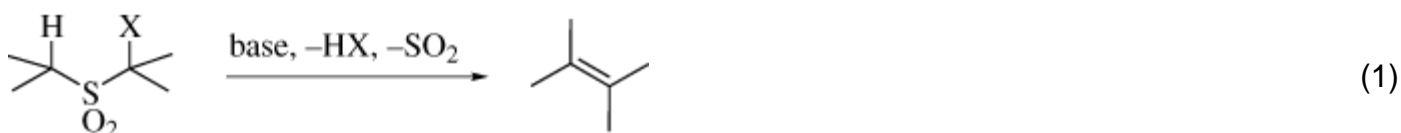


The Ramberg-Bäcklund Reaction

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1. Introduction

The base-mediated conversion of α -halosulfones into regio-defined alkenes was first described by Ludwig Ramberg and Birger Bäcklund. (1) This transformation, generalized in Eq. 1, has proved to be of wide synthetic value and is now known as the Ramberg-Bäcklund reaction. (Also referred to as the Ramberg-Bäcklund rearrangement, and abbreviated herein as RBR).



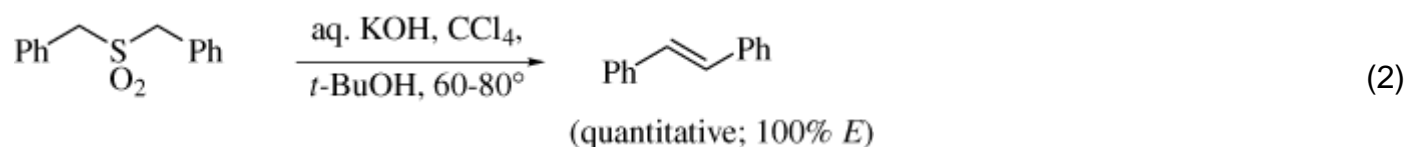
The facile nature of the RBR is surprising given the difficulties encountered when attempting to carry out nucleophilic substitution reactions on α -halosulfones. (2) In contrast to halogens adjacent to carbonyls and related electron-withdrawing groups, (3) polar, steric, and field effects appear to combine leading to the marked deactivation of α -halosulfones. The stereochemical outcome of the reaction was also unexpected: a predominance of Z-alkenes is often observed with relatively weak bases (e.g. sodium hydroxide) whereas stronger bases [e.g. potassium *tert*-butoxide] tend to favor E-alkenes. The mechanism of the RBR was therefore the subject of intense interest, particularly in the 1950's and 1960's; mechanistic aspects are reviewed in the next section.

From the synthetic viewpoint, the RBR is attractive for a number of reasons:

- i. The accessibility of the precursor sulfides and sulfones,
- ii. The conjunctive nature of the process,
- iii. The unambiguous location of the resulting double bond,
- iv. The absence of alkene rearrangement processes due to the alkaline reaction conditions,
- v. The applicability of the procedure to all alkene substitution patterns including tetra-substituted variants,
- vi. The efficiency with which strained alkenes such as cyclobutenes and cyclophanes can be prepared,
- vii. The availability of polyenes via the RBR,
- viii. The availability of deuterated alkenes by carrying out the RBR in deuterated solvents,
- ix. The applicability of the procedure to complex, multifunctional molecules, provided certain base-sensitive groups are absent or protected.

Organic sulfones are readily available but the preparation of α -halosulfones can be problematic. In view of this, perhaps the most significant synthetic advance concerning the RBR has been the development of Meyers' modification, (4) which involves an in situ halogenation-RBR sequence and enables sulfones to be converted directly into alkenes. This procedure therefore avoids the need to prepare α -halogenated sulfones in advance. Eq. 2 shows one of the first examples of this type: first,

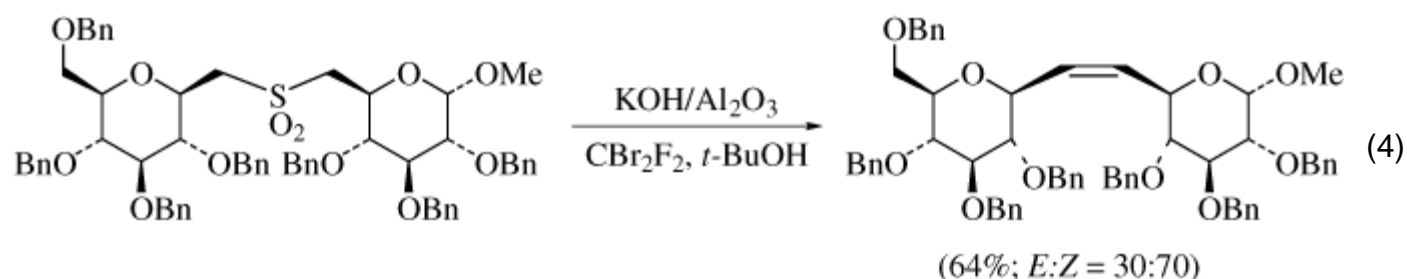
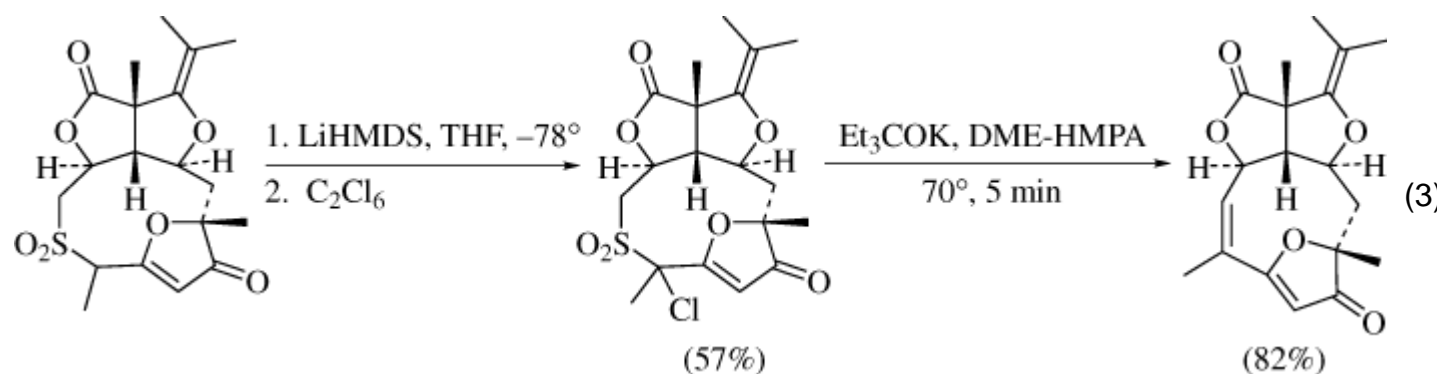
the α -sulfonyl anion undergoes halogenation by the solvent; the product then undergoes cyclization and subsequent olefin formation in the normal manner.



The following sections discuss the mechanism of the RBR, its scope and limitations, applications of the reaction in natural product synthesis, and comparison of the RBR with related procedures. Representative experimental procedures are also given.

The RBR has been well reviewed over the years, (5-7) the seminal contribution being the *Organic Reactions* chapter by Paquette. (5) The aim of the current chapter is to update the Paquette review with minimal duplication. Particular emphasis is therefore given to major developments in the reaction since 1977 as well as to the isolation and synthetic utility of thiirane dioxides. The Tabular Survey covers all publications since the previous review in *Organic Reactions*. For a comprehensive listing of published RBR processes, therefore, both Chapters should be consulted.

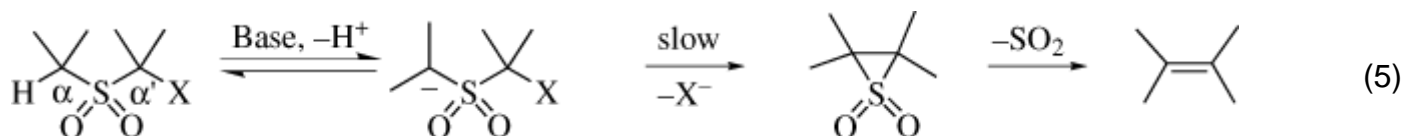
To conclude this introductory section, two examples are included to illustrate the utility of the RBR. Eq. 3 shows the key RBR of a pre-formed α -halosulfone during a synthesis of the antitumor natural product eremantholide A, (8) and Eq. 4 shows the use of the Meyers modification, en route to methyl C-gentiobioside. (9)



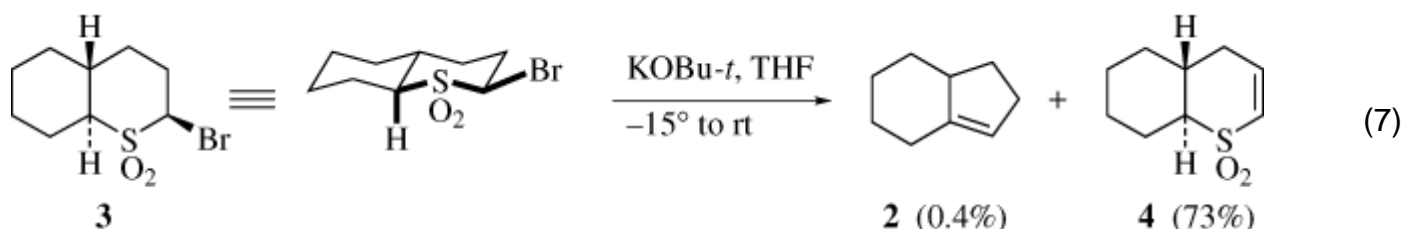
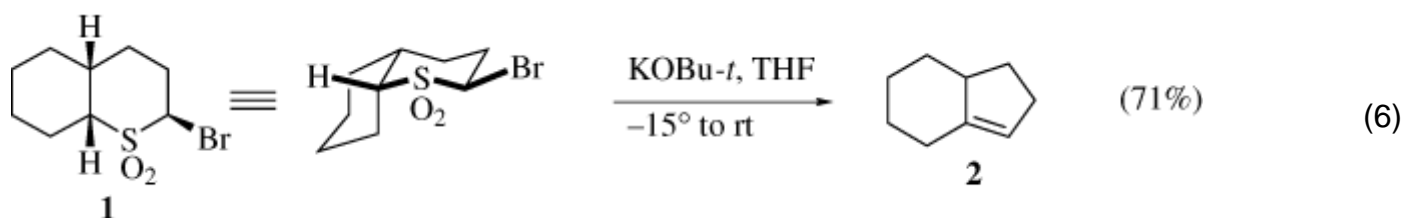
2. Mechanism and Stereochemistry

Extensive studies have been carried out to elucidate the mechanism of the RBR and these investigations have been well reviewed. (5, 10-13) Thus, only an overview will be presented here, with emphasis on advances reported after 1977.

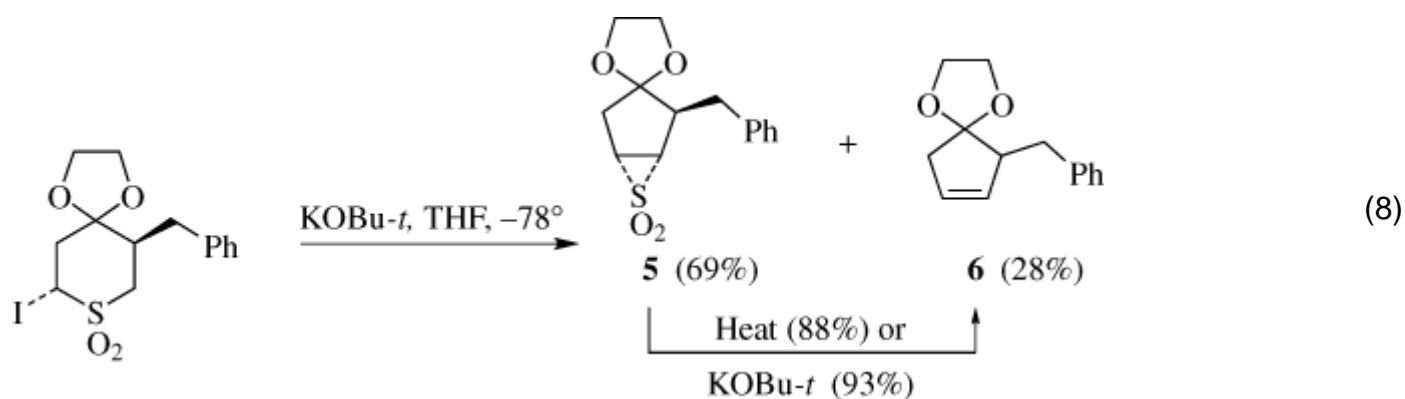
The intermediacy of thiirane dioxides (episulfones) was first proposed in 1951. (2) Later studies confirmed this hypothesis and produced the generally accepted anionic mechanism for the RBR shown in Eq. 5. Other proposals, such as carbenoid and dipolar mechanisms, were considered but dismissed after experimentation. (12, 14)



Thus, rapid and reversible formation of the α -sulfonyl anion (which is in equilibrium with the α^- -anion if the substrate can form one) is followed by the rate-determining step, the loss of halide in a 1,3-cyclization process (with $k_1 > k_{Br} > k_{Cl}$), generating the thiirane dioxide intermediate. The intramolecular nature of this process ensures that the carbanionic center is remote from the polar sulfonyl oxygens (15) and therefore avoids the unfavorable electronic factors present in the intermolecular displacements of α -halosulfones. (2) There is a stereoelectronic preference for the so-called "W-plan" co-planar arrangement of the proton and leaving group adjacent to the sulfonyl group. This is nicely shown in Eqs. 6 and 7. (16) The cis-fused system **1**, which possesses the W-plan arrangement, undergoes facile RBR giving alkene **2**, whereas with the trans-fused isomer **3** the major product **4** results from 1,2-elimination. It should be noted that inversion of configuration at both reacting centers is required to convert **1** into the corresponding thiirane dioxide.

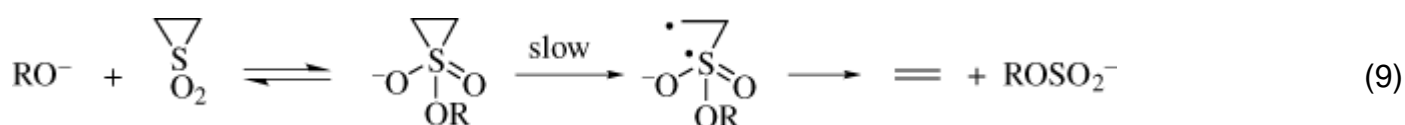


Indirect support for the intermediacy of thiirane dioxides was obtained by first preparing them by other procedures, and then showing that they are converted into alkenes under the conditions of the RBR. (17-19) However, in 1989 it was shown that treatment of α -iodothiirane dioxides with bases at low temperature gives thiirane dioxides as the major products (Eq. 8). (20, 21) Heating thiirane dioxide **5**, or treating it with potassium *tert*-butoxide, converts **5** into the expected RBR alkene product **6**. Further aspects of the formation and reactivity of thiirane dioxides are discussed later.



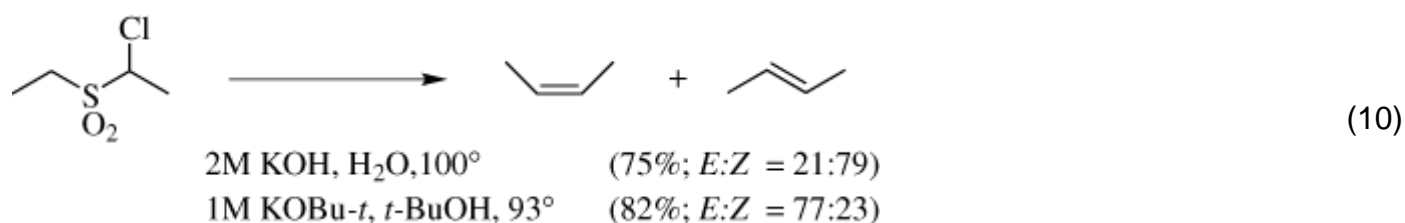
The conversion of thirane dioxides into alkenes has been well studied and reviewed. (22) In general, on heating (usually in the range between room temperature and 110°) thirane dioxides lose sulfur dioxide to give the corresponding alkenes in a stereospecific process. There have been a number of mechanistic proposals for this thermal desulfonylation reaction. (12, 19, 23, 24) Concerted, linear cheletropic loss is symmetry forbidden and therefore dipolar and diradical stepwise mechanisms were initially considered, with the proviso that loss of sulfur dioxide must occur at a faster rate than rotation around the carbon-carbon bond in order to accommodate the observed stereospecificity. The intermediacy of 1,3-diradicals possessing significant rotational barriers is consistent with experimental evidence, (19) and this mechanism was advocated by Bordwell et al. (19) However, Woodward and Hoffman subsequently stated that “the available evidence is also consistent with the view that the elimination follows the concerted symmetry-allowed non-linear cheletropic pathway” (23) and more recent theoretical studies are in accord with this statement. (25)

The rate of thirane dioxide decomposition is increased by base (19) and in general the reactions are stereospecific when hydroxide ion is employed. Again, there have been numerous mechanistic proposals; (12, 19, 24, 26, 27) Bordwell's mechanism is shown in Eq. 9. (19) The initial step, involving addition to the sulfone group, now seems to be generally accepted. (26, 27) Whether the subsequent decomposition occurs via a rotationally restricted diradical anionic intermediate as shown, or via a non-linear cheletropic extrusion from the initially formed hypervalent intermediate, (23) still has to be confirmed.

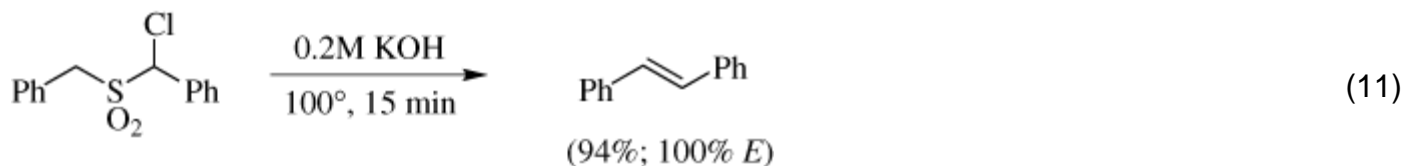


2.1. Stereoselectivity

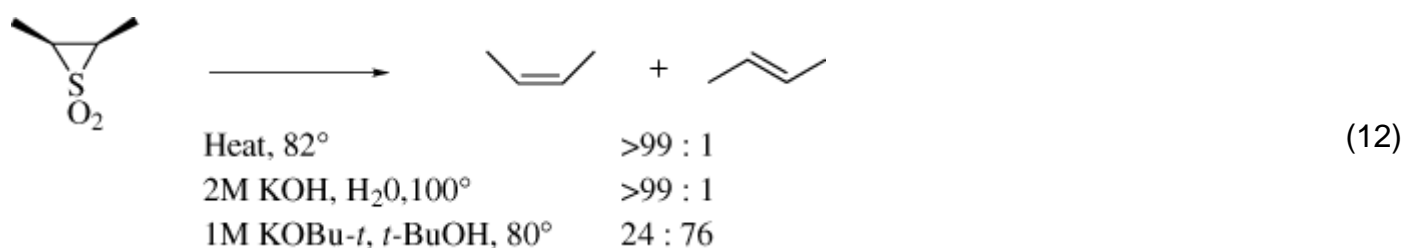
The original publication made the surprising claim that Z-alkenes predominate from the treatment of α -bromoethyl and α -bromopropyl ethyl sulfone. These observations were later confirmed and extended to other sulfones. In the same study, it was established that the E:Z ratio is remarkably consistent over a range of solvents and bases. However, when the strong base potassium *tert*-butoxide in *tert*-butanol (or toluene) is employed there is a dramatic change and the E-isomer predominates, as shown in Eq. 10. (17)



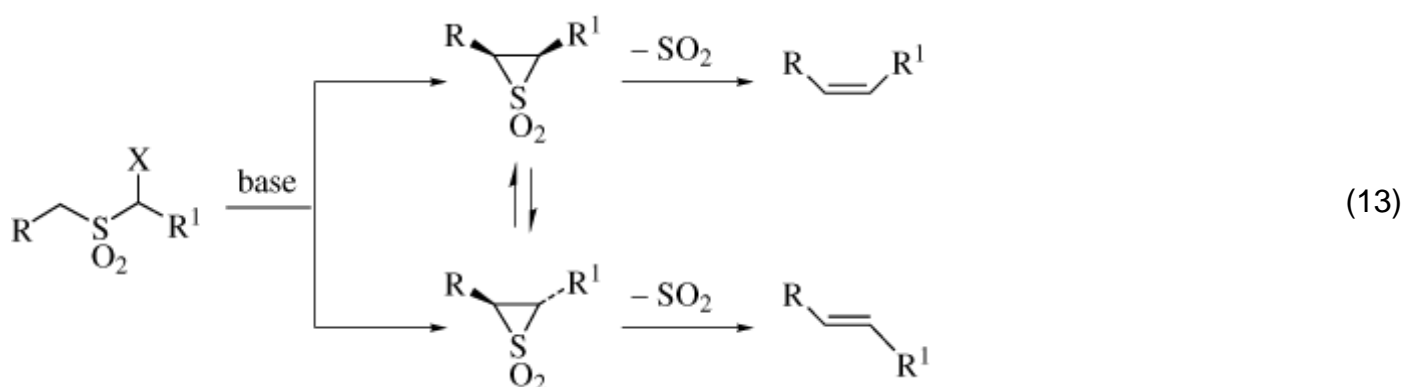
A second anomaly is that α -chlorobenzyl benzyl sulfone was reported to give only (*E*)-stilbene on treatment with hydroxide as shown in Eq. 11. (2)



In order to solve this stereochemical conundrum, experiments were carried out on isolated thiirane dioxides. (17-19) Thus, with *cis*-1,2-dimethylthiirane dioxide, thermolysis or treatment with hydroxide gives only (*Z*)-but-2-ene, whereas treatment with *tert*-butoxide gives predominantly the *E*-alkene (Eq. 12). (17) With *cis*-1,2-diphenylthiirane dioxide, thermal decomposition is again stereospecific but treatment with hydroxide or methoxide yields predominantly (*E*)-stilbene. (19, 24)

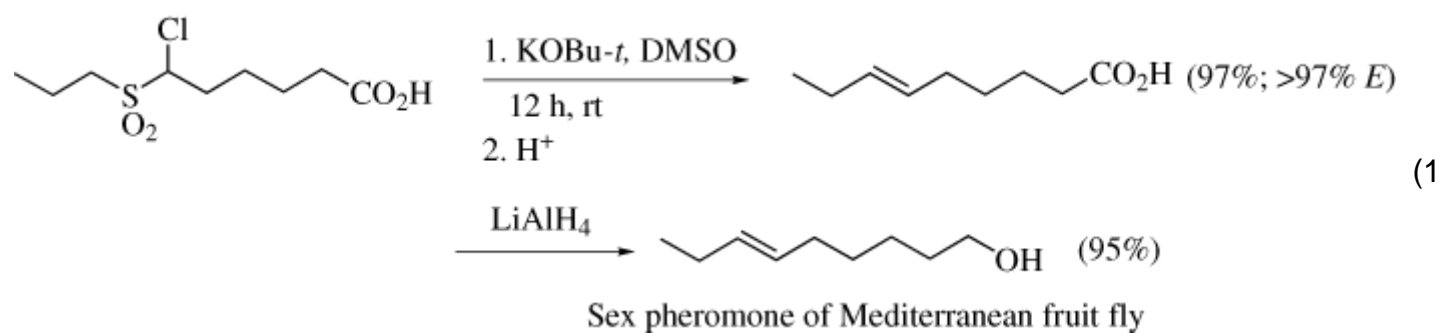


These results have been rationalized as shown in Eq. 13. In most reactions, the ratio of the *trans*- and *cis*-disubstituted thiirane dioxide established in the intramolecular cyclization step is reflected in the final *E*:*Z*-alkene ratio since the thermal or base-mediated loss of sulfur dioxide from the thiirane dioxide intermediates occurs in a stereospecific manner. However, when a stronger base such as *tert*-butoxide is employed, or when there are additional acidifying substituents (e.g. phenyl) attached to the thiirane dioxide, epimerization can occur to favor the *trans*-disubstituted thiirane dioxide and ultimately the *E*-alkene.



Of course, the question remains as to why *cis*-disubstituted thiirane dioxides predominate in the cyclization step. Various theories (including preferential formation of one diastereomeric carbanion, attractive dispersion forces, and steric attraction theory) have been put forward to explain this “*cis* effect” (10-12, 17, 25, 28) but a definitive explanation is still required. The reader is referred to these articles and reviews for more detailed discussions.

In recent studies, the above mechanistic suggestions concerning thiirane dioxide isomerization have been confirmed in more complex systems (29-31) and exploited synthetically. Eq. 14 illustrates this in the stereoselective preparation of an insect pheromone. (32)



3. Scope and Limitations

3.1. Preparation of α -Halosulfones for the Classical RBR

The classical method (as opposed to the Meyers variant) utilizes pre-formed α -halosulfones. Preparative routes to these compounds are well reviewed by Paquette and elsewhere. (5, 33, 34) This section will therefore provide just an overview of the standard methods, with more detailed coverage of the more recently developed procedures.

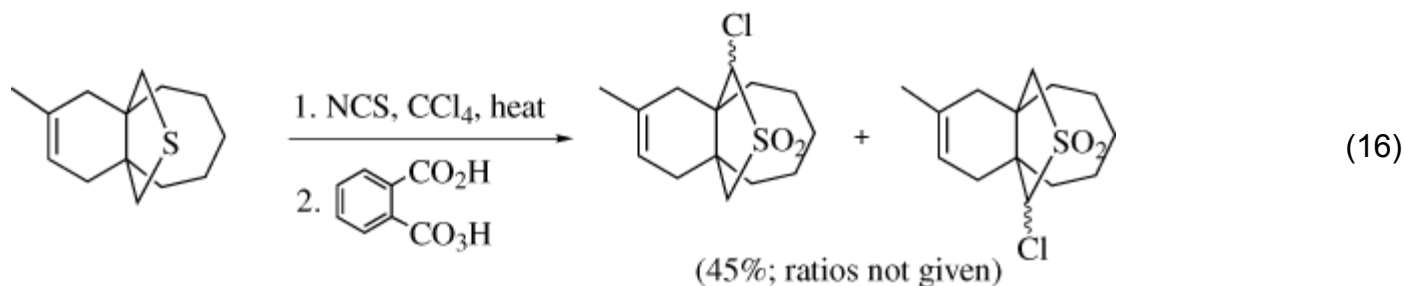
3.1.1. Preparation and Oxidation of α -Chlorosulfides

The most commonly employed procedure for the preparation of α -chlorosulfones involves chlorination of the corresponding sulfide followed by direct oxidation of the intermediate α -chlorosulfide. A recent example is illustrated in Eq. 15. (35)



The sulfide halogenation is usually carried out using *N*-chlorosuccinimide (NCS), although other electrophilic chlorine donors such as chlorine, sulfuryl chloride, and Chloreal^z (trichloroisocyanuric acid) can also be employed. Further details of these procedures, together with mechanistic discussions, are available in review articles. (5, 33) Other routes to α -chlorosulfides include the condensation of an aldehyde and a thiol in the presence of hydrogen chloride, the reactions of diazocarbonyl compounds with sulfenyl chlorides, and Pummerer-type rearrangements of sulfoxides. These alternative approaches have been reviewed. (5, 33)

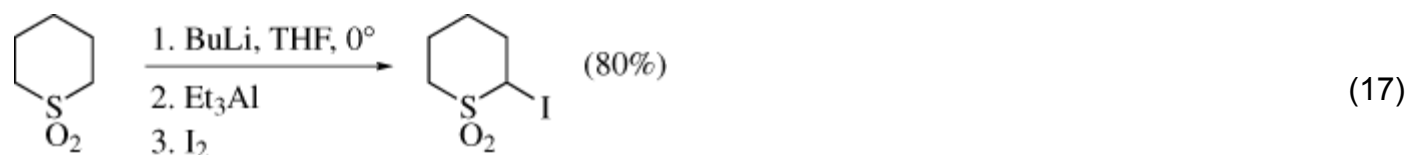
The intermediate α -chlorosulfides are extremely susceptible to hydrolysis and so are usually oxidized directly using anhydrous conditions. A range of oxidants has been used (5) but *m*-chloroperoxybenzoic acid (*m*-CPBA) in chloroform or dichloromethane solution is most commonly employed (ethereal monoperoxyphthalic acid was used in a number of early studies). Sulfides undergo rapid oxidation and double bonds are usually unaffected (Eq. 16). (36)



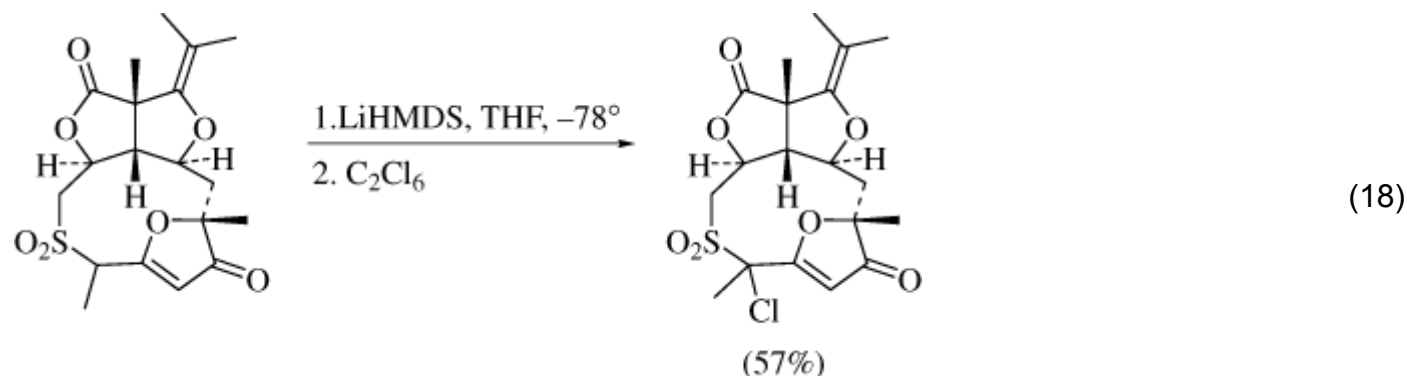
3.1.2. Halogenation of α -Sulfonyl Carbanions

The halogenation of α -sulfonyl carbanions has also been widely used to prepare RBR precursors, although the procedure has been less popular in recent years with the advent of the Meyers modification and the use of more densely functionalized substrates. Butyllithium is most often employed to deprotonate sulfones lacking additional acidifying groups, and a range of halogenating reagents have been employed [e.g. NCS, trichloromethanesulfonyl chloride, bromine, *N*-bromosuccinimide (NBS), 2-bromo-2,2-dimethyl-1,3-dioxan-4,6-dione, iodine, cyanogen bromide]; these reactions have been well reviewed. (5) An iodination example is shown in Eq. 17,

(37) the modification using alanate intermediates (38) having proved useful. (37, 39)



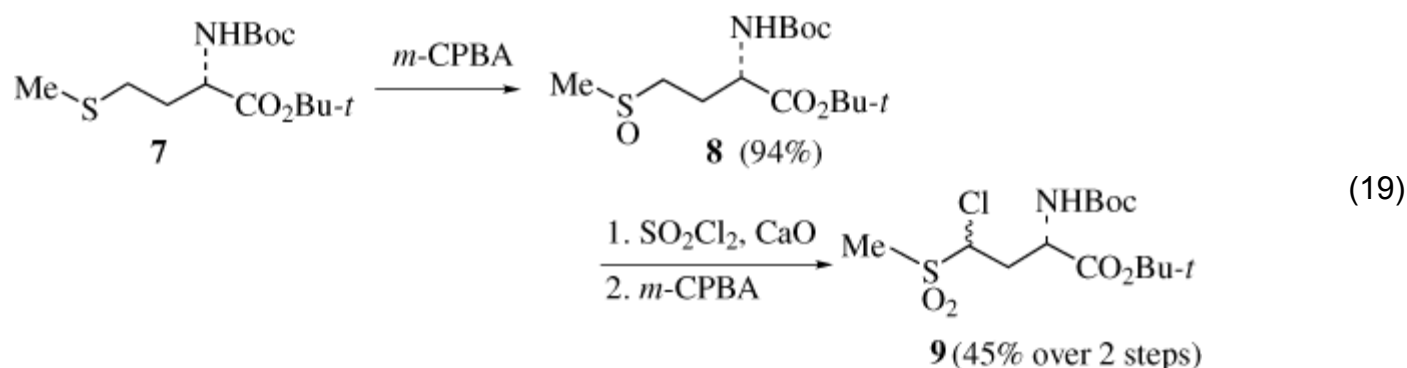
Hexachloroethane has been employed as chlorinating agent in two more recent examples. (8, 40) In the case shown, the α -sulfonyl proton is doubly activated and an amide base was sufficient for deprotonation (Eq. 18). (8)



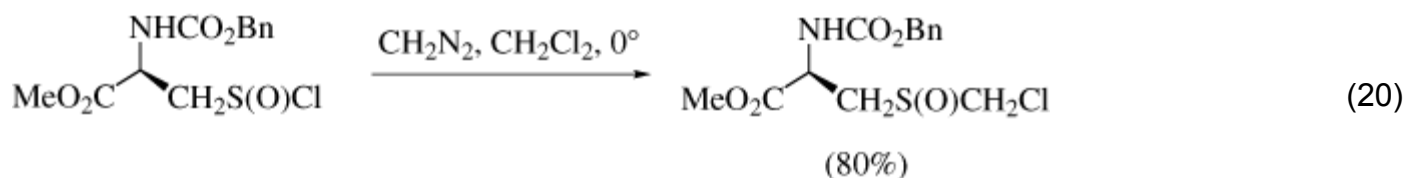
3.1.3. Other Methods

3.1.3.1. Via α -Halosulfoxides

In certain systems the preferred route to α -halosulfones has involved proceeding by initial chlorination of the corresponding sulfoxides following Durst's procedure. (41) Thus, the conversion of methionine derived sulfide **7** into α -chlorosulfone **9** is carried out by initial oxidation to sulfoxide **8** and then chlorination using sulfuryl chloride followed by a second oxidation step (Eq. 19). (42) The corresponding sequence proceeding via the α -chlorosulfide was non-reproducible and the route via α -sulfonyl anion chlorination was unsuccessful. A similar sequence was employed in the preparation of enediyne precursors. (43)

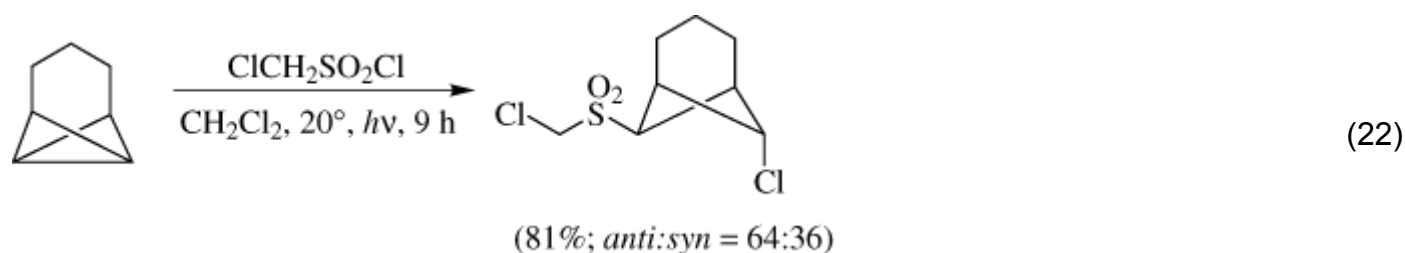
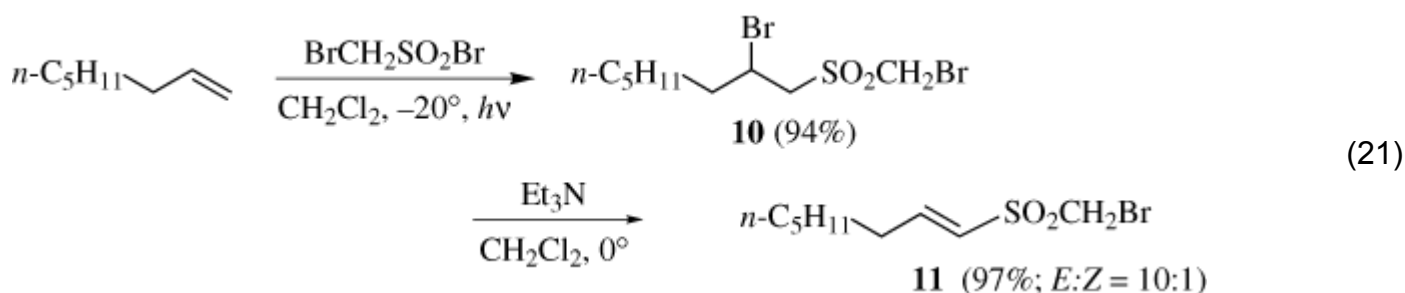


α -Chlorosulfoxides can also be prepared by treatment of readily available sulfinyl chlorides (44, 45) with diazomethane (Eq. 20). (45)



3.1.3.2. Via Sulfonyl Halide Addition Reactions

The photochemical addition of bromomethanesulfonyl bromide to alkenes provides a convenient route to α -bromosulfones (Eq. 21). (46-48) The initially formed dibromides **10** are usually converted into vinyl sulfones **11**, which are employed as precursors for the vinylogous RBR. A similar sequence has been applied to tricycloheptanes (Eq. 22). (49-51) In this system, both bromomethanesulfonyl bromide and chloromethanesulfonyl chloride are employed in the addition step.



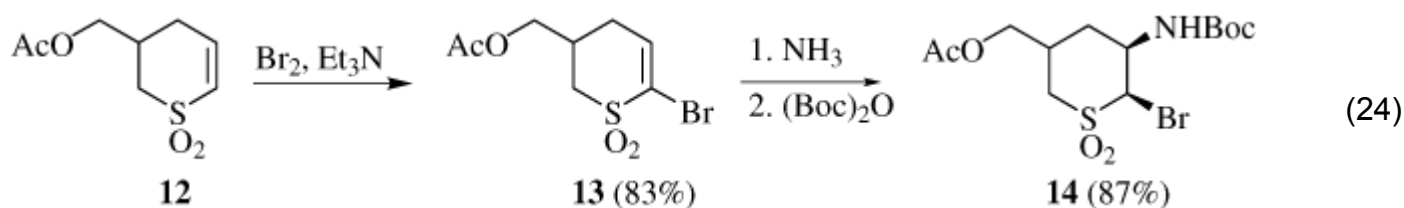
3.1.3.3. Via α,β -Unsaturated Sulfones

γ -Keto- α,β -unsaturated sulfones are readily converted into α -halosulfonyl ketals by treatment with a trimethylsilyl halide and an alcohol or a diol (Eq. 23). (21, 52) This process works most efficiently with trimethylsilyl iodide, and the resulting α -iodosulfones undergo the RBR at low temperatures. This methodology has been used to prepare the natural product tetrahydrodicranenone B. (52) In addition, the intermediate α -iodosulfones may be transformed into isolable thiirane dioxides on treatment with one equivalent of base at low temperatures. (21)



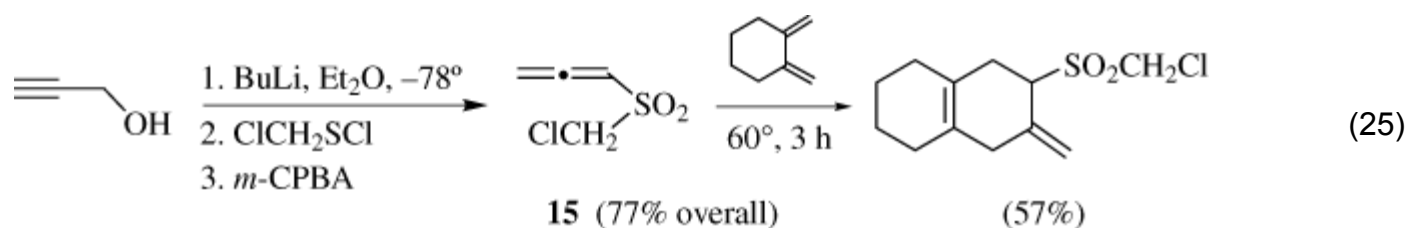
In a related approach, vinyl sulfone **12** is converted into bromovinyl derivative **13**, which undergoes

an efficient conjugate addition reaction with ammonia giving Ramberg-Bäcklund precursor **14** after *N*-protection (Eq. 24). (53) It should be noted that addition of ammonia to **12** is much slower (5 days vs 3 hours). This methodology has been extended to develop a tandem conjugate addition-RBR sequence. (54)

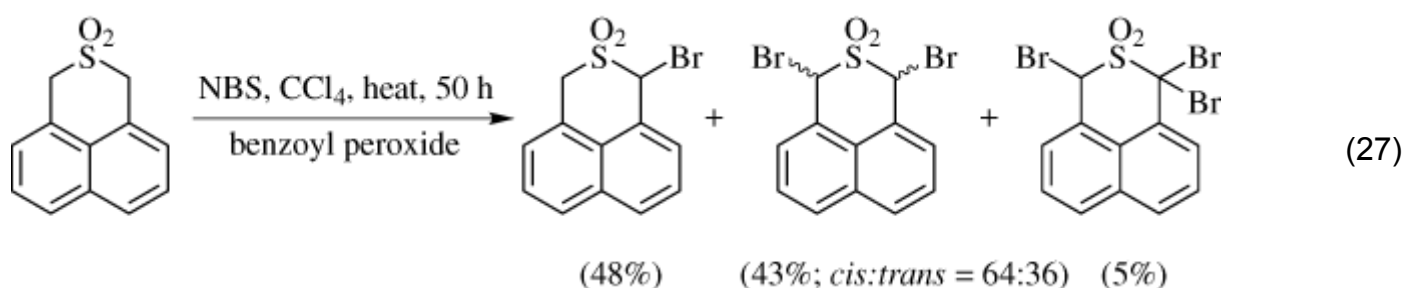
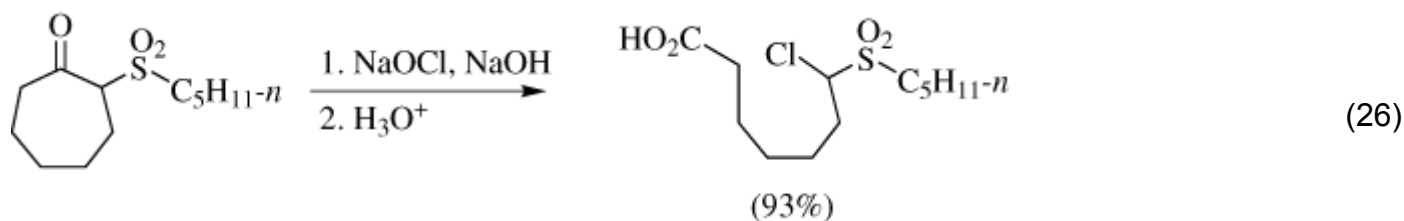


3.1.3.4. Miscellaneous Methods

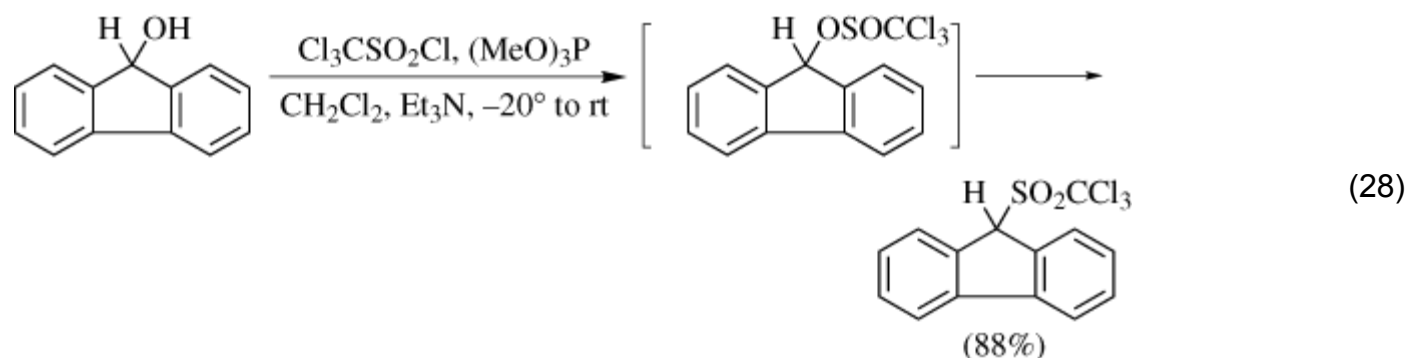
A number of other preparative routes to α -halosulfones have been employed on a more limited basis. The halogenative decarboxylation of α -carboxyalkyl sulfones, the reaction of sodium arylsulfonates with dihalocarbenes, the reactions of halosulfenes with diazoalkanes, and Diels-Alder reactions of α -bromovinyl sulfones are covered in Paquette's review. (5) A more recent Diels-Alder approach to the requisite α -chlorosulfones is shown in Eq. 25. (55) The allenyl α -chlorosulfone **15** is prepared from the corresponding sulfoxide, which in turn is obtained from propargyl alcohol by a [2,3]-sigmatropic process. A related Diels-Alder approach to trichlorosulfones has also been reported. (56)



Another little-used, but potentially useful, procedure is the halogenative ring opening of β -keto sulfones (Eq. 26). (32, 57, 58) The free-radical bromination of benzylic sulfones has also been employed occasionally (59, 60) and an example is shown in Eq. 27. (60)



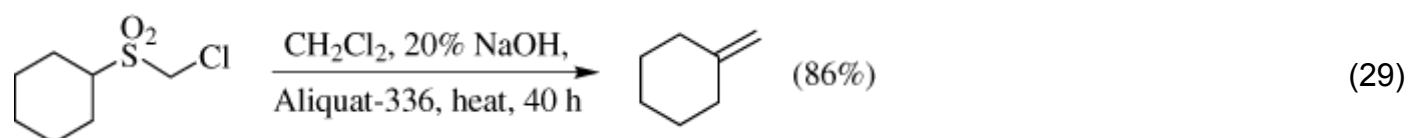
Di- and trihalosulfones are usually prepared by sequential sulfide halogenation followed by oxidation. (61, 62) Trichloromethylsulfones have also been prepared by rearrangement of the corresponding trichloromethanesulfinates: these can be obtained by reaction of the alcohol with trichloromethanesulfinyl chloride generated in situ from the sulfonyl chloride and trimethyl phosphite (Eq. 28). (63)



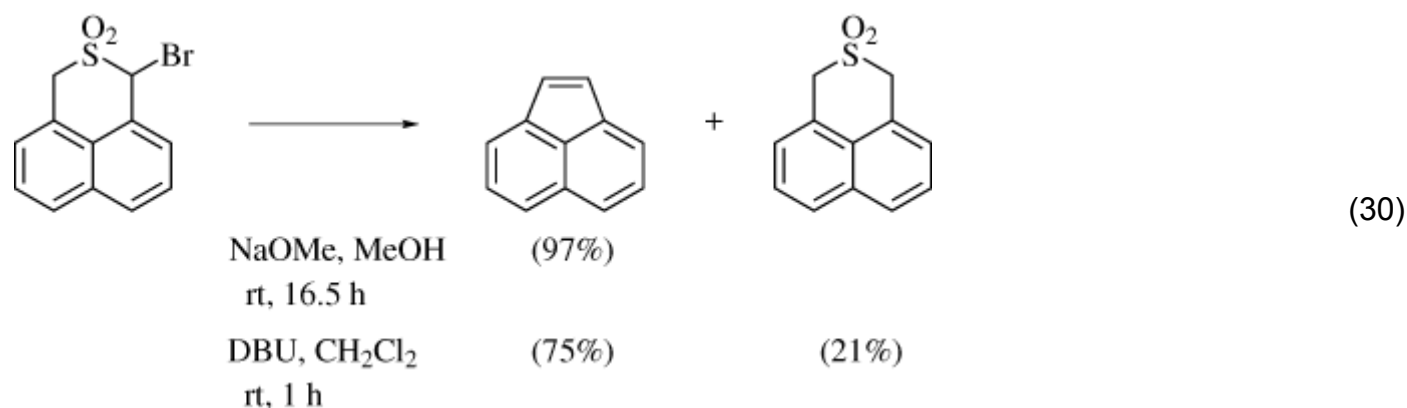
3.2. RBR of α -Halosulfones

3.2.1. Reaction Conditions

The original conditions employed (1) involved heating the α -halosulfones in aqueous potassium hydroxide at 100°. Solubility is often a problem under these conditions although dioxane can be used as a cosolvent. (49-51, 64) Alternatively, phase transfer conditions (58, 65, 66) can be employed as shown in Eq. 29. (65)

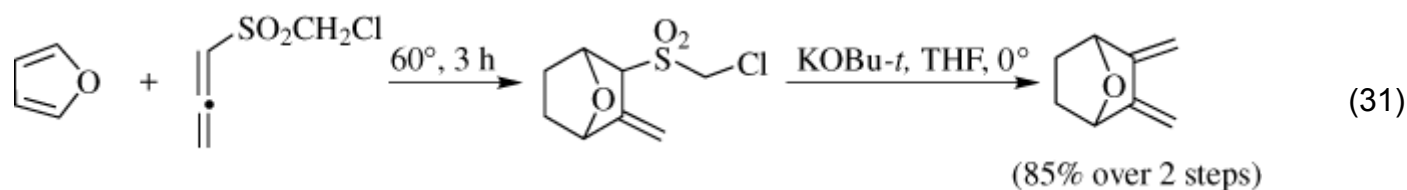


In general, however, solutions of methoxide/ethoxide/*tert*-butoxide in the corresponding alcohols are employed if polar solvents are required. A typical example is shown in Eq. 30. (60) It is interesting to note that the same transformation can be accomplished using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane but that debromination accompanies the RBR.

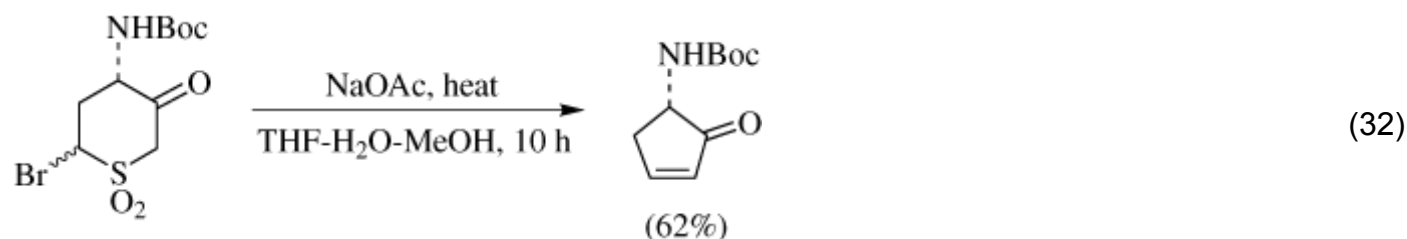


The most common base-solvent combination, however, is potassium *tert*-butoxide in tetrahydrofuran (THF) as shown in Eq. 31. (55) Other solvents have also been employed with potassium *tert*-butoxide including diethyl ether, (35) 1,2-dimethoxyethane (DME), (67, 68) dimethylformamide (DMF), (30) hexamethylphosphoramide (HMPA), (30) and dimethyl sulfoxide (DMSO). (30, 49)

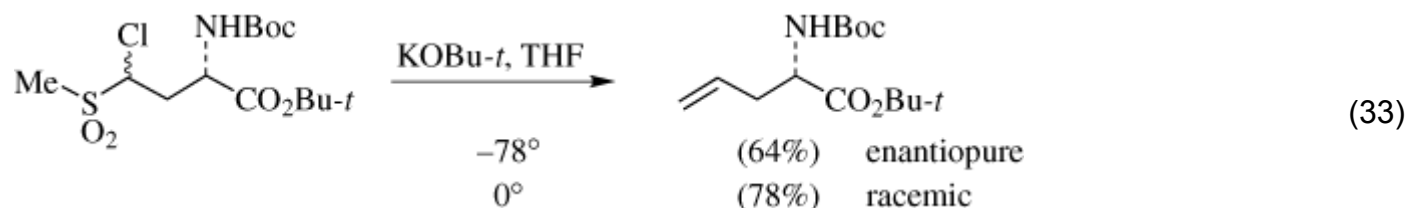
Similar combinations include sodium phenoxide-diglyme (59) and potassium 3-ethyl-3-pentoxide-DME-HMPA. (8) It should be recalled, however, that the use of stronger bases, such as *tert*-butoxide, may influence the stereochemical outcome of the process.



In rare cases (usually when more standard base-solvent combinations proved unsuccessful), stronger bases such as methyl lithium (see Eq. 132) (43) and butyllithium (69) have been employed. On the other hand, α -halosulfones possessing acidifying groups can undergo RBR on treatment with weaker bases such as sodium acetate in aqueous THF-methanol (Eq. 32), (70) DBU in dichloromethane (Eq. 30), (60) 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in dichloromethane or ethanol (see Eq. 35), (47) triethylamine in dichloromethane, (71) and morpholine in chloroform. (63)

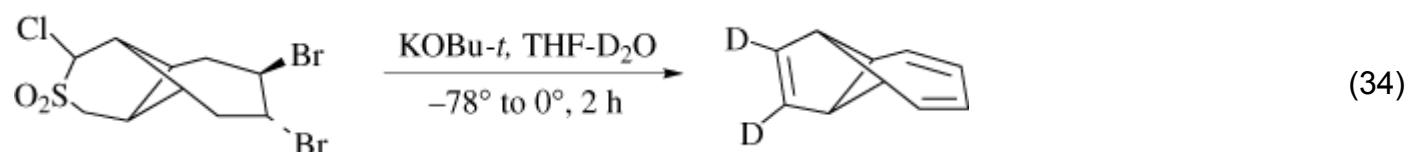


Stronger bases permit the use of lower temperatures for the RBR of α -halosulfones; reactions are now routinely carried out at room temperature and there are a number that proceed at -78° . These low temperatures may enable the intermediate thiirane dioxides to be isolated (21) and minimize side reactions (including racemization of labile stereocenters, e.g. Eq. 33 (42)).



3.2.2. Substrate Scope

Earlier studies concentrated on the utility of the RBR for the formation of strained ring systems. The ability to form deuterated alkenes was also exploited. These topics, illustrated by the example in Eq. 34, (72-74) have been well reviewed. (5, 6)

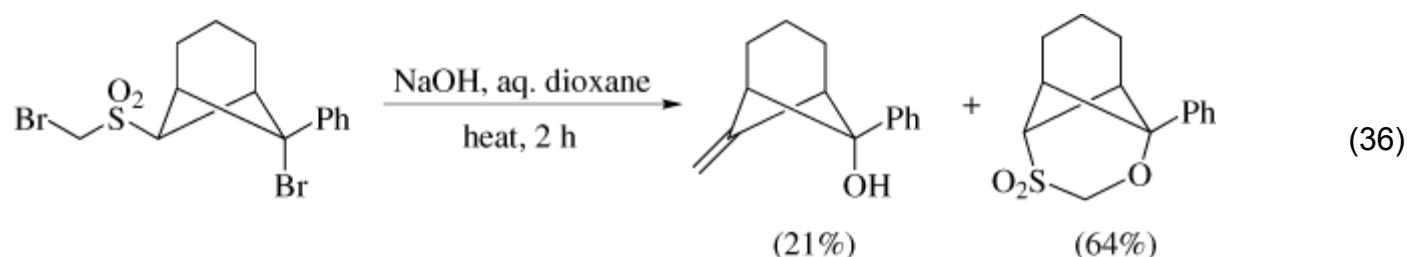
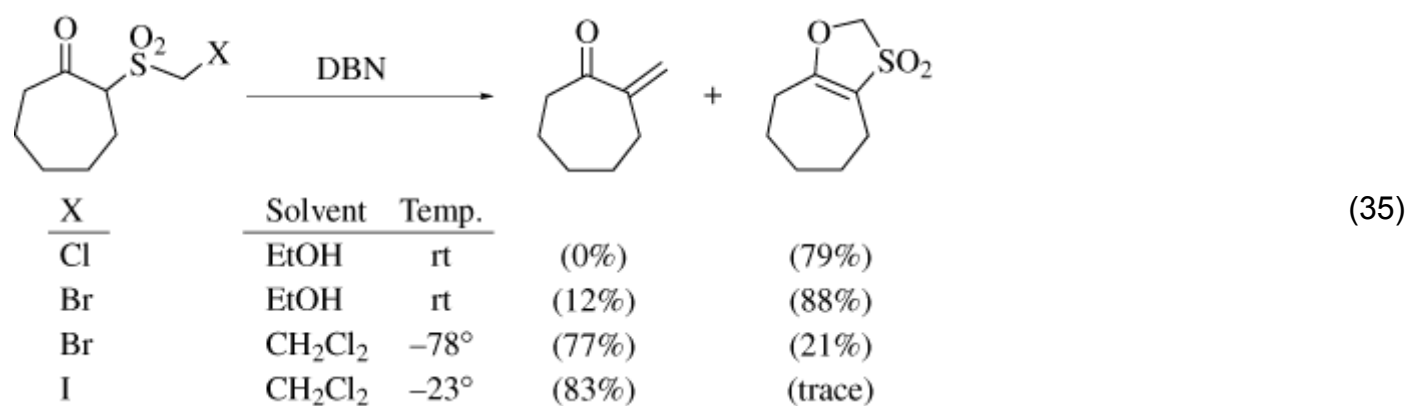


More recently, however, the scope of the RBR has been extended to encompass stereoselective

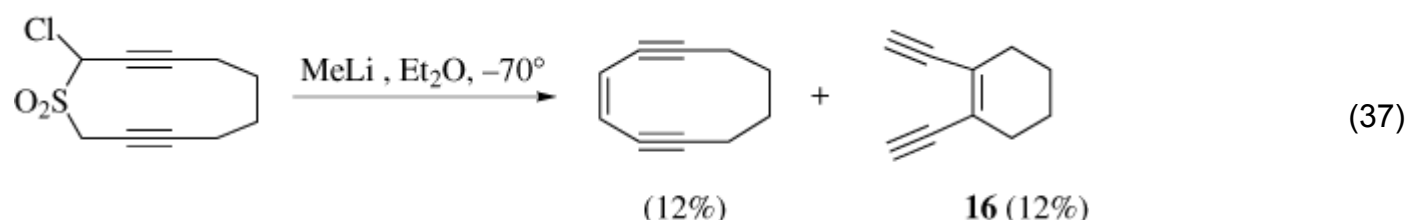
alkene and polyene syntheses as well as carbocycle and heterocycle syntheses with a range of ring sizes. In addition, highly functionalized systems have been employed as substrates for the RBR and its value in natural product synthesis has been established. The advent of the Meyers modification has further increased the scope of the reaction.

