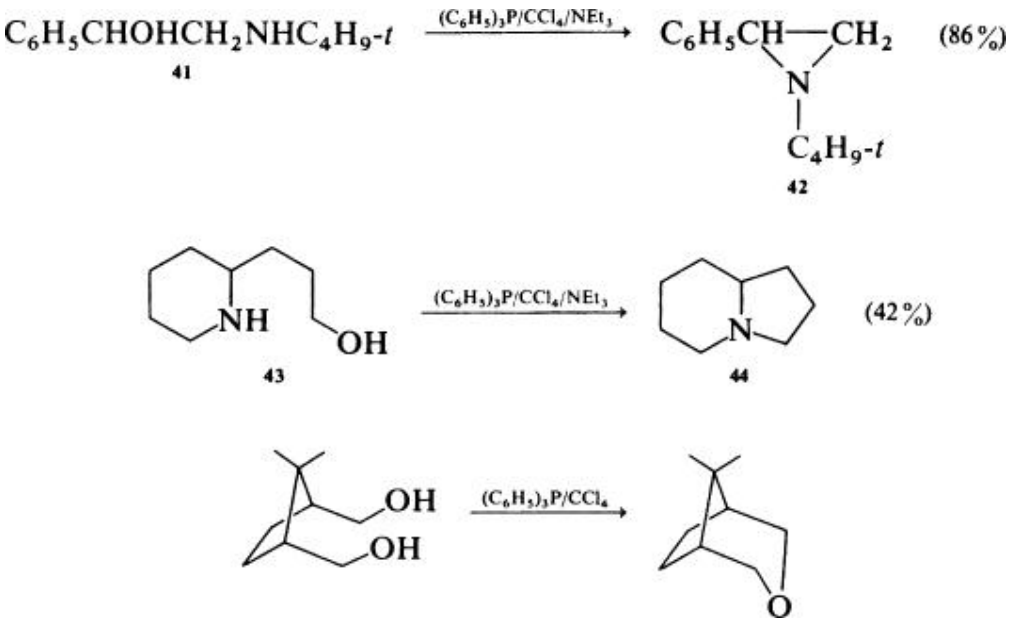
A one-pot synthesis of alkyl azides can be carried out by performing the triphenylphosphine–carbon tetrabromide–alcohol reaction in the presence of lithium azide. (164-168)



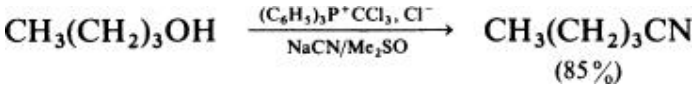
Dimethylformamide must be used as the solvent, rather than pyridine or

hexamethylphosphortriamide. Triphenyl phosphite–methiodide and triphenylphosphine–diethyl azodicarboxylate are much less effective than triphenylphosphine–carbon tetrachloride.

Reaction of the 2-aminoalcohol **41** with the carbon tetrachloride reagent in the presence of triethylamine effects cyclization to the aziridine **42**, (169) and similar aziridine syntheses have been carried out. (170, 171) The same reagent converts the 4-aminoalcohol **43** into octahydroindolizine (**44**). (172) Ring closure of 5-aminoalcohols to piperidines can be effected, (173) as can the analogous cyclization of 1,5-diols. (174)



Alcohols can be converted directly to nitriles by reaction with triphenylphosphine–carbon tetrachloride in the presence of sodium or potassium cyanide and dimethyl sulfoxide. (153, 175)

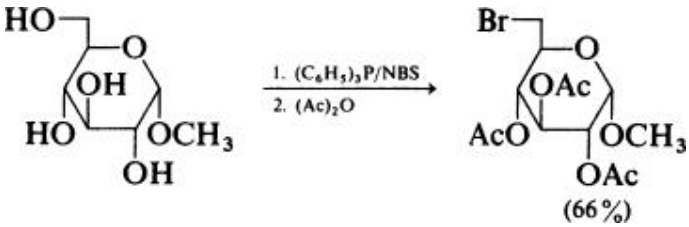


Reaction of triphenylphosphine–carbon tetrachloride with secondary alcohols in excess carbon tetrachloride generally leads to formation of chlorides; however, with acetonitrile as the solvent dehydration of the alcohol is frequently the principal reaction. (176, 177) The latter reaction can be a useful method for preparing olefins.

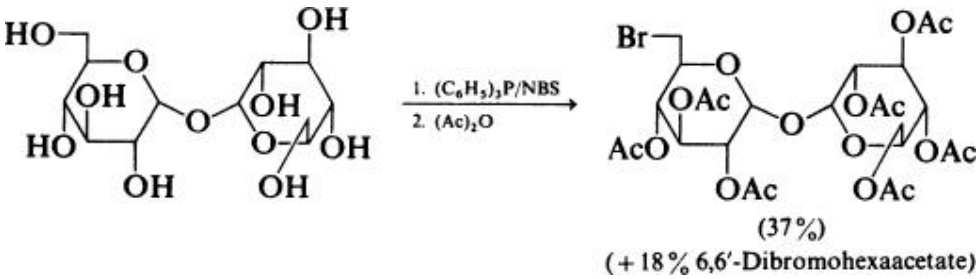
$$C_2H_5CHOHCH_3 \xrightarrow[CH_3CN]{(C_6H_5)_3P^+CCl_3,\ Cl^-} C_2H_5CH{=}CH_2 \quad (74\%)$$

3.5. The Triphenylphosphine–N-Halosuccinimide Reagent

The triphenylphosphine–N-halosuccinimide reagent is used principally for replacement of primary hydroxyl groups, with good primary/secondary selectivity. The reaction is generally carried out in dimethylformamide, and the oxidant can be N-bromo-(NBS), N-chloro-, or N-iodosuccinimide. The reagent is useful in the preparation of halides from tetrahydrofurfuryl alcohol (178) and from carbohydrates and nucleosides. (179-184) An example of the reaction is shown in Eq. 38. (180) It is possible to achieve some selectivity in replacing only one of two primary hydroxyl groups by using a 2:1 ratio of reagent to substrate (Eq. 39). (183) A large excess is needed to achieve the disubstitution.

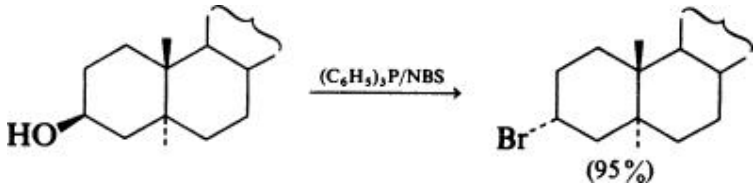


(38)



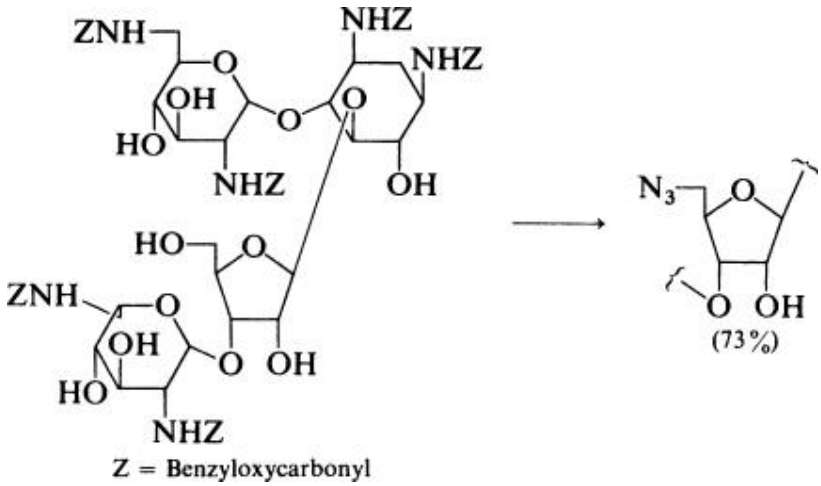
(39)

There is one report of the replacement of the 3-hydroxy group in a steroid with inversion of configuration (Eq. 40), (185) but generally mixtures of α and β isomers are obtained. Use of triphenyl phosphite and N-haloacetamides gives similar results. (185)



(40)

The one-step conversion of alcohols to azides does not occur with this reagent because the azide ion reacts with the phosphorus intermediate, attacking the phosphorus and deactivating the hydroxyl group. However, the conversion can be accomplished by carrying out the reaction in two steps without isolating the intermediate bromide. (184) This technique provides a route to aminoglycoside antibiotics; thus only the primary hydroxyl group of penta(benzyloxycarbonyl)neomycin can be replaced by an azido group in 73% yield.



3.6. The Tris(dimethylamino)phosphine–Carbon Tetrachloride Reagent

Tris(dimethylamino)phosphine reacts with carbon tetrachloride to give a trichloromethylphosphonium salt. (186) In the presence of an alcohol, alkyl chlorides are formed above 0°. When the reaction is carried out at –78°, an insoluble alkoxyphosphonium chloride is formed, which can be converted into a stable alkoxyphosphonium hexafluorophosphate by treatment with aqueous ammonium hexafluorophosphate. (187) The stability of the alkoxyphosphonium chloride is very solvent dependent, and is enhanced by polar solvents; the salts are completely stable in water. (188) The chloride ion can be replaced by stronger nucleophiles such as iodide, phenylthio, cyanide, thiocyanide, or azide, and even with a weaker nucleophile such as an amine, if

the oxyphosphonium salt is isolated with a non-nucleophilic anion such as perchlorate or hexafluorophosphate. (189)

Alkoxy(trisdimethylamino)phosphonium salts are versatile reagents that can undergo substitution reactions with a variety of nucleophiles. Although a two-step reaction is required, it is characterized by high yields, good selectivity, and easy workup owing to the water solubility of the by-products, hexamethylphosphoramide and hexafluorophosphates.

The preparation of the salt is usually performed in the temperature range –20° to –45°. A dilute solution of the aminophosphine is prepared in a solvent such as tetrahydrofuran, dichloromethane, pyridine, aceto nitrile, or dimethylformamide. This solution is added very slowly, e.g., using a motor-driven syringe, to a solution of the alcohol and carbon tetrachloride in the same solvent. A slight molar excess of carbon tetrachloride relative to alcohol is used.

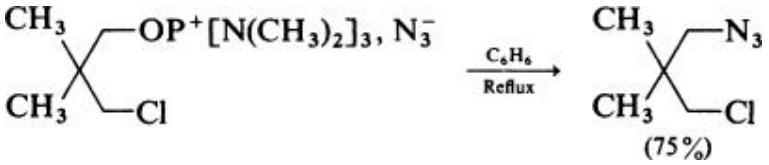
The reaction is generally complete at the end of the addition; however, if alcohol can be detected by TLC, additional tris(dimethylamino)phosphine can be added. The reaction mixture is then poured into water, and solvents and unreacted alcohol are removed by washing with diethyl ether or ethyl acetate. Addition of potassium hexafluorophosphate usually precipitates the salt; if the salt is water-soluble it can be extracted with dichloromethane.

Some mono-oxyphosphonium salts of polyols are not extractable because of the remaining hydroxyl groups; these can be acetylated with acetic anhydride and pyridine, and they either precipitate or become extractable. (190) This technique is generally used with carbohydrates. (191)

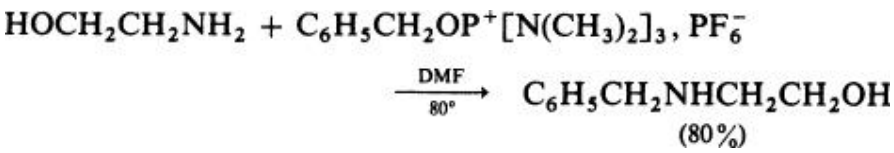
Extraction with dichloromethane is feasible only with salts of large, hydrophobic anions such as perchlorate, hexafluorophosphate, iodide, azide, and thiocyanate; salts involving bromide and cyanide are borderline, and salts of chloride and fluoride are not extractable. (192) This characteristic permits the use of phase-transfer systems, in which the organic phase “catalyzes” the reaction. For example, a water solution of sodium azide and an alkoxy(trisdimethylamino)phosphonium chloride does not react at 60°; addition of chloroform extracts the alkoxyphosphonium azide into the organic phase, where nucleophilic substitution occurs. (188)

$$C_6H_5CH_2OP^+[N(CH_3)_2]_3, Cl^- + NaN_3 \xrightarrow[H_2O/30^\circ]{CH_2Cl_2} C_6H_5CH_2N_3$$

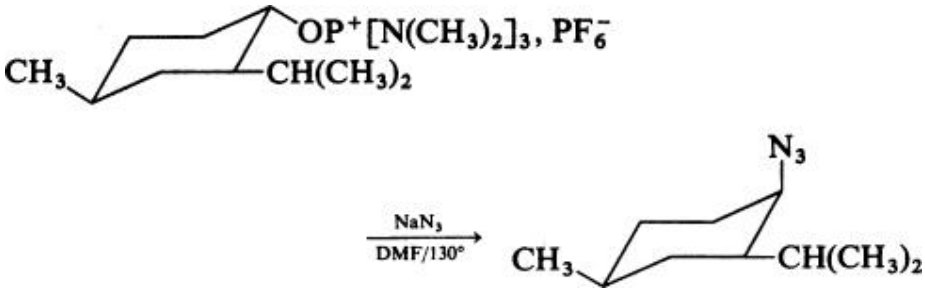
Alternatively, the oxyphosphonium azide can first be extracted with dichloromethane, isolated, and suspended in boiling benzene; complete solution signals completion of the reaction.



More often, the isolated hexafluorophosphate is reacted with the nucleophile in dimethylformamide at 80–110°. This procedure permits the selective monoalkylation of primary amines (Eq. 41) (189) or the formation of azides from alcohols (Eq. 42). (40)

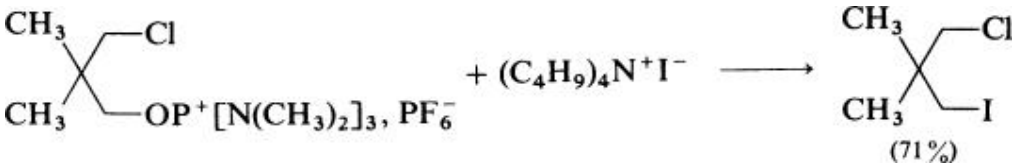


(41)



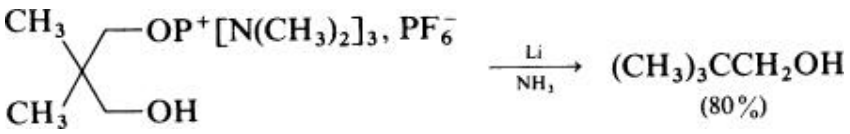
(42)

A similar technique can be used to prepare halides, using tetrabutylammonium halides as the source of halide ion. (193)

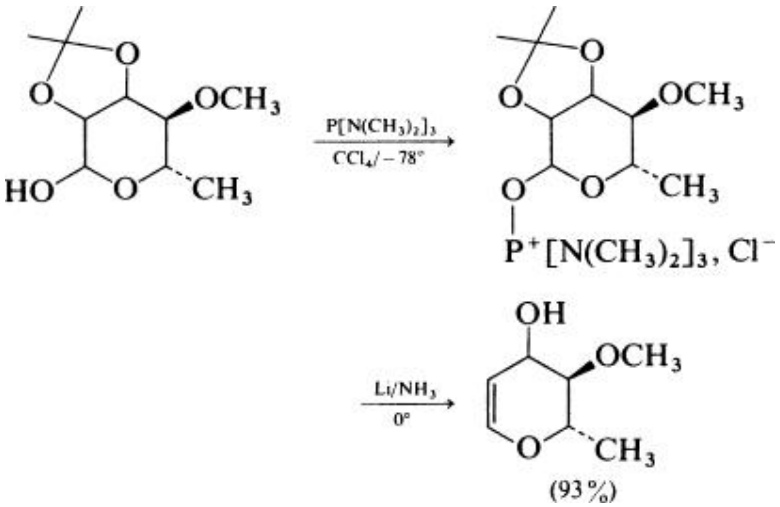


Carbon — sulfur bonds can be formed by using triethylammonium thioacetate (190) or ammonium thiocyanate (188) as the nucleophile. Aryl thioethers are prepared by using triethylammonium (190) or potassium (194) aryl thiolates.

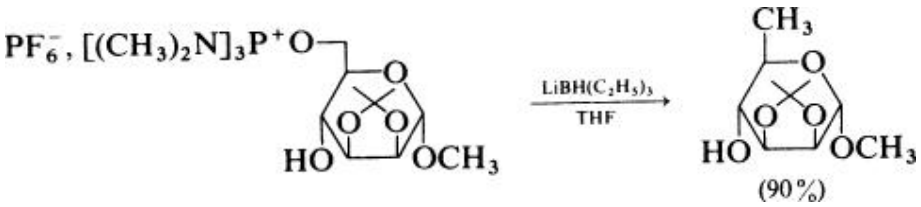
Nitriles are prepared by reaction of the oxyphosphonium salt with potassium cyanide. Reductive cleavage of the oxyphosphonium salt with lithium in liquid ammonia results in replacement of oxygen by hydrogen. (192)



If an electronegative substituent is present in the β position to the salt group, reductive cleavage may be accompanied by elimination. (195)



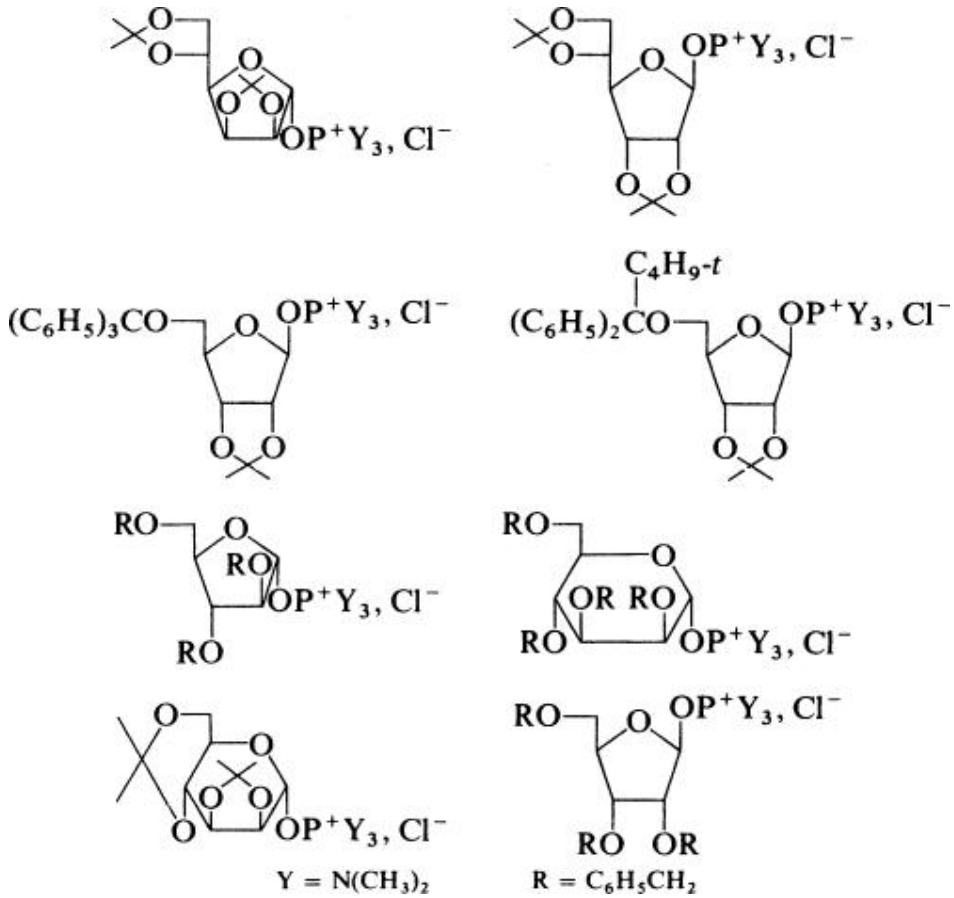
This reaction probably involves the intermediate glycosyl chloride formed on warming to 0°. Reductive cleavage of oxyphosphonium salts can be effected in high yield with lithium triethyl borohydride. (196)



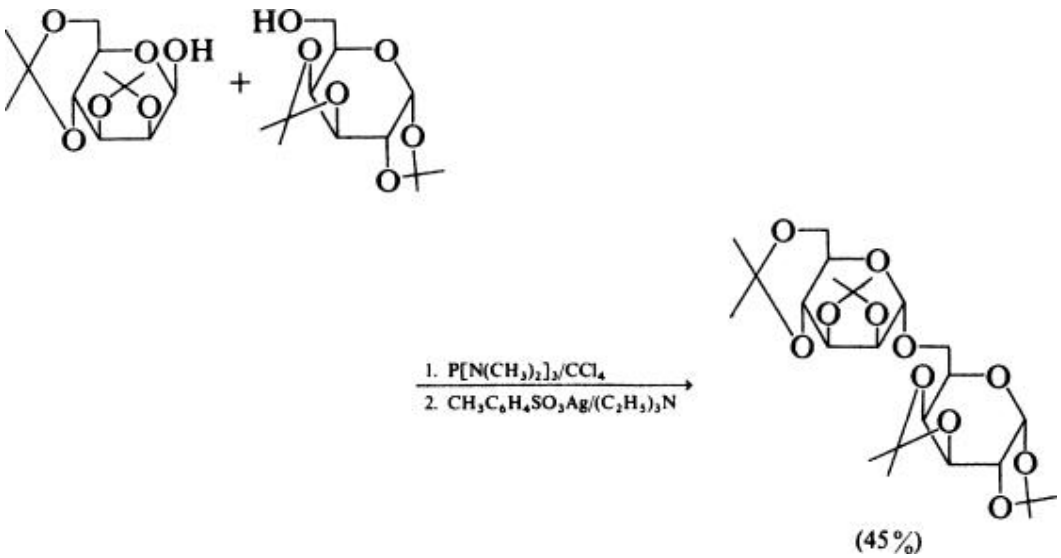
3.6.1.1. Activation of the Anomeric Position of Carbohydrates

The behavior of oxyphosphonium salts of anomeric hydroxyl groups of carbohydrates depends largely on the structure of the carbohydrate. 2,3,4,6-Tetra-O-acetylglucose gives two anomeric salts, both stable at –40°. The α -*cis* isomer can be isolated as a hexafluorophosphate in 55% yield; the β -*trans* isomer is readily hydrolyzed to the starting materials.

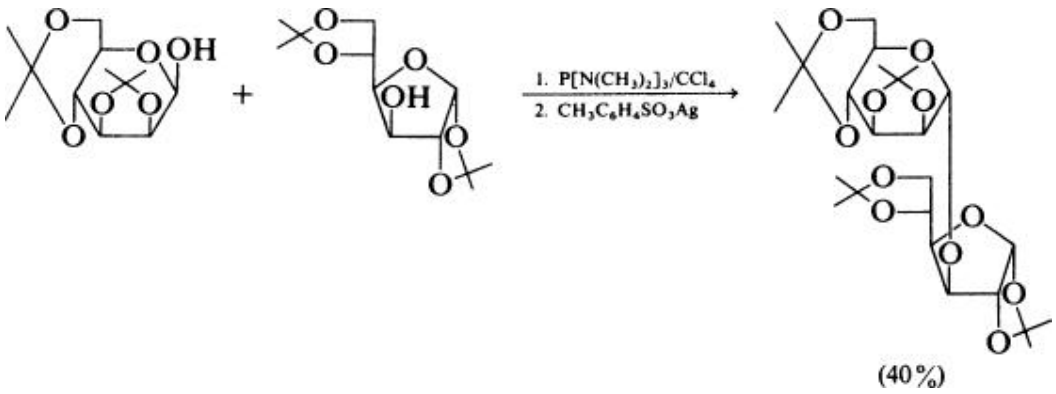
2,3,4,6-Tetra-O-acetylmannose gives only one salt, with the α -*trans* configuration. This salt is stable only below –20°, and is converted into the chloride at higher temperatures. Similar behavior is observed with salts of carbohydrates with isopropylidene blocking groups: diacetone mannose, diacetone allose, and 5-O-trityl-2,3-O-isopropylideneribose. Whereas 2,3,4,6-tetra-O-benzylmannose gives a salt in the alpha configuration that is stable up to –20°, 2,3,4,6-tetra-O-benzylglucose gives the glycosyl chloride directly even at –100°; the existence of an oxyphosphonium salt could not be established by ^{31}P NMR. (197) The following oxyphosphonium salts of carbohydrates have been detected in solution below –20°:



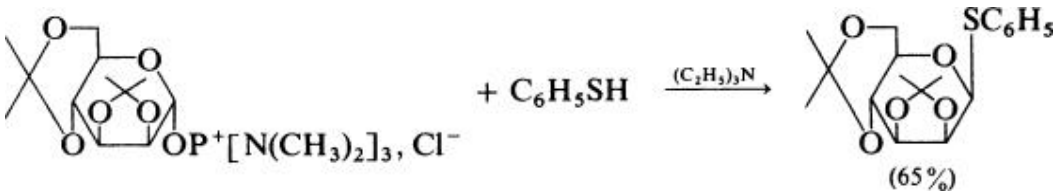
In the presence of an aglycone the formation of glycosides requires precipitation of the chloride ion with a silver salt, such as silver tosylate (198) or silver hexafluorophosphate. (38) With the former reagent a reactive tosyl glycoside is formed. Glycosidation generally proceeds through an S_N1 process; although the stereoselectivity is poor with the lighter alcohols, it is better with hindered aglycones. (199)



Use of a tertiary base such as triethylamine can suppress the reaction; the following reaction does not proceed in the presence of triethylamine. (199)

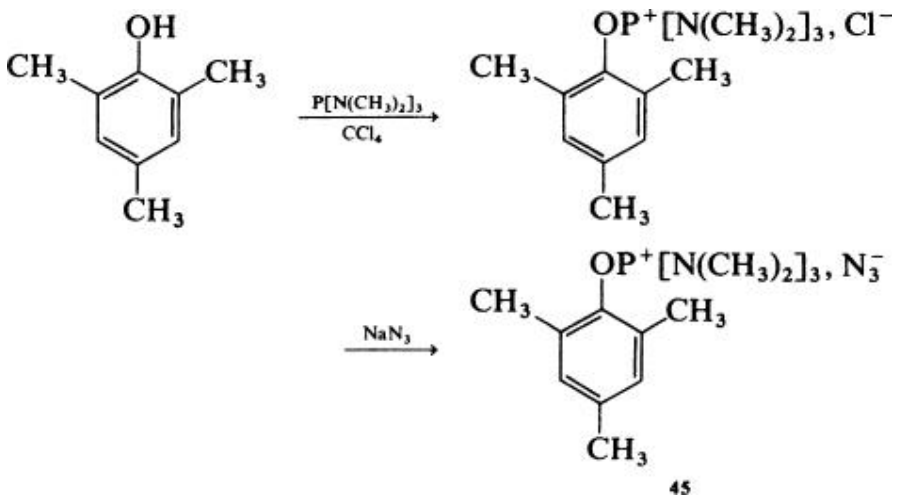


Arylthioglycosylation can be effected in high yield directly from the oxyphosphonium chloride and an arylthiotriethylammonium salt. The reaction occurs with complete inversion of configuration, and can be used to determine the anomeric configuration of an oxyphosphonium salt. (199)

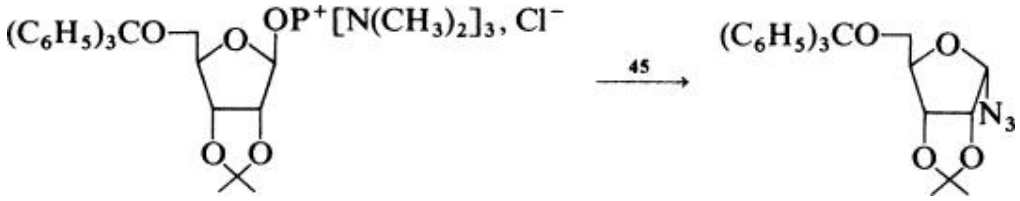


Glycosyl azides are readily obtained, generally with inversion of configuration,

by reaction of an azide anion with an oxyphosphonium chloride (Eq. 44). The azide ion is conveniently introduced as a soluble, crystalline, non-hygroscopic aryloxyphosphonium salt (**45**) (Eq. 43). This aryloxyphosphonium cation is completely unreactive, but provides a much more easily handled form of soluble azide than does tetrabutylammonium azide. (200) Glycosyl azides are easily converted into 1,2,3-triazolonucleosides.



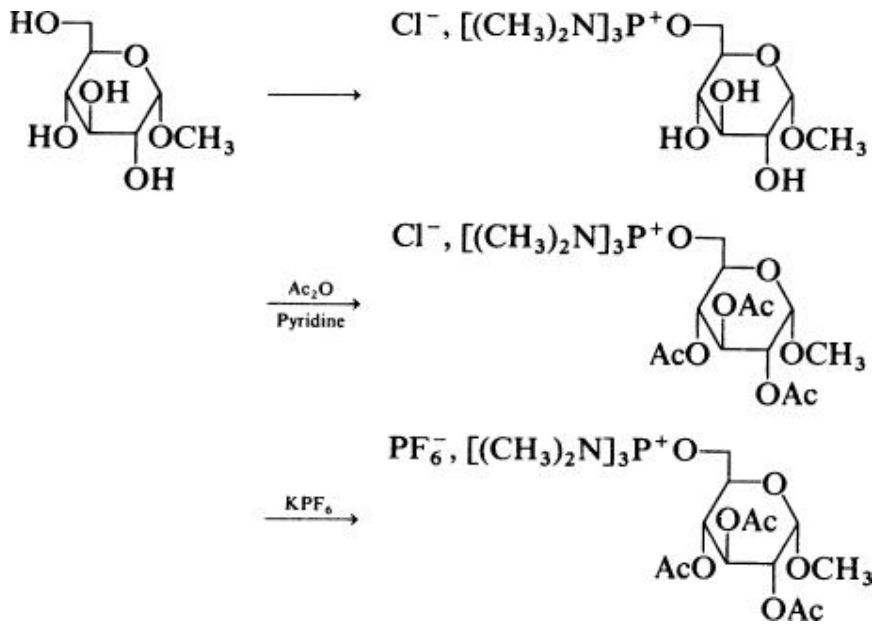
(43)



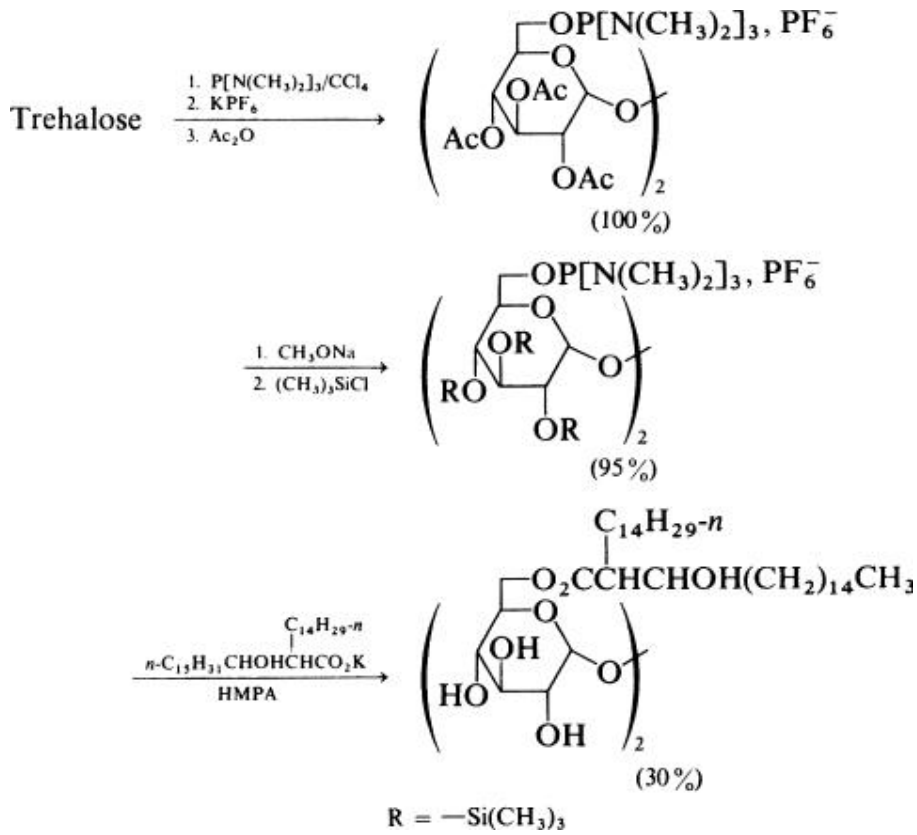
(44)

3.6.1.2. Selectivity

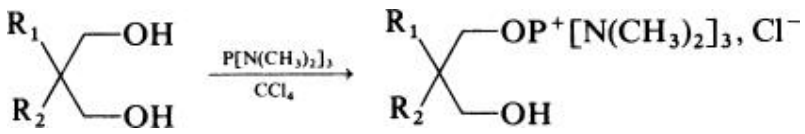
The formation of alkoxy(trisdimethylamino)phosphonium salts is very selective for primary over secondary alcohols. This effect can be used in selective salt formation from carbohydrates. (201)



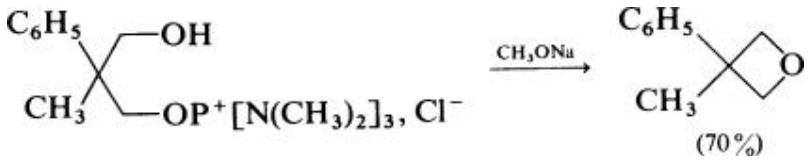
This technique has been used to synthesize Cord-Factor, an immunostimulant. (202)



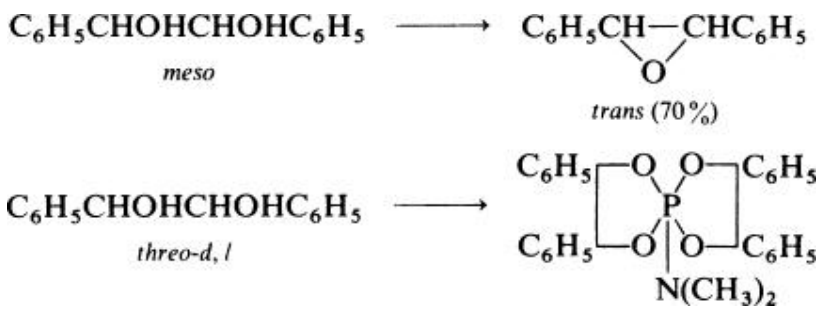
Biprimary alcohols, such as 1,3-glycols, can be activated selectively at only



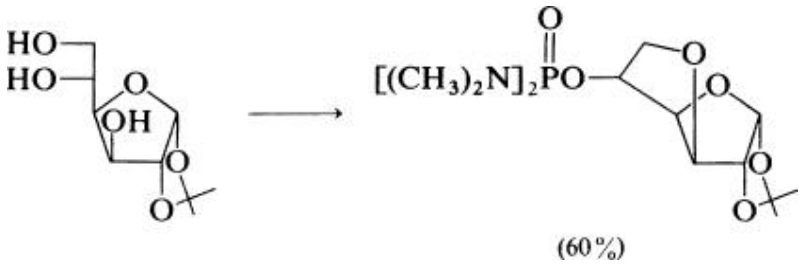
one of the two hydroxyl groups. These oxyphosphonium salts of 1,3-glycols are easily cyclized into oxetanes. (203)



Treatment of 1,2-glycols with hexamethylphosphoramide–carbon tetrachloride gives either an epoxide or a pentacoordinated spirophosphorane, depending on the configuration of the glycol. (204)



1,2-O-Isopropylideneglucofuranose is converted into an amidophosphite by nucleophilic substitution of the phosphorane intermediate. (205)



Mono salts of ω -biprimary glycols can be obtained by using a solvent such as tetrahydrofuran that is a solvent for the glycol but not for the mono salt. (249)

$$HO(CH_2)_{10}OH \xrightarrow[THF,\ -20^\circ]{P[N(CH_3)_2]_3,\ CCl_4} HO(CH_2)_{10}OP^+[N(CH_3)_2]_3,\ Cl^-$$

$$\xrightarrow{KPF_6} HO(CH_2)_{10}OP^+[N(CH_3)_2]_3,\ PF_6^- \xrightarrow{NaN_3} HO(CH_2)_{10}N_3$$

This synthesis provides an excellent route to ω -substituted alcohols.

4. Experimental Procedures

4.1.1.1. 1-(3'-Azido-3'-desoxy-2',5'-di-O-trityl- β -D-xylofuranosyl)uracil (Use of Triphenylphosphine–Diethyl Azodicarboxylate–Hydrazoic Acid) (59)

2 ,5 -Di-O-trityluridine (219 mg, 0.3 mmol) and triphenylphosphine (94 mg, 0.36 mmol) were dissolved in 4 mL of anhydrous benzene and mixed with a 0.36 millimoles of hydrazoic acid in benzene solution; diethyl azodicarboxylate (63 mg, 0.36 mmol) was then added, and the mixture was refluxed for 10 minutes. After evaporation of the solvent, the crude product was chromatographed on 30 g of Kieselgel and eluted with benzene–ethyl acetate (4:1). There was obtained 196 mg (87%) of 1-(3′-azido-3′-desoxy-2′,5′-di-O-trityl- β -D-xylofuranosyl)uracil. After solution in ether and precipitation with cyclohexane the compound had mp 136–139°; IR: 3370 (NH), 2115 (N_3), 1720, 1695 (CO) cm^{-1}; NMR (100 MHz) δ : 2.60 (d, 3 *H*), 3.12 (dd, 5 b*H*), 3.52 (dd, 5 a*H*), 4.01 (d, 2 *H*), 4.10 (ddd, 4 *H*), 5.60 (dd, 5 *H* of uracil), 6.46 (d, 1 *H*), 7.30 (m, aromatic H), 9.32 (s, b, NH) ppm.

4.1.1.2. Methyl 3 β -Formyloxy-12 α -hydroxycholanate (Use of Triphenylphosphine–Diethyl Azodicarboxylate–Formic Acid) (67)

A solution of methyl deoxycholate (2.03 g, 5 mmol), triphenylphosphine (2.62 g, 10 mmol), and formic acid (0.46 g, 10 mmol) in dry tetrahydrofuran was stirred at room temperature. There was added dropwise a solution of 1.74 g (10 mmol) of diethyl azodicarboxylate in 10 mL of tetrahydrofuran. Removal of the tetrahydrofuran under reduced pressure afforded a syruplike product that was chromatographed on a Florisil column. The first five fractions (50 mL each) obtained with benzene–hexane (6:4) as the eluant gave 2.1 g (97%) of methyl 3 β -formyloxy-12 α -hydroxycholanate, mp 160–161°.

4.1.1.3. Triphenoxyphosphonium Methiodide (120)

Triphenyl phosphite (52 mL, 0.2 mol) and methyl iodide (16 mL, 0.26 mol) were mixed in a 250-mL flask fitted with a very efficient 3-ft condenser and a thermometer well. The flask was placed in a 90° oil bath, and the temperature was slowly raised to 125° over 8 hours while the pot temperature rose slowly from 70° to 85° and then rapidly to 115°. This temperature was maintained for 12–14 hours and, on cooling and seeding, the mixture crystallized to a solid brown mass. Dry ether (100 mL) was added, the product was broken up with a spatula, and the resulting crystalline material was then washed repeatedly with fresh, dry ethyl acetate until the washings were only light-colored. The amber crystals were dried and stored *in vacuo*, giving 80 g (90%) of product suitable for direct use; NMR (rigorously dry $CDCl_3$) δ : 3.11 (d, 3*H*, $J_{P,H}$ = 16.5 Hz, PCH_3), 7.45 (m, 15*H*, aromatic) ppm. If the sample is not prepared in a drybox, appreciable amounts of diphenyl methyl phosphonate are formed, as indicated

by a doublet ($J_{P,H}$ = 18 Hz) at δ 1.84 ppm. The reagent should always be weighed and handled in a drybox under a nitrogen atmosphere.

4.1.1.4. 3 α -Iodocholestane (Use of Triphenoxyphosphonium Methiodide) (120)

Cholestanol (0.78 g, 2.0 mmol) and triphenoxyphosphonium methiodide (1.81 g, 4.0 mmol) were dissolved in anhydrous dimethylformamide (10 mL), and the solution was stored for 2 hours at 25°. After addition of methanol (1 mL), the mixture was diluted with chloroform and extracted with dilute aqueous sodium thiosulfate followed by water. After drying (Na_2SO_4), the solvent was evaporated and the residue was chromatographed on a column of silicic acid with hexane. The product from the major peak was evaporated to give 640 mg of 3 α -iodocholestane. Crystallization from acetone gave 562 mg (57%) of pure product, mp 112–113°; $[\alpha]_D^{23} + 36.9°$; NMR ($CDCl_3$) δ : 0.65 (s, 3*H*, $C_{18}H_3$), 0.79 (s, 3*H*, $C_{19}H_3$), 0.86 (d, 6*H*, *J* = 6 Hz, $C_{26}H_3$ and $C_{27}H_3$), 0.90 (d, 3*H*, *J* = 6 Hz, $C_{21}H_3$), 4.95 (m, 1*H*, C_3H) ppm.

4.1.1.5. 3-Bromo-2-cyclohexen-1-one (Use of Triphenylphosphine–Bromine) (147)

To an ice-cold, stirred solution of triphenylphosphine (576 mg, 2.2 mmol, freshly recrystallized from ethyl acetate–methanol) in 20 mL of dry benzene was added dropwise 2.2 mL of a 1.0 M solution of bromine in benzene. To the resulting suspension was added triethylamine (220 mg, 2.2 mmol, freshly distilled from lithium aluminum hydride) and 1,3-cyclohexanedione (224 mg, 2.0 mmol); stirring was continued at room temperature for 3 hours. The mixture was filtered through a short column of silica gel, and the column was eluted with ether. Concentration of the eluant, followed by distillation (air-bath temperature 95–105°) of the residual material under reduced pressure (11 mm), gave 342 mg (97%) of 3-bromo-2-cyclohexen-1-one as a clear, colorless oil; IR: 1682, 1605 cm^{-1}; NMR δ : 1.80–3.00 (m, 6*H*), 6.50 (m, 1*H*) ppm.

4.1.1.6. (S)-(–)-5-(Chloromethyl)-2-pyrrolidinone (Use of Triphenylphosphine–Carbon Tetrachloride) (206)

A solution of triphenylphosphine (6.75 g, 25.7 mmol) in 25 mL of dry carbon tetrachloride was added by syringe to a solution of 1.94 g (16.7 mmol) of (*S*)-(+)-5-(hydroxymethyl)-2-pyrrolidinone in 15 mL of dry chloroform. After 5 minutes the solution became cloudy. The mixture was then heated at 55° for 6 hours, cooled to room temperature, and the solvent was evaporated. The residue was extracted with benzene in a Soxhlet extractor for 15 hours. After cooling to room temperature, the benzene solution was filtered and concentrated. The resulting residue was triturated three times with 45 mL of distilled water. The combined aqueous extract was filtered through Celite, and the filtrate was concentrated to give 2.39 g of a semisolid. This yellow residue

was vacuum-distilled to give 1.91 g (86%) of a colorless oil that crystallized to a white solid on cooling in ice, bp 106.5–107° (0.15 mm); mp 53–55°; $[\alpha]_D^{20} - 18°$ (*c* 2.5, ethanol); NMR ($CDCl_3$) δ : 2.2 (m, 4*H*), 3.5 (d, 2*H*, *J* = 5 Hz), 4.0 (m, 1*H*), 7.5 (br, 1*H*) ppm; IR (Nujol): 3200 (br), 1690 (s), 1282 (m), 765 (br), 645 (s) cm^{-1}. Anal. Calcd. for C_5H_8ClNO : C, 44.96; H, 6.04; N, 10.49. Found: C, 45.35; H, 6.24; N, 10.36.

4.1.1.7. Methyl 6-Chloro-6-desoxy- α -D-glucopyranoside (Use of Triphenylphosphine–Carbon Tetrachloride in Pyridine) (156)

Methyl α -D-glucopyranoside (1 g, 5 mmol) was dissolved in 10 mL of pyridine, and the solution was cooled to 0°. There was added 2.75 g (10.5 mmol) of triphenylphosphine followed by 0.8 g (5.2 mmol) of carbon tetrachloride. The mixture was protected from moisture, heated with stirring to 65° for 12 minutes, and cooled slightly; 10 mL of methanol was added to decompose any excess reagent. The solvent was evaporated, and the residue was chromatographed on silica gel with chloroform–methanol (20:1). Noncarbohydrate materials were removed by elution with chloroform, and further elution with chloroform–methanol (20:1) gave 1.07 g (98%) of methyl 6-chloro-6-desoxy- α -D-glucopyranoside. Crystallization from chloroform–hexane gave product, mp 111–112°; $[\alpha]_D^{25} + 153°$.

4.1.1.8. 3-Chloro-2,2-dimethylpropanol [Use of Tris(dimethylamino)phosphine–Carbon Tetrachloride] (192, 193)

To a well-stirred solution of 2,2-dimethylpropane-1,3-diol (5.20 g, 50 mmol) and 5 mL (8 g, 52 mmol) of carbon tetrachloride in 100 mL of tetrahydrofuran at –30° there was added slowly a solution of 8.15 g (50 mmol) of tris(dimethylamino)phosphine in 15 mL of tetrahydrofuran. (Too rapid an addition caused the mixture to darken.) The mixture was allowed to come to room temperature and was stirred for 2 hours. Evaporation of the solvent gave crystalline (3-hydroxy-2,2-dimethyl)propoxytris(dimethylamino)-phosphonium chloride (14.7 g, 98%); after crystallization from methanol–ether, mp 61°d.

The salt was dissolved in 80 mL of dimethylformamide and heated at 90–100° for 6 hours. The reaction mixture was poured into 150 mL of water and extracted with ethyl acetate, the organic phase was washed with dilute hydrochloric acid, and the solvent was evaporated. Distillation gave 5.2 g (85%) of 3-chloro-2,2-dimethylpropanol, bp 67° (19 mm); mp 30°; n_D^{24} 1.448; IR (film): 720 (C — Cl), 3350 (OH) cm^{-1}; NMR (CCl_4) δ : 0.97 (s, CH_3), 3.38 (s, CH_2Cl), 3.4 (s, CH_2O) ppm.

4.1.1.9. N-(2,3:5,6-Di-O-isopropylidene- β -D-mannofuranosyl)phthalimide (Use of Triphenylphosphine–Diethyl Azodicarboxylate–Phthalimide) (51)

To a solution of 2,3:5,6-di-O-isopropylidene-D-mannofuranose (260 mg, 1 mmol), phthalimide (147 mg, 1 mmol), and triphenylphosphine (262 mg, 1 mmol) in 5 mL of tetrahydrofuran was added 190 mg (1.1 mmol) of diethyl azodicarboxylate. A slight exothermic reaction was observed. The reaction mixture was left at room temperature for 24 hours and then evaporated to dryness under reduced pressure. The residue was fractionated on a silica gel column, using benzene–diethyl ether (9:1). There was obtained 98 mg (25%) of N-(2,3:5,6-di-O-isopropylidene- β -D-mannofuranosyl)phthalimide, mp 133–134°;[α]$_D$ + 37°; IR (KBr): 1790, 1730, 1620, 725 cm^{-1};^{1}H NMR δ : 7.88 (phthalimide *H*), 5.82 (d, *J* = 3.7 Hz, 1*H*) ppm. Anal. Calcd. for $C_{20}H_{23}NO_7$: C, 61.7; H, 6.0; N, 3.6. Found: C, 61.5; H, 6.0; N, 3.6.

There was also obtained 19 mg (5%) of the α isomer, mp 125°; [α]$_D$ + 19°; IR (KBr): 1780, 1720 (phthalimide C ═ O), 1610, 725 cm^{-1}; ^{1}H NMR δ : 7.90 (m, 4 aromatic *H*), 5.96 (s, 1*H*) ppm. Anal. Calcd. for $C_{20}H_{23}NO_7$: C, 61.7; H, 6.0; N, 3.6. Found: C, 61.8; H, 5.9; N, 3.5.

4.1.1.10. 2-Phthalimidoacrylic Acid (Use of Triphenylphosphine–Diethyl Azodicarboxylate to Dehydrate an Alcohol) (100)

To a solution of 0.91 g (4.1 mmol) of (*S*)-3-hydroxy-2-phthalimidopropionic acid in 15 mL of tetrahydrofuran were added 1.07 g (4.1 mmol) of triphenylphosphine and 0.71 g (4.1 mmol) of diethyl azodicarboxylate, and the solution was stirred for 4 hours. The solvent was removed under reduced pressure, the oily residue was dissolved in benzene, and the precipitated N,N-diethoxycarbonylhydrazine was removed by filtration. The filtrate was chromatographed on a silica gel column with benzene, and the resulting 2-phthalimidoacrylic acid was recrystallized from diethyl ether–hexane (1:30). There was obtained 0.61 g (65%) of a solid, mp 111–112°; ^{1}H NMR ($CDCl_3$) δ : 3.7 (OCH_3), 5.9, 6.6 (vinyl *H*), 7.7 (phthalimido *H*) ppm.

4.1.1.11. 3 α -Cyanocholestane (Use of Triphenylphosphine–Diethyl Azodicarboxylate to Replace an Alcoholic Hydroxyl Group with Cyano) (11)

To a stirred solution of 3 β -cholestanol (390 mg, 1 mmol) and triphenylphosphine (288 mg, 1.1 mmol) in 5 mL of dry benzene was added at room temperature a solution of hydrogen cyanide (30 mg, 1.1 mmol) in 2 mL of dry benzene and then a solution of diethyl azodicarboxylate (191 mg, 1.1 mmol) in 2 mL of dry benzene. The reaction mixture warmed slightly, and a precipitate appeared. After 1 hour the benzene was removed by distillation under reduced pressure, and the residue was chromatographed on a Kieselgel column with benzene–petroleum ether (1:1). The two principal fractions were 3 α-cyanocholestane (25%) and ethyl 3 β -cholestanyl carbonate (25%). These compounds were separated by preparative liquid chromatography using petroleum ether–ethyl acetate (9:1), and the 3 α -cyanocholestane was recrystallized from diethyl ether–ethanol, mp 165–170°; $[\alpha]_D^{20}$ 20.8°(*c* 1%,

$CHCl_3$); IR (CN): 2210 cm^{-1}. Anal. Calcd. for $C_{28}H_{47}N$: C, 84.56; H, 11.91; N, 3.52. Found: C, 84.66; H, 11.58; N, 3.4.

4.1.1.12. Methyl 6-Desoxy-2,3-O-benzyl- α -D-glucopyranoside [Use of Tris(dimethylamino)phosphine–Carbon Tetrachloride] (196)

A solution of tris(dimethylamino)phosphine (0.66 g, 4 mmol) in tetrahydrofuran was added dropwise to a cold (–45°), stirred solution of methyl 2,3-di-O-benzyl- α -D-glucopyranoside (1.125 g, 3 mmol) and carbon tetrachloride (0.912 g, 6 mmol) in 10 mL of tetrahydrofuran. The reaction was monitored by TLC, using silica gel and 1:4 methanol–ethyl acetate as eluant. When the reaction was complete, a 1 *M* solution (12 mL, 12 mmol) of lithium triethylborohydride in tetrahydrofuran was added, and the mixture refluxed under an inert atmosphere for 3 hours, then allowed to cool. Excess hydride was destroyed by the addition of 0.5 mL of water. The mixture was filtered, the solvent removed under reduced pressure, and the gummy product chromatographed on a silica gel column using diethyl ether–petroleum ether (25:75) as eluant. The product was dissolved in 50 mL of diethyl ether, and the solution was washed with 1 *N* hydrochloric acid (3 × 2 mL), 1 *N* aqueous sodium hydroxide (3 × 2 mL), and water to neutrality. The solution was dried over magnesium sulfate and filtered, and the solvent removed under reduced pressure to obtain methyl 6-desoxy-2,3-O-benzyl- α -D-glucopyranoside (0.968 g, 90%), n_D^{20}1.5330; $[\alpha]_D^{25} + 33.4°$(*c* 5.3%, CCl_4).

4.1.1.13. 2,3:5,6-Di-O-isopropylidene- β -D-mannofuranosyl Azide [Use of Tris(dimethylamino)phosphine–Carbon Tetrachloride] (200)

A solution of 2,4,6-trimethylphenol (13.6 g, 0.1 mol) in dry methylene chloride (500 mL) containing carbon tetrachloride (20 g, 0.13 mol) was cooled to –40° under an inert atmosphere. The mixture was stirred while a solution of tris(dimethylamino)-phosphine (19.56 g, 0.12 mol) in 20 mL of dry methylene chloride was added dropwise over 3 hours. The mixture was allowed to warm to room temperature, and a solution of 21 g (0.32 mol) of sodium azide in 20 mL of water was added with stirring. The organic layer was separated, dried over magnesium sulfate, and evaporated under reduced pressure to give a yellow syrup. The syrup was dissolved in 70 mL of water and washed with diethyl ether (3 × 100 mL) to remove excess tris(dimethylamino)phosphine. The aqueous layer was extracted with methylene chloride (3 × 200 mL), and the extracts were dried over magnesium sulfate and evaporated to give crude mesityloxy-tris(dimethylamino)-phosphonium azide. The crude product was dissolved in 20 mL of acetone and precipitated by addition of dry diethyl ether; yield, 23.1 g (68%); mp 110–112°; IR (film): 2030 $(N_3^-)$$cm^{-1}$; ^1H NMR ($CDCl_3$) δ : 2.29 (s, 9*H*, 3 CH_3), 2.87 (d, 18*H*, *J* = 10.33 Hz), 6.90 (s, 2*H*) ppm.

A solution of 2,3:5,6-di-O-isopropylidene-D-mannofuranose (260 mg, 1 mmol) in 15 mL of dry methylene chloride containing carbon tetrachloride (308 mg,

2 mmol) was cooled to –40° under an inert atmosphere. The mixture was stirred while a solution of tris(dimethylamino)phosphine (200 mg, 1.23 mmol) in dry methylene chloride was added dropwise over 1 hour. Mesityloxy-tris(dimethylamino)phosphonium azide (680 mg, 2 mmol) was added to the cold solution, and the mixture was stirred at –10° for 3 hours. The solvent was evaporated, and the glycosyl azide was dissolved in 200 mL of hexane, washed with water (3 × 20 mL), dried over magnesium sulfate, and evaporated. The resulting syrup was chromatographed on silica gel using diethyl ether–petroleum ether (1:4) as eluant. There was obtained 0.185 g (65%) of 2,3:5,6-di-O-isopropylidene- β -D-mannofuranosyl azide, $[\alpha]_D^{25} + 2.7°$(*c* 3.32%, $CHCl_3$); IR (film): 2150 cm^{-1} (C — N_3); ^1H NMR ($CDCl_3$) δ : 1.37, 1.44, 1.55 (3 s, 12*H*), 3.43–4.87 (m, 7*H*) ppm.

4.1.1.14. trans-2,3-Di-(o-methoxyphenyl)oxirane [Use of Tris(dimethylamino)phosphine–Carbon Tetrachloride] (204)

To a solution of *meso*-1,2-di(*o*-methoxyphenyl)-1,2-ethanediol (2.74 g, 10 mmol) and carbon tetrachloride (3.24 g, 20 mmol) in methylene chloride cooled to –40° was added tris(dimethylamino)-phosphine (3.26 g, 20 mmol) dissolved in methylene chloride. After the addition, the solvent was removed under reduced pressure, the residue was hydrolyzed and extracted with pentane, and the solution was dried over magnesium sulfate. After evaporation of the solvent, the residue was crystallized from cyclohexane–ethyl acetate to obtain 1.5 g (66%) of *trans*-2,3-di-(*o*-methoxyphenyl)oxirane, mp 150–152°; ^1H NMR ($CDCl_3$) δ : 6.7–7.4 (m, aromatic *H*), 4.18 (s, CH), 3.78 (s, CH_3) ppm.

5. Tabular Survey

The tables appear in the order in which the various reagent combinations are discussed in the text. Coverage of the literature extends to April 1981.

The Conditions column includes the temperature, solvent, and reaction time if provided in the reference; a dash indicates that the conditions were not given. Yields that were not given in the reference are marked (—) in the Products column.

Abbreviations used for a few large substituents in the structures of starting compounds and products are defined in footnotes to the tables. Abbreviations used in the Conditions column are as follows:

Ac	Acetyl
Bz	Benzoyl
Bzl	Benzyl
DMF	Dimethylformamide
DMAc	Dimethylacetamide
Et_2O	Diethyl ether
HMPA	Hexamethylphosphoroustriamide
Methyl carbitol	Diethylene glycol monomethyl ether
Py	Pyridine
Tetralin	1,2,3,4-Tetrahydronaphthalene
THF	Tetrahydrofuran
Triglyme	Triethylene glycol dimethyl ether
Ts	*p*-Toluenesulfonyl

Table I. Replacement of Hydroxyl Groups by Nitrogen Nucleophiles Using Triphenylphosphine–Diethyl Azodicarboxylate

View PDF

Table II. Formation of Esters Using Triphenylphosphine–Diethyl Azodicarboxylate

View PDF

Table III. Formation of Ethers and Glycosides Using Triphenylphosphine–Diethyl Azodicarboxylate

View PDF

Table IV. Glycol Cyclizations Using Triphenylphosphine–Diethyl Diazodicarboxylate

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Table V. Preparation of Alkyl Iodides Using Triphenyl Phosphite–Methiodide

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Table VI. Preparation of Alkyl Halides Using Triphenyl Phosphite–Halogen

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Table VII. Preparation of Alkyl Halides Using Triphenylphosphine–Halogen

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Table VIII. Preparation of Alkyl Halides Using Triphenylphosphine–Carbon Tetrahalides

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Table IX. Preparation of Alkyl Halides and Azides Using Triphenylphosphine–N-Halosuccinimide

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Table X. Preparation of Alkyl Halides Using Alkoxy(trisdimethylamino)phosphonium Salts

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Table XI. Formation of Carbon — Nitrogen Bonds Using Alkoxy(trisdimethylamino)phosphonium Salts

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Table XII. Formation of Ethers and Glycosides Using Alkoxy(trisdimethylamino)phosphonium Salts

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Table XIII. Formation of Carbon — Sulfur Bonds Using Alkoxy(trisdimethylamino)phosphonium Salts

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Table XIV. Formation of Carbon —Hydrogen and Carbon —Carbon Bonds Using Alkoxy(trisdimethylamino)phosphonium Salts

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Table XV. Formation of Oxetanes from 1,3-Glycols Using 3-Hydroxy(trisdimethylamino)phosphonium Chlorides

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TABLE I. REPLACEMENT OF HYDROXYL GROUPS BY NITROGEN NUCLEOPHILES USING TRIPHENYLPHOSPHINE–DIETHYL AZODICARBOXYLATE

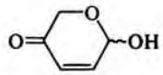
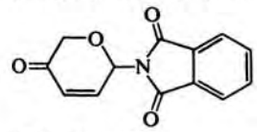
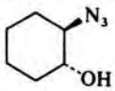
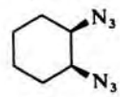
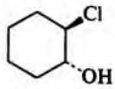
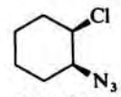
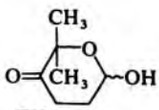
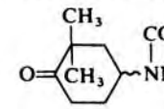
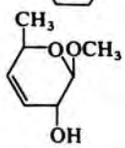
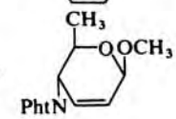
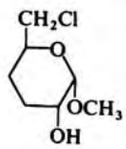
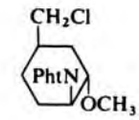
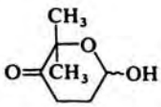
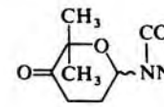
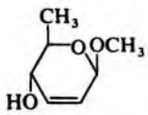
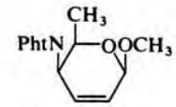
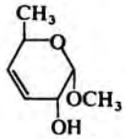
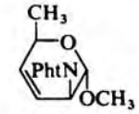
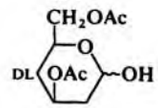
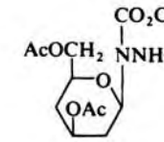
	Alcohol	Nucleophile	Conditions	Products and Yields (%)	Ref.
C_2	C_2H_5OH	Phthalimide	25°, THF	N-Ethylphthalimide (91)	48
		$C_6H_5CONHCO_2CH_2C_6H_5$	"	$C_6H_5CON(C_2H_5)CO_2CH_2C_6H_5$ (66)	48
C_3	$CH_2{=}CHCH_2OH$	None	25°, Et_2O, overnight	$C_2H_5O_2CNCH_2CH{=}CH_2$ (73) | $C_2H_5O_2CNH$	8
	n-C_3H_7OH	Phthalimide	25°, THF	N-n-Propylphthalimide (93)	48
C_4	n-C_4H_9OH	"	"	N-n-Butylphthalimide (81)	48
		Succinimide	"	N-n-Butylsuccinimide (76)	48
		$C_6H_5CONHCO_2CH_2C_6H_5$	"	$C_6H_5CON(C_4H_9\text{-}n)CO_2CH_2C_6H_5$ (66)	54
	$CH_3CHOHC_2H_5$	Phthalimide	"	N-*sec*-Butylphthalimide (75)	48
C_5	$C_2H_5O_2CCHOHCH_3$	"	"	$C_2H_5O_2CCH(CH_3)N(CO)_2C_6H_4\text{-}o$ (58)	48
	(±)-$CH_3CHOHCO_2C_2H_5$	"	25°, THF, 12 hr	(±)-$CH_3CH(CO_2C_2H_5)N(CO)_2C_6H_4\text{-}o$ (58)	50
	$(CH_3)_2COHCO_2CH_3$	"	"	$(CH_3)_2C(CO_2CH_3)N(CO)_2C_6H_4\text{-}o$ (15)	50
		Phthalimide	25°, THF, 24 hr	 (43)	51
C_6	Cyclohexanol	$(C_6H_5O)_2P(O)N_3$	"	$C_6H_{11}N_3$ (60)	65
		HN_3	25°, C_6H_6, 1 hr	 (81)	11
		"	"	 (—)	11
C_7	$C_6H_5CH_2OH$	None	Reflux, THF	$C_6H_5CH_2N(CO_2C_2H_5)NHCO_2C_2H_5$ (69) + $C_6H_5CH_2N(CO_2C_2H_5)N(CO_2C_2H_5)_2$ (8)	44
		"	25°, Et_2O, 2 days	$C_6H_5CH_2N(CO_2C_2H_5)NHCO_2C_2H_5$ (70)	8
		"	"	 (44)	45
		Phthalimide	Reflux, C_6H_6, 10 min	 (67)[a]	45
		"	"	 (47)[a]	49
		— (dibutyl azodicarboxylate as the oxidant)	25°, THF, 24 hr	 (47)	45
		Phthalimide	"	 (41)[a]	52
		"	"	 (75)[a]	52
		— (dibutyl azodicarboxylate as the oxidant)	25°, THF, 1 hr	 (45)	45

TABLE I. REPLACEMENT OF HYDROXYL GROUPS BY NITROGEN NUCLEOPHILES USING TRIPHENYLPHOSPHINE–DIETHYL AZODICARBOXYLATE (*Continued*)

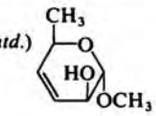
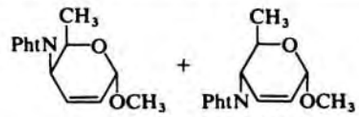
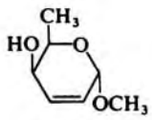
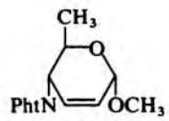
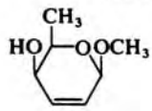
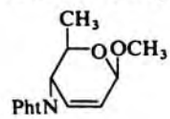
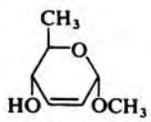
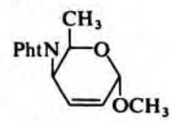
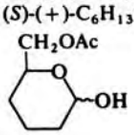
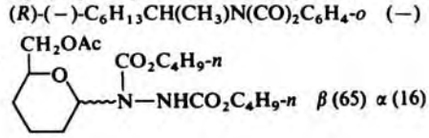
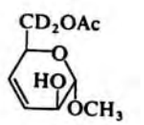
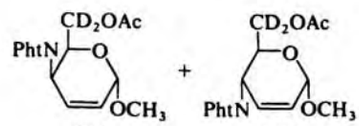
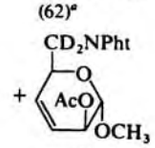
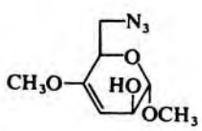
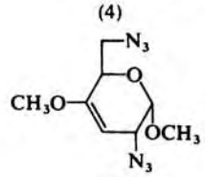
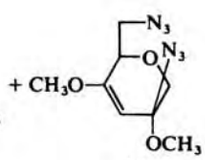
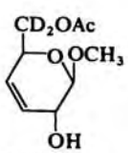
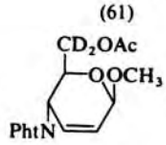
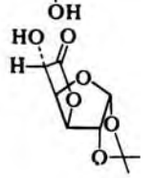
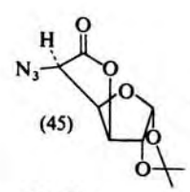
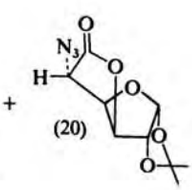
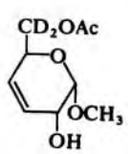
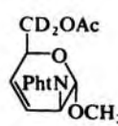
	Alcohol	Nucleophile	Conditions	Products and Yields (%)	Ref.
C_7 (*Contd.*)		Phthalimide	Reflux, C_6H_6, 10 min	 (40)[a] + (17)[a]	52
		"	Reflux, C_6H_6	 (44)[a]	52
		"	"	 (69)[a]	52
		"	"	 (54)[a]	52
C_8	(±)-$C_6H_5CHOHCH_3$	"	25°, THF	$C_6H_5CH(CH_3)N(CO)_2C_6H_4$-*o* (82)	48
	$C_2H_5O_2CCH_2CHOHCO_2C_2H_5$	HN_3	25°, C_6H_6, 1 hr	$C_2H_5O_2CCH_2CH(N_3)CO_2C_2H_5$ (75)	11
	(*S*)-(+)-$C_6H_{13}CHOHCH_3$	Phthalimide	25°, THF	(*R*)-(−)-$C_6H_{13}CH(CH_3)N(CO)_2C_6H_4$-*o* (—)	48
		— (dibutyl azodicarboxylate as the oxidant)	Reflux, C_6H_6, 10 min	 β (65) α (16)	45
		Phthalimide	"	 (62)[a] + (12)[a]	52
				 (4)	
		HN_3	25°, C_6H_6, 2 hr	 (61) +  (8)	165
		Phthalimide	Reflux, C_6H_6, 10 min	 (63)[a]	52
C_9		HN_3	25°, C_6H_6, 2 hr	 (45) +  (20)	61
C_{10}		Phthalimide	Reflux, C_6H_6, 10 min	 (100)[a]	52

TABLE I. REPLACEMENT OF HYDROXYL GROUPS BY NITROGEN NUCLEOPHILES USING TRIPHENYLPHOSPHINE–DIETHYL AZODICARBOXYLATE (*Continued*)

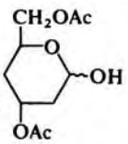
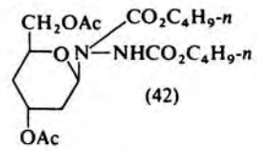
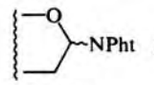
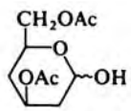
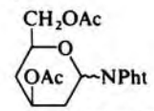
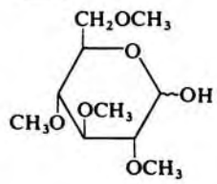
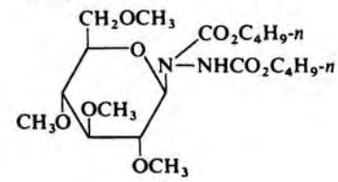
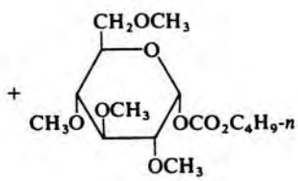
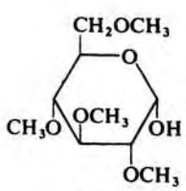
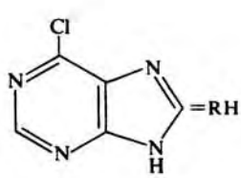
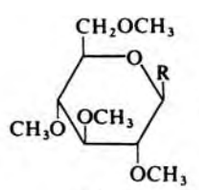
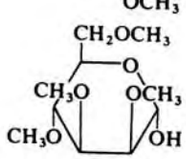
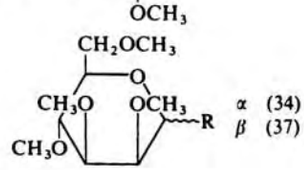
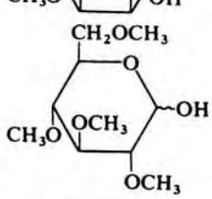
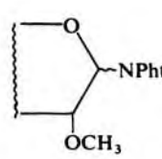
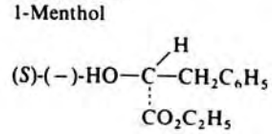
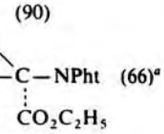
Alcohol	Nucleophile	Conditions	Products and Yields (%)	Ref.
C_{10} DL (*Contd.*) 	— (dibutyl azodicarboxylate as the oxidant)	25°, THF, 1 hr	 (42)	52
	Phthalimide	25°, THF, 24 hr	 β (43)[a]	83
	"	25°, THF, 24 hr	 α (33)[a] β (8)[a]	51
	— (dibutyl azodicarboxylate as the oxidant)	25°, THF, 1 hr	 (55) +  (18)	45
		25°, THF, 12 hr, $CH_3P(C_6H_5)_2$ as the phosphine	 (66)	57
	"	25°, THF, 12 hr, $CH_3P(C_6H_5)_2$ as the phosphine	 α (34) β (37)	57
	Phthalimide	25°, THF, 24 hr	 α (4)[a] β (37)	51
n-$C_{10}H_{23}OH$	$(C_6H_5O)_2PON_3$	"	n-$C_{10}H_{23}N_3$ (68)	65
1-Menthol	"	"	(+)-Menthyl azide (90)	65
C_{11} (*S*)-(−)- 	Phthalimide	25°, THF, 24 hr	(*R*)-(+)-  (66)[a]	