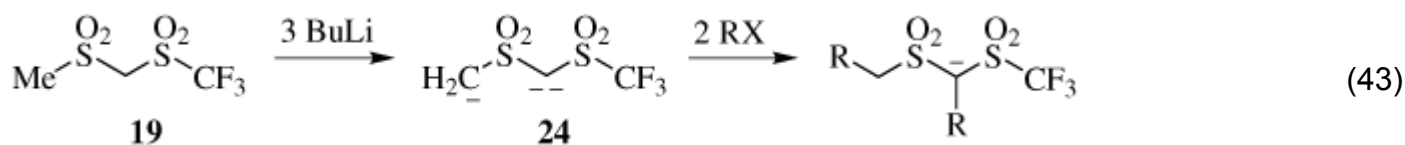
3.2.3. Compatibility of Functional Groups: Side Reactions

Diverse functionality is compatible with the basic conditions required for the classic RBR. Thus, alkenes, alkynes, aryl and heteroaryl groups present no problem. Successful examples with unprotected alcohols are known but they are normally protected as ethers or silyl ethers (although β -alkoxy and silyloxy sulfones can undergo elimination (75)). In addition, acids, esters, lactones, amides, carbamates, enones, and even ketones are compatible, although ketones are normally protected as ketals unless they are β to the sulfone. However, β -keto sulfones containing an α -halogen group can undergo heterocycle formation in a competitive process (Eq. 35). (47) In this example, the product ratio was found to vary according to the nature of the solvent, the leaving group, and the reaction temperature. Remote halogens have also been reported to be compatible with the RBR, but in the example shown in Eq. 36, alkene production is accompanied by alcohol and ether formation. (50, 51) It was assumed that conversion of the bromide into the alcohol occurs first, and that the ether arises by base-catalyzed epimerization of the sulfone group followed by cyclization, rather than by alkoxide attack on an intermediate thiirane dioxide. Under appropriate conditions, remote halogens can also undergo elimination (see Eq. 34). (73, 74)

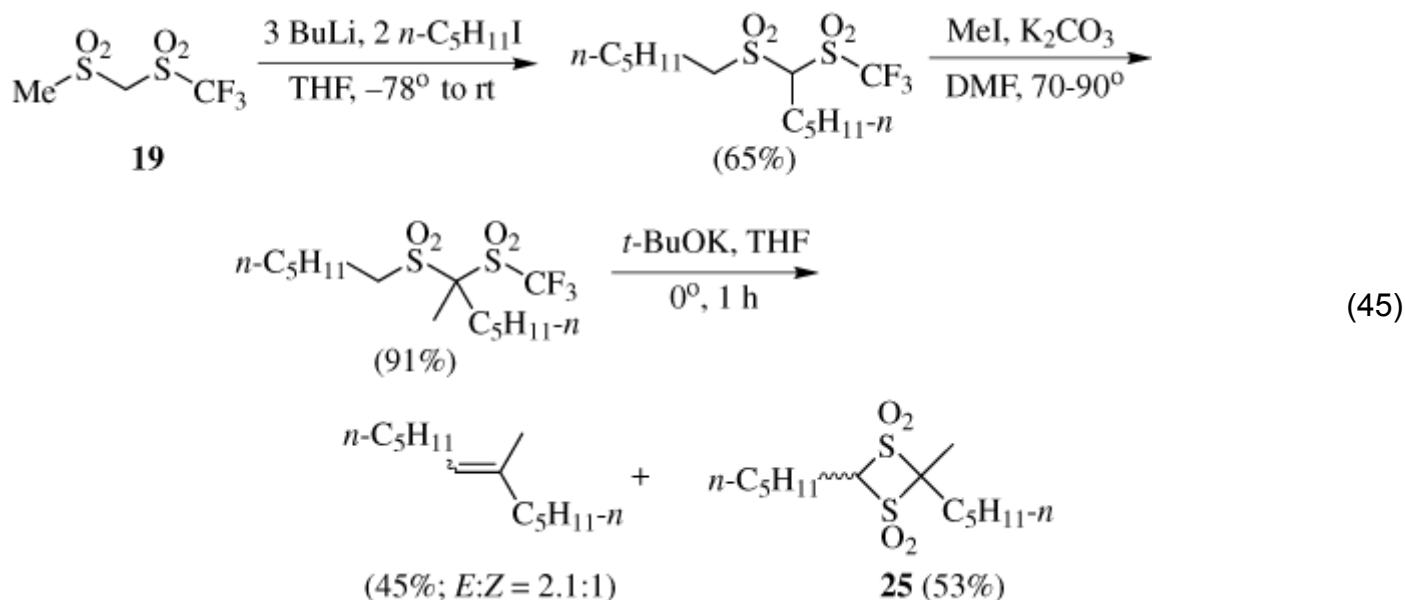
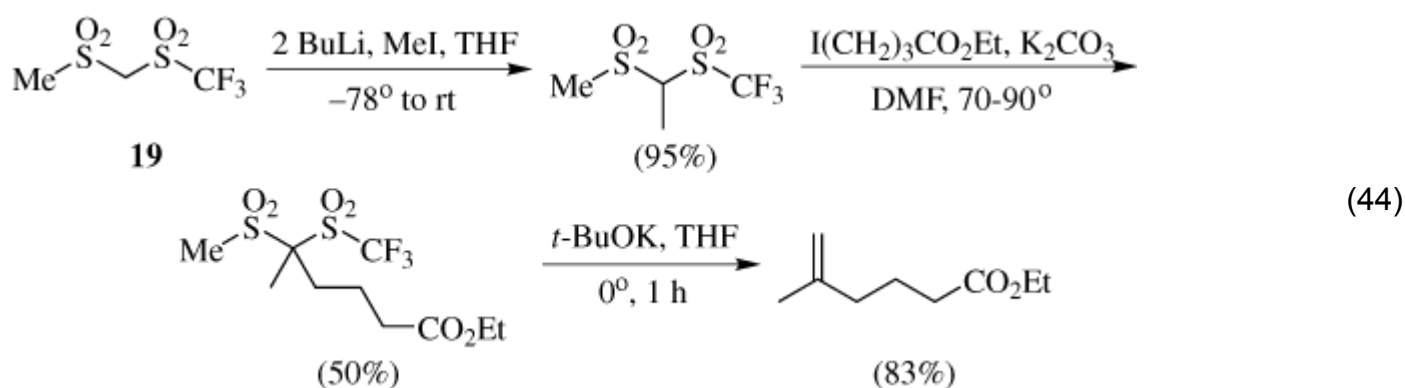


In an example within a strained system (Eq. 37), the RBR is accompanied by the unexpected formation of the disubstituted cyclohexene **16**. (43) It was proposed that **16** forms as a result of a Cope-type rearrangement of the intermediate thiirane dioxide followed by further rearrangement with loss of sulfur dioxide.

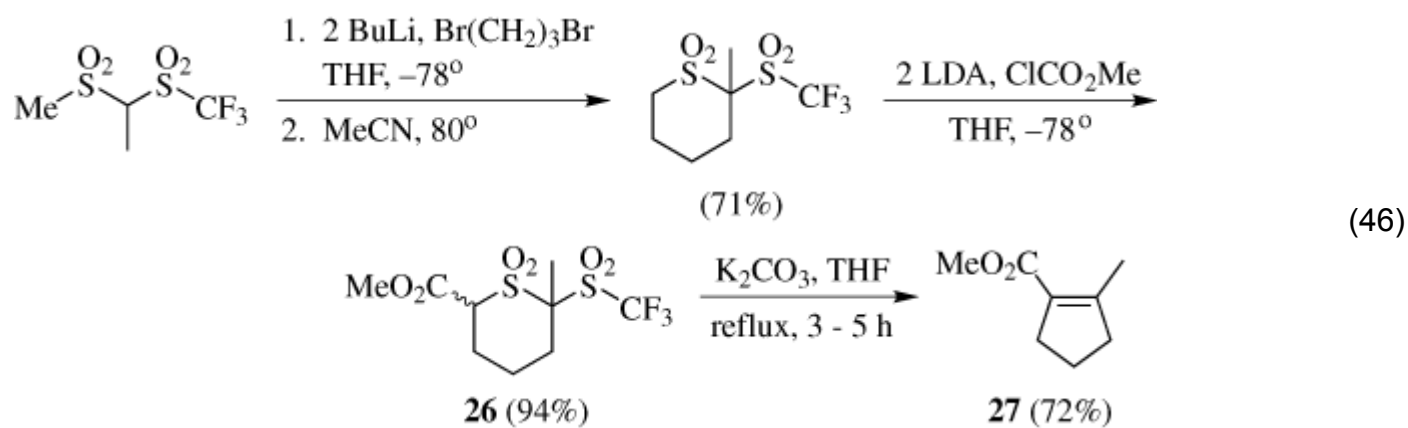




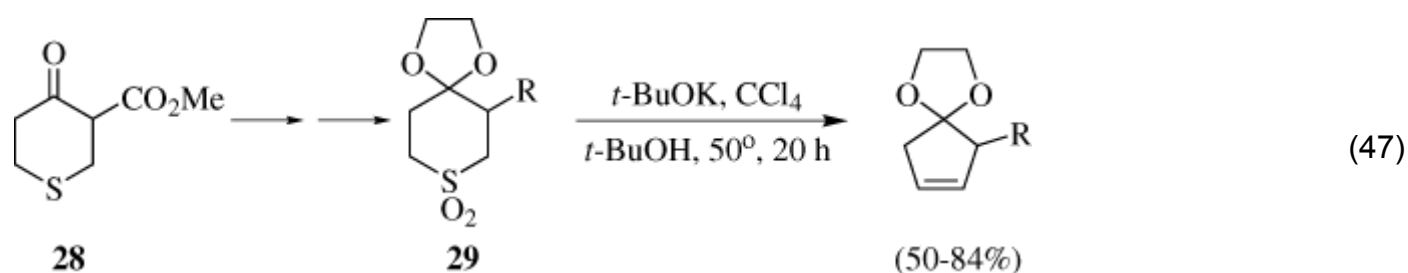
Eqs. 44–46 show representative examples of the synthesis of alkenes from disulfone **19**, and contrast reactions that are viable as preparative methods with nonviable applications. (82, 83) For the synthesis of a 1,1-disubstituted alkene, use of a weak base in the second alkylation step provides the requisite regiocontrol (Eq. 44). For the synthesis of a 1,1,2-trisubstituted alkene, proceeding via trianion generation in the first step, stereocontrol in the RBR is poor and the cyclic disulfone **25** is the major isolated product (Eq. 45). Eq. 46 shows the synthesis of a tetrasubstituted cyclic alkene, in which the first step entails the use of 1,3-dibromopropane as a bifunctional annulating agent. Subsequent acylation at low temperature requires two equivalents of base, since the product **26** is more acidic than the starting material. The final ring contraction proceeds smoothly to give cyclopentene **27** in good yield.

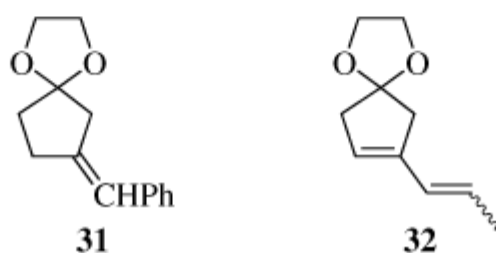
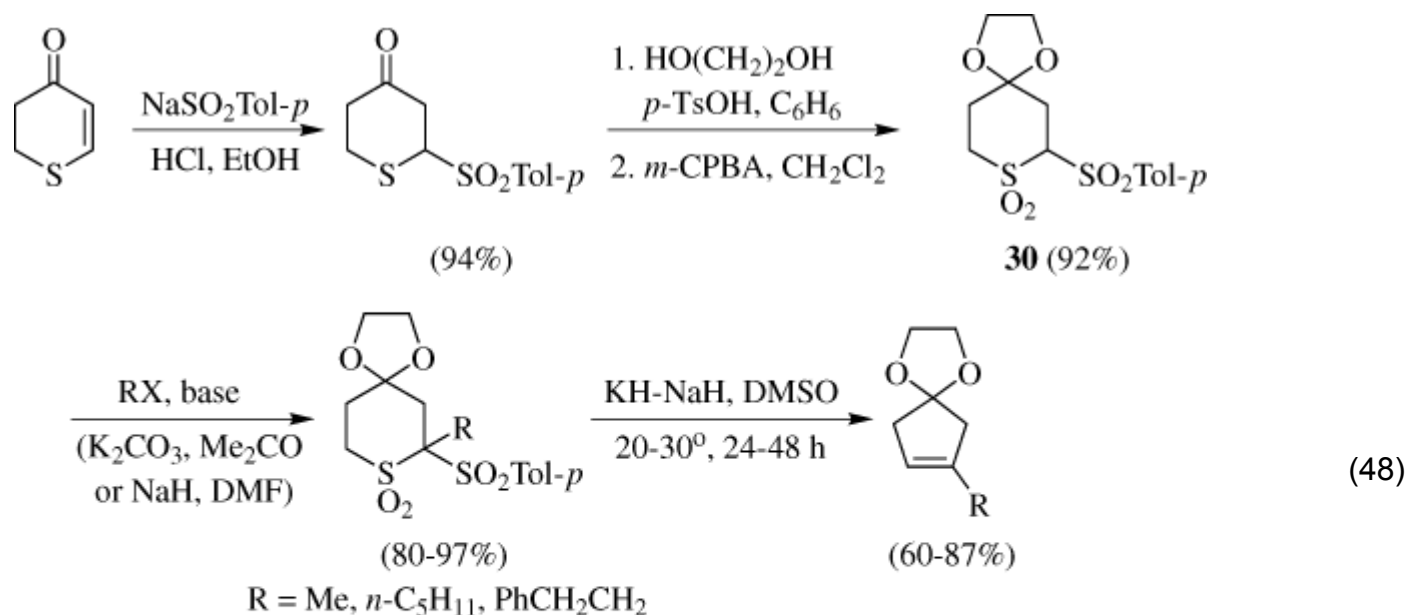


Later studies have demonstrated that arylsulfone groups are also effective in RBR chemistry. Use of the *p*-toluenesulfonyl group as both an activating and leaving group provides the basis of one of a pair of complementary methodologies to prepare 2- and 3-alkyl-3-cyclopentenones from ketal-protected 4-thianone-1,1-dioxides. (84) Preparation of protected 2-alkyl-3-cyclopentenones is accomplished by the sequence of standard transformations depicted in Eq. 47. Alkylation of the β-keto ester **28** followed by saponification/decarboxylation, ketalization, and sulfide

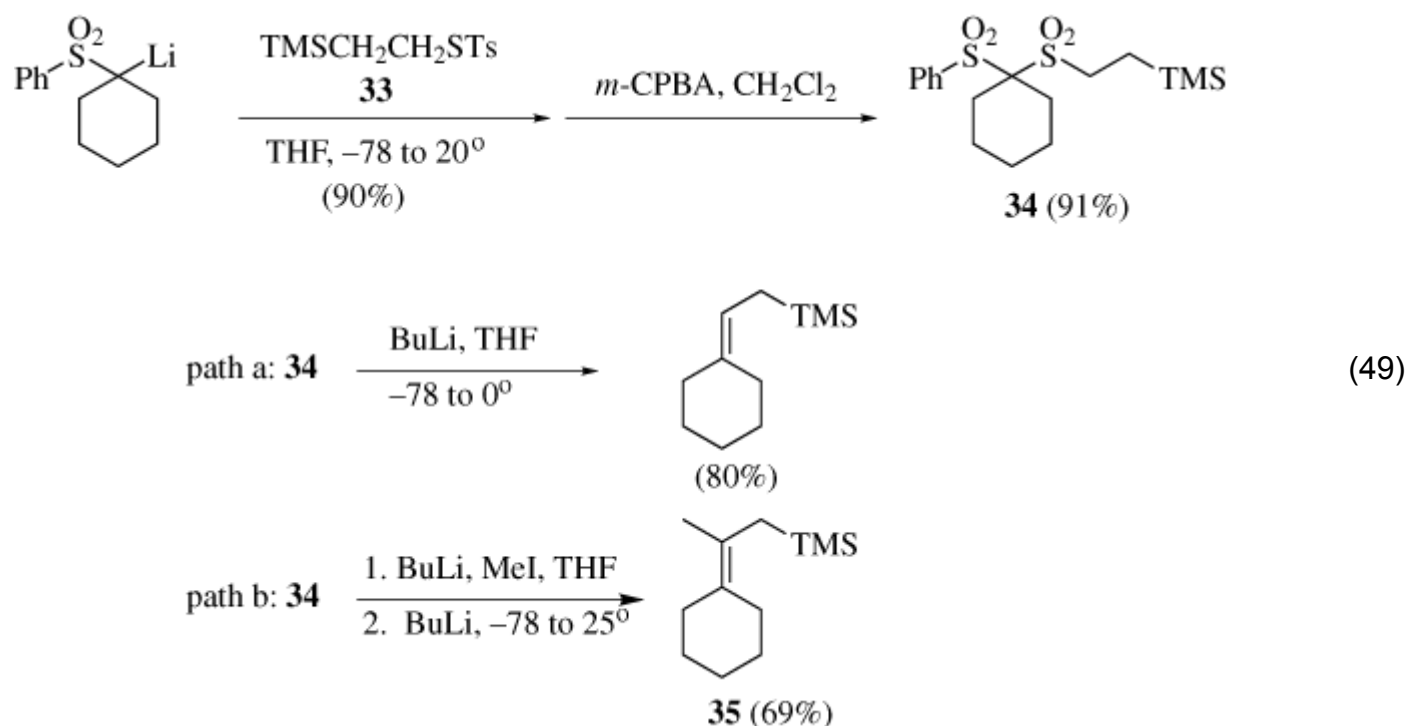


oxidation gives the sulfone **29** as a substrate for RBR via in situ halogenation. To prepare protected 3-alkyl-3-cyclopentenones a novel approach was required (Eq. 48), in which the pivotal disulfone intermediate **30** is prepared in three steps from 2,3-dihydrothiophen-4-one via conjugate addition of the *p*-toluenesulfonyl group. Subsequently, alkylation of disulfone **30** is carried out with a range of alkyl halides, both activated (e.g. benzyl bromide) and non-activated (e.g. 1-iodopentane). Lastly, RBR of disulfones substituted with simple alkyl groups is accomplished in good yield by treatment with alkali metal hydrides. In contrast, benzyl- and allyl-substituted disulfones give rise to isomerized products **31** (as a minor by-product) and **32** (as the only isolable product), respectively.

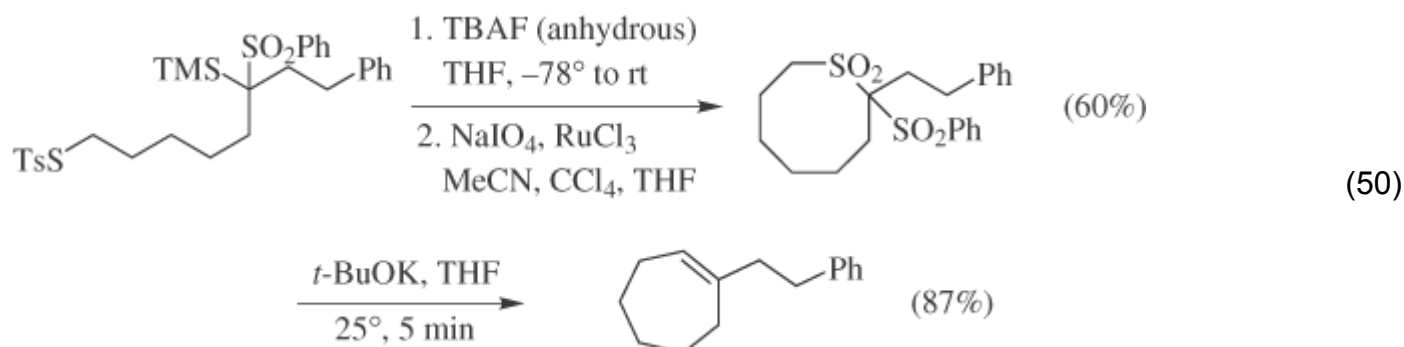




Use of phenylsulfone as a leaving group in RBR chemistry was first demonstrated in a general synthesis of exocyclic allylsilanes. (85) As depicted in Eq. 49, the electrophilic sulfenylating agent **33** is used to prepare the disulfone intermediate **34**. The RBR is effected by treatment with butyllithium, followed by warming (path a). Alternatively, in situ alkylation could be incorporated affording a β -substituted allylsilane, e.g. **35** (path b).

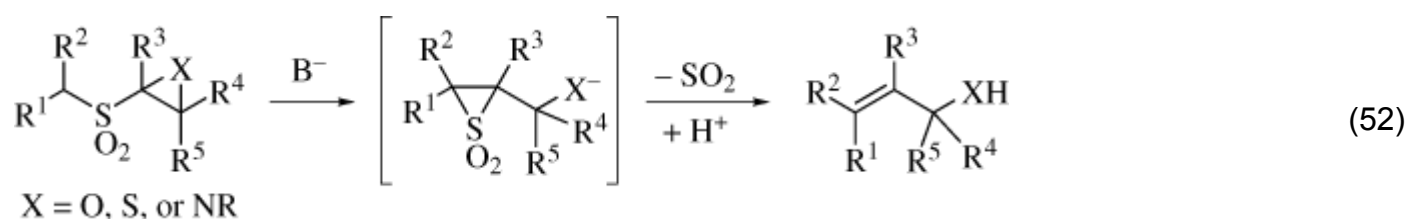
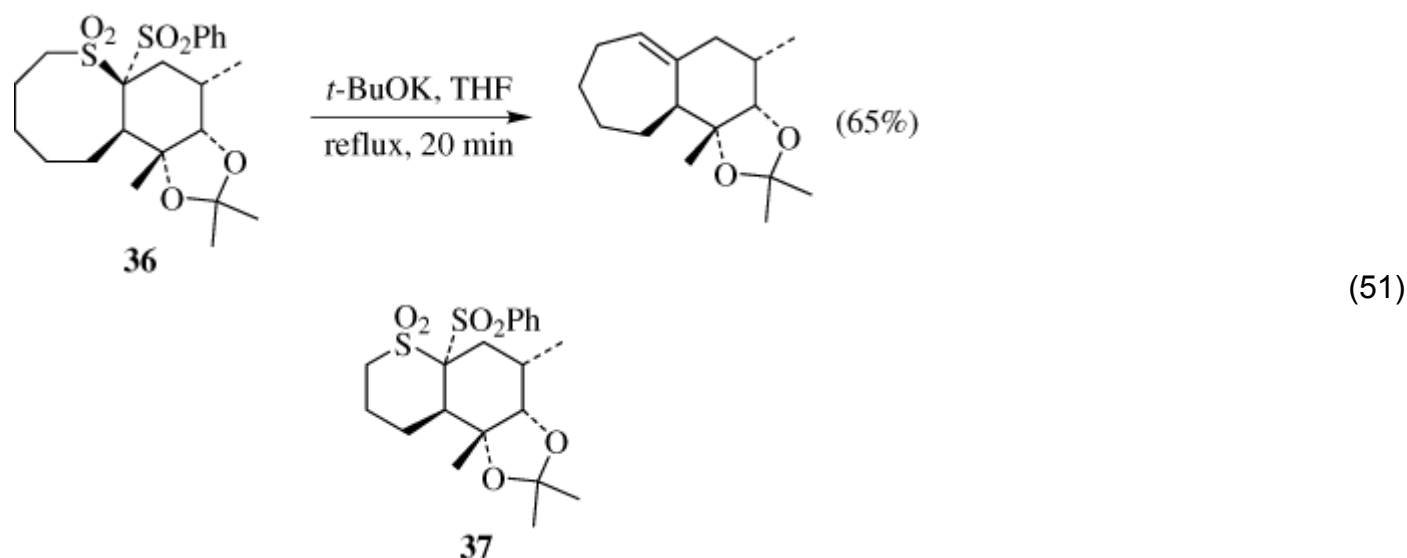


In related methodology to prepare 5- to 7-membered cycloalkenes, a distinctive feature is the fluoride-induced intramolecular sulfenylation of α -silyl sulfones. (86) Eq. 50 shows a representative example from model studies in which the RBR ring contraction is remarkably facile. This cyclization protocol was utilized successfully for the synthesis and rearrangement of the bicyclic disulfone **36** (Eq. 51), although the smaller ring homolog **37** resists ring contraction, a finding attributed to the strain required to form the requisite thiirane dioxide intermediate.



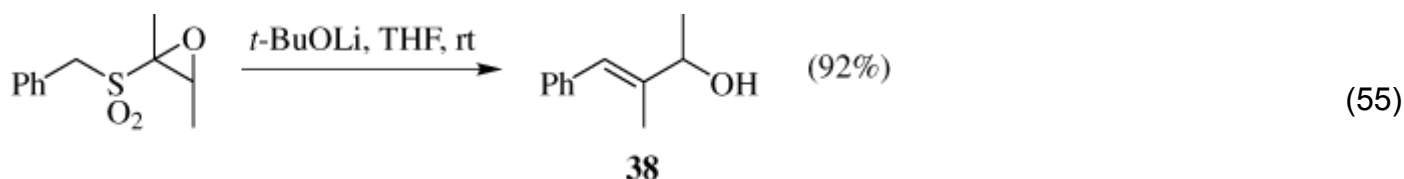
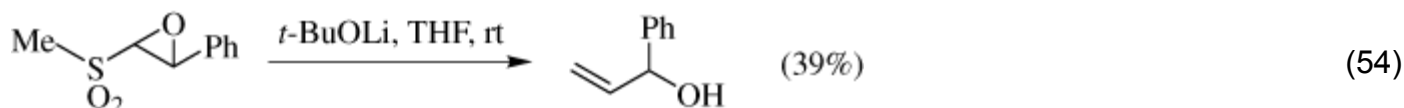
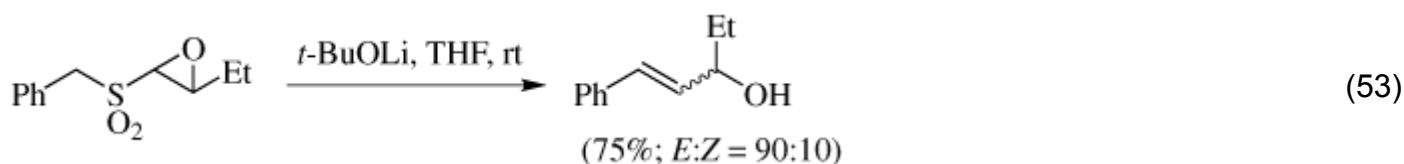
3.3.2. The Epoxy-RBR

A novel variant of the RBR, conceived and developed by Taylor and Evans, (87) is the so-called epoxy-Ramberg-Bäcklund reaction (ERBR), in which an α,β -epoxysulfone is converted into an allylic alcohol. This process, which has been conceptualized more generally to encompass episulfide and aziridine variants (Eq. 52), has the benefit that alkene formation is accompanied by the introduction of functionality in the adjacent position.



Representative examples of the methodology are shown in Eqs. 53–55. Substrates are prepared by nucleophilic epoxidation (lithium *tert*-butylperoxide) of the corresponding vinyl sulfones. In most

cases lithium *tert*-butoxide in THF is the reagent of choice. Both benzylic sulfones (Eq. 53) and non-benzylic sulfones (Eq. 54) can undergo the reaction, although the latter are less reactive. Stereocontrol in the ERBR is variable, but notably good in the synthesis of the trisubstituted alkene **38** (Eq. 55).



3.4. RBR With in Situ Halogenation: Meyers' Variant

The most widely used variant of the RBR, frequently referred to as the Meyers modification, involves the one-pot conversion of a sulfone into an alkene via in situ halogenation. The reaction is effected by treatment with base and a suitable electrophilic halogenating agent.

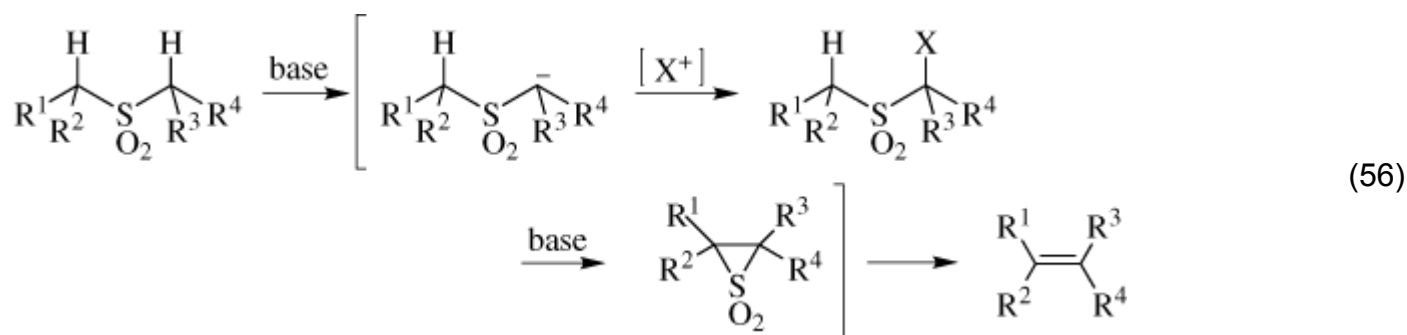
This section summarizes the development of the method since its discovery by Meyers in 1969. (4) Scope, limitations, choice of reaction conditions and mechanistic aspects will be addressed. Tables 3A and 3B provide a comprehensive listing of synthetic applications published since 1978; salient examples will also be highlighted in this section.

A review article by Meyers (88) provides further insight into the discovery and development of the one-pot halogenative RBR. Meyers and coworkers also patented the method as a means of alkene synthesis. (89) It is interesting to note that US 3,830,862, which was issued in 1974 and expired in 1991, highlights carbon tetrachloride as the preferred halogenating agent but also describes the use of alternative agents, including dibromodifluoromethane. The latter is a key component of the protocol introduced by Chan in 1994, (90) described below.

3.4.1. Scope of Reaction and Choice of Conditions

Where use of the Ramberg-Bäcklund reaction is contemplated in a novel synthetic sequence, the one-pot halogenative methods should normally be attempted first. The traditional RBR approach requires a separate halogenation step in which formation and separation of regioisomeric and/or diastereomeric mixtures may be an additional complication, whereas the Meyers modification and related protocols proceed directly from the sulfone.

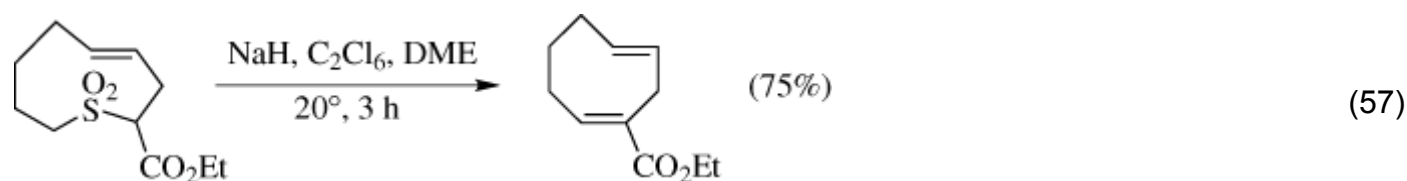
The one-pot method can be applied to a wide range of sulfones. In principle, any sulfone possessing hydrogen atoms on the α - and α' -carbons can be transformed into an alkene according to the pathway depicted in Eq. 56. An early demonstration by Meyers of the synthetic utility of the method was in the conversion of dibenzyl sulfone into (*E*)-stilbene in quantitative yield (Eq. 2). (4) However, for other types of substrates, careful choice of conditions is critical for the suppression of side reactions and optimization of yield.



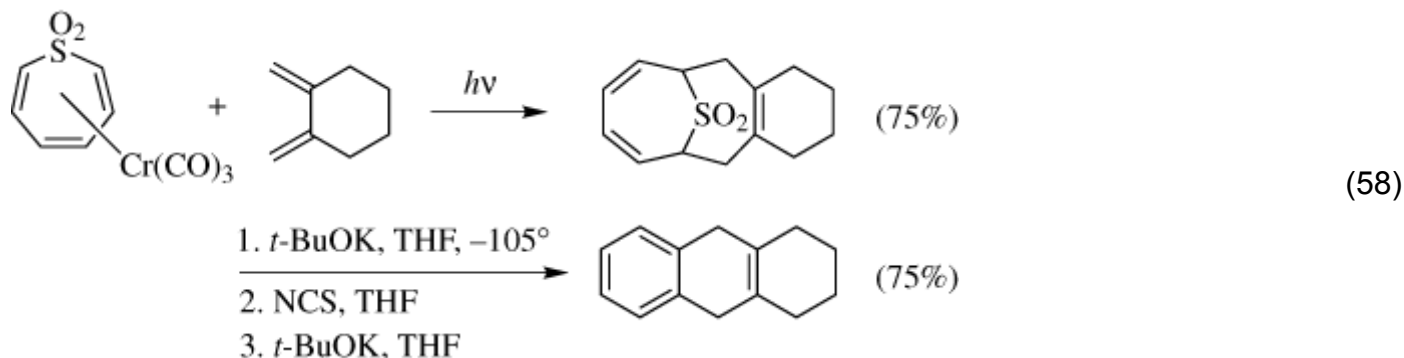
Meyers' original conditions for the one-pot halogenative RBR entail treatment of the substrate with excess powdered potassium hydroxide and carbon tetrachloride in *tert*-butanol. Typically, the reaction is carried out at room temperature for activated substrates (e.g. benzylic and allylic sulfones), for which carbanion formation is relatively facile, or by heating to 50–60° for other substrates. Although water is included as an additive in the original conditions reported by Meyers, in many cases it is not required since powdered potassium hydroxide prepared from commercial pellets contains about 15% w/w water. (88) The alcohol is essential in order to ensure that a high, local concentration of alkoxide, required for proton abstraction, is attained at the surface of potassium hydroxide. *tert*-Butanol is the preferred alcohol, although it may be replaced by methanol if the α - and α' -hydrogen atoms both have enhanced acidity. (91) carbon tetrachloride may be replaced by a congener such as hexachloroethane, (92) although this practice is uncommon. A phase-transfer variant of the Meyers' modification (65) utilizes potassium hydroxide/carbon tetrachloride/*tert*-butyl alcohol with water in a two-phase system, for which Aliquat-336 (tricaprylmethylammonium chloride) is the preferred transfer agent. However, these and similar (66) conditions have only been applied successfully to the prototypical substrate dibenzyl sulfone.

Although Meyers' original conditions have been widely used, the modification (90) introduced by Chan in 1994 extends the scope of the one-pot halogenative RBR considerably, as will be evident from the examples presented below. The Chan procedure comprises treatment of the substrate with alumina-supported potassium hydroxide, dibromodifluoromethane, and *tert*-butanol. As with Meyers' conditions, the reaction is typically carried out at or below room temperature for activated substrates (e.g. benzylic and allylic sulfones) or by heating to 50–80° for other substrates. When heating is required, the volatility of dibromodifluoromethane (bp 22–23°) may be problematic. When this occurs, improved yields are obtained by using 1,2-dibromotetrafluoroethane (bp 47°) as halogenating agent and cosolvent. (93) It is not always necessary to use a protic solvent; dichloromethane is preferred for diallylic sulfones and is essential for dipropargylic sulfones. Experiments comparing potassium hydroxide with potassium hydroxide-alumina revealed that the alumina has a role in suppressing dihalogenation. Although the reason for this effect is unclear, the efficacy of the potassium hydroxide-alumina reagent is believed to be a consequence of dispersion of potassium hydroxide across a large and activated surface.

A third protocol for halogenative RBR, discovered by Vedejs, comprises treatment of the substrate with sodium hydride and hexachloroethane in DME at room temperature. (40) However, use of these milder reaction conditions is limited to sulfones in which the α -position bears a single hydrogen atom, an ester group, and another substituent. Eq. 57 depicts the application of this method to a cyclic sulfone; acyclic substrates have also been employed.



It is also possible to convert sulfones into alkenes in a one-pot operation comprising the sequential addition of one equivalent of a strong base, one equivalent of halogenating agent, and a second equivalent of base. It would be inaccurate to describe this as a general method since only a few examples are reported in the literature. Eq. 58 depicts application of this method in conjunction with chromium(0)-promoted $[6\pi + 4\pi]$ -cycloaddition to effect benzannulation. (94) A reaction temperature of -105° is required in this sequence in order to prevent decomposition of the metallated dihydrothiepine 1,1-dioxides formed in situ.



The suitability of particular reaction conditions for a given substrate is influenced by the nature of each group flanking the sulfone moiety. This is described in detail in the following sections. For doubly activated substrates, with flanking groups selected from benzyl, benzhydryl, or allyl, the Meyers and Chan procedures are both applicable. However, when both flanking groups are selected from *n*-alkyl, *sec*-alkyl, or cycloalkyl, the Chan procedure gives superior results. Borderline cases include substrates where one flanking substituent is an activating group and the other is nonactivating. It is also evident from published examples that cyclic sulfones are less prone to side reactions, as are alkyl sulfones branched at the β -position; for such substrates either procedure may be suitable.

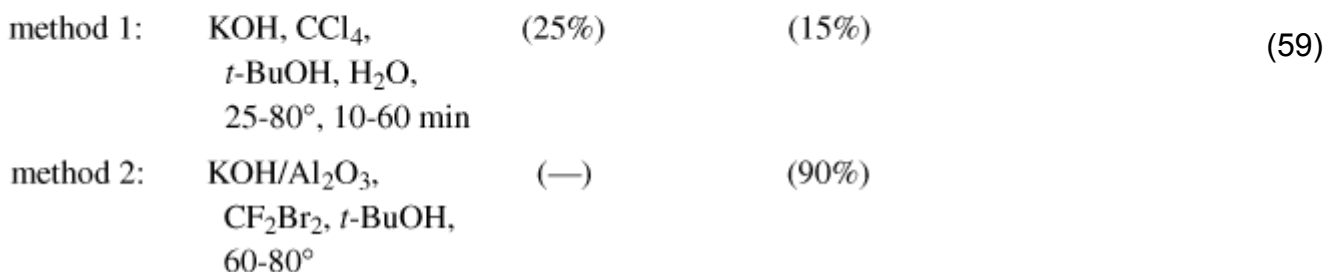
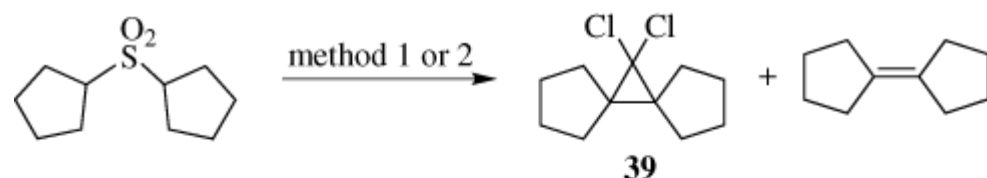
Functional group compatibility in the halogenative RBR is another important consideration. Protecting groups are usually required for alcohols, and for base-sensitive groups such as aldehydes and ketones. Remote halogen substituents may be compatible with the RBR (Eq. 62) or may lead to side reactions (Eq. 63). (51) Esters and lactones do not usually withstand the RBR conditions, except when Vedejs' protocol is used, although exceptions are known (e.g. Eq. 66). (95)

3.4.2. Side Reactions; Synthesis of Acyclic Alkenes

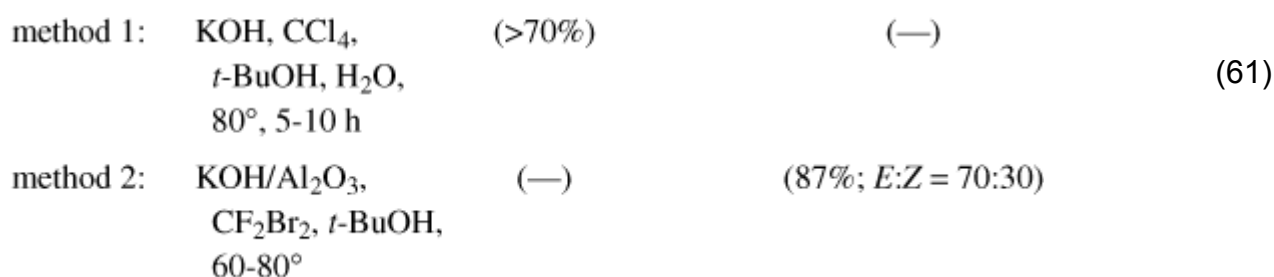
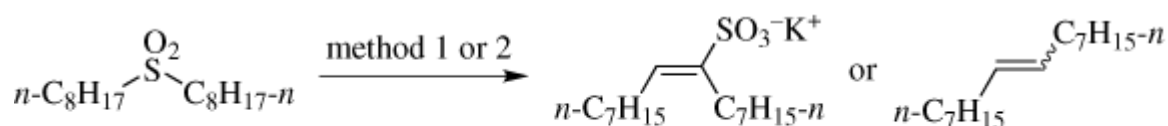
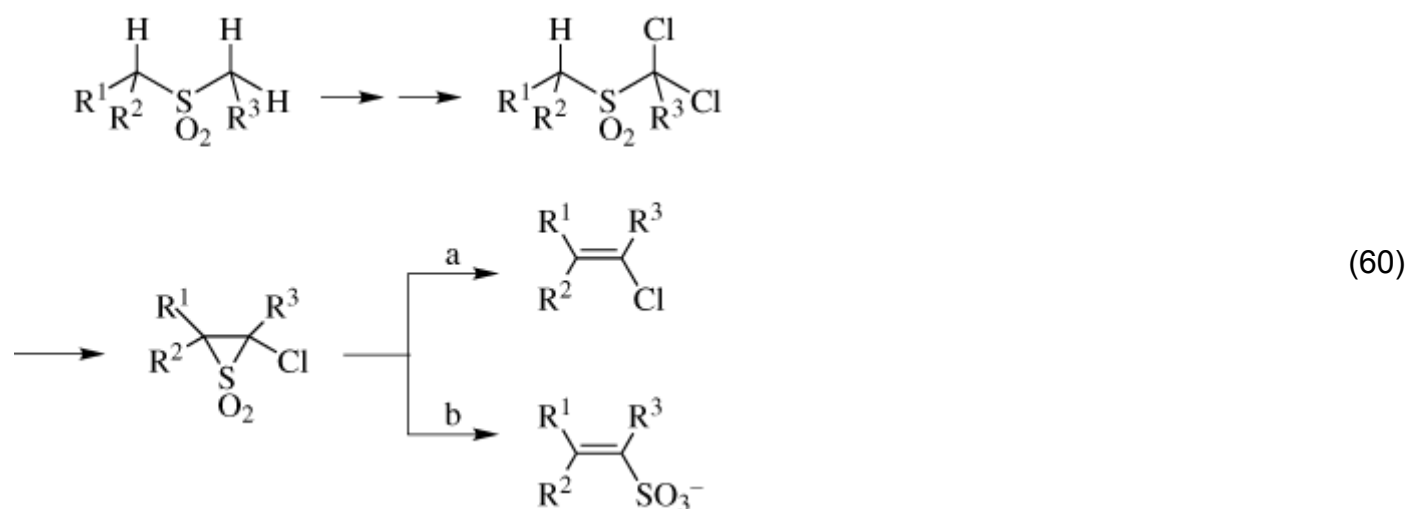
Meyers' original conditions involve chlorine transfer from carbon tetrachloride to the sulfone generating the trichloromethyl anion, which can lose chloride to produce the highly reactive dichlorocarbene that can undergo addition to the desired alkene product to form *gem*-dichlorocyclopropane side-products. This side reaction is most prevalent with highly substituted, electron-rich alkenes such as those derived from di-*sec*-alkyl sulfones. For example, reaction of dicyclopentyl sulfone with potassium hydroxide/carbon tetrachloride/*tert*-butanol/water gives the carbene adduct 39 as the major product (Eq. 59, method 1). (4) Two approaches to suppress this side reaction have been reported. The addition of phenol or a sacrificial alkene as carbene scavenger provides one method, (88) although it is difficult to find comparative examples of this in the open literature. Alternatively, Chan's procedure replaces carbon tetrachloride with dibromodifluoromethane, a halogen source from which the less reactive difluorocarbene may be generated. Consequently, conversion of dicyclopentyl sulfone into bicyclopentylidene using potassium hydroxide/alumina-dibromodifluoromethane-*tert*-butanol is a viable preparative method (Eq. 59; method 2). A separate experiment in which powdered potassium hydroxide was used instead of potassium hydroxide/alumina gave a comparable result. (90)

When additional hydrogen atoms are present at α - and α' -carbons of the substrate, a second

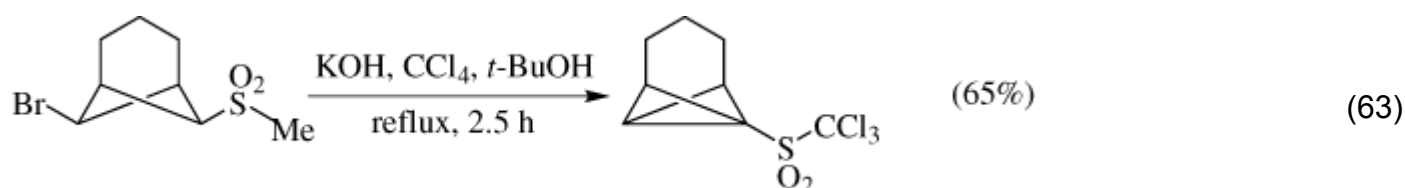
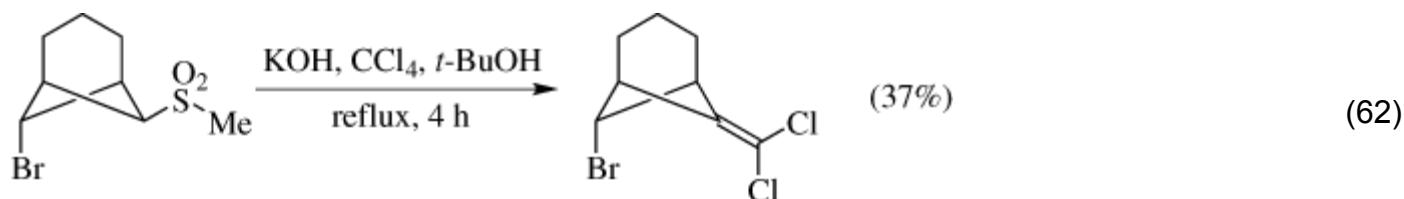
chlorination at either position can compete with the desired Ramberg-Bäcklund reaction (Eq. 60). Subsequent 1,3-elimination of hydrogen chloride



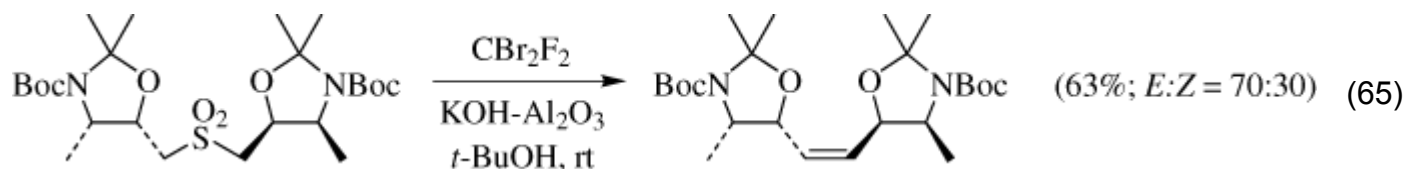
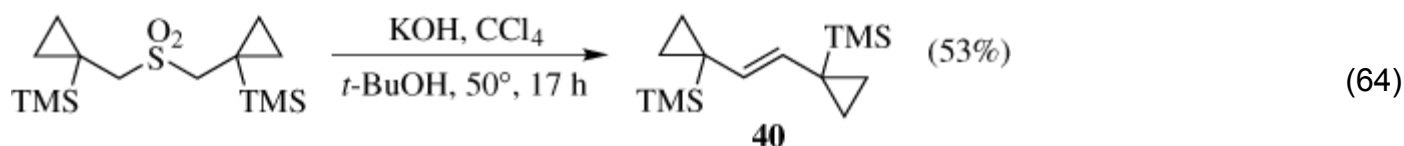
from the resulting dichlorosulfone may lead to a chloroalkene by-product (Eq. 60, path a), although, more commonly, reaction with hydroxide leads to formation of an alkene sulfonate (Eq. 60, path b). The latter pathway proceeds via a thiirene dioxide intermediate that can also extrude sulfur dioxide to produce an alkyne. Di-*n*-alkyl sulfones are particularly susceptible to polychlorination and thus one-pot halogenative RBR of these substrates cannot be effected under the original Meyers conditions. Instead, the major product is an alkene sulfonate salt formed via a dichlorosulfone, as is illustrated in Eq. 61 (method 1) for di-*n*-octyl sulfone. (96) In marked contrast (Eq. 61, method 2), the Chan procedure allows clean conversion of the same substrate into 8-hexadecene, albeit as a mixture of isomers. (90) Prior to the discovery of these alternative conditions, using a preformed α -halo dialkyl sulfone was preferred. (42)



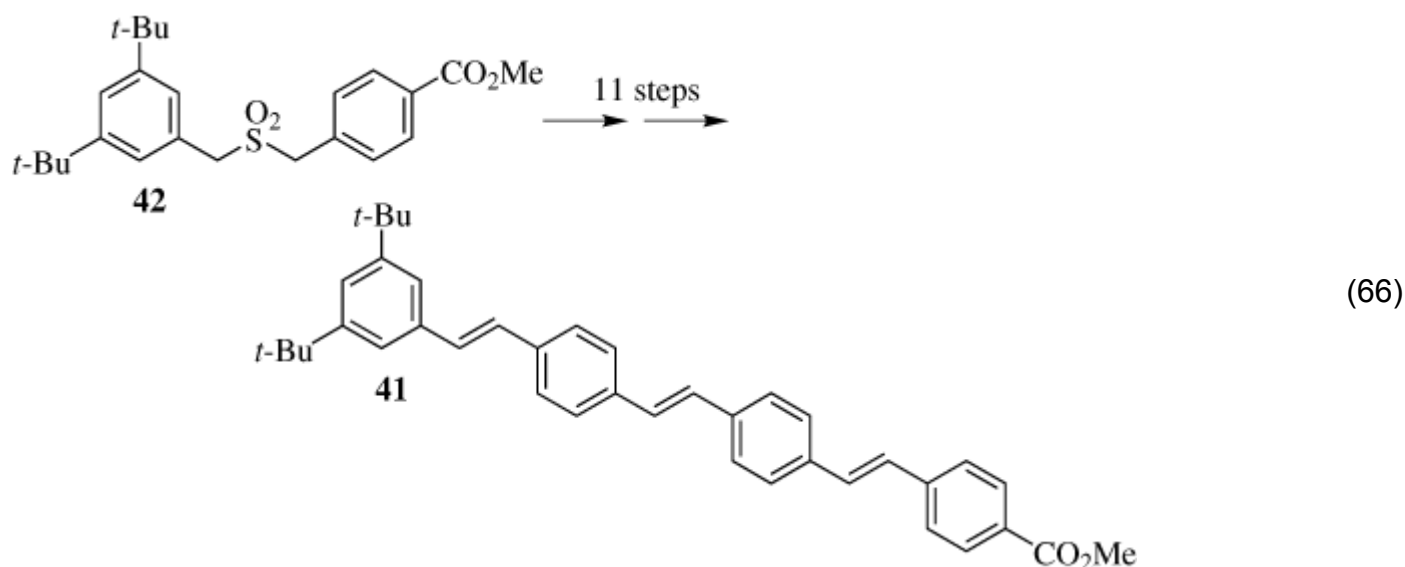
Multiple α -chlorination can also occur in sulfones in which the α -hydrogen is hindered, as is evident for the 7-*endo*-(bromo)bicyclo[3.1.1]heptane in Eq. 62. The corresponding 7-*exo* isomer also undergoes exhaustive α -chlorination but subsequent intramolecular displacement of the remote halogen occurs to form a tricyclo[4.1.0.0]heptane in preference to RBR (Eq. 63). (51)



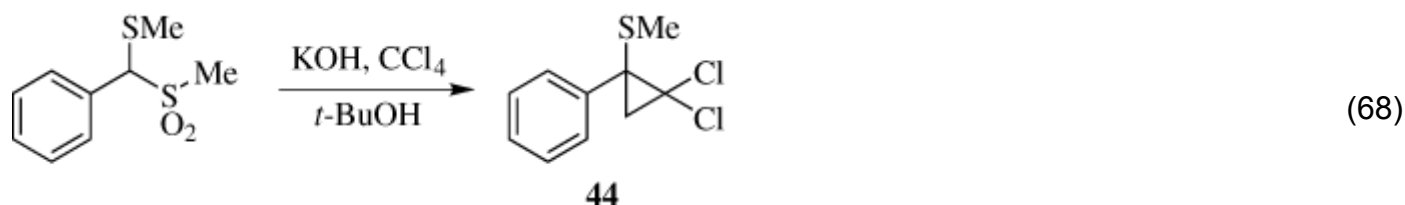
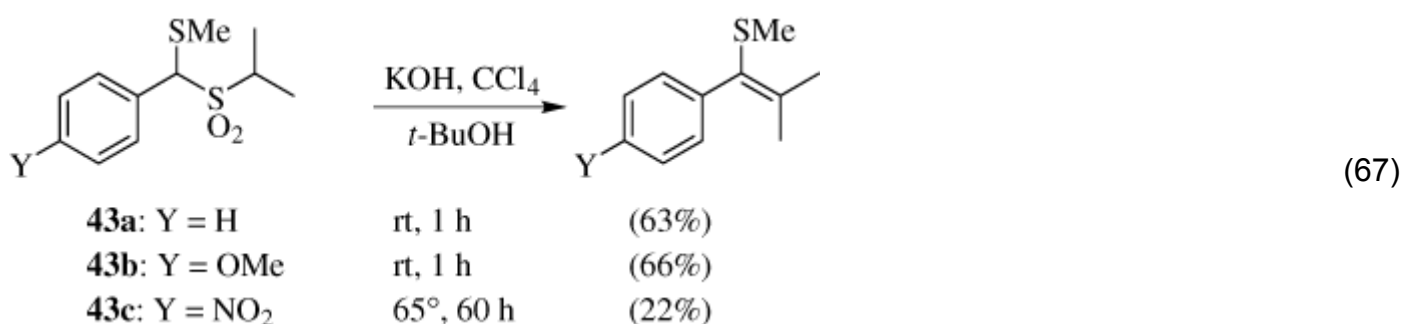
The aforementioned limitations of the Meyers procedure in rearrangements of di-*n*-alkyl sulfones do not apply to sulfones with β -branched alkyl groups. This is evident in the synthesis of (*E*)-1,2-bis[1-(trimethylsilyl)cyclopropyl]ethene (**40**) en route to dicyclopropylideneethane (Eq. 64). (97) The absence of side reactions may be a consequence of steric hindrance favoring 1,3-elimination of hydrogen chloride over dichlorination. β -Branched dialkyl sulfones have also been successfully transformed using Chan's conditions, as demonstrated in the preparation of enantiomerically pure 2,7-diamino-3,6-octenediol derivatives. (98) Eq. 65 shows a representative example, in which the assembly of two α -amino alcohol moieties is achieved.