TABLE I. REPLACEMENT OF HYDROXYL GROUPS BY NITROGEN NUCLEOPHILES USING TRIPHENYLPHOSPHINE–DIETHYL AZODICARBOXYLATE (*Continued*)

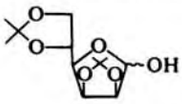
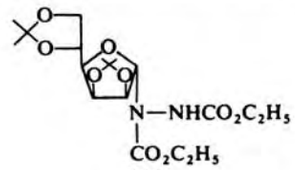
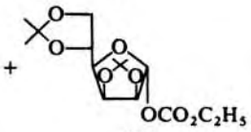
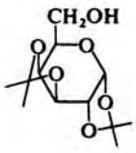
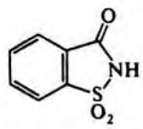
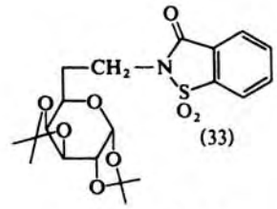
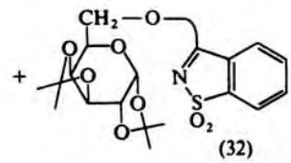
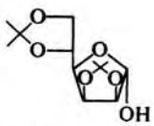
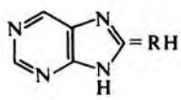
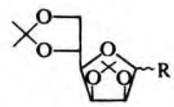
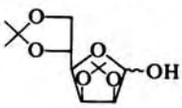
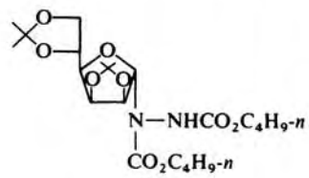
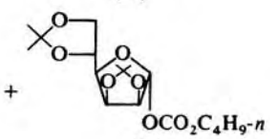
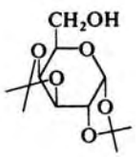
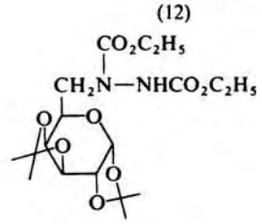
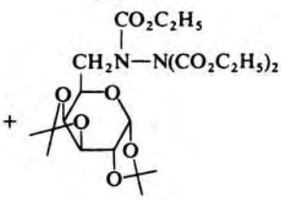
Alcohol	Nucleophile	Conditions	Products and Yields (%)	Ref.
C_{12} 	None	25°, THF, 1 hr	 (77) +  (10)	45
		25°, THF, 12 hr	 (33) +  (32)	56
		25°, THF, 12 hr, $CH_3P(C_6H_5)_2$ as the phosphine	 β (63) α (16)	57
	None (dibutyl azodicarboxylate as the oxidant)	25°, THF, 1 hr	 (79) +  (12)	45
	None	Reflux, THF	 (13) +  (75)	44

TABLE I. REPLACEMENT OF HYDROXYL GROUPS BY NITROGEN NUCLEOPHILES USING TRIPHENYLPHOSPHINE–DIETHYL AZODICARBOXYLATE (*Continued*)

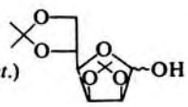
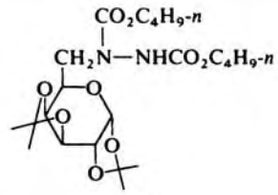
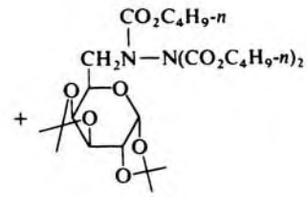
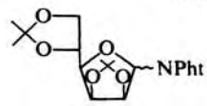
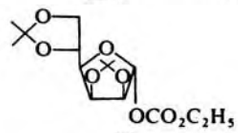
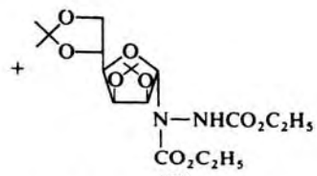
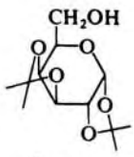
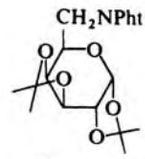
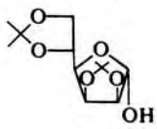
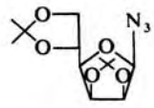
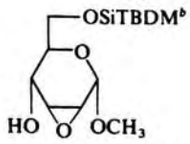
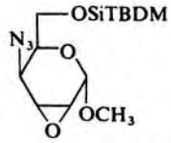
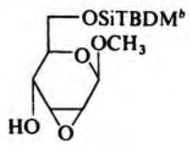
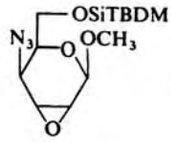
Alcohol	Nucleophile	Conditions	Products and Yields (%)	Ref.
C_{12} (*Cont.*) 	None (dibutyl azodicarboxylate as the oxidant)	Reflux, THF	 (35)	44
			 (58)	
	Phthalimide	25°, THF, 24 hr	 α (5)[a] β (25)	51
			 (2)	
			 (2)	
	"	"	 (66)[a]	49
	HN_3	25°, C_6H_6, 30 min	 (75)	207
C_{13} 	"	"	 (70)[b]	207
	"	"	 (70)[b]	207

TABLE I. REPLACEMENT OF HYDROXYL GROUPS BY NITROGEN NUCLEOPHILES USING TRIPHENYLPHOSPHINE–DIETHYL AZODICARBOXYLATE (*Continued*)

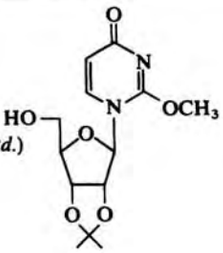
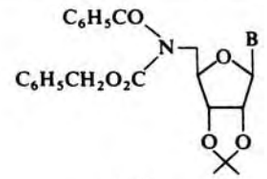
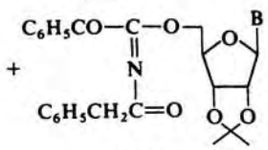
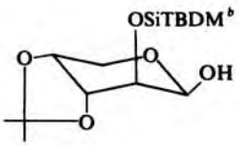
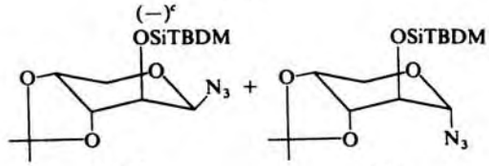
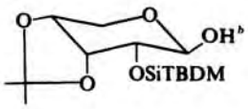
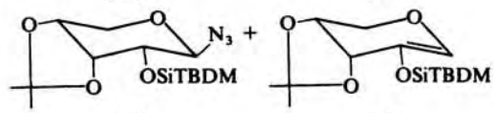
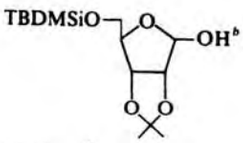
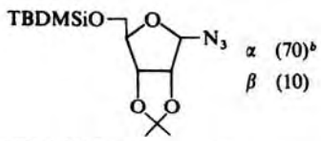
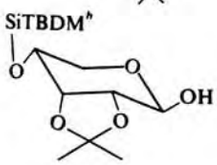
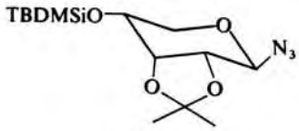
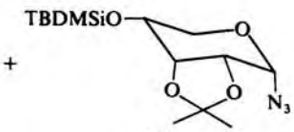
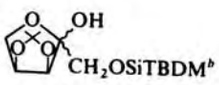
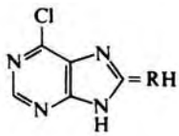
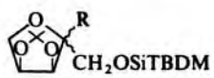
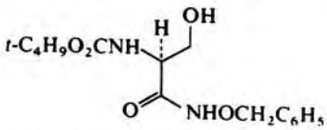
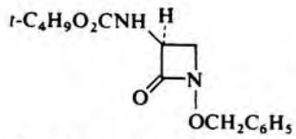
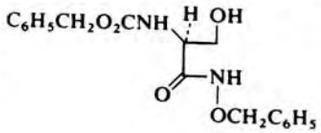
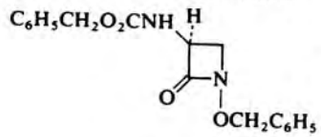
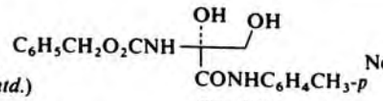
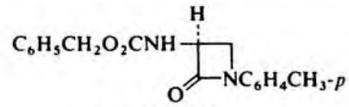
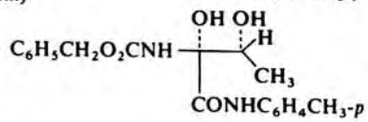
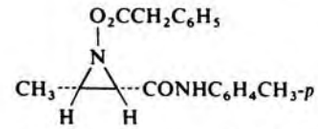
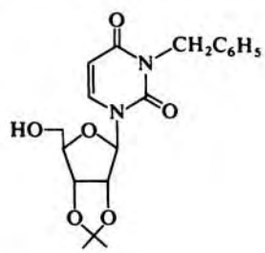
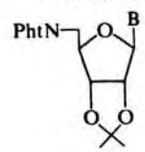
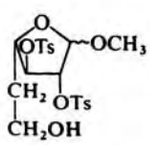
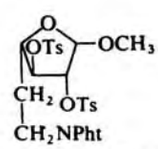
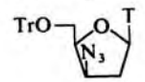
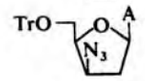
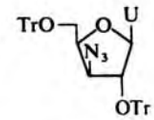
Alcohol	Nucleophile	Conditions	Products and Yields (%)	Ref.
C_{13} (*Contd.*) 	$C_6H_5CH_2O_2CNHCOC_6H_5$	25°, C_6H_6, 30 min	 (20)[c]  (–)[c]	53
C_{14} 	HN_3	"	 (57)[b] (29)	207
	"	"	 (49)[b] (49)	207
	"	"	 α (70)[b] β (10)	207
	"	"	 (49)[b] +  (49)	207
		25°, THF, 12 hr, $CH_3P(C_6H_5)_2$ as the phosphine	 (48)[b]	57
C_{15} 	None	20°, THF, 20 hr	 (90)	208
C_{18} 	"	"	 (82)	208

TABLE I. REPLACEMENT OF HYDROXYL GROUPS BY NITROGEN NUCLEOPHILES USING TRIPHENYLPHOSPHINE–DIETHYL AZODICARBOXYLATE (*Continued*)

	Alcohol	Nucleophile	Conditions	Products and Yields (%)	Ref.
C_{18} (*Contd.*)		None	25°, THF, 24 hr	 (53)	209
C_{19}		"	"	 (57)	209
	17β-Hydroxy-5α-androstan-3-one	HN_3	Reflux, C_6H_6, 10 min	17α-Azido-5α-androstan-3-one (73)	58
		$(C_6H_5O)_2P(O)N_3$	25°, THF, 24 hr	No reaction	65
	3β-Hydroxy-5α-androstan-17-one	"	"	3α-Azido-5α-androstan-17-one (75)	65
	3α-Hydroxy-5-androsten-17-one	"	"	3α-Azido-5-androsten-17-one (68)	65
	Testosterone	HN_3	Reflux, C_6H_6, 10 min	17α-Azidoandrosten-3-one (86)	58
	3β,17β-Diacetoxy-5α-androstan-6β-ol	"	"	3β,17β-Diacetoxy-6α-azido-5α-androstane (13) + 3β,17β- diacetoxyandrost-5-ene (63)	58
		Phthalimide	25°, THF, 18 hr	 (47)[a,c]	
C_{21}		"	25°, THF, 24 hr	 (66)[a]	49
	11α-Hydroxyprogesterone	HN_3	Reflux, C_6H_6/THF, 15 min	11β-Azidoprogesterone (59)	58
C_{27}	5α-Cholestan-3α-ol	"	25°, C_6H_6, 10 min	3β-Azido-5α-cholestane (77) + cholestene (traces)	58
		$(C_6H_5O)_2P(O)N_3$	25°, THF, 24 hr	No Reaction	65
	5α-Cholestan-3β-ol	"	"	3α-Azido-5α-cholestane (78)	65
	Cholesterol	"	"	3α-Azido-5-cholestene (80)	65
	Vitamin D_3	HN_3	25°, C_6H_6, 10 min	3-Desoxy-3-epiazido-vitamin D_3 (75)	60
	Epi-vitamin D_3	"	"	3-Desoxy-3-azido-vitamin D_3 (71)	60
C_{29}	5′-O-Trityl-2′-desoxythymidine	"	25°, THF, 1 hr	 (90)[d,e]	59
	5′-O-Trityl-2′-desoxyadenosine	"	Reflux, THF/C_6H_6, 10 min	 (65)[d,f]	59
C_{49}	2′,5′-Di-O-trityluridine	"	Reflux, C_6H_6, 10 min	 (87)[d,g]	59

[a] Pht = *o*-phthaloyl.
[b] TBDM = *t*-butyldimethyl.
[c] B = base group in the starting alcohol.
[d] Tr = trityl.
[e] T = 1-desoxythymidyl.
[f] A = 1-desoxyadenosyl.
[g] U = 1-uridyl.

TABLE II. FORMATION OF ESTERS USING TRIPHENYLPHOSPHINE–DIETHYL AZODICARBOXYLATE

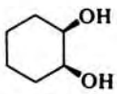
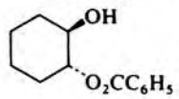
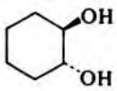
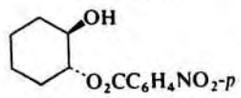
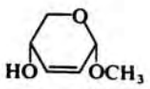
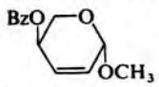
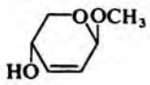
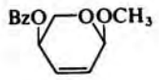
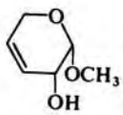
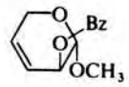
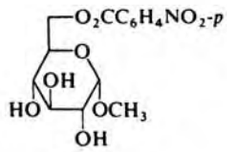
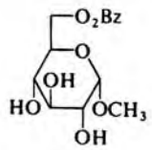
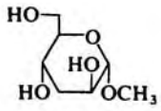
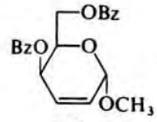
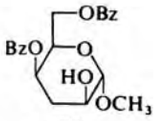
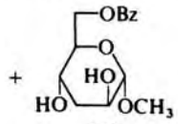
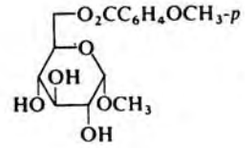
	Alcohol	Acid	Conditions	Esters and Yields (%)	Ref.
C_2	C_2H_5OH	n-$C_4H_9CO_2H$	25°, Et_2O, 8 hr	n-$C_4H_9CO_2C_2H_5$ (34)	66
		$C_6H_5CO_2H$	"	$C_6H_5CO_2C_2H_5$ (85)	66
C_3	i-C_3H_7OH	n-$C_4H_9CO_2H$	"	n-$C_4H_9CO_2C_3H_7$-i (43)	66
	$CH_2{=}CHCH_2OH$	"	"	n-$C_4H_9CO_2CH_2CH{=}CH_2$ (35)	66
		$C_6H_5CO_2H$	"	$C_6H_5CO_2CH_2CH{=}CH_2$ (85)	66
	$CH_3CHOHCH_2OH$	"	25°, THF, 14 hr	$CH_3CHOHCH_2O_2CC_6H_5$ + $CH_3CH(O_2CC_6H_5)CH_2O_2CC_6H_5$ (5)	107
C_4	$CH_3CHOHCH_2CH_2OH$	"	"	$CH_3CHOHCH_2CH_2O_2CC_6H_5$ (70) + $CH_3CH(O_2CC_6H_5)CH_2CH_2O_2CC_6H_5$ (7)	107
	$CH_3CHOHCHOHCH_3$	"	"	$CH_3CHOHCH(CH_3)O_2CC_6H_5$ (8)	107
C_5	$CH_3CHOHCH_2CHOHCH_3$	"	"	$CH_3CHOHCH_2CH(CH_3)O_2CC_6H_5$ (57) + $CH_3CH(O_2CC_6H_5)CH_2CH(CH_3)O_2CC_6H_5$ (20)	107
C_6		"	"	 (22)	107
		p-$O_2NC_6H_4CO_2H$	Reflux, $(i\text{-}C_3H_7)_2O$, 14 hr	 (49)	11
		$C_6H_5CO_2H$	25°, Et_2O, 18 hr	Cyclohexene oxide (68)	107
		"	25°, THF, 1 hr	 (94)	14
		"	"	 (90)	14
		"	"	 (88)	14
C_7	Methyl-α-D-glucopyranoside	p-$O_2NC_6H_4CO_2H$	Reflux, dioxane/Py, 4 hr	 (92)	210
		$C_6H_5CO_2H$	"	 (71)	210
		$C_6H_5CO_2H$	25°, THF, 31 hr	 (23) +  (47) +  (12)	13
	Methyl-α-D-glucopyranoside	p-$CH_3OC_6H_4CO_2H$	Reflux, dioxane/Py, 4 hr	 (75)	210

TABLE II. FORMATION OF ESTERS USING TRIPHENYLPHOSPHINE–DIETHYL AZODICARBOXYLATE (*Continued*)

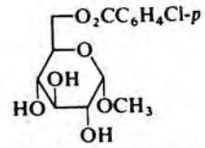
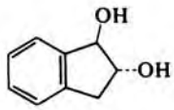
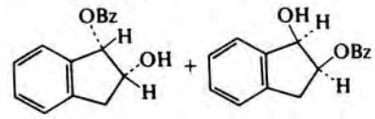
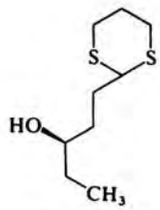
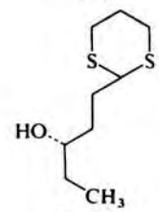
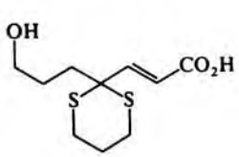
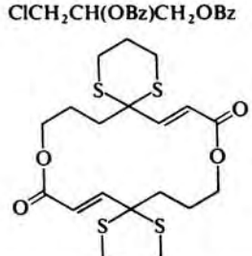
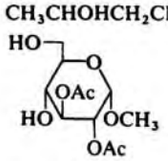
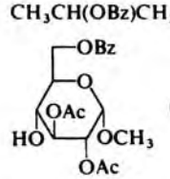
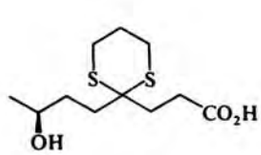
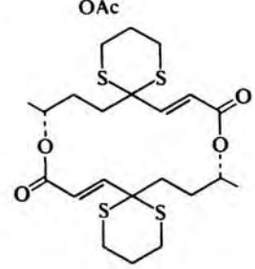
	Alcohol	Acid	Conditions	Esters and Yields (%)	Ref.
	C- Methyl-α-D-glucopyranoside (*Contd.*)	p-$ClC_6H_4CO_2H$	Reflux, dioxane/Py, 4 hr	 (79)	210
C_8	$C_6H_5CHOHCH_2OH$	$C_6H_5CO_2H$	25°, Et_2O, 18 hr	$C_6H_5CHOHCH_2OBz$ (47) + $C_6H_5CH(OBz)CH_2OBz$ (5) + $C_6H_5CH—CH_2$ (27) (O)	107
C_9	 *trans*	"	"	 (29) (21)	107
	 $[\alpha]_D^{20} = -14.1°$	1. $C_6H_5CO_2H$ 2. CH_3ONa	—	 (Quant.) $[\alpha]_D^{20} = +14.0°$	211
	Uridine	$C_6H_5CO_2H$	25°, Dioxane/HMPA, 18 hr	5′-O-Benzoyluridine (77)	68
		p-$O_2NC_6H_4CO_2H$	"	5′-O-p-Nitrobenzoyluridine (50)	68
C_{10}	Thymidine	$C_6H_5CO_2H$	25°, HMPA, 18 hr	5′-O-Benzoylthymidine (74)	80
		p-$O_2NC_6H_4CO_2H$	"	5′-O-p-Nitrobenzoylthymidine (84)	80
		p-$NCC_6H_4CO_2H$	"	5′-O-p-Cyanobenzoylthymidine (79)	80
		p-$CH_3OC_6H_4CO_2H$	"	5′-O-p-Methoxybenzoylthymidine (65)	80
		p-$CH_3C_6H_4CO_2H$	"	5′-O-p-Methylbenzoylthymidine (65)	80
		CH_3CO_2H	25°, HMPA/dioxane, 18 hr	5′-O-Acetylthymidine (55)	80
	Adenosine	p-$O_2NC_6H_4CO_2H$	Reflux, HMPA/dioxane, 18 hr	5′-O-p-Nitrobenzoyladenosine (43)	68
	$ClCH_2CHOHCH_2O_2CC_6H_5$	$C_6H_5CO_2H$	25°, Et_2O, 18 hr	$ClCH_2CH(OBz)CH_2OBz$ (81)	107
		None	−40°, +25°, Toluene, 52 hr	 (60)	76
C_{11}	$CH_3CHOHCH_2CH_2OBz$	$C_6H_5CO_2H$	"	$CH_3CH(OBz)CH_2CH_2OBz$ (63)	107
		"	25°, THF, 31 hr	 (71)	13
		None	−40°, −4°, Toluene, 84 hr	 (84)	76

TABLE II. FORMATION OF ESTERS USING TRIPHENYLPHOSPHINE–DIETHYL AZODICARBOXYLATE (*Continued*)

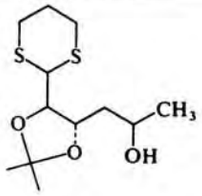
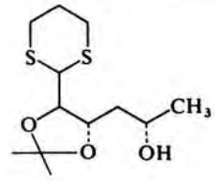
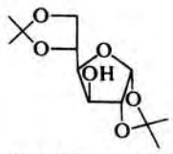
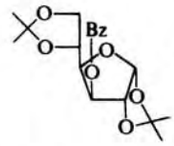
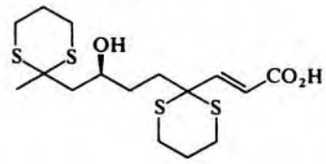
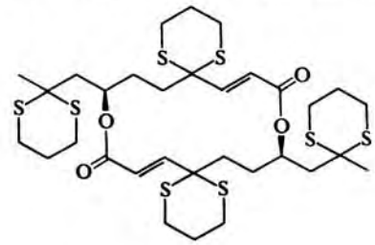
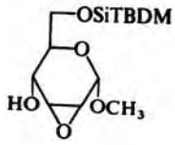
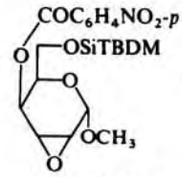
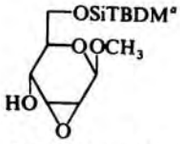
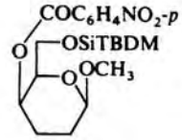
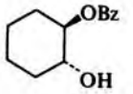
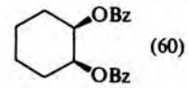
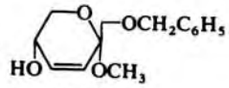
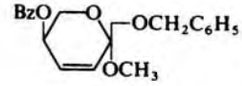
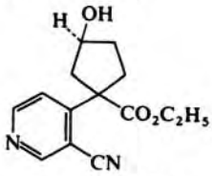
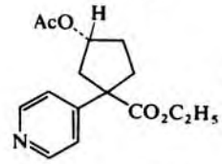
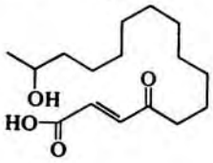
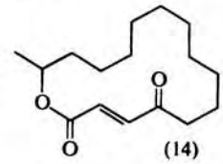
	Alcohol	Acid	Conditions	Esters and Yields (%)	Ref.
C_{12}		$C_6H_5CO_2H$	1. THF 2. CH_3ONa	 (86)	212
		"	25°, THF, 48 hr	 (18)	70
	2′,3′-O-Isopropylideneuridine	"	25°, HMPA/dioxane, 18 hr	2′,3′-O-Isopropylidene-5′-O-benzoyluridine (43)	68
		p-$O_2NC_6H_4CO_2H$	"	2′,3′-O-Isopropylidene-5′-O-p-nitrobenzoyluridine (65)	68
C_{13}	2′,3′-O-Isopropylideneadenosine	"	"	2′,3′-O-Isopropylidene-5′-O-p-nitrobenzoyladenosine (63)	68
		None	−28°; +12°, Toluene, 12 hr	 (24)	76
		p-$O_2NC_6H_4CO_2H$	Reflux, THF, 1 hr	 (56)[a]	64
		"	"	 (46)[a]	64
	$CH_3CH(OBz)CH_2CH_2CHOHCH_3$	$C_6H_5CO_2H$	"	$CH_3CH(OBz)CH_2CH_2CH(OBz)CH_3$ (75)	107
		"	"	 (60)	107
C_{14}		"	25°, THF, 1 hr	 (87)	14
		CH_3CO_2H	25°, THF, 20 hr	 (91)	213
C_{16}		None	−30°, Toluene, 15 hr	 (14) + dimer (4)	214

TABLE II. FORMATION OF ESTERS USING TRIPHENYLPHOSPHINE–DIETHYL AZODICARBOXYLATE (*Continued*)

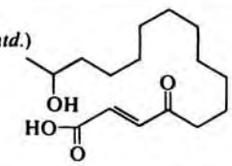
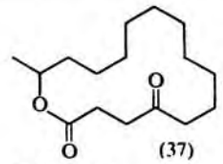
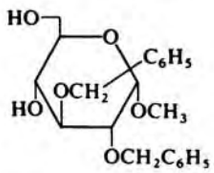
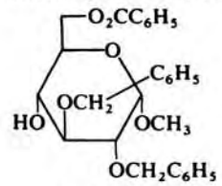
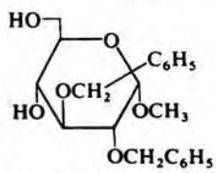
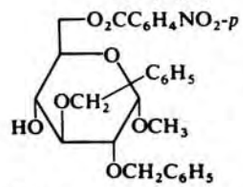
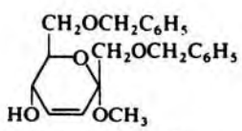
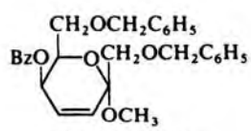
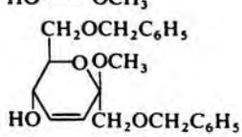
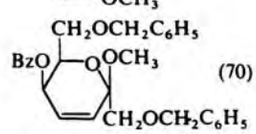
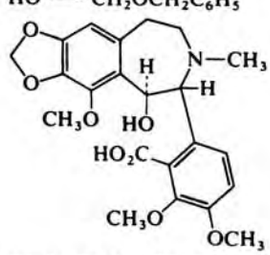
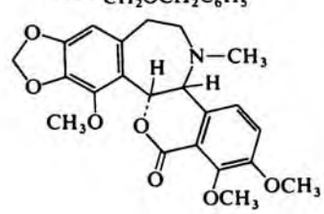
	Alcohol	Acid	Conditions	Esters and Yields (%)	Ref.
C_{16} (*Contd.*)		None	−20°, THF, 2 hr	 + dimer (17) (37)	214
C_{19}	4-Androsten-17β-ol-3-one	$C_6H_5CO_2H$	25°, THF, 14 hr	No reaction	67
		"	Reflux, C_6H_6, 15 min	17α-Benzoyloxyandrost-4-en-3-one (64)	58
	5-Androsten-3β, 16α-diol	"	25°, THF, 14 hr	5-Androsten-3α, 16β-diol dibenzoate (75)	67
	5α-Androsten-3β-ol-17-one	HCO_2H	"	3α-Formyloxy-5α-androsten-17-one (85)	67
C_{21}		$C_6H_5CO_2H$	25°, THF	 (69)	210
		p-$O_2NC_6H_4CO_2H$	"	 (83)	210
C_{22}	16α-Methyl-5α-pregnan-3β-ol-20-one	HCO_2H	25°, THF, 14 hr	3α-Formyloxy-16α-methyl-5α-pregnan-20-one (75)	67
		$C_6H_5CO_2H$	25°, THF, 1 hr	 (82)	14
		"	"	 (70)	14
		None	20°, THF, 90 min		215
C_{24}	Methyl 3α, 12α-dihydroxycholanate	HCO_2H	25°, THF, 14 hr	Methyl 3β-formyloxy-12α-hydroxycholanate (97)	67
	Methyl 3α, 7α, 12α-trihydroxycholanate	"	"	Methyl 3β-formyloxy-7α, 12α-dihydroxycholanate (75)	67
C_{27}	5α-Cholestan-3β, 6β-diol	$C_6H_5CO_2H$	25°, THF, 15 hr	3α-Benzoyloxy-5α-cholestan-6β-ol (92)	69
	5α-Cholestan-3β-ol	HCO_2H	"	3α-Formyloxy-5α-cholestane (97)	67
		$C_6H_5CH_2CO_2H$	"	5α-Cholestan-3α-ol phenylacetate (90)	67
		$C_6H_5CO_2H$	"	5α-Cholestan-3α-ol benzoate (100)	67
	5α-Cholestan-3α-ol	"	"	No reaction	67
		"	25°, C_6H_6, 15 min	3β-Benzoyloxy-5α-cholestane (73) + 2-cholestene (25)	11
	Δ^4-Cholestan-3-ol	"	25°, THF, 10 min	Δ^4-Cholesten-3α-ol benzoate (81)	14
		"	25°, THF, 24 hr	" (81)	15
		CH_3CO_2H	"	Δ^4-Cholesten-3α-ol acetate (47)	15
		$C_2H_5CO_2H$	"	Δ^4-Cholesten-3α-ol propionate (48)	15

TABLE II. FORMATION OF ESTERS USING TRIPHENYLPHOSPHINE–DIETHYL AZODICARBOXYLATE (*Continued*)

Alcohol	Acid	Conditions	Esters and Yields (%)	Ref.
C_{27} Δ^4-Cholestan-3-ol (*Contd.*)	$C_2H_5CO_2H$	25°, THF, 14 hr	Δ^4-Cholesten-3β-ol propionate (68)	15
	CH_3CO_2H	"	Δ^4-Cholesten-3β-ol acetate (85)	15
	$C_6H_5CO_2H$	"	Δ^4-Cholesten-3β-ol benzoate (72)	15
Cholesterol	"	0°, Et_2O, 3 hr	Cholest-5-en-3α-yl benzoate (11) + cholest-5-en-3β-yl benzoate (20) + 3,5-cyclocholest-6β-yl benzoate (23) + 3,5-cyclocholest-6α-yl benzoate (14) + cholesta-3,5-diene (10) + 3,5-cyclocholest-6-ene (10)	17
C_{28} (*R*)-HO(CH$_2$OC$_{18}$H$_{37}$-*n*)(CH$_2$O$_2$CC$_6$H$_5$)-H	CH_3CO_2H	25°, Et_2O	(*S*)-H(CH$_2$OC$_{18}$H$_{37}$-*n*)(CH$_2$O$_2$CC$_2$H$_5$)-OAc	16
"	$C_6H_5CO_2H$	"	(*S*)-H(CH$_2$OC$_{18}$H$_{37}$-*n*)(CH$_2$O$_2$CC$_6$H$_5$)-OBz	16
C_{37} (±)-H(CH$_2$O$_2$CC$_{15}$H$_{31}$-*n*)(CH$_2$O$_2$CC$_{17}$H$_{35}$-*n*)-OH	"	"	(±)-H(CH$_2$O$_2$CC$_{15}$H$_{31}$-*n*)(CH$_2$—O$_2$CC$_{17}$H$_{35}$-*n*)-OBz	16
"	Oleic acid	"	(±)-H(CH$_2$O$_2$CC$_{15}$H$_{31}$-*n*)(CH$_2$O$_2$CC$_{17}$H$_{35}$-*n*)-O$_2$CC$_{17}$H$_{33}$	16

[a] TBDM = *t*-butyldimethyl.

TABLE III. FORMATION OF ETHERS AND GLYCOSIDES USING TRIPHENYLPHOSPHINE–DIETHYL AZODICARBOXYLATE

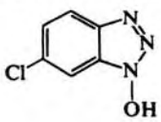
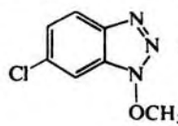
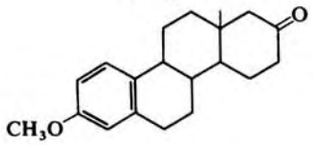
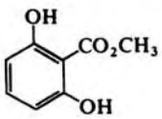
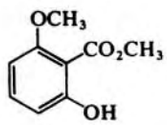
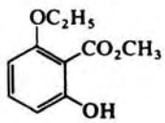
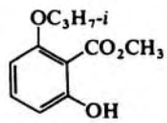
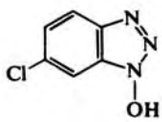
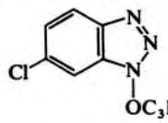
	Alcohol	Nucleophilic Hydroxyl Compound	Conditions	Products and Yields (%)	Ref.
C_1	CH_3OH		25°, THF, 12 hr	 (90)	90
		Estrone	25°, THF, 1–4 days	 (—)	93
			25°, THF, 2 hr	 (76)	216
C_2	C_2H_5OH	"	"	 (61)	216
C_3	i-C_3H_7OH	"	"	 (55)	216
			25°, THF, 12 hr	 (84)	90

TABLE III. FORMATION OF ETHERS AND GLYCOSIDES USING TRIPHENYLPHOSPHINE–DIETHYL AZODICARBOXYLATE (*Continued*)

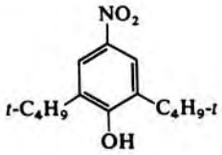
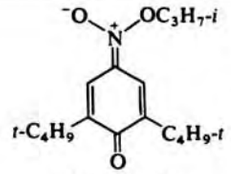
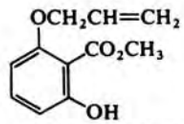
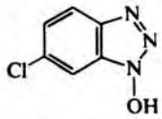
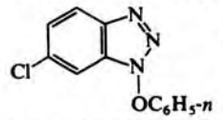
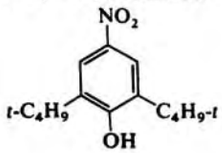
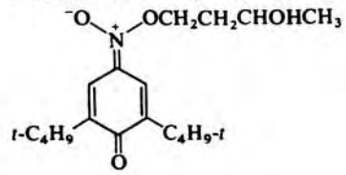
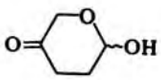
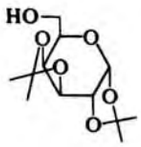
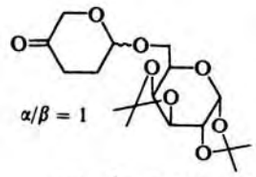
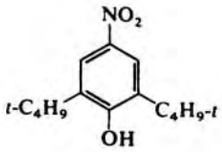
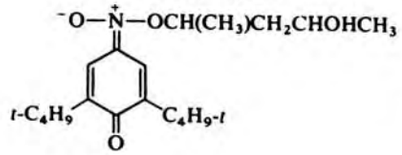
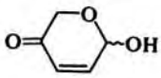
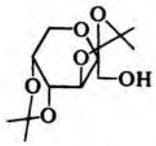
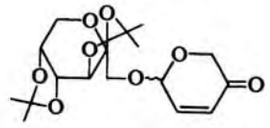
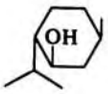
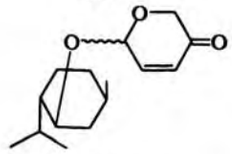
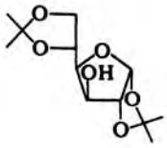
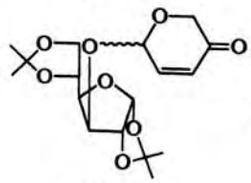
Alcohol	Nucleophilic Hydroxyl Compound	Conditions	Products and Yields (%)	Ref.
C_3 i-C_3H_7OH (*Contd.*)		25°, 24 hr	 (79)	99
$CH_2{=}CHCH_2OH$	"	"	 (62)	216
	N-Hydroxyphthalimide	—	o-$C_6H_4(CO)_2NOCH_2CH{=}CH_2$ (80)	87
C_4 n-C_4H_9OH	N-Hydroxyphthalimide	25°, THF, 24 hr	o-$C_6H_4(CO)_2NOC_4H_9$-n (91)	87
		25°, THF, 12 hr	 (80)	90
$CH_3CH_2CHOHCH_3$	N-Hydroxyphthalimide	25°, THF, 24 hr	o-$C_6H_4(CO)_2NOCH(CH_3)CH_2CH_3$ (76)	87
$CH_3CHOHCH_2CH_2OH$		25°, 24 hr	 (69)	99
C_5 		25°, THF, 12 hr, catalyst $HgBr_2$	 $\alpha/\beta = 1$ (36)	98
$CH_3CHOHCH_2CHOHCH_3$		25°, 24 hr	 (68)	99
		25°, THF, 12 hr, catalyst $HgBr_2$	 $\alpha/\beta = 1$ (17)	98
		25°, THF, 12 hr,	 $\alpha/\beta = 1$ (48)	98
		"	 $\alpha/\beta = 1$ (32)	98

TABLE III. FORMATION OF ETHERS AND GLYCOSIDES USING TRIPHENYLPHOSPHINE–DIETHYL AZODICARBOXYLATE (*Continued*)

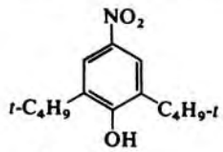
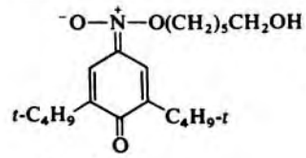
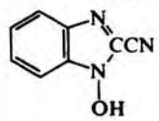
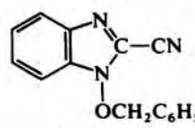
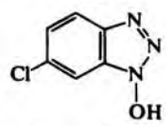
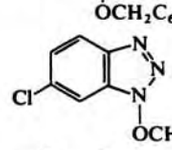
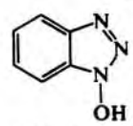
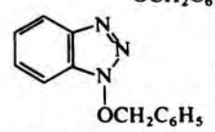
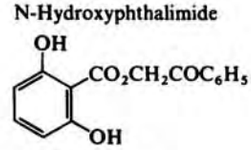
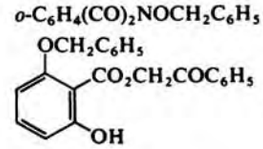
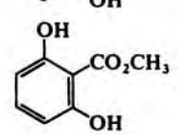
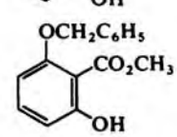
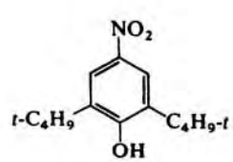
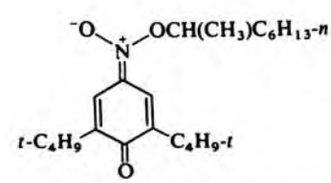
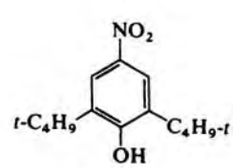
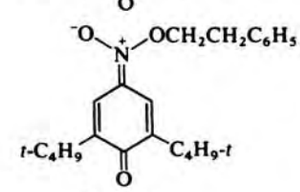
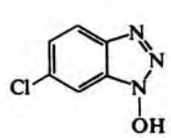
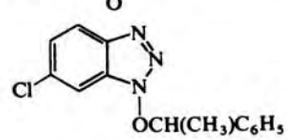
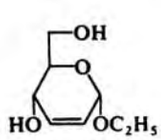
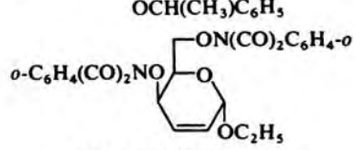
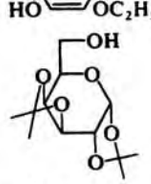
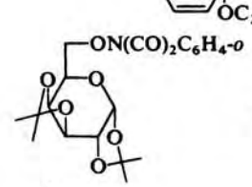
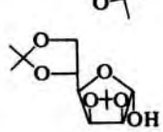
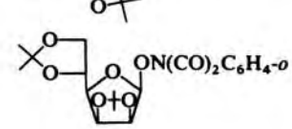
	Alcohol	Nucleophilic Hydroxyl Compound	Conditions	Products and Yields (%)	Ref.
C_6	$HOCH_2(CH_2)_4CH_2OH$		25°, 24 hr	 (68)	99
C_7	$C_6H_5CH_2OH$		25°, THF, 12 hr	 (68)	90
			"	 (85)	90
			"	 (80)	90
		N-Hydroxyphthalimide	25°, THF, 24 hr	o-$C_6H_4(CO)_2NOCH_2C_6H_5$ (92)	87
			25°, THF, 2 hr	 (70)	216
			"	 (73)	216
C_8	n-$C_6H_{13}CHOHCH_3$		25°, 24 hr	 (76)	99
	$C_6H_5CH_2CH_2OH$		"	 (83)	99
	$C_6H_5CHOHCH_3$		25°, THF, 12 hr	 (79) + α anomer (11)	90
		N-Hydroxyphthalimide	25°, THF, 24 hr	 (78)	88
C_{12}		N-Hydroxyphthalimide	"	 (54)	88
		N-Hydroxyphthalimide	"	 (65)	88

TABLE III. FORMATION OF ETHERS AND GLYCOSIDES USING TRIPHENYLPHOSPHINE–DIETHYL AZODICARBOXYLATE (*Continued*)

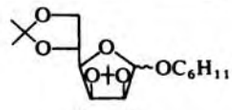
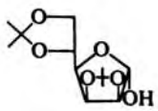
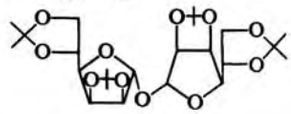
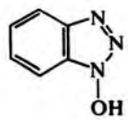
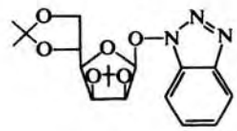
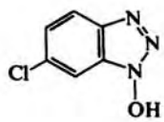
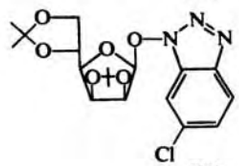
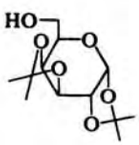
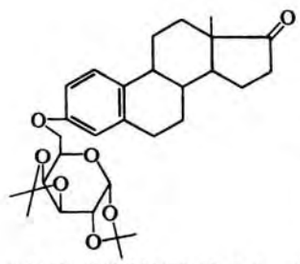
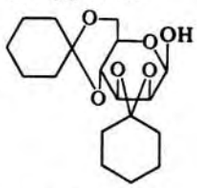
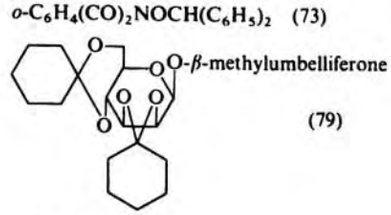
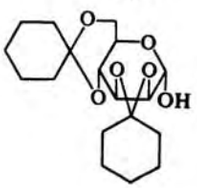
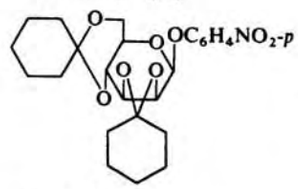
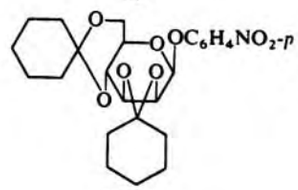
Alcohol	Nucleophilic Hydroxyl Compound	Conditions	Products and Yields (%)	Ref.
C_{12} (*Contd.*)	Cyclohexanol	Reflux, THF, 3 hr, catalyst $HgBr_2$	 (72) $\alpha/\beta = 2.6$	97
		25°, THF, 12 hr, catalyst $HgBr_2$	 (21)	97
		25°, THF, 12 hr	 + α isomer (—) (66)	90
		"	 + α isomer (—) (90)	90
		Estrone	25°, THF, 1–4 days  (43)	93
C_{13} $(C_6H_5)_2CHOH$	N-Hydroxyphthalimide	25°, THF, 24 hr	o-$C_6H_4(CO)_2NOCH(C_6H_5)_2$ (73)	87
C_{18} 	β-Methylumbelliferone	25°, Toluene	 O-β-methylumbelliferone (79) + α isomer (11)	217
	p-$O_2NC_6H_4OH$	25, Toluene, 1 hr	 (58)	96
	"	25°, Toluene	 + α isomer (22) (72)	217

TABLE III. FORMATION OF ETHERS AND GLYCOSIDES USING TRIPHENYLPHOSPHINE–DIETHYL AZODICARBOXYLATE (*Continued*)

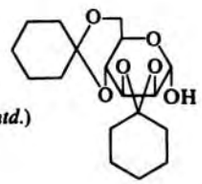
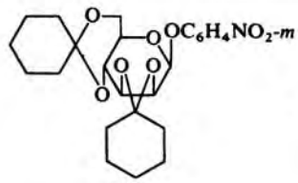
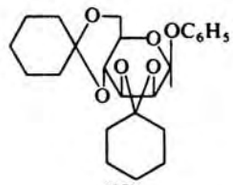
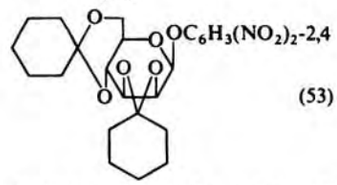
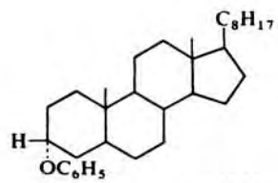
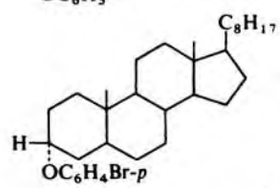
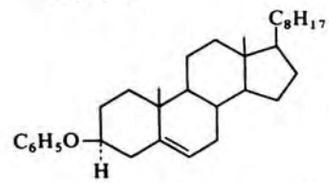
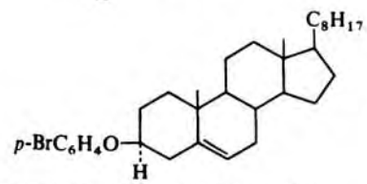
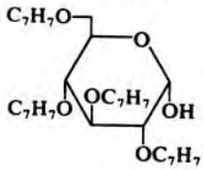
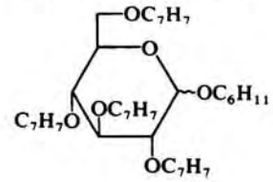
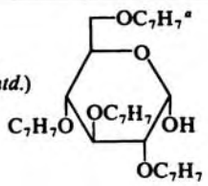
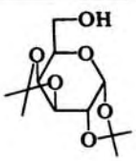
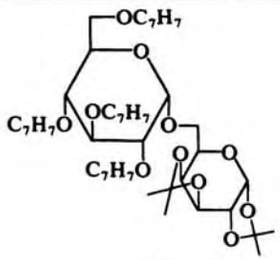
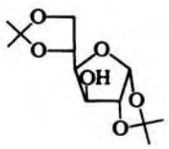
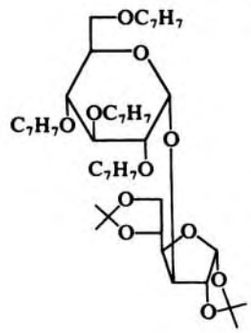
Alcohol	Nucleophilic Hydroxyl Compound	Conditions	Products and Yields (%)	Ref.
C_{18} (*Contd.*) 	m-$O_2NC_6H_4OH$	25°, Toluene	 (81) + α isomer (8)	217
	C_6H_5OH	"	 (82) + α isomer (4)	217
	2,4-$(O_2N)_2C_6H_3OH$	25°, Toluene	 (53) + α isomer (37)	217
C_{21} Hydrocortisone	N-Hydroxyphthalimide	25°, THF, 24 hr	21-Phthalimidoxyhydrocortisone (86)	89
Epi-Hydrocortisone	"	"	21-Phthalimidoxy-*epi*-hydrocortisone (80)	89
C_{24} Desoxycholic acid	"	"	3β-Phthalimidoxy-12α-hydroxy-24-O-cholanoyl-N-hydroxyphthalimide (75)	89
C_{27} Cholestan-5α, 3β-ol	C_6H_5OH	25°, THF, 1–4 days	 (80)	93
Cholestan-5α,3β-ol	p-BrC_6H_4OH	"	 (65)	93
Cholesterol	C_6H_5OH	"	 (65)	93
	p-BrC_6H_4OH	"	 (60)	93
Cholestan-3β-ol	N-Hydroxyphthalimide	25°, THF, 24 hr	3α-Phthalimidoxycholestane (96)	89
Cholest-5-en-3β-ol	"	"	3α-Phthalimidoxycholest-5-ene (50)	89
C_{34} 	Cyclohexanol	25°, THF, 12 hr, catalyst $HgBr_2$	 (80)[a]	97

TABLE III. FORMATION OF ETHERS AND GLYCOSIDES USING TRIPHENYLPHOSPHINE–DIETHYL AZODICARBOXYLATE (*Continued*)

Alcohol	Nucleophilic Hydroxyl Compound	Conditions	Products and Yields (%)	Ref.
C_{34} (*Contd.*) 		25°, THF, 24 hr, catalyst $HgBr_2$	 (80)[a]	97
		"	 (38)[a]	97
	None	25°, THF, 48 hr, catalyst HgI_2, phosphine $CH_3P(C_6H_5)_2$	Octa-O-benzyl-α,α′-trehalose (40)	97

[a] $C_7H_7 = C_6H_5CH_2$

TABLE IV. GLYCOL CYCLIZATIONS USING TRIPHENYLPHOSPHINE–DIETHYL DIAZODICARBOXYLATE

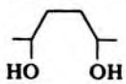
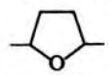
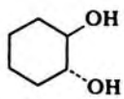
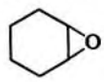
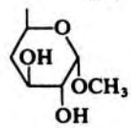
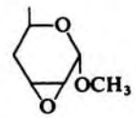
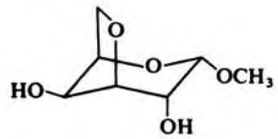
	Glycol	Conditions	Products and Yields (%)	Ref.
C_3	$CH_3CHOHCH_2OH$	0°, Toluene, 10 min	2-Methyloxirane (100)	94
	$HOCH_2CH_2CH_2OH$	20°, $CDCl_3$, 10 min	Oxetane (98)	94
C_4	$CH_3CHOHCHOHCH_3$	20°, THF, 10 min	2,3-Dimethyloxirane (100)	94
	$HOCH_2(CH_2)_2CH_2OH$	5°, Tetralin, 10 min	Tetrahydrofuran (100)	94
	$O(CH_2CH_2OH)_2$	25°, Tetralin, 10 min	1,4-Dioxane (96)	94
	$(CH_3)_2CH(NH_2)CH_2OH$	20°, Tetralin, 10 min	2,2-Dimethylaziridine (100)	94
C_5	$CH_2(CH_2CH_2OH)_2$	5°, $CDCl_3$, 10 min	Tetrahydropyran (95)	94
C_6	$HOCH_2(CH_2)_4CH_2OH$	"	Oxepane (94)	94
	trans-1,2-Cyclohexanediol	20°, THF, 10 min	Cyclohexene oxide (100)	94
		25°, Et_2O, 12 hr	 (48) (stereochemistry not specified)	107
		"	 (68)	107
C_7		Reflux, C_6H_6	 (75)	218
	Methyl-α-D-galactopyranoside	Reflux, dioxane/Py	 (80)	210

TABLE IV. GLYCOL CYCLIZATIONS USING TRIPHENYLPHOSPHINE–DIETHYL DIAZODICARBOXYLATE (*Continued*)

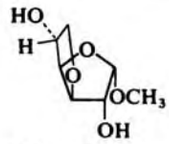
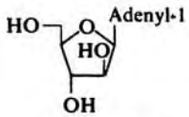
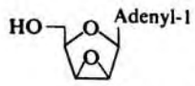
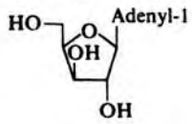
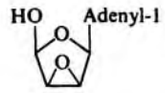
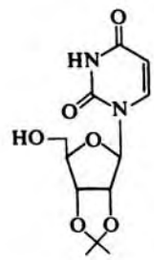
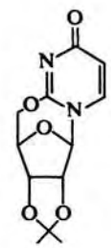
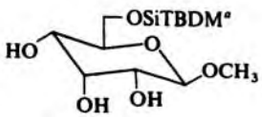
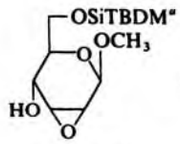
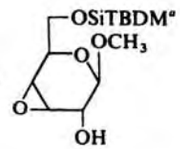
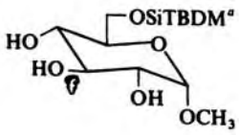
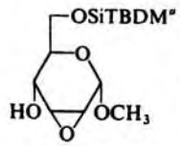
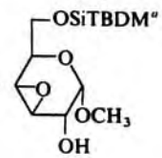
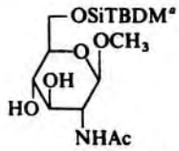
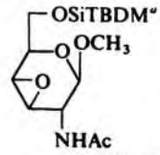
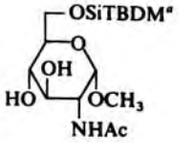
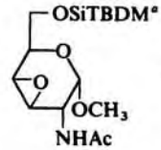
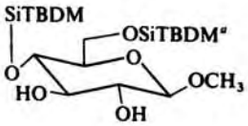
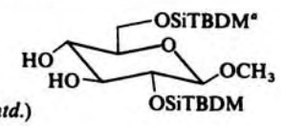
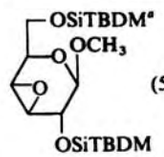
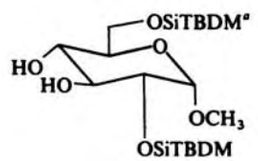
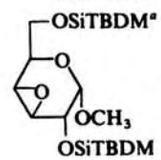
	Glycol	Conditions	Products and Yields (%)	Ref.
C_7 (*Cont.*)	Methyl-α-D-glucopyranoside	Reflux, dioxane/Py	 (85)	210
C_8	$C_6H_5CHOHCH_2OH$	21°, $CDCl_3$, 10 min	2-Phenyloxirane (100)	94
		25°, Et_2O, 12 hr	" (27)	107
C_{10}		70°, Dioxane, 40 min	 (90)	108
		70°, Dioxane, 6 hr	 (60)	108
C_{12}			 (80)	54
C_{13}		Reflux, C_6H_6, 30 min	 (46) +  (23)	64
		"	 (56) +  (10)	64
C_{15}		0°, C_6H_6, 30 min	 (80)	64
		60°, C_6H_6, 30 min	 (80)	64
C_{19}		Reflux, C_6H_6, 3 min	(71)	64

TABLE IV. GLYCOL CYCLIZATIONS USING TRIPHENYLPHOSPHINE–DIETHYL DIAZODICARBOXYLATE (*Continued*)

	Glycol	Conditions	Products and Yields (%)	Ref.
C_{19} (*Contd.*)		Reflux, C_6H_6, 30 min	 (54)	64
		"	 (68)	64
C_{27}	2β,3α-Dihydroxy-5α-cholestane	80°, C_6H_6, 10 min	2β,3β-Epoxy-5α-cholestane (—) + 2α,3β-Epoxy-5α-cholestane (—)	58

[a] TBDM = *t*-butyldimethyl.

TABLE V. PREPARATION OF ALKYL IODIDES USING TRIPHENYL PHOSPHITE–METHIODIDE

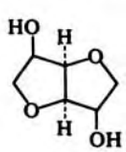
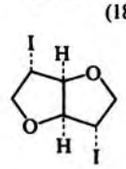
	Alcohol	Conditions	Products and Yields (%)	Ref.
C_3	$CH_3CHOHCH_3$	25°	CH_3CHICH_3 (75)	115
	$CH_2{=}CHCH_2OH$	0°, 30 min	$CH_2{=}CHCH_2I$ (84)	115
	$HC{\equiv}CCH_2OH$	0°, CH_2Cl_2, 3 hr	$HC{\equiv}CCH_2I$ (65) + $CH_2{=}C{=}CHI$ (7)	116
		100°, DMF, 30 min	$HC{\equiv}CCH_2I$ (11) + $CH_2{=}C{=}CHI$ (43)	116
	$HO(CH_2)_3OH$	—	$I(CH_2)_3I$ (95)	219, 115
C_4	n-C_4H_9OH	25°, 30 min	n-C_4H_9I (72)	115
	$C_2H_5CHOHCH_3$	25°, 2 hr	$C_2H_5CHICH_3$ (60)	115
	t-C_4H_9OH	50°, 1 hr	$(CH_3)_3CI$ (76)	115
	$CH_3CH{=}CHCH_2OH$	0°, 30 min	$CH_3CH{=}CHCH_2I$ (83)	115
	$HC{\equiv}CCHOHCH_3$	100°, DMF, 30 min	$ICH{=}C{=}CHCH_3$ (53)	116
C_5	$(CH_3)_3CCH_2OH$	70°	$(CH_3)_3CCH_2I$ (74)	115
			" (55) + $C_2H_5(CH_3)_2CI$ (6)	127
	$CH_3CHOHCO_2C_2H_5$	25°, 12 hr	$CH_3CHICO_2C_2H_5$ (92)	115
	$HC{\equiv}CCHOHCH{=}CH_2$	40°, 15 min	$ICH_2CH{=}CHC{\equiv}CH$ (46)	116
	$HC{\equiv}CCHOHC{\equiv}CH$	100°, DMF, 30 min	$ICH{=}C{=}CHC{\equiv}CH$ (42)	116
	$HOCH_2C(CH_3)_2CH_2OH$	—	$ICH_2C(CH_3)_2CH_2I$ (—)	114a
C_6	Cyclohexanol	25°, 18 hr	Iodocyclohexane (75)	115
	$HC{\equiv}CCHOH(CH_2)_2CH_3$	80°, DMF, 2 hr	$ICH{=}C{=}CH(CH_2)_2CH_3$ (60)	116
	$HC{\equiv}CCHOHCH(CH_3)_2$	15°, DMF, 7 days	$ICH{=}CHCH{=}C(CH_3)_2$ (18) + $ICH{=}C{=}CHCH(CH_3)_2$ (25)	116
		25°, C_6H_6, 24 hr	 (100)	105

TABLE V. PREPARATION OF ALKYL IODIDES USING TRIPHENYL PHOSPHITE–METHIODIDE (*Continued*)

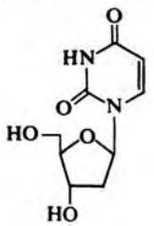
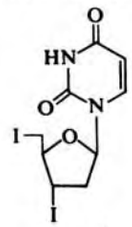
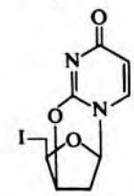
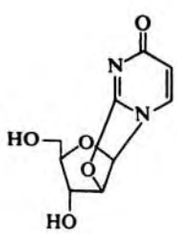
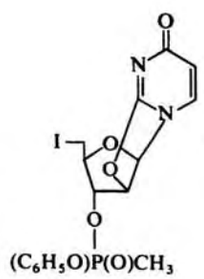
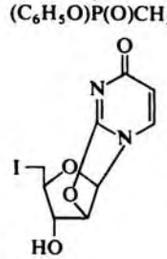
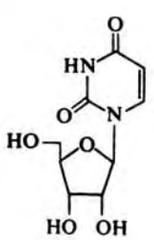
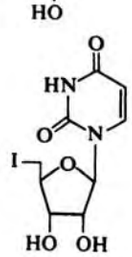
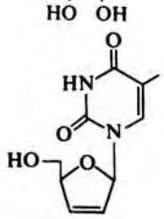
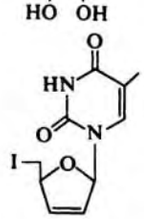
	Alcohol	Conditions	Products and Yields (%)	Ref.
C_7	$C_6H_5CH_2OH$	25°, 1 hr	$C_6H_5CH_2I$ (95)	115
	$HC{\equiv}CCHOH(CH_2)_3CH_3$	Not specified	$ICH{=}C{=}CH(CH_2)_3CH_3$ (20)	116
	$HC{\equiv}CCHOHC(CH_3)_3$	80°, DMF, 2 hr	$ICH{=}C{=}CHC(CH_3)_3$ (67)	116
C_8	$C_6H_{13}CHOHCH_3$	80°, 20 hr	$C_6H_{13}CHICH_3$ (80)	115
	$C_6H_5CH_2OHCH_3$	25°, 1 hr	$C_6H_5CHICH_3$ (95)	115
	$C_6H_5CH_2CH_2OH$	"	$C_6H_5CH_2CH_2I$ (92)	115
	$HC{\equiv}CCHOH(CH_2)_4CH_3$	—	$ICH{=}C{=}CH(CH_2)_4CH_3$ (43)	116
C_9	$HC{\equiv}CCHOHC{\equiv}CC(CH_3)_3$	Distil.	$ICH{=}C{=}CHC{\equiv}CC(CH_3)_3$ (41)	116
	$HC{\equiv}CCHOHC_6H_5$	25°, DMF	$ICH{=}C{=}CHC_6H_5$ (21)	116
		25°, DMF, 12 hr	 (84)	122, 121
		25°, Py, 1 hr	 (43)	120
		25°, DMF, 15 min + $(i\text{-}C_3H_7)_2NC_2H_5$	 (42)	120
		25°, DMF, 10 min	 (31)	120
		25°, DMF, 1 hr	 (65)	120
C_{10}		25°, DMF, 3 min	 (82)	125

TABLE V. PREPARATION OF ALKYL IODIDES USING TRIPHENYL PHOSPHITE–METHIODIDE (*Continued*)

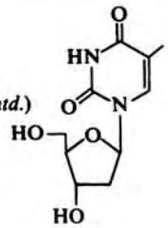
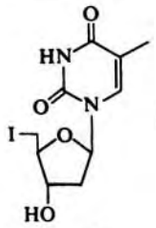
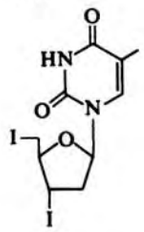
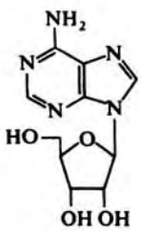
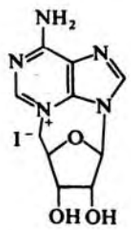
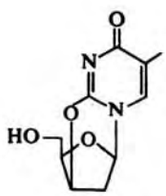
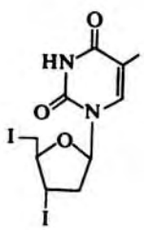
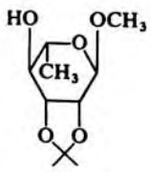
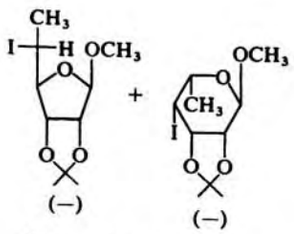
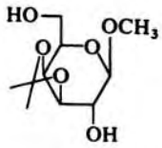
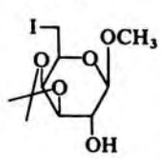
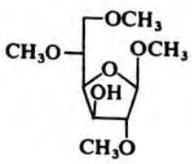
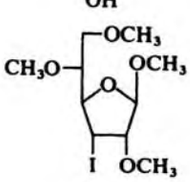
Alcohol	Conditions	Products and Yields (%)	Ref.
C_{10} (*Contd.*) 	25°, DMF, 10 min	 (63)	122, 120
	25°, DMF, 12 hr	 (76)	121
	25°, DMF, 5 min	 (50)	120
	25°, DMF	 (58)	122
	–	 (–) (–)	129, 119
	25°, C_6H_6, 2 days	 (60)	105
	55°, C_6H_6, 12 hr	 (31)	105

TABLE V. PREPARATION OF ALKYL IODIDES USING TRIPHENYL PHOSPHITE–METHIODIDE (*Continued*)

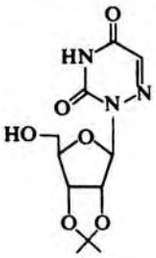
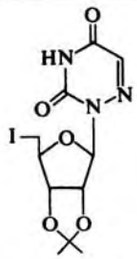
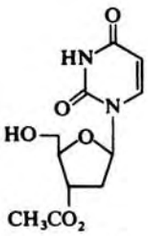
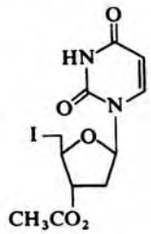
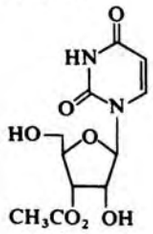
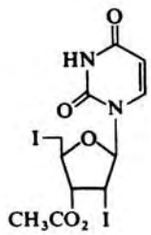
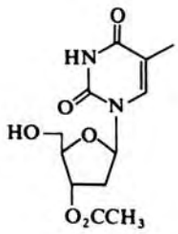
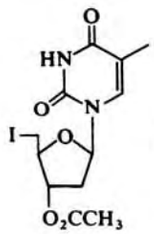
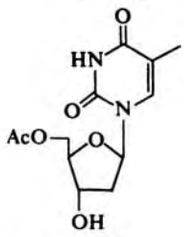
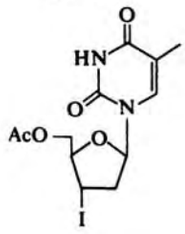
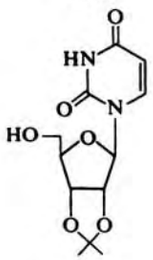
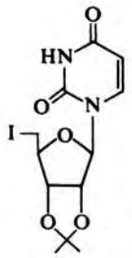
Alcohol	Conditions	Products and Yields (%)	Ref.
C_{11} 	25°, DMF, 30 min	 (48)	120
	25°, DMF, 18 hr	 (50)	122
	25°, DMF, 20 hr	 (46)	121
C_{12} 	25°, DMF, 1 hr	 (88)	120
	25°, DMF, 24 hr	 (50)	121
	25°, DMF, 15 min	 (96)	122, 120

TABLE V. PREPARATION OF ALKYL IODIDES USING TRIPHENYL PHOSPHITE–METHIODIDE (*Continued*)

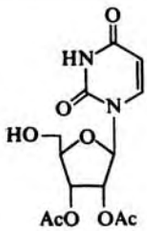
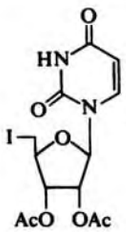
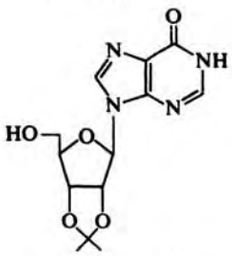
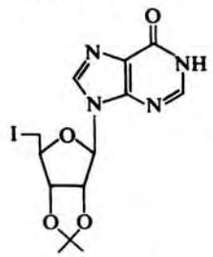
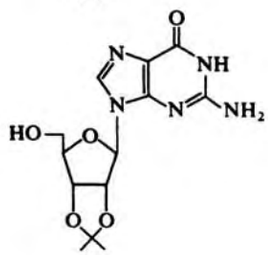
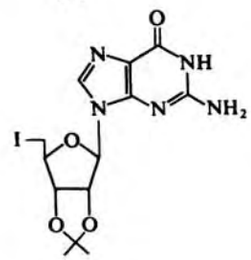
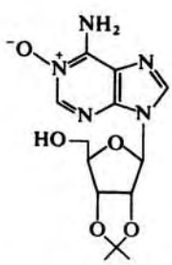
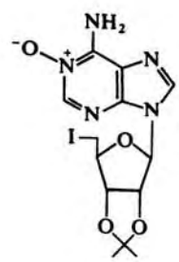
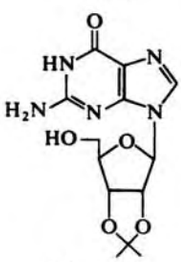
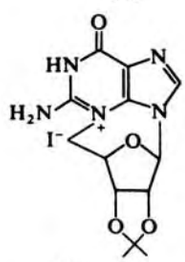
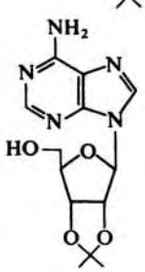
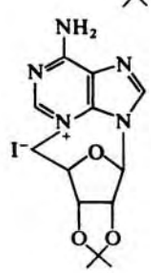
Alcohol	Conditions	Products and Yields (%)	Ref.
C_{13} 	25°, DMF, 2 hr	 (84)	123, 120
	−78°, THF, 3 hr	 (87)	126
	−78°, THF, 4 hr	 (58)	—
	25°, DMF, 24 hr	 (74)	220
	25°, DMF, 5 min	 (87)	122, 120
	25°, DMF, 12 hr	 (96)	122, 120

TABLE V. PREPARATION OF ALKYL IODIDES USING TRIPHENYL PHOSPHITE–METHIODIDE (*Continued*)

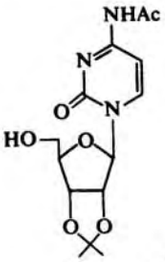
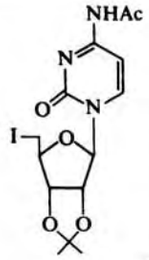
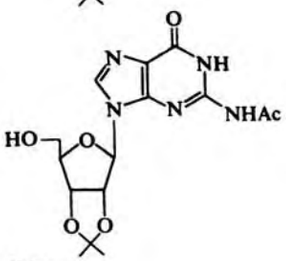
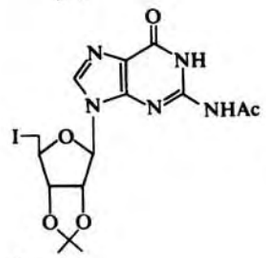
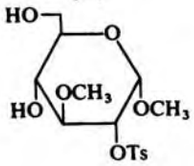
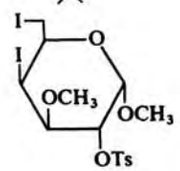
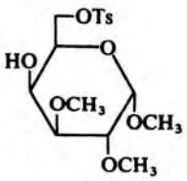
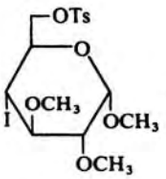
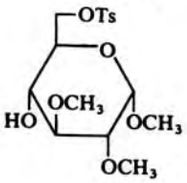
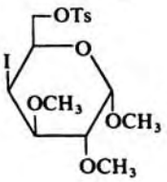
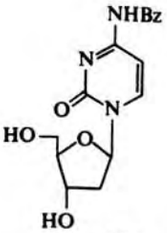
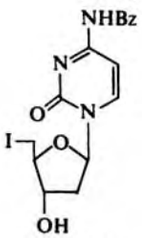
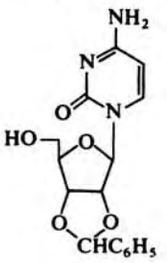
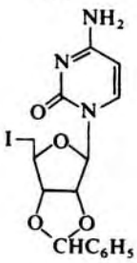
Alcohol	Conditions	Products and Yields (%)	Ref.
C_{14} 	25°, DMF, 3 hr	 (91)	125
C_{15} 	−78°, THF, 1.5 hr	 (84)	126
	50°, C_6H_6, 30 hr	 (85)	118
C_{16} 	50°, C_6H_6, 10 hr	 (58)	118
	55°, C_6H_6, 7 hr	 (80)	105
	25°, DMF, 10 min	 (15)	125
	25°, DMF, 12 hr	 (89)	120