The utility of the Meyers modification for the conversion of simple dibenzyl sulfones into *E*-stilbenes (see Eq. 2) is evident from the original report (4) and in examples previously reviewed. (5) Subsequent applications to more elaborate dibenzyl sulfones include the synthesis of a homologous series of oligo (phenylenevinylenes) terminated with porphyrins, for use in the field of molecular electronics. (91) Similar oligo (phenylenevinylenes), for example **41**, have been constructed by employing the Chan procedure three times in an iterative sequence commencing from the monosulfone **42** (Eq. 66). (95)



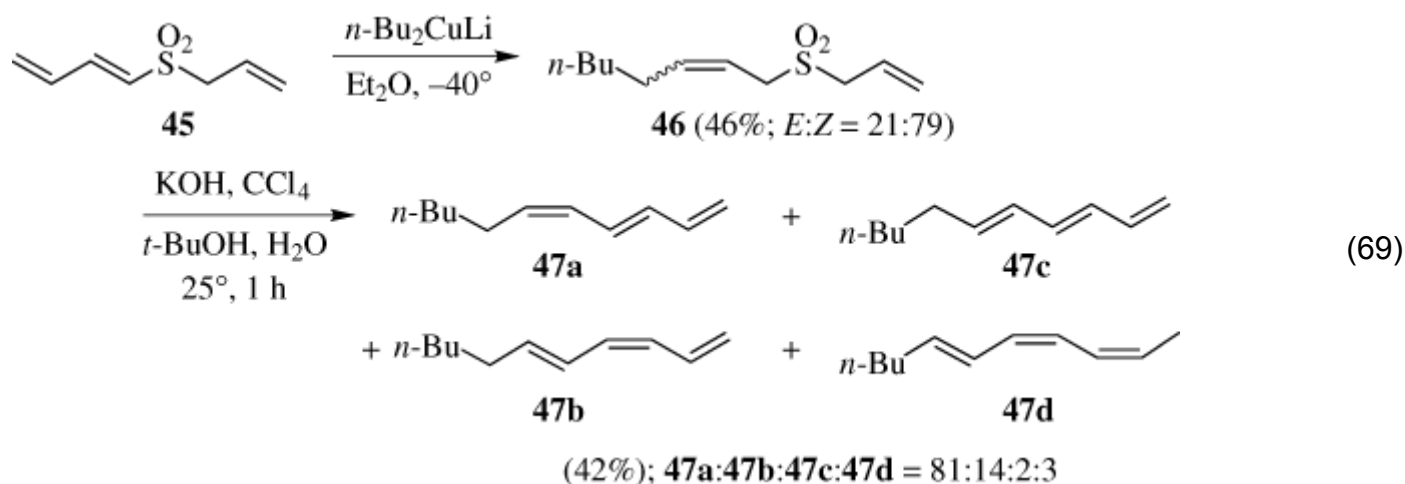
The Meyers modification has been applied to monobenzyllic substrates where the second group flanking the sulfone moiety is alkyl. (99) A study targeted at a series of vinyl sulfides highlights the effects of para-substitution in the benzyl group. (100) As shown in Eq. 67, the conversion of benzyl isopropyl sulfones **43a** and **43b** into the corresponding vinyl sulfides proceeds in reasonable yield at room temperature. In contrast, reaction of the para-nitro substrate **43c** requires forcing conditions and gives a lower yield, a result ascribed to greater stabilization of the initially formed benzylic carbanion, which inhibits chlorination. In a related study, (101) reaction of the methyl sulfone analog of **43a** gives dichlorocarbene adduct **44** as the sole product (Eq. 68).



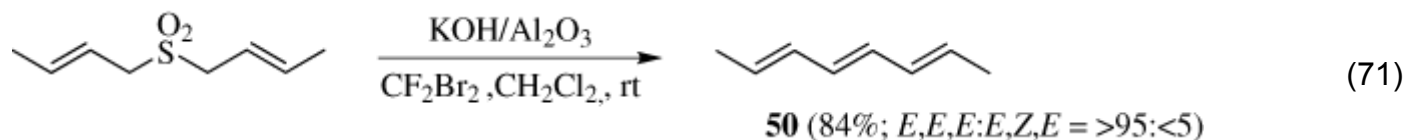
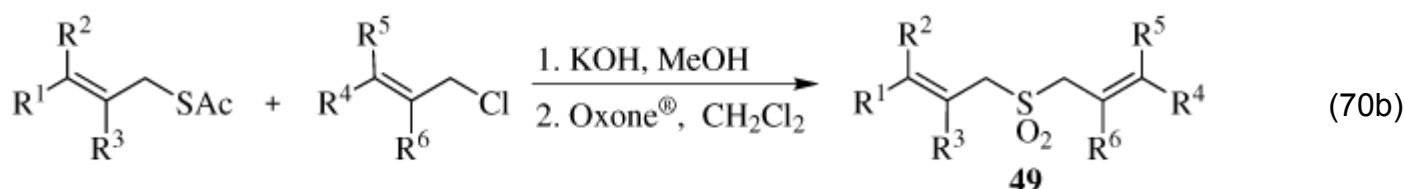
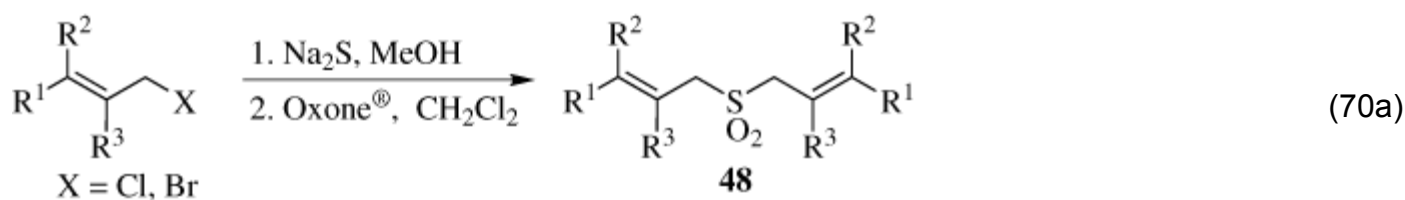
3.4.3. Synthesis of Polyenes

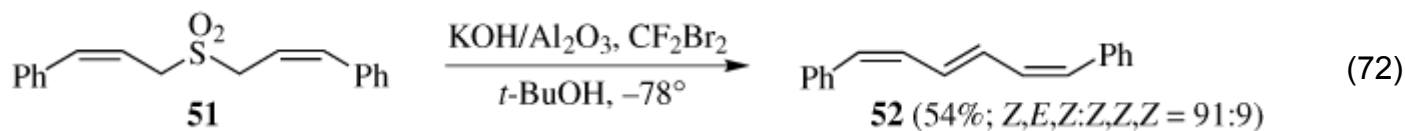
In pioneering studies by Büchi and Freidinger, (102) reviewed previously, (5) it was established that diallyl sulfones undergo facile conversion into conjugated trienes using the Meyers modification. In general, these reactions are characterized by retention of the geometry of pre-existing double bonds, and the preferential formation of the third double bond with E-configuration. The degree of stereocontrol is also dependent on the substitution pattern of allyl groups in the substrate. Furthermore, a limitation evident in early applications is the difficulty in preparing geometrically pure diallyl sulfones. Consequently, halogenative RBR inevitably gives complex product mixtures. These features are evident in work directed towards naturally occurring polyenes for use as fragrance

compounds. (103) As shown in Eq. 69, reaction of (*E*)-1,3-butadienyl allyl sulfone [45; containing 5% of the *Z*-isomer] with lithium dibutylcuprate gives the adduct 46 as a geometric mixture [E:Z = 21:79]. Subsequent in situ chlorination and rearrangement gives a mixture of four compounds 47a-d, the predominant pathway being conversion of (*Z*)-46 into (3*E*,5*Z*)-triene 47a.

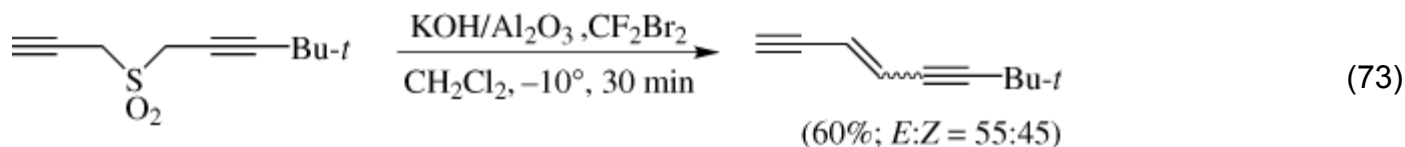


More preparatively viable applications developed later use geometrically pure substrates. In a systematic survey of halogenative RBR of diallyl sulfones using the Chan procedure, (104) substrates were prepared by coupling of the requisite *E*- and *Z*-allyl alcohol/halide/thioacetate precursors, followed by chemoselective sulfide oxidation using Oxone[®]. (105) Eqs. 70a and 70b illustrate these general approaches for the synthesis of the symmetrical and unsymmetrical sulfones 48 and 49, respectively. Notable examples of triene synthesis from this work are shown in Eqs. 71 and 72. With pre-existing double bonds both of *E*-configuration, the expected *E,E,E*-triene 50 is obtained in high yield (Eq. 71). A related example using Meyers' conditions produces an *E,E,E*-triene intermediate for carotenoid synthesis. (106, 107) Likewise, the *Z,Z*-diallyl sulfone 51 gives the *Z,E,Z*-triene 52 as the major product (Eq. 72). However, reaction at -78° in *tert*-butanol-dibromodifluoromethane (1:1) solution is required in order to achieve acceptable stereocontrol, a finding corroborated in later work directed at galbanolene natural products. (108)



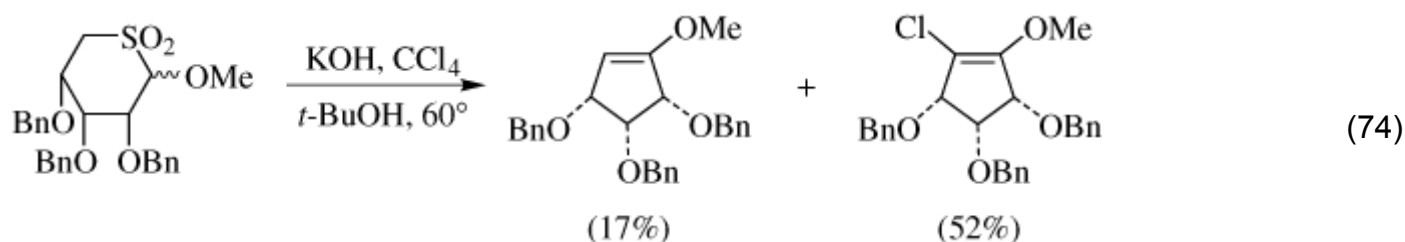


A novel application of the halogenative RBR, using the Chan procedure, is the synthesis of acyclic enediynes from dipropargylic sulfones. (109) The example shown in Eq. 73 is typical; the reaction is facile but gives essentially no stereocontrol. It is essential to use dichloromethane as the reaction solvent, since *tert*-butanol gives intractable mixtures.



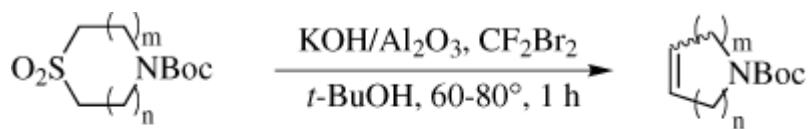
3.4.4. Synthesis of Cyclic Alkenes

The Meyers modification has been successfully applied to make cycloalkenes and heterocyclic compounds of variable ring size and functionality. For reasons that are unclear, it also appears that small- and medium-ring cyclic sulfones are generally less susceptible to side reactions than their acyclic counterparts. A general route to masked 3-cyclopentenones has been described (Eq. 47) (84) and related procedures have been employed to prepare an enantiomerically pure prostaglandin precursor (92) and a variety of polyoxygenated cyclopentenenes (e.g. Eq. 74) (110) and cyclohexenes (111, 112) from thiosugar derived sulfones.



General methodology utilizing Chan's procedure has been demonstrated for the synthesis of Boc-protected azacycles of varying ring size (Eq. 75). (31) In 7- and 8-membered ring products, only the *Z*-alkene is formed, whereas products of ring sizes 9–13 are formed as mixtures of *E*- and *Z*-isomers. For these larger ring sizes greater stereocontrol in favor of the *Z*-alkene is achieved by classical RBR of the corresponding pre-formed α -chlorosulfones.

With larger ring sizes, a recurring theme has been the conversion of disulfones of ring size (*m*) into cyclic dienes of ring size (*m*-2). This approach has been used in the synthesis of stereoisomers of tetrabenzo- and tetranaphtho[*a,c,g,i*]cyclododecene. (113) Certain compounds of this type exist as stable atropisomers, due to the

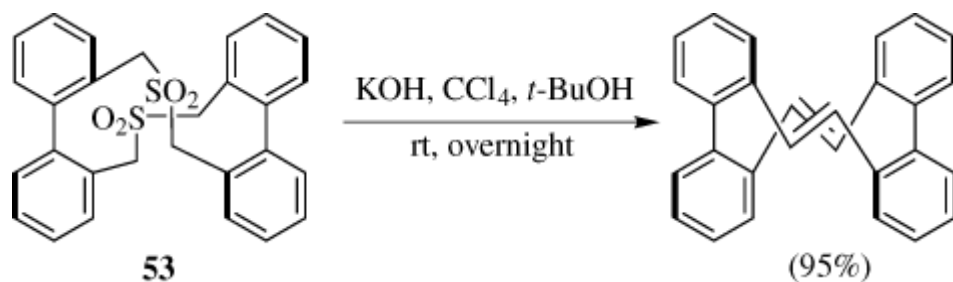


m	n	Z:E	yield ^a
2	2	100:0	(63%)
3	2	100:0	(33%)
3	3	35:65	(59%)
4	3	40:60	(67%)
4	4	27:73	(68%)
5	4	15:85	(62%)
5	5	39:61	(53%)

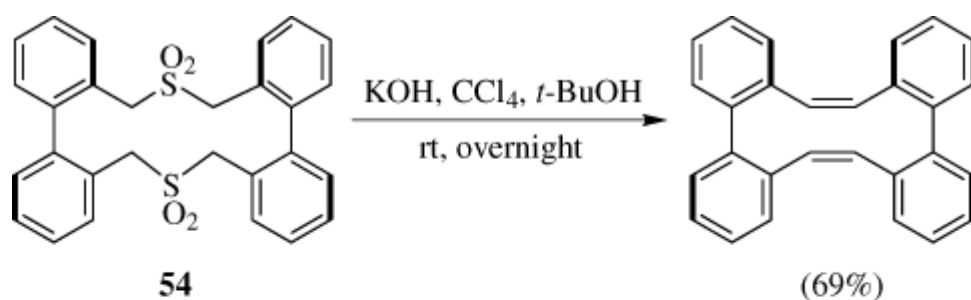
^aover 2 steps from sulfide

(75)

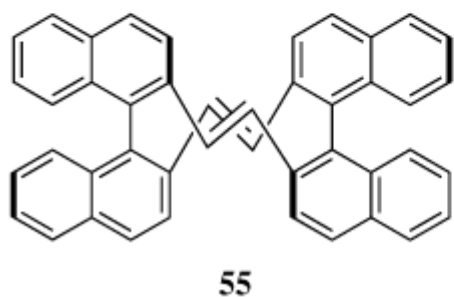
presence of chiral axes, rotation about which is hindered by bridging. In the tetrabenzo series, reaction of the racemic disulfone **53** results in the formation of E-double bonds (Eq. 76), whereas the *meso*-isomer **54** gives achiral Z-alkenes exclusively (Eq. 77). Work in the tetranaphtho series extends to the preparation of single atrop-*i*-somers, e.g. **55**, and is facilitated by the availability of enantiomerically pure precursors **56**. In contrast, analogous precursors in the tetrabenzo series are achiral due to unrestricted rotation of the 1,1'-biphenyl moiety. In a similar application, Chan's procedure is used to prepare the dienes **57** and subsequently both enantiomers of **58** en route to optically active [12][12]-paracyclophanes (Eq. 78). (114) Meyers' conditions have also been used as the basis of a general route to adamantophanes. (115)



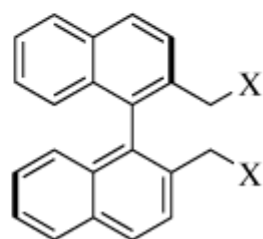
(76)



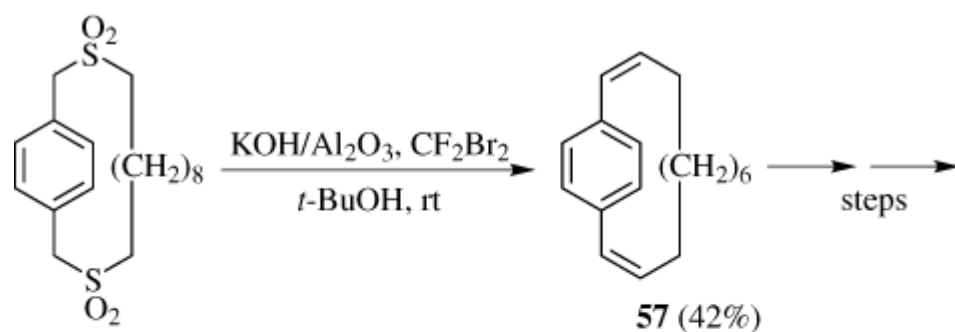
(77)



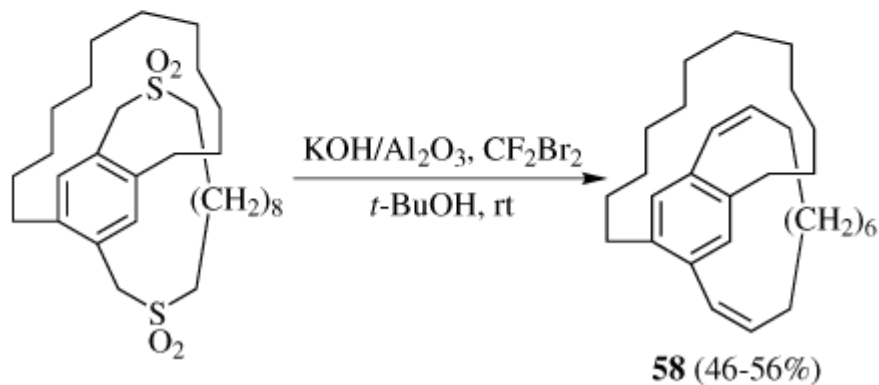
55



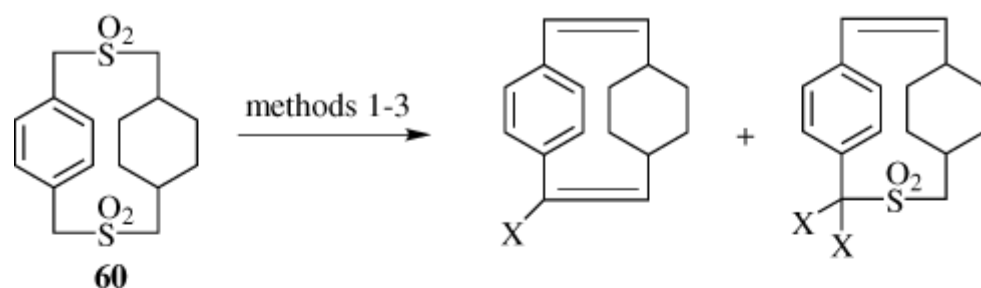
56: X = SH or Br



(78)

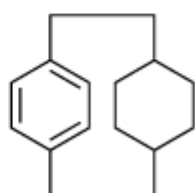


Lastly, studies directed at hexahydro[2.2]paracyclophane (**59**) indicate that the double RBR strategy for the preparation of cyclic dienes has its limitations. (116) As depicted in Eq. 79, a variety of methods for halogenative RBR were attempted for the conversion of disulfone **60** into diene **61**. In all cases, the first ring contraction is effected as required. However, presumably as a consequence of the highly strained nature of the targeted ring system, dihalogenation at the remaining benzylic carbon occurs prior to rearrangement, resulting in the formation of vinyl halide products. The paracyclophane **59** was eventually obtained by pyrolysis of the disulfone **60**.

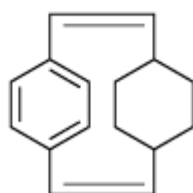


method 1:	KOH, CCl ₄ , <i>t</i> -BuOH, 27°, 13 h	(8.4%) X = Cl	(22%) X = Cl
method 2:	KOH/Al ₂ O ₃ , CCl ₄ , <i>t</i> -BuOH, 27°, 24 h	(16.8%) X = Cl	(—)
method 3:	KOH/Al ₂ O ₃ , CF ₂ Br ₂ , <i>t</i> -BuOH, 27°, 24 h	(6.2%) X = Br	(—)

(79)



59



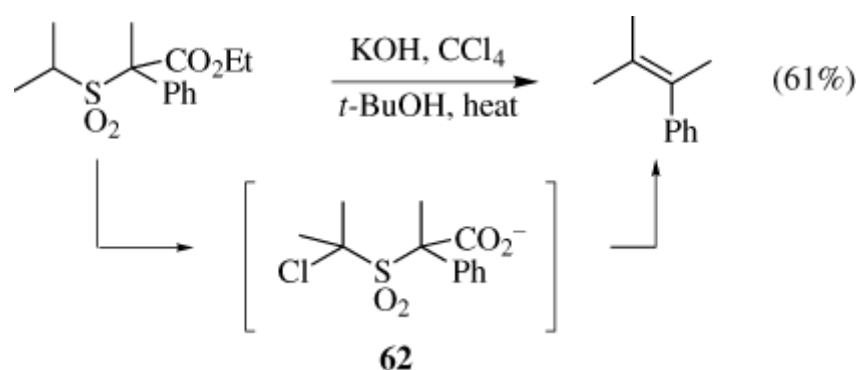
61

In conclusion, the foregoing examples attest to the versatility of the one-pot methods for halogenative RBR. The method has become increasingly prevalent, and there are now very few cases in which a separate halogenation step is a necessity.

3.5. Other Variants of the RBR

3.5.1. Decarboxylative RBR

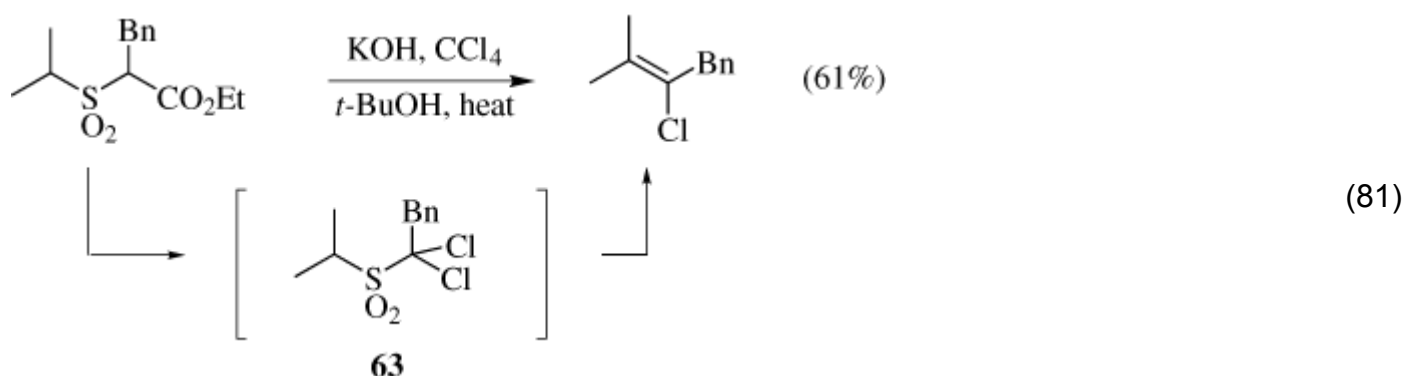
A limited number of α,α -disubstituted ethyl isopropylsulfonylacetates have been reported to undergo a decarboxylative RBR under Meyers' conditions (e.g. Eq. 80). (117) It was established that, in the absence of carbon tetrachloride, saponification takes place but decarboxylation is not observed. In view of this surprising result, it was proposed that the key intermediate is a chlorinated carboxylate **62** and that this undergoes ready decarboxylation followed by RBR.



(80)

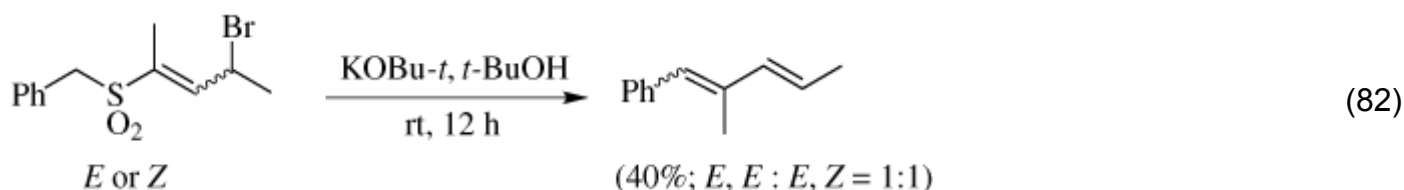
With the corresponding α -monosubstituted esters, vinyl chlorides are obtained as secondary

products or, in one example (Eq. 81) as the sole product. To account for this observation, initial chlorination adjacent to the ester group was proposed followed by saponification/decarboxylation/chlorination to give the key dichloro intermediate **63** that would then undergo RBR.

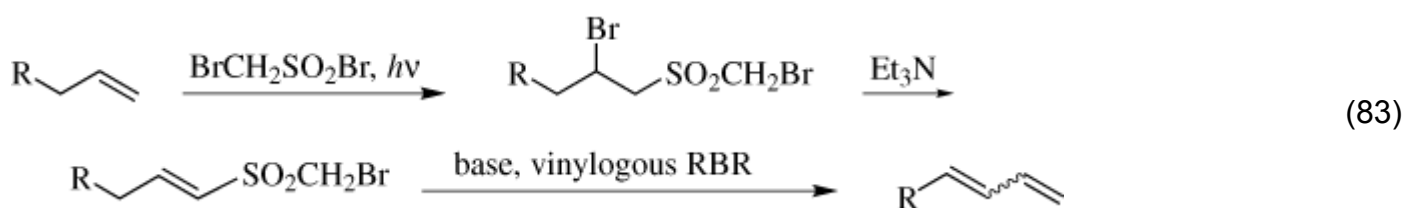


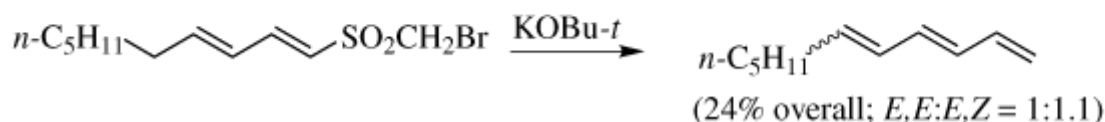
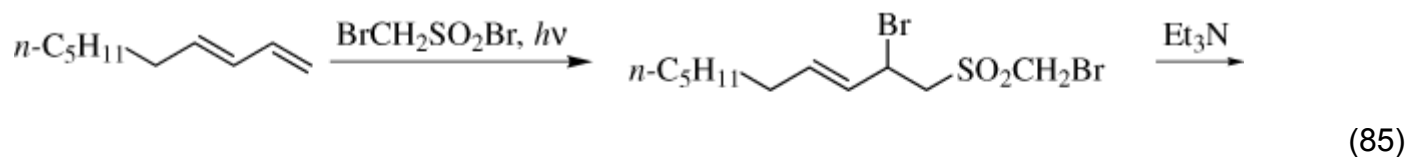
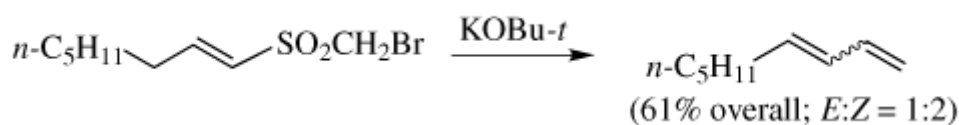
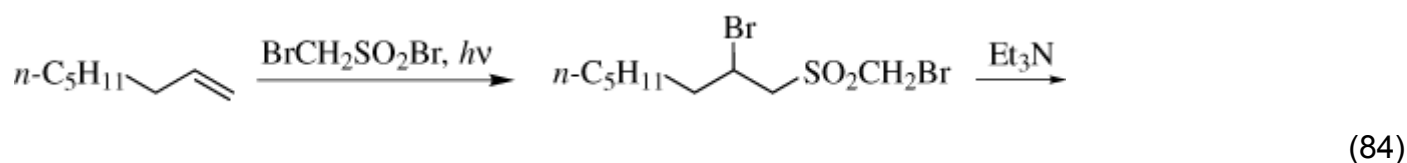
3.5.2. Vinylogous RBR

Vinylogous variants of the Ramberg-Bäcklund reaction, in which an additional double bond participates in the process and dienes are formed, have also been devised. The first type of vinylogous RBR, in which the leaving group is allylically disposed to the sulfone, was reported in 1975 (Eq. 82). (118) The bromide precursors for this type of vinylogous RBR are not readily available, however, and no further examples have been reported.

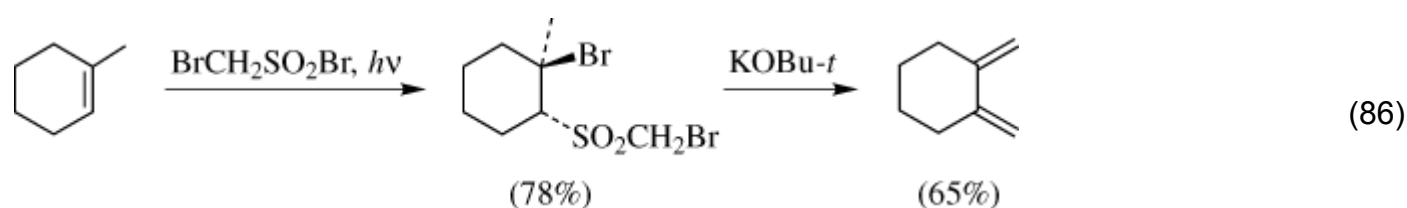


More recently, Block et al. have published a number of examples of the alternative vinylogous process which employs vinyl sulfones bearing an α -halogen group (Eq. 83). (46-48, 119-122) The requisite α -halo- α,β -unsaturated sulfones are readily prepared from alkenes by the photochemical addition of bromomethanesulfonyl bromide followed by elimination of hydrogen bromide. The vinylogous RBR then proceeds efficiently, using potassium *tert*-butoxide. The overall process thus represents a three-step procedure for the transformation of alkenes into 1,3-dienes. Eqs. 84–87 depict representative cases. Eq. 84 illustrates diene formation, and Eq. 85 shows that conjugated dienes can be elaborated to prepare trienes using this methodology. (47) However, conjugated trienes do not undergo addition with bromomethanesulfonyl bromide and so conjugated tetraenes are not available using this procedure.

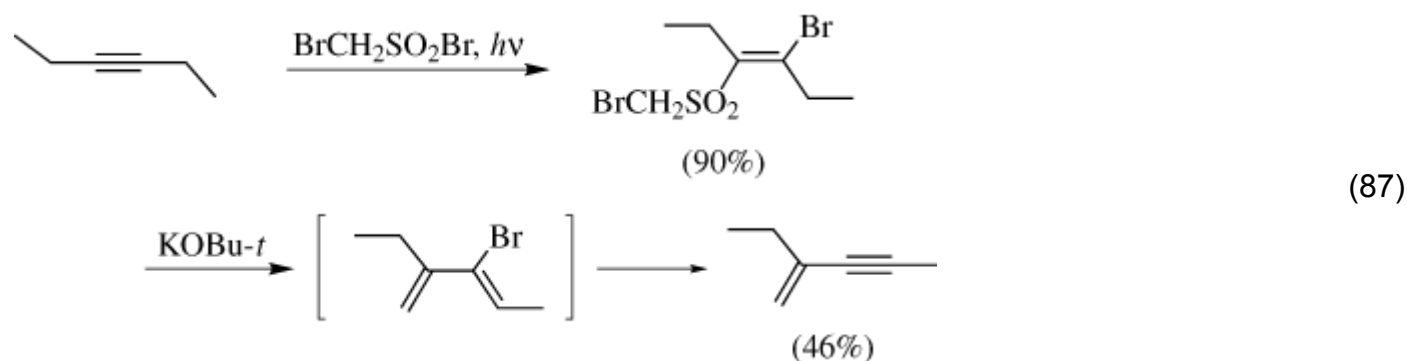




As can be seen, the stereocontrol in acyclic examples is often poor, although the use of lithium *tert*-butoxide can lead to improved stereoselectivity in the synthesis of 2-alkyl-1,3-butadienes. (121) For this reason, the sequence is most useful in cases where geometric isomers are not possible: this is illustrated in Eq. 86, and this example also shows that the hydrogen bromide elimination and vinylogous RBR can be accomplished in a single operation. (47, 122) This methodology has subsequently been utilized in the preparation of chiral dienyl boronates. (123)



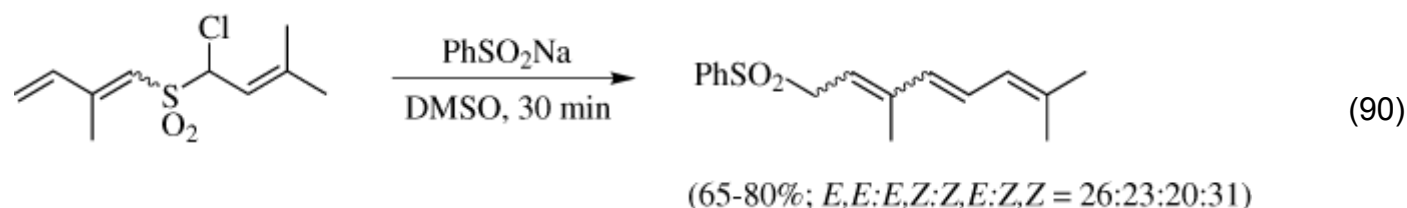
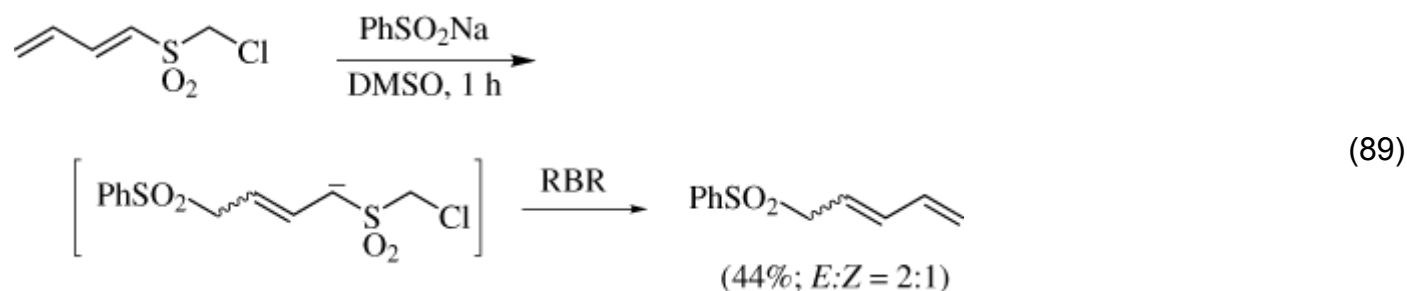
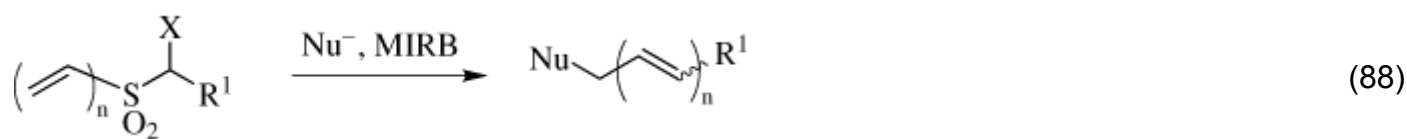
Eq. 87 illustrates the extension of the methodology to alkynes: treatment of the bromomethylsulfonyl adduct with base presumably gives an initial vinylogous RBR followed by dehydrobromination. (6)



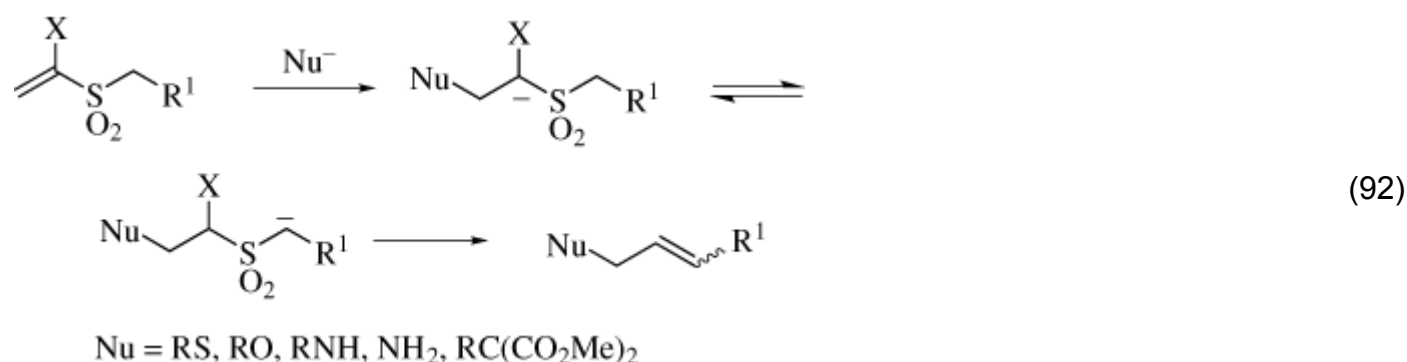
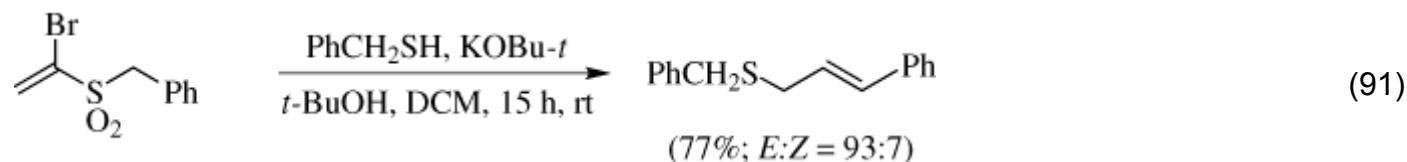
3.5.3. Michael-induced RBR (MIRBR)

The α -sulfonyl anions needed for the Ramberg-Bäcklund reaction have also been generated indirectly. In 1977, De Waard introduced the Michael-induced Ramberg-Bäcklund (MIRBR) variant (Eq. 88). (124) In principle, this is an extremely useful modification as it allows the introduction of

functionality (e.g. Nu = arylsulfonyl, (124, 125) alkoxide, or phenoxide (47)) during the reaction. In practice, however, the process is of limited utility because of the apparent (6) requirement for a dienyl sulfone (n = 2); similar reactions involving vinyl sulfones (n = 1) are unknown. Within these limitations, however, the process is a valuable route to functionalized dienes (Eq. 89) (124) and, if allylic halides are employed, functionalized trienes. The latter approach has been used for isoprenoid synthesis, although with a low level of stereocontrol (Eq. 90). (125)

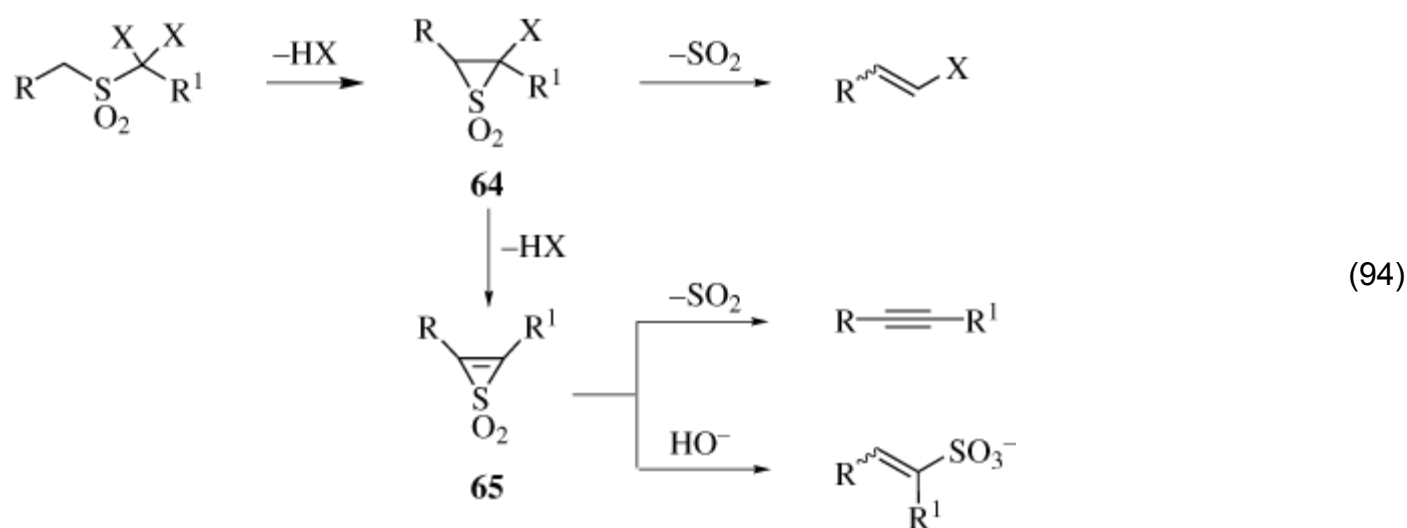
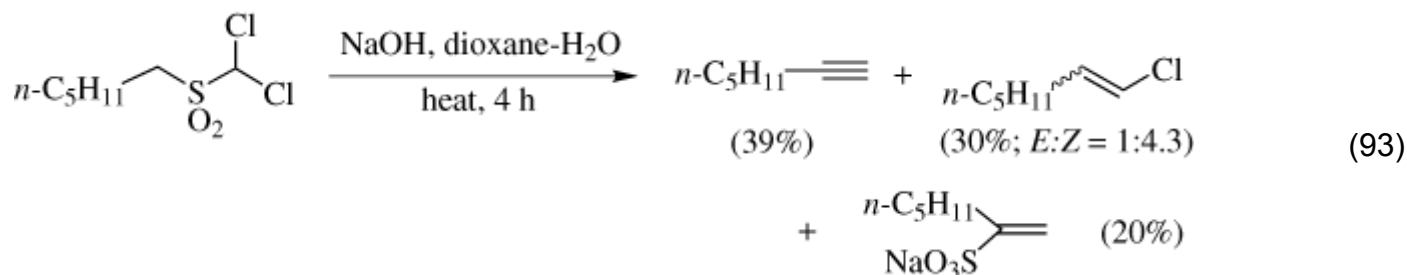


More recently, a new variant of the MIRBR reaction has been developed which utilizes α -halovinyl sulfones as substrates and has been carried out using thiolate (Eq. 91), alkoxide, amine, and malonate nucleophiles. (54) The E:Z ratios reflect the basicity of the reagent; with weak amine bases, Z-isomers predominate, whereas methoxide and *tert*-butoxide (and benzylthiolate) favor formation of the E-alkenes. This process involves a one-pot tandem conjugate addition-proton exchange-RBR process (Eq. 92).

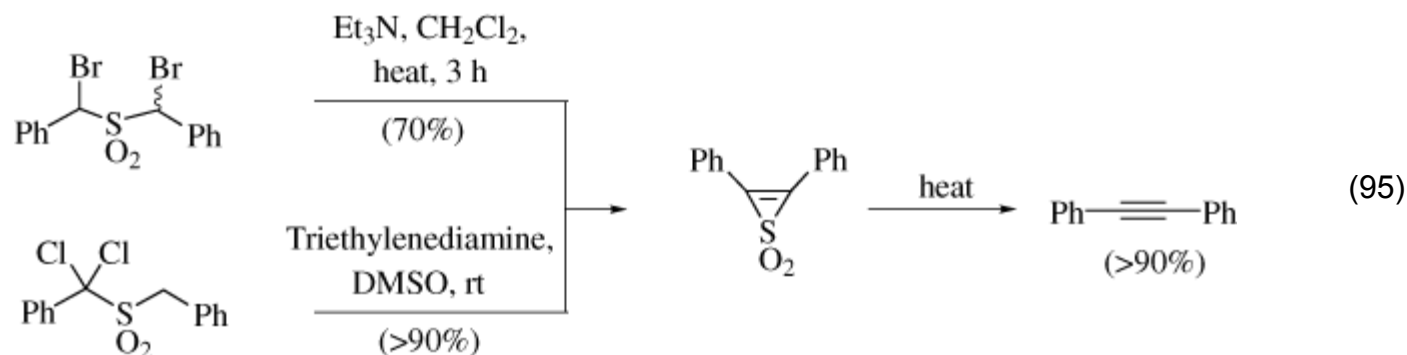


3.5.4. Preparation of Alkynes and Vinyl Halides

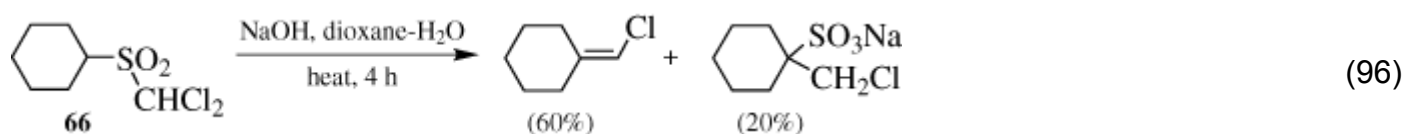
(RBR on dihalo- and trihalosulfones). α,α -Dihalosulfones and α,α' -dihalosulfones can undergo base-mediated rearrangements to produce vinyl halides, alkynes, or α,β -unsaturated sulfonic acids. Similar products can be obtained directly from sulfones via Meyers' variant, as discussed earlier. In some cases (e.g. Eq. 93) all three types of product are observed. (61) The formation of these products has been rationalized by the mechanistic scheme shown in Eq. 94. (11, 61) Thus, the presumed α -halothiirane dioxide intermediate **64** can either undergo loss of sulfur dioxide to generate a vinyl halide, or undergo dehydro-halogenation to give thiirene dioxide **65**. Intermediate **65** can then lose sulfur dioxide to generate an alkyne or react with hydroxide to give the vinylsulfonate.



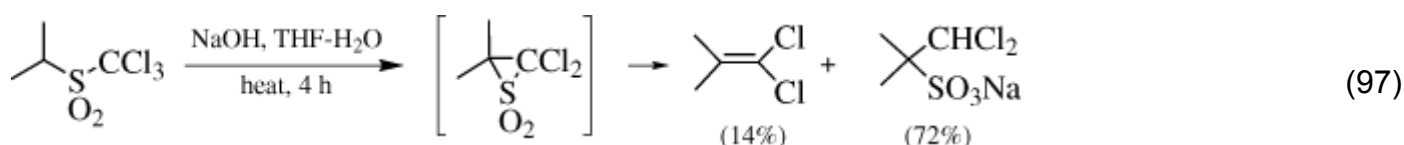
Thiirene dioxides can be prepared from dihalosulfones using weak bases (Eq. 95), and they give alkynes on thermolysis, (71, 126) adding support to the above mechanistic hypothesis.



In other examples, the range of products is restricted for structural reasons. For example, (61) alkyne formation is precluded in the reaction of dichlorosulfone **66** (Eq. 96).

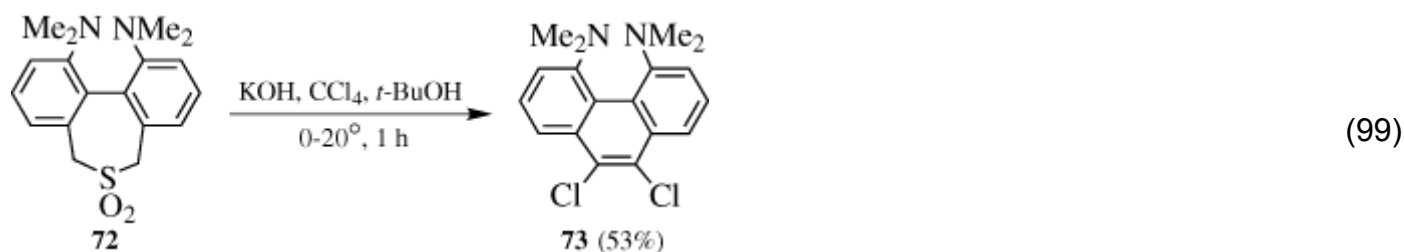
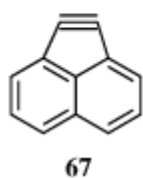
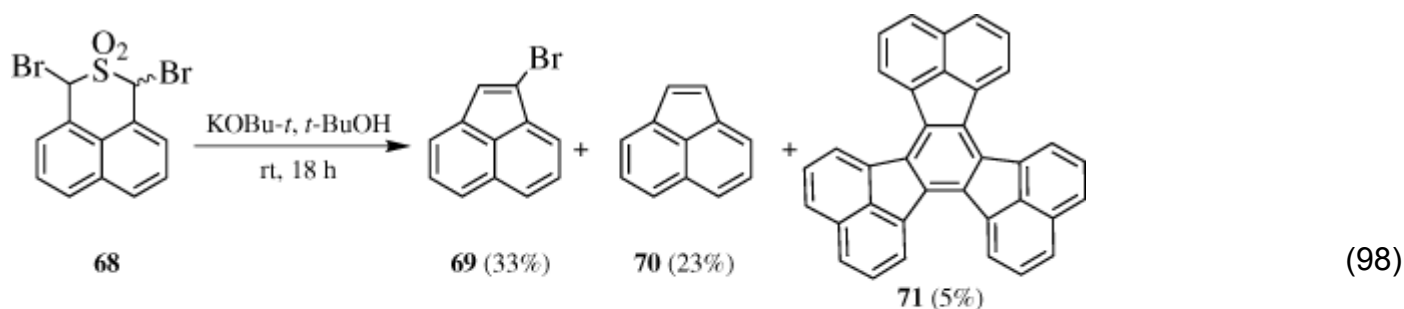


1,1,1-Trichlorosulfones have also been studied and in general it was found that sulfonate formation predominates (e.g. Eq. 97). (62)

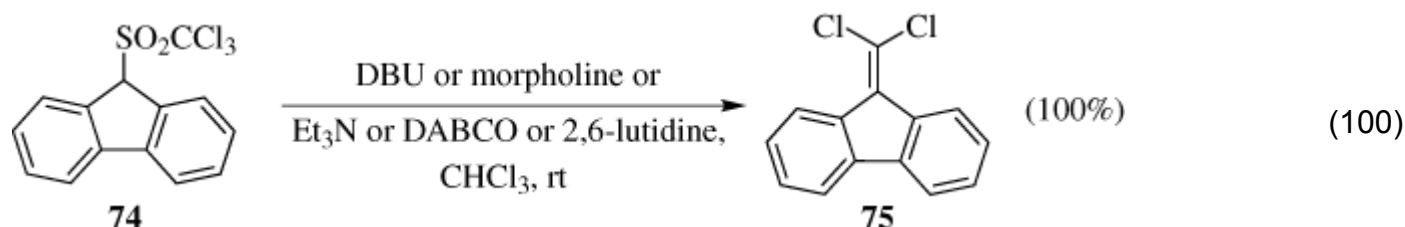


The above area has been well reviewed by Paquette (5, 12) and only a few additional examples have been published in recent years. A selection of these recent examples is covered here. In the search for a route to acenaphthylene **67**, treatment of dibromide **68** with base was explored (Eq. 98). (60) The major product is vinyl bromide **69** although the corresponding alkene **70** and decacyclene **71** are also formed. It was proposed that sulfite reduction of dibromide **68** to the corresponding monobromide, followed by RBR, gives rise to **70**, and that the formation of **71** (by a [2 + 2 + 2]-cycloaddition process) confirms the intermediacy of acenaphthylene **67** formed from the corresponding thiirene dioxide.

In a related example (Eq. 99), the disubstituted dichlorophenanthrene **73** is produced directly from sulfone **72** under Meyers' conditions, presumably by way of an intermediate trichlorosulfone. (127) It should be noted that the classic RBR on related α -chlorosulfones is not a useful procedure for preparing substituted phenanthrenes. (14)



The trichloromethylsulfone **74** undergoes quantitative conversion into 9-dichloromethylene-fluorene **75** on treatment with weak bases (Eq. 100). (63) A number of related examples are reported also giving 1,1-dichloroalkenes. (56, 63) The conversion shown in Eq. 100 is a dramatic exception to Paquette's generalization that 1,1,1-trichlorosulfones mainly produce sulfonates on treatment with base, (62) although the use of an amine base and non-aqueous conditions are probably crucial. Reactions of the corresponding sulfoxide have also been studied, and on treatment with DBU a modest yield (12%) of dichloroalkene **75** is obtained along with several other by-products. (128)

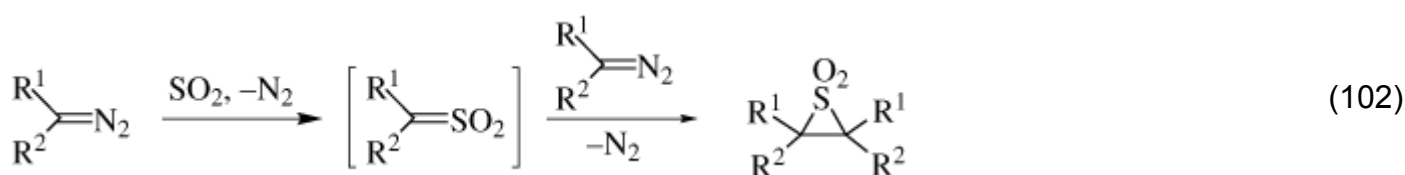
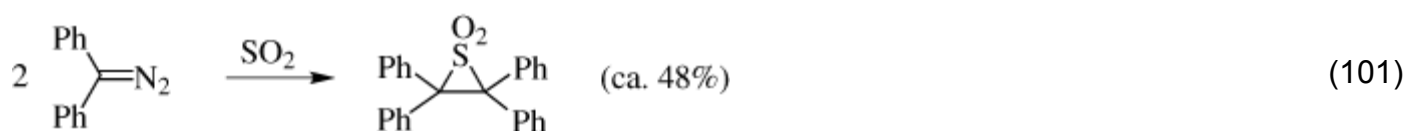


3.6. Preparation and Synthetic Utility of Thiirane Dioxides

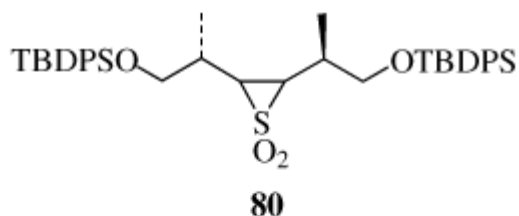
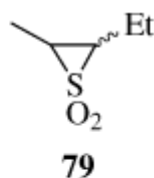
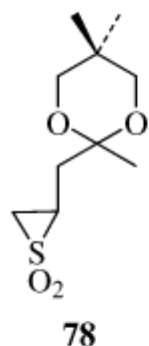
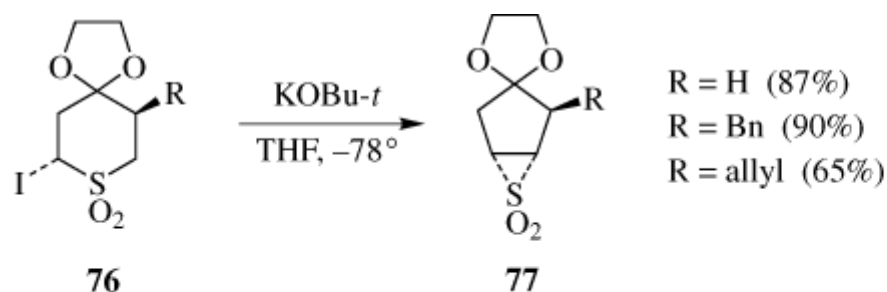
At the time they were first proposed as intermediates in the RBR, (2) only a few stable thiirane dioxides were known. Since that time new procedures have been introduced for their preparation and a more detailed study of their synthetic potential has been undertaken. This topic has been well reviewed (7, 22, 129-131) and the following section will concentrate on recent advances.

3.6.1. Isolation of Thiirane Dioxides

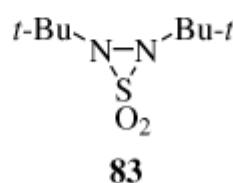
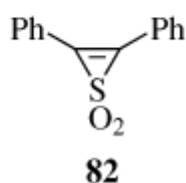
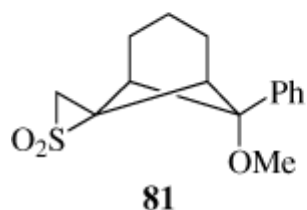
The first reported thiirane dioxide (episulfone) preparation was by Staudinger and Pfenninger in 1916. (132) They showed (Eq. 101) that treatment of sulfur dioxide with excess diphenyldiazomethane generated tetraphenylthiirane dioxide. This process proceeds by way of an intermediate sulfene, which then reacts with a second equivalent of diazoalkane (Eq. 102).