TABLE V. PREPARATION OF ALKYL IODIDES USING TRIPHENYL PHOSPHITE–METHIODIDE (*Continued*)

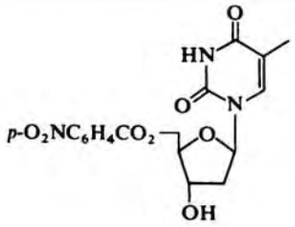
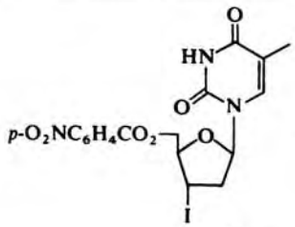
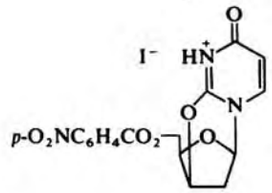
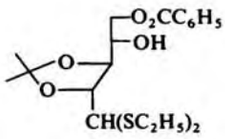
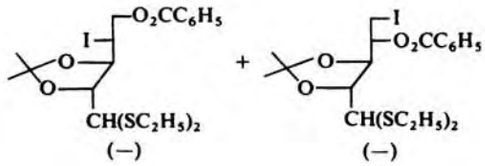
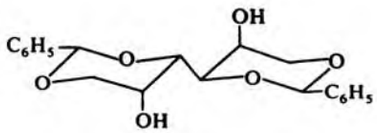
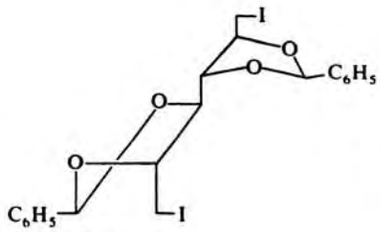
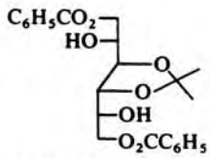
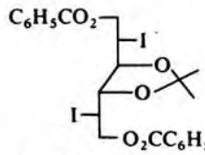
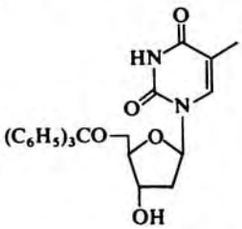
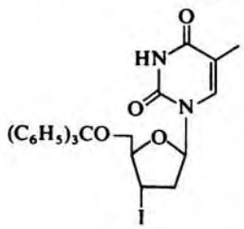
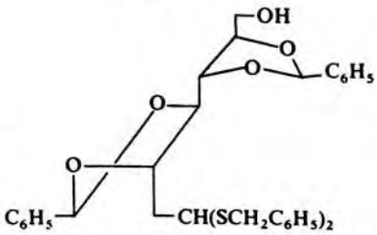
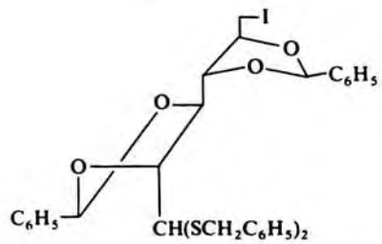
Alcohol	Conditions	Products and Yields (%)	Ref.
C_{17} 	25°, DMF, 24 hr	 (85)	122, 121
	25°, DMF, 15 min	 (53)	121
C_{19} 	50°, C_6H_6, 24 hr	 (–) + (–)	105
C_{20} 	25°, C_6H_6, 80 hr	 (60)	105
C_{23} 	50°, C_6H_6, 48 hr	 (90)	105
C_{27} Cholesterol	50°, Neat, 1 hr	Cholesteryl iodide (30)	115
Cholestanol	25°, DMF, 2 hr	3-α-Iodocholestane (57)	120
C_{29} 	25°, DMF, 24 hr	 (67)	121
C_{35} 	50°, C_6H_6, 30 hr	 (98)	105

TABLE VI. PREPARATION OF ALKYL HALIDES USING TRIPHENYL PHOSPHITE–HALOGEN

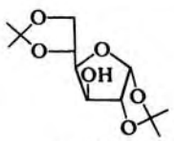
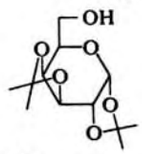
	Alcohol	Halogen	Conditions	Product and Yield (%)	Ref.
C_3	$CH_2{=}CHCH_2OH$	Br_2	10°	$CH_2{=}CHCH_2Br$ (75)	134
	$HO(CH_2)_3OH$	Cl_2	0°	$Cl(CH_2)_3Cl$ (63)	134
		Br_2	0°	$Br(CH_2)_3Br$ (92)	134
C_4	n-C_4H_9OH	I_2	25°	n-C_4H_9I (87)	134
	t-C_4H_9OH	"	25°, 30 min	t-C_4H_9I (83)	134
	n-C_4H_9OH	Br_2	0°	n-C_4H_9Br (76)	134
		Cl_2	80°	n-C_4H_9Cl (76)	134
C_5	$CH_3CHOHCO_2C_2H_5$	"	0°	$CH_3CHClCO_2C_2H_5$ (79)	134
		Br_2	0°	$CH_3CHBrCO_2C_2H_5$ (82)	134
C_6	Cyclohexanol	Cl_2	25°, 12 hr	Chlorocyclohexane (34)	134
C_8	$C_6H_5CH_2CH_2OH$	"	0°	$C_6H_5CH_2CH_2Cl$ (78)	134
		Br_2	0°	$C_6H_5CH_2CH_2Br$ (82)	134
C_{12}		"	1. 25° (C_6H_6), 48 hr 2. H_2SO_4	6-Bromo-6-desoxy-D-glucose (16)	105
		"	1. 25° (C_6H_6), 48 hr 2. H_2SO_4	6-Bromo-6-desoxy-D-galactose (20)	105
C_{27}	Cholesterol	"	60°, 15 min	Cholesteryl bromide (—)	134

TABLE VII. PREPARATION OF ALKYL HALIDES USING TRIPHENYLPHOSPHINE–HALOGEN

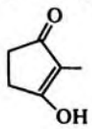
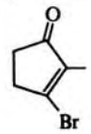
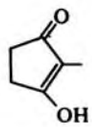
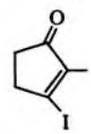
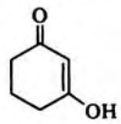
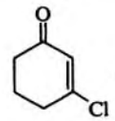
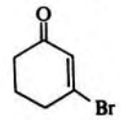
	Alcohol	Reagent	Conditions	Product and Yield (%)	Ref.
C_2	C_2H_5OH	$(C_6H_5)_3PBr_2$	80°, CCl_4, 20 min	C_2H_5Br (30)	140
C_4	n-C_4H_9OH	"	55°, DMF	n-C_4H_9Br (91)	139
C_5	$(CH_3)_2CHCHOHCH_3$	"	40°, C_6H_6, 1 hr	$(CH_3)_2CHCHBrCH_3$ (26)	144
	$(CH_3)_3CCH_2OH$	"	84°, DMF	$(CH_3)_3CCH_2Br$ (91)	139
		$(C_6H_5)_3PCl_2$	Reflux, DMF	$(CH_3)_3CCH_2Cl$ (92)	139
	$CH_3CHOH(CH_2)_3OH$	$(C_6H_5)_3PBr_2$	−5°, DMF, 36 hr	$CH_3CH(O_2CH)(CH_2)_3Br$ (50)	148
C_6	n-$C_6H_{13}OH$	"	80°, CCl_4, 20 min	n-$C_6H_{13}Br$ (55)	140
	p-Chlorophenol	"	200°, neat	p-Chlorobromobenzene (90)	139
		"	25°, C_6H_6, 4 hr	 (93)	147
		$(C_6H_5)_3PI_2$	25°, C_6H_6, 24 hr	 (71)	147
		$(C_6H_5)_3PCl_2$	25°, C_6H_6, 1 hr	 (91)	147
		$(C_6H_5)_3PBr_2$	25°, C_6H_6, 4 hr	 (97)	147

TABLE VII. PREPARATION OF ALKYL HALIDES USING TRIPHENYLPHOSPHINE–HALOGEN (*Continued*)

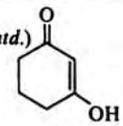
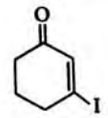
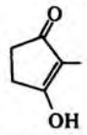
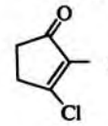
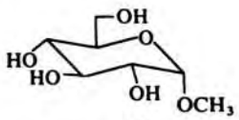
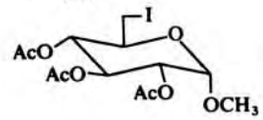
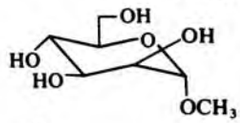
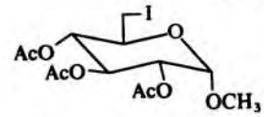
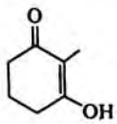
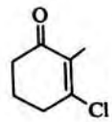
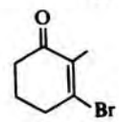
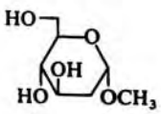
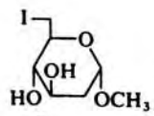
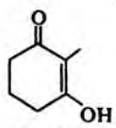
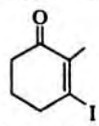
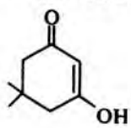
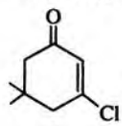
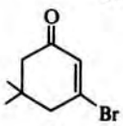
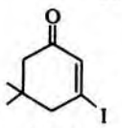
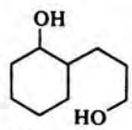
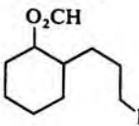
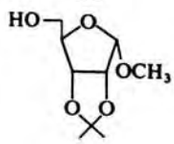
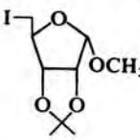
Alcohol	Reagent	Conditions	Product and Yield (%)	Ref.
C_6 (*Contd.*) 	$(C_6H_5)_3PI_2$	25°, CH_3CN, 4 days	 (72)	147
	$(C_6H_5)_3PCl_2$	25°, C_6H_6, 4 hr	 (92)	147
C_7 $C_6H_5CH_2OH$	$(C_6H_5)_3PBr_2$	80°, CCl_4, 20 min	$C_6H_5CH_2Br$ (76)	140
	$(C_6H_5)_3PBrCN$	80°, C_6H_6, 20 min	" (70)	140
	1. $(C_6H_5)_3P/I_2$/imidazole 2. Ac_2O	Toluene	 (80)	103
	1. $(C_6H_5)_3P/I_2$/imidazole 2. Ac_2O	Toluene	 (70)	103
	$(C_6H_5)_3PCl_2$	25°, C_6H_6, 4 hr	 (97)	147
	$(C_6H_5)_3PBr_2$	"	 (96)	147
	I_2/imidazole	75°, Toluene, 5 hr	 (76)	220a
	$(C_6H_5)_3PI_2$	25°, C_6H_6, 4 days	 (73)	147
C_8 $CH_3(CH_2)_5CHOHCH_2OH$	"	−5°, DMF, 24 hr	$CH_3(CH_2)_5CH(O_2CH)CH_2Br$ (90)	148
	$(C_6H_5)_3PCl_2$	25°, C_6H_6, 1 hr	 (94)	147
	$(C_6H_5)_3PBr_2$	25°, C_6H_6, 3 hr	 (93)	147
	$(C_6H_5)_3PI_2$	25°, CH_3CN, 4 days	 (83)	147
C_9 	$(C_6H_5)_3PBr_2$	−5°, DMF, 96 hr	 (78)	148
	$(C_6H_5)_3P/I_2$/imidazole	Toluene	 (92)	103

TABLE VII. PREPARATION OF ALKYL HALIDES USING TRIPHENYLPHOSPHINE–HALOGEN (*Continued*)

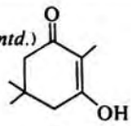
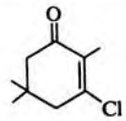
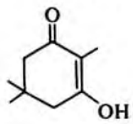
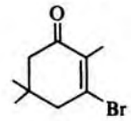
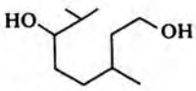
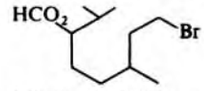
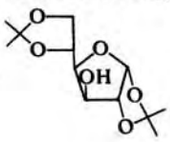
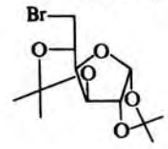
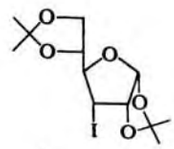
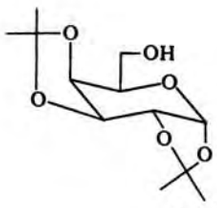
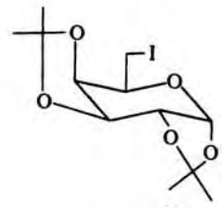
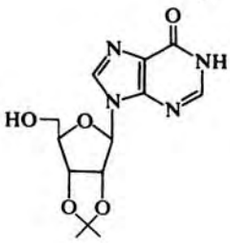
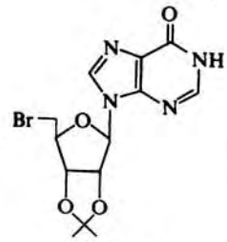
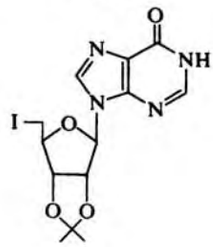
	Alcohol	Reagent	Conditions	Product and Yield (%)	Ref.
C_9 (*Contd.*)		$(C_6H_5)_3PCl_2$	25°, C_6H_6, 7 hr	 (90)	147
		$(C_6H_5)_3PBr_2$	25°, C_6H_6, 4 hr	 (91)	147
C_{10}	n-$C_{10}H_{21}OH$	"	80°, CCl_4, 20 min	n-$C_{10}H_{21}Br$ (73)	140
	l-Menthol	$(C_6H_5)_3PCl_2$	—	*neo*-Menthyl chloride (93)	140
		$(C_6H_5)_3PBr_2$	—	*neo*-Menthyl bromide (45)	140
		"	−5°, DMF, 36 hr	 (66)	148
	β-Naphthol	"	CH_3CN	2-Bromonaphthalene (85)	146
C_{11}	$CH_3CHOH(CH_2)_8CH_2OH$	"	−20°, DMF, 120 hr	$CH_3CH(O_2CH)(CH_2)_8CH_2Br$ (64)	148
C_{12}		"	25°, C_6H_6, 48 hr	 (−)	105
		$(C_6H_5)_3P/I_2$/imidazole	Toluene	 (60)	103
		$(C_6H_5)_3P/I_2$/imidazole	Toluene	 (94)	103
C_{13}		$(C_6H_5)_3PBr_2$	80°, $OP(OC_2H_5)_3$, 15 min	 (50)	145
		$(C_6H_5)_3PBrCN$	25°, $OP(OC_2H_5)_3$, 5 min	" (60)	145
		$(C_6H_5)_3PI_2$	25°, $OP(OC_2H_5)_3$, 30 min	 (60)	145

TABLE VII. PREPARATION OF ALKYL HALIDES USING TRIPHENYLPHOSPHINE–HALOGEN (*Continued*)

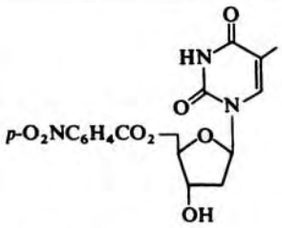
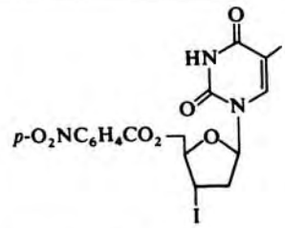
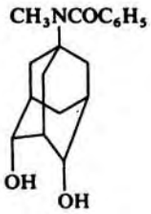
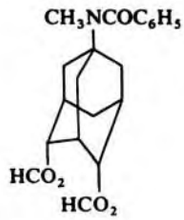
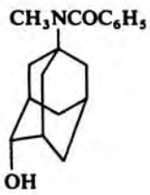
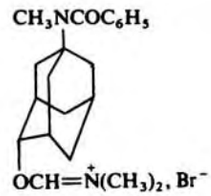
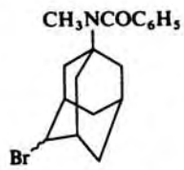
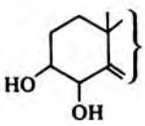
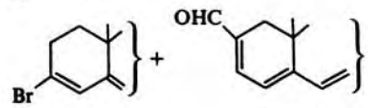
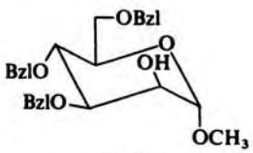
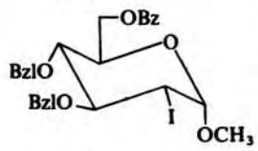
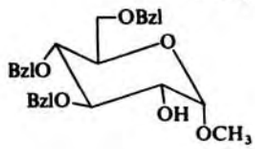
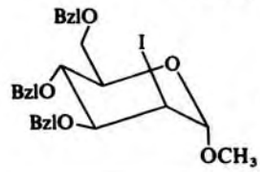
Alcohol	Reagent	Conditions	Product and Yield (%)	Ref.
C_{17} 	$(C_6H_5)_3PI_2$	23°, DMF, 14 days	 (47)	124
C_{18} Lincomycin	$(C_6H_5)_3PBr_2$	25°, CH_3CN, 3 hr	Clindamycin (73)	154
	"	1. 0°, DMF, 1 hr 2. H_2O	 (33)	143
	"	0°, DMF, 15 min	 (80)	143
	"	1. 0°, DMF, 15 min 2. 200°, neat, 15 min	 (–)	143
C_{27} 	$(C_6H_5)_3PBr_2$	80°, DMF, 16 hr	 (–) (–)	149
C_{28} 	$(C_6H_5)_3PI_2$/imidazole	Toluene	 (67)	103
	$(C_6H_5)_3PI_2$/imidazole	Toluene	 (75)	103

TABLE VIII. PREPARATION OF ALKYL HALIDES USING TRIPHENYLPHOSPHINE–CARBON TETRAHALIDES

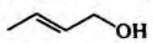
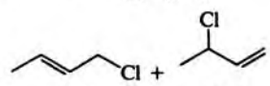
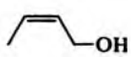
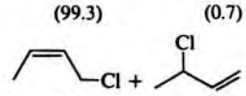
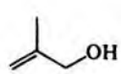
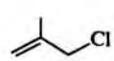
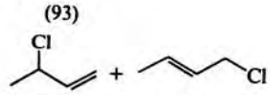
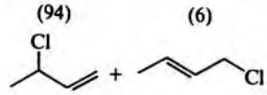
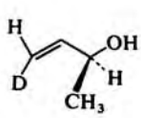
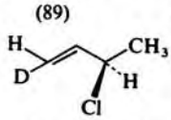
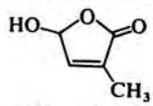
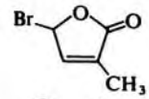
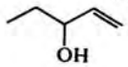
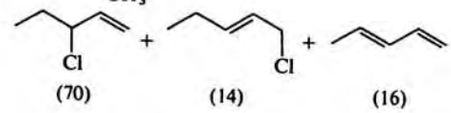
	Alcohol	CX_4	Conditions	Products and Yields (%)	Ref.
C_1	CH_3OH	CCl_4	—	CH_3Cl (78)	23
C_2	C_2H_5OH	"	—	C_2H_5Cl (68)	23
	$HOCH_2CH_2OH$	"	80°, CCl_4, 12 hr	$ClCH_2CH_2OH$ + $ClCH_2CH_2Cl$ (20) (54)	
		"	—	$ClCH_2CH_2Cl$ + $ClCH_2CH_2OH$ (60) (30)	221
					23
C_3	n-C_3H_7OH	"	—	n-C_3H_7Cl (94)	23
	$CH_3OCH_2CH_2OH$	"	80°, CCl_4, 15 min	$CH_3OCH_2CH_2Cl$ (82)	221
C_4	n-C_4H_9OH	"	—	n-C_4H_9Cl (89)	23
	i-C_4H_9OH	"	—	i-C_4H_9Cl (—)	23
	$CH_3CHOHC_2H_5$	"	65°, CCl_4, 0.3 hr	$CH_3CHClC_2H_5$ (65)	176
		"	CCl_4, 5 min	" (60)	222
		$CCl_4/P(C_8H_{17})_3$	—	" (65)	23
	$HOCH_2CO_2C_2H_5$	"	80°, CCl_4, 15 min	$ClCH_2CO_2C_2H_5$ (—)	223
	$HO(CH_2)_3OH$	"	80°, CCl_4	$Cl(CH_2)_3Cl$ (—)	221
	$C_2H_5CHOHCH_2OH$	"	"	$C_2H_5CHClCH_2Cl$ (—)	221
	$CH_3CHOHCHOHCH_3$	"	"	$CH_3CHClCHClCH_3$ (—)	221
		CCl_4	25°, CCl_4, 48 hr	(100)	224
		$(CCl_3)_2CO$	0–15°, $(CCl_3)_2CO$, 30 min	 (99.3) (0.7)	30
		"	"	 (98) (0.5)	30
		"	"	 (93)	30
		"	"	 (94) (6)	30
		"	25°, CCl_4, 48 hr	 (89) (11)	224
		"	"	 (—) (inversion ≥99%)	30
	$(CH_3)_3COH$	CCl_4	—	$(CH_3)_3CCl$ (76)	23
		"	80°, CCl_4	" (—)	221
C_5	n-$C_5H_{11}OH$	$CBr_4/P(C_8H_{17})_3$	Et_2O, 5 min	n-$C_5H_{11}Br$ (80)	222
		CCl_4	—	n-$C_5H_{11}Cl$ (99)	23
	$(CH_3)_2CHCHOHCH_3$	CBr_4	25°, THF, 1 hr	$(CH_3)_2CHCHBrCH_3$ + $(CH_3)_2CBrCH_2CH_3$ (39) (10)	144
	$HO(CH_2)_2CO_2C_2H_5$	CCl_4	80°, CCl_4, 15 min	$Cl(CH_2)_2CO_2C_2H_5$ (—)	223
	$CH_3CHOHCO_2C_2H_5$	"	80°, CCl_4, 15 min	$CH_3CHClCO_2C_2H_5$ (—)	223
		CBr_4	0°, CH_2Cl_2, 6 hr	 (68)	225
		CCl_4	25°, CCl_4, 24 hr	 (70) (14) (16)	29

TABLE VIII. PREPARATION OF ALKYL HALIDES USING TRIPHENYLPHOSPHINE–CARBON TETRAHALIDES (*Continued*)

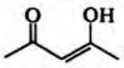
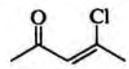
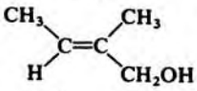
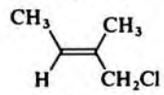
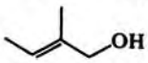
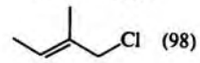
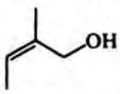
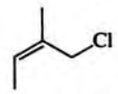
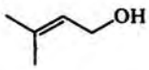
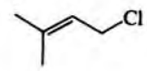
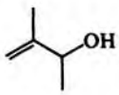
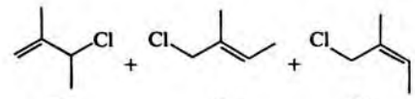
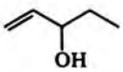
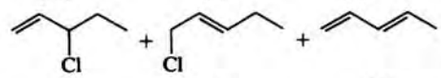
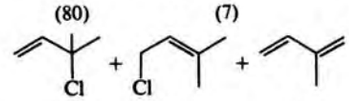
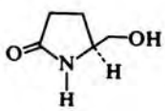
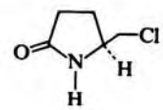
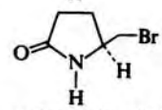
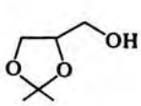
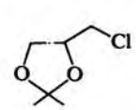
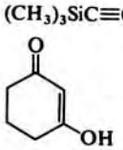
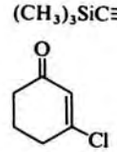
	Alcohol	CX_4	Conditions	Products and Yields (%)	Ref.
C_5 (*Contd.*)		CCl_4	50°, CCl_4, 4 hr	 (81)	22
		"	—	 (Quant.)	226
		$(CCl_3)_2CO$	0–15°, $(CCl_3)_2CO$, 30 min	 (98)	30
		"	"	 (100)	30
		"	"	 (91)	30
		"	"	 (92) (2) (1)	30
		"	"	 (80) (7) (12)	30
		"	"	 (21) (43) (17)	30
		CCl_4	55°, $CCl_4/CHCl_3$, 6 hr	 (86)	206
		CBr_4	20°, CH_3CN, 12 hr	 (74)	206
C_6	n-$C_6H_{13}OH$	CCl_4	—	n-$C_6H_{13}Cl$ (83)	23
	Cyclohexanol	CCl_4, polymer-supported phosphine	—	Chlorocyclohexane (40)	160
		"	80°, CCl_4, 2 hr	" (60)	159
		CCl_4	Reflux, $CHCl_3$, 4 hr	" (82)	227
	$C_2H_5CHOHCO_2C_2H_5$	"	80°, CCl_4, 15 min	$C_2H_5CHClCO_2C_2H_5$ (—)	223
	$HO(CH_3)_3CO_2C_2H_5$	"	"	$Cl(CH_2)_3CO_2C_2H_5$ (—)	223
	n-$C_4H_9OCH_2CH_2OH$	CCl_4, polymer-supported phosphine	—	n-$C_4H_9OCH_2CH_2Cl$ (94)	160
		CCl_4	80°, CCl_4, 15 min	 (76)	221
		CCl_4, polymer-supported phosphine	—	" (78)	160
	$(CH_3)_3SiC{\equiv}CCH_2OH$	CCl_4	—	$(CH_3)_3SiC{\equiv}CCH_2Cl$	228
		"	50°, CCl_4, 4 hr	 (85)	22

TABLE VIII. PREPARATION OF ALKYL HALIDES USING TRIPHENYLPHOSPHINE–CARBON TETRAHALIDES (*Continued*)

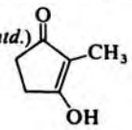
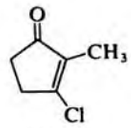
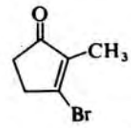
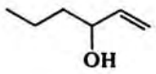
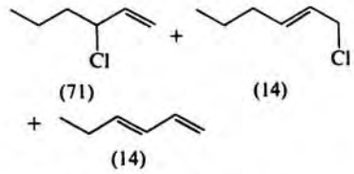
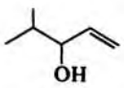
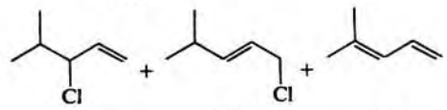
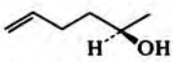
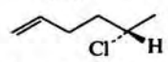
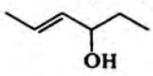
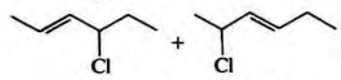
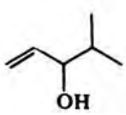
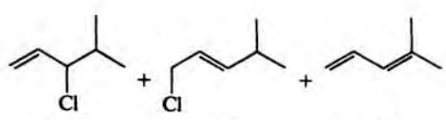
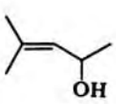
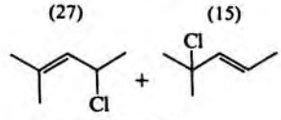
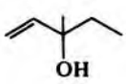
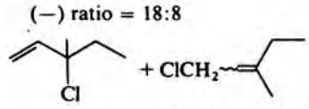
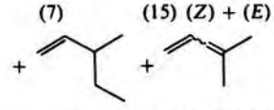
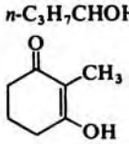
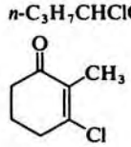
Alcohol	CX_4	Conditions	Products and Yields (%)	Ref.
C_6 (*Contd.*) 	CCl_4	50°, CCl_4, 3 hr	 (73)	22
	CBr_4	50°, $CHCl_3$, 3 hr	 (75)	22
	CCl_4	25°, CCl_4, 24 hr	 (71) (14) (14)	29
	"	"	 (23) (18) (58)	29
	"	80°, CCl_4, 2.5 hr	 (40) (Racemization ≥24%)	229
	$(CCl_3)_2CO$	0–15°, $(CCl_3)_2CO$, 30 min	 (53) (26)	30
	"	"	 (27) (15) (61)	30
	"	"	 (−) ratio = 18:8	30
	"	"	 (7) (15) (*Z*) + (*E*) (50/50)	30
			 (9) (37); (*Z*) + (*E*)	30
C_7 n-$C_7H_{15}OH$	CCl_4	"	n-$C_7H_{15}Cl$ (−)	23
$C_6H_5CH_2OH$	"/$P(C_8H_{17})_3$	(CCl_4), 5 min	$C_6H_5CH_2Cl$ (100)	222
	CCl_4	—	" (83)	23
	CCl_4, polymer-supported phosphine	—	" (88)	160
	"	80°, CCl_4, 2 hr	" (99)	159
Cycloheptanol	CCl_4, polymer-supported phosphine	"	Chlorocycloheptane (92)	159
n-$C_3H_7CHOHCO_2C_2H_5$	CCl_4	80°, CCl_4, 15 min	n-$C_3H_7CHClCO_2C_2H_5$ (−)	223
	"	50°, CCl_4, 4 hr	 (81)	22

TABLE VIII. PREPARATION OF ALKYL HALIDES USING TRIPHENYLPHOSPHINE–CARBON TETRAHALIDES (*Continued*)

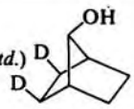
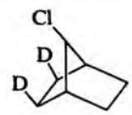
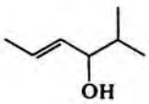
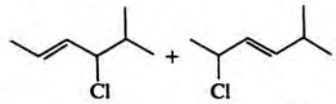
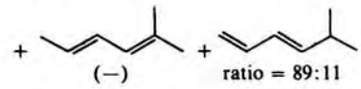
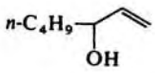
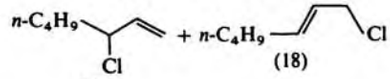
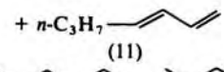
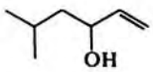
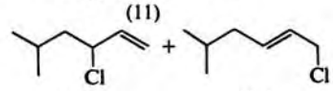
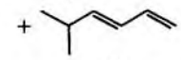
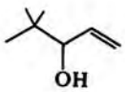
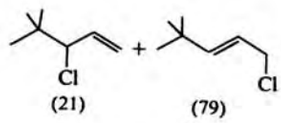
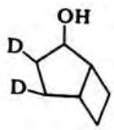
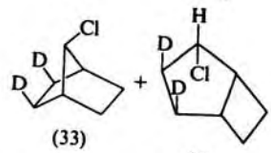
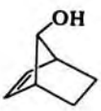
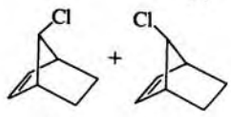
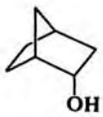
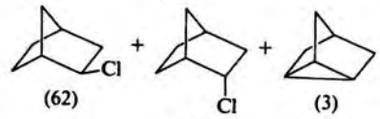
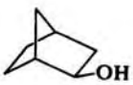
Alcohol	CX_4	Conditions	Products and Yields (%)	Ref.
C_7 (*Contd.*) 	CCl_4	1. 25°, CCl_4, 24 hr 2. 175°	 (53)	24
	$(CCl_3)_2CO$	0–15°, $(CCl_3)_2CO$, 30 min	 (–) ratio = 62:38	30
			 (–) ratio = 89:11	
	CCl_4	25°, CCl_4, 24 hr	 (70) (18)	29
			 (11)	
	"	"	 (50) (26)	29
			 (23)	
	"	"	 (21) (79)	29
	"	25°, CCl_4, 65 hr	 (33) (7)	24
	"	60°, CCl_4, 2.5 hr	 (42) (6)	230
	"	80°, CCl_4, 3.5 hr	 (62) (3) (3)	230
	"	80°, CCl_4, 1.75 hr	(8) (28) (27)	230
$(CH_3)_3SiC(CH_3)=CHCH_2OH$	"	—	$(CH_3)_3SiC(CH_3)=CHCH_2Cl$ (60)	228

TABLE VIII. PREPARATION OF ALKYL HALIDES USING TRIPHENYLPHOSPHINE–CARBON TETRAHALIDES (*Continued*)

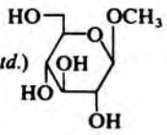
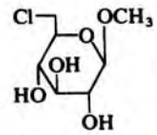
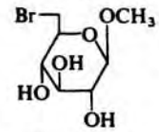
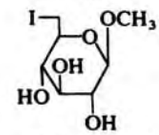
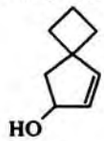
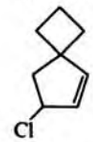
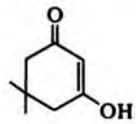
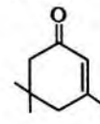
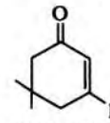
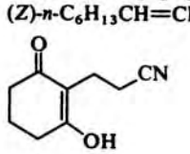
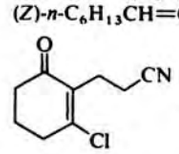
	Alcohol	CX_4	Conditions	Products and Yields (%)	Ref.
C_7 (*Contd.*)		CCl_4	65°, Py, 0.2 hr	 (98)	156
		CBr_4	"	 (93)	156
		CI_4	25°, Py, 18 hr	 (97)	156
C_8	n-$C_8H_{17}OH$	$CCl_4/P(C_8H_{17})_3$	CCl_4, 5 min	n-$C_8H_{17}Cl$ (88)	222
		CCl_4, polymer-supported phosphine	—	" (98)	160
		"	80°, CCl_4, 2 hr	" (90)	159
	$CH_3CHOHC_6H_{13}$-n	CBr_4	0°, CH_2Cl_2	n-$C_8H_{17}Br$ (91)	231
		"	"	$CH_3CHBrC_6H_{13}$-n (90)	231
	D-$CH_3CHOHC_6H_{13}$-n	CCl_4	80°, CCl_4, 6 hr	L-$CH_3CHClC_6H_{13}$-n (45)	133
		CBr_4	—	L-$CH_3CHBrC_6H_{13}$-n (38)	133
		CCl_4	60°, CCl_4, 4 hr	L-$CH_3CHClC_6H_{13}$-n (50) $(\alpha)_D^{20} = -34.2°$	230
		$CCl_4/P(C_8H_{17})_3$	CCl_4, 5 min	L-$CH_3CHClC_6H_{13}$-n (80) (optical purity 90%)	222
	n-$C_4H_9CH(C_2H_5)CH_2OH$	CCl_4	—	n-$C_4H_9CH(C_2H_5)CH_2Cl$ (82)	23
	(−)-$C_2H_5O_2CCH_2CHOHCO_2C_2H_5$	"	80°, CCl_4	D(+)-$C_2H_5O_2CH_2CHClCO_2C_2H_5$ (−)	223
	threo-$C_6H_5CHDCHDOH$	"	60°, CCl_4, 6 hr	*erythro*-$C_6H_5CHDCHDCl$ (75)	230
	$C_6H_5CH_2CH_2OH$	$CCl_4/P(C_8H_{17})_3$	CCl_4, 5 min	$C_6H_5CH_2CH_2Cl$ (66)	222
		CCl_4	80°, CCl_4, 1 hr	 (−)	232
		"	50°, CCl_4, 4 hr	 (82)	22
		CBr_4	50°, $CHCl_3$, 3 hr	 (85)	22
C_9	$C_6H_5(CH_2)_3OH$	CCl_4	—	$C_6H_5(CH_2)_3Cl$ (80)	23
	endo-Norborneol	"	80°, CCl_4, 6 hr	*exo*-Norbornyl chloride (57)	133
		CBr_4	—	*exo*-Norbornyl bromide (64)	133
	$HO(CH_2)_6CO_2C_2H_5$	CCl_4	80°, CCl_4, 15 min	$Cl(CH_2)_6CO_2C_2H_5$ (−)	223
	(*Z*)-n-$C_6H_{13}CH{=}CHCH_2OH$	CBr_4	0°, CH_2Cl_2	(*Z*)-n-$C_6H_{13}CH{=}CHCH_2Cl$ (89)	231
		CCl_4	50°, CCl_4, 4 hr	 (79)	22