The Staudinger-Pfenninger method is therefore limited to the formation of symmetrically substituted thiirane dioxides, but unsymmetrical systems can be obtained by generation of the sulfenes, usually from sulfonyl chlorides and tertiary amines, in the presence of a diazoalkane (Eq. 103). (133, 134) Until recently, these diazoalkane methods were the only efficient routes to thiirane dioxides and they have been widely used, (22, 129, 135) with a number of recent applications. (136-142) In addition, as mentioned earlier, thiirane dioxides obtained via this procedure have proved invaluable in mechanistic studies of the RBR.



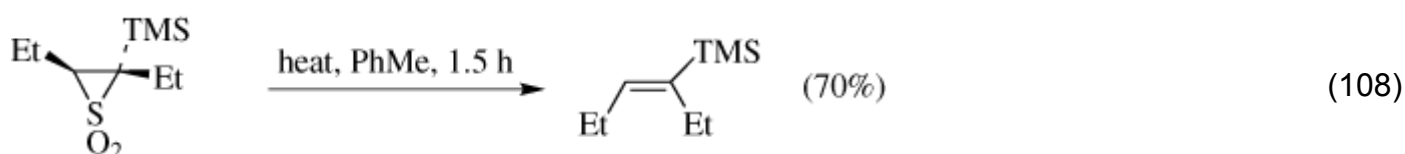
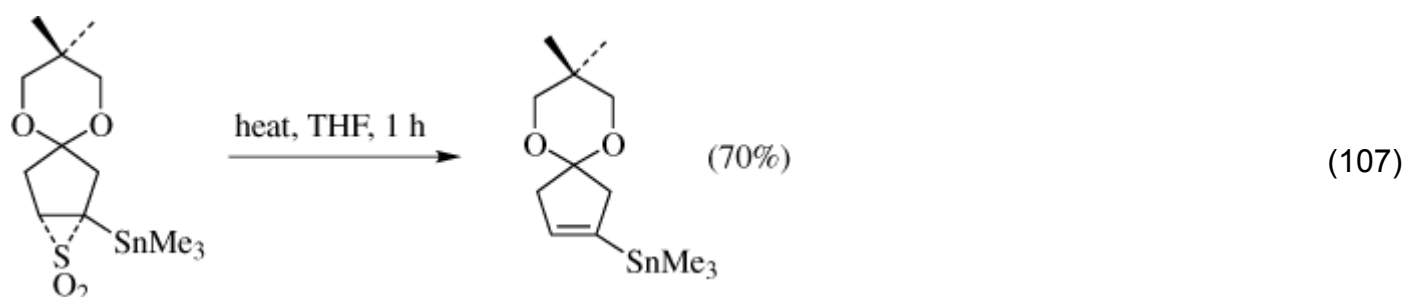
(106)

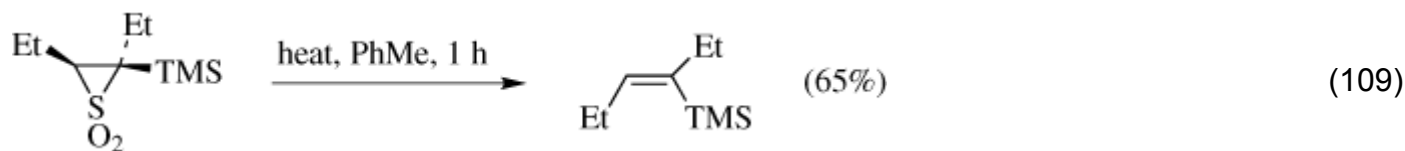


Thiirane dioxides (e.g. **82**) ([71](#), [126](#)) are also readily prepared by the treatment of dihalosulfones with amine bases in organic solvents, and are accessible by other procedures. ([22](#), [71](#), [129](#)) In addition, several nitrogen-containing analogs of thiirane dioxides (e.g. thiaziridine dioxides, and thiadiaziridine dioxides such as **83** ([151](#))) have been described, either as isolated compounds or as reaction intermediates. ([152](#))

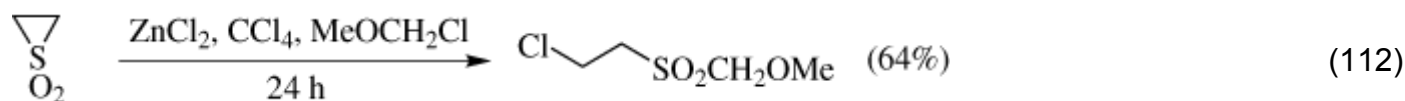
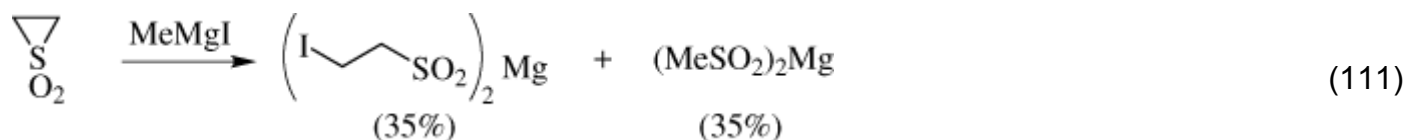
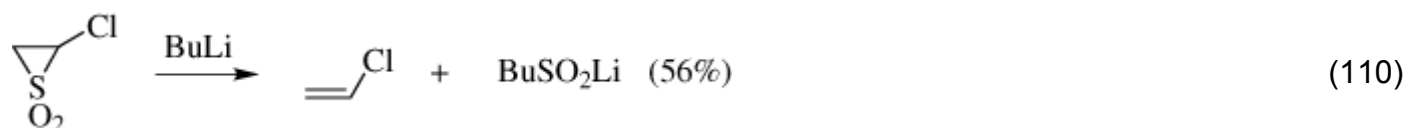
3.6.2. Reactions Of Thiirane Dioxides

The reactions of thiirane (and thiirane) dioxides were comprehensively reviewed in 1983, ([22](#)) 1988, ([129](#)) and 1996. ([130](#), [131](#)) The most studied reaction of thiirane dioxides involves their conversion into alkenes either thermally or on treatment with base. This topic has been well reviewed and was discussed in more detail earlier in this review. Examples are shown in Eqs. [107–109](#). ([153](#))

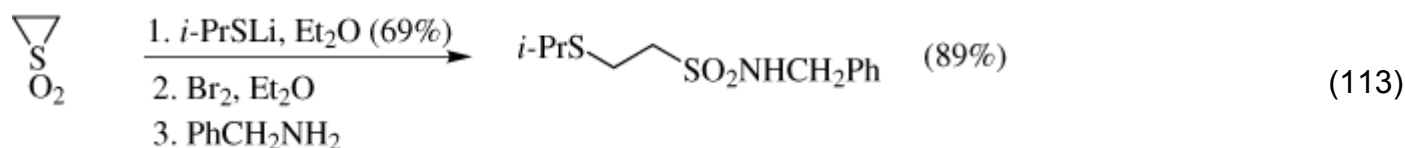




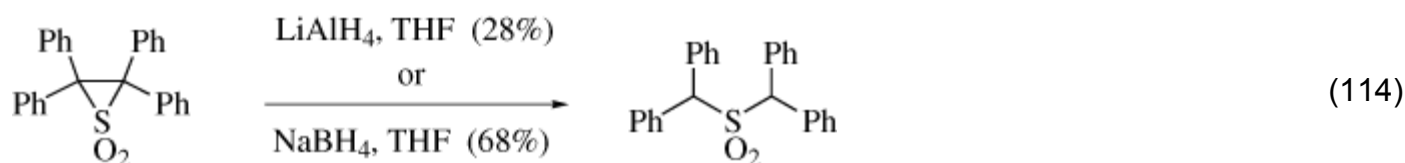
Reaction of thiirane dioxides with alkyllithium and dialkylmagnesium reagents gives mainly the corresponding alkenes accompanied by the alkylsulfinate salt (Eq. 110). (24, 154) Initial attack at sulfur would again appear to be in operation here. By contrast, the use of Grignard reagents generates a significant amount of the haloethylsulfinate salt resulting from halide attack at carbon (Eq. 111). (154) Similar reactions have been observed with metal halides, (155, 156) and by the combined use of zinc(II) chloride/chloromethyl methyl ether the intermediate sulfinate can be S-alkylated in situ (Eq. 112). (155)

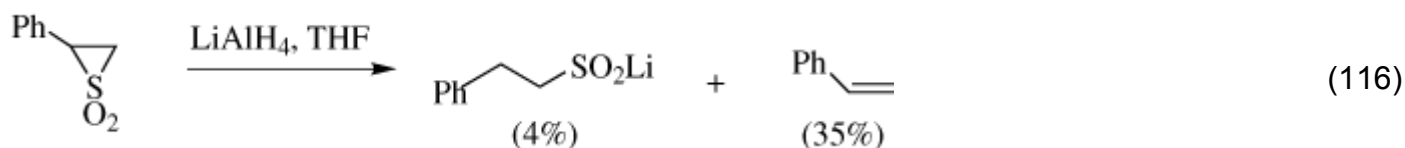
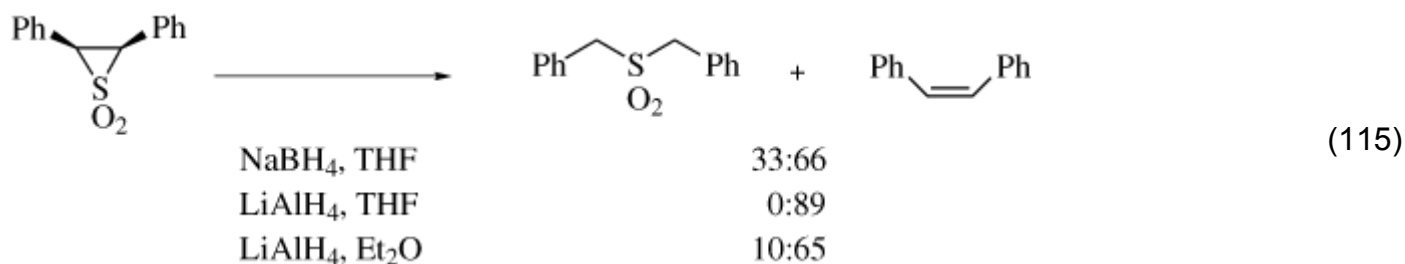


Thiolates and related sulfur-based nucleophiles also appear to attack thiirane dioxides at carbon rather than sulfur, giving a synthetically useful route to a range of ethanesulfonates. (157, 158) Eq. 113 illustrates a route to functionalized sulfonamides using this methodology. (157)

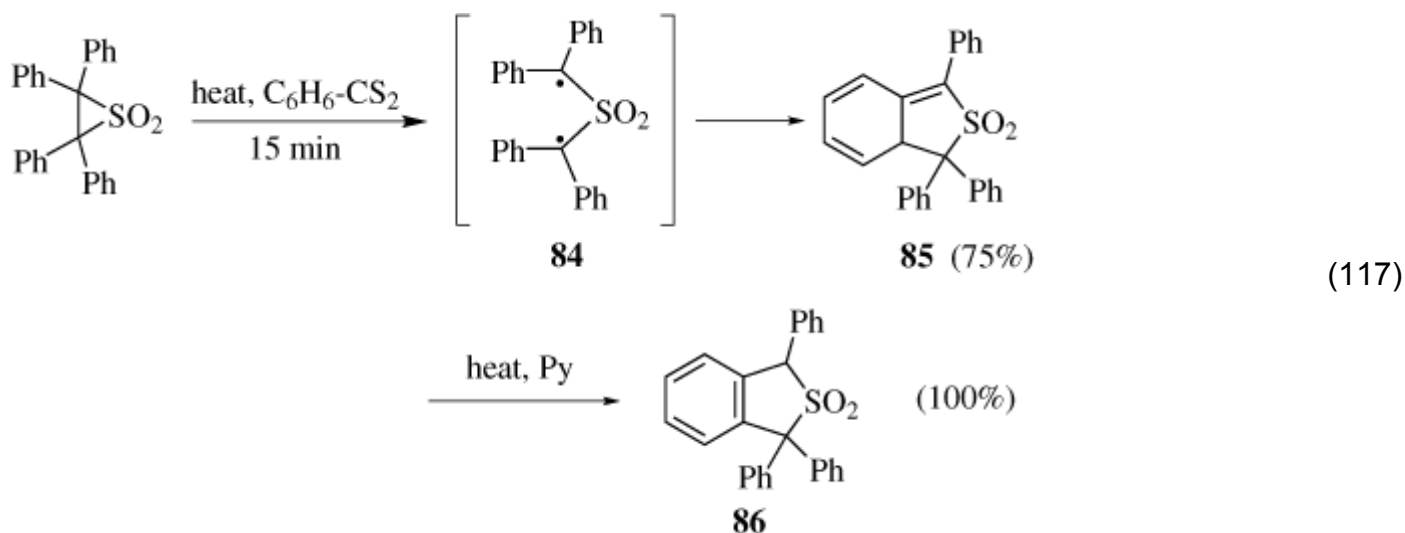


Hydride reductions have been studied and the outcome shown to be highly dependent on the substitution pattern of the thiirane dioxide, the particular reducing agent, and the reaction solvent (Eqs. 114–116). (159) The noteworthy aspect of this study is the observation of reductive cleavage of the thiirane dioxide carbon-carbon bond in the tetraphenyl- and diphenyl-substituted systems.

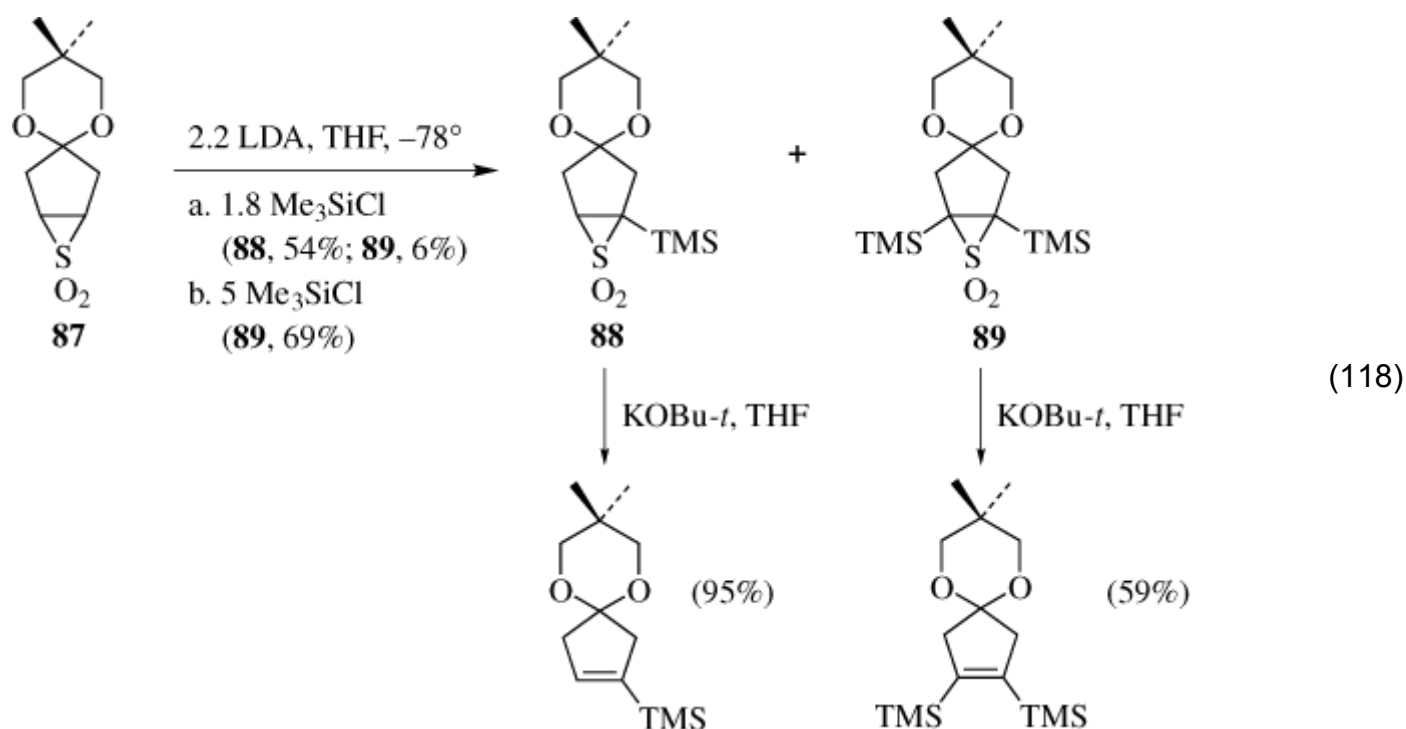




Carbon-carbon bond cleavage is also seen during the thermolysis of tetraphenylthiirane dioxide in carbon disulfide-benzene (Eq. 117). (160) The mechanistic proposal is that the diradical intermediate **84** undergoes intramolecular cyclization to give **85**, which isomerizes to the benzannulated thiolane dioxide **86** on treatment with base.

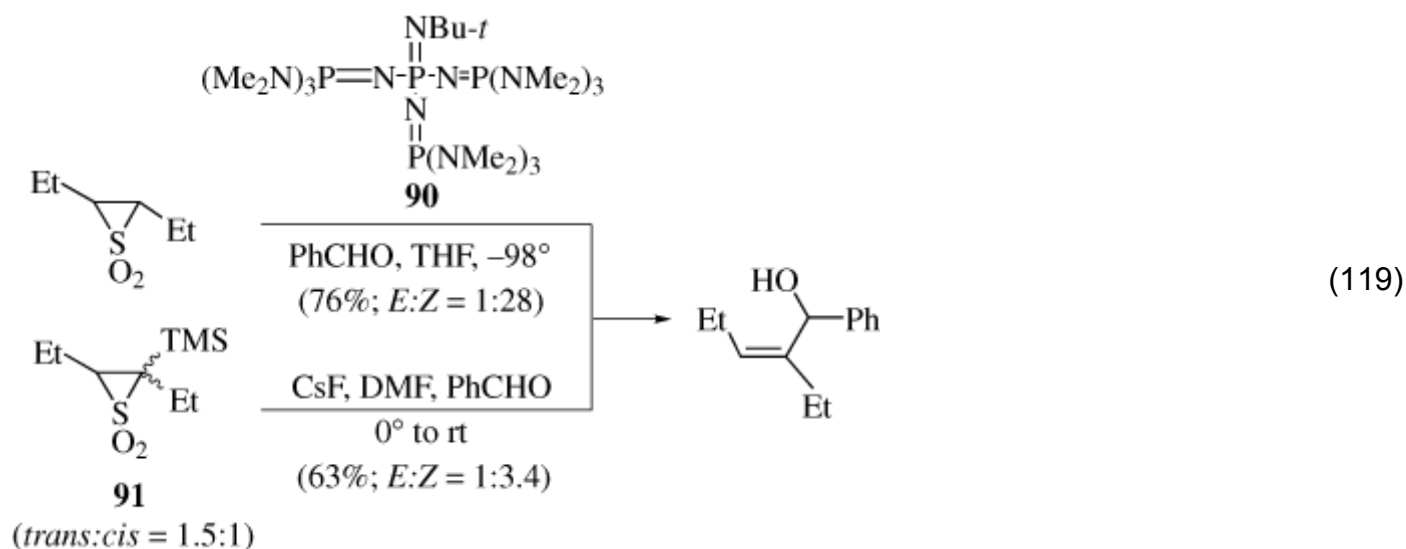


Building on the mechanistic work concerning thiirane dioxide epimerization discussed earlier, recent studies have shown that thiirane dioxides can be quantitatively deprotonated and the resulting α -sulfonyl anions trapped with a range of electrophiles. (153, 161-164) Thus, as shown in Eq. 118, thiirane dioxide **87** can be deprotonated using lithium diisopropylamide (LDA) and the anion trapped using trimethylsilyl chloride as an in situ electrophilic quenching agent. (153) By varying the stoichiometry of the electrophile, mono- or disilylated adducts (**88** or **89**, respectively) can be obtained. The structure of adduct **89** was confirmed by X-ray crystallography, the long carbon-sulfur bond length (1.686 Å) being particularly noteworthy. Other chlorosilanes, as well as chlorostannanes, can be employed in this process but in all cases in situ trapping of the anion is a requirement for success. The resulting thiirane dioxides can be readily converted into the corresponding alkenes (Eq. 118): this methodology therefore constitutes a novel means of preparing unusual vinyl silanes (and vinyl stannanes).



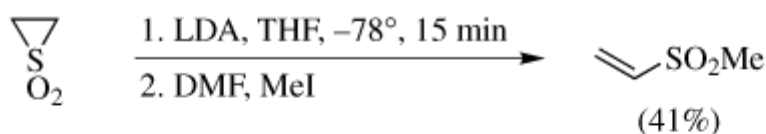
The requirement for in situ trapping of the α -sulfonyl anions proves problematic where carbon-centered electrophiles are concerned. Using the LDA conditions with benzoyl chloride or benzoyl imidazole as electrophile gave only low yields of the acylated thiirane dioxide. (153) However, it was found that the phosphazene base **90** was compatible with aromatic aldehydes in the thiirane dioxide deprotonation-trapping procedure, although the process was accompanied by desulfonylation (Eq. 119). (39, 162) The same transformation could be accomplished by anion generation from the silylated thiirane dioxide **91** (Eq. 119); in addition to aromatic aldehydes, 2,2,2-trifluoroacetophenone, benzenesulfonyl fluoride, benzoyl fluoride, diphenyldisulfide, and diphenyldiselenide could be employed as electrophiles in this desilylation-trapping-desulfonylation sequence. (39, 162)

Although the in situ alkylation of the thiirane dioxide derived anions does not appear to be an efficient process, it has been established that the sequential deprotonation-alkylation reaction provides a useful route to alkenyl sulfones (Eq. 120). (24, 39, 163)

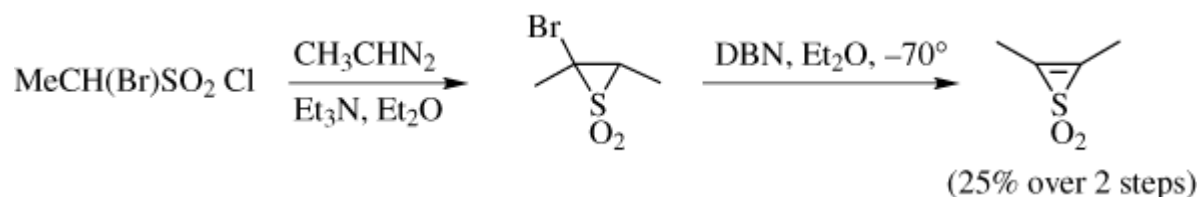
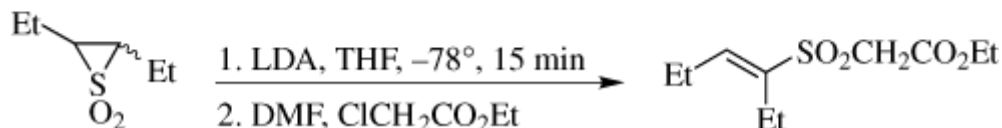


It is assumed that this transformation proceeds by way of a ring opening rearrangement to generate an intermediate alkenylsulfinate. Similar results have been obtained with thiirane oxides. (165) Gas

phase and theoretical studies (165, 166) on the deprotonation of thiirane, thiirane oxide, and thiirane dioxide are in accord with these experimental studies.



(120)



(121)

Finally in this section, it should also be noted that a bromo-substituted thiirane dioxide has been shown to undergo dehydrobromination on treatment with DBN to produce dimethylthiirene dioxide (Eq. 121). (71)

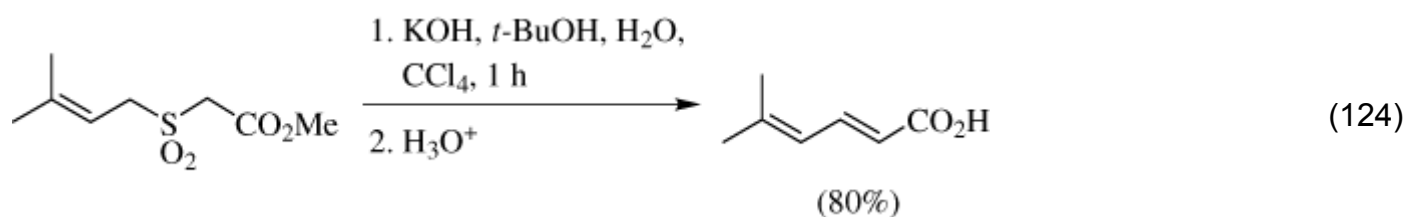
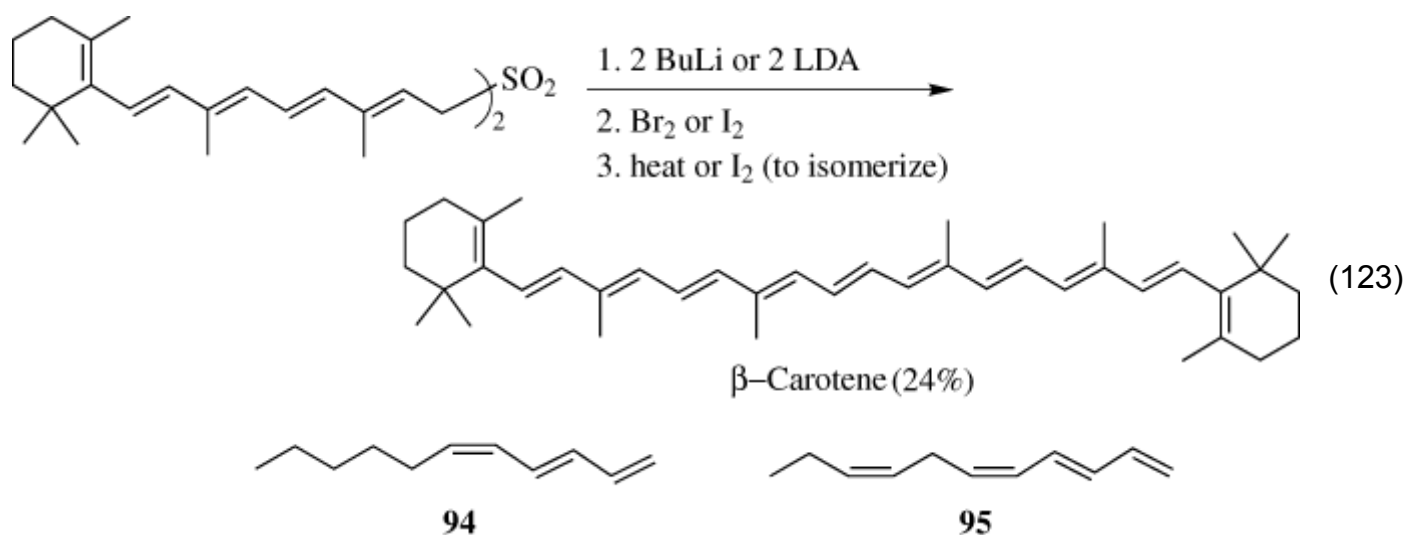
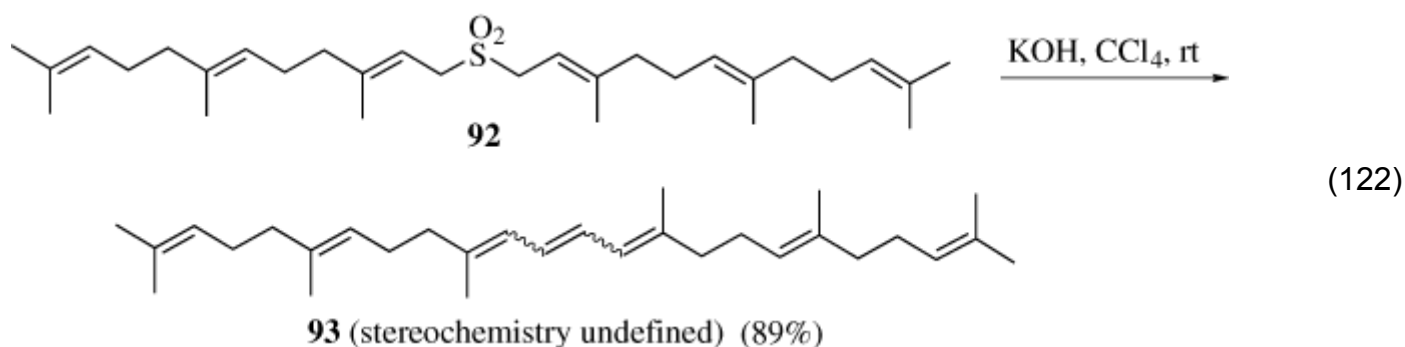
3.7. Applications of the RBR in Natural Product and Bioactive target Molecule Synthesis

The RBR found many early applications for the preparation of strained cycloalkenes such as cyclobutenes, unsaturated cyclophanes, and related bridged systems. These applications have been well reviewed. (5, 6) A number of applications of the reaction in natural product synthesis and related areas, many published relatively recently, are discussed in this section. Attention is concentrated on the key RBR process, and the reader is referred to the original literature for the complete synthetic scheme. It should be noted, however, that these applications illustrate the scope of the RBR in terms of substrates (acyclic, carbocyclic, and heterocyclic with a range of ring sizes), and its utility in terms of a conjunctive synthetic procedure with complete regiocontrol with respect to alkene construction. The importance of any synthetic methodology is often judged by its utility in the synthesis of complex, polyfunctional natural products: the following examples illustrate the increasingly recognized value of the RBR in this regard.

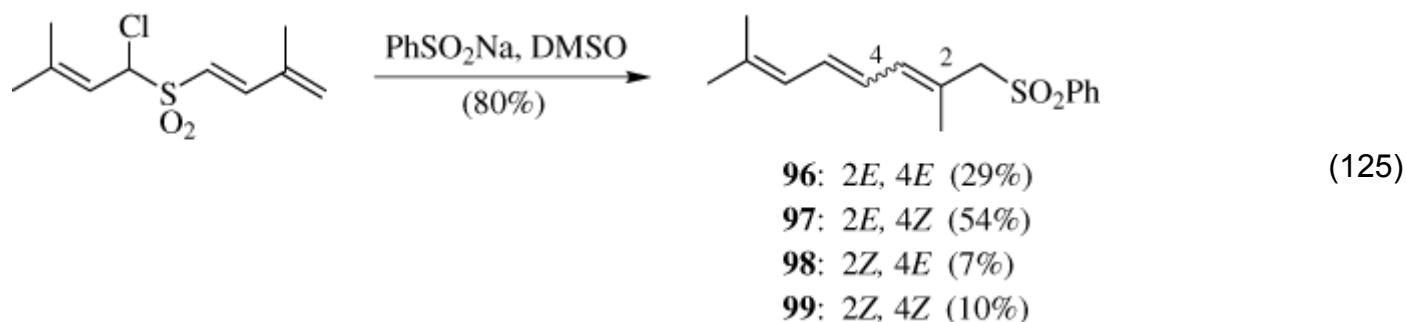
3.7.1. Isoprenoids and Related Polyenes

The first application of the RBR in natural product synthesis was by Büchi who described two routes to isoprenoids (Eqs. 122 and 123). (102) The Meyers modification was employed to convert a range of diallyl sulfones (e.g. 92) into the corresponding conjugated trienes (e.g. 93) as shown in Eq. 122. In the synthesis of the β -carotene shown in Eq. 123, Meyers' procedure was unsuccessful and a variant based on the halogenation of an α,α -sulfonyl dianion (167) was employed. However, a synthesis of β -carotene using Meyers' method has recently been successfully accomplished. (106, 107)

Further applications of the RBR in the isoprenoid area have been reported, (168) and it has also been employed for the preparation of naturally occurring trienes and tetraenes such as 94 and 95, (103) which have been isolated from a number of sources including the seaweed *Dictyopterus plagiogramma*. A related route to polyunsaturated acids has also been described (Eq. 124). (169)



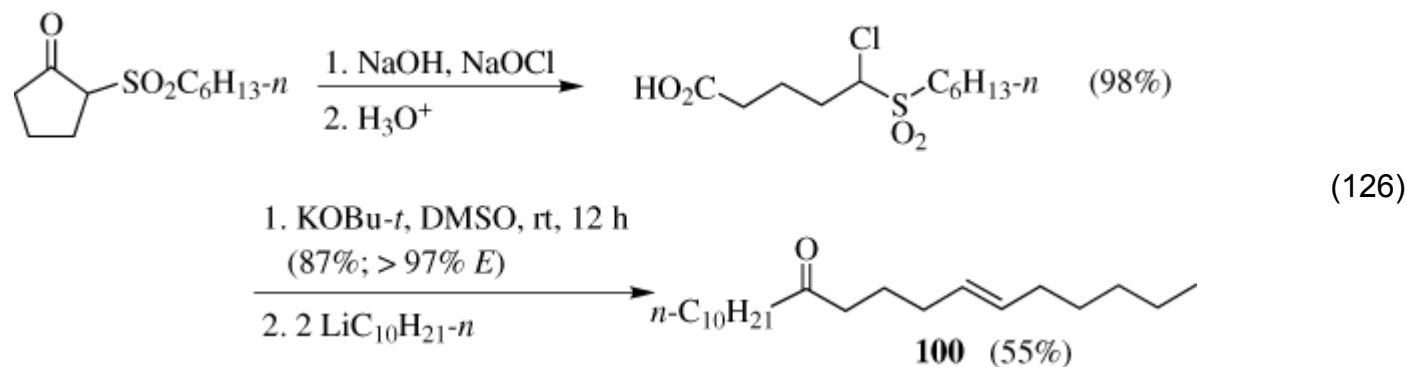
The MIRBR has subsequently been employed to prepare a range of conjugated isoprenoids, but, as shown in Eq. 125, the degree of stereocontrol is often disappointing, as evidenced by the distribution of products **96–99**. However, iodine-catalyzed isomerization gives a quantitative yield of an equilibrium mixture containing isomers **96** and **98** (70:30). (125)



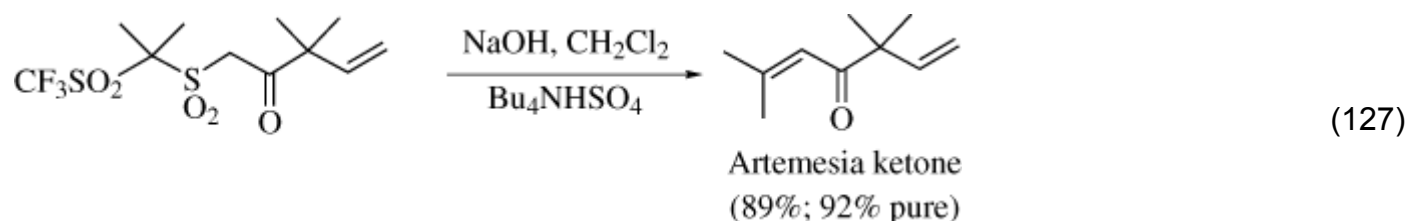
3.7.2. Insect Pheromones and Related Natural Products

Several simple insect pheromones have been prepared using the RBR. (32, 58) Eq. 126 shows the

synthesis of (*E*)-heneicos-6-en-11-one (**100**); (*E*)-dodec-7-enyl acetate is prepared in a similar manner. (32) The use of the halogenative ring opening (57) of 2-alkylsulfonylcycloalkanones to give RBR precursors is noteworthy.

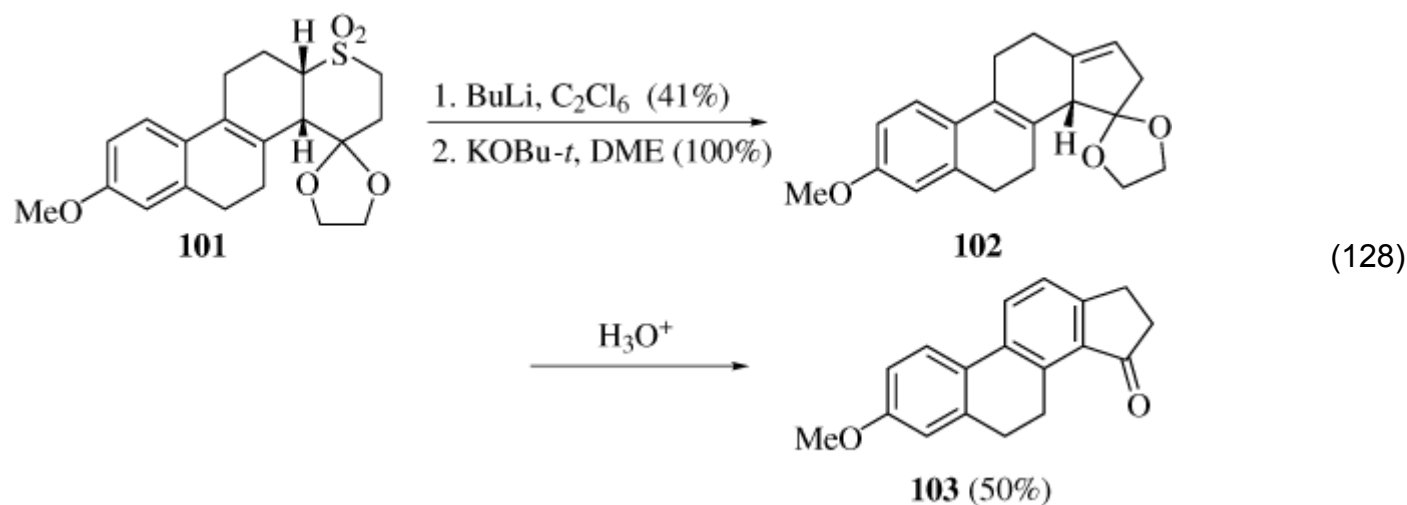


Artemisia ketone, obtained from the herb *Artemisia annua* and used in the perfumery industry, has been prepared efficiently using the triflone methodology outlined in Eq. 127. (83)



3.7.3. Steroid Synthesis

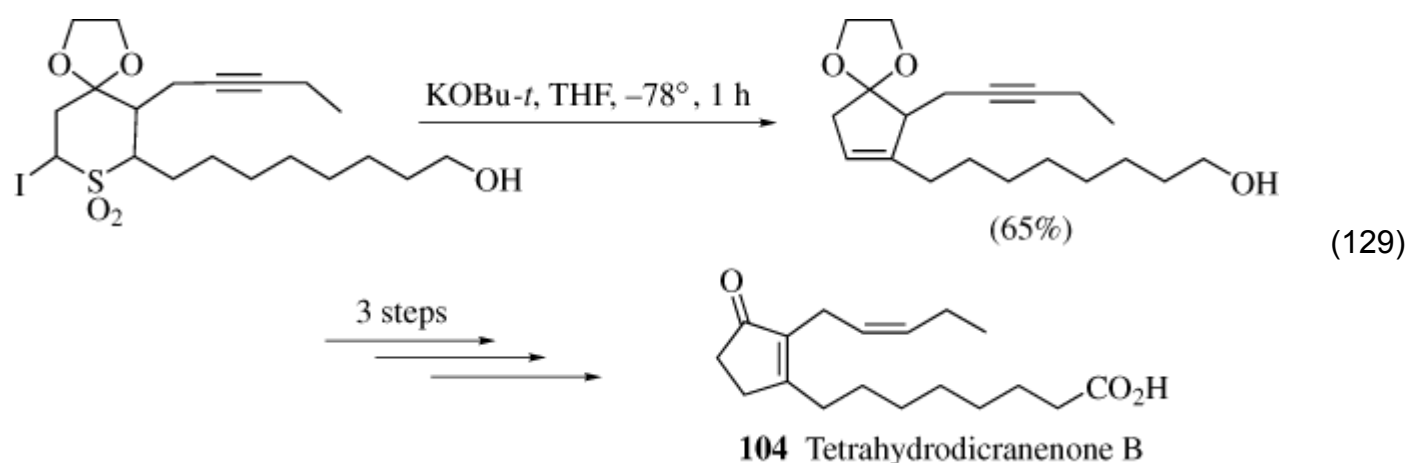
An early application of the RBR to steroid synthesis is shown in Eq. 128. (67) Chlorination of the anion derived from sulfone **101** followed by RBR gives cyclopentene **102** which, on acidic hydrolysis and in situ aromatization, produces the novel estrone analog **103**. More recently, the RBR has been utilized to prepare E- Δ^{22} -steroids, (150) and in a formal total synthesis of brassinolide. (170)



3.7.4. Cyclopentenoid and Dihydrofuran Natural Products

The antimicrobial natural product tetrahydrodicranenone B (**104**) has been prepared using the RBR as the key step (Eq. 129). (52, 171) The mild reaction conditions (-78° , THF) are noteworthy. In a similar transformation, the bromosulfone **105** gives aminocyclopentene **106**, which is converted into

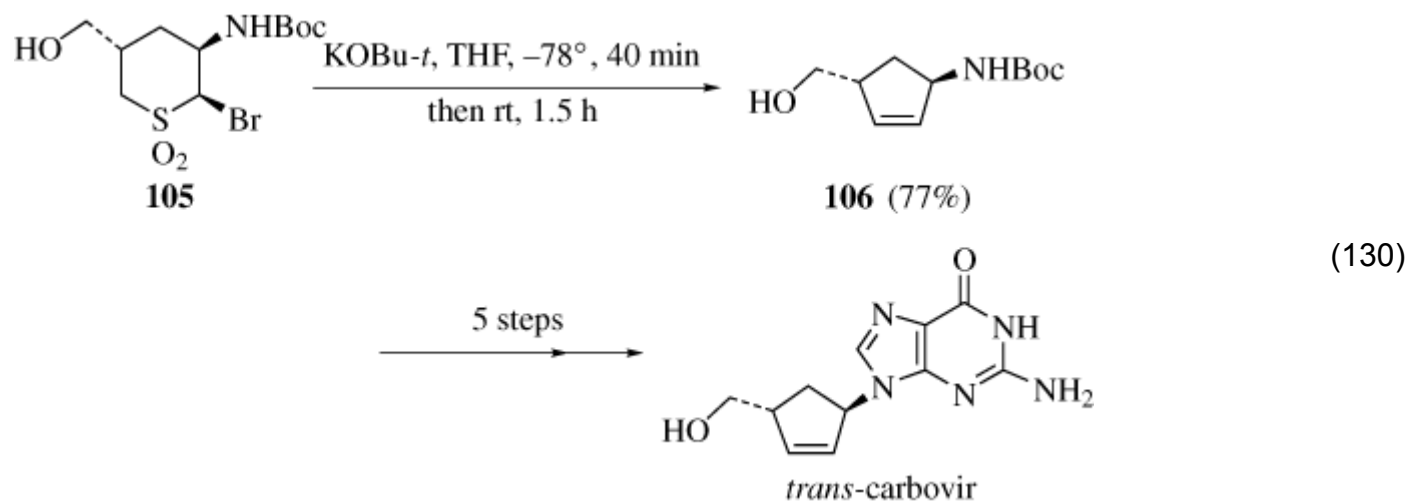
trans-carbovir in five steps (Eq. 130). (53) *cis*-Carbovir is a fraudulent nucleoside which acts as a potent inhibitor of HIV reverse transcriptase. A related thiane dioxide transformation, but employing a modified Meyers procedure with hexachloroethane, is used to prepare optically pure prostaglandin precursors. (92)

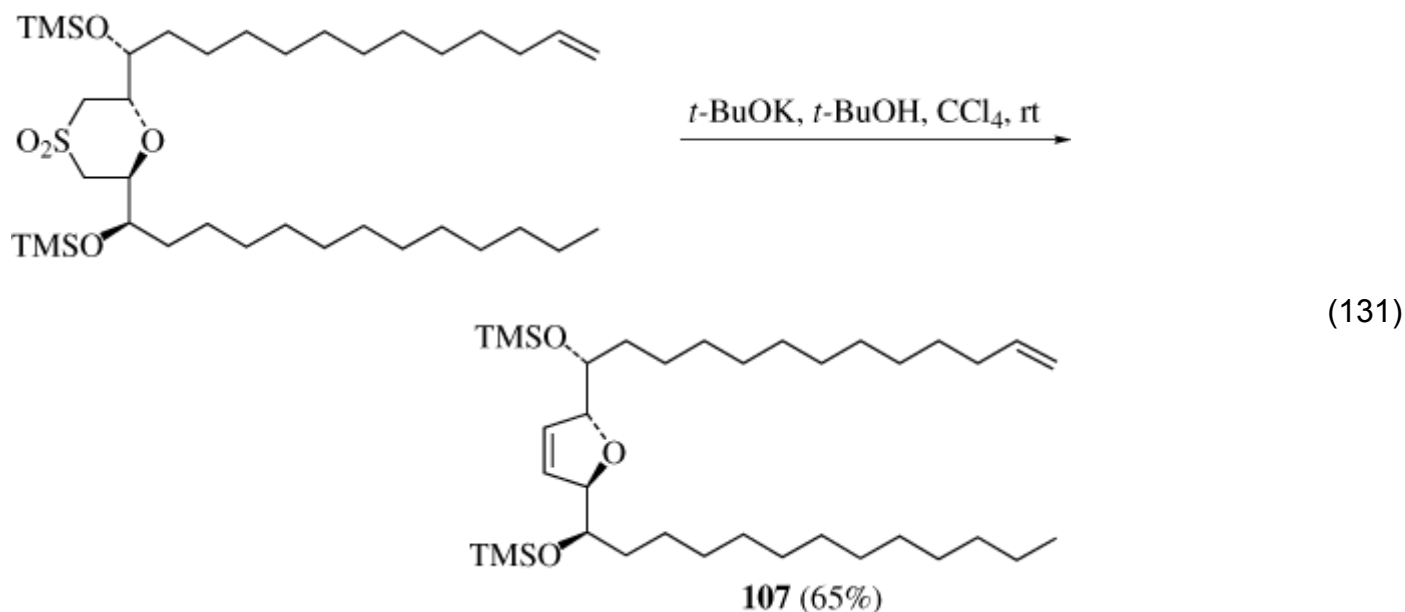


The RBR was employed to construct the 2,5-dihydrofuran unit of (+)-solamin precursor **107** as shown in Eq. 131. (172) Difficulties were encountered using the conventional procedure but success was achieved using Meyers' modification.

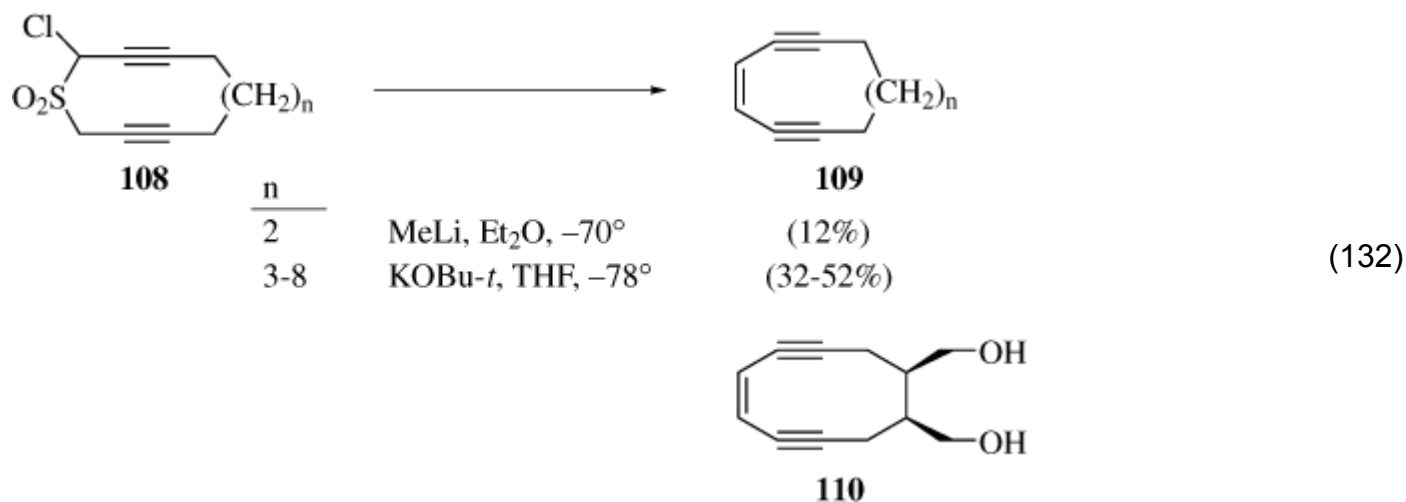
3.7.5. Ene-diyne Analogs

The discovery of the enediyne natural products (calicheamycins, esperamycins, dynemycins etc.) generated tremendous interest, particularly when it was realized that their antitumor and antibacterial activity were due to their ability to cause DNA cleavage. The key process is Bergman cycloaromatization of the enediyne moiety generating benzenoid diradicals. The RBR was employed



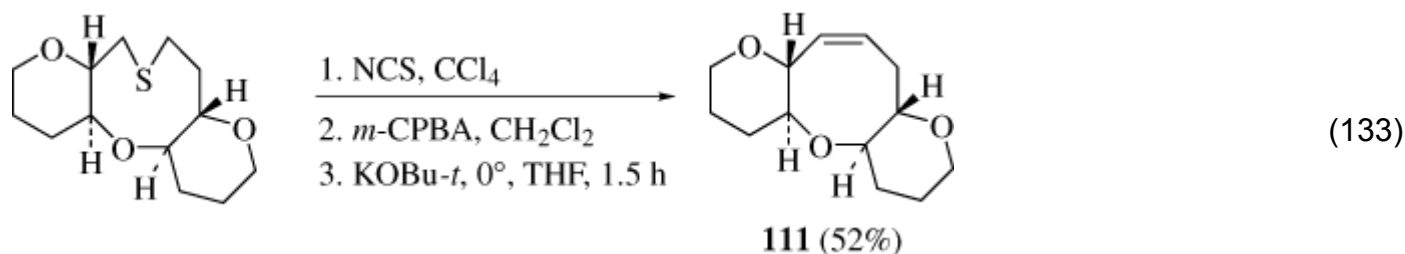


in a landmark study to prepare simple monocyclic enediyne analogs (Eq. 132). (43, 173) Classic RBR conditions were used to convert α -chlorosulfones **108** ($n = 3-8$) into enediynes **109** ($n = 3-8$). In the case of isomer **108** ($n = 2$), potassium *tert*-butoxide gives a complex mixture but methyl lithium generates the required enediyne **109** ($n = 2$), albeit in low yield. Compound **109** ($n = 2$) undergoes the required Bergman cyclization to give tetrahydronaphthalene on warming to 50° . Using the same RBR-based methodology, the water-soluble analog **110** is prepared: this was the first enediyne analog to show potent DNA cleaving properties. (43) A photochemical sulfone ring contraction has been used to prepare a related diyne. (174)



3.7.6. Other Medium Ring Natural Products

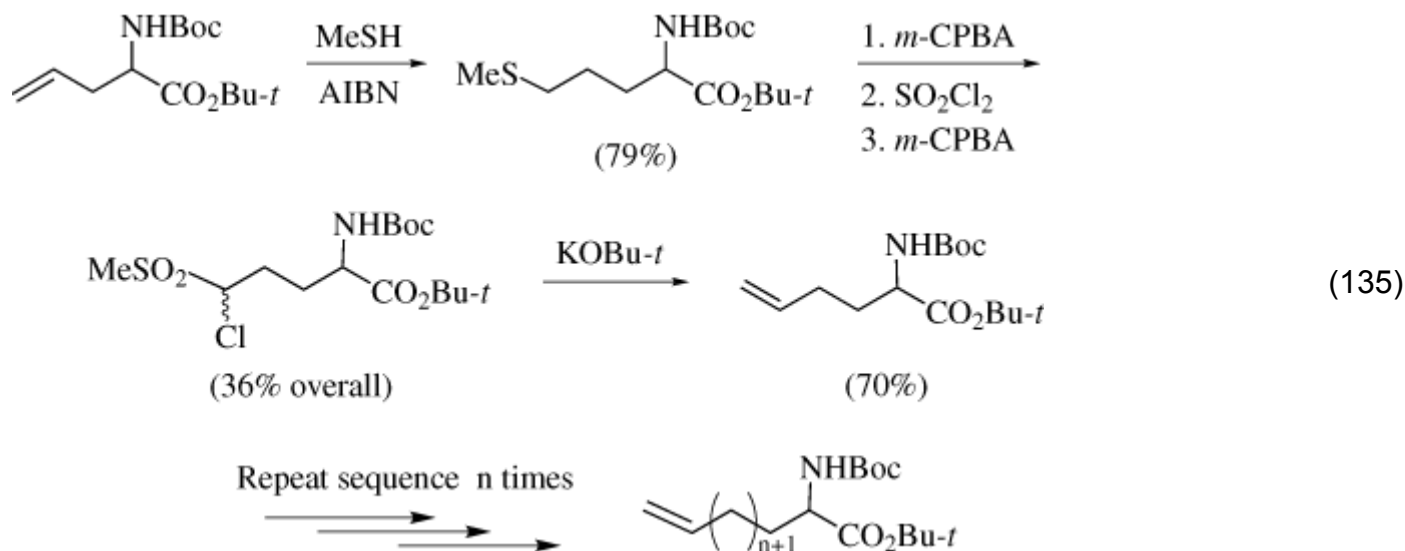
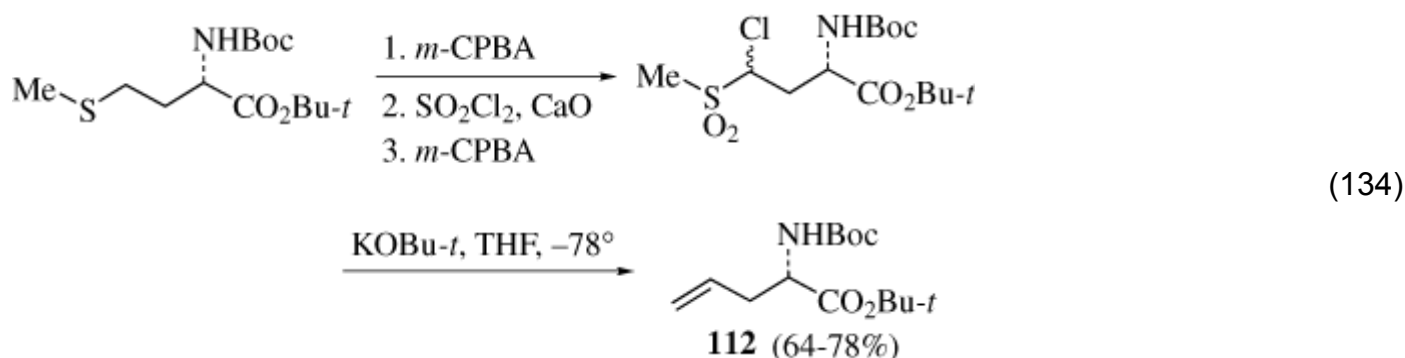
The RBR was a key step in an elegant synthesis of (+)-eremantholide A, a highly strained, tetracyclic anti-tumor natural product discussed earlier (Eq. 3). (8) During studies to devise a synthetic route to ciguatoxin, the RBR was employed to generate the tricyclic polyether **111** (Eq. 133). (175, 176)



The RBR has also been utilized to prepare the (*Z*)-azacycloundecene unit during a total synthesis of manzamine C. (31)

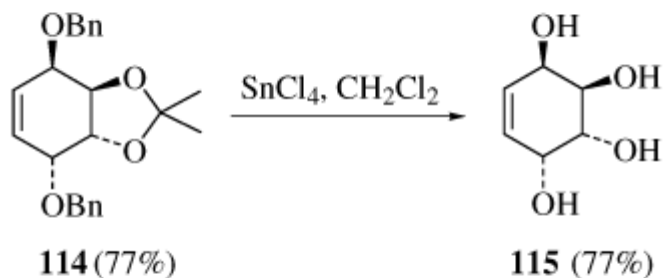
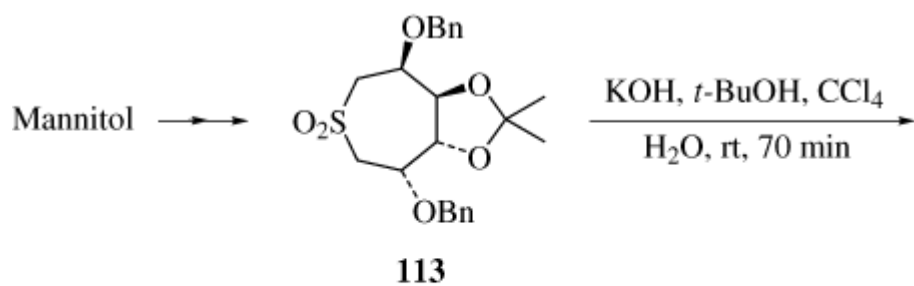
3.7.7. Unsaturated Amino Acids

The RBR has been used to convert methionine into the allyl glycine derivative **112** as shown in Eq. 134. (42) Racemization is avoided by carrying out the reaction at low temperature (when the reaction is carried out at 0°, the product is racemic **112**). By utilizing the radical addition of methanethiol to alkenes, this sequence can be employed in an iterative manner as shown in Eq. 135. (7)