TABLE VIII. PREPARATION OF ALKYL HALIDES USING TRIPHENYLPHOSPHINE–CARBON TETRAHALIDES (*Continued*)

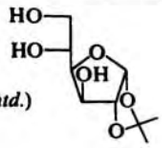
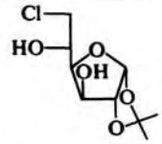
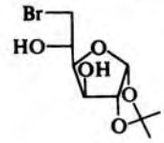
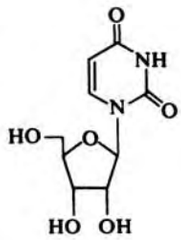
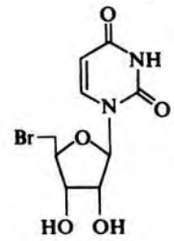
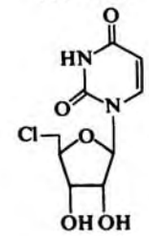
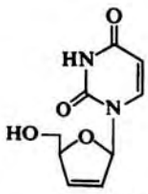
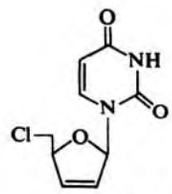
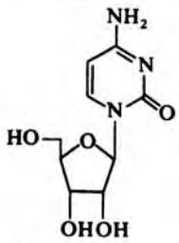
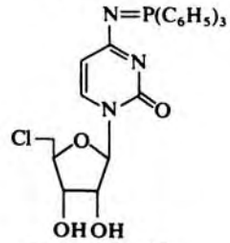
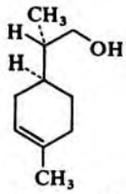
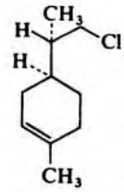
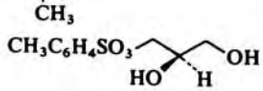
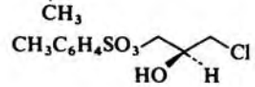
Alcohol	CX_4	Conditions	Products and Yields (%)	Ref.
C_9 (*Contd.*) 	CCl_4	5°, Py, 20 hr	 (96)	156
	CBr_4	60°, Py, 0.15 hr	 (95)	156
	"	23°, DMF, 24 hr	 (55)	124
	CCl_4	25°, Py, 18 hr	 (92)	156
	"	25°, DMF, 12 hr	 (57)	233
	"	23°, DMF, 4 hr	 (27)	124
C_{10} n-$C_{10}H_{21}OH$	CCl_4, polymer-supported phosphine	80°, CCl_4, 2 hr	n-$C_{10}H_{21}Cl$ (89)	159
$C_6H_5CHOHCO_2C_2H_5$	CCl_4	80°, CCl_4, 15 min	$C_6H_5CHClCO_2C_2H_5$ (—)	223
Geraniol	"	80°, CCl_4, 2 hr	Geranyl chloride (54)	234
	CBr_4	0°, CH_2Cl_2	Geranyl bromide (82)	231
	"	"	 (93)	235
	CCl_4	50°, DMF, 3 hr		236

TABLE VIII. PREPARATION OF ALKYL HALIDES USING TRIPHENYLPHOSPHINE–CARBON TETRAHALIDES (*Continued*)

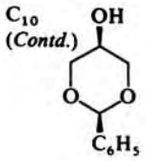
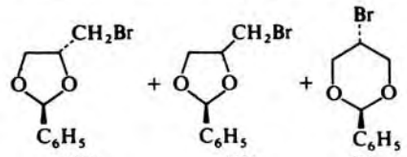
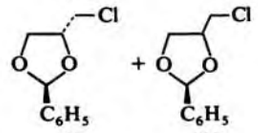
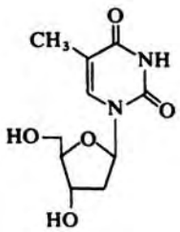
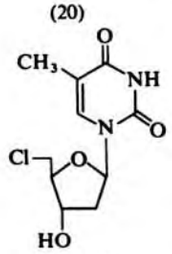
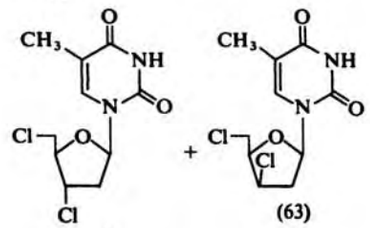
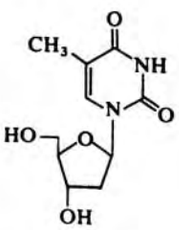
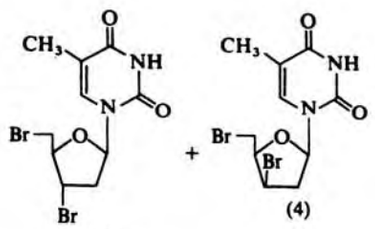
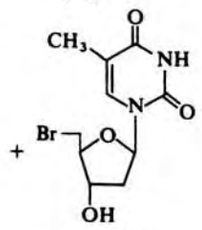
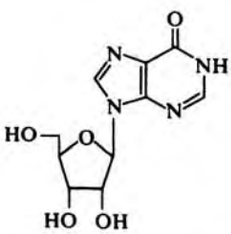
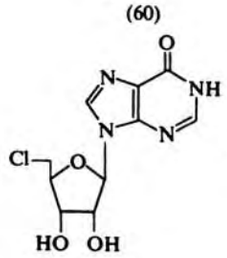
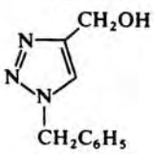
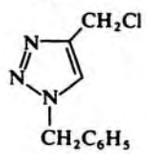
Alcohol	CX_4	Conditions	Products and Yields (%)	Ref.
C_{10} (*Contd.*) 	CBr_4	80°, C_6H_6, 1 hr	 (22) + (22) + (3)	237
	CCl_4	80°, CCl_4	 (20) + (20)	237
	CCl_4	23°, CCl_4, 24 hr	 (73)	124
	"	23°, DMF, 10 hr	 (5) + (63)	124
	CBr_4	23°, DMF, 7 hr	 (12) + (4)	124
			 (60)	
	CCl_4	65°, Py, 0.2 hr	 (94)	156
	"	20°, CH_3CN, 12 hr	 (47)	238

TABLE VIII. PREPARATION OF ALKYL HALIDES USING TRIPHENYLPHOSPHINE–CARBON TETRAHALIDES (*Continued*)

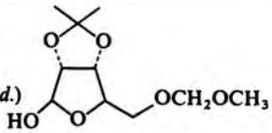
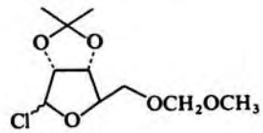
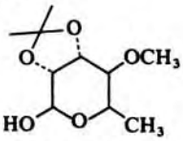
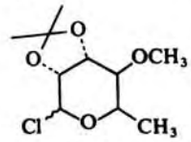
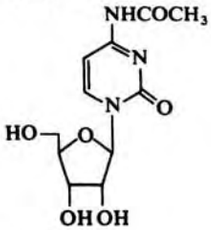
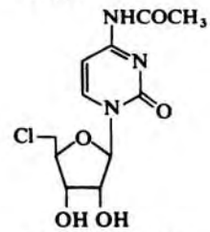
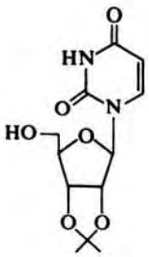
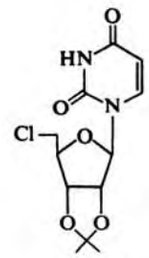
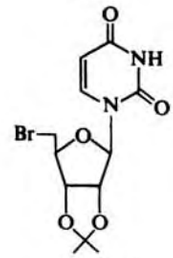
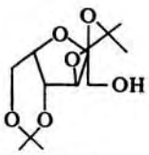
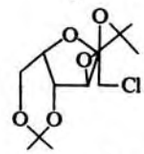
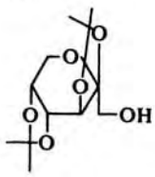
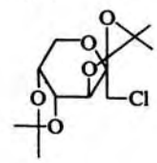
Alcohol	CX_4	Conditions	Products and Yields (%)	Ref.
C_{10} (*Contd.*) 	CCl_4	80°, CCl_4, 3 hr	 (93)	195
	"	"	 (89)	195
C_{11} n-$C_{11}H_{23}OH$	CCl_4, polymer-supported phosphine	80°, CCl_4, 2 hr	n-$C_{11}H_{23}Cl$ (99)	159
$C_6H_{13}CH{=}C{=}CH(CH_2)_2OH$	CBr_4	0°, CH_2Cl_2	$C_6H_{13}CH{=}C{=}CH(CH_2)_2Br$ (88)	231
	CCl_4	20°, DMF, 48 hr	 (58)	124
C_{12} n-$C_{12}H_{25}OH$	CCl_4, polymer-supported phosphine	80°, CCl_4, 2 hr	n-$C_{12}H_{25}Cl$ (71)	159
	CCl_4	23°, DMF, 18 hr	 (70)	124
	CBr_4	"	 (55)	124
	CCl_4	80°, CCl_4, 48 hr	 (56)	104
	"	"	 (57)	104

TABLE VIII. PREPARATION OF ALKYL HALIDES USING TRIPHENYLPHOSPHINE–CARBON TETRAHALIDES (*Continued*)

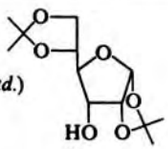
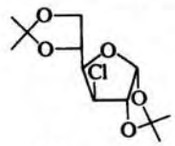
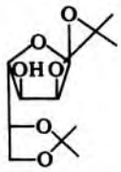
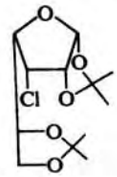
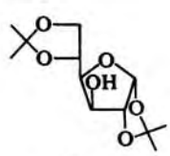
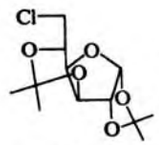
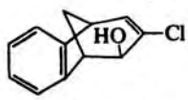
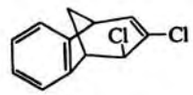
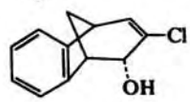
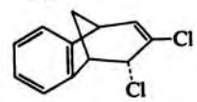
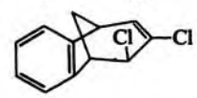
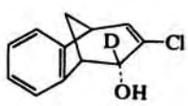
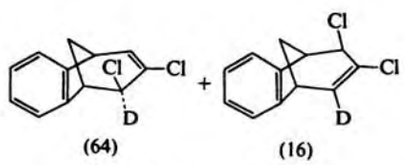
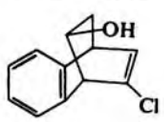
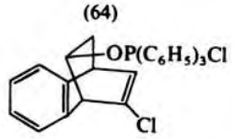
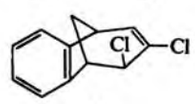
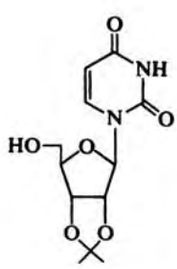
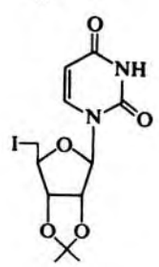
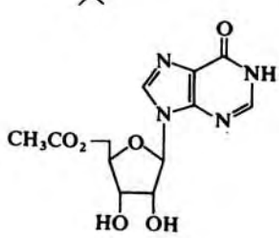
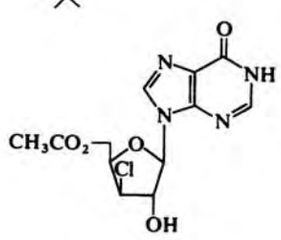
Alcohol	CX_4	Conditions	Products and Yields (%)	Ref.
C_{12} (*Contd.*) 	CCl_4	80°, CCl_4, 48 hr	 (85)	104
	"	"	 (57)	104
	"	"	 (79)	104
	CCl_4	25°, CCl_4, 24 hr	 (70)	27
	"	25°, CCl_4, 5 days	 (20)	27
	"	70°, CCl_4, 25 hr	 (68)	27
	"	"	 (64) + (16)	27
	"	25°, CH_3CN, 3 hr	 (Quant.)	27
	"	70°, CH_3CN, 1 hr	 (Quant.)	27
	CI_4	23°, Py, 16 hr	 (76)	124
	CCl_4	11°, $OP(OC_2H_5)_3$, 6 hr	 (19)	143

TABLE VIII. PREPARATION OF ALKYL HALIDES USING TRIPHENYLPHOSPHINE–CARBON TETRAHALIDES (*Continued*)

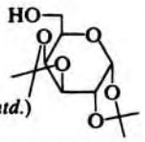
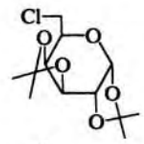
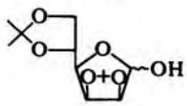
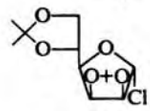
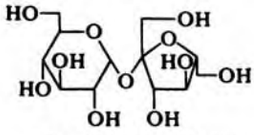
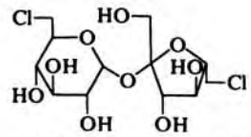
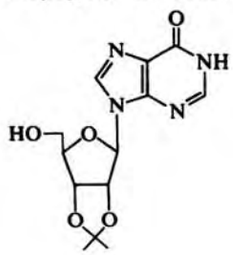
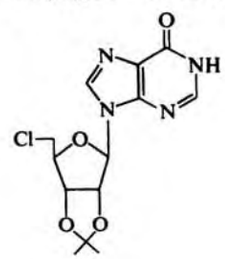
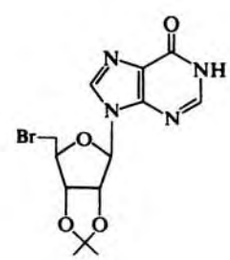
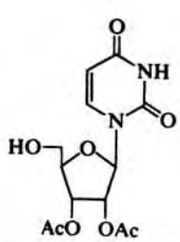
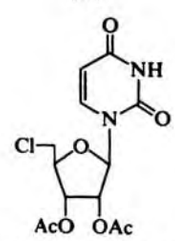
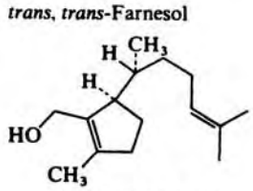
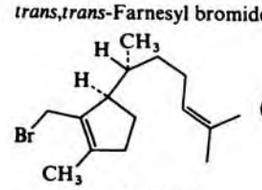
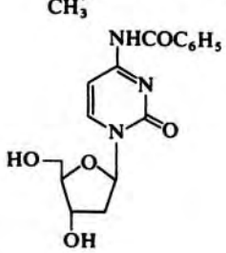
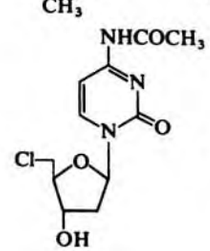
Alcohol	CX_4	Conditions	Products and Yields (%)	Ref.
C_{12} (*Contd.*) 	CCl_4	80°, CCl_4, 3 hr		221
	"	80°, CCl_4, 45 min	 (50)	31
	"	70°, Py, 2 hr	 (92)	156
C_{13} n-$C_8H_{17}CH{=}C{=}CHCH_2CH_2OH$	CBr_4	0°, CH_2Cl_2	n-$C_8H_{17}CH{=}C{=}CHCH_2CH_2Br$ (76)	231
	CCl_4	23°, DMF, 12 hr	 (80)	124
	"	100°, $OP(OC_2H_5)_3$, 5 min	" (86)	145
	CBr_4	23°, DMAc, 16 hr	 (49)	124
	CCl_4	20°, CCl_4, 18 hr	 (50)	124
C_{15} *trans, trans*-Farnesol	"	25°, CH_3CN, 3 hr	*trans,trans*-Farnesyl bromide (90)	155
	CBr_4	"	 (−)	235
C_{16} 	CCl_4	23°, DMF, 16 hr	 (10)	124

TABLE VIII. PREPARATION OF ALKYL HALIDES USING TRIPHENYLPHOSPHINE–CARBON TETRAHALIDES (*Continued*)

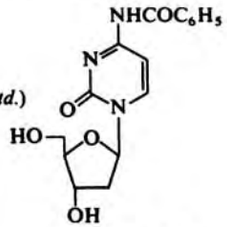
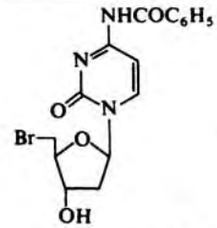
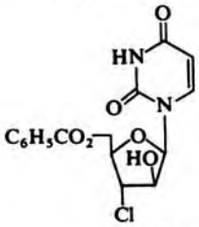
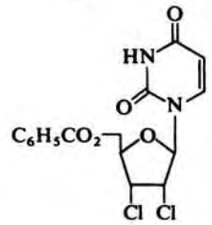
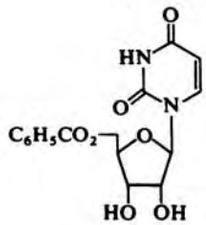
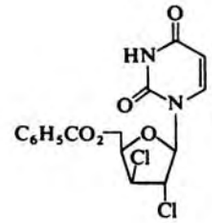
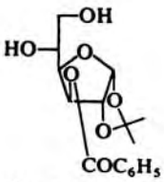
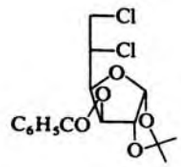
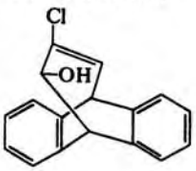
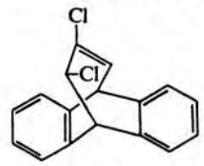
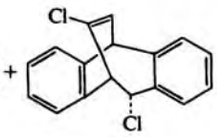
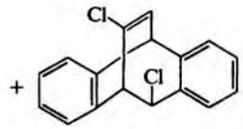
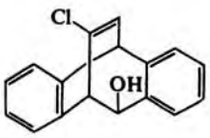
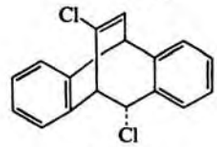
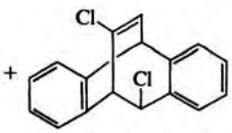
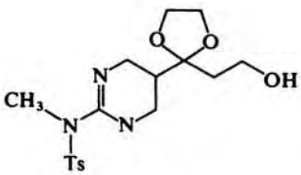
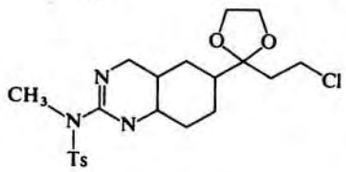
Alcohol	CX_4	Conditions	Products and Yields (%)	Ref.
C_{16} (*Contd.*) 	CBr_4	25°, DMAc, 4 hr	 (57)	125
	CCl_4	80°, $(C_2H_5O)_3PO$, 4 hr	 (64)	158
	"	80°, $(C_2H_5O)_3PO$, 5 hr	 (–)	158
	CCl_4	80°, CCl_4, 5 hr	 (72)	239
Hexadecyl alcohol	CCl_4, polymer-supported phosphine	—	Hexadecyl chloride (98)	160
C_{17} 	CCl_4	50°, CCl_4, 19 hr	 (75) +  (20)	27
			+  (5)	
	"	70°, CCl_4, 36 hr	 (70) +  (17)	27
	"	80°, CCl_4, 6 hr	 (47)	240

TABLE VIII. PREPARATION OF ALKYL HALIDES USING TRIPHENYLPHOSPHINE–CARBON TETRAHALIDES (*Continued*)

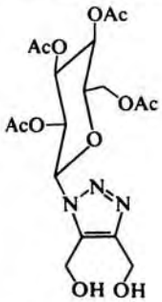
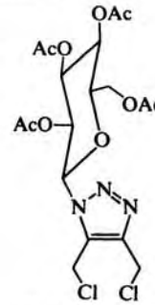
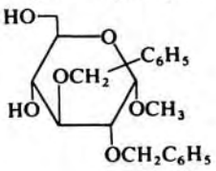
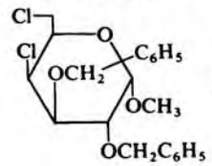
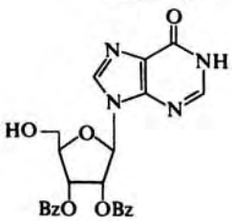
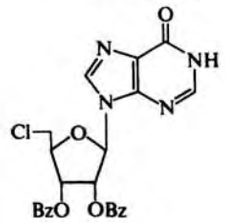
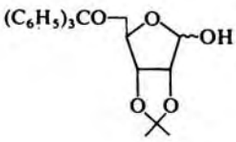
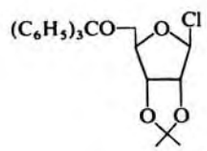
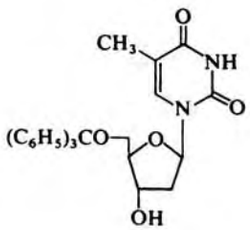
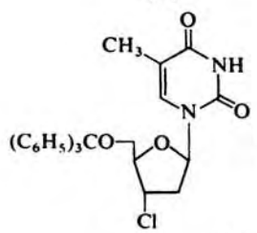
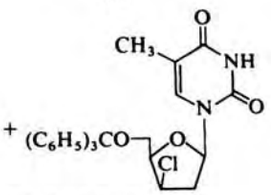
	Alcohol	CX_4	Conditions	Products and Yields (%)	Ref.
C_{18}		CCl_4	20°, CH_3CN, 12 hr	 (80)	238
	Lincomycin	"	25°, CH_3CN, 18 hr	Clindamycin (67)	154
C_{19}	Ethyl D-12-hydroxystearate	"	80°, CCl_4, 6 hr	Ethyl L-12-chlorostearate (92)	133
C_{21}		"	80°, CCl_4, 36 hr	 (84)	241
C_{24}		"	23°, DMF, 24 hr	 (86)	124
C_{27}	Cholesterol	"	80°, CCl_4, 8 hr	3-α-Chlorocholest-5-ene (8) + 3-β-chlorocholest-5-ene (28) + cholesta-3,5-diene (13) + 3,5-cyclocholest-6-ene (34)	26
	Isocholesterol	"	"	3-β-Chlorocholest-5-ene (30) + 3,5-cyclocholest-6-ene (48)	26
	5-β-Cholan-24-ol	CCl_4, polymer-supported phosphine	—	24-Chloro-5-β-cholane (78)	160
		CCl_4	25°, DMF, 1 hr	 (55)	242
C_{29}		"	23°, DMF, 24 hr	 (15) +  (35)	124
C_{39}	$CH_2OCOC_{17}H_{35}$-*n* | CHOH | $CH_2OCOC_{17}H_{35}$-*n*	"	80°, CCl_4	$CH_2OCOC_{17}H_{35}$-*n* | ClCH | $CH_2OCOC_{17}H_{35}$-*n* (95)	243

TABLE IX. PREPARATION OF ALKYL HALIDES AND AZIDES USING TRIPHENYLPHOSPHINE–N-HALOSUCCINIMIDE

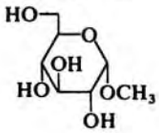
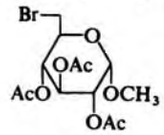
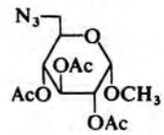
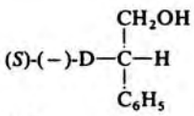
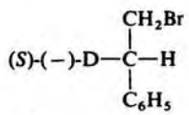
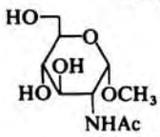
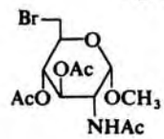
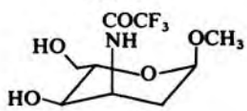
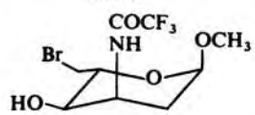
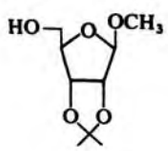
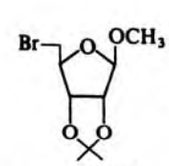
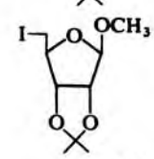
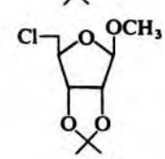
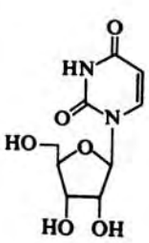
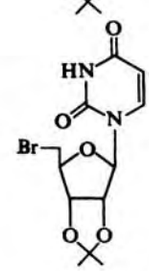
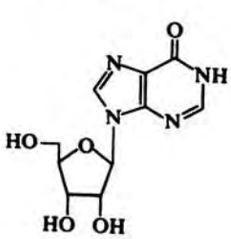
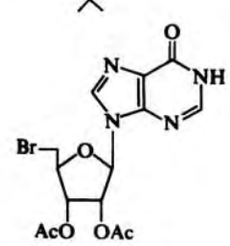
	Substrate	N-Halosuccinimide	Conditions	Products and Yields (%)	Ref.
C_2	C_2H_5OH	Br	—	C_2H_5Br (—)	244
C_7	Cycloheptanol	"	25°, THF, 2 hr	Bromocycloheptane (78)	185
		"	1. 50°, DMF, 2 hr 2. Ac_2O	 (66)	180
		"	1. 55°, DMF, 2 hr 2. NaN_3, 80°, CH_3OH 3. Ac_2O	 (75)	184
C_8		"	—	 (—)	245
C_9		"	1. 50°, DMF, 2 hr 2. Ac_2O	 (55)	180
		"	DMF	 (—)	246
		"	25°, CH_2Cl_2 or 50°, DMF, 15 min	 (95)	180
		I	50°, DMF, 20 min	 (71)	180
		Cl	"	 (95)	180
		Br	1. 50°, DMF, 3 hr 2. $(CH_3)_2CO$	 (70)	180
C_{10}		"	1. 50°, DMF, 2.5 hr 2. Ac_2O	 (59)	180

TABLE IX. PREPARATION OF ALKYL HALIDES AND AZIDES USING TRIPHENYLPHOSPHINE–N-HALOSUCCINIMIDE (*Continued*)

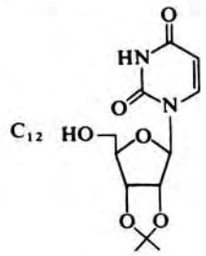
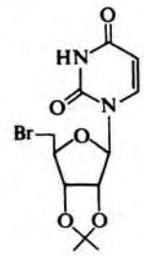
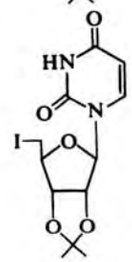
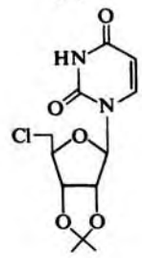
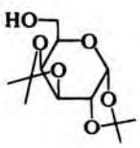
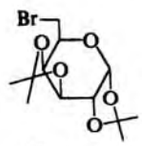
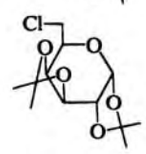
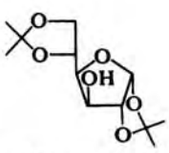
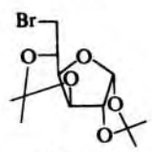
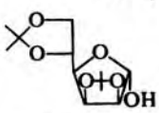
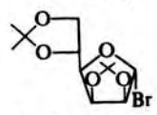
Substrate	N-Halosuccinimide	Conditions	Products and Yields (%)	Ref.
	Br	50°, DMF, 3.5 hr	 (79)	180
	I	50°, DMF, 2.5 hr	 (67)	180
	Cl	"	 (89)	180
	Br	50°, DMF, 2 hr	 (70)	180
	Cl	"	 (68)	180
	Br	50°, DMF, 1 hr	 (85)	180
	"	50°, DMF, 4 hr	 (95)	180
α,α-Trehalose	"	1. 25°, DMF, 60 hr 2. Ac_2O	6,6′-Dibromo-6,6′-didesoxy-α,α-trehalose hexaacetate (62)	182
	"	1. 25°, DMF, 43 hr 2. Ac_2O	6-Bromo-6-desoxy-α,α-trehalose heptaacetate (37) + dibromo derivative (11)	182
	I	1. 25°, DMF, 48 hr 2. Ac_2O	6-Iodo-6-desoxy-α,α-trehalose heptaacetate (21) + diiodo derivative (5)	182
	"	1. 50°, DMF, 50 hr 2. Ac_2O	6,6′-Didesoxy-6,6′-diiodo-α,α-trehalose hexaacetate (55)	182
	Cl	1. 25°, DMF, 48 hr 2. Ac_2O	6-Chloro-6-desoxy-α,α-trehalose heptaacetate (13) + dichloro derivative (2)	182
	"	50°, DMF, 75 hr	6,6′-Dichloro-6,6′-didesoxy-α,α-trehalose hexaacetate (42)	182

TABLE IX. PREPARATION OF ALKYL HALIDES AND AZIDES USING TRIPHENYLPHOSPHINE–N-HALOSUCCINIMIDE (*Continued*)

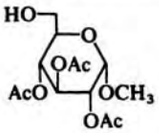
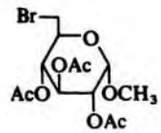
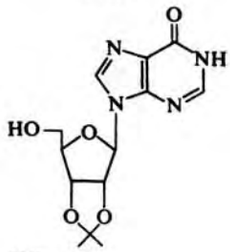
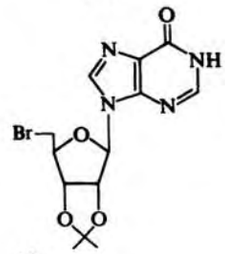
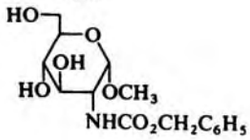
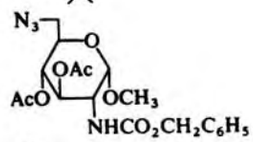
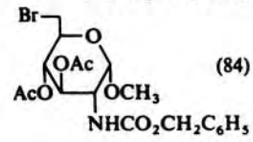
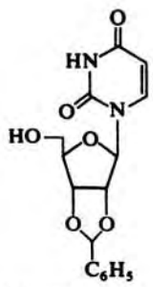
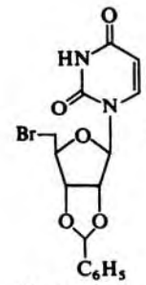
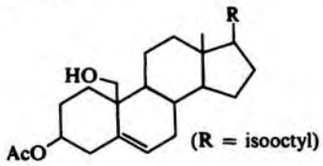
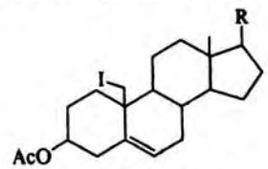
	Substrate	N-Halosuccinimide	Conditions	Products and Yields (%)	Ref.
C_{13}		Br	50°, DMF, 1 hr	 (77)	180
		"	50°, DMF, 1.5 hr	 (50)	180
C_{15}		"	1. 25°, DMF, 2 hr 2. NaN_3, CH_3OH, 80° 3. Ac_2O	 (84)	184
		"	1. 25°, DMF, 2 hr 2. Ac_2O	 (84)	184
C_{16}		"	50°, DMF, 4 hr	 (64)	180
C_{18}	4-Estren-17β-ol-3-one	"	25°, THF, 1 hr	17α-Bromo-4-estren-3-one (75)	185
C_{19}	5-Androsten-3β-ol-17-one	"	"	3-Bromo-5-androsten-17-one (75 (3α/3β = 4:1)	185
C_{27}	3β-Cholestanol	Br	"	3α-Cholestanyl bromide (95)	185
		I	"	3α-Cholestanyl iodide (85)	185
	Cholesterol	Br	"	Cholesteryl bromide (3α/3β = 3:1) (65)	185
	 (R = isooctyl)	I	25°, THF, 90 min	 (19)	247
C_{62}	Penta-N-benzyloxycarbonylneomycin	Br	1. 55°, HMPA, 4 hr 2. NaN_3, 55°, HMPA, 4 hr	5′-Azido-5′-desoxypenta-N-benzyloxycarbonylneomycin (73)	181
		"	55°, HMPA, 4 hr	5′-Bromo-5′-desoxypenta-N-benzyloxycarbonylneomycin (91)	181

TABLE X. PREPARATION OF ALKYL HALIDES USING ALKOXY(TRISDIMETHYLAMINO)PHOSPHONIUM SALTS

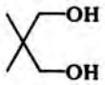
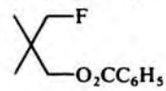
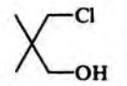
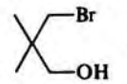
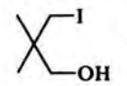
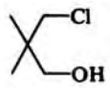
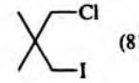
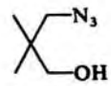
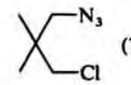
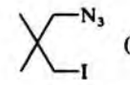
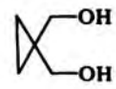
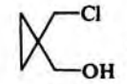
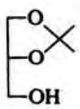
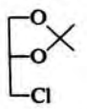
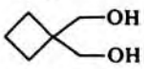
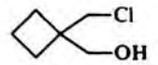
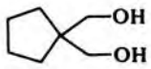
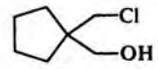
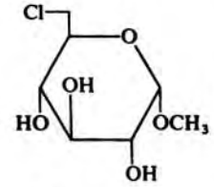
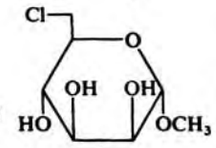
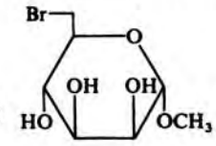
	Alcohol	Anion for Salt Isolation and Yield (%)	Nucleophile	Conditions	Products and Yields from Alcohol (%)	Ref.
C_4	n-C_4H_9OH	Cl^-	None	25°, Et_2O	n-C_4H_9Cl (81)	187
C_5	n-$C_5H_{11}OH$	"	"	"	n-$C_5H_{11}Cl$ (61)	187
		F^- (benzoylated)	"	1. 135°, DMF, 15 hr 2. C_6H_5COCl	 (20)	192, 193
		Cl^- (98)	"	90°, DMF, 6 hr	 (85)	192, 193
		ClO_4^- (95)	n-$C_4H_9N(C_2H_5)_3Br$	100°, DMF, 6 hr	 (60)	188, 189
		ClO_4^- (95)	KI	100°, DMF, 10 hr	 (87)	192, 193
		I^- (extraction)	None	80°, C_6H_6, 10 hr	 (81)	192, 193
		Cl^-	"	"	 (75)	192, 193
		I^- (extraction)	"	110°, toluene, 20 hr	 (65)	192, 193
		Cl^- (93)	"	100°, DMF, 8 hr	 (80)	192, 193
C_6	n-$C_6H_{13}OH$	None	KI	30°, CH_2Cl_2, H_2O, 180 min	n-$C_6H_{13}I$ (80)	188
		Cl^-	None	25°, Et_2O	1-Chlorohexane (67)	187
		"	"	"	 (70)	187
		" (95)	"	100°, DMF, 8 hr	 (82)	192, 193
C_7	n-$C_7H_{15}OH$	"	"	25°, Et_2O	n-$C_7H_{15}Cl$ (87)	187
	$C_6H_5CH_2OH$	None	KI	40°, CH_2Cl_2, H_2O, 120 min	$C_6H_5CH_2I$ (80)	188
		Cl^- (96)	None	100°, DMF, 9 hr	 (81)	192, 193
	Methyl-α-D-glucopyranoside	Cl^- (acetylated)	LiCl	1. 110°, DMF, 24 hr 2. CH_3ONa, CH_3OH	 (52)	248, 201
	Methyl-α-D-mannopyranoside	PF_6^- [acetylated (88)]	$(CH_3)_4NCl$	1. 95°, DMF, 8 hr 2. CH_3ONa, CH_3OH	 (76)	201
		"	$(C_2H_5)_4NBr$	1. 90°, DMF, 2 hr 2. CH_3ONa, CH_3OH	 (82)	201

TABLE X. PREPARATION OF ALKYL HALIDES USING ALKOXY(TRISDIMETHYLAMINO)PHOSPHONIUM SALTS (*Continued*)

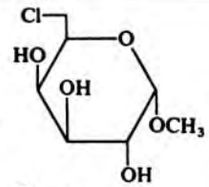
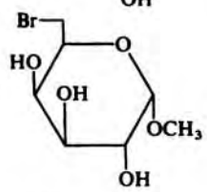
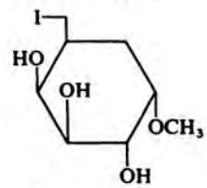
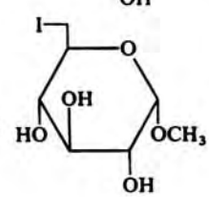
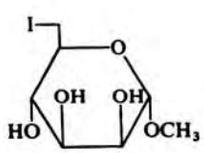
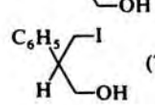
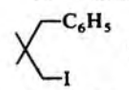
	Alcohol	Anion for Salt Isolation and Yield (%)	Nucleophile	Conditions	Products and Yields from Alcohol (%)	Ref.
C_7 (*Contd.*)	Methyl-α-D-galactopyranoside	PF_6^- [acetylated (85)]	$(CH_3)_4NCl$	1. 110°, DMF, 1 hr 2. CH_3ONa, CH_3OH	 (76)	210
		"	$(C_2H_5)_4NBr$	1. 90°, DMF, 6 hr 2. CH_3ONa, CH_3OH	 (75)	201
		"	KI	1. 90°, DMF, 20 hr 2. CH_3ONa, CH_3OH	 (60)	201
	Methyl-α-D-glucopyranoside	BF_4^- (100) (acetylated)	"	1. 80°, DMF, 24 hr 2. CH_3ONa, CH_3OH	 (64)	248, 201
	Methyl-α-D-mannopyranoside	PF_6^- [acetylated (88)]	"	1. 90°, DMF, 3 hr 2. CH_3ONa, CH_3OH	 (79)	201
C_8	n-$C_8H_{17}OH$	Cl^-	None	25°, Et_2O	n-$C_8H_{17}Cl$ (73)	187
	n-$C_6H_{13}CHOHCH_3$	"	"		n-$C_6H_{13}CHClCH_3$ (60)	133
	n-$C_5H_{11}CHOHC{\equiv}CH$	Cl^- (—)	"	65°, THF, 30 min	n-$C_5H_{11}CHClC{\equiv}CH$ (62)	39
C_9	C_6H_5–CH(OH)–CH$_2$–OH	F^-	"	120°, toluene, 15 hr	C_6H_5–CH(F)–CH$_2$–OH (57)	192, 193
		ClO_4^- (80)	KI	100°, DMF, 6 hr	 (78)	192, 193
C_{10}	$C_6H_5C(CH_3)_2CH_2OH$	I^- (extraction)	None	110°, toluene, 20 hr	 (70)	192, 193
	$HOCH_2(CH_2)_8CH_2OH$	PF_6^- (90)	KI	80°, DMF, 3 hr	$ICH_2(CH_2)_8CH_2OH$ (72)	249
C_{11}	C_6H_5–C(OH)(C$_2$H$_5$)–CH$_2$–OH	ClO_4^- (85)	"	100°, DMF, 6 hr	C_6H_5–C(I)(CH$_3$)–CH$_2$–OH (77)	192, 193
		Cl^- (98)	None	"	C_6H_5–C(Cl)(C$_2$H$_5$)–CH$_2$–OH (60)	192, 193
		I^- (extraction)	"	80°, C_6H_6, 15 hr	C_6H_5–C(I)(C$_2$H$_5$)–CH$_2$–OH (77)	192, 193
C_{12}	$HOCH_2(CH_2)_{10}CH_2OH$	PF_6^- (88)	KI	80°, DMF, 7 hr	$ICH_2(CH_2)_{10}CH_2OH$ (64)	249

TABLE X. PREPARATION OF ALKYL HALIDES USING ALKOXY(TRISDIMETHYLAMINO)PHOSPHONIUM SALTS (*Continued*)

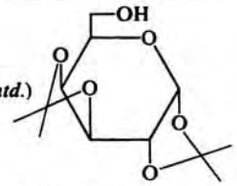
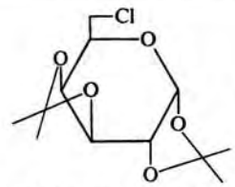
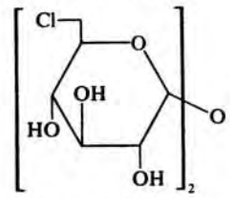
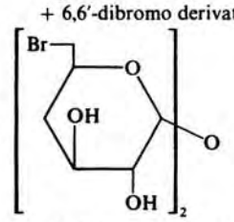
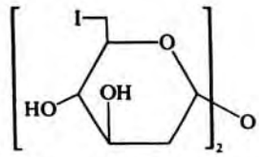
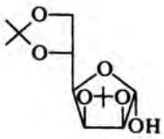
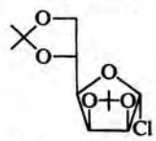
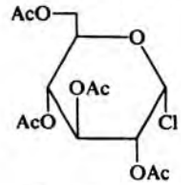
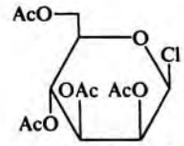
Alcohol	Anion for Salt Isolation and Yield (%)	Nucleophile	Conditions	Products and Yields from Alcohol (%)	Ref.
C_{12} (*Contd.*) 	PF_6^- (88)	Cl^-	25°, Et_2O	 (65)	187
α,α′-Trehalose	PF_6^- (acetylated)	$(CH_3)_4NCl$	70°, DMF, 2 hr	6-Chloro-6-desoxy-α,α′-trehalose heptaacetate (37) + 6,6′-dichloro derivative (19)	35
"	PF_6^- (acetylated) (85)	$(CH_3)_4NCl$	1. 80°, DMF, 10 hr 2. CH_3ONa, CH_3OH	 (72)	201
	PF_6^- (acetylated)	$(C_2H_5)_4NBr$	90°, DMF, 4 hr	6-Bromo-6-desoxy-α,α′-trehalose heptaacetate (39) + 6,6′-dibromo derivative (19)	35
	PF_6^- (acetylated) (85)	"	1. 85°, DMF, 10 hr 2. CH_3ONa, CH_3OH	 (75)	201
	PF_6^- (acetylated)	KI	90°, DMF, 3 hr	6-Iodo-6-desoxy-α,α′-trehalose heptaacetate (40) + 6,6′-diiodo derivative (14)	35
	PF_6^- (acetylated) (85)	"	1. 80°, DMF, 8 hr 2. CH_3ONa, CH_3OH	 (76)	201
Saccharose	PF_6^- (acetylated)	$(CH_3)_4NCl$	110°, DMF, 24 hr	6-Chloro-6-desoxysaccharose heptaacetate (49) + 6,6′-dichloro derivative (15)	35
	"	$(C_2H_5)_4NBr$	"	6-Bromo-6-desoxysaccharose heptaacetate (34) + 6,6′-dibromo derivative (15)	35
	"	KI	"	6-Iodo-6-desoxysaccharose heptaacetate (38) + 6,6′-diiodo derivative (12)	35
	Cl^-	None	25°, CH_2Cl_2, 2 hr	 (92)	198
C_{14} 2,3,4,6-Tetra-O-acetyl-β-D-glucopyranose	"	"	"	 (80)	37
2,3,4,6-Tetra-O-acetyl-mannopyranose	"	"	25°, CH_2Cl_2, 3 hr	 (19) + α anomer (40)	40

TABLE XI. Formation of Carbon–Nitrogen Bonds Using Alkoxy(trisdimethylamino)phosphonium Salts

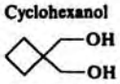
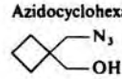
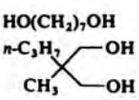
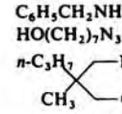
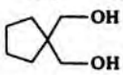
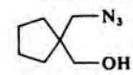
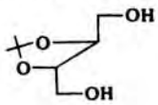
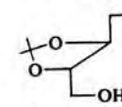
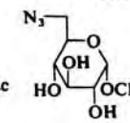
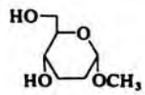
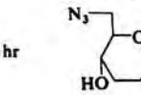
	Alcohol	Anion Used for Salt Isolation (%)	Nucleophile	Conditions	Products and Yields from Alcohol (%)	Ref.
C_1	CH_3OH	ClO_4^- (100)	$C_6H_5NH_2$	130°, DMF, 10 hr	$C_6H_5NHCH_3$ (70)	189
C_3	$HC{\equiv}CHCH_2OH$	"	CH_3NH_2	70°, DMF, 3 hr	$HC{\equiv}CCH_2NHCH_3$ (60)	189
		"	$HOCH_2CH_2NH_2$	80°, DMF, 3 hr	$HC{\equiv}CCH_2NHCH_2CH_2OH$ (57)	189
		"	Pyrrolidine	"	N-Propargylpyrrolidine (83)	189
		"	Morpholine	"	N-Propargylmorpholine (80)	189
		"	Cyclohexylamine	"	N-Propargylcyclohexylamine (77)	189
		"	$C_6H_5NH_2$	130°, DMF, 10 hr	$C_6H_5NHCH_2C{\equiv}CH$ (68)	189
C_4	$CH_3CH{=}CHCH_2OH$	ClO_4^- (not isolated)	CH_3NH_2	70°, DMF, 3 hr	$CH_3CH{=}CHCH_2NHCH_3$ (53)	189
		"	$HOCH_2CH_2NH_2$	80°, DMF, 3 hr	$CH_3CH{=}CHCH_2NHCH_2CH_2OH$ (52)	189
		"	Pyrrolidine	"	N-Crotylpyrrolidine (60)	189
		"	Morpholine	"	N-Crotylmorpholine (60)	189
		"	Cyclohexylamine	"	N-Crotylcyclohexylamine (51)	189
		"	$C_6H_5NH_2$	130°, DMF, 3 hr	$C_6H_5NHCH_2CH{=}CHCH_3$ (60)	189
C_5	n-$C_5H_{11}OH$	ClO_4^- (100)	$H_2NCH_2CH_2OH$	80°, DMF, 3 hr	n-$C_5H_{11}NHCH_2CH_2OH$ (55)	189
		"	Morpholine	"	N-n-Pentylmorpholine (75)	189
		"	Cyclohexylamine	"	N-n-Pentylcyclohexylamine (68)	189
		"	"	130°, DMF, 10 hr	n-$C_5H_{11}NHC_5H_{11}$-n (60)	189
		None	NaN_3	30°, THF, H_2O, 4 hr	n-$C_5H_{11}N_3$ (70)	189
		ClO_4^- (100)	Pyrrolidine	80°, DMF, 3 hr	N-n-Pentylpyrrolidine (81)	189
		N_3^- (extraction)	None	80°, C_6H_6, 10 hr	(66)	192, 193
		N_3^- (extraction)	"	80°, C_6H_6, 4 hr	(80)	192, 193
		PF_6^- (80)	NaN_3	100°, DMF, 10 hr	(68)	192, 193
C_6	n-$C_6H_{13}OH$	ClO_4^- (100)	CH_3NH_2	70°, DMF, 3 hr	n-$C_6H_{13}NHCH_3$ (60)	189
		—	NaN_3	30°, THF, H_2O, 4 hr	n-$C_6H_{13}N_3$ (70)	188
	$(CH_3)_2CH(CH_2)_2CH_2OH$	ClO_4^- (100)	Morpholine	80°, DMF, 3 hr	N-(2-Methylpentyl)morpholine (56)	189
		"	Cyclohexylamine	80°, DMF, 10 hr	N-(2-Methylpentyl)cyclohexylamine (60)	189
	Cyclohexanol	PF_6^- (91)	NaN_3	130°, DMF, 10 hr	Azidocyclohexane (57)	39
		ClO_4^- (90)	"	100°, DMF, 10 hr	 (72)	192, 193
C_7	$C_6H_5CH_2OH$	None	"	30°, THF, H_2O, 3 hr	$C_6H_5CH_2N_3$ (75)	188
		ClO_4^- (100)	CH_3NH_2	70°, DMF, 3 hr	$C_6H_5CH_2NHCH_3$ (70)	189
		"	$HOCH_2CH_2NH_2$	80°, DMF, 3 hr	$C_6H_5CH_2NHCH_2CH_2OH$ (70)	189
		"	Pyrrolidine	"	N-Benzylpyrrolidine (83)	189
		"	Morpholine	"	N-Benzylmorpholine (75)	189
		"	Cyclohexylamine	"	N-Benzylcyclohexylamine (70)	189
		"	$C_6H_5NH_2$	130°, DMF, 10 hr	$C_6H_5CH_2NHC_6H_5$ (66)	189
	$HO(CH_2)_7OH$	PF_6^- (81)	NaN_3	80°, DMF, 3 hr	$HO(CH_2)_7N_3$ (74)	249
		N_3^- (extraction)	None	80°, C_6H_6, 4 hr	 (80)	192, 193
		ClO_4^- (80)	NaN_3	100°, DMF, 10 hr	 (71)	192, 193
		PF_6^- (90)	"	80°, DMF, 3 hr	 (60)	249
	Methyl-α-D-glucopyranoside	BF_4^- (100) (acetylated)	"	1. 80°, DMF, 8 hr 2. CH_3ONa, CH_3OAc	 (90)	248, 201
		Br^- (CBr_4)	"	−50°; 60°, DMF, 6 hr	 (78)	250

TABLE XI. FORMATION OF CARBON–NITROGEN BONDS USING ALKOXY(TRISDIMETHYLAMINO)PHOSPHONIUM SALTS (*Continued*)

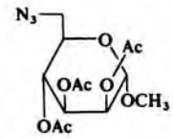
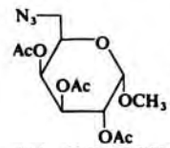
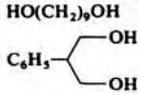
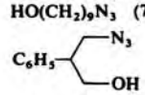
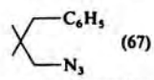
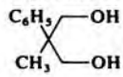
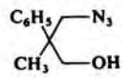
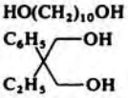
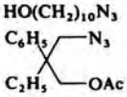
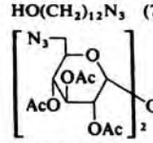
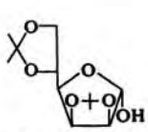
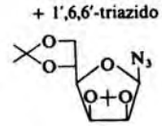
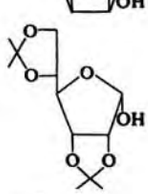
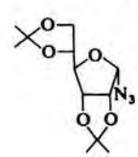
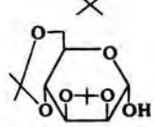
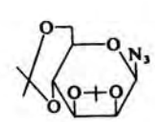
	Alcohol	Anion Used for Salt Isolation (%)	Nucleophile	Conditions	Products and Yields from Alcohol (%)	Ref.
C_7 (*Contd.*)	Methyl-α-D-mannopyranoside	PF_6^- [acetylated (88)]	NaN_3	90°, DMF, 3 hr	 (87)	201
	Methyl-α-D-galactopyranoside	PF_6^- [acetylated (85)]	"	90°, DMF, 15 hr	 (80)	201
C_8	(−)-*n*-$C_6H_{13}CHOHCH_3$	PF_6^- (97) (diisopropylchloramine as oxidant)	"	130°, DMF, 5 hr	(+)-*n*-$C_6H_{13}CH(N_3)CH_3$ (75)	39
	$HO(CH_2)_8OH$	PF_6^- (77)	"	80°, DMF, 3 hr	$HO(CH_2)_8N_3$ (70)	249
	$C_6H_5NHCH_2CH_2OH$	PF_6^- (97)	"	"	$C_6H_5NHCH_2CH_2N_3$ (87)	251
C_9	$HO(CH_2)_9OH$	PF_6^- (77)	"	80°, DMF, 3 hr	$HO(CH_2)_9N_3$ (70)	249
		N_3^- (extraction)	None	80°, C_6H_6, 4 hr	 (70)	192, 193
C_{10}	4-*t*-Butylcyclohexanol (*cis*–*trans* = 30:70)	PF_6^- (75)	NaN_3	130°, DMF, 10 hr	1-Azido-4-*t*-butylcyclohexane (67) (*cis*–*trans* = 90:10)	39
	$C_6H_5C(CH_3)_2CH_2OH$	ClO_4^-	None	100°, DMF, 20 hr	 (67)	192, 193
	(−)-Menthol	PF_6^- (86)	NaN_3	130°, DMF, 10 hr	(+)-Azidomenthane (52)	39
		N_3^- (extraction)	—	80°, C_6H_6, 4 hr	 (71)	192, 193
	$HO(CH_2)_{10}OH$	PF_6^- (90)	NaN_3	80°, DMF, 3 hr	$HO(CH_2)_{10}N_3$ (82)	249
C_{11}		ClO_4^- [acetylated (85)]	"	100°, DMF, 10 hr	 (70)	192, 193
C_{12}	$HO(CH_2)_{12}OH$	PF_6^- (88)	"	80°, DMF, 3 hr	$HO(CH_2)_{12}N_3$ (75)	249
	α,α′-Trehalose	PF_6^- [acetylated (85)]	"	90°, DMF, 9 hr	 (81)	201
		PF_6^- (acetylated)	"	90°, DMF, 4 hr	6-Azido-6-desoxy-α,α′-trehalose heptaacetate (33) + 6,6′-diazido derivative (2)	35
	Saccharose	"	"	"	6-Azido-6-desoxysaccharose heptaacetate (38) + 6,6′-diazido (11) + 1′,6,6′-triazido derivatives (2)	35
		None	$(CH_3)_3C_6H_2O\overset{+}{P}(N(CH_3)_2)_3N_3^-$	−10°, CH_2Cl_2, 3 hr	 (65)	200
		"	"	"	 (70)	200
		"	"	"	 (80)	200

TABLE XI. FORMATION OF CARBON–NITROGEN BONDS USING ALKOXY(TRISDIMETHYLAMINO)PHOSPHONIUM SALTS (*Continued*)

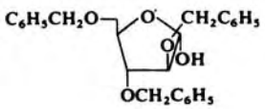
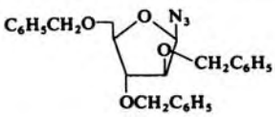
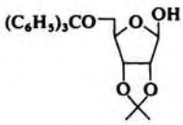
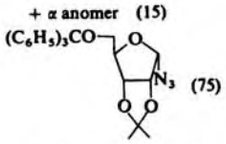
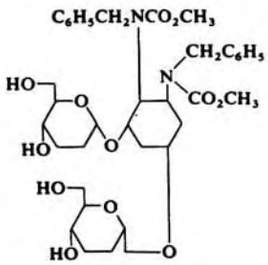
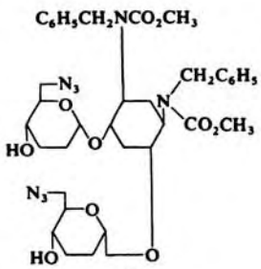
	Alcohol	Anion Used for Salt Isolation (%)	Nucleophile	Conditions	Products and Yields from Alcohol (%)	Ref.
C_{26}		None	$(CH_3)_3C_6H_2O\overset{+}{P}(N(CH_3)_2)_3N_3^-$	$-10°$, CH_2Cl_2, 3 hr	 (70) + α anomer (15)	200
C_{27}		"	"	"	 (75)	200
C_{37}		"	NaN_3	$-50°$, $+80°$, DMF, 8 hr	 (70)	252

TABLE XII. FORMATION OF ETHERS AND GLYCOSIDES USING ALKOXY(TRISDIMETHYLAMINO)PHOSPHONIUM SALTS

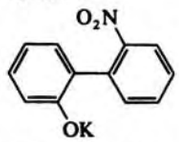
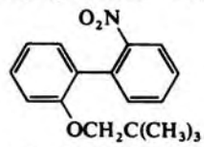
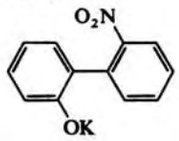
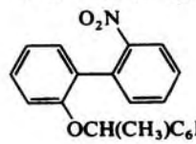
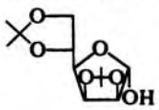
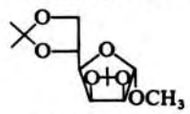
	Alcohol	Anion Used for Salt Isolation	Nucleophile	Conditions	Products and Yields from Salt (%)	Ref.
C_3	$CH_2{=}CHCH_2OH$	PF_6^-	C_6H_5OK	150°, DMF, 15 hr	$C_6H_5OCH_2CH{=}CH_2$ (79)	194
C_5	$(CH_3)_3CCH_2OH$	"		"	 (90)	194
		"	p-$O_2NC_6H_4OK$	"	p-$O_2NC_6H_4OCH_2C(CH_3)_3$ (42), p-$O_2NC_6H_4N(CH_3)_2$ (29)	194
		"	p-$CH_3OC_6H_4OK$	"	p-$CH_3OC_6H_4OCH_2C(CH_3)_3$ (66)	194
		"	C_6H_5OK	"	$C_6H_5OCH_2C(CH_3)_3$ (75)	194
C_8	n-$C_6H_{13}CHOHCH_3$	PF_6^-		"		194
		"	p-$O_2NC_6H_4OK$	"	n-$C_6H_{13}CH(CH_3)OC_6H_4NO_2$-$p$ (80)	194
		"	p-$CH_3OC_6H_4OK$	"	n-$C_6H_{13}CH(CH_3)OC_6H_4OCH_3$-$p$ (68)	194
		"	C_6H_5OK	"	n-$C_6H_{13}CH(CH_3)OC_6H_5$ (99)	194
C_{10}	1,10-Decanediol	"	$NaOCH_3$	60°, CH_3OH, 4 hr	10-Methoxy-1-decanol (76)	249
C_{12}		$CH_3C_6H_4SO_3^-$	$CH_3OH/N(C_2H_5)_3$	25°, CH_2Cl_2, 4 hr	 (34) + β isomer (41)	198

TABLE XII. FORMATION OF ETHERS AND GLYCOSIDES USING ALKOXY(TRISDIMETHYLAMINO)PHOSPHONIUM SALTS (*Continued*)

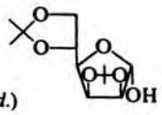
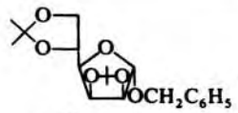
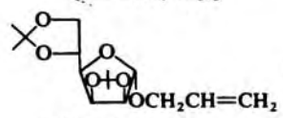
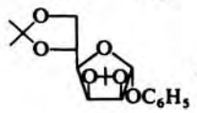
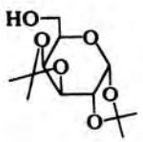
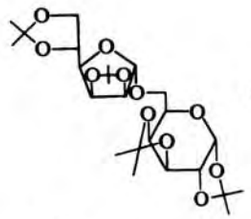
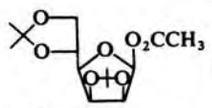
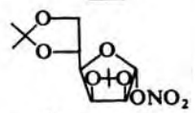
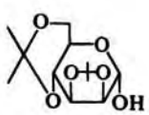
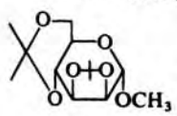
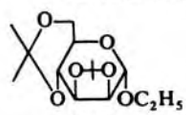
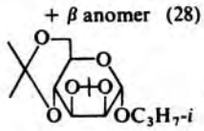
Alcohol	Anion Used for Salt Isolation	Nucleophile	Conditions	Products and Yields from Salt (%)	Ref.
C_{12} (*Contd.*) 	$CH_3C_6H_4SO_3^-$	$C_6H_5CH_2OH/N(C_2H_5)_3$	"	 (52) + β isomer (22)	198
	"	$(CH_3)_2CHOH/N(C_2H_5)_3$	"	(72)	198
	"	$(CH_3)_3COH/N(C_2H_5)_3$	"	(90)	198
	"	$CH_2{=}CHCH_2OH/N(C_2H_5)_3$	"	 (41) + β isomer (34)	198
	$CH_3C_6H_4SO_3^-$	$C_6H_5OH/N(C_2H_5)_3$	25°, CH_2Cl_2, 4 hr	 (80)	198
	"		"	 (60)	198
	None	CH_3CO_2Ag	25°, CH_2Cl_2, 2 hr	 (80)	198
	"	$AgNO_3$	"	 (85)	198
	$CH_3C_6H_4SO_3^-$	$CH_3OH/N(C_2H_5)_3$	25°, CH_2Cl_2, 3 hr	 (51) + β anomer (38)	199
	"	$C_2H_5OH/N(C_2H_5)_3$	"	 (45) + β anomer (28)	199
	"	$i\text{-}C_3H_7OH/N(C_2H_5)_3$	25°, CH_2Cl_2, 3 hr	 (50) + β anomer (33)	199

TABLE XII. FORMATION OF ETHERS AND GLYCOSIDES USING ALKOXY(TRISDIMETHYLAMINO)PHOSPHONIUM SALTS (*Continued*)

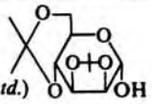
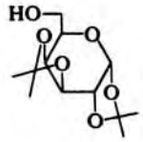
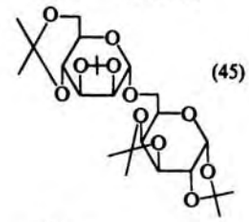
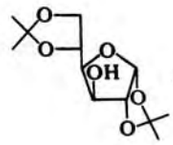
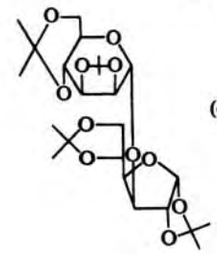
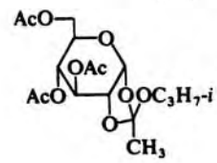
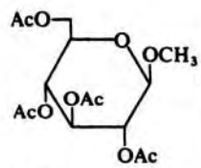
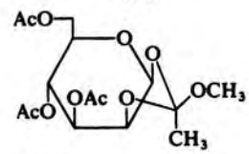
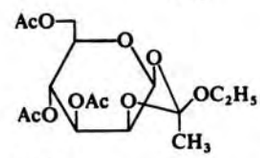
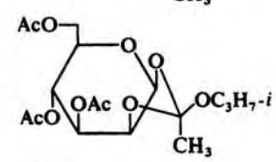
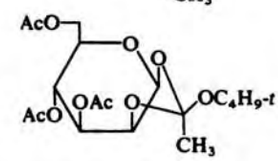
Alcohol	Anion Used for Salt Isolation	Nucleophile	Conditions	Products and Yields from Salt (%)	Ref.
C_{12} (*Contd.*) 	$CH_3C_6H_5SO_3^-$	t-$C_4H_9OH/N(C_2H_5)_3$	25°, CH_2Cl_2, 4 hr	(50)	199
	"	 $/N(C_2H_5)_3$	"	 (45)	199
	"	 $/N(C_2H_5)_3$	"	 (40)	199
C_{14} 2,3,4,6-Tetra-O-acetyl-β-D-glucopyranose	None	i-$C_3H_7OH/N(C_2H_5)_3$	"	 (80)	37
	PF_6^- [α anomer (55)]	CH_3OH/Pyridine	"	 (40)	37
2,3,4,6-Tetra-O-acetylmannopyranose	None	$CH_3OH/N(C_2H_5)_3$	60°, CH_3CN, 30 min	 (82)	40
	"	$C_2H_5OH/N(C_2H_5)_3$	70°, CH_3CN, 30 min	 (85)	40
	"	i-$C_3H_7OH/N(C_2H_5)_3$	70°, CH_3CN, 1 hr	 (43)	40
	"	t-$C_4H_9OH/N(C_2H_5)_3$	70°, CH_3CN, 2 hr	 (40)	40

TABLE XIII. Formation of Carbon-Sulfur Bonds Using Alkoxy(trisdimethylamino)phosphonium Salts

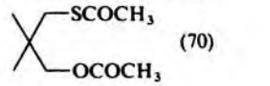
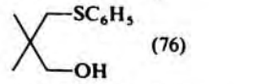
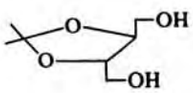
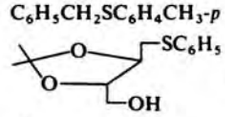
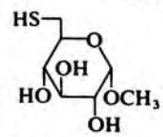
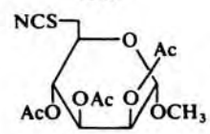
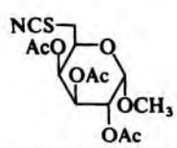
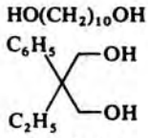
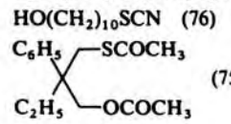
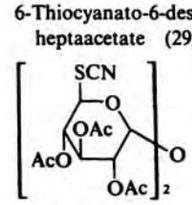
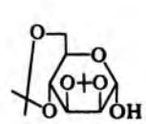
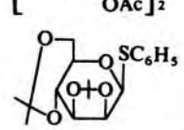
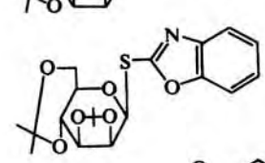
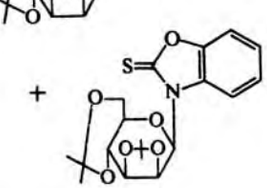
	Alcohol	Anion for Salt Isolation and Yield (%)	Nucleophile	Conditions	Products and Yields from Alcohol	Ref.
C_3	$CH_2{=}CHCH_2OH$	PF_6^-	p-$CH_3C_6H_4SK$	150°, DMF, 15 hr	p-$CH_3C_6H_4SCH_2CH{=}CH_2$ (97)	194
		"	C_6H_5SH/KOH	"	$C_6H_5SCH_2CH{=}CH_2$ (90)	
C_5	n-$C_5H_{11}OH$	None	NH_4SCN	30°, THF, 2 hr	n-$C_5H_{11}SCN$ (70)	188
		"	$C_6H_5SH/N(C_2H_5)_3$	−60°, THF, 20 min	n-$C_5H_{11}SC_6H_5$ (70)	188
		ClO_4^- [acetylation (80)]	$CH_3COSH/N(C_2H_5)_3$	1. 100°, DMF, 10 hr 2. Ac_2O	 (70)	192, 193
		ClO_4^- (95)	$C_6H_5SH/N(C_2H_5)_3$	100°, DMF, 10 hr	 (76)	192, 193
C_6	n-$C_6H_{13}OH$	None	NH_4SCN	30°, THF, 2 hr	n-$C_6H_{13}SCN$ (70)	188
		"	$C_6H_5SH/N(C_2H_5)_3$	−60°, THF, 20 min	n-$C_6H_{13}SC_6H_5$ (70)	188
C_7	$C_6H_5CH_2OH$	"	NH_4SCN	30°, THF, 90 min	$C_6H_5CH_2SCN$ (80)	188
		"	$C_6H_5SH/N(C_2H_5)_3$	−60°, THF, 20 min	$C_6H_5CH_2SC_6H_5$ (85)	188
		PF_6^-	C_6H_5SK	150°, DMF, 15 hr	" (83)	194
		"	p-$CH_3C_6H_4SK$	"	$C_6H_5CH_2SC_6H_4CH_3$-p (98)	194
		PF_6^- (90)	$C_6H_5SH/N(C_2H_5)_3$	80°, DMF, 5 hr	 (50)	249
	Methyl-α-D-glucopyranoside	BF_4^- [acetylation (100)]	$CH_3COSH/N(C_2H_5)_3$	1. 80°, DMF, 8 hr 2. CH_2ONa, CH_3OH	 (54)	248, 201
	Methyl-α-D-mannopyranoside	PF_6^- [acetylation (88)]	NH_4SCN	90°, DMF, 10 hr	 (83)	201
	Methyl-α-D-galactopyranoside	PF_6^- [acetylation (85)]	"	100°, DMF, 20 hr	 (46)	201
C_8	$C_6H_{11}CHOHCH_3$	PF_6^-	C_6H_5SK	150°, DMF, 15 hr	$C_6H_{11}CH(CH_3)SC_6H_5$ (61)	194
		"	p-$CH_3C_6H_4SK$	"	$C_6H_{11}CH(CH_3)SC_6H_4CH_3$-$p$ (68)	194
C_{10}	$HO(CH_2)_{10}OH$	PF_6^- (90)	NH_4SCN	80°, DMF, 3 hr	$HO(CH_2)_{10}SCN$ (76)	249
C_{11}		ClO_4^- [acetylation (85)]	$CH_3COSH/N(C_2H_5)_3$	100°, DMF, 10 hr	 (75)	192, 193
C_{12}	α,α′-Trehalose	PF_6^- (acetylation)	NH_4SCN	90°, DMF, 7 hr	6-Thiocyanato-6-desoxy-α,α′-trehalose heptaacetate (29)	35
		PF_6^- [acetylation (88)]	NH_4SCN	90°, DMF, 7 hr	 (78)	35
		None	C_6H_5SH, $N(C_2H_5)_3$	25°, CH_2Cl_2, 3 hr	 (65)	199
		"	2-Thiobenzoxazole	"	 (50)	199
					+  (15)	