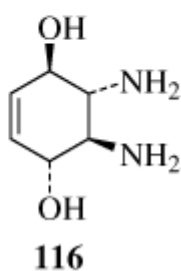


3.7.8. Conduritols

The RBR has been employed to prepare conduritols and related analogs. (111, 177, 178) Thus, sulfone **113**, readily obtained from mannitol, undergoes efficient RBR under Meyers' conditions (Eq. 136). Deprotection of product **114** gives (–)-conduritol E (**115**). (111) The novel 2,3-diaminoconduritol analog **116** is prepared using a related route. (112, 178)

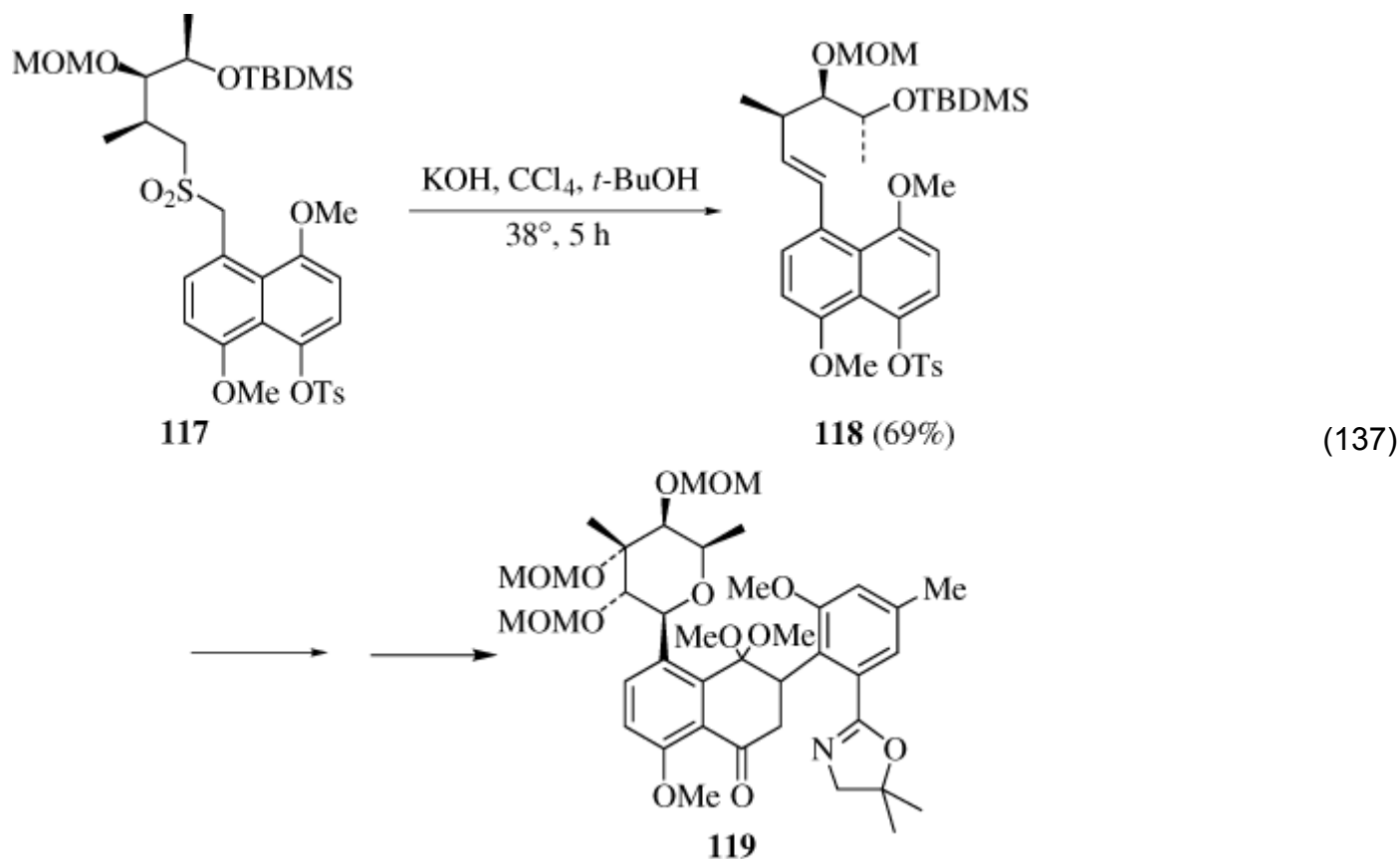


(136)

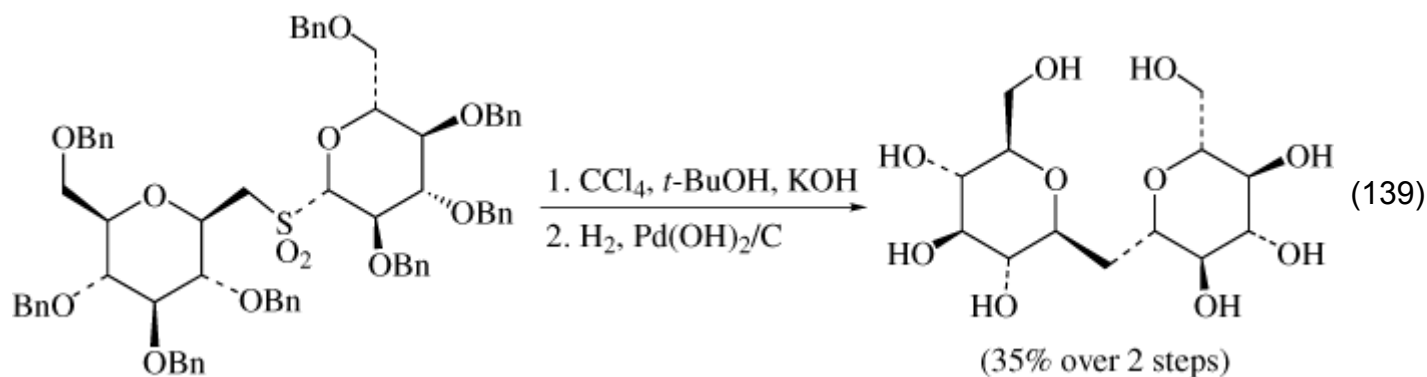
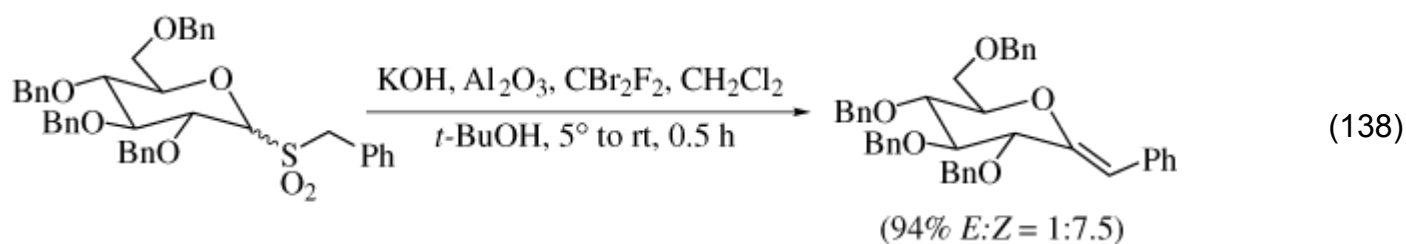


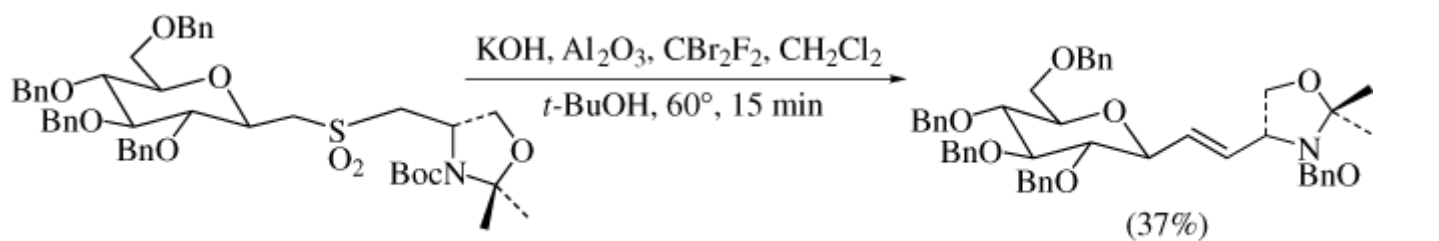
3.7.9. C-Glycosides

The chrysomycins are members of the C-aryl glycoside family of antitumor antibiotics. The RBR has been employed in synthetic studies directed towards the total synthesis of these compounds (Eq. 137). (99) Meyers' modification is employed to convert the highly functionalized sulfone **117** into E-alkene **118**, which is then transformed into **119**, an advanced intermediate en route to chrysomycin A.

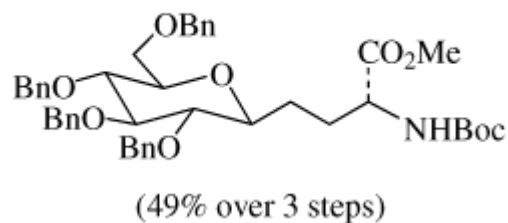


A more direct route to C-glycosides, which utilizes the RBR of S-glycoside dioxides under Meyers or Chan conditions, has since been developed (Eq. 138). (179-181) This approach, which is compatible with 2-oxygenated substituents, has been applied to a range of carbohydrates (galactose, mannose, fucose, and ribose), and can produce terminal alkenes, which are unsubstituted, monosubstituted, or disubstituted. The chemistry has also been extended to prepare novel C-linked disaccharides (Eq. 139), (9) C-linked glycosyl amino acids (Eq. 140), (182) C-glycolipids (Eq. 141), (91) glucosamine-derived glycolipids, (183) and porphyrin C- and S-glycoconjugates. (184)

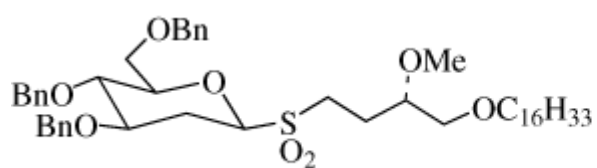




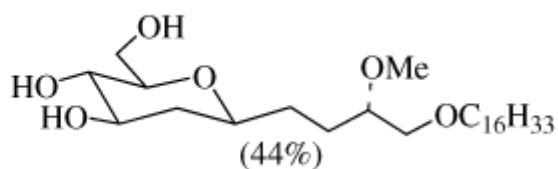
1. TsNHNH₂,
NaOAc, 85°
2. Jones reagent
3. CH₂N₂



(14)



1. KOH, Al₂O₃, C₂Br₂F₄,
heat, 15 min (60%)
2. Et₃SiH, TFA, then
H₂, 10% Pd/C



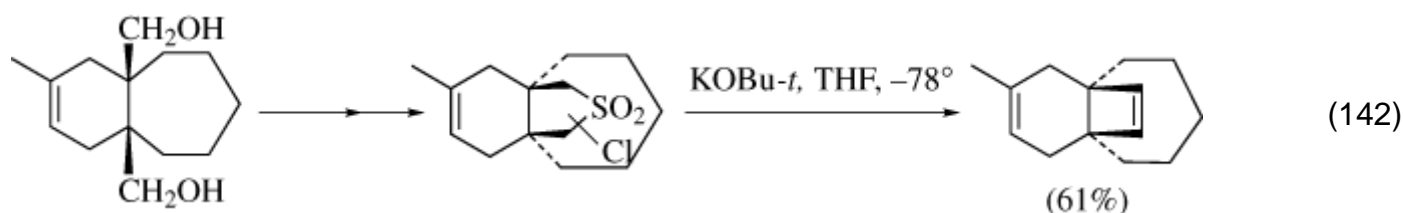
(141)

4. Comparison with other Methods

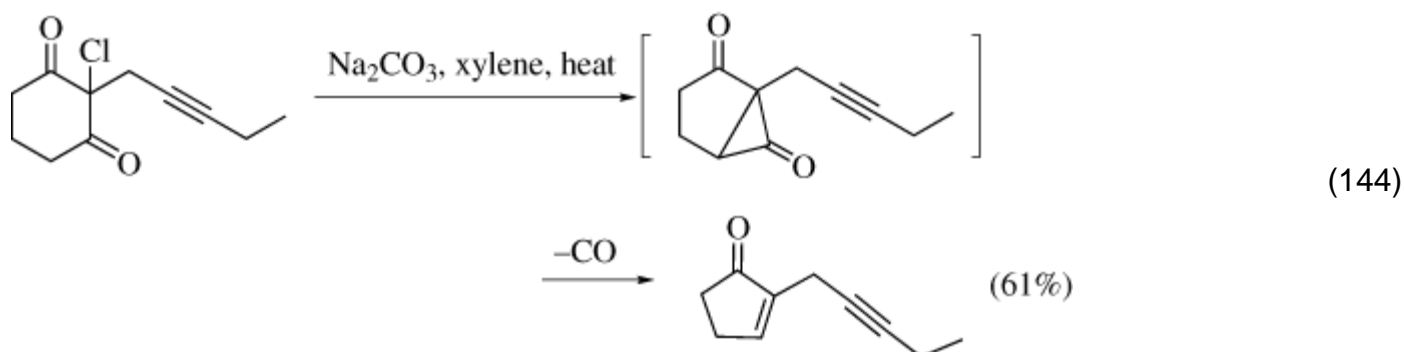
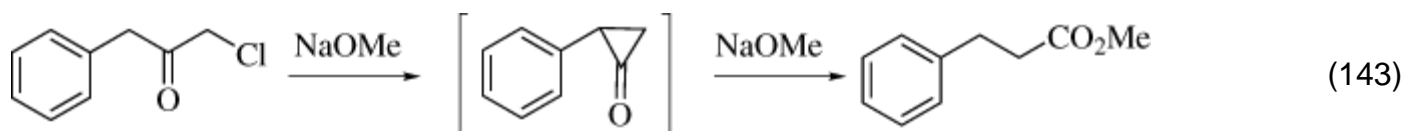
4.1. Overview

The RBR is a conjunctive procedure that introduces the new alkene with complete regiocontrol. There are a number of related procedures based on sulfur and phosphorus, and these will be reviewed in the following sections. From a general synthetic viewpoint, however, the Wittig reaction (185-187) and related processes, (188) such as the Horner-Wadsworth-Emmons reaction (189) and the Peterson reaction, (190) are the main competitors to the RBR. Given the predictable stereocontrol often achievable in such processes, they are frequently the protocols of choice.

However, it should be noted that the RBR involves initial linking of the two organic moieties using sulfur: this pre-organization can be valuable, in the synthesis of cyclobutenes for example, where the initially formed ring is five-membered and the strained four-membered system is generated in the subsequent step (Eq. 142). (36)



The RBR is also related to the Favorskii rearrangement of α -haloketones, a classic example of which is shown in Eq. 143. (191) The deprotonation followed by cyclization to a three-membered intermediate closely resembles the RBR pathway, although in most Favorskii rearrangements the intermediate cyclopropanone undergoes ring opening with alkoxide or hydroxide to give a carboxylate product. (192, 193) However, in the absence of a nucleophilic base, decarbonylation can occur producing alkenes. The most useful example of this type involves the conversion of 2-alkyl-2-chlorocyclohexanediones into 2-alkylated cyclopentenones (Eq. 144). (194)

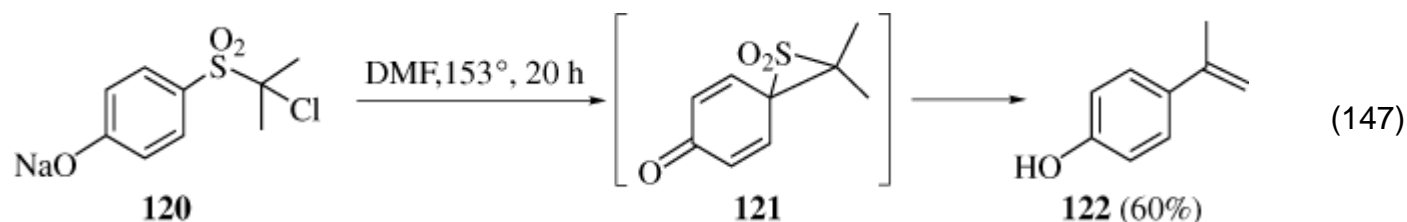
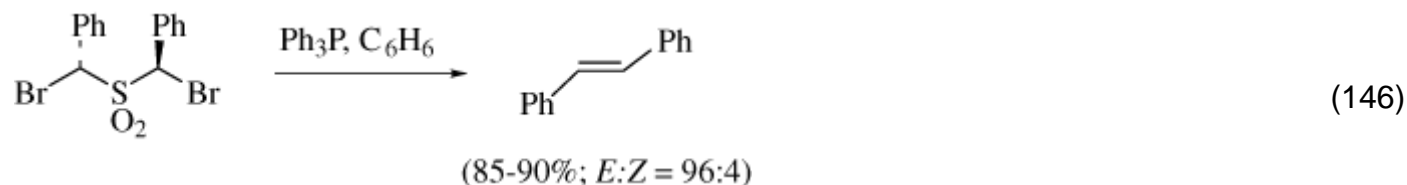
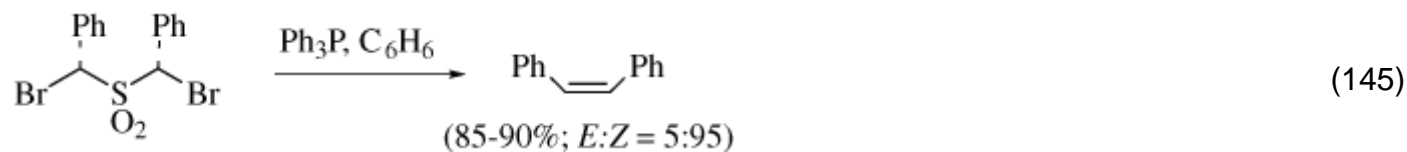


4.2. Related Sulfur Extrusion Reactions

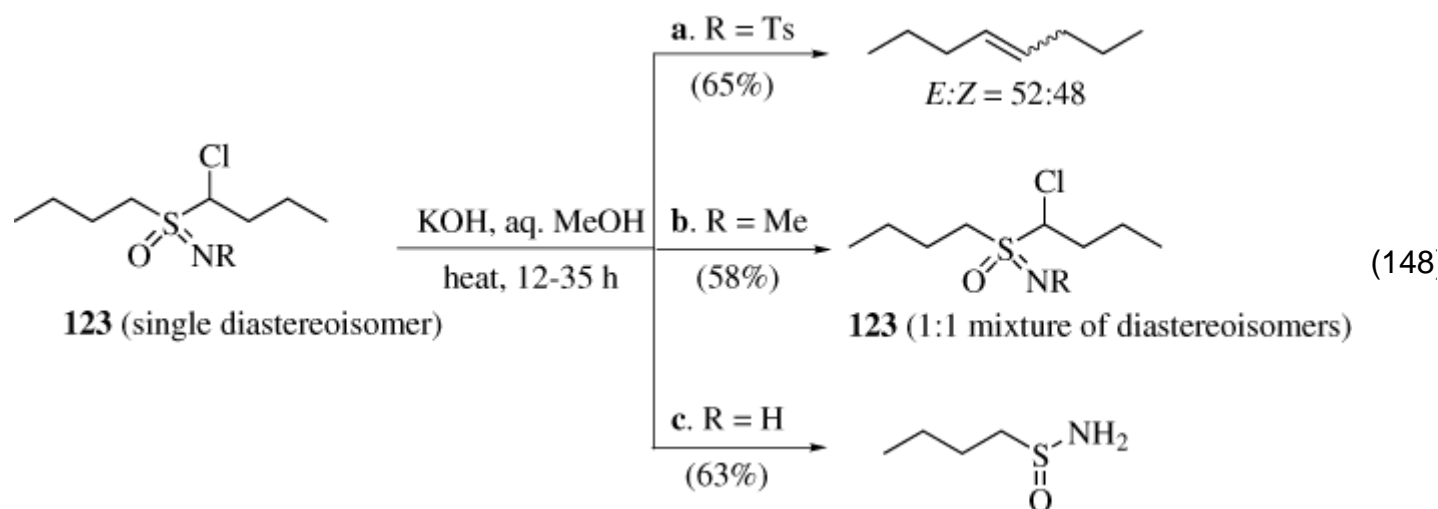
Sulfur extrusion reactions have been well reviewed, (195-199) and examples producing alkanes by thermal and photochemical means are covered in these reviews and in recent publications. (116, 127, 174) Only those reactions that produce alkenes will be considered in the following sections.

4.2.1. α -Halogenated Systems

Processes closely related to the RBR have been reported using α -halosulfones. (200-202) For example, α, α' -dibromosulfones give alkenes on treatment with triphenylphosphine (Eqs. 145 and 146), (201) and thermolysis of the α -chlorosulfone phenolate **120** in the presence of base gives alkene **122** via the presumed thirane dioxide intermediate **121** resulting from a 1,7-elimination (Eq. 147). (200)

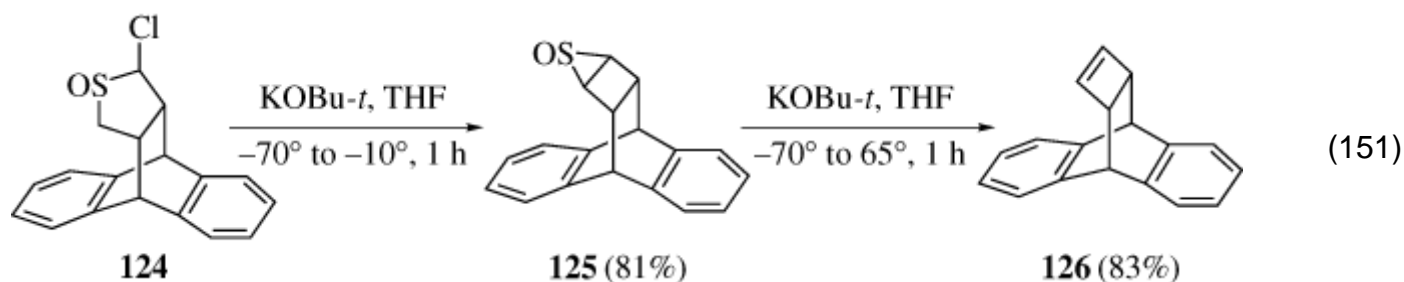
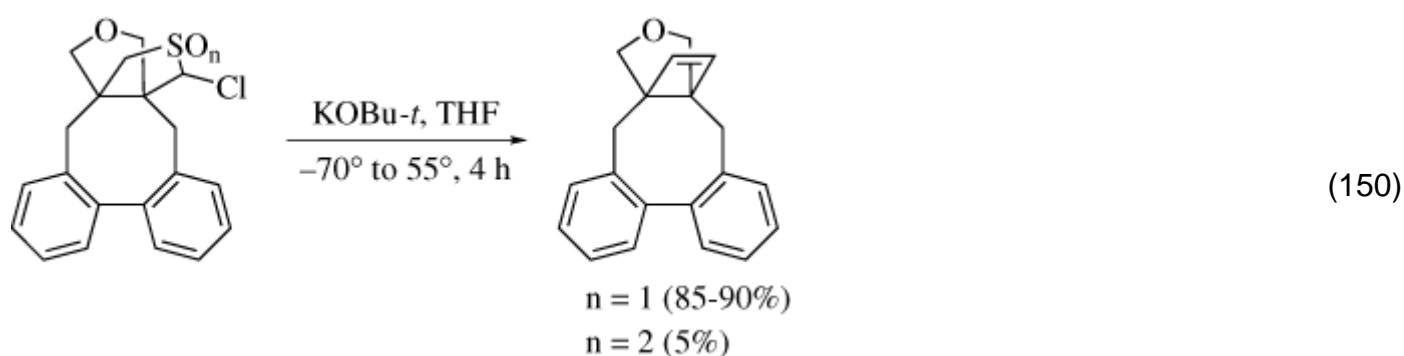
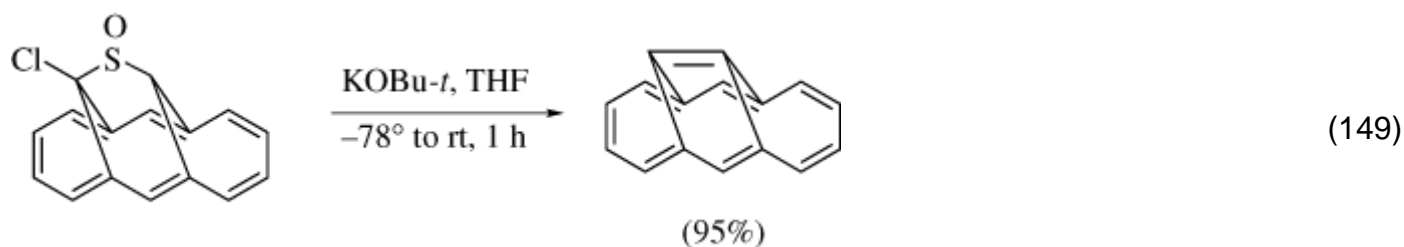


Processes like the Ramberg-Bäcklund reaction have been reported for α -halosulfoximines, α -halosulfoxides and α -halosulfides. With α -halosulfoximines, the choice of *N*-substituent is crucial (Eq. 148). (203) The *N*-tosyl derivative **123a** undergoes Ramberg-Bäcklund type reaction whereas the corresponding *N*-methyl derivative **123b** simply epimerizes at the α -chloro center and the unsubstituted analog **123c** undergoes a fragmentation reaction. In dialkyl examples (e.g. Eq. 148), the reactions show essentially no stereoselectivity, but when the halide is benzylic, high *Z*-stereoselectivity is observed in the formation of (*Z*)-stilbene.



Alkene formation by the treatment of α -chlorosulfoxides with base has also been reported.

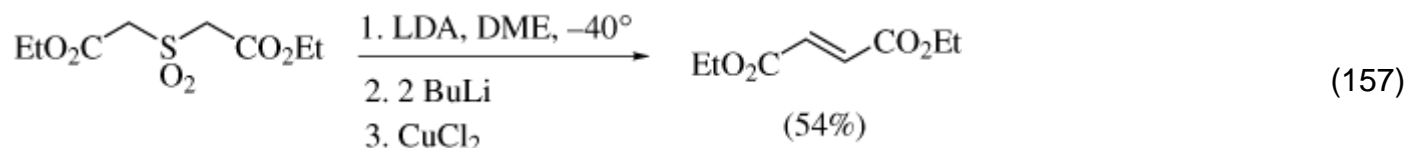
(204-210) In examples shown in Eqs. 149 and 150, the cyclic alkene products are obtained in almost quantitative yield. (204, 205) It is noteworthy that the conventional RBR corresponding to the latter transformation proceeds in extremely low yield. (205) In a related system (Eq. 151), treatment of α -chlorosulfoxide **124** with base gives an isolable thiirane oxide intermediate **125**, which is independently converted into alkene **126** using potassium *tert*-butoxide. (208)



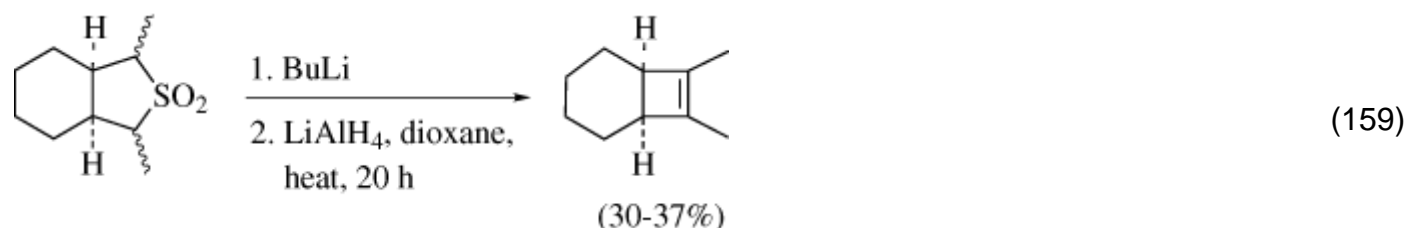
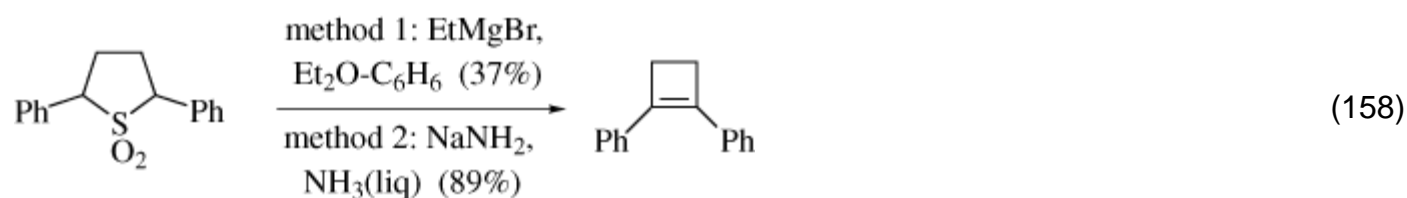
It should be noted that the high yields obtained in the α -chlorosulfoxide reactions shown in Eqs. 149–151 may not be typical of this process. More recent work has established that acyclic systems often produce little or no alkene, the intermediate thiirane oxides undergoing base-induced ring opening to give vinyl sulfoxides after alkylation. (209, 210) An RBR-type process on a trichlorosulfoxide has also been reported. (128)

There are a few reports of α -halosulfides being converted into alkenes. As shown in Eqs. 152 and 153, this conversion can be achieved using base (211) or by thermolysis. (212) The presumption is that the reactions proceed by way of thiirane intermediates, and in one example the intermediate thiirane has been isolated: (213) the desulfurization of thiiranes to give alkenes is a well-established process. (196, 197)

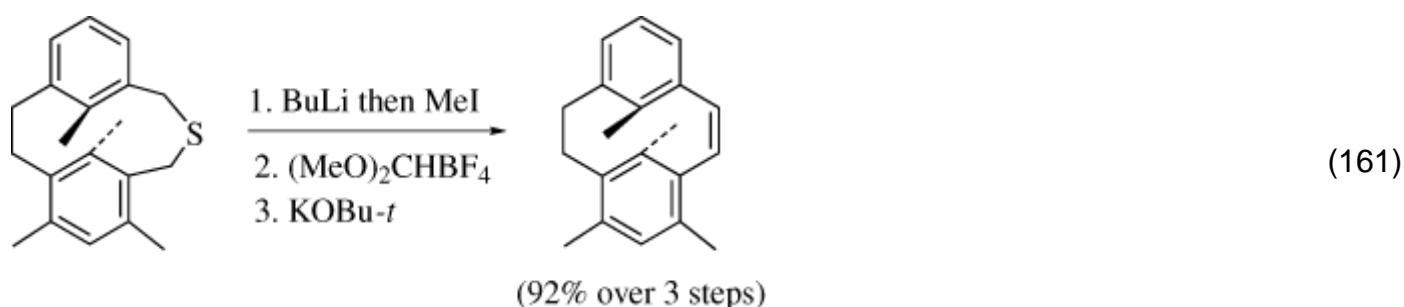
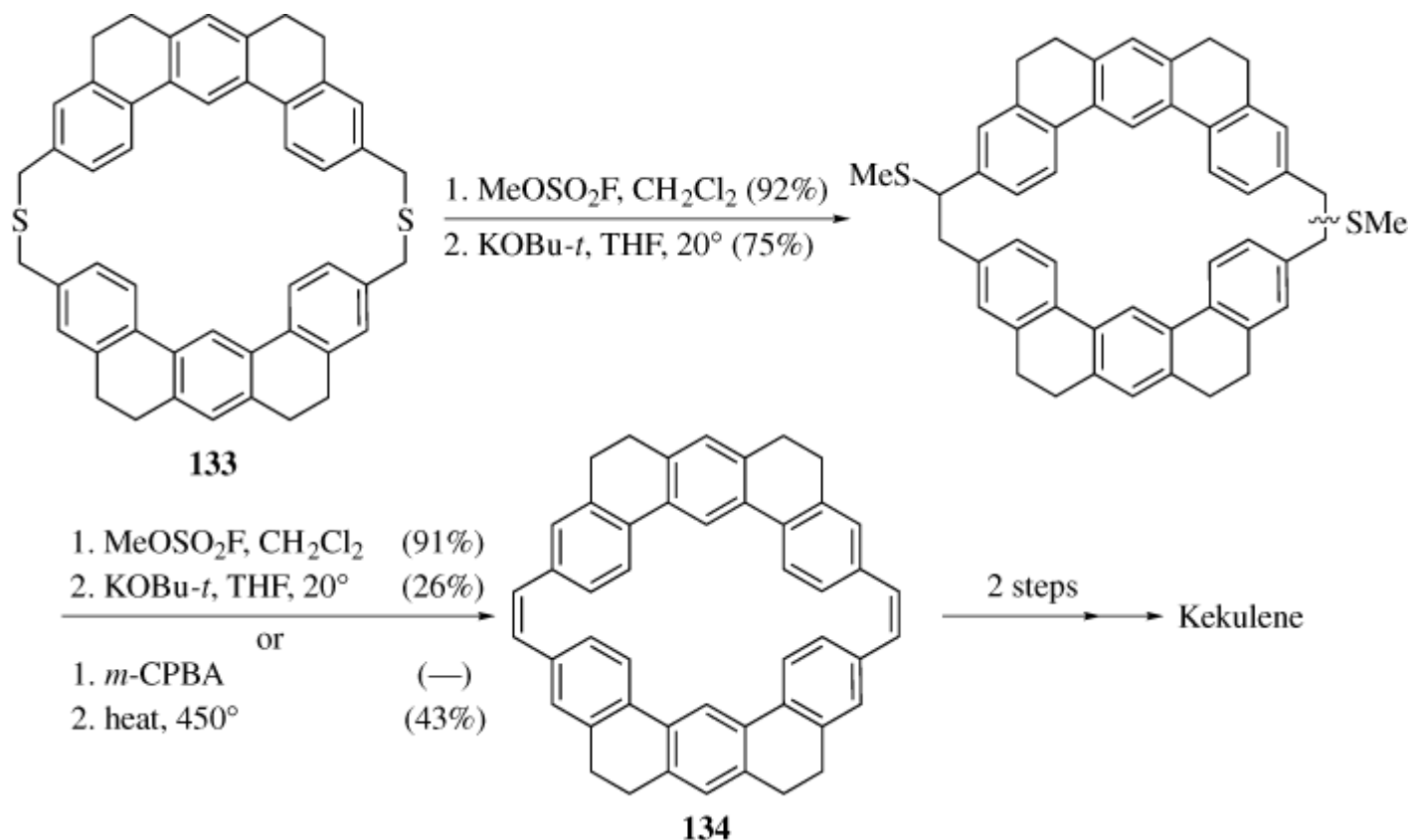
into alkenes (102, 217) and this procedure has been employed to prepare β -carotene (Eq. 123). (102) It is not known whether the iodine-mediated method proceeds via a two-electron oxidation or the intermediacy of an α -iodosulfone.



Alkenes have also been obtained by the treatment of sulfones with Grignard reagents (Eq. 158), (218, 219) sodamide (Eq. 158), (219) butyllithium-lithium aluminum hydride, (220-225) and lithium aluminum hydride alone. (220) No mechanistic evidence is available for these processes. The Paquette-Photis (butyllithium-lithium aluminum hydride) procedure has proved to be particularly valuable for the preparation of annulated 1,2-dimethylated cyclobutenes (Eq. 159), (225) although in a comparison study on the preparation of a less substituted cyclobutene the classical RBR gave a higher overall yield. (223)

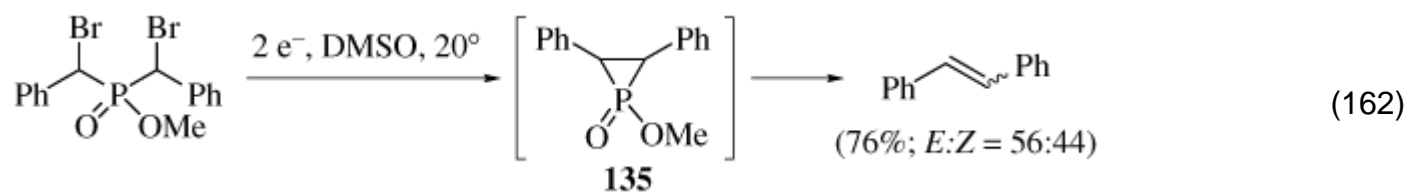


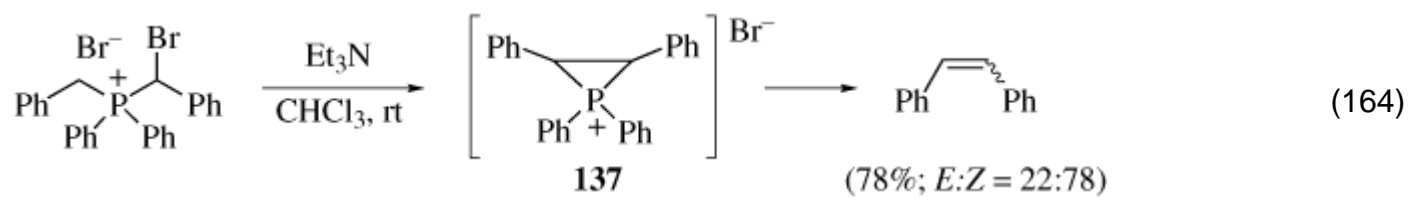
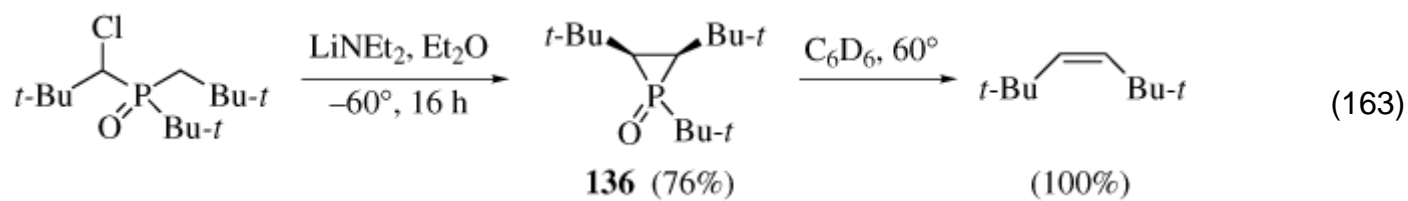
As discussed earlier, there are numerous examples of sulfones being converted into *alkanes* by thermal or photochemical means. (116, 127, 174, 195-199) Mention should also be made of the 1,2-Stevens rearrangement of sulfonium ylids, often used in combination with a subsequent sulfonium salt elimination for the conversion of cyclic sulfides into ring-contracted alkenes. (226) This sequence has proved particularly valuable for cyclophane synthesis, the key steps in the synthesis of Kekulene being shown in Eq. 160. (227) It should be noted that the disulfone corresponding to 133 was prepared and its direct conversion into 134 via the RBR reaction was attempted: using Meyers' conditions 134 is obtained in only 1.2% yield. A more recent Stevens rearrangement example is shown in Eq. 161. (228)



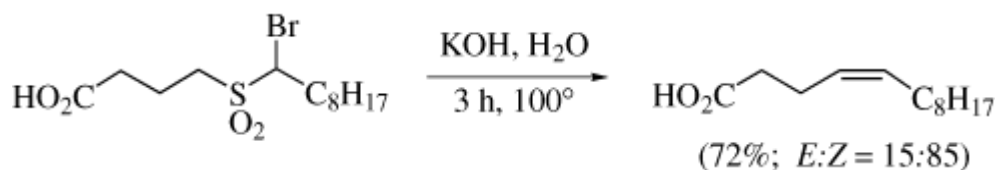
4.2.3. Ramberg-Bäcklund Variants Based on Phosphorus

Ramberg-Bäcklund-like reactions have been reported for several types of phosphorus compounds bearing an adjacent leaving group and an α -proton (Eqs. 162–164). (152) In one of the earliest examples, electrolysis of an α, α' -dibromophosphinate produced stilbene via the presumed intermediacy of oxyphosphirane **135** (Eq. 162). (229, 230) Subsequently, an α -halophosphine oxide was converted into an isolable phosphirane oxide **136**, which produced a quantitative yield of the corresponding Z-alkene on heating to 60° (Eq. 163). (231–233) More recently, related phosphonium species (e.g. **137**) have been proposed as the intermediates in the base-mediated conversion of α -halophosphonium salts into alkenes (Eq. 164). (234, 235)



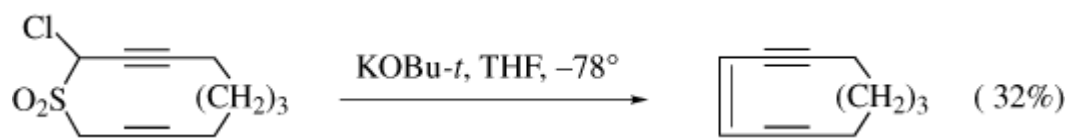


5. Experimental Procedures



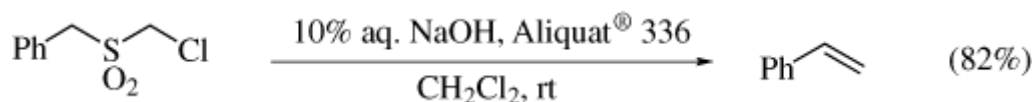
5.1.1. 4-Tridecenoic Acid [RBR of an α -Halosulfone Using Aqueous Potassium Hydroxide] (29)

The α -bromosulfone (714 mg, 2.0 mmol) was added to a solution of KOH (276 mg, 5 mol) in water (6 mL). The mixture was heated to 100° for 3 hours. After cooling to room temperature, the mixture was extracted twice with Et₂O, acidified, and extracted three times with EtOAc. The EtOAc layers were combined, dried, and the solvent removed in vacuo. The oily residue was purified by chromatography on silica gel using CHCl₃ as the eluant. This produced the title compound (305 mg, 72%) as a mixture of isomers (*Z:E* = 85:15): ¹H NMR (CDCl₃): δ 0.66–1.47 (m, 15 H), 1.71–2.16 (m, 2 H), 2.16–2.51 (m, 4 H), 5.13–5.51 (m, 2 H), 10.55 (br s, 1 H).



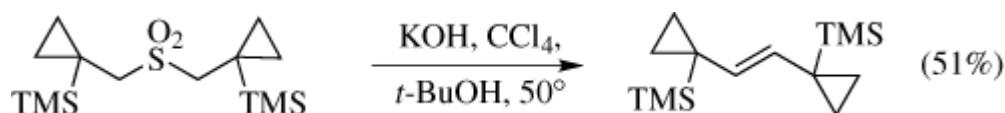
5.1.2. Cycloundeca-1,5-diyne-3-ene [RBR of an α -Halosulfone Using Potassium *tert*-Butoxide/THF] (43)

To a solution of the α -chlorosulfone (1.205 g, 4.9 mmol) in THF (30 mL) at –78° was added KOtBu (1.414 g, 12.6 mmol). After 3 hours the reaction mixture was added to saturated, aqueous NH₄Cl and Et₂O (50 mL). The organic layer was washed with water (30 mL) and brine (30 mL), dried (Na₂SO₄), and the solvent removed in vacuo. The residue was purified by column chromatography (2.5 to 5% Et₂O in hexanes) to give the title compound (0.228 g, 32%) as a white solid, mp 35–36°; ¹H NMR (CDCl₃) δ 1.59 (qn, *J* = 3.3 Hz, 4 H), 2.01 (qn, *J* = 3.5 Hz, 2 H), 2.45 (t, *J* = 3.1 Hz, 4 H), 5.78 (s, 2 H).



5.1.3. Styrene [Phase-Transfer RBR of an α -Halosulfone] (65)

To a solution of benzyl chloromethyl sulfone (20.4 g, 0.1 mol) in CH₂Cl₂ (340 mL) was added 10% aqueous NaOH (170 mL) and Aliquat 336 (5.0 g, 0.01 mol). The mixture was stirred vigorously with a magnetic bar and the progress of the reaction monitored by analysis of the organic layer using GLC and TLC. When the reaction was complete (1.5 hours), the organic phase was separated, washed with water and brine and then dried (Na₂SO₄). The solvent was distilled carefully through a 24-inch Vigreux column. Distillation of the remainder through a 5-inch Vigreux column gave the title compound (8.5 g, 82%), bp 145–146°/760 mm Hg (lit. (236) bp 145.2°/760 mm Hg).

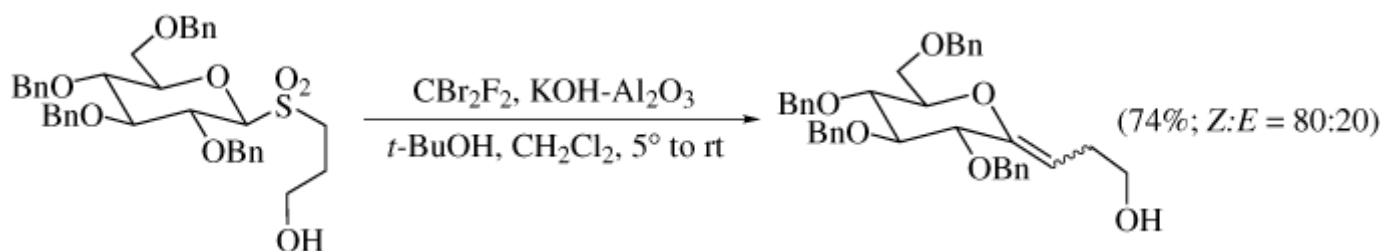


5.1.4. (*E*)-1,2-bis[1-(Trimethylsilyl)cyclopropyl]ethylene [Stereoselective RBR Under Classical Meyers Conditions] (97)

The sulfone starting material (7.0 g, 22.0 mmol), powdered KOH (62 g, 1.11 mmol), anhydrous *t*-BuOH (308 mL), and CCl₄ (728 mL) were combined and heated at 50° for 17 hours. The mixture was cooled to room temperature, washed with water and brine, dried, and then concentrated under reduced pressure. The residue was combined with that obtained from a second preparation involving 6.5 g (20.4 mmol) of the sulfone, and this combined sample was distilled under reduced pressure to give the title compound (5.69 g, 51%) as a nearly colorless oil, bp 75°/0.8 mm Hg; ¹H NMR (CDCl₃) δ 0.00 (s, 18 H), 0.35–0.55 (m, 8 H), 5.40 (s, 2 H); Anal. Calcd for C₁₄H₂₈Si₂: C, 66.56; H, 11.20. Found: C, 66.75; H, 11.20.

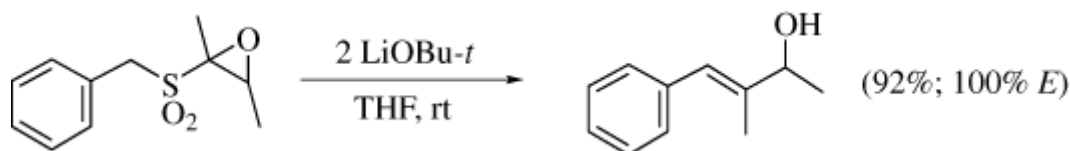
5.1.5. Alumina-Supported Potassium Hydroxide [Preparation of the Reagent for RBR under Meyers-Chan Conditions] (88)

A mixture of three parts by weight of neutral alumina (E. Merck, grade 1, 20–230 mesh) and a methanolic solution of one part by weight of commercial KOH pellets was thoroughly stirred at room temperature. The solvent was then removed by rotary evaporation at 40–60° until a free-flowing powder of constant weight was obtained. (When kept in a tightly closed container, this material remains active for several months.)



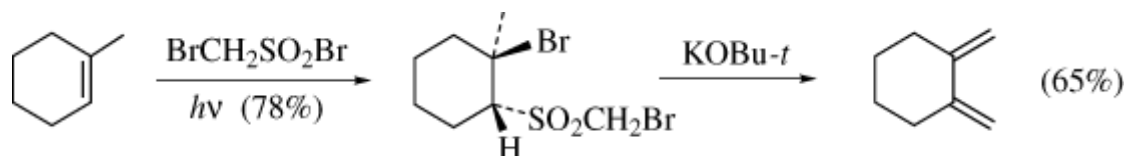
5.1.6. 4,8-Anhydro-5,6,7,9-tetra-O-benzyl-2,3-dideoxy-D-gluco-non-3-enitol [RBR Under Meyers-Chan Conditions] (180)

Dibromodifluoromethane (0.5 mL, 5.3 mmol) was added dropwise during one minute to a vigorously stirred mixture of the starting sulfone (270 mg, 0.42 mmol) and alumina-supported KOH (2.60 g) in *t*-BuOH (6 mL) and CH₂Cl₂ (3 mL) kept at 5° under N₂. The mixture was then stirred at room temperature for 3.5 hours after which it was diluted with CH₂Cl₂ and the supported base removed by suction filtration through a pad of CeliteTM. The reaction vessel and the filter cake were rinsed thoroughly with CH₂Cl₂ and the combined filtrates concentrated. The crude product was purified by silica gel chromatography (EtOAc-hexanes, 4:1 to 1:1) to afford the title compound (178 mg, 74%; Z:E = 80:20) as a colorless oil, *R*_f 0.1 (EtOAc-hexanes, 1:4); ¹H NMR (CDCl₃) δ 2.05–3.21 and 2.32–2.45 (m, 3 H), 3.60 (t, *J* = 6.5 Hz, 2 H), 3.67–3.79 (m, 4 H), 3.93 (br d, *J* = 6.5 Hz, 1 H), 4.33–4.83 (m, 9 H), 4.98 [t, *J* = 7.5 Hz, 1 H; (3-H, *Z*-isomer)], 5.21 [t, *J* = 8.7 Hz, 1 H (3-H, *E*-isomer)], 7.13–7.17 and 7.24–7.36 (m, 20 H); HRMS: [M + Na]⁺ calcd for C₃₇H₄₀O₆, 603.27226; found, 603.27187.



5.1.7. (E)-3-Methyl-4-phenyl-3-buten-2-ol [Epoxy RBR] (87)

Under N₂ at room temperature, the starting cis-epoxide (96 mg, 0.424 mmol, 1 eq.) in dry THF (5 mL) was treated dropwise with a solution of LiOBu-*t* (68 mg, 0.849 mmol, 2 eq.) in THF (2 mL). Stirring was continued for 4 hours before TLC analysis indicated the consumption of starting material. Saturated aq. NH₄Cl solution (10 mL) was added and the resultant mixture was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (35 mL) and dried over MgSO₄. Filtration followed by solvent removal under reduced pressure afforded the crude material which was purified by flash column chromatography (hexanes-EtOAc, 3:1) to give the title compound (63 mg, 92%) as a clear oil, R_f 0.30 (hexanes-EtOAc, 3:1), which showed spectroscopic properties fully consistent with the literature data. (237, 238)



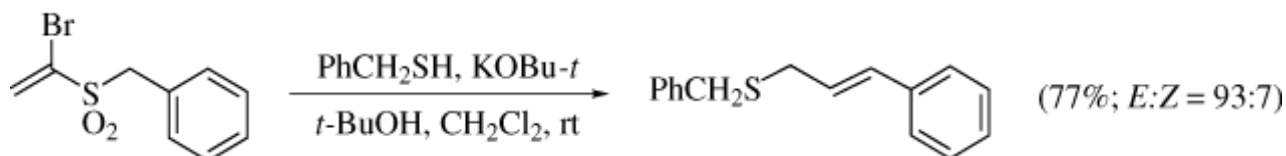
5.1.8. 1,2-Dimethylenecyclohexane [Vinylogous RBR] (47, 122)

a. 1-Bromo-1-methyl-2-(bromomethylsulfonyl)cyclohexane:

Four Pyrex test tubes (2.5 × 20 cm) were charged with redistilled 1-methylcyclohexene (5.0 g per test tube; total weight 20.0 g, 0.21 mol). CH₂Cl₂ (12 mL) was added to each test tube, which was cooled in ice. An ice-cold solution of bromomethanesulfonyl bromide (13.6 g of bromomethanesulfonyl bromide per test tube; total weight 54.4 g, 0.23 mol) in CH₂Cl₂ (12 mL) was added to each test tube with mixing at 0°. The test tubes were attached with the help of several rubber bands to a Pyrex immersion well equipped with a Hanovia 450-W mercury lamp. The immersion well was cooled by circulation of ice water and immersed in a cooling bath maintained at -15°. The reaction mixture was irradiated for 2 hours. Solid K₂CO₃ (1.5 g) was added to each test tube and the contents of the test tubes were filtered through a small column with a glass wool plug into a 250-mL round-bottomed flask. CH₂Cl₂ was removed, first on a rotary evaporator and then with a vacuum pump (1 mm Hg), to give an oil, which gradually solidified (68.3 g, 98%). Crystallization from 95% ethanol (100 mL) gave white crystals, mp 59–61°. The first crop (47.0 g) was followed by two other crops (5.2 and 2.1 g), obtained by concentrating and cooling the mother liquor, giving in total 54.3 g (78%) of the title compound.

b. 1,2-Dimethylenecyclohexane:

An oven-dried, 1-L, three necked, round-bottomed flask equipped with a mechanical stirrer, pressure-equalized dropping funnel, and a stopper was charged with KOBU-*t* (59.5 g, 0.53 mol) dissolved in *t*-BuOH-THF (both distilled from CaH₂; 9:1, 400 mL total) and cooled in ice. A solution of 1-bromo-1-methyl-2-(bromomethylsulfonyl)cyclohexane (54.0 g, 0.16 mol) in *t*-BuOH-THF (9:1, 100 mL) (warming was required to dissolve the solid in this solvent) was added dropwise over a 1 hour period. After the addition was complete, the reaction mixture was stirred at room temperature for 0.5 hour and then poured into a 2-L separatory funnel containing water (500 mL). This solution was extracted with pentane (2 × 150 mL). The combined pentane extracts were washed with water (8 × 500 mL; the first four washings were done with gentle agitation to avoid emulsion formation), dried over anhydrous MgSO₄, and filtered. The pentane was removed by distillation at atmospheric pressure using an efficient Vigreux column and the residue was distilled under reduced pressure to give 1,2-dimethylenecyclohexane (11.4 g, 65%) as a colorless liquid, bp 69–70°/90 mm Hg (lit. bp 60–61°/90 mm Hg). (239, 240) The first cut of the distillate (ca. 1–2 mL) coming below 60° was discarded.



5.1.9. (E)-3-Benzylthio-1-phenylprop-1-ene [Michael-Induced RBR] (54)

To a stirred solution of benzyl mercaptan (0.12 mL, 1.01 mmol) in dry *t*-BuOH (10 mL) under N₂ at room temperature was added a solution of KO*t*-Bu in THF (1 M, 1.11 mL, 1.11 mmol). After 10 minutes, a solution of benzyl 1-bromovinyl sulfone (264 mg, 1.01 mmol) in dry CH₂Cl₂ (2 mL) was added and stirring continued for 15 hours. Saturated NH₄Cl solution (10 mL) was added and the resultant mixture was extracted with EtOAc (4 × 30 mL). The combined extracts were washed with brine, dried (MgSO₄) and the solvent removed in vacuo. Purification by flash chromatography (silica, hexanes-EtOAc, 9:1) gave the title sulfide (188 mg, 77%) as a clear oil, *R*_f 0.5 (hexanes-EtOAc, 9:1); HRMS: calcd for C₁₆H₁₆S, 240.0973; found: 240.0976. Spectroscopic properties were fully consistent with the literature data. (241)

6. Notes Added in Proof

Several relevant papers have been published during the editing of the review (up to mid-2002). These are briefly summarized below.

Ring closing metathesis has been employed to prepare a range of cyclic unsaturated sulfones, two of which were converted into 1-phenyl-cyclohexa-1,4-diene and 2-phenyl-cyclohepta-1,4-diene using Chan's in situ RBR conditions. (1) Similar conditions have been employed to convert polyunsaturated sulfones into a range of all *trans*-1,3,5,7-octatetraenes. (2)

Full papers on the RBR route to *exo*-glycals and derived C-glycosides, C-linked disaccharides, and C-glycosyl amino acids have been published. (3, 4) This methodology has been applied to the preparation of C-GlcNHAc-*N*-Fmoc-serine, (5) and as part of a synthetic route towards altromycin B. (6)

Finally, two reviews have been published which incorporate the RBR. (7, 8) The first covers α -oxygenated-sulfones (7) and the second deals with rearrangements of sulfoxides and sulfones in the total synthesis of natural products. (8)

1. Yao, Q. *Org. Lett.* 2002, **4**, 427.
2. Cao, X. P. *Tetrahedron* 2002, **58**, 1301.
3. Griffin, F. K.; Paterson, D. E.; Murphy, P. V.; Taylor, R. J. K. *Eur. J. Org. Chem.* 2002, 1305.
4. Paterson, D. E.; Griffin, F. K.; Alcaraz, M.-L.; Taylor, R. J. K. *Eur. J. Org. Chem.* 2002, 1323.
5. Ohnishi, Y.; Ichikawa, Y. *Bioorg. Med. Chem. Lett.* 2002, **12**, 997.
6. Pasetto, P.; Frank, R. W. *Abstr. 223rd ACS Meeting 2002 (CARB-069)*; *Chem. Abstr.* 2002, 186314. Pasetto, P.; Franck, R. W. *Abstr. 221st ACS Meeting 2001 (ORGN104)*; *Chem. Abstr.* 2001, 202590.
7. Chemla, F. J. *Chem. Soc., Perkin Trans. 1* 2002, 275.
8. Prilezhaeva, E. N. *Russ. Chem. Rev.* 2001, **70**, 897.

7. Tabular Survey

We have attempted to include all examples of the RBR published since the previous chapter in *Organic Reactions* in 1977 and up to and including those appearing in 2000. For a comprehensive listing of published RBR processes, therefore, both Chapters should be consulted. The tables are arranged in parallel with the text and entries are in order of increasing carbon number of the starting material, and within each carbon-number group, in order of increasing hydrogen count. All protecting groups attached to heteroatoms are excluded from the carbon and hydrogen counts. Similar groups of substrates are grouped together as a range, for example C₆₋₉ precedes C₇. Numbers in parenthesis are yields of isolated pure products, whereas a dash (—) indicates that no yield is reported.

The following abbreviations are used in the tables:

Ac	acetyl
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Bz	benzoyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBN	1,5-diazabicyclo[3.4.0]-5-nonene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DME	1,2-dimethoxyethane
DMSO	dimethyl sulfoxide
ERBR	Epoxy Ramberg-Bäcklund Reaction
GC	gas chromatography
GC-MS	gas chromatography — mass spectrometry
HMPA	hexamethylphosphoramide
<i>hν</i>	ultraviolet light
MIRBR	Michael-Induced Ramberg-Bäcklund Reaction
MOM	methoxymethyl
MPA	monoperphthalic acid
NCS	<i>N</i> -chlorosuccinimide
NIS	<i>N</i> -iodosuccinimide
RBR	Ramberg-Bäcklund Reaction
TBDMS	<i>tert</i> -butyldimethylsilyl
TBDPS	<i>tert</i> -butyldiphenylsilyl
THF	tetrahydrofuran
TMS	trimethylsilyl

Table 1A. RBR of Preformed α -Halo Sulfones: Acyclic Substrates

Table 1B. RBR of Preformed α -Halo Sulfones: Cyclic Substrates

[View PDF](#)

Table 2. RBR of other α -Substituted Sulfones

[View PDF](#)

Table 3A. RBR with in Situ Halogenation: Acyclic Substrates

[View PDF](#)

Table 3B. RBR with in Situ Halogenation: Cyclic Substrates

[View PDF](#)

Table 4. Vinylogous RBR of Vinyl Sulfones

[View PDF](#)

Table 5. Decarboxylative RBR

[View PDF](#)

Table 6. Michael-Induced RBR

[View PDF](#)

TABLE 1A. RBR OF PREFORMED α -HALO SULFONES: ACYCLIC SUBSTRATES

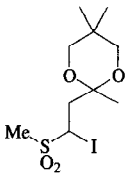
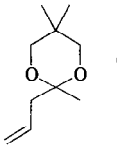
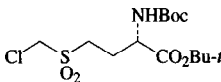
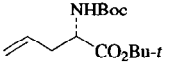
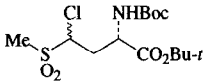
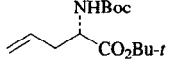
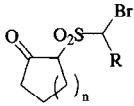
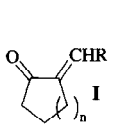
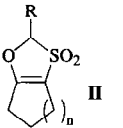
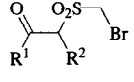
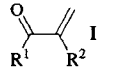
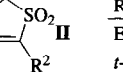
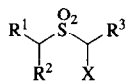
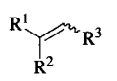
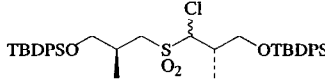
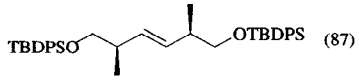
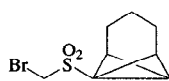
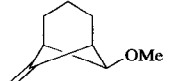
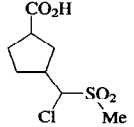
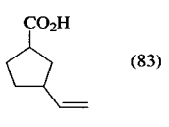
Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.																																																	
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	<i>t</i> -BuOK, THF, -78 to -30°	 (64-78)	42																																																	
C ₆₋₉ 	DBN, CH ₂ Cl ₂ , -23° or EtOH, 23°	 I +  II	47																																																	
		<table border="1"> <thead> <tr> <th>R</th> <th>n</th> <th>I^a</th> <th>E:Z</th> <th>II^a</th> </tr> </thead> <tbody> <tr> <td>H</td> <td>1</td> <td>(30)</td> <td>—</td> <td>(—)</td> </tr> <tr> <td>H</td> <td>2</td> <td>(32)</td> <td>—</td> <td>(32)</td> </tr> <tr> <td>Me</td> <td>2</td> <td>(12)</td> <td>12:1</td> <td>(6)</td> </tr> <tr> <td>H</td> <td>3</td> <td>(61)</td> <td>—</td> <td>(17)</td> </tr> <tr> <td>Me</td> <td>3</td> <td>(13)</td> <td>20:1</td> <td>(2)</td> </tr> </tbody> </table>	R	n	I ^a	E:Z	II ^a	H	1	(30)	—	(—)	H	2	(32)	—	(32)	Me	2	(12)	12:1	(6)	H	3	(61)	—	(17)	Me	3	(13)	20:1	(2)																				
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C ₈ 	<i>t</i> -BuOK, THF, rt, 4 h	 (87)	150																																																	
	NaOMe, MeOH, 100°, 20 h, sealed tube	 (31)	49																																																	
	NaOEt, EtOH, rt, 3 h	 (83)	243																																																	

TABLE 1A. RBR OF PREFORMED α -HALO SULFONES: ACYCLIC SUBSTRATES (Continued)

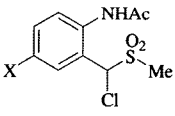
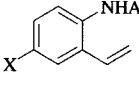
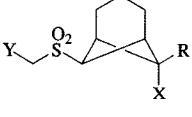
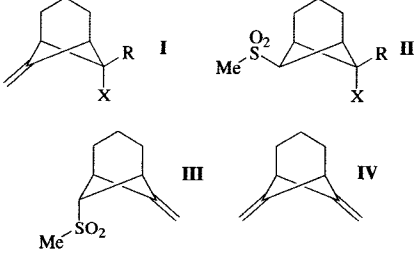
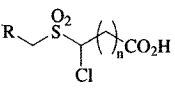
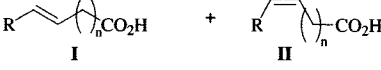
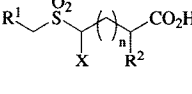
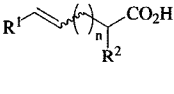
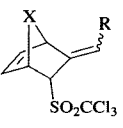
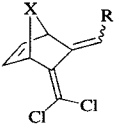
Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.																																													
<p>C₈₋₉</p> 	<p><i>t</i>-BuOK, <i>t</i>-BuOH, THF, 25-60°, 1.5 h</p>	 <table border="1"> <tr><td>X</td><td></td></tr> <tr><td>Me</td><td>(77)</td></tr> <tr><td>H</td><td>(76)</td></tr> <tr><td>CO₂Et</td><td>(62)</td></tr> </table>	X		Me	(77)	H	(76)	CO ₂ Et	(62)	242																																					
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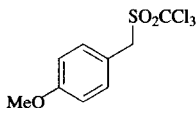
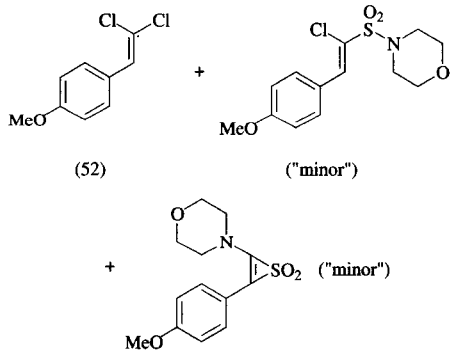
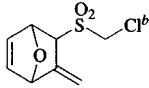

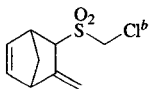

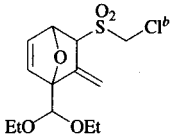
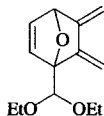
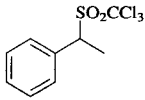
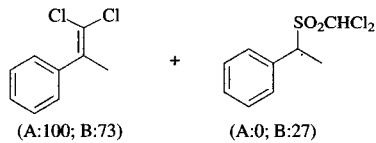
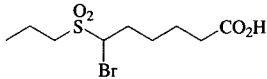

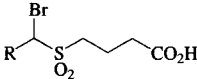

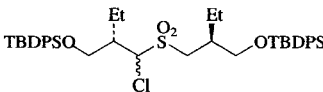
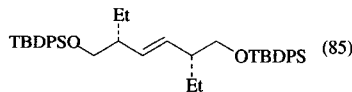
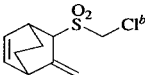

Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.																					
C ₈ 	Morpholine, DABCO, toluene, reflux, 12 h	 (52) ("minor")	63																					
424 	<i>t</i> -BuOK, THF, 0°	 (85) ^c	55																					
C ₉ 	<i>t</i> -BuOK, THF, 0°	 (85) ^c	55																					
	<i>t</i> -BuOK, THF, 0°	 (68) ^c	55																					
	A. Morpholine, DABCO, toluene, reflux or B. DBU, CHCl ₃ , rt, 15 min	 (A:100; B:73) (A:0; B:27)	63																					
	NaOEt, EtOH, reflux, 45 min	 (80)	58																					
C ₉₋₁₆ 	A. KOH, reflux, 3 h or B. <i>t</i> -BuOK, <i>t</i> -BuOH, reflux, 4 h	 R <table border="1" data-bbox="921 1593 1298 1793"> <thead> <tr> <th>R</th> <th>Conditions</th> <th><i>E:Z</i></th> </tr> </thead> <tbody> <tr> <td><i>n</i>-Bu</td> <td>A</td> <td>(74) 18:82</td> </tr> <tr> <td><i>n</i>-Bu</td> <td>B</td> <td>(83) 76:24</td> </tr> <tr> <td><i>n</i>-C₈H₁₇</td> <td>A</td> <td>(72) 15:85</td> </tr> <tr> <td><i>n</i>-C₈H₁₇</td> <td>B</td> <td>(85) 78:22</td> </tr> <tr> <td><i>n</i>-C₁₀H₂₀CO₂H</td> <td>A</td> <td>(65) 20:80</td> </tr> <tr> <td><i>n</i>-C₁₀H₂₀CO₂H</td> <td>B</td> <td>(68) 75:25</td> </tr> </tbody> </table>	R	Conditions	<i>E:Z</i>	<i>n</i> -Bu	A	(74) 18:82	<i>n</i> -Bu	B	(83) 76:24	<i>n</i> -C ₈ H ₁₇	A	(72) 15:85	<i>n</i> -C ₈ H ₁₇	B	(85) 78:22	<i>n</i> -C ₁₀ H ₂₀ CO ₂ H	A	(65) 20:80	<i>n</i> -C ₁₀ H ₂₀ CO ₂ H	B	(68) 75:25	29
R	Conditions	<i>E:Z</i>																						
<i>n</i> -Bu	A	(74) 18:82																						
<i>n</i> -Bu	B	(83) 76:24																						
<i>n</i> -C ₈ H ₁₇	A	(72) 15:85																						
<i>n</i> -C ₈ H ₁₇	B	(85) 78:22																						
<i>n</i> -C ₁₀ H ₂₀ CO ₂ H	A	(65) 20:80																						
<i>n</i> -C ₁₀ H ₂₀ CO ₂ H	B	(68) 75:25																						
C ₁₀ 	<i>t</i> -BuOK, THF, -78 to 0°, 3 h	 (85)	170																					
425 	<i>t</i> -BuOK, THF, 0°	 (60) ^c	55																					

TABLE 1A. RBR OF PREFORMED α -HALO SULFONES: ACYCLIC SUBSTRATES (Continued)

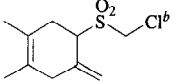
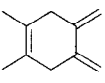
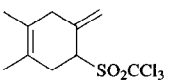
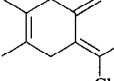
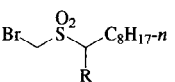
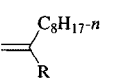
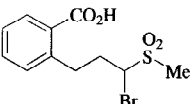
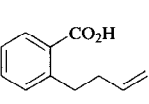
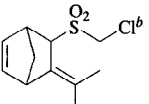
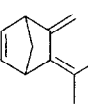
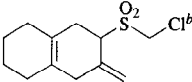
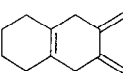
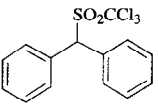
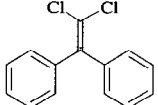
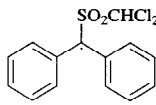
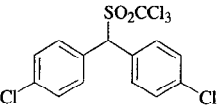
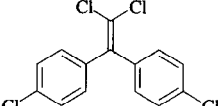
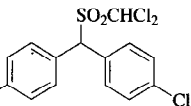
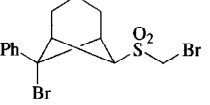
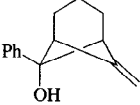
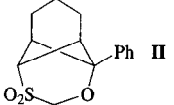
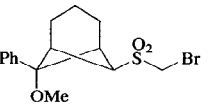
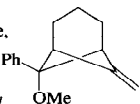
Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.								
	<i>t</i> -BuOK, THF, 0°	 (57) ^c	55								
	DBU, CHCl ₃ , 0° to rt, 2.5 h	 (77)	56								
C ₁₀₋₁₄ 	NaOEt, EtOH, reflux, 45 min	 <table border="0" style="margin-left: 20px;"> <tr> <td>R</td> <td></td> </tr> <tr> <td>H</td> <td>(83)</td> </tr> <tr> <td>Et</td> <td>(84)</td> </tr> <tr> <td><i>n</i>-Bu</td> <td>(78)</td> </tr> </table>	R		H	(83)	Et	(84)	<i>n</i> -Bu	(78)	58
R											
H	(83)										
Et	(84)										
<i>n</i> -Bu	(78)										
C ₁₁ 	NaOEt, EtOH, rt, 45 min	 (71)	243								
	<i>t</i> -BuOK, THF, 0°	 (85) ^c	55								
C ₁₂ 	<i>t</i> -BuOK, THF, 0°	 (57) ^c	55								
C ₁₄ 	A. Morpholine, DABCO, toluene, reflux or B. DBU, CHCl ₃ , rt, 15 min	 (A:100; B:74) +  (A:0; B:26)	63								
	A. Morpholine, DABCO, toluene, reflux or B. DBU, CHCl ₃ , rt, 15 min	 (A:100; B:63) +  (A:0; B:37)	63								
	NaOH, H ₂ O, 1,4-dioxane, reflux, 2 h	 I +  II (85) I:II = 25:75	50, 244								
	A. NaOH, H ₂ O, 1,4-dioxane, reflux, 2 h or B. 1. <i>t</i> -BuOK, THF, 0°, 2 h ^d 2. 1,4-dioxane, reflux, 1 h	 (A:98; B:26)	50, 244								

TABLE 1A. RBR OF PREFORMED α -HALO SULFONES: ACYCLIC SUBSTRATES (Continued)

	Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₁₅		NaOEt, EtOH, rt, 3 h	(88)	243
C ₁₆		<i>t</i> -BuOK, THF, 0°	(85)	55
C ₁₈		DBU, CHCl ₃ , 0° to rt, 2.5 h	(86)	56
C ₁₉₋₂₀		<i>t</i> -BuOK, THF, 0°	(49) ^c $\frac{X}{O}$ (60) ^c CH ₂	55
C ₂₀		<i>t</i> -BuOK, THF, 0°	(85) ^c	55
C ₂₇₋₂₉		<i>t</i> -BuOK (3.5 eq), THF, rt, 3-4 h	(73) ^f $\frac{R}{H}$ (70) ^f Et	150

^a This was the overall yield from the TMS enol ether precursor of reactant.

^b The reactant was generated in situ by Diels-Alder cycloaddition of diene and allenyl sulfone.

^c This was the overall yield for 2 stages from diene precursor of reactant.

^d An episulfone intermediate was isolated after this stage.

^e The substrate was an undefined mixture of regio- and diastereoisomers.

^f This was the overall yield for 3 steps (chlorination, oxidation, rearrangement) from a sulfide precursor.

TABLE 1B. RBR OF PREFORMED α -HALO SULFONES: CYCLIC SUBSTRATES



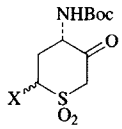

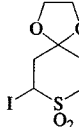

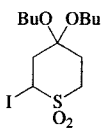

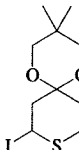
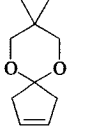
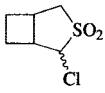

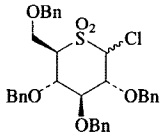
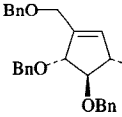
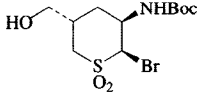

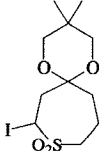
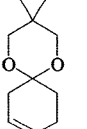
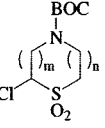

Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₄ 	NaOPh, diglyme, 160°, 24 h	 (74) ^d	59
C ₅ 	AcONa, THF, H ₂ O, MeCN, reflux, 10 h	 X Cl (48) ^b Br (62) ^b	70
	<i>t</i> -BuOK, THF, -78° to rt, 6 h	 (—) ^c	21
	<i>t</i> -BuOK, THF, rt, 2 h	 (93)	21
	<i>t</i> -BuOK, THF, rt, 1 h	 (86)	21
C ₆ 	NaOPh, diglyme, 140°, 24 h	 (68)	59
	<i>t</i> -BuOK, THF, -78°	 (40)	110
	1. <i>t</i> -BuOK, THF, -78° 2. HCl, MeOH	 (77)	53
	<i>t</i> -BuOK, THF, -78°, 2 min	 (82)	37
C ₆₋₁₂ 	A. <i>t</i> -BuOK, THF, DMSO rt, 10 min or B. KOH (2M), reflux, 1-3 h or C. DBU, toluene 110°, 1 h	 m n Conditions Z:E 2 2 A 100:0 (66) ^d 2 2 A 100:0 (43) ^d 3 2 B 100:0 (41) ^d 3 2 B 100:0 (33) ^d 3 3 A 6:94 (100) ^d 4 3 A 5:95 (54) ^d 4 4 A 2:98 (97) ^d 4 4 B 39:61 (57) ^d 4 4 C 43:57 (56) ^d 5 4 A 1:99 (76) ^d 5 4 B 38:62 (70) ^d 5 5 A 6:94 (93) ^d 5 5 B 56:44 (79) ^d	31, 245

TABLE 1B. RBR OF PREFORMED α -HALO SULFONES: CYCLIC SUBSTRATES (Continued)

	Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.												
C ₇		<i>t</i> -BuOK, Et ₂ O	<table border="1"> <tr> <td>X</td> <td>Y</td> <td></td> </tr> <tr> <td>Cl</td> <td>Cl</td> <td>(22)</td> </tr> <tr> <td>Br</td> <td>Br</td> <td>(17)</td> </tr> <tr> <td>Cl</td> <td>Br</td> <td>(30)</td> </tr> </table>	X	Y		Cl	Cl	(22)	Br	Br	(17)	Cl	Br	(30)	35
X	Y															
Cl	Cl	(22)														
Br	Br	(17)														
Cl	Br	(30)														
C ₈		<i>t</i> -BuOK, THF, -30° to rt	I (-) + II (-) <i>y</i>	246												
		<i>t</i> -BuOK, THF, -78° to rt, 16 h	(87)	21												
C ₈₋₉		<i>t</i> -BuOK, THF, 0°, 4-5 h	<table border="1"> <tr> <td>n</td> <td></td> </tr> <tr> <td>1</td> <td>(40)^d</td> </tr> <tr> <td>2</td> <td>(40)^d</td> </tr> </table>	n		1	(40) ^d	2	(40) ^d	176						
n																
1	(40) ^d															
2	(40) ^d															
C ₉		1. <i>t</i> -BuOK, THF, -78 to 0° 2. SiO ₂ chromatography	(86)	21												
		<i>t</i> -BuOK, THF, -15°, 6 h	(71)	16												
		<i>t</i> -BuOK, THF, -75°, 11 h	(21) ^b	16												
		<i>t</i> -BuOK, THF, 0° to reflux, 4 days	(1)	247												
C ₉₋₁₀		MeLi, Et ₂ O, -78°	<table border="1"> <tr> <td>n</td> <td>Time</td> <td>I</td> <td>II</td> </tr> <tr> <td>1</td> <td>10 min</td> <td>(0)</td> <td>(24)</td> </tr> <tr> <td>2</td> <td>quench immediately</td> <td>(12)</td> <td>(12)</td> </tr> </table>	n	Time	I	II	1	10 min	(0)	(24)	2	quench immediately	(12)	(12)	43
n	Time	I	II													
1	10 min	(0)	(24)													
2	quench immediately	(12)	(12)													
C ₁₀		<i>t</i> -BuOK, THF, 0° to reflux, 4 days	(26)	247												
		<i>t</i> -BuOK, THF	(-) <i>y</i>	249												
		<i>t</i> -BuOK, THF, rt, 1 h	(-)	73, 74												
		<i>t</i> -BuOK, THF, 0° to rt, 2 h	(82)	73, 74												
		<i>t</i> -BuOK, THF, 0°, 1 h	I + II I:II = 10:1	73, 74												

TABLE 1B. RBR OF PREFORMED α -HALO SULFONES: CYCLIC SUBSTRATES (Continued)

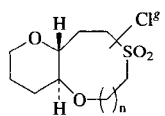
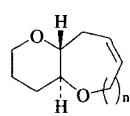
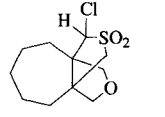
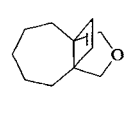
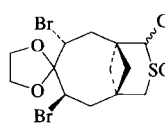
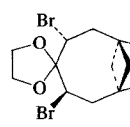
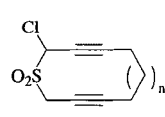
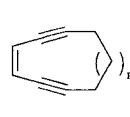
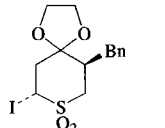
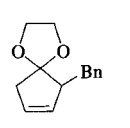
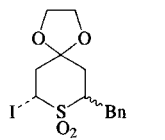
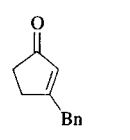
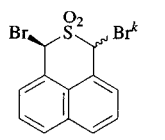
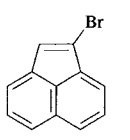
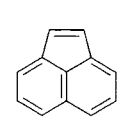
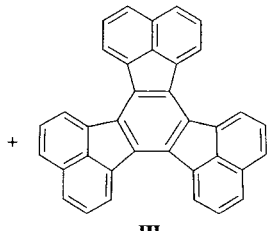
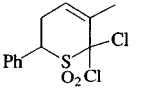
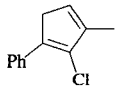
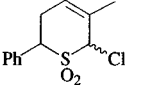
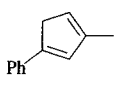
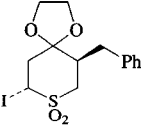
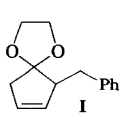
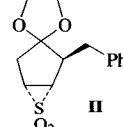
Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.												
C ₁₀₋₁₁ 	<i>t</i> -BuOK, THF, 0°, 4-5 h	 $\frac{n}{2}$ (37) ^d $\frac{n}{3}$ (48) ^d	176												
C ₁₁ 	<i>t</i> -BuOK, THF, 0° to reflux, 4 days	 (28)	247												
	<i>t</i> -BuOK, THF, -78°, 10 min	 (—)	249												
C ₁₁₋₁₆ 434 	<i>t</i> -BuOK, THF, -78°, 3 h	 $\frac{n}{3}$ (32) $\frac{n}{4}$ (33) (62% using KOH) $\frac{n}{5}$ (24) $\frac{n}{6}$ (49) $\frac{n}{7}$ (32) $\frac{n}{8}$ (44)	43												
C ₁₂ 	<i>t</i> -BuOK, THF, -23° to rt, 3 h	 (85)	21												
	1. <i>t</i> -BuOK, THF, -78° to rt 2. SiO ₂ chromatography	 (62)	21												
	A. NaOMe, MeOH, rt, 18 h or B. <i>t</i> -BuOK, <i>t</i> -BuOH, 27°, 18 h	 I +  II	60												
		 III	<table border="1"> <thead> <tr> <th>Conditions</th> <th>I</th> <th>II</th> <th>III</th> </tr> </thead> <tbody> <tr> <td>A</td> <td>(75)</td> <td>(9)</td> <td>(trace)</td> </tr> <tr> <td>B</td> <td>(33)</td> <td>(23)</td> <td>(5)</td> </tr> </tbody> </table>	Conditions	I	II	III	A	(75)	(9)	(trace)	B	(33)	(23)	(5)
Conditions	I	II	III												
A	(75)	(9)	(trace)												
B	(33)	(23)	(5)												
	<i>n</i> -BuLi, THF, -78° to rt	 (26)	69												
	<i>n</i> -BuLi, THF, -78° to rt	 (30)	69												
	<i>t</i> -BuOK, THF	 I +  II	20												
		<table border="1"> <thead> <tr> <th>Mol. eq. <i>t</i>-BuOK</th> <th>Temp</th> <th>I</th> <th>II</th> </tr> </thead> <tbody> <tr> <td>2.5</td> <td>-20° to rt</td> <td>(85)</td> <td>(0)</td> </tr> <tr> <td>1.2</td> <td>-78° to rt</td> <td>(28)</td> <td>(69)</td> </tr> </tbody> </table>	Mol. eq. <i>t</i> -BuOK	Temp	I	II	2.5	-20° to rt	(85)	(0)	1.2	-78° to rt	(28)	(69)	
Mol. eq. <i>t</i> -BuOK	Temp	I	II												
2.5	-20° to rt	(85)	(0)												
1.2	-78° to rt	(28)	(69)												

TABLE 1B. RBR OF PREFORMED α -HALO SULFONES: CYCLIC SUBSTRATES (Continued)

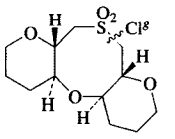
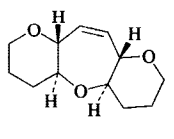
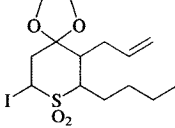
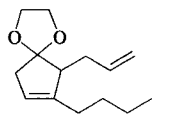
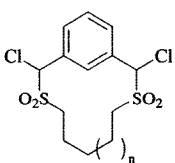
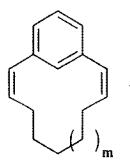
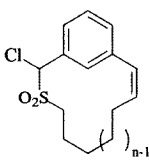
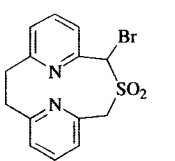
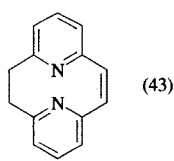
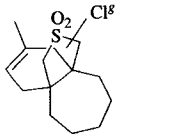
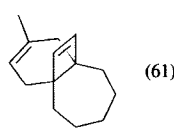
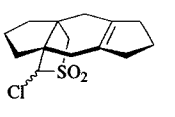
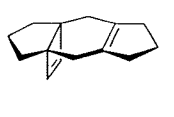
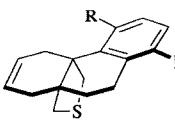
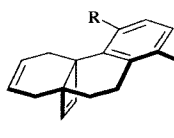
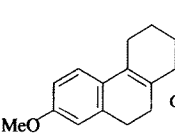
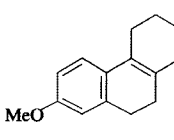
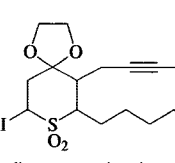
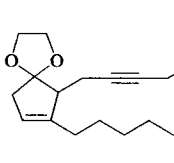
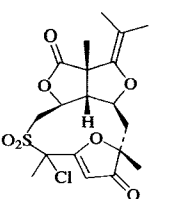
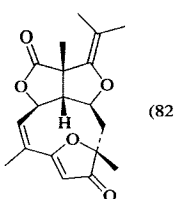
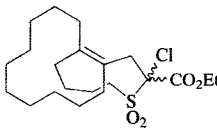
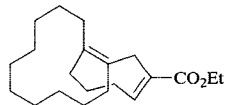
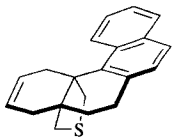
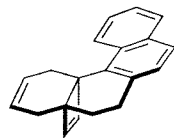
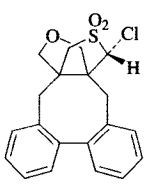
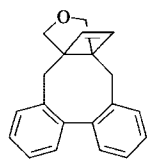
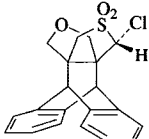

Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.												
	<i>t</i> -BuOK, THF, 0°, 1.5 h	 (52) ^d	175												
	single diastereoisomer configuration undefined <i>t</i> -BuOK, THF, -78°, 30 min	 (78)	171												
C ₁₄₋₁₅ 	<i>t</i> -BuOK, THF, rt, 21 h	 I +  II <table border="1" style="display: inline-table; vertical-align: middle;"> <tr> <td>n</td> <td>m</td> <td>I^d</td> <td>II^d</td> </tr> <tr> <td>2</td> <td>0</td> <td>(32)</td> <td>(25)</td> </tr> <tr> <td>3</td> <td>1</td> <td>(25)</td> <td>(—)</td> </tr> </table>	n	m	I ^d	II ^d	2	0	(32)	(25)	3	1	(25)	(—)	251
n	m	I ^d	II ^d												
2	0	(32)	(25)												
3	1	(25)	(—)												
C ₁₄ 	NaOH, 1,4-dioxane, rt, 2 h	 (43)	64												
	<i>n</i> -BuLi, THF, -78° to rt	 (61)	36												
	<i>t</i> -BuOK, THF, 0° to reflux, > 4 h	 (29)	250												
C ₁₆₋₁₈ 	1. NCS, CCl ₄ , reflux, 3 h 2. MPA, Et ₂ O, CHCl ₃ , -23° to rt, 6-7.5 h 3. <i>t</i> -BuOK, THF, reflux, 3 - 3.5 h	 <table border="1" style="display: inline-table; vertical-align: middle;"> <tr> <td>R</td> <td></td> </tr> <tr> <td>H</td> <td>(81)</td> </tr> <tr> <td>Me</td> <td>(53)</td> </tr> </table>	R		H	(81)	Me	(53)	223						
R															
H	(81)														
Me	(53)														
C ₁₇ 	<i>t</i> -BuOK, DME	 (—)	67												
C ₁₈ 	<i>t</i> -BuOK, THF, -78°, 30 min	 (65)	171												
C ₁₉ 	single diastereoisomer Et ₃ COK, HMPA, DME, 70°, 5 min	 (82)	8												

TABLE 1B. RBR OF PREFORMED α -HALO SULFONES: CYCLIC SUBSTRATES (Continued)

Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.
	<i>t</i> -BuOK, DME, rt, 2 h	 (64)	68
	1. NCS, CCl ₄ , reflux, 29 h 2. MPA, Et ₂ O, CHCl ₃ , -23° to rt, 10 h 3. <i>t</i> -BuOK, THF, reflux, 20 h	 (40)	223
	<i>t</i> -BuOK, THF, -70° to reflux, 4 h	 (5) ^l	208
	<i>t</i> -BuOK, THF, -70° to reflux, 4 h	 (6) ^m	208

^a The product was isolated in a methanol-dry ice cold trap.

^b Substantial racemization occurred during the reaction.

^c Due to volatility of product the yield was not determined.

^d The yield is over 3 steps from a sulfide starting material.

^e The compound was a mixture of 3 regio- and stereoisomers.

^f The products were identified by GC-MS.

^g The substrate was an undefined mixture of regio- and diastereoisomers.

^h Separate experiments on diastereomerically pure *endo*- and *exo*-bromides gave yields up to 35 and 49%, respectively, as determined by GC analysis.

ⁱ The starting material was an isomeric mixture.

^j The product was isolated in a mixture with four other unidentified products; purification was effected by preparative GC.

^k This was used as a 64:36 mixture of *cis*- and *trans*-stereoisomers.

^l Yields of 90% and 85% were obtained from reaction of the corresponding *erythro*- and *threo*- α -chlorosulfoxides, respectively.

^m A yield of 25% was obtained from reaction of the corresponding *threo*- α -chlorosulfoxide.

TABLE 2. RBR OF OTHER α -SUBSTITUTED SULFONES^a

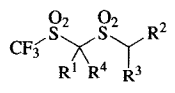
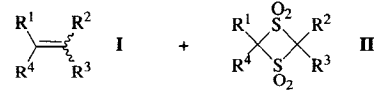
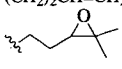
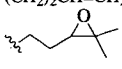
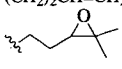
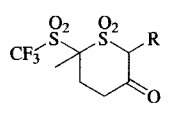
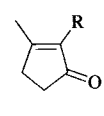
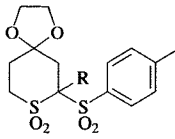
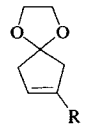
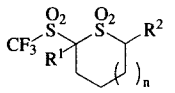
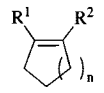
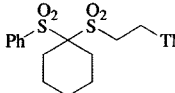
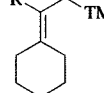
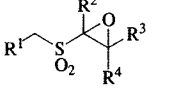
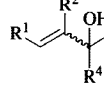
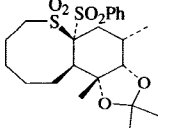
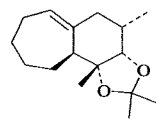
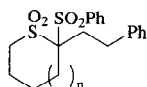
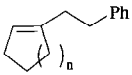
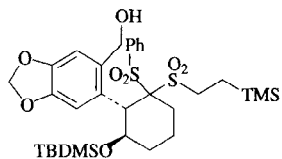
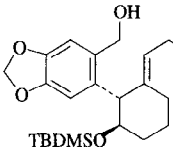
Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.																																																																																																								
C5-18 	A. <i>t</i> -BuOK, THF, 0°, 1 h or B. NaOH (10%), CH ₂ Cl ₂ , Bu ₄ N ⁺ HSO ₄ ⁻ , rt, overnight		83																																																																																																								
<table border="1"> <thead> <tr> <th>R¹</th> <th>R²</th> <th>R³</th> <th>R⁴</th> <th>Conditions</th> <th>I</th> <th>II</th> </tr> </thead> <tbody> <tr> <td>Me</td> <td>H</td> <td>CO₂Me</td> <td>Me</td> <td>B</td> <td>(62)</td> <td>(—)</td> </tr> <tr> <td>CH₂OBn</td> <td>H</td> <td>CO₂Me</td> <td>Me</td> <td>B</td> <td>(91)</td> <td>(—)</td> </tr> <tr> <td><i>n</i>-Pr</td> <td>H</td> <td>H</td> <td>Me</td> <td>A</td> <td>(80)</td> <td>(20)</td> </tr> <tr> <td>(CH₂)₂CO₂Et</td> <td>H</td> <td>H</td> <td>Me</td> <td>A</td> <td>(83)</td> <td>(7)</td> </tr> <tr> <td>Me</td> <td>H</td> <td>H</td> <td>(CH₂)₃CO₂Et</td> <td>A</td> <td>(83)</td> <td>(—)</td> </tr> <tr> <td>Me</td> <td>H</td> <td>COBu-<i>t</i></td> <td>Me</td> <td>B</td> <td>(67)</td> <td>(—)</td> </tr> <tr> <td><i>n</i>-Pr</td> <td><i>n</i>-Pr</td> <td>H</td> <td>Me</td> <td>A</td> <td>(38)</td> <td>(62)^b</td> </tr> <tr> <td>Me</td> <td>H</td> <td>COCMe₂CH=CH₂</td> <td>Me</td> <td>B</td> <td>(90)</td> <td>(—)</td> </tr> <tr> <td>(CH₂)₂CH=CH₂</td> <td>H</td> <td>CO₂Me</td> <td>Me</td> <td>B</td> <td>(89)</td> <td>(—)</td> </tr> <tr> <td></td> <td>H</td> <td>CO₂Me</td> <td>Me</td> <td>B</td> <td>(84)</td> <td>(—)</td> </tr> <tr> <td>Me</td> <td>H</td> <td>Bz</td> <td>Me</td> <td>B</td> <td>(86)</td> <td>(—)</td> </tr> <tr> <td><i>n</i>-Bu</td> <td><i>n</i>-Bu</td> <td>H</td> <td>Me</td> <td>A</td> <td>(45)^c</td> <td>(53)^b</td> </tr> <tr> <td>Me</td> <td><i>n</i>-C₅H₁₁</td> <td>CO₂Me</td> <td><i>n</i>-C₅H₁₁</td> <td>B</td> <td>(100)</td> <td>(—)</td> </tr> <tr> <td>Me</td> <td><i>n</i>-C₅H₁₁</td> <td><i>n</i>-C₅H₁₁</td> <td><i>n</i>-C₅H₁₁</td> <td>A</td> <td>(64)</td> <td>(—)</td> </tr> </tbody> </table>	R ¹	R ²	R ³	R ⁴	Conditions	I	II	Me	H	CO ₂ Me	Me	B	(62)	(—)	CH ₂ OBn	H	CO ₂ Me	Me	B	(91)	(—)	<i>n</i> -Pr	H	H	Me	A	(80)	(20)	(CH ₂) ₂ CO ₂ Et	H	H	Me	A	(83)	(7)	Me	H	H	(CH ₂) ₃ CO ₂ Et	A	(83)	(—)	Me	H	COBu- <i>t</i>	Me	B	(67)	(—)	<i>n</i> -Pr	<i>n</i> -Pr	H	Me	A	(38)	(62) ^b	Me	H	COCMe ₂ CH=CH ₂	Me	B	(90)	(—)	(CH ₂) ₂ CH=CH ₂	H	CO ₂ Me	Me	B	(89)	(—)		H	CO ₂ Me	Me	B	(84)	(—)	Me	H	Bz	Me	B	(86)	(—)	<i>n</i> -Bu	<i>n</i> -Bu	H	Me	A	(45) ^c	(53) ^b	Me	<i>n</i> -C ₅ H ₁₁	CO ₂ Me	<i>n</i> -C ₅ H ₁₁	B	(100)	(—)	Me	<i>n</i> -C ₅ H ₁₁	<i>n</i> -C ₅ H ₁₁	<i>n</i> -C ₅ H ₁₁	A	(64)	(—)		
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C6-11 	K ₂ CO ₃ , THF, reflux, 3-5 h		<table border="1"> <thead> <tr> <th>R</th> <th>Yield (%)</th> </tr> </thead> <tbody> <tr> <td>H</td> <td>(50)</td> </tr> <tr> <td>Me</td> <td>(100)</td> </tr> <tr> <td><i>n</i>-C₅H₁₁</td> <td>(100)</td> </tr> </tbody> </table>	R	Yield (%)	H	(50)	Me	(100)	<i>n</i> -C ₅ H ₁₁	(100)	83																																																																																															
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C6-13 	KH, NaH, DMSO, 20-30°, 24-48 h		<table border="1"> <thead> <tr> <th>R</th> <th>Yield (%)</th> </tr> </thead> <tbody> <tr> <td>Me</td> <td>(60)</td> </tr> <tr> <td><i>n</i>-C₅H₁₁</td> <td>(87)</td> </tr> <tr> <td>PhCH₂CH₂</td> <td>(70)</td> </tr> </tbody> </table>	R	Yield (%)	Me	(60)	<i>n</i> -C ₅ H ₁₁	(87)	PhCH ₂ CH ₂	(70)	84																																																																																															
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C7-12 	A. <i>t</i> -BuOK, THF, 0°, 1 h or B. K ₂ CO ₃ , THF, reflux, 3-5 h		<table border="1"> <thead> <tr> <th>n</th> <th>R¹</th> <th>R²</th> <th>Conditions</th> <th>Yield (%)</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>Me</td> <td>CO₂Me</td> <td>B</td> <td>(72)</td> </tr> <tr> <td>2</td> <td>Me</td> <td>CO₂Me</td> <td>B</td> <td>(100)</td> </tr> <tr> <td>1</td> <td><i>n</i>-C₅H₁₁</td> <td>H</td> <td>A</td> <td>(65)</td> </tr> <tr> <td>1</td> <td>Me</td> <td><i>n</i>-C₅H₁₁</td> <td>A</td> <td>(64)</td> </tr> <tr> <td>2</td> <td>Me</td> <td><i>n</i>-C₅H₁₁</td> <td>A</td> <td>(70)</td> </tr> </tbody> </table>	n	R ¹	R ²	Conditions	Yield (%)	1	Me	CO ₂ Me	B	(72)	2	Me	CO ₂ Me	B	(100)	1	<i>n</i> -C ₅ H ₁₁	H	A	(65)	1	Me	<i>n</i> -C ₅ H ₁₁	A	(64)	2	Me	<i>n</i> -C ₅ H ₁₁	A	(70)	83																																																																									
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C8-15 	1. <i>n</i> -BuLi, THF, -78° 2. RX, -78 to -20° 3. <i>n</i> -BuLi, -20 to 25°		<table border="1"> <thead> <tr> <th>R</th> <th>X</th> <th>Yield (%)</th> </tr> </thead> <tbody> <tr> <td>H</td> <td>—</td> <td>(80)^d</td> </tr> <tr> <td>CH₂CH=CH₂</td> <td>Br</td> <td>(62)</td> </tr> <tr> <td>Bn</td> <td>Br</td> <td>(80)</td> </tr> <tr> <td>Me</td> <td>I</td> <td>(69)</td> </tr> <tr> <td>TMS</td> <td>Cl</td> <td>(85)</td> </tr> </tbody> </table>	R	X	Yield (%)	H	—	(80) ^d	CH ₂ CH=CH ₂	Br	(62)	Bn	Br	(80)	Me	I	(69)	TMS	Cl	(85)	85																																																																																					
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C9-15 	<i>t</i> -BuOLi, THF or DMSO, rt		<table border="1"> <thead> <tr> <th>R¹</th> <th>R²</th> <th>R³</th> <th>R⁴</th> <th>solvent</th> <th>Yield (%)</th> <th><i>E</i>:<i>Z</i></th> </tr> </thead> <tbody> <tr> <td>H</td> <td>H</td> <td>Ph</td> <td>H</td> <td>THF</td> <td>(39)^e</td> <td>—</td> </tr> <tr> <td>Ph</td> <td>H</td> <td>H</td> <td>H</td> <td>THF</td> <td>(75)</td> <td>65:35</td> </tr> <tr> <td>Ph</td> <td>H</td> <td>Et</td> <td>H</td> <td>THF</td> <td>(91)</td> <td>90:10</td> </tr> <tr> <td>Ph</td> <td>Me</td> <td>H</td> <td>Me</td> <td>THF</td> <td>(91)</td> <td>100:0</td> </tr> <tr> <td>Ph</td> <td>H</td> <td>Ph</td> <td>H</td> <td>DMSO^f</td> <td>(82)</td> <td>50:50</td> </tr> </tbody> </table>	R ¹	R ²	R ³	R ⁴	solvent	Yield (%)	<i>E</i> : <i>Z</i>	H	H	Ph	H	THF	(39) ^e	—	Ph	H	H	H	THF	(75)	65:35	Ph	H	Et	H	THF	(91)	90:10	Ph	Me	H	Me	THF	(91)	100:0	Ph	H	Ph	H	DMSO ^f	(82)	50:50	87																																																													
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C13 	<i>t</i> -BuOK, THF, reflux, 20 min		(65)	86																																																																																																							

TABLE 2. RBR OF OTHER α -SUBSTITUTED SULFONES^a (Continued)

Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.								
C ₁₃₋₁₅ 	<i>t</i> -BuOK, THF, 25°, 5 min	 <table style="display: inline-table; vertical-align: middle;"> <tr> <td>n</td> <td></td> </tr> <tr> <td>1</td> <td>(94)</td> </tr> <tr> <td>2</td> <td>(93)</td> </tr> <tr> <td>3</td> <td>(87)</td> </tr> </table>	n		1	(94)	2	(93)	3	(87)	86
n											
1	(94)										
2	(93)										
3	(87)										
C ₁₅ 	<i>n</i> -BuLi, THF, -78 to 0°	 (91)	85								

^a Carbon atoms in the leaving group are not included in the carbon count.

^b The product was obtained with an *E:Z trans:cis* ratio of 3:2.

^c The product was obtained with an *E:Z* ratio of 2.2:1.

^d This was the yield from reaction with *n*-BuLi at -78 to 0° without electrophile addition.

^e The yield was 64% based on recovered starting material.

^f The reaction in THF gave dimerized ether product (81%).

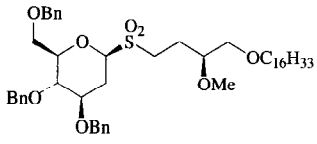
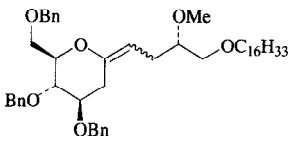
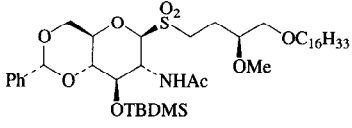
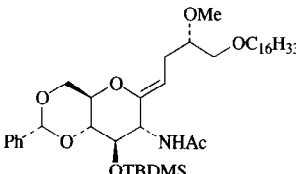
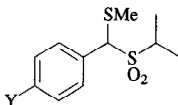
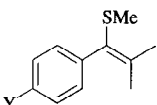
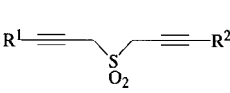
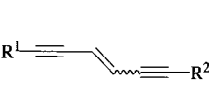
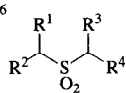

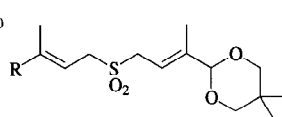
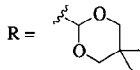
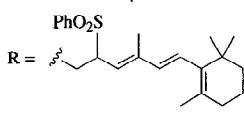
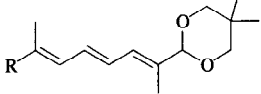
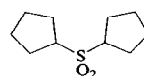
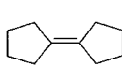
TABLE 3A. RBR WITH IN SITU HALOGENATION: ACYCLIC SUBSTRATES

Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₆₋₇ 	NaH, C ₂ Cl ₆ , DME, 20°, 3 - 24 h	 R <i>E:Z</i> Me (54) 1:1 Cl (—) —	40
C ₇ 	CBr ₂ F ₂ , KOH/Al ₂ O ₃ , <i>t</i> -BuOH, CH ₂ Cl ₂ , 5° to rt	 (58) <i>E:Z</i> = 50:50	179
C ₇₋₁₃ 	A. CBr ₂ F ₂ , KOH/Al ₂ O ₃ , <i>t</i> -BuOH, CH ₂ Cl ₂ , 5° to rt or B. CCl ₄ , KOH, <i>t</i> -BuOH, H ₂ O, 60°	 R Conditions <i>E:Z</i> H A (54) ^a — H B (72) — Me A (75) 20:80 Et A (71) 8:92 (CH ₂) ₂ OH A (74) 20:80 Ph A (94) 12:88	179-181
C ₈ 	KOH, CCl ₄ , <i>t</i> -BuOH, 50°, 1 h	 (70)	252
	KOH, CCl ₄ , <i>t</i> -BuOH, 50°, 17 h	 (53)	97
	CBr ₂ F ₂ , KOH/Al ₂ O ₃ , <i>t</i> -BuOH, CH ₂ Cl ₂ , 5° to rt	 (56) <i>E:Z</i> = 25:75	179

TABLE 3A. RBR WITH IN SITU HALOGENATION: ACYCLIC SUBSTRATES (Continued)

Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.
	CBr ₂ F ₂ , KOH/Al ₂ O ₃ , <i>t</i> -BuOH, rt	 (63) <i>E:Z</i> = 70:30	98
	CBr ₂ F ₂ , KOH/Al ₂ O ₃ , <i>t</i> -BuOH, rt	 (71)	98
C ₈₋₁₈ 	CBr ₂ F ₂ , KOH/Al ₂ O ₃ , CH ₂ Cl ₂ , rt	 <i>E:Z</i>	104
R ¹ R ² R ³ R ⁴ R ⁵			
Me H Me H H		(84) >95:<5	
Me H H H Me		(90) >95:<5	
Me Me Me Me H		(82) 75:25	
Ph H H H H		(86) >95:<5	
Ph H Me H H		(88) >95:<5	
Ph H H H Me		(92) >95:<5	
Ph H Me Me H		(87) 87:13	
Ph H TMS H H		(84) >95:<5	
H Ph TMS H H		(90) ^b 90:10	
Ph H Ph H H		(89) >95:<5	
Ph H H Ph H		(90) >95:<5	
H Ph H Ph H		(54) ^{b,c} 91:9	
C ₈₋₁₄ 	KOH, CCl ₄ , <i>t</i> -BuOH, reflux, 1-6 h	 R X Y	51
		H H H (40) ^d	
		H Br H (37)	
		H Cl H (36)	
		H Br Br (49)	
		H Cl Cl (41)	
		Me Br Br (32)	
		Ph Br H (11)	
		Ph MeO H (47)	
C ₉ 	KOH, CCl ₄ , <i>t</i> -BuOH, H ₂ O, 60°	 (51)	179
C ₉₋₁₄ 	KOH, CCl ₄ , <i>t</i> -BuOH, rt	 (-) ^e	101
R = Me, Ph			
C ₁₀ 	NaOH (50%), CCl ₄ , CH ₂ Cl ₂ , BnEt ₃ N ⁺ Cl ⁻ , rt, 20 h	 (97) + (2)	66
	CBr ₂ F ₂ , KOH/Al ₂ O ₃ , <i>t</i> -BuOH, 60°	 (37)	182

TABLE 3A. RBR WITH IN SITU HALOGENATION: ACYCLIC SUBSTRATES (Continued)

Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.																																																																																																
	CBr ₂ FCBr ₂ F, KOH/Al ₂ O ₃ , <i>t</i> -BuOH, reflux, 6 h	 (60) <i>E:Z</i> = 50:50	93																																																																																																
	CBr ₂ FCBr ₂ F, KOH/Al ₂ O ₃ , <i>t</i> -BuOH, reflux	 (70) <i>Z</i> = 100%	183																																																																																																
C ₁₀₋₁₁ 	KOH, CCl ₄ , <i>t</i> -BuOH, rt, 1 h	 <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th>Y</th> <th>Yield (%)</th> </tr> </thead> <tbody> <tr> <td>H</td> <td>(63)</td> </tr> <tr> <td>Me</td> <td>(67)</td> </tr> <tr> <td>OMe</td> <td>(66)</td> </tr> <tr> <td>Cl</td> <td>(67)</td> </tr> <tr> <td>NO₂</td> <td>(22)</td> </tr> </tbody> </table>	Y	Yield (%)	H	(63)	Me	(67)	OMe	(66)	Cl	(67)	NO ₂	(22)	100																																																																																				
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C ₁₀₋₁₈ 	CBr ₂ F ₂ , KOH/Al ₂ O ₃ , CH ₂ Cl ₂ , -10°, 30 min	 <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th>R¹</th> <th>R²</th> <th>Yield (%)</th> <th><i>E:Z</i></th> </tr> </thead> <tbody> <tr> <td>H</td> <td><i>t</i>-Bu</td> <td>(60)</td> <td>55:45</td> </tr> <tr> <td>H</td> <td><i>n</i>-C₅H₁₁</td> <td>(80)</td> <td>54:46</td> </tr> <tr> <td>Ph</td> <td>H</td> <td>(94)</td> <td>52:48</td> </tr> <tr> <td><i>n</i>-C₅H₁₁</td> <td>Ph</td> <td>(60)</td> <td>55:45</td> </tr> <tr> <td><i>t</i>-Bu</td> <td>Ph</td> <td>(90)</td> <td>48:52</td> </tr> <tr> <td><i>n</i>-C₅H₁₁</td> <td><i>n</i>-C₅H₁₁</td> <td>(81)</td> <td>51:49</td> </tr> <tr> <td>Ph</td> <td>Ph</td> <td>(80)</td> <td>50:50</td> </tr> </tbody> </table>	R ¹	R ²	Yield (%)	<i>E:Z</i>	H	<i>t</i> -Bu	(60)	55:45	H	<i>n</i> -C ₅ H ₁₁	(80)	54:46	Ph	H	(94)	52:48	<i>n</i> -C ₅ H ₁₁	Ph	(60)	55:45	<i>t</i> -Bu	Ph	(90)	48:52	<i>n</i> -C ₅ H ₁₁	<i>n</i> -C ₅ H ₁₁	(81)	51:49	Ph	Ph	(80)	50:50	109																																																																
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C ₁₀ 	CBr ₂ F ₂ , KOH/Al ₂ O ₃ , <i>t</i> -BuOH, 60-80°	 (90)	90																																																																																																

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447

TABLE 3A. RBR WITH IN SITU HALOGENATION: ACYCLIC SUBSTRATES (Continued)

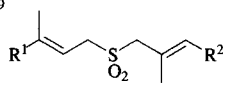
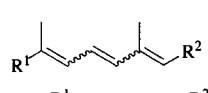
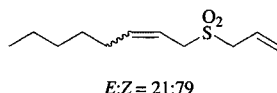
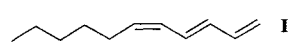
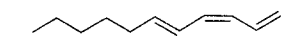
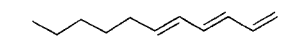
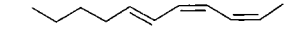
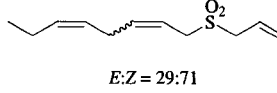
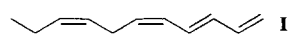
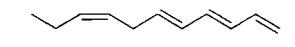
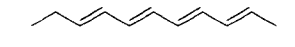
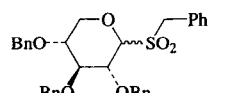
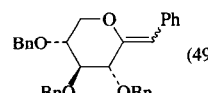
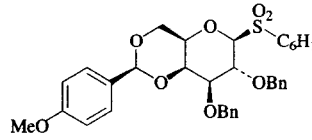
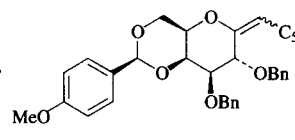
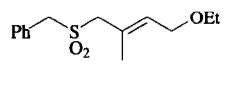
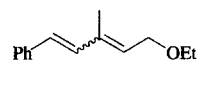
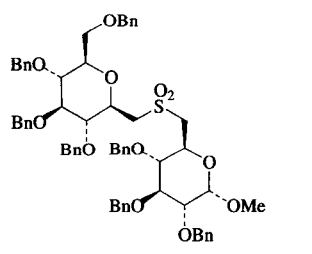
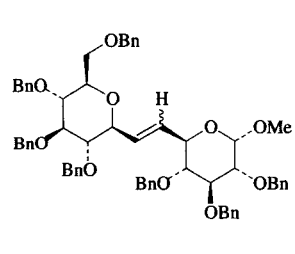
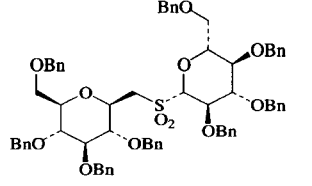
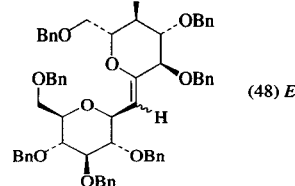
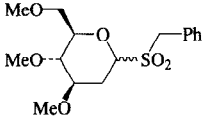
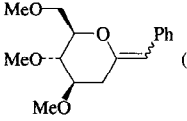
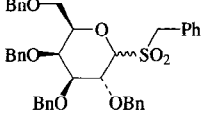
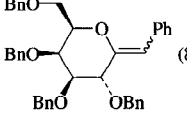
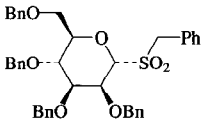
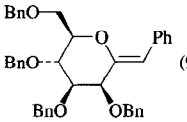
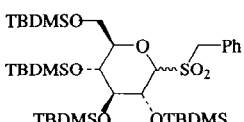
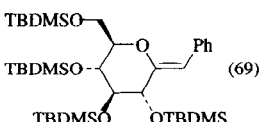
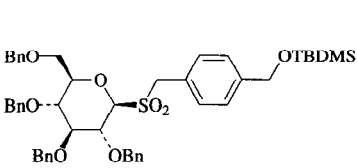
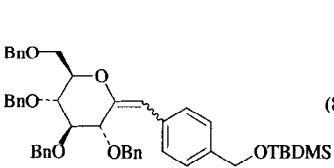
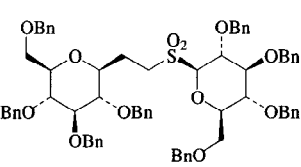
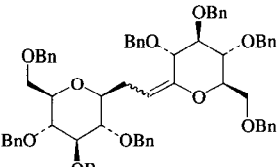
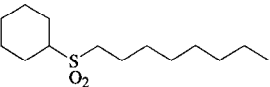
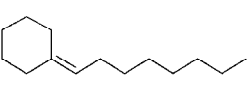
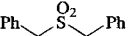
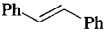