TABLE XIII. FORMATION OF CARBON-SULFUR BONDS USING ALKOXY(TRISDIMETHYLAMINO)PHOSPHONIUM SALTS (*Continued*)

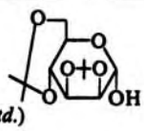
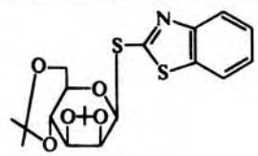
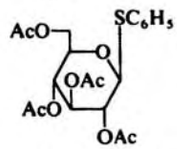
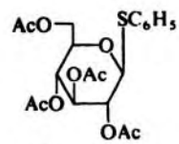
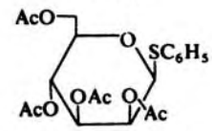
	Alcohol	Anion for Salt Isolation and Yield (%)	Nucleophile	Conditions	Products and Yields from Alcohol	Ref.
C_{12} (*Contd.*)		None	2-Thiobenzothiazole	25°, CH_2Cl_2, 3 hr	 (65)	199
C_{14}	2,3,4,6-Tetra-O-acetyl-β-D-glucopyranose	"	$C_6H_5SH/N(C_2H_5)_3$	25°, CH_2Cl_2, 4 hr	 (65) + α anomer (15)	39
		PF_6^-, α anomer (59)	"	"	 (38)	39
	2,3,4,6-Tetra-O-acetylmannopyranose	None	$C_6H_5SH/N(C_2H_5)_3$	25°, CH_2Cl_2, 1 hr	 (58)	40

TABLE XIV. FORMATION OF CARBON–HYDROGEN AND CARBON–CARBON BONDS USING ALKOXY(TRISDIMETHYLAMINO)PHOSPHONIUM SALTS

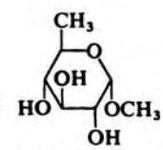
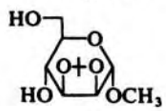
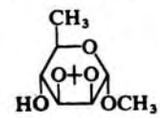
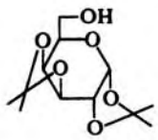
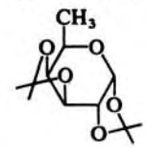
	Alcohol	Anion for Salt Isolation and Yield (%)	Nucleophile	Conditions	Products and Yields from Alcohol (%)	Ref.
C_6	n-$C_6H_{13}OH$	None	KCN	30°, CH_2Cl_2, H_2O 3 hr	n-$C_6H_{13}CN$ (65)	188
C_7	Methyl-α-D-glucopyranoside	None (acetylation)	$LiAlH_4$	1. 65°, THF, 25 hr 2. CH_3ONa, CH_3OH	 (60)	248, 201
C_{10}	$HO(CH_2)_{10}OH$	PF_6^- (90)	KCN	80°, DMF, 3 hr	$HO(CH_2)_{10}CN$ (70)	249
		PF_6^-	$LiBH(C_2H_5)_3$	70°, THF, 3 hr	 (90)	196
C_{12}		"	"	"	 (92)	196

TABLE XIV. FORMATION OF CARBON-HYDROGEN AND CARBON-CARBON BONDS USING ALKOXY(TRISDIMETHYLAMINO)PHOSPHONIUM SALTS (*Contd.*)

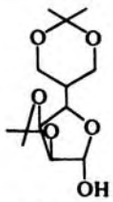
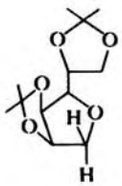
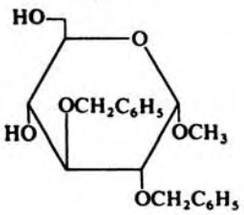
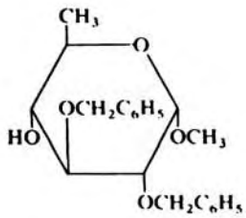
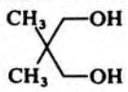
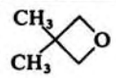
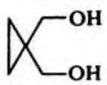
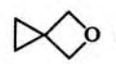
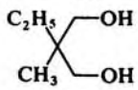
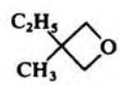
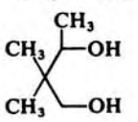
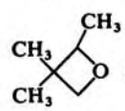
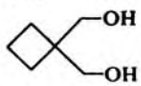
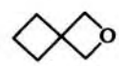
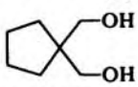
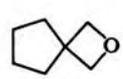
Alcohol	Anion for Salt Isolation and Yield (%)	Nucleophile	Conditions	Products and Yields from Alcohol (%)	Ref.
C_{13} 	None	"	"	 (92)	196
C_{21} 	PF_6^- (96)	"	"	 (91)	254, 196

TABLE XV. FORMATION OF OXETANES FROM 1,3-GLYCOLS USING 3-HYDROXY(TRISDIMETHYLAMINO)PHOSPHONIUM CHLORIDES

	Salt from Glycol	Conditions	Product and Yield (%)	Ref.
C_5		150°, Na/Methyl carbitol	 (63)	203
		"	 (10)	203
C_6		"	 (70)	203
		"	 (65)	203
		"	 (55)	203
C_7		"	 (60)	203
C_9	$C_6H_5CH(CH_2OH)_2$	70°, Na/CH_3OH	3-Phenyloxetane (35)	203
C_{10}	$C_6H_5C(CH_3)(CH_2OH)_2$	"	3-Methyl-3-phenyloxetane (70)	203
C_{11}	$C_6H_5C(C_2H_5)(CH_2OH)_2$	"	3-Ethyl-3-phenyloxetane (60)	203

6. Acknowledgment

I gratefully acknowledge the expert extensive assistance of Dr. Robert M. Joyce in preparing the manuscript for publication.

End Notes

* For a review of this reaction see ref. 7.

References

1. A. Michaelis and R. Kaehne, Ber., **31**, 1048 (1898).
2. A. E. Arbuzov, J. Russ. Phys. Chem. Soc., **38**, 687 (1906) [Chem. Zentralbl., 1906, **II**, 1639].
3. J. I. G. Cadogan and R. K. Mackie, Chem. Soc. Rev., **3**, 87 (1974).
4. R. Appel, Angew. Chem., Int. Ed. Engl., **14**, 801 (1975).
5. T. Mukaiyama, Angew. Chem., Int. Ed. Engl., **15**, 94 (1976).
6. R. K. Mackie, in *Organophosphorus Reagents in Organic Chemistry*, J. I. G. Cadogan, Ed., Academic Press, London, 1979.
7. O. Mitsunobu, Synthesis, **1981**, 1.
8. O. Mitsunobu, M. Yamada, and T. Mukaiyama, Bull. Chem. Soc. Jpn., **40**, 935 (1967).
9. E. Brunn and R. Huisgen, Angew. Chem., Int. Ed. Engl., **8**, 513 (1969).
10. O. Mitsunobu and M. Iguchi, Bull. Chem. Soc. Jpn., **44**, 2327 (1971).
11. H. Loibner and E. Zbiral, Helv. Chim. Acta, **59**, 2100 (1976).
12. B. A. Arbuzov, N. A. Polezhaeva, and V. S. Vinogradova, Izv. Akad. Nauk SSSR, Ser. Khim., **1968**, 2525 [C.A., **70**, 87682r (1969)].
13. G. Alfredsson and P. J. Garegg, Acta Chem. Scand., Ser. B, **27**, 724 (1973).
14. G. Grynkiewicz and H. Burynska, Tetrahedron, **32**, 2109 (1976).
15. M. Gligorijevic and M. J. Gasic, Bull. Soc. Chim. Beograd, **41**, 353 (1976).
16. R. Aneja, A. P. Davies, A. Harkes, and J. A. Knaggs, J. Chem. Soc., Chem. Commun., **1974**, 963.
17. R. Aneja, A. P. Davies, and J. A. Knaggs, Tetrahedron Lett., **1975**, 1033.
18. R. Appel, F. Knoll, W. Michel, W. Morbach, H. D. Wihler, and H. Veltmann, Chem. Ber., **109**, 58 (1976).
19. A. J. Speziale and K. W. Ratts, J. Am. Chem. Soc., **84**, 857 (1962).
20. R. Appel and K. Warning, Chem. Ber., **108**, 606 (1975).
21. R. Appel and H. Veltmann, Tetrahedron Lett., **1977**, 399.
22. L. Gruber, I. Tömösközi, and L. Radics, Synthesis, **1975**, 708.
23. I. M. Downie, J. B. Holmes, and J. B. Lee, Chem. Ind. (Lond.), **28**, 900 (1966).
24. R. G. Weiss and E. I. Snyder, J. Org. Chem., **35**, 1627 (1970).
25. L. A. Jones, C. E. Summer, Jr., B. Franzus, T. T. S. Huang, and E. I. Snyder, J. Org. Chem., **43**, 2821 (1978).
26. R. Aneja, A. P. Davies, and J. A. Knaggs, Tetrahedron Lett., **1974**, 67.
27. S. J. Cristol, R. M. Strom, and D. P. Stull, J. Org. Chem., **43**, 1150

(1978).
28. R. G. Weiss and E. I. Snyder, J. Org. Chem., **36**, 403 (1971).
29. C. Georgoulis and G. Ville, Bull. Soc. Chim. Fr., **1975**, 607.
30. R. M. Magid, O. S. Fruchey, W. L. Johnson, and T. G. Allen, J. Org. Chem., **44**, 359 (1979).
31. J. B. Lee and T. J. Nolan, Tetrahedron, **23**, 2789 (1967).
32. B. Castro, R. Burgada, G. Lavielle, and J. Villieras, C. R. Hebd. Seances Acad. Sci., Ser. C., **268**, 1067 (1969).
33. B. Castro, R. Burgada, G. Lavielle, and J. Villieras, Bull. Soc. Chim. Fr., **1969**, 2770.
34. B. Castro, J. Villieras, R. Burgada, and G. Lavielle, in *Chimie Organique du Phosphore*, Ed. du CNRS, Paris, 1970, p. 235.
35. B. Castro, Y. Chapleur, and B. Gross, Carbohydr. Res., **36**, 412 (1974).
36. B. Castro, M. Nacro, and C. Selve, Tetrahedron, **35**, 481 (1979).
37. B. Castro, Y. Chapleur, and B. Gross, Bull. Soc. Chim. Fr., **1975**, 875.
38. R. A. Boigegrain, B. Castro, and B. Gross, Tetrahedron Lett., **1975**, 3947.
39. Y. Chapleur, B. Castro, and B. Gross, Tetrahedron, **33**, 1609 (1977).
40. Y. Chapleur, B. Castro, and B. Gross, Synth. Commun., **7**, 143 (1977).
41. D. Neibecker and B. Castro, J. Organomet. Chem., **134**, 105 (1977).
42. D. C. Morrison, J. Org. Chem., **23**, 1072 (1958).
43. V. A. Ginsburg, M. N. Vasil'eva, S. S. Dubov, and A. Yakubovitch, Zh. Obshch. Khim., **30**, 2854 (1960) [C. A., **55**, 17477b (1961)].
44. G. Grynkiewicz, J. Jurczak, and A. Zamojski, Bull. Acad. Pol. Sci., **24**, 83 (1976).
45. G. Grynkiewicz and J. Jurczak, Carbohydr. Res., **43**, 188 (1975).
46. G. Grynkiewicz, Bull. Acad. Pol. Sci., **26**, 537 (1978).
47. G. Grynkiewicz, J. Jurczak, and A. Zamojski, J. Chem. Soc., Chem. Commun., **1974**, 413.
48. O. Mitsunobu, M. Wada, and T. Sano, J. Am. Chem. Soc., **94**, 679 (1972).
49. A. Zamojski, W. A. Szarek, and K. N. Jones, Carbohydr. Res., **23**, 460 (1972).
50. M. Wada, T. Sano, and O. Mitsunobu, Bull. Chem. Soc. Jpn., **46**, 2833 (1973).
51. J. Jurczak, G. Grynkiewicz, and A. Zamojski, Carbohydr. Res., **39**, 147 (1975).
52. A. Banaszek, B. Szechner, J. Mieczkowski, and A. Zamojski, Rocz. Chem., **50**, 105 (1976).

53. O. Mitsunobu, S. Takizawa, and H. Morimoto, J. Am. Chem. Soc., **98**, 7858 (1976).
54. M. Wada and O. Mitsunobu, Tetrahedron Lett., **1972**, 1279.
55. H. Morimoto, T. Furukawa, K. Miyazima, and O. Mitsunobu, Chem. Lett., **1973**, 821.
56. W. A. Szarek, C. Depew, and J. K. N. Jones, J. Heterocycl. Chem., **13**, 1131 (1976).
57. W. A. Szarek, C. Depew, H. C. Jarrell, and J. K. N. Jones, J. Chem. Soc., Chem. Commun., **1975**, 648.
58. H. Loibner and E. Zbiral, Helv. Chim. Acta, **60**, 417 (1977).
59. H. Loibner and E. Zbiral, Justus Liebigs Ann. Chem., **1978**, 78.
60. H. Loibner and E. Zbiral, Tetrahedron, **34**, 713 (1978).
61. J. Schweng and E. Zbiral, Tetrahedron Lett., **1978**, 119.
62. W. Reischi and E. Zbiral, Justus Liebigs Ann. Chem., **1978**, 745.
63. H. Brandstetter and E. Zbiral, Helv. Chim. Acta, **61**, 1832 (1978).
64. H. Brandstetter and E. Zbiral, Helv. Chim. Acta, **63**, 327 (1980).
65. B. Lal, B. N. Pramanik, M. S. Manhas, and A. K. Bose, Tetrahedron Lett., **1977**, 1977.
66. O. Mitsunobu and M. Yamada, Bull. Chem. Soc. Jpn., **40**, 2380 (1967).
67. A. K. Bose, B. Lal, W. A. Hoffman, and M. S. Manhas, Tetrahedron Lett., **1973**, 1619.
68. S. Shimokawa, J. Kimura, and O. Mitsunobu, Bull. Chem. Soc. Jpn., **49**, 3357 (1976).
69. L. P. L. Piacenza, J. Org. Chem., **42**, 3778 (1977).
70. G. Grynkiewicz, Rocz. Chem., **50**, 1449 (1976).
71. H. Kunz and O. Schmidt, Z. Naturforsch., B, **33**, 1009 (1978).
72. J. Mulzer and G. Brüntrup, Angew. Chem., Int. Ed. Engl., **16**, 255 (1977).
73. J. Mulzer, A. Pointner, A. Chucholowski, and G. Brüntrup, J. Chem. Soc., Chem. Commun., **1979**, 52.
74. J. Mulzer, G. Brüntrup, and A. Chucholowski, Angew. Chem., Int. Ed. Engl., **18**, 622 (1979).
75. T. Kurihara, Y. Nakajima, and O. Mitsunobu, Tetrahedron Lett., **1976**, 2455.
76. B. Seuring and D. Seebach, Justus Liebigs Ann. Chem., **1978**, 2044.
77. Y. Fukuyama, C. L. Kirkemo, and J. D. White, J. Am. Chem. Soc., **99**, 646 (1977).
78. T. A. Hase and E. L. Nylund, Tetrahedron Lett., **1979**, 2633.
79. A. I. Myers and R. A. Amos, J. Am. Chem. Soc., **102**, 870 (1980).
80. O. Mitsunobu, J. Kimura, and Y. Fujisawa, Bull. Chem. Soc. Jpn., **45**,

245 (1972).
81. E. Grochowski and J. Jurczak, Synthesis, **4**, 277 (1977).
82. B. Castro, J. R. Dormoy, G. Evin, and C. Selve, J. Chem. Res., (S), **1977**, 182.
83. G. Grynkiewicz, J. Jurczak, and A. Zamojski, Tetrahedron, **31**, 1411 (1975).
84. M. Furukawa, T. Okawara, Y. Noguchi, and M. Nishikawa, Synthesis, **1978**, 441.
85. O. Mitsunobu, K. Kato, and J. Kimura, J. Am. Chem. Soc., **91**, 6510 (1969).
86. B. Mlotkowska and A. Zwierzak, Pol. J. Chem., **53**, 359 (1979).
87. E. Grochowski and J. Jurczak, Carbohydr. Res., **1976**, C15.
88. E. Grochowski and J. Jurczak, Synthesis, **10**, 682 (1976).
89. E. Grochowski, E. Falent, and J. Jurczak, Pol. J. Chem., **52**, 335 (1978).
90. E. Grochowski and E. Falent-Kwastowa, J. Chem. Res., (S), **1978**, 300.
91. R. S. Glass and R. J. Swedo, J. Org. Chem., **43**, 2291 (1978).
92. S. Bittner and Y. Assaf, Chem. Ind. (Lond.), **1975**, 281.
93. M. S. Manhas, W. H. Hoffman, B. Lal, and A. K. Bose, J. Chem. Soc., Perkin Trans. 1, **1975**, 461.
94. J. T. Carlock and M. P. Mack, Tetrahedron Lett., **1978**, 5153.
95. G. Grynkiewicz, Carbohydr. Res., **53**, C11 (1977).
96. P. J. Garregg, T. Iverson, and T. Norberg, Carbohydr. Res., **73**, 313 (1979).
97. W. A. Szarek, H. D. Jarrell, and J. K. N. Jones, Carbohydr. Res., **57**, C13 (1977).
98. G. Grynkiewicz and A. Zamojski, Synth. Commun., **8**, 491 (1978).
99. J. Kimura, A. Kawashima, M. Sugizaki, N. Nemoto, and O. Mitsunobu, J. Chem. Soc., Chem. Commun., **1979**, 303.
100. H. Wojciechowska, R. Pawlowicz, R. Andruszkiewicz, and J. Grybowska, Tetrahedron Lett., **1978**, 4063.
101. F. DiNinno, J. Am. Chem. Soc., **100**, 3251 (1978).
102. H. Kunz and P. Schmidt, Tetrahedron Lett., **1979**, 2123.
103. P. J. Garregg and B. Samuelsson, J. Chem. Soc., Chem. Commun., **1979**, 978.
104. C. R. Haylock, L. D. Melton, K. N. Slessor, and A. S. Tracey, Carbohydr. Res., **16**, 375 (1971).
105. N. K. Kochetkov and A. I. Usov, Tetrahedron, **19**, 973 (1963).
106. K. Kato and O. Mitsunobu, J. Org. Chem., **35**, 4227 (1970).
107. O. Mitsunobu, J. Kimura, K. Inzumi, and N. Yanagida, Bull. Chem. Soc.

Jpn., **49**, 510 (1976).

108. R. Mengel and M. Bartke, Angew. Chem., Int. Ed. Engl., **17**, 679 (1978).
109. R. Boigegrain and B. Castro, Tetrahedron Lett., **1965**, 3459.
110. J. Kimura, Y. Fujisawa, T. Sawada, and O. Mitsunobu, Chem. Lett., **1974**, 691.
111. J. Kimura, Y. Hashimoto, and O. Mitsunobu, Chem. Lett., **1974**, 1473.
112. J. Kimura, K. Yagi, H. Suzuki, and O. Mitsunobu, Bull. Chem. Soc. Jpn., **53**, 3670 (1980).
113. H. R. Hudson, R. C. Rees, and J. E. Weekes, J. Chem. Soc., Chem. Commun., **1971**, 1297.
114. S. R. Landauer and H. N. Rydon, Chem. Ind. (Lond.), **1951**, 313.

114a A. Campbell and H. N. Rydon, Chem. Ind. (Lond.), **1951**, 312.

.

115. S. R. Landauer and H. N. Rydon, J. Chem. Soc., **1953**, 2224.
116. C. S. L. Baker, P. D. Landor, S. R. Landor, and A. N. Patel, J. Chem. Soc., **1965**, 4348.
117. N. K. Kochetkov, L. Z. Kudryasov, and A. Z. Uzov, Dokl. Akad. Nauk SSSR, **133**, 1091 (1960) [C.A., **55**, 27066i (1961)].
118. N. K. Kochetkov and A. I. Usov, Tetrahedron Lett., **1963**, 519.
119. K. S. Adamyants, N. K. Kochetkov, and A. I. Usov, Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transi.), **1967**, 1262.
120. J. P. H. Verheyden and J. G. Moffatt, J. Org. Chem., **35**, 2319 (1970).
121. J. P. H. Verheyden and J. G. Moffatt, J. Org. Chem., **35**, 2868 (1970).
122. J. P. H. Verheyden and J. G. Moffatt, J. Am. Chem. Soc., **86**, 2094 (1964).
123. J. P. H. Verheyden and J. G. Moffatt, J. Am. Chem. Soc., **88**, 5684 (1966).
124. J. P. H. Verheyden and J. G. Moffatt, J. Org. Chem., **37**, 2289 (1972).
125. J. P. H. Verheyden and J. G. Moffatt, J. Org. Chem., **39**, 3573 (1974).
126. S. D. Dimitrijevich, J. P. H. Verheyden, and J. G. Moffatt, J. Org. Chem., **44**, 400 (1979).
127. N. Kornblum and D. C. Iffland, J. Am. Chem. Soc., **77**, 6653 (1955).
128. J. B. Lee and M. M. El Sawi, Chem. Ind. (Lond.), **1960**, 839.
129. K. Kerfurt, J. Jary, and Z. Samek, J. Chem. Soc., D, **1969**, 213.
130. E. Santaniello, Gazz. Chim. Ital., **108**, 131 (1978).
131. R. O. Hutchins, M. G. Hutchins, and C. A. Milewski, J. Org. Chem., **37**, 4190 (1972).
132. E. S. Lewis, B. J. Walker, and L. M. Ziurys, J. Chem. Soc., Chem. Commun., **1978**, 424.

133. D. Brett, I. M. Downie, J. B. Lee, and M. F. S. Matought, Chem. Ind. (Lond.), **1969**, 1017.
134. D. G. Coe, S. R. Landauer, and H. N. Rydon, J. Chem. Soc., **1954**, 2281.
135. D. G. Coe, H. N. Rydon, and B. L. Tonge, J. Chem. Soc., **1957**, 323.
136. A. W. Franck and C. F. Baranaukas, J. Org. Chem., **31**, 872 (1966).
137. G. S. Harris and D. S. Payne, J. Chem. Soc., **1956**, 3038.
138. H. N. Rydon and B. L. Tonge, J. Chem. Soc., **1956**, 3043.
139. G. A. Wiley, R. L. Hershkowitz, B. M. Rein, and B. C. Chung, J. Am. Chem. Soc., **86**, 964 (1964).
140. L. Horner, H. Oediger, and H. Hoffmann, Justus Liebigs Ann. Chem., **626**, 26 (1959).
141. G. A. Wiley, B. M. Rein, and R. L. Hershkowitz, Tetrahedron Lett., **1964**, 2509.
142. L. Kaplan, J. Org. Chem., **31**, 3454 (1966).
143. M. E. Herr and R. A. Johnson, J. Org. Chem., **37**, 310 (1972).
144. R. A. Arain and M. K. Hargreaves, J. Chem. Soc., C. **1970**, 67.
145. K. Haga, M. Yoshikawa, and T. Kato, Bull. Chem. Soc. Jpn., **43**, 3922 (1970).
146. J. P. Schaeffer and J. Higgins, J. Org. Chem., **32**, 1607 (1967).
147. E. Piers and I. Nagakura, Synth. Commun., **5**, 193 (1975).
148. R. K. Boeckman, Jr., and B. Ganem, Tetrahedron Lett., **1974**, 913.
149. T. Dahl and R. Stevenson, J. Org. Chem., **36**, 3243 (1971).
150. P. Caubere and M. S. Mourad, Tetrahedron, **30**, 3439 (1974).
151. I. Okada, K. Ichimura, and R. Sudo, Bull. Chem. Soc. Jpn., **43**, 1185 (1970).
152. H. M. Relles and R. W. Schluenz, J. Am. Chem. Soc., **96**, 6469 (1974).
153. D. Brett, I. M. Downie, and J. B. Lee, J. Org. Chem., **32**, 855 (1967).
154. R. D. Birkenmeyer and F. Kagan, J. Med. Chem., **13**, 616 (1970).
155. E. H. Axelrod, G. M. Milne, and E. E. Van Tamelen, J. Am. Chem. Soc., **92**, 2139 (1970).
156. M. Anisuzzaman and R. L. Whistler, Carbohydr. Res., **61**, 511 (1978).
157. L. M. Beacham, J. Org. Chem., **44**, 3100 (1979).
158. S. David and G. de Sennyer, Carbohydr. Res., **77**, 79 (1979).
159. S. L. Regen and D. P. Lee, J. Org. Chem., **40**, 1669 (1975).
160. P. Hodge and G. Richardson, J. Chem. Soc., Chem. Commun., **1975**, 622.
161. C. R. Harrison and P. Hodge, J. Chem. Soc., Chem. Commun., **1978**, 813.

162. R. M. Magid, O. S. Fruchey, and W. L. Johnson, Tetrahedron Lett., **1977**, 2999.
163. P. J. Garregg and B. Samuelsson, Synthesis, **1979**, 813.
164. T. Hata, I. Yamamoto, and M. Sekine, Chem. Lett., **1975**, 977.
165. J. C. Florent, C. Monneret, and Q. Khuong-Huu, Tetrahedron, **34**, 909 (1978).
166. A. V. Azhayev, A. A. Krayevsky, and J. Smrt, Coll. Czech. Chem. Commun., **44**, 792 (1979).
167. I. Yamamoto, M. Sekine, and T. Hata, J. Chem. Soc., Perkin Trans. 1, **1980**, 306.
168. T. Adachi, Y. Arai, and I. Inoue, Carbohydr. Res., **78**, 66 (1980).
169. R. Appel and R. Kleinstück, Chem. Ber., **107**, 5 (1974).
170. H. Fukase, N. Mizokami, and S. Horii, Carbohydr. Res., **60**, 289 (1978).
171. T. Kametani, Y. Rigawa, and M. Ihara, Tetrahedron, **35**, 313 (1979).
172. V. Stoilava, L. S. Trifonov, and A. S. Orahovats, Synthesis, **1979**, 105.
173. D. Barbry, D. Couturier, and G. Ricart, Synthesis, **1980**, 387.
174. G. W. Erickson and J. L. Fry, J. Org. Chem., **45**, 970 (1980).
175. A. Mizumo, Y. Hamada, and T. Shioiri, Synthesis, **1980**, 1007.
176. R. Appel and H. D. Wihler, Chem. Ber., **109**, 3446 (1976).
177. Y. Kashman and A. Groweiss, J. Org. Chem., **45**, 3814 (1980).
178. E. E. Schweizer, W. S. Creazy, K. K. Light, and E. T. Schaffer, J. Org. Chem., **34**, 212 (1969).
179. M. M. Ponpipom and S. Hanessian, Carbohydr. Res., **18**, 342 (1971).
180. S. Hanessian, M. M. Ponpipom, and P. Lavallée, Carbohydr. Res., **24**, 45 (1972).
181. S. Hanessian, R. Massé, and M. L. Capmeau, J. Antibiot., **30**, 893 (1977).
182. S. Hanessian and P. Lavallée, Carbohydr. Res., **28**, 303 (1973).
183. S. Hanessian and P. Lavallée, J. Antibiot., **25**, 683 (1972).
184. S. Hanessian, D. Ducharme, R. Massé, and M. L. Capmau, Carbohydr. Res., **63**, 265 (1978).
185. A. K. Bose and B. Lal, Tetrahedron Lett., **1973**, 3937.
186. W. Ried and H. Appel, Chem. Ber., **679**, 51 (1964).
187. I. M. Downie, J. B. Lee, and M. F. S. Matough, J. Chem. Soc., Chem. Commun., **1968**, 1350.
188. B. Castro and C. Selve, Bull. Soc. Chim. Fr., **1971**, 2296.
189. B. Castro and C. Selve, Bull. Soc. Chim. Fr., **1971**, 4368.
190. B. Castro, M. Ly, and C. Selve, Tetrahedron Lett., **1973**, 4455.

191. B. Castro, Y. Chapleur, and B. Gross, Tetrahedron Lett., **1974**, 2313.
192. B. Castro and C. Selve, Bull. Soc. Chim. Fr., Part 2, **1974**, 3004.
193. B. Castro and C. Selve, Bull. Soc. Chim. Fr., Part 2, **1974**, 3009.
194. I. M. Downie, H. Heaney, and G. Kemp, Tetrahedron Lett., **1975**, 3951.
195. R. E. Ireland, S. Thaisrivongs, N. Vanier, and C. S. Wilcox, J. Org. Chem., **45**, 48 (1980).
196. P. Simon, J. C. Ziegler, and B. Gross, Synthesis, **1979**, 951.
197. F. Chrétien, Thesis, University of Nancy, 1977.
198. R. A. Boigegrain, B. Castro, and B. Gross, Bull. Soc. Chim. Fr., **1974**, 2623.
199. F. Chrétien, Y. Chapleur, B. Castro, and B. Gross, J. Chem. Soc., Perkin Trans. 1, **1980**, 381.
200. F. Chrétien, B. Castro, and B. Gross, Synthesis, **1979**, 937.
201. B. Castro, Y. Chapleur, and B. Gross, Bull. Soc. Chim. Fr., Part 2, **1973**, 3034.
202. R. Toubiana, C. Pizza, Y. Chapleur, and B. Castro, J. Carbohydr., Nucleosides, Nucleotides, **5**, 127 (1978).
203. B. Castro and C. Selve, Tetrahedron Lett., **1973**, 4459.
204. R. Boigegrain and B. Castro, Tetrahedron, **32**, 1283 (1976).
205. R. Boigegrain and B. Castro, J. Carbohydr., Nucleosides, Nucleotides, **3**, 335 (1976).
206. R. B. Silverman and M. A. Levy, J. Org. Chem., **45**, 815 (1980).
207. W. Schörkhuber and E. Zbiral, Justus Liebigs Ann. Chem., **1980**, 1455.
208. P. G. Mattingly, J. F. Kerwin, Jr., and M. J. Miller, J. Am. Chem. Soc., **101**, 3983 (1979).
209. A. K. Bose, D. P. Sahu, and M. S. Manhas, J. Org. Chem., **46**, 1229 (1981).
210. G. Grynkiewicz, Pol. J. Chem., **53**, 2501 (1979).
211. H. Redlich and W. Francke, Angew. Chem., Int. Ed. Engl., **19**, 630 (1980).
212. H. Redlich, B. Schneider, and W. Francke, Tetrahedron Lett., **1980**, 3013.
213. K. Tomioka and K. Koga, Tetrahedron Lett., **1980**, 2321.
214. M. Asaoka, N. Yanagida, and H. Takei, Tetrahedron Lett., **1980**, 4611.
215. R. Hohlbrugger and W. Klötzer, Chem. Ber., **112**, 3486 (1979).
216. R. J. Bass, B. J. Banks, and M. Snarey, Tetrahedron Lett., **1980**, 769.
217. K. Akerfelot, P. J. Garregg, and T. Iverson, Acta Chem. Scand., Ser. B, **1979**, 1815.
218. O. Mitsunobu, T. Kudo, M. Nishida, and N. Tsuda, Chem. Lett., **1980**,

1614.

219. A. Campbell and H. N. Rydon, Chem. Ind. (Lond.), **1951**, 312.

220. M. McCoss, E. K. Ryu, R. S. White, and R. L. Last, J. Org. Chem., **45**, 788 (1980).

220a. P. L. Durette, Synthesis, **1980**, 1037.

221. J. B. Lee and T. J. Nolan, Can. J. Chem., **44**, 1331 (1966).

222. J. Hooz and S. S. H. Gilani, Can. J. Chem., **46**, 86 (1968).

223. J. B. Lee and I. M. Downie, Tetrahedron, **23**, 359 (1967).

224. E. I. Snyder, J. Org. Chem., **37**, 1466 (1972).

225. J. B. Heather, R. S. D. Mittal, and C. J. Sih, J. Am. Chem. Soc., **98**, 3661 (1971).

226. H. L. Goering and S. L. Trenbeath, J. Am. Chem. Soc., **98**, 5016 (1976).

227. I. Tomoskozi, L. Gruber, and L. Radics, Tetrahedron Lett., **1975**, 2473.

228. G. Stork, M. E. Jung, E. Calvin, and Y. Noel, J. Am. Chem. Soc., **96**, 3684 (1974).

229. A. W. Friederang and D. S. Tarbell, J. Org. Chem., **33**, 7797 (1968).

230. R. G. Weiss and E. I. Snyder, J. Chem. Soc., Chem. Commun., **1968**, 1358.

231. P. J. Kocienski, G. Cornigliaro, and G. Feldstein, J. Org. Chem., **42**, 353 (1977).

232. R. D. Miller, M. Schneider, and D. L. Dolce, J. Am. Chem. Soc., **95**, 8469 (1973).

233. T. C. Jain, D. Jenkins, A. F. Russel, J. D. H. Verheyden, and J. G. Moffat, J. Org. Chem., **39**, 30 (1974).

234. L. B. Hunt, D. F. MacSweeny, and R. Ramage, Tetrahedron, **27**, 1491 (1971).

235. E. E. van Tamelen and R. J. Anderson, J. Am. Chem. Soc., **94**, 8225 (1972).

236. J. J. Baldwin, A. W. Raab, K. Mensler, B. H. Arison, and D. E. McClure, J. Org. Chem., **43**, 4876 (1978).

237. R. Aneja and A. P. Davies, J. Chem. Soc., Perkin Trans. 1, **1974**, 141.

238. F. G. de la Heras, R. Alonson, and G. Alonso, J. Med. Chem., **22**, 496 (1979).

239. C. W. Chiu and R. L. Whistler, J. Org. Chem., **38**, 832 (1973).

240. R. A. Houghten, R. A. Simpson, R. N. Hanson, and H. Rapoport, J. Org. Chem., **44**, 4536 (1979).

241. B. T. Lawton, W. A. Szarek, and J. K. N. Jones, Carbohydr. Res., **14**, 255 (1970).

242. R. S. Klein, H. Ohrui, and I. J. Fox, J. Carbohydr., Nucleosides, Nucleotides, **1975**, 265.
243. R. Aneja, A. P. Davies, and J. A. Knaggs, J. Chem. Soc., Chem. Commun., **1973**, 110.
244. S. Trippett, J. Chem. Soc., **1962**, 2337.
245. J. D. Morrison, J. E. Tomaszewski, H. S. Mosher, J. Dale, D. Miller, and R. L. Elsenbaumer, J. Am. Chem. Soc., **99**, 3167 (1977).
246. F. Arcamone, A. Bargiotti, G. Cassinelli, S. Penco, and S. Hanessian, Carbohydr. Res., **46**, C3 (1976).
247. H. E. Hadd, Steroids, **31**, 453 (1978).
248. B. Castro, Y. Chapleur, B. Gross, and C. Selve, Tetrahedron Lett., **1972**, 5001.
249. R. Boigegrain, B. Castro, and C. Selve, Tetrahedron Lett., **1975**, 2529.
250. A. Canas-Rodriguez, A. Martinez-Tobed, A. Gomez-Sanchez, and C. Martin-Madero, Carbohydr. Res., **56**, 289 (1977).
251. R. Boigegrain, Thesis, University of Nancy, 1975.
252. A. Canas-Rodriguez and A. Martinez-Tobed, Carbohydr. Res., **68**, 43 (1979).
253. I. M. Downie, H. Heaney, and G. Kemp, Angew. Chem., Int. Ed. Engl., **14**, 370 (1975).
254. P. Simon, J. C. Ziegler, and B. Gross, Carbohydr. Res., **64**, 257 (1978).