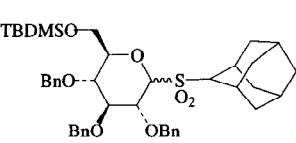
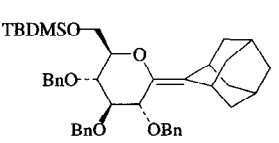
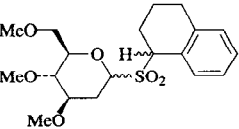
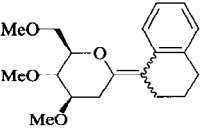
Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.																		
C ₁₀₋₁₉ 	"Meyers conditions or two-step procedure" (no more details given)	 <table border="1"> <thead> <tr> <th>R¹</th> <th>R²</th> <th>Yield (%)</th> </tr> </thead> <tbody> <tr> <td>Me</td> <td>CH₂OEt</td> <td>(82)</td> </tr> <tr> <td>Me₂C=CHCH₂</td> <td>CH₂OEt</td> <td>(55)</td> </tr> <tr> <td>Me₂C=CHCH₂</td> <td>(E)-CH=CHCOMe</td> <td>(50)</td> </tr> <tr> <td>Me₂C=CHCH₂</td> <td>CH₂CH₂C(Me)OHCH=CH₂</td> <td>(91)</td> </tr> <tr> <td>Me₂C=CHCH₂</td> <td>(E)-CH=CHC(Me)OHCH=CH₂</td> <td>(70)</td> </tr> </tbody> </table>	R ¹	R ²	Yield (%)	Me	CH ₂ OEt	(82)	Me ₂ C=CHCH ₂	CH ₂ OEt	(55)	Me ₂ C=CHCH ₂	(E)-CH=CHCOMe	(50)	Me ₂ C=CHCH ₂	CH ₂ CH ₂ C(Me)OHCH=CH ₂	(91)	Me ₂ C=CHCH ₂	(E)-CH=CHC(Me)OHCH=CH ₂	(70)	168
R ¹	R ²	Yield (%)																			
Me	CH ₂ OEt	(82)																			
Me ₂ C=CHCH ₂	CH ₂ OEt	(55)																			
Me ₂ C=CHCH ₂	(E)-CH=CHCOMe	(50)																			
Me ₂ C=CHCH ₂	CH ₂ CH ₂ C(Me)OHCH=CH ₂	(91)																			
Me ₂ C=CHCH ₂	(E)-CH=CHC(Me)OHCH=CH ₂	(70)																			
C ₁₁  E:Z = 21:79	KOH, CCl ₄ , <i>t</i> -BuOH, H ₂ O, 50°, 1 h	 I +  II +  III +  IV (42) I:II:III:IV = 81:14:2:3	103																		
 E:Z = 29:71		 I +  II +  III (48) I:II:III = 77.5:14.5:8	103																		
C ₁₂ 	CBF ₂ F ₂ , KOH/Al ₂ O ₃ , <i>t</i> -BuOH, CH ₂ Cl ₂ , 5° to rt	 (49) E:Z = 13:87	179																		
	CBF ₂ FCBr ₂ F, KOH/Al ₂ O ₃ , <i>t</i> -BuOH, reflux, 6 h	 (83) E:Z = 40:60	93																		
	"Meyers conditions or two-step procedure" (no more details given)	 (81)	168																		
C ₁₃ 	CBF ₂ F ₂ , KOH/Al ₂ O ₃ , <i>t</i> -BuOH, 60°	 (64) E:Z = 30:70	9																		
	KOH, CCl ₄ , <i>t</i> -BuOH, H ₂ O, 60°, 1 h	 (48) E:Z = 9:91	9																		

TABLE 3A. RBR WITH IN SITU HALOGENATION: ACYCLIC SUBSTRATES (Continued)

Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.
	CBr_2F_2 , $\text{KOH}/\text{Al}_2\text{O}_3$, $t\text{-BuOH}$, CH_2Cl_2 , 5° to rt	 (72) <i>E:Z</i> :endo = 76:15:9	181
	CBr_2F_2 , $\text{KOH}/\text{Al}_2\text{O}_3$, $t\text{-BuOH}$, CH_2Cl_2 , 5° to rt	 (83) <i>E:Z</i> = 38:62	179
	CBr_2F_2 , $\text{KOH}/\text{Al}_2\text{O}_3$, $t\text{-BuOH}$, CH_2Cl_2 , 5° to rt	 (94)	179
	CBr_2F_2 , $\text{KOH}/\text{Al}_2\text{O}_3$, $t\text{-BuOH}$, CH_2Cl_2 , 5° to rt	 (69)	180
	CBr_2F_2 , $\text{KOH}/\text{Al}_2\text{O}_3$, $t\text{-BuOH}$, CH_2Cl_2 , 5° to rt	 (88) <i>E:Z</i> = 80:20	184
	KOH , CCl_4 , $t\text{-BuOH}$, H_2O , 60° , 1 h	 (57) <i>E:Z</i> = 12:88	9
	CBr_2F_2 , $\text{KOH}/\text{Al}_2\text{O}_3$, $t\text{-BuOH}$, 60 to 80°	 (82)	90
	NaOH (10-20%), CCl_4 , CH_2Cl_2 , Aliquat-336, reflux, 1.5 h	 (94)	65
	NaOH (50%), CCl_4 , CH_2Cl_2 , $\text{BnEt}_3\text{N}^+\text{Cl}^-$, rt, 20 h	 (100)	66
	CBr_2F_2 , $\text{KOH}/\text{Al}_2\text{O}_3$, $t\text{-BuOH}$, CH_2Cl_2 , 5° to rt	 (20)	179
	CBr_2F_2 , $\text{KOH}/\text{Al}_2\text{O}_3$, $t\text{-BuOH}$, CH_2Cl_2 , 5° to rt	 (76) <i>E:Z</i> = 55:45	181

450

C₁₄

451

C₁₆

TABLE 3A. RBR WITH IN SITU HALOGENATION: ACYCLIC SUBSTRATES (Continued)

	Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.								
C ₁₇		CBr ₂ F ₂ , KOH/Al ₂ O ₃ , <i>t</i> -BuOH, CH ₂ Cl ₂ , 5° to rt	(70)	181								
		KOH, CCl ₄ , <i>t</i> -BuOH, 38°, 5 h	(69)	99								
C ₁₉		CCl ₄ , KOH, <i>t</i> -BuOH, H ₂ O, 60°	(57)	179								
C ₂₀		CBr ₂ F ₂ , KOH/Al ₂ O ₃ , <i>t</i> -BuOH, rt	(59) <i>E:Z</i> = 70:30	98								
C ₂₃₋₃₉		CBr ₂ F ₂ , KOH/Al ₂ O ₃ , <i>t</i> -BuOH, 5-10°	 I: R = Me II: R = H <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th>n</th> <th>I:II</th> </tr> </thead> <tbody> <tr> <td>0 (80)</td> <td>0:100</td> </tr> <tr> <td>1 (90)</td> <td>3:2</td> </tr> <tr> <td>2 (—)</td> <td>10:1</td> </tr> </tbody> </table>	n	I:II	0 (80)	0:100	1 (90)	3:2	2 (—)	10:1	95
n	I:II											
0 (80)	0:100											
1 (90)	3:2											
2 (—)	10:1											
C ₂₄		CBr ₂ F ₂ , KOH/ Al ₂ O ₃ , <i>t</i> -BuOH, reflux, 6 h	(85) <i>E:Z</i> = 1:1	93								
C ₃₀		CBr ₂ F ₂ , KOH/Al ₂ O ₃ , <i>t</i> -BuOH, rt, 1-2 h	(54)	90								

452

453

TABLE 3A. RBR WITH IN SITU HALOGENATION: ACYCLIC SUBSTRATES (Continued)

Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.										
<p>C₅₄</p>	<p>CBr₂F₂, KOH/Al₂O₃, <i>t</i>-BuOH, 5-10°</p>	<p>(81)^h</p>	95										
<p>C₆₂</p>	<p>CBr₂F₂, KOH/Al₂O₃, <i>t</i>-BuOH, 5-10°</p>	<p>(70)ⁱ</p>	95										
<p>C₁₀₄₋₁₃₆</p> <p>Ar =</p>	<p>NaOH, CCl₄, MeOH, THF, rt, 10 h</p>	<table border="1"> <tr> <td>n</td> <td></td> </tr> <tr> <td>1</td> <td>(87)</td> </tr> <tr> <td>2</td> <td>(84)</td> </tr> <tr> <td>3</td> <td>(75)</td> </tr> <tr> <td>4</td> <td>(73)</td> </tr> </table>	n		1	(87)	2	(84)	3	(75)	4	(73)	91
n													
1	(87)												
2	(84)												
3	(75)												
4	(73)												

^a A second product [(32% *E:Z* = 25:75] wherein R = Br was also formed.

^b The solvent was *t*-BuOH instead of CH₂Cl₂.

^c The reaction temperature was -78°.

^d A dichlorocarbene adduct (15%) was also isolated.

^e Dichlorocarbene adducts were also formed.

^f This reaction was run at 65° for 60 h.

^g This reaction was run at 60-80°.

^h This was the overall yield for two steps from the corresponding bis-sulfide.

ⁱ This was the overall yield for two steps from the corresponding sulfide.

TABLE 3B. RBR WITH IN SITU HALOGENATION: CYCLIC SUBSTRATES

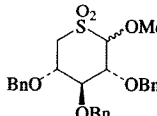
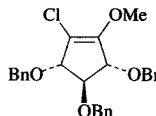
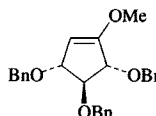
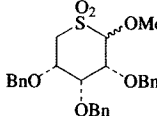
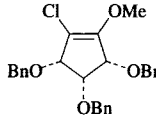
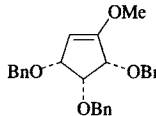
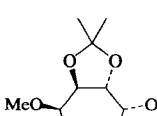
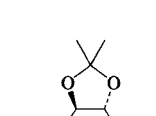
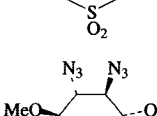
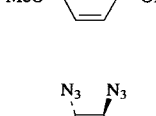
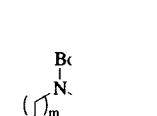





















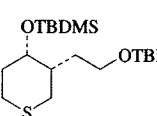
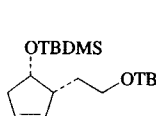
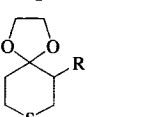
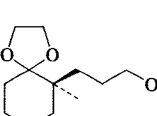
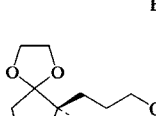
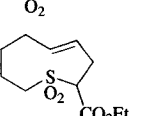
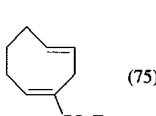
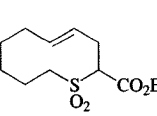
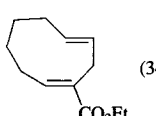
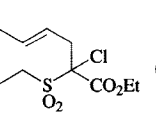
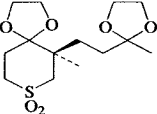
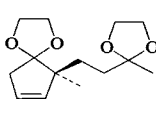
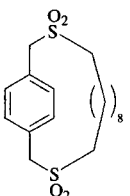
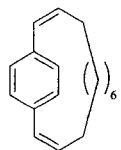
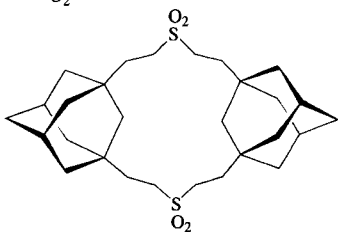
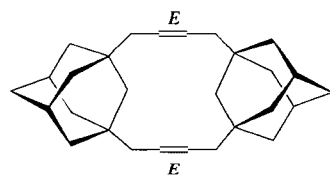
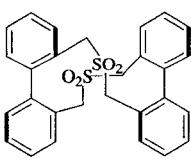
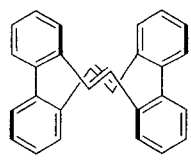
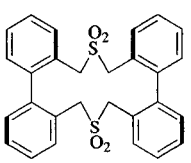
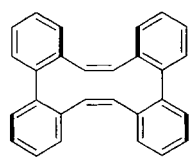
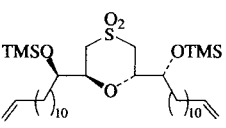
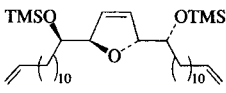
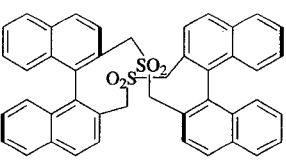
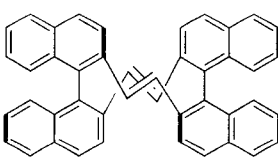
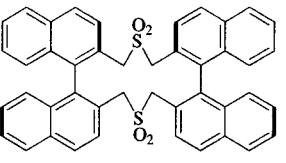
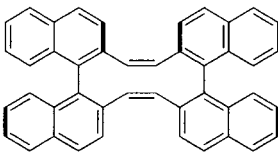
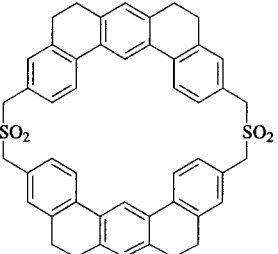
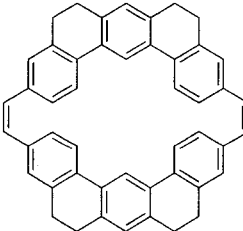
Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.																																								
C ₅ 	CCl ₄ , KOH, <i>t</i> -BuOH, 60°	 (50) +  (11)	110																																								
	CCl ₄ , KOH, <i>t</i> -BuOH, 60°	 (52) +  (17)	110																																								
C ₆ 	CCl ₄ , KOH, <i>t</i> -BuOH, H ₂ O, rt, 2 h	 (94)	177																																								
	CCl ₄ , KOH, <i>t</i> -BuOH, H ₂ O, rt, 2 h	 (78)	178																																								
C ₆₋₁₂ 	CBr ₂ F ₂ , KOH/Al ₂ O ₃ , <i>t</i> -BuOH, 60-80°, 1 h	<table border="1" data-bbox="920 941 1249 1170"> <thead> <tr> <th>Boc</th> <th>m</th> <th>n</th> <th><i>E</i>:<i>Z</i></th> <th></th> </tr> </thead> <tbody> <tr> <td></td> <td>2</td> <td>2</td> <td>0:100</td> <td>(63°)</td> </tr> <tr> <td></td> <td>3</td> <td>2</td> <td>0:100</td> <td>(33°)</td> </tr> <tr> <td></td> <td>3</td> <td>3</td> <td>65:35</td> <td>(59°)</td> </tr> <tr> <td></td> <td>4</td> <td>3</td> <td>60:40</td> <td>(67°)</td> </tr> <tr> <td></td> <td>4</td> <td>4</td> <td>73:27</td> <td>(68°)</td> </tr> <tr> <td></td> <td>5</td> <td>4</td> <td>85:15</td> <td>(62°)</td> </tr> <tr> <td></td> <td>5</td> <td>5</td> <td>61:39</td> <td>(53°)</td> </tr> </tbody> </table>	Boc	m	n	<i>E</i> : <i>Z</i>			2	2	0:100	(63°)		3	2	0:100	(33°)		3	3	65:35	(59°)		4	3	60:40	(67°)		4	4	73:27	(68°)		5	4	85:15	(62°)		5	5	61:39	(53°)	31
Boc	m	n	<i>E</i> : <i>Z</i>																																								
	2	2	0:100	(63°)																																							
	3	2	0:100	(33°)																																							
	3	3	65:35	(59°)																																							
	4	3	60:40	(67°)																																							
	4	4	73:27	(68°)																																							
	5	4	85:15	(62°)																																							
	5	5	61:39	(53°)																																							
C ₇ 	<i>t</i> -BuOK, C ₂ Cl ₆ , THF, rt	 (66)	92																																								
C ₈₋₁₂ 	<i>t</i> -BuOK, CCl ₄ , <i>t</i> -BuOH, 50°, 20 h	<table border="1" data-bbox="920 1377 1249 1561"> <thead> <tr> <th>R</th> <th></th> </tr> </thead> <tbody> <tr> <td><i>n</i>-Pr</td> <td>(60)</td> </tr> <tr> <td>CH₂CH=CH₂</td> <td>(73)</td> </tr> <tr> <td><i>n</i>-C₅H₁₁</td> <td>(50)</td> </tr> <tr> <td>(<i>E</i>)-CH₂CH=CH₂Et</td> <td>(77)</td> </tr> <tr> <td>Bn</td> <td>(84)</td> </tr> </tbody> </table>	R		<i>n</i> -Pr	(60)	CH ₂ CH=CH ₂	(73)	<i>n</i> -C ₅ H ₁₁	(50)	(<i>E</i>)-CH ₂ CH=CH ₂ Et	(77)	Bn	(84)	84																												
R																																											
<i>n</i> -Pr	(60)																																										
CH ₂ CH=CH ₂	(73)																																										
<i>n</i> -C ₅ H ₁₁	(50)																																										
(<i>E</i>)-CH ₂ CH=CH ₂ Et	(77)																																										
Bn	(84)																																										
C ₉ 	<i>t</i> -BuOK, CCl ₄ , <i>t</i> -BuOH, 50°, 4 h	 (71)	253																																								
	NaH, C ₂ Cl ₆ , DME, 20°, 3 h	 (75)	40																																								
C ₁₀ 	NaH, C ₂ Cl ₆ , DME, 20°, 24 h	 (34) +  (54)	40																																								
	<i>t</i> -BuOK, CCl ₄ , <i>t</i> -BuOH, 50°, 4 h	 (60)	254																																								

TABLE 3B. RBR WITH IN SITU HALOGENATION: CYCLIC SUBSTRATES (Continued)

Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. <i>t</i> -BuOK, THF, -105° 2. NCS 3. <i>t</i> -BuOK, -105°	 (81) ^b	94
	1. <i>t</i> -BuOK, THF, -105° 2. NCS 3. <i>t</i> -BuOK, -105°	 (38) ^b	94
C ₁₁ 	1. <i>t</i> -BuOK, THF, -105° 2. NCS 3. <i>t</i> -BuOK, -105°	 (38) ^{b,c}	94
C ₁₂ 	1. <i>t</i> -BuOK, THF, -105° 2. NCS 3. <i>t</i> -BuOK, -105°	 (36) ^b	94
C ₁₄ 	1. <i>t</i> -BuOK, THF, -105° 2. NCS 3. <i>t</i> -BuOK, -105°	 (75) ^b	94
	KOH, CCl ₄ , <i>t</i> -BuOH, 0-20°, 1 h	 (53)	127
C ₁₆ 	A. KOH, CCl ₄ , <i>t</i> -BuOH, 27°, 13 h or B. KOH/Al ₂ O ₃ , CCl ₄ , <i>t</i> -BuOH, 27°, 24 h or C. KOH/Al ₂ O ₃ , CBr ₂ F ₂ , <i>t</i> -BuOH, 27°, 24 h	 I + II Conditions X I II A Cl (8) (22) B Cl (17) (—) C Br (6) (—)	116
C ₁₇ 	1. <i>t</i> -BuOK, THF, -105° 2. NIS 3. <i>t</i> -BuOK, -105°	 (45) ^b	94
	1. <i>t</i> -BuOK, THF, -105° 2. NIS 3. <i>t</i> -BuOK, -105°	 (52) ^b	94
C ₁₈ 	1. <i>t</i> -BuOK, THF, -105° 2. NIS 3. <i>t</i> -BuOK, -105°	 (62) ^b	94
	1. <i>t</i> -BuOK, THF, -105° 2. NCS 3. <i>t</i> -BuOK, -105°	 (60)	255

TABLE 3B. RBR WITH IN SITU HALOGENATION: CYCLIC SUBSTRATES (Continued)

	Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₁₈		CF ₂ Br ₂ , KOH/Al ₂ O ₃ , <i>t</i> -BuOH, rt	 (42)	114
C ₂₈		KOH, CCl ₄ , <i>t</i> -BuOH, 50°	 (50) ^d	115
460		KOH, CCl ₄ , <i>t</i> -BuOH, rt, overnight	 (95)	113
		KOH, CCl ₄ , <i>t</i> -BuOH, rt, overnight	 (69)	113
C ₃₀		<i>t</i> -BuOK, CCl ₄ , <i>t</i> -BuOH, rt	 (65)	172
461		KOH, CCl ₄ , <i>t</i> -BuOH, rt, overnight	 (49)	113
		KOH, CCl ₄ , <i>t</i> -BuOH, rt, overnight	 (30)	113
C ₄₈		KOH, CCl ₄ , <i>t</i> -BuOH	 (1-2)	227

^a The yields are for two steps from a sulfide.

^b This was the overall yield for four steps from a triene-Cr(CO)₃ cycloaddition precursor.

^c This product was formed by spontaneous aromatization of the initially generated RBR product.

^d A mono adduct with dichlorocarbene (8%) and the *E,Z*-diene (10%) were also isolated.

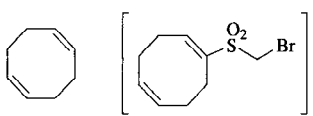
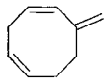
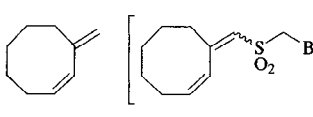
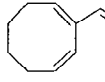
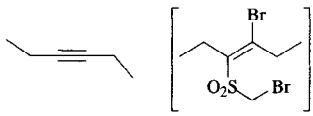
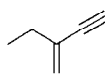
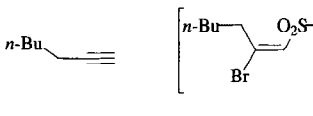
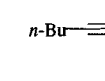
TABLE 4. VINYLOGOUS RBR OF VINYL SULFONES

Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.																		
A. Preformed Vinyl Sulfones																					
C ₁₂ 	<i>t</i> -BuOK, <i>t</i> -BuOH, rt, 12 h	(40) <i>E</i> : <i>Z</i> = 50:50	118																		
	<i>t</i> -BuOK, <i>t</i> -BuOH, rt, 12 h	(—) <i>E</i> : <i>Z</i> = 50:50	118																		
B. Vinyl Sulfones Formed In Situ; Terminal Alkenes ^{a,b}																					
C ₃ 	1. BrCH ₂ SO ₂ Br, CH ₂ Cl ₂ , <i>hν</i> 2. Et ₃ N, CHCl ₃ 3. <i>t</i> -BuOK, <i>t</i> -BuOH	(81)	123																		
C ₃₋₁₁ 	1. BrCH ₂ SO ₂ Br, CH ₂ Cl ₂ , <i>hν</i> 2. Et ₃ N, CH ₂ Cl ₂ 3. <i>t</i> -BuOK, <i>t</i> -BuOH, THF, rt	<table border="1"> <thead> <tr> <th>R</th> <th><i>E</i>:<i>Z</i></th> </tr> </thead> <tbody> <tr> <td>PhO</td> <td>(54) 1:9</td> </tr> <tr> <td>TMS</td> <td>(41) (—)</td> </tr> <tr> <td><i>n</i>-Pr</td> <td>(38) 1:2</td> </tr> <tr> <td><i>n</i>-C₅H₁₁</td> <td>(61) 1:2</td> </tr> <tr> <td><i>n</i>-C₆H₁₃</td> <td>(52) 1:2</td> </tr> <tr> <td>Ph</td> <td>(85) 8:1</td> </tr> <tr> <td>CH₂=CH(CH₂)₅</td> <td>(49) (—)</td> </tr> <tr> <td>HO(CH₂)₈</td> <td>(86) 1:5</td> </tr> </tbody> </table>	R	<i>E</i> : <i>Z</i>	PhO	(54) 1:9	TMS	(41) (—)	<i>n</i> -Pr	(38) 1:2	<i>n</i> -C ₅ H ₁₁	(61) 1:2	<i>n</i> -C ₆ H ₁₃	(52) 1:2	Ph	(85) 8:1	CH ₂ =CH(CH ₂) ₅	(49) (—)	HO(CH ₂) ₈	(86) 1:5	47
R	<i>E</i> : <i>Z</i>																				
PhO	(54) 1:9																				
TMS	(41) (—)																				
<i>n</i> -Pr	(38) 1:2																				
<i>n</i> -C ₅ H ₁₁	(61) 1:2																				
<i>n</i> -C ₆ H ₁₃	(52) 1:2																				
Ph	(85) 8:1																				
CH ₂ =CH(CH ₂) ₅	(49) (—)																				
HO(CH ₂) ₈	(86) 1:5																				
C ₈₋₁₂ 	1. BrCH ₂ SO ₂ Br, CH ₂ Cl ₂ , <i>hν</i> 2. Et ₃ N, CH ₂ Cl ₂ 3. <i>t</i> -BuOK, <i>t</i> -BuOH, THF, rt	<table border="1"> <thead> <tr> <th>R</th> <th>Yield (%)</th> </tr> </thead> <tbody> <tr> <td><i>n</i>-C₅H₁₁</td> <td>(79)</td> </tr> <tr> <td><i>i</i>-BuCH₂</td> <td>(63)</td> </tr> <tr> <td><i>n</i>-C₆H₁₃</td> <td>(73)</td> </tr> <tr> <td>Me₂C=CH(CH₂)₂</td> <td>(65)</td> </tr> <tr> <td><i>c</i>-C₆H₁₁</td> <td>(62)</td> </tr> <tr> <td><i>n</i>-C₉H₁₉</td> <td>(59)</td> </tr> </tbody> </table>	R	Yield (%)	<i>n</i> -C ₅ H ₁₁	(79)	<i>i</i> -BuCH ₂	(63)	<i>n</i> -C ₆ H ₁₃	(73)	Me ₂ C=CH(CH ₂) ₂	(65)	<i>c</i> -C ₆ H ₁₁	(62)	<i>n</i> -C ₉ H ₁₉	(59)	47				
R	Yield (%)																				
<i>n</i> -C ₅ H ₁₁	(79)																				
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<i>n</i> -C ₆ H ₁₃	(73)																				
Me ₂ C=CH(CH ₂) ₂	(65)																				
<i>c</i> -C ₆ H ₁₁	(62)																				
<i>n</i> -C ₉ H ₁₉	(59)																				
C. Vinyl Sulfones Formed In Situ; Internal Alkenes ^{a,b}																					
C ₆₋₁₄ 	1. BrCH ₂ SO ₂ Br, CH ₂ Cl ₂ , <i>hν</i> 2. Et ₃ N, CH ₂ Cl ₂ 3. <i>t</i> -BuOK, <i>t</i> -BuOH, THF	<table border="1"> <thead> <tr> <th>R</th> <th>Yield (%)</th> </tr> </thead> <tbody> <tr> <td>Me</td> <td>(58)</td> </tr> <tr> <td><i>n</i>-Pr</td> <td>(68)</td> </tr> <tr> <td><i>n</i>-C₅H₁₁</td> <td>(71)</td> </tr> </tbody> </table>	R	Yield (%)	Me	(58)	<i>n</i> -Pr	(68)	<i>n</i> -C ₅ H ₁₁	(71)	47										
R	Yield (%)																				
Me	(58)																				
<i>n</i> -Pr	(68)																				
<i>n</i> -C ₅ H ₁₁	(71)																				
C ₈ 	1. BrCH ₂ SO ₂ Br, CH ₂ Cl ₂ , <i>hν</i> 2. Et ₃ N, CH ₂ Cl ₂ 3. <i>t</i> -BuOK, <i>t</i> -BuOH, THF	(52) + (15)	47																		
D. Vinyl Sulfones Formed In Situ; Conjugated Dienes ^{a,b}																					
C ₅₋₁₀ 	1. BrCH ₂ SO ₂ Br, CH ₂ Cl ₂ , <i>hν</i> 2. Et ₃ N, CH ₂ Cl ₂ 3. <i>t</i> -BuOK, <i>t</i> -BuOH, THF, rt	<table border="1"> <thead> <tr> <th>R</th> <th>Yield (%)</th> <th><i>E</i>:<i>Z</i></th> </tr> </thead> <tbody> <tr> <td>H</td> <td>(22)</td> <td><i>E</i>:<i>Z</i> = >98:<2</td> </tr> <tr> <td>Et</td> <td>(16)</td> <td><i>E</i>:<i>E</i>:<i>Z</i> = 1:1.7</td> </tr> <tr> <td><i>n</i>-C₅H₁₁</td> <td>(24)</td> <td><i>E</i>:<i>E</i>:<i>Z</i> = 1:1.1</td> </tr> </tbody> </table>	R	Yield (%)	<i>E</i> : <i>Z</i>	H	(22)	<i>E</i> : <i>Z</i> = >98:<2	Et	(16)	<i>E</i> : <i>E</i> : <i>Z</i> = 1:1.7	<i>n</i> -C ₅ H ₁₁	(24)	<i>E</i> : <i>E</i> : <i>Z</i> = 1:1.1	47						
R	Yield (%)	<i>E</i> : <i>Z</i>																			
H	(22)	<i>E</i> : <i>Z</i> = >98:<2																			
Et	(16)	<i>E</i> : <i>E</i> : <i>Z</i> = 1:1.7																			
<i>n</i> -C ₅ H ₁₁	(24)	<i>E</i> : <i>E</i> : <i>Z</i> = 1:1.1																			

TABLE 4. VINYLOGOUS RBR OF VINYL SULFONES (Continued)

	Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₇		1. BrCH ₂ SO ₂ Br, CH ₂ Cl ₂ , <i>hν</i> 2. Et ₃ N, CH ₂ Cl ₂ 3. <i>t</i> -BuOK, <i>t</i> -BuOH, THF, rt	(33) + (17)	47
E. Vinyl Sulfones Formed In Situ; Other Polyenes ^{a,b}				
C ₅		1. BrCH(Me)SO ₂ Br, CH ₂ Cl ₂ , <i>hν</i> 2. Et ₃ N, CH ₂ Cl ₂ 3. <i>t</i> -BuOK, <i>t</i> -BuOH, THF, rt	(8)	47
C ₆₋₁₄		1. BrCH ₂ SO ₂ Br, CH ₂ Cl ₂ , <i>hν</i> 2. Et ₃ N, CH ₂ Cl ₂ 3. <i>t</i> -BuOK, <i>t</i> -BuOH, THF, rt	 X (-) (8) SiMe ₂ (38) (CH ₂) ₂ (57) 80% Z,Z (CH ₂) ₄ (40) (CH ₂) ₈ (41)	47
C ₇		1. BrCH ₂ SO ₂ Br, CH ₂ Cl ₂ , <i>hν</i> 2. Et ₃ N, CH ₂ Cl ₂ 3. <i>t</i> -BuOK, <i>t</i> -BuOH, THF, rt	(23)	47
C ₈		1. BrCH ₂ SO ₂ Br, CH ₂ Cl ₂ , <i>hν</i> 2. Et ₃ N, CH ₂ Cl ₂ 3. <i>t</i> -BuOK, <i>t</i> -BuOH, THF, rt	(14)	47
C ₁₀		1. BrCH ₂ SO ₂ Br, CH ₂ Cl ₂ , <i>hν</i> 2. Et ₃ N, CH ₂ Cl ₂ 3. <i>t</i> -BuOK, <i>t</i> -BuOH, THF, rt	(23)	47
F. Vinyl Sulfones Formed In Situ; Cyclic Substrates ^{a,b}				
C ₆₋₈		1. BrCH ₂ SO ₂ Br, CH ₂ Cl ₂ , <i>hν</i> 2. Et ₃ N, CH ₂ Cl ₂ 3. <i>t</i> -BuOK, <i>t</i> -BuOH, THF, rt	 n 1 (41) 2 (31) 3 (49)	47
C ₇₋₈		1. BrCH ₂ SO ₂ Br, CH ₂ Cl ₂ , <i>hν</i> 2. Et ₃ N, CH ₂ Cl ₂ 3. <i>t</i> -BuOK, <i>t</i> -BuOH, THF, rt	 n 1 (51) 2 (43)	47
		1. BrCH ₂ SO ₂ Br, CH ₂ Cl ₂ , <i>hν</i> 2. Et ₃ N, CH ₂ Cl ₂ 3. <i>t</i> -BuOK, <i>t</i> -BuOH, THF, rt	 I + II n 1 (51) 1:3 2 (43) 1:1.4	47
C ₇₋₉		1. BrCH ₂ SO ₂ Br, CH ₂ Cl ₂ , <i>hν</i> 2. Et ₃ N, CH ₂ Cl ₂ 3. <i>t</i> -BuOK, <i>t</i> -BuOH, THF, rt	 n 1 (74) 2 (75) 3 (41)	47

TABLE 4. VINYLOGOUS RBR OF VINYL SULFONES (Continued)

	Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₈		1. BrCH ₂ SO ₂ Br, CH ₂ Cl ₂ , <i>hν</i> 2. <i>t</i> -BuOK, <i>t</i> -BuOH, THF, rt	 (35)	47
C ₉		1. BrCH ₂ SO ₂ Br, CH ₂ Cl ₂ , <i>hν</i> 2. Et ₃ N, CH ₂ Cl ₂ 3. <i>t</i> -BuOK, <i>t</i> -BuOH, THF, rt	 (53)	47
G. Vinyl Sulfones Formed In Situ; Alkynes ^{a,b}				
C ₆		1. BrCH ₂ SO ₂ Br, CH ₂ Cl ₂ , <i>hν</i> 2. <i>t</i> -BuOK, <i>t</i> -BuOH, THF, rt	 (39)	47
C ₇		1. BrCH ₂ SO ₂ Br, CH ₂ Cl ₂ , <i>hν</i> 2. <i>t</i> -BuOK, <i>t</i> -BuOH, THF, rt	 (29)	47

^a The yields were over the three steps of the reaction.^b The intermediates are shown in brackets.

TABLE 5. DECARBOXYLATIVE RBR

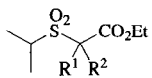
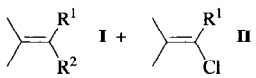
Reactant	Conditions	Product(s) and Yield(s) (%) ^a	Refs.																														
C ₁₁₋₁₉ 	KOH, CCl ₄ , <i>t</i> -BuOH		117																														
<table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th>R¹</th> <th>R²</th> <th>I</th> <th>II</th> <th>I:II</th> </tr> </thead> <tbody> <tr> <td>Ph</td> <td>H</td> <td>(—)</td> <td>(—)</td> <td>3:1</td> </tr> <tr> <td>Ph</td> <td>Me</td> <td>(61)</td> <td>(0)</td> <td></td> </tr> <tr> <td>Bn</td> <td>H</td> <td>(0)</td> <td>(61)</td> <td></td> </tr> <tr> <td><i>p</i>-MeC₆H₄</td> <td>H</td> <td>(—)</td> <td>(—)</td> <td>3:2</td> </tr> <tr> <td>Bn</td> <td>Bn</td> <td>(59)</td> <td>(0)</td> <td></td> </tr> </tbody> </table>	R ¹	R ²	I	II	I:II	Ph	H	(—)	(—)	3:1	Ph	Me	(61)	(0)		Bn	H	(0)	(61)		<i>p</i> -MeC ₆ H ₄	H	(—)	(—)	3:2	Bn	Bn	(59)	(0)				
R ¹	R ²	I	II	I:II																													
Ph	H	(—)	(—)	3:1																													
Ph	Me	(61)	(0)																														
Bn	H	(0)	(61)																														
<i>p</i> -MeC ₆ H ₄	H	(—)	(—)	3:2																													
Bn	Bn	(59)	(0)																														

TABLE 6. MICHAEL-INDUCED RBR

Reactant	Conditions	Product(s) and Yield(s) (%)	Refs.																																																
C ₅ 	PhSO ₂ Na, DMSO, rt, 1 h	SO ₂ Ph (44) <i>E:Z</i> = 2:1	124																																																
	(<i>E</i>)-CH ₂ =CHCH=CHSO ₂ Na	SO ₂ (—)	124																																																
C ₉ 		Ph Nu I + Ph Nu II	54																																																
		<table border="1"> <thead> <tr> <th>Nu</th> <th>Temp</th> <th>Time</th> <th>I</th> <th><i>E:Z</i></th> <th>II</th> </tr> </thead> <tbody> <tr> <td>MeO</td> <td>rt</td> <td>15 h</td> <td>(52)</td> <td>75:25</td> <td>(26)</td> </tr> <tr> <td>BnS</td> <td>rt</td> <td>15 h</td> <td>(77)</td> <td>93:7</td> <td>(—)</td> </tr> <tr> <td>BnNH</td> <td>rt</td> <td>7 h</td> <td>(60)</td> <td>25:75</td> <td>(20)</td> </tr> <tr> <td><i>t</i>-BuNH</td> <td>rt</td> <td>4 h</td> <td>(55)</td> <td>20:80</td> <td>(—)</td> </tr> <tr> <td>(<i>S</i>)-PhCH(Me)NH</td> <td>rt</td> <td>12 h</td> <td>(53)</td> <td>21:79</td> <td>(38)</td> </tr> <tr> <td>1. NH₄OH, DMSO 2. Boc₂O</td> <td>rt</td> <td>15 h</td> <td>(73)</td> <td>14:86</td> <td>(—)</td> </tr> <tr> <td>MeC(CO₂Me)₂, NaH, THF</td> <td>rt</td> <td>12 h</td> <td>(71)</td> <td>80:20</td> <td>(—)</td> </tr> </tbody> </table>	Nu	Temp	Time	I	<i>E:Z</i>	II	MeO	rt	15 h	(52)	75:25	(26)	BnS	rt	15 h	(77)	93:7	(—)	BnNH	rt	7 h	(60)	25:75	(20)	<i>t</i> -BuNH	rt	4 h	(55)	20:80	(—)	(<i>S</i>)-PhCH(Me)NH	rt	12 h	(53)	21:79	(38)	1. NH ₄ OH, DMSO 2. Boc ₂ O	rt	15 h	(73)	14:86	(—)	MeC(CO ₂ Me) ₂ , NaH, THF	rt	12 h	(71)	80:20	(—)	
Nu	Temp	Time	I	<i>E:Z</i>	II																																														
MeO	rt	15 h	(52)	75:25	(26)																																														
BnS	rt	15 h	(77)	93:7	(—)																																														
BnNH	rt	7 h	(60)	25:75	(20)																																														
<i>t</i> -BuNH	rt	4 h	(55)	20:80	(—)																																														
(<i>S</i>)-PhCH(Me)NH	rt	12 h	(53)	21:79	(38)																																														
1. NH ₄ OH, DMSO 2. Boc ₂ O	rt	15 h	(73)	14:86	(—)																																														
MeC(CO ₂ Me) ₂ , NaH, THF	rt	12 h	(71)	80:20	(—)																																														
	PhSO ₂ Na, DMSO, rt	SO ₂ Ph (73) <i>2E,4E:2E,4Z</i> = 23:77	125																																																
C ₁₀ 	PhSO ₂ Na, DMSO, rt	SO ₂ Ph (80) <i>2E,4E:2E,4Z:2Z,4E:2Z,4Z</i> = 29:54:7:10	125																																																
or	PhSO ₂ Na, DMSO, rt, 30 min	SO ₂ Ph (65-80) <i>2E,4E:2E,4Z:2Z,4E:2Z,4Z</i> = 26:23:20:31	125																																																
or	SO ₂ K DMSO, rt, 68 h	SO ₂ (68) <i>2E,4E & 2E,4Z & 2Z,4E:2Z,4Z</i> = 71:29	125																																																

8. Acknowledgments

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The α -Hydroxy Ketone (α -Ketol) and Related Rearrangements

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Abstract

Treatment of suitable α -hydroxy aldehydes and ketones with a base, a Bronsted or Lewis acid, or simply with heat has long been known to induce the 1,2-shift of an alkyl or aryl substituent to form an isomeric product. The synthetic utility of the process was considerably expanded when applied to steroidal D-ring homoannulations, and has more recently encompassed novel ring expansion to numerous complex target ring systems. The classical α -ketol rearrangement shares, in common with other base-promoted ketogenic isomerizations, the property of advancing from an alkoxide to a carbonyl group as the migrating center relocates its bonding electrons to the adjacent trigonal center. A distinctive feature of the title reaction, however, is its reversibility, such that the more stable α -hydroxy carbonyl isomer is favored. The process has sometimes been termed the acyloin rearrangement.

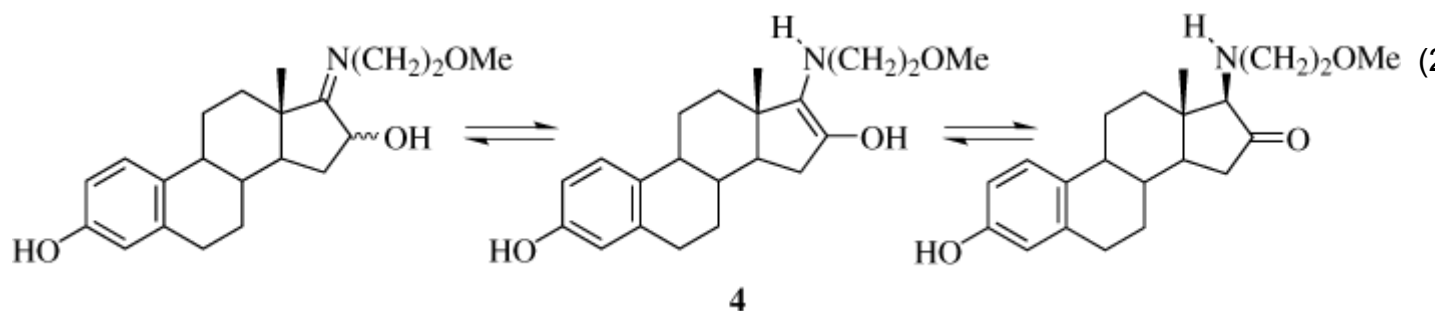
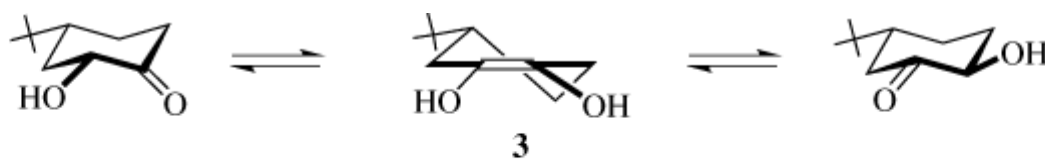
This chapter focuses on the isomerization of α -hydroxy ketones, aldehydes, and imines under various reaction conditions exclusive of photochemical activation. The literature coverage extends to 2000.

Since many of the steroidal transformations were carried out in early days when products were not always adequately characterized; errors in structural assignment were occasionally made. Experimental detail was sometimes lacking. To alleviate this problem, we have included only experiments that lead to reasonably pure products of established structure.

1. Introduction

Treatment of suitable α -hydroxy aldehydes and ketones with a base, a Brønsted or Lewis acid, or simply with heat has long been known to induce the 1,2-shift of an alkyl or aryl substituent to form an isomeric product. The synthetic utility of the process was considerably expanded when applied to steroidal D-ring homoannulations, (1, 2) and has more recently encompassed novel ring expansion approaches to numerous complex target ring systems. The classical α -ketol rearrangement shares, (3, 4) in common with other base-promoted ketogenic isomerizations, the property of advancing from an alkoxide to a carbonyl group as the migrating center relocates its bonding electrons to the adjacent trigonal center. A distinctive feature of the title reaction, however, is its reversibility, such that the more stable α -hydroxy carbonyl isomer is favored. (5, 6) The process has sometimes been termed the acyloin rearrangement. (7-9)

This chapter focuses on the isomerization of α -hydroxy ketones, aldehydes, and imines, as represented by 1 and 2, under various reaction conditions exclusive of photochemical activation (Eq. 1). (10, 11) The literature coverage extends to mid-2002. The scope does not encompass mechanistically related transformations (e.g., benzilic acid rearrangements), (12) enzyme-catalyzed rearrangements are not specifically addressed, (13-16) and no attempt has been made to deal with the mass spectrometry of α -ketols. (17-19) Also excluded are those transformations of secondary α -keto carbinols that isomerize via enediol 3 and enol amine intermediates 4 through simple tautomerization (Eq. 2). (20, 21) Such processes bear different names such as the Lobry de Bruyn-Albert van Ekenstein transformation, (13, 22) the Heyns and Amadori rearrangements, (23) and the Voight (24) and Bilik reactions, (25) to reflect their relative importance to the field of glycoscience.

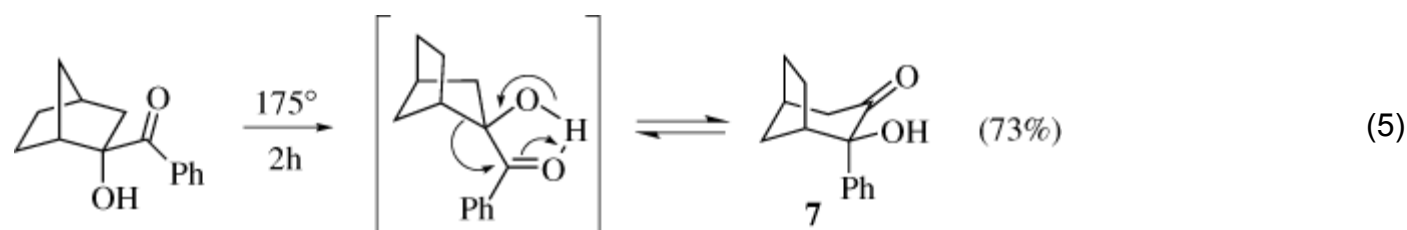
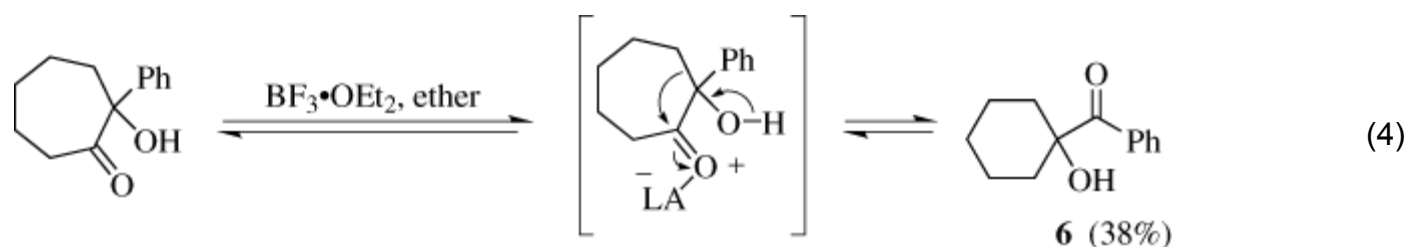


Since many of the steroidal transformations were carried out in early days when products were not always adequately characterized, errors in structural assignment were occasionally made. In addition, experimental detail is sometimes lacking. For example, yields are infrequently cited. To alleviate this problem somewhat, we have included in Tables 1-D and 2 only experiments that lead

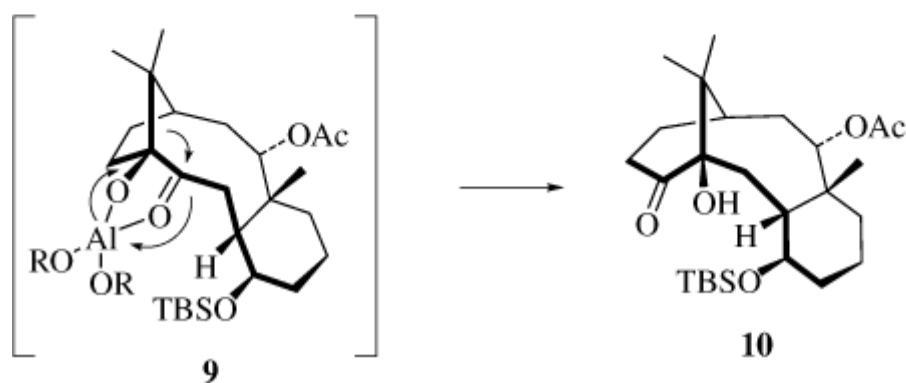
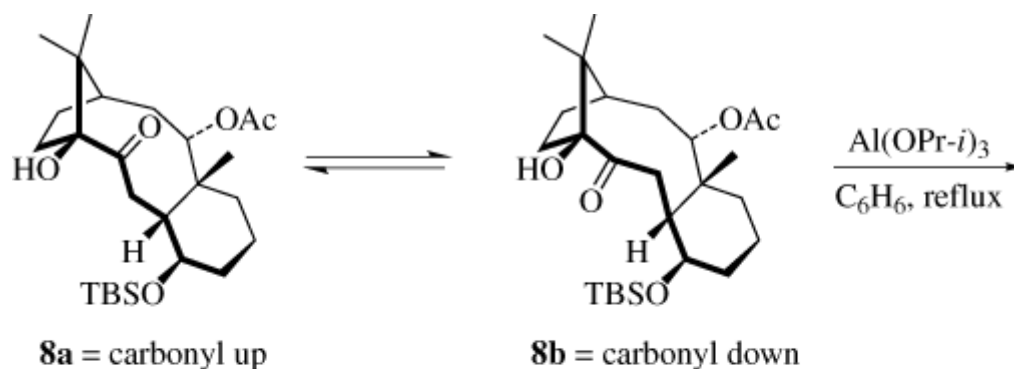
to reasonably pure products of established structure, and trust that these clarifying restrictions will not limit a reader's appreciation for the scope of the α -ketol rearrangement.

2. Mechanistic Considerations

The mechanistic features of the α -ketol rearrangement have been clearly established in a number of contexts. Since tertiary α -keto carbinols are involved, enolization is unavailable and a substituent must migrate to effect isomerization. When these reactions are performed under basic conditions (NaOH, NaOMe, Al(BuO-*t*)₃, KH, etc), deprotonation of the hydroxy group initiates reaction (8, 26-28) (Eq. 3). The alternate use of protic or Lewis acidic conditions (CF₃CO₂H, BF₃·OEt₂, ZnCl₂, NiO₂, SiO₂, etc) results in coordination to the carbonyl oxygen as the preliminary step to bond migration (28-32) (Eq. 4). Advancement to product under purely thermal conditions occurs via intramolecular proton transfer (33-36) (Eq. 5). In view of the intrinsic reversibility of the α -ketol rearrangement, the conversions into α -keto carbinols 5-7 imply them to be more thermodynamically stable than their precursors. When strained ring systems are involved as starting materials, the initial bond migration will relieve strain and be accelerated relative to its back-reaction. (37) The ring expansion that gives rise to 7 constitutes a suitable example (Eq. 5). (34)

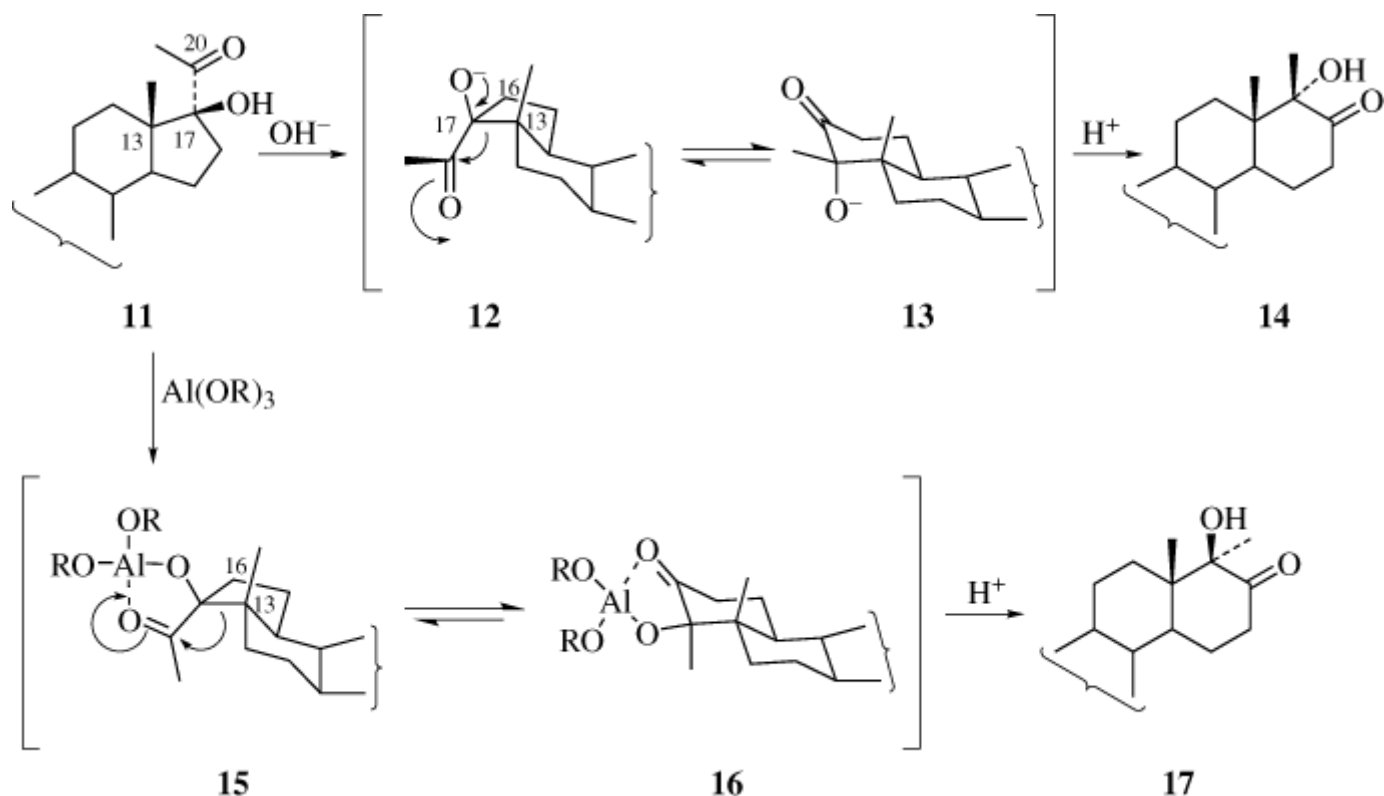


Various metal salts also promote the α -ketol rearrangement. Of these, PbO (as Pb(NO₃)₂ and KOH), (30, 38) FeCl₃/ SiO₂, (35) Ba(OMe)₂, (39) and MnO₂ (40) have seen use and join alumina, silica gel, and boron trifluoride etherate as suitable catalysts. In some cases, specific coordination by a metal salt can help orient a migrating group and thereby favor its rearrangement stereoelectronically. For example, in the conversion of the [6.2.1] bicyclic 8 into its [5.3.1] isomer 10 (Eq. 6), coordination with the aluminum salt insures co-planarity between the free hydroxy group and the carbonyl (see transition state 9). This latter conformation aligns the C=O favorably to receive the migrating bond and speeds the rearrangement. (5, 6, 41, 42) This acceleration is independent of the question of which α -ketol isomer is the more stable. If kinetics and thermodynamics favor the same rearrangement product, the conversion is notably facilitated.



(6)

The α -ketol rearrangement of stereoisomeric 17-hydroxy-20-keto steroids to effect D-homoannulations was intensively pursued over several decades and has been discussed extensively. An unusually high interest at the mechanistic level appears to have focused on two aspects, namely: (a) the dependence of product structure on reagents used for D-homoannulation, and (b) the prospect that selective bond migrations triggered by different reagents arose from conformational control. (2, 43) For 17 β -hydroxy-20-keto derivatives of type **11**, exposure to hydroxide ion affords stereospecifically the D-homo ketol **14** (Eq. 7). This ring expansion involves



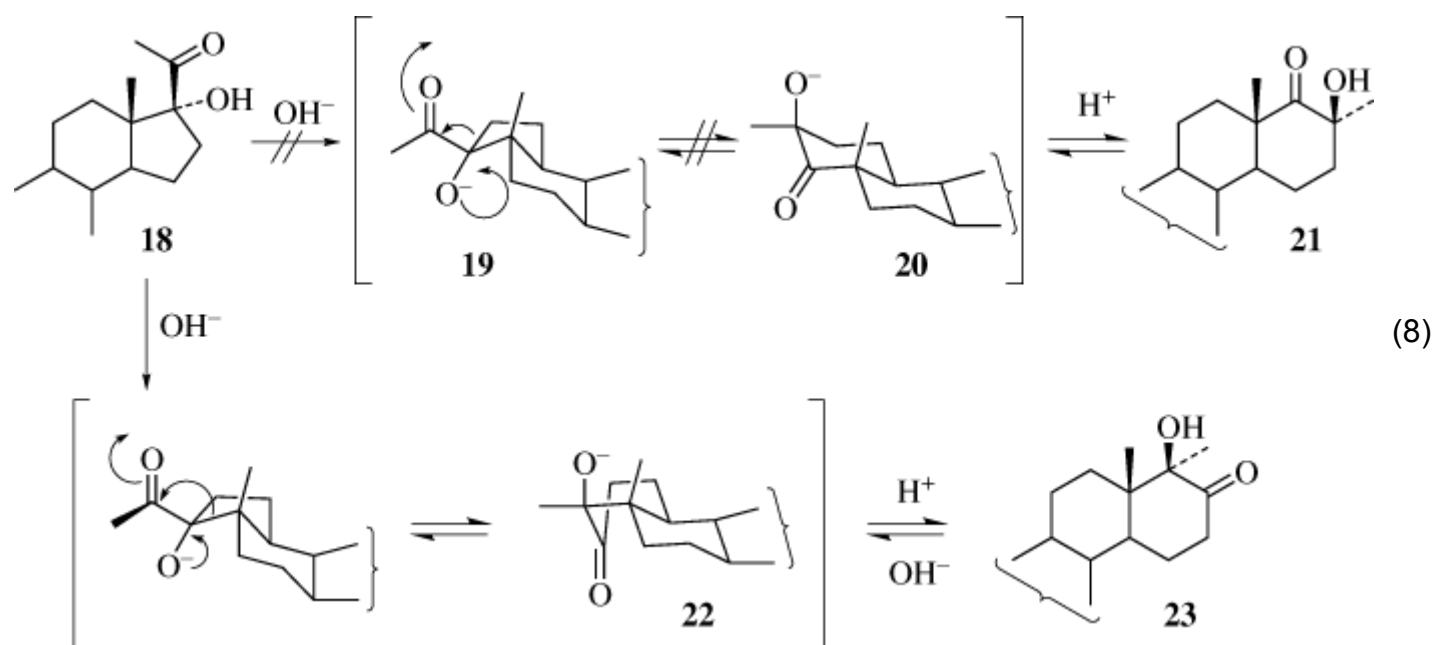
(7)

1,2-shift of C-13 (the more highly substituted ring carbon) from conformer **12**, where the two oxygens are anti-oriented to minimize dipole repulsion. Note that the hydroxy group in compounds

13 and **14** ends up axial rather than equatorial. Migration of C-16 in conformer **12** would require ring D to expand via a boat-like transition state. Thus, there seems to be an electronic and steric preference for C-13 migration.

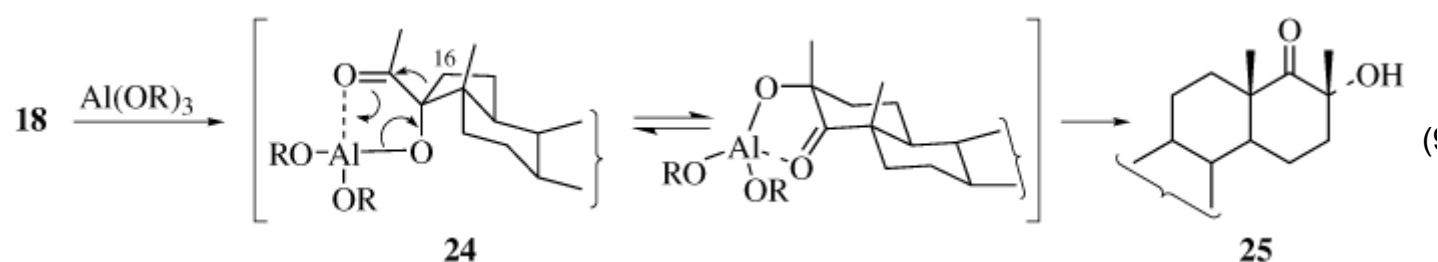
In comparison, Lewis acid catalyzed D-homoannulation of **11** likewise induces migration of C-13, but here coordination to the carbonyl oxygen as in transition structure **15** is thought to make the difference. This reagent-imposed syn orientation of the two relevant oxygenated substituents now stereoelectronically favors passage via chair arrangement **16** to product ketone **17**.

Steroids in the 17α -hydroxy-20-keto series (e.g., **18**) are also amenable to D-homoannulation but with greater difficulty and less stereoselectivity. As before, four possible isomeric ketols can arise, yet a quite strong preference for formation of one product is seen. The alkali-catalyzed rearrangement of steroid **18** proved initially enigmatic, since product **21** was expected on the basis of an anti conformation (viz. **19**) and chair-intermediate **20** was not observed (Eq. 8); the product was steroid **23** instead. An early suggestion that **21** is in fact kinetically favored but rapidly reverses through starting ketol **18** to the thermodynamically favored ring expansion product **23** was ultimately disproved. (44) The strain relief on conversion to a transfused decalin is seemingly adequate to allow the α -ketol rearrangement of C-17 via a boat-like transition state resembling **22**. (45)

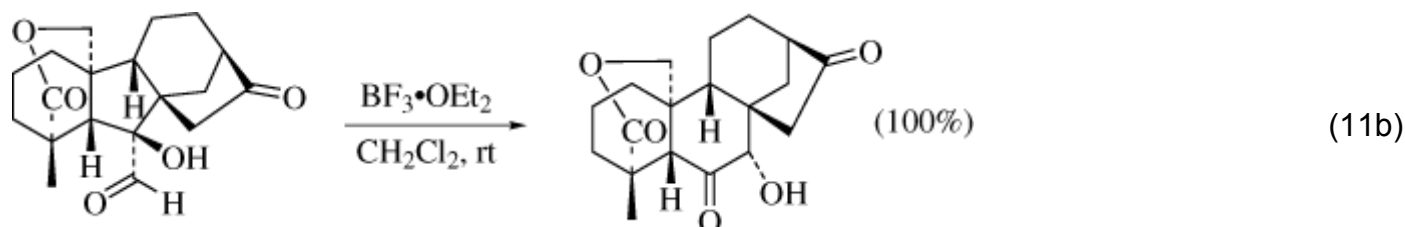
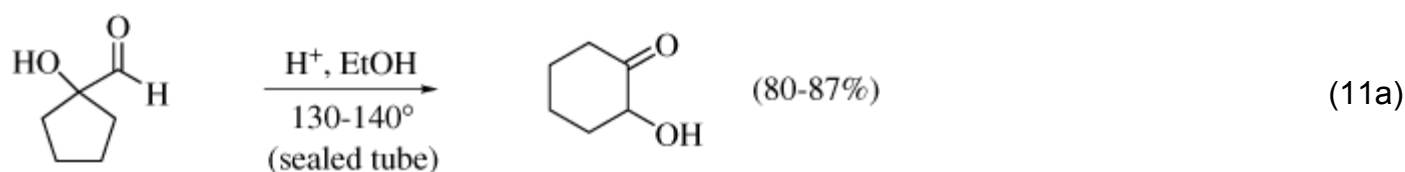
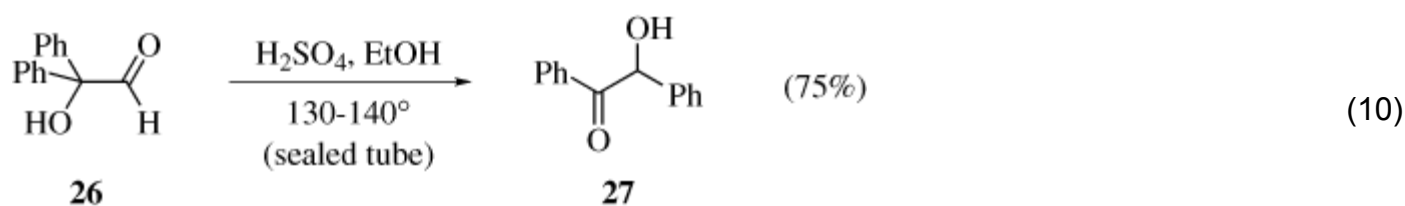


Lewis acid catalyzed isomerizations of steroid **18** involve the shift of C-16 and afford product **25** (Eq. 9). Presumably, this outcome is mediated by a cyclic coordination species **24** (akin to transition state **15**), which stereoelectronically favors the migration of C-16 along a chair-like path to ultimate product **25**.

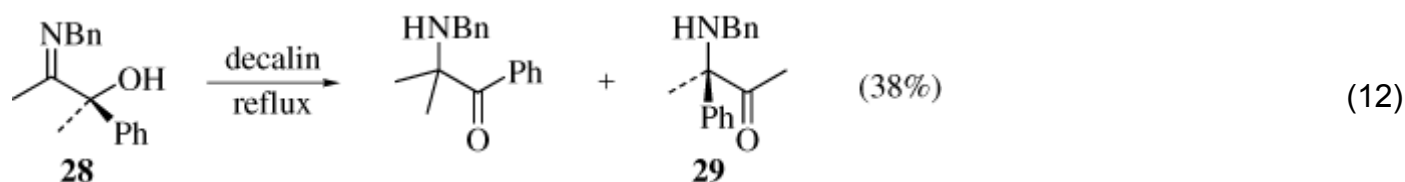
Mechanistic details of α -ketol rearrangements can largely be carried over to α -hydroxy aldehyde counterparts. The major element of contrast is the intrinsic gain in thermodynamic stability that often materializes. The total conversion of α -keto

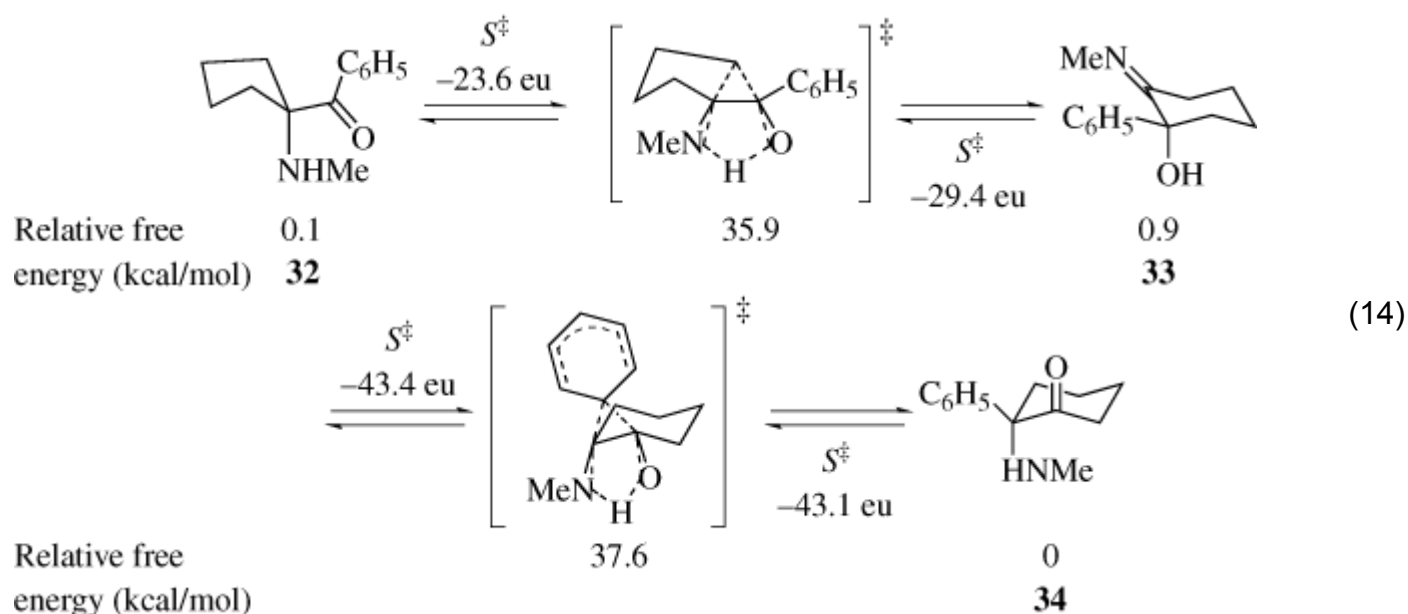
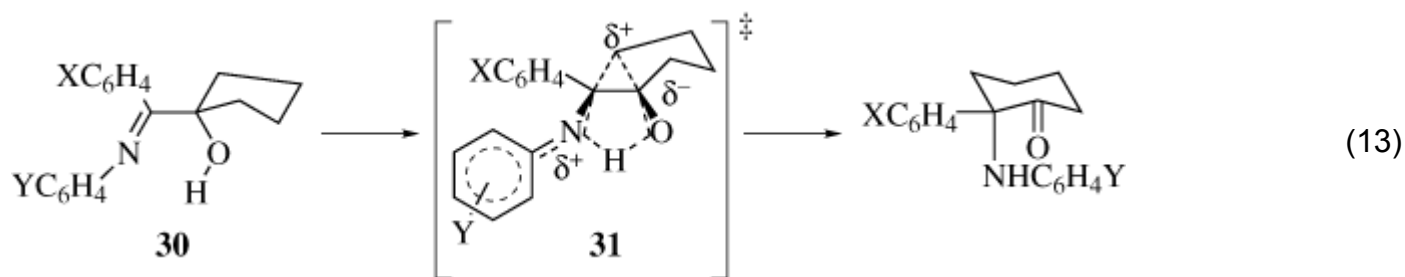


carbinol **26** to isomer **27** when heated in the presence of a catalytic amount of acid is exemplary (Eq. 10). (46) In more complex examples, this gain in stability can be overshadowed by other thermodynamic factors such as the relief of ring strain (Eq. 11a) or steric compression (Eq. 11b). (47, 48) The stereochemical course of α -hydroxy aldehyde rearrangements derives its basis directly from the principles governing α -ketol reactivity and will not be discussed independently.

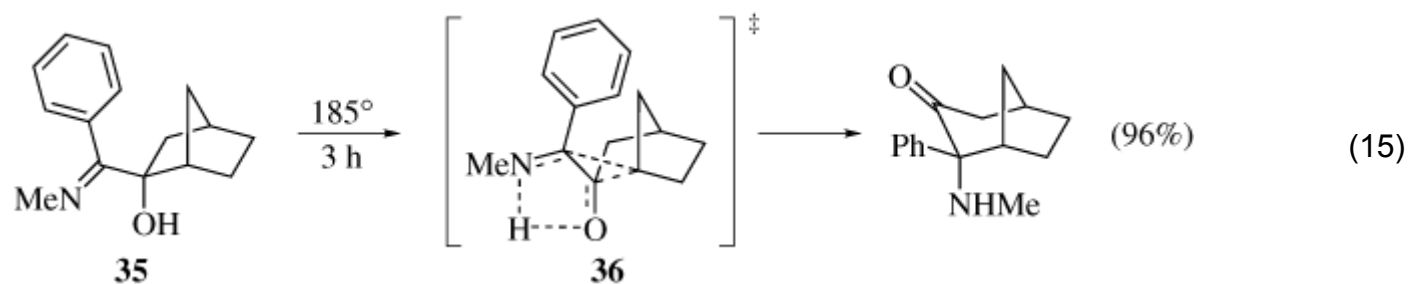


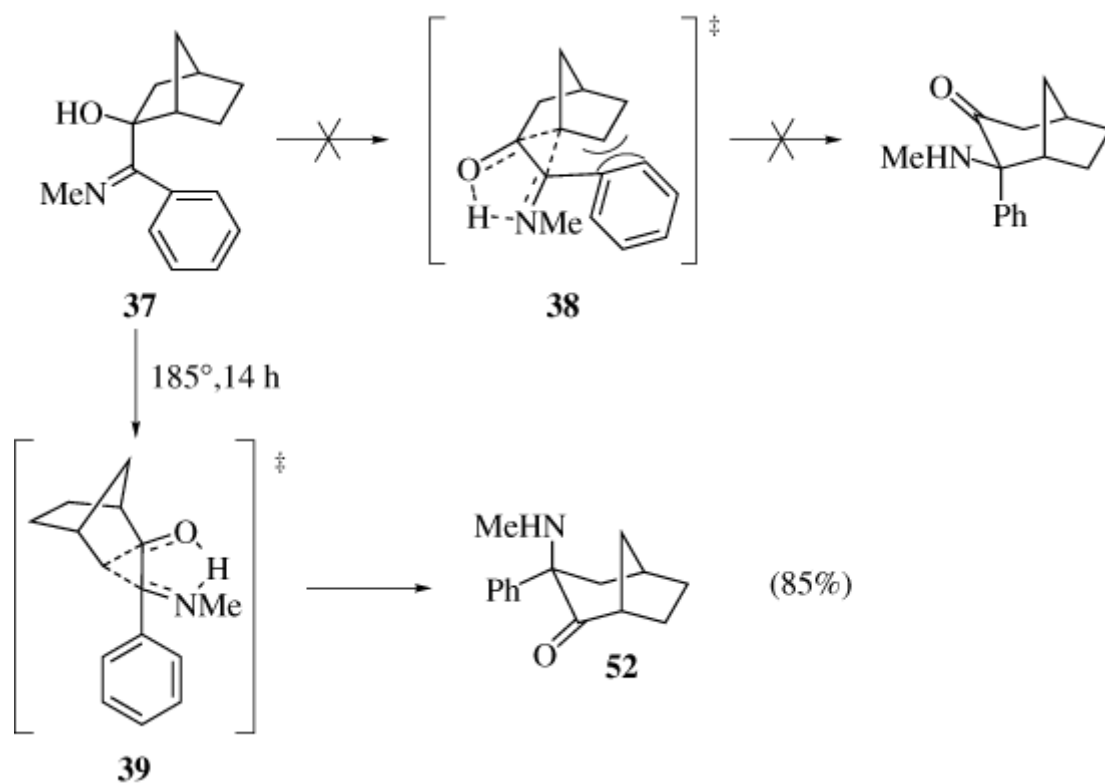
A more distinct variation of the α -ketol rearrangement is that involving α -hydroxy imines. Imines vicinal to tertiary carbinols are amenable to skeletal rearrangement and provide α -amino ketones (Eq. 12). (49) Distinct from α -hydroxy ketone rearrangements, the preferred steric course of these reactions is well defined regardless of the involvement of catalysts as reflected in the complete transfer of chirality from imine **28** to amine **29**. The response of imine **30** for rearranging under thermal conditions has been examined by Hammett σ_{p} analysis (Eq. 13). (50) Rate enhancement is seen when electron-withdrawing groups are present at either position X or Y, consistent with transition state structure **31** ($\rho = -0.32$). Further evidence for a concerted intramolecular transition structure is gained from kinetic analysis of the thermal equilibration of α -amino ketones **32** and **34** via the α -hydroxy imine **33** (Eq. 14). (51) The most notable feature of the associated thermodynamics is the uncharacteristically large and negative entropy of activation associated with the formation of each transition structure, which allows for concerted movement of the proton and carbon involved in each conversion. Of equal importance is the lack of a dominant thermodynamic sink among the equilibrating components. This feature is not uncommon for α -hydroxy imine equilibria and allows subtle changes in structure to dictate the reaction course. Factors such as imine basicity, the electron-donating character of substituents, catalysts, solvent, and ring strain are often overshadowed by the requirement that the *s-cis* transition structure be realized in the transition state.





Comparison of the thermal rearrangement of the diastereomeric imines **35** (Eq. 15) and **37** (Eq. 16) illustrates the interplay of structure and well-defined transition state features in dictating the reaction course. (52) The rearrangement of norbornanol **35** proceeds as one might predict. The *s*-cis conformation is adopted in transition state **36** and the most substituted carbon migrates to stabilize the developing positive charge at the imine carbon. However, the steric course of the rearrangement of hydroxy imine **37** is altered by steric compression in transition structure **38** that would allow migration of the most substituted carbon. The alternative *s*-cis transition structure **39** is consequently operative, allowing migration of the methylene carbon. The energetic penalty for necessary recourse to alternate transition state **39** is reflected in the relatively slow conversion of **37** (14 h vs. 3 h for **35**).





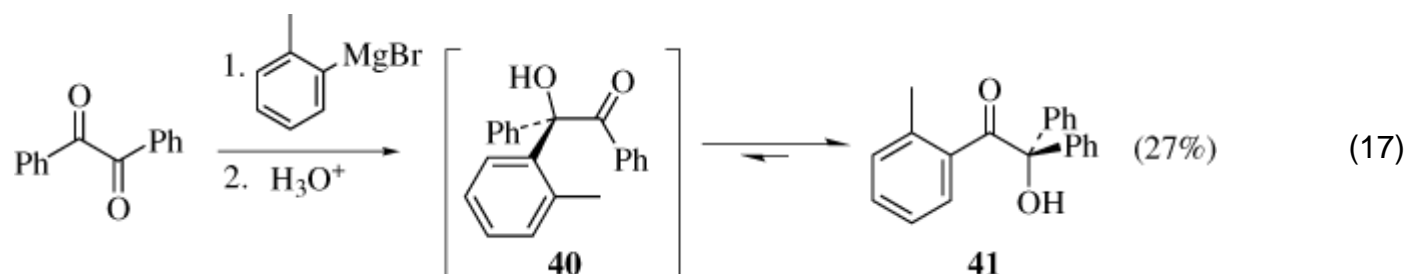
(16)

While catalysis by Lewis acids, Brønsted acids, or base is possible, in many cases the most effective means to drive the direction of the α -amino ketone rearrangement is the use of protic acids, which lead to the formation of amine-HX salts. The latter are not partners to the equilibrium.

3. Scope and Limitations

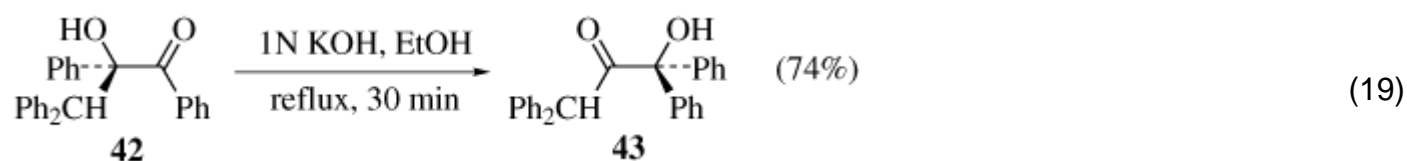
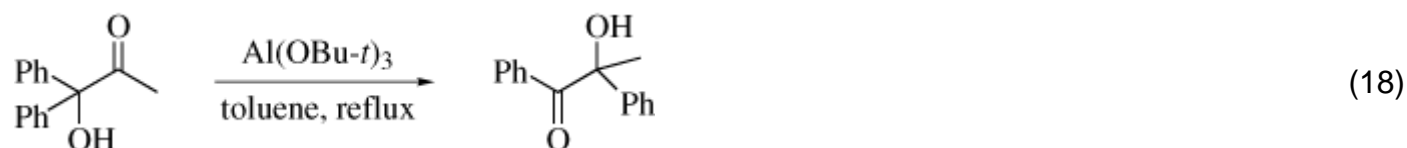
3.1. Acyclic α -Hydroxy Ketones

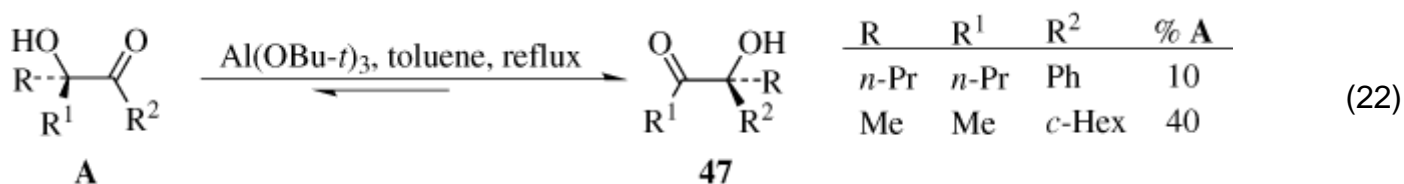
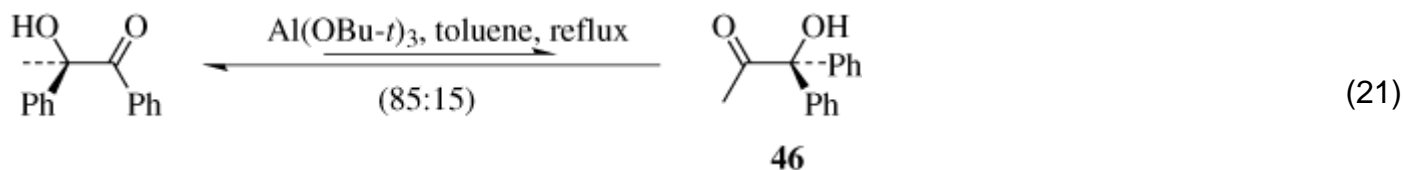
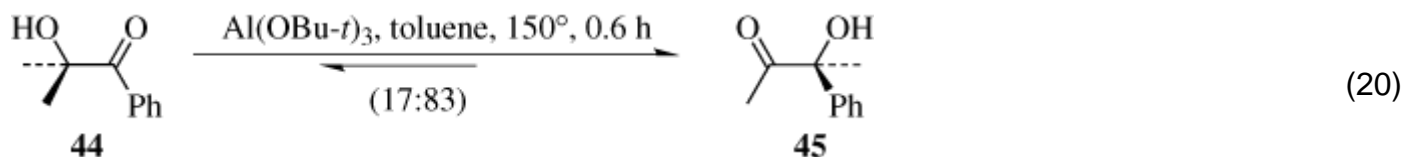
The possibility always exists that an α -ketol, when produced under basic conditions such as those involved in the benzoin condensation or upon addition of one mole equivalent of an organometallic reagent to an α -diketone, may already have experienced rearrangement to a lesser or greater extent. A classic example is shown in Eq. 17. (53) For more than 30 years, the product from coupling *o*-tolylmagnesium bromide



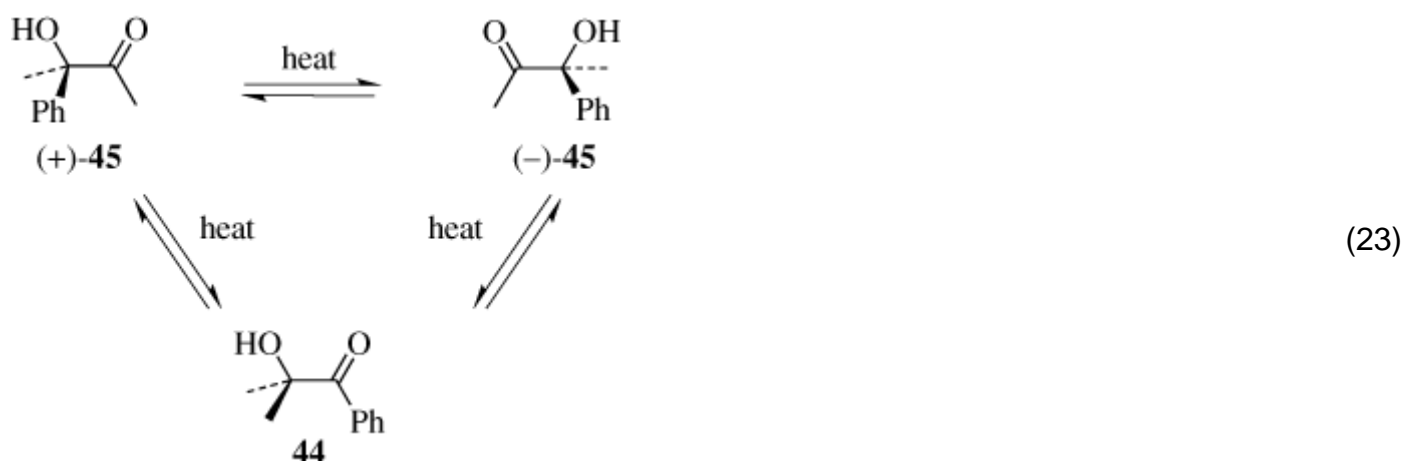
to benzil was believed to be hydroxy ketone **40** rather than **41**. (54) With the advent of an independent, unequivocal synthesis of **40**, it was made clear that thermodynamics favored **41**. (55) Several additional examples of related phenomena have been identified, (56-58) so caution must be exercised in these situations.

Although relative stability can sometimes be judged intuitively on the basis of conventional electronic effects (Eq. 18), (59) many cases have been reported where additional factors dictate the outcome. For example, in the base-catalyzed rearrangement of α -ketol **42** to isomer **43**, direct conjugation of the carbonyl with the neighboring phenyl is lost (Eq. 19). The greater thermodynamic stability of product **43** is attributed to decreased nonbonded interactions in this isomer. (60) These early observations were so prevalent that they led to formulation of a so-called Favorsky rule. According to this empirical dictum, an equilibrium associated with an α -ketol isomer pair favors placement of a carbonyl group adjacent to methyl (Eq. 20) or distal to phenyl when such structural conditions apply. (3, 59, 61-65) Although exceptions are numerous (Eq. 21), this rule did reconcile a significant number of isolated facts during that era. The results of more recent equilibration studies such as those defined by Eq. 22 (66) reveal that a COMe group does not in fact confer any notable stability to α -ketols. Steric factors can substantially influence the relative stability of one member of an isomer pair, as can perhaps also intramolecular hydrogen bonding and its associated geometric demands. Researchers have also considered possible homoconjugative interactions between the phenyl and carbonyl in isomers **43**, **45**, **46** and **47**. Although each of these factors alone might not outweigh the resonance stabilization provided by a COPh unit, under the proper circumstances their total contribution could control the equilibrium.

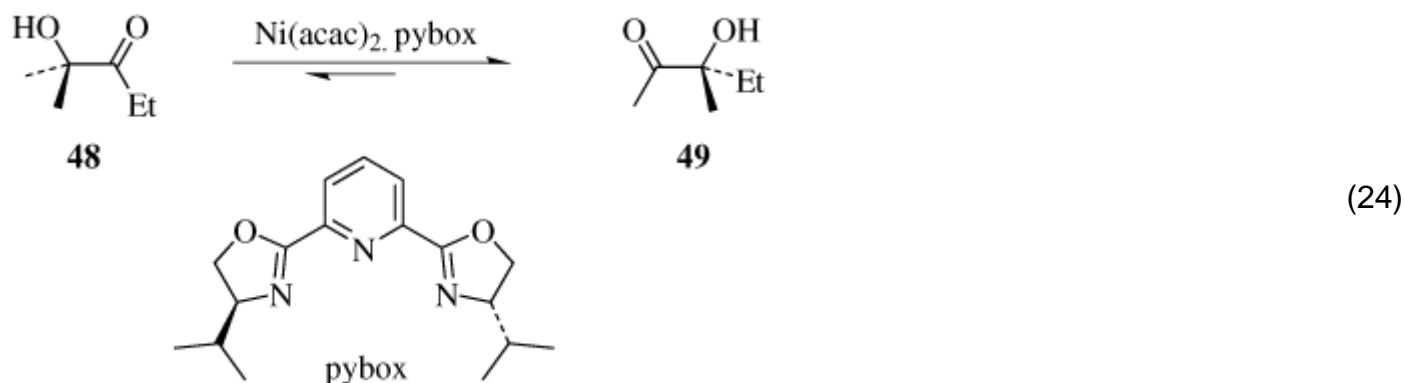




Ketols **44** and **45** also interconvert in molten biphenyl at temperatures above 200°. Although the equilibration confirms methyl shifting, any phenyl migration escapes notice because that rearrangement is degenerate. Phenyl shifting was proven by kinetic studies on optically active samples of α -ketol **45**. (33) Since the experimentally determined initial rate of loss of optical activity of (+)-**45** is 4–5 times faster than that of its isomerization to **44**, this more rapid change must be associated with translocation of the phenyl group. Proper control experiments confirmed that (+)-**45**, (–)-**45**, and **44** do indeed revert to the same equilibrium mixture of the three components (Eq. 23).



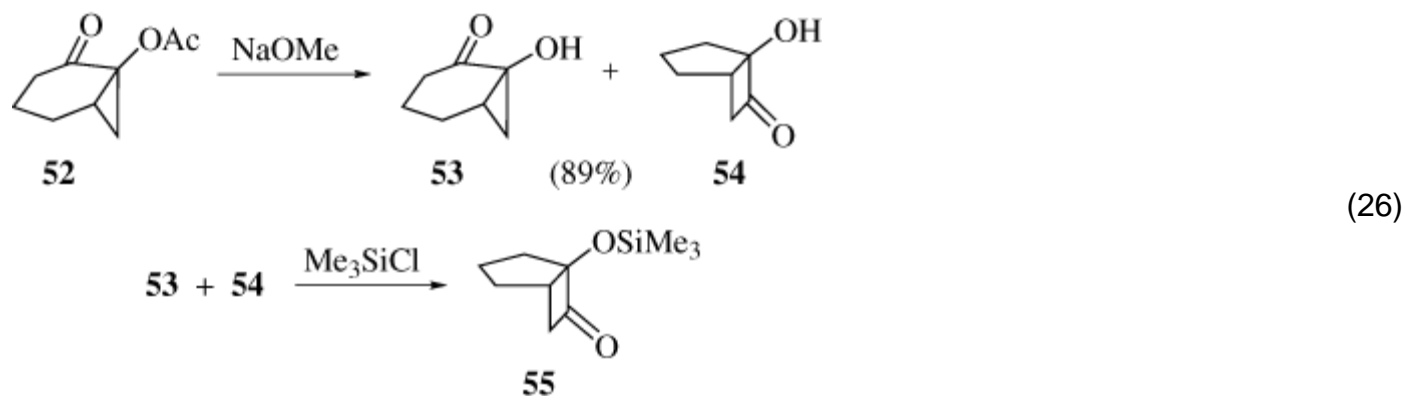
The rearrangements of α -ketols **44** and **48** generate chiral centers, and the possibility exists for asymmetric induction in their conversion to isomers **45** and **49**, respectively (Eq. 24). (29) The rates of migration of the pro-*S* and pro-*R* methyl groups must have different values. An enantio-enriched catalyst (or other chiral influence) must necessarily be present for this rate differential to manifest itself. The system Ni(acac)₂/2,6-bis[(*S*)-4-isopropyl(oxazolin-2-yl)]pyridine (colloquially known as pybox)/**48** at a mole ratio of 0.5:1:100 and a temperature of 130° catalyzes the conversion to α -keto carbinol **49** (70% at equilibrium) with a maximum enantiomeric excess of 37%.



3.2. Cyclic α -Ketols

Strain release can be used to advantage as a driving force in α -ketol rearrangements. The smooth, unidirectional conversion of cyclopropanol **50** into **51** (Eq. 25) under alkaline (0.1 M NaOH, 100°), acidic (HCl, CCl₄), or thermal conditions (230°, sealed tube, 5 min) is representative. (67)

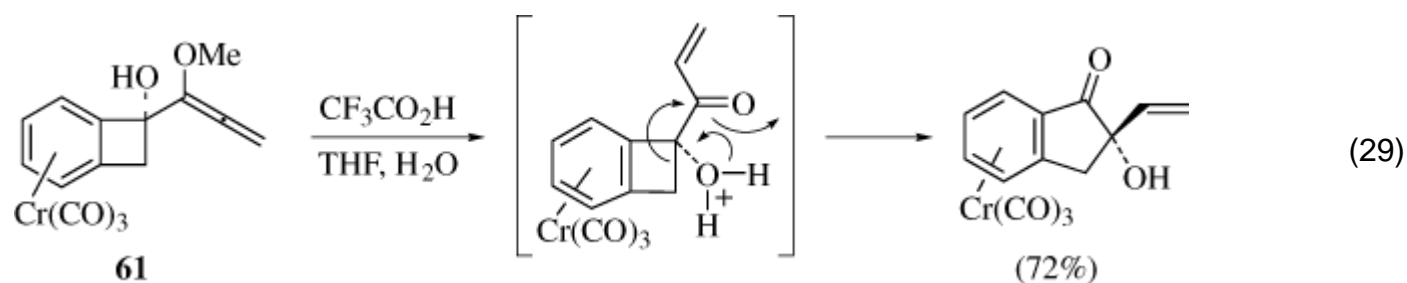
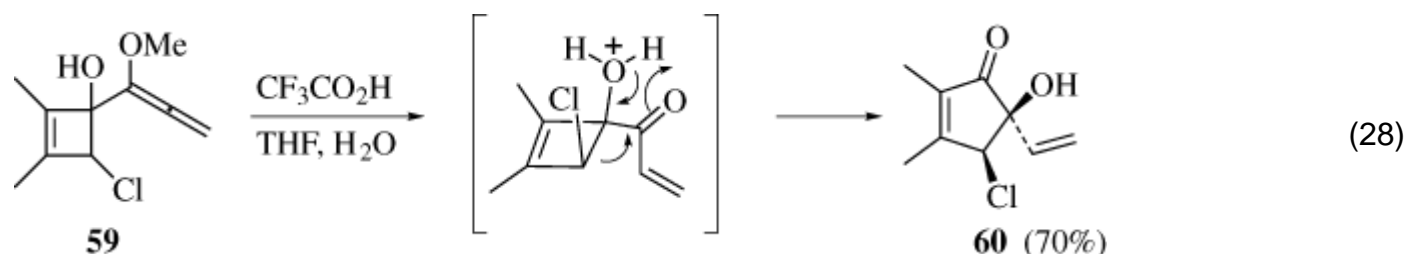
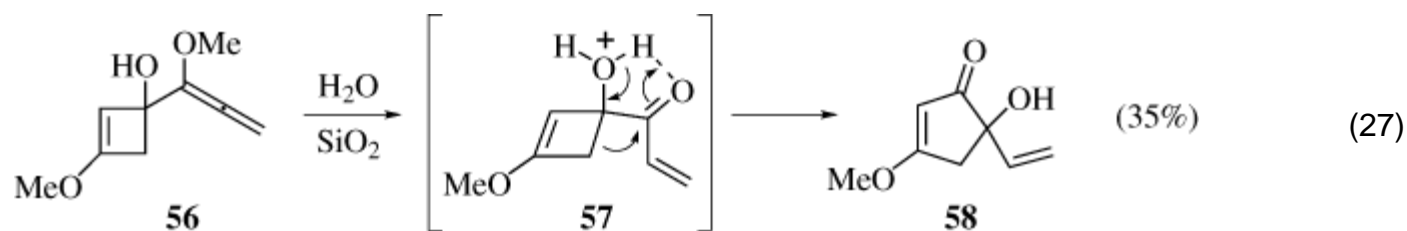
Treatment of acetoxy ketone **52** with sodium methoxide gives a mixture of ketols **53** and **54**. This partial rearrangement is completed upon silylation of the mixture with trimethylchlorosilane, as reflected in the isolation of four-membered ketone **55** in 80% overall yield (Eq. 26). (68)



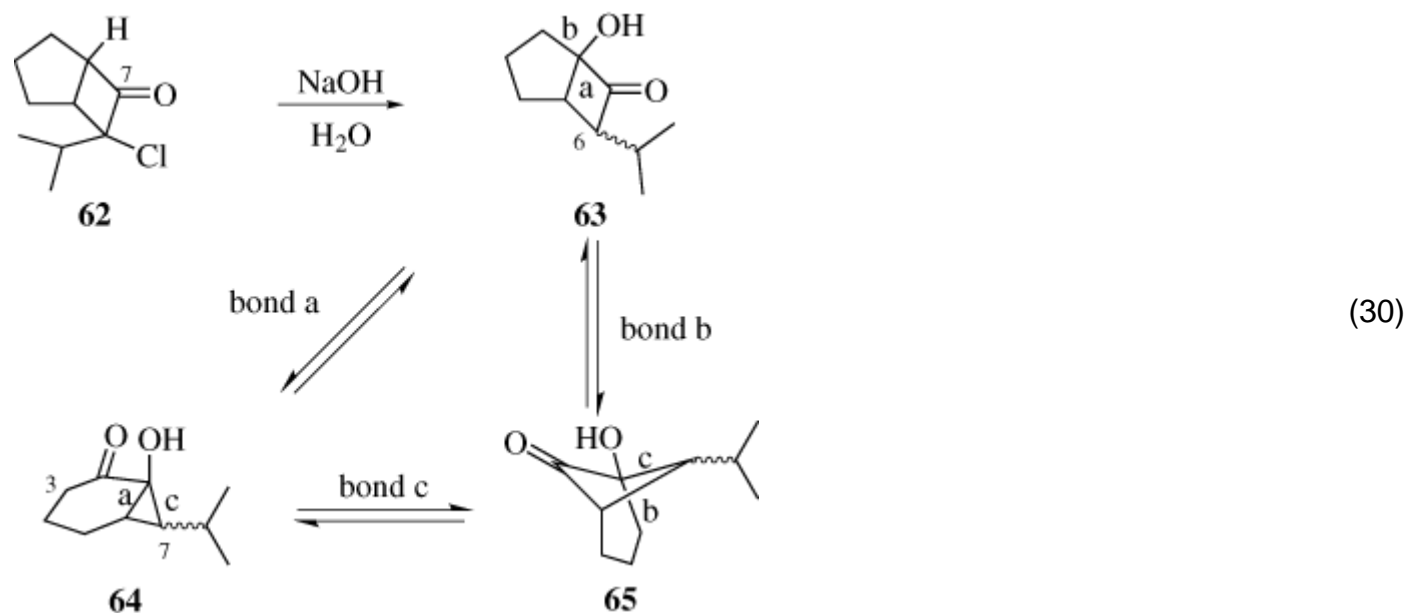
The conversion of cyclobutenol **56** to cyclopentenone **58** involves hydrolytic in situ generation of an α -ketol intermediate akin to **57** (Eq. 27). Mild conditions (aqueous tetrahydrofuran in the presence of silica gel, 1 h, 30°) were required to prevent unwanted hydrolysis of the endocyclic enol ether moiety. (31) In more highly functionalized analogs of compound **56** (Eqs. 28 and 29), high diastereoselectivity is observed for the ring expansion step, and intramolecular hydrogen bonding as in transition state **57** is cited as a controlling factor. (28, 31) In the conversion of cyclobutenol **59** into cyclopentenone **60** (Eq. 28), this factor leads to a cis relationship between the Cl and OH in product **60**; and when (benzocyclobutenone)chromium tricarbonyl complexes such as **61** are involved, the OH ends up cis to the metal center (Eq. 29).

When the hydrolysis of chlorocyclobutanol **62** is performed with NaOD in D₂O, α -ketol **63** containing three deuterium atoms (after proton exchange of the labile OD substituent) results. This

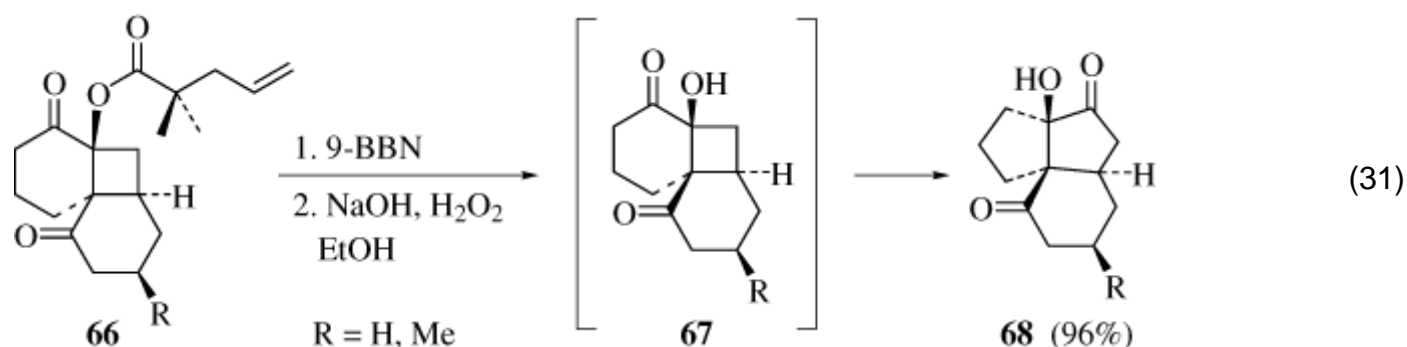
level of isotopic incorporation can be attributed to facile



base-catalyzed isotopic exchange at C-6 in **63** and of both H-3's in **64** (Eq. 30). (69) The equilibration between isomers **63** and **64** is also readily established under chromatographic conditions. It is noteworthy that bond (a) which migrates in α -ketol **63** during conversion to product **64** is not stereoelectronically aligned with the carbonyl π cloud. Bond (b) is far better placed for the α -ketol rearrangement. However, the more highly strained nature of α -keto carbinol **65** obviously precludes its spectroscopic detection. Proof that intermediate **65** is nevertheless very much involved in the cyclic equilibrium was gained by labeling C-7 in compound **64** with ^{14}C . Following sequential exposure to lithium benzyloxide in benzyl alcohol, hydrogenolysis, and controlled degradation, the carbon-14 labels are shared between C-7 and the remainder of the molecule as required of rapid interconversion between all three α -ketol tautomers.



Hydroboration of substrate **66** with 9-borabicyclononane and subsequent oxidation under alkaline conditions liberates α -ketol **67**, which spontaneously isomerizes to the tricyclic diquinane system **68** (Eq. 31). (70)



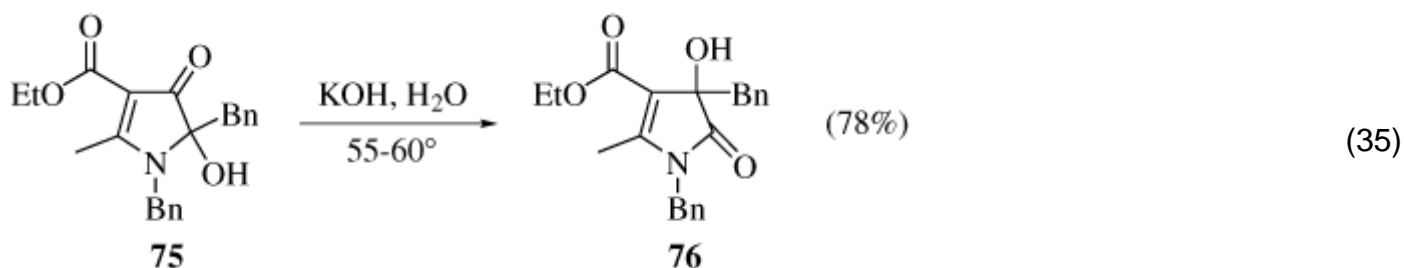
The α -ketol ring expansion of 1-acetyl- and 1-benzoylcyclopentanone (**69**) can be achieved under a variety of conditions (Eq. 32). Catalysts include $\text{Pb}(\text{NO}_3)_2/\text{KOH}$, (**38**) solid NaOH or KOH , (**27**) aluminum tri-*tert*-butoxide, (**59**) and boron trifluoride etherate. (**30**) The chiral catalyst $\text{NiCl}_2/\text{pybox}$ converts cyclopentanone **69** ($\text{R} = \text{Ph}$) to (*R*)-**70** ($\text{R} = \text{Ph}$) with an enantiomeric excess of 34% after 120 hours at 65° . (**37**) The smaller ring analog of compound **69**, 1-benzoylcyclobutanol, behaves analogously but rearranges at a lower temperature (25°). Heating the higher analog, 1-benzoylcyclohexanol, with $\text{NiCl}_2/\text{pybox}$ at 130° for 96 hours led to no observable chemical change. This finding conforms to an earlier discovery that the seven-membered α -ketol **71** unidirectionally contracts to cyclohexanol **72** under basic conditions (Eq. 33). (3, 38)



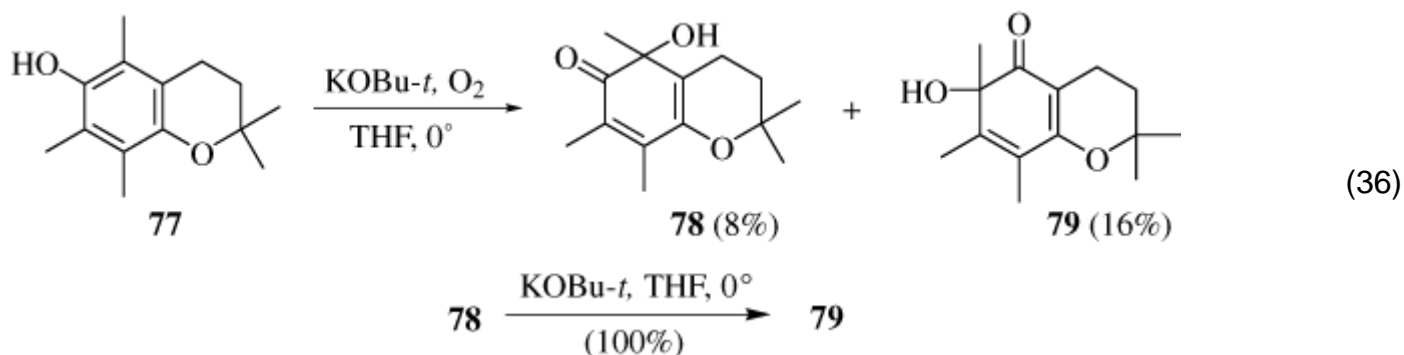
α -Ketol rearrangements that retain ring size are well known. The degenerate behavior of 2-hydroxy-2-methylcyclobutanone is revealed by hydrogen/deuterium exchange in D_2O /0.8 M in pyridine. The ^1H NMR signals attributable to its C-3 and C-4 methylene groups disappear at approximately equal rates whereas the methyl singlet is unaffected, indicating that isomerization via 1,2-methyl shift is faster than enolization and that homoenolization at methyl is not involved. In the case of ketol **73**, equilibration with isomer **74** also occurs readily under basic conditions and follows pseudo first order kinetics (Eq. 34). (71) The equilibrium constant is close to 0.8–1.2 in various solvents, and their free energies differ by less than 0.1 kcal/mol.



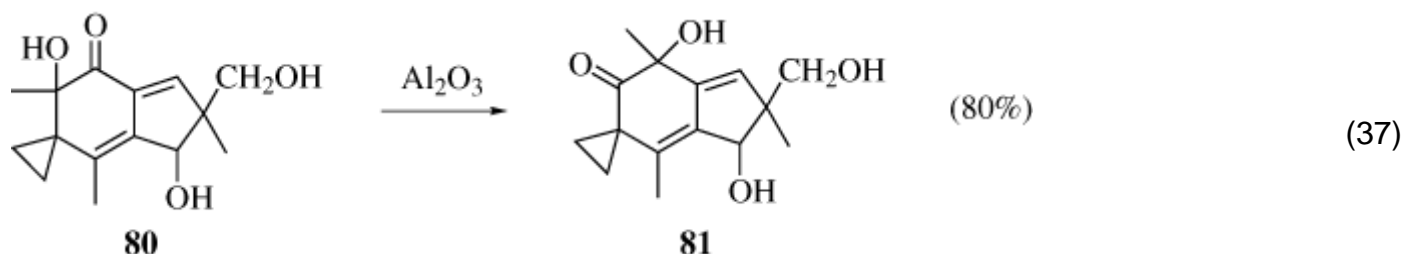
5-Hydroxypyrrolinones related to **75** isomerize to their 4-hydroxy isomers **76** when treated with aqueous KOH at 25–65° (Eq. 35). (8) Presumably, these structurally unusual heterocyclic products are thermodynamically favored by their extended conjugation. Indeed, product **76** and its congeners share in common the ability to emit a characteristic fluorescence when illuminated with near-ultraviolet light.



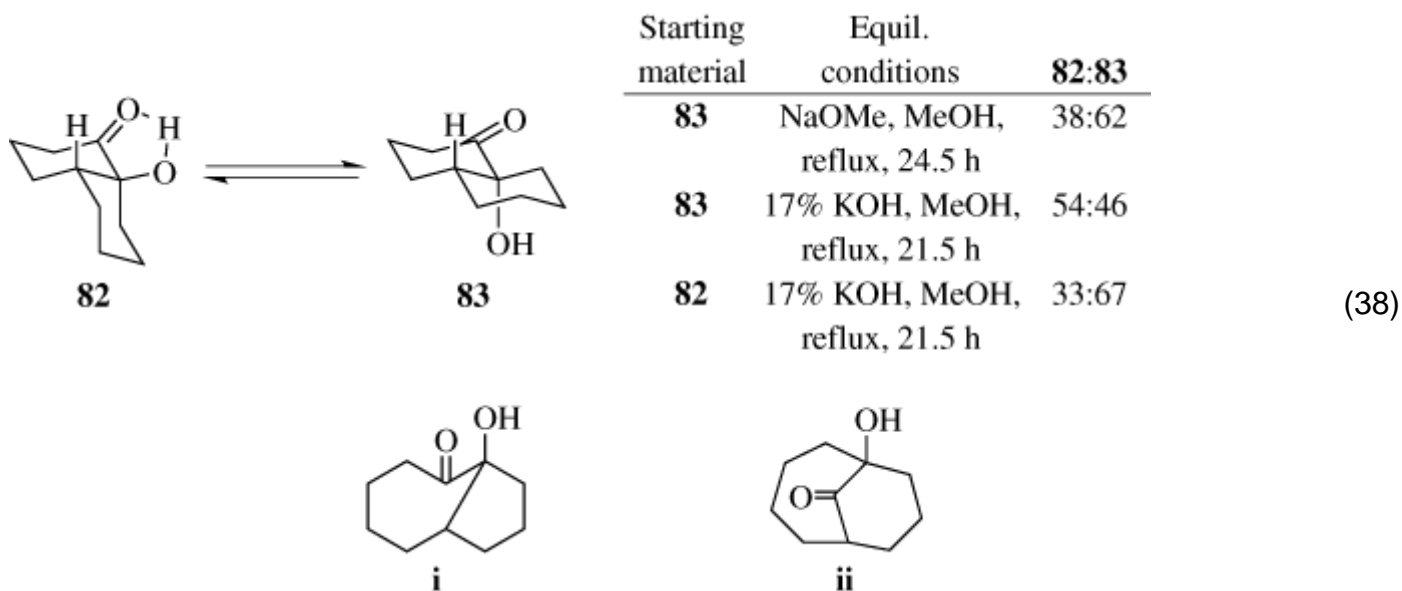
Air oxidation of cold (0°) tetrahydrofuran solutions of the α -tocopherol mimic **77** in the presence of potassium *tert*-butoxide leads to cyclohexadienones **78** (8%) and **79** (16%) in addition to other products (Eq. 36). (72) The researchers proved that **79** arises from an intervening α -ketol rearrangement by resubmitting **78** to the original alkaline medium, which furnishes cyclohexadienone **79** in quantitative yield.



A related rearrangement is observed when the antitumor agent lampterol (also known as illudin S, **80**) is chromatographed on alumina (Eq. 37). (73) In isolampterol (**81**), the carbonyl group continues to reside in a six-membered ring but is adjacent to a cyclopropane unit. Evidently, this change is sufficient to favor heavily the iso product **81** at equilibrium.

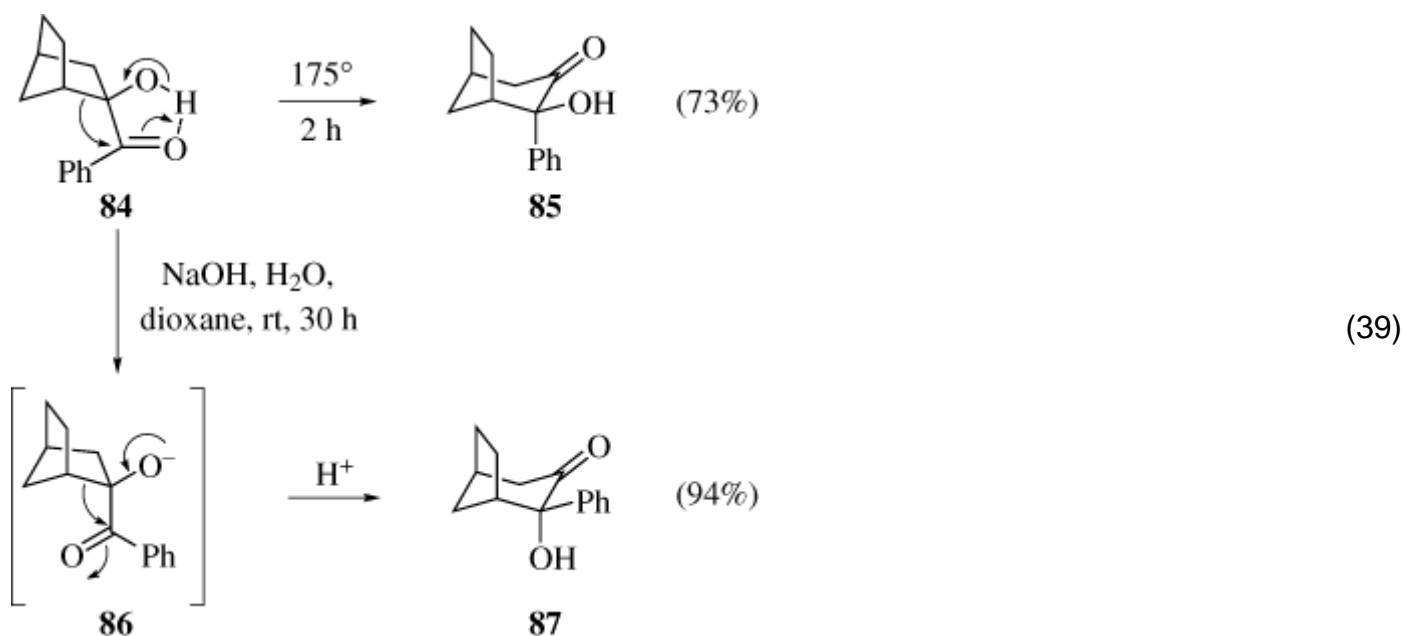


The cis and trans decalyl ketols **82** and **83** are equilibrated in alkaline media (Eq. 38). (74) Although exhaustive examination did not prove possible because of competing side reactions, sufficient information is available to indicate that the relative stability of the trans isomer is hardly overwhelming. The possibility exists that the cis-decalyl system profits from intramolecular hydrogen bonding. It is not known which of the two intermediate ketols (**i** and **ii**) are involved.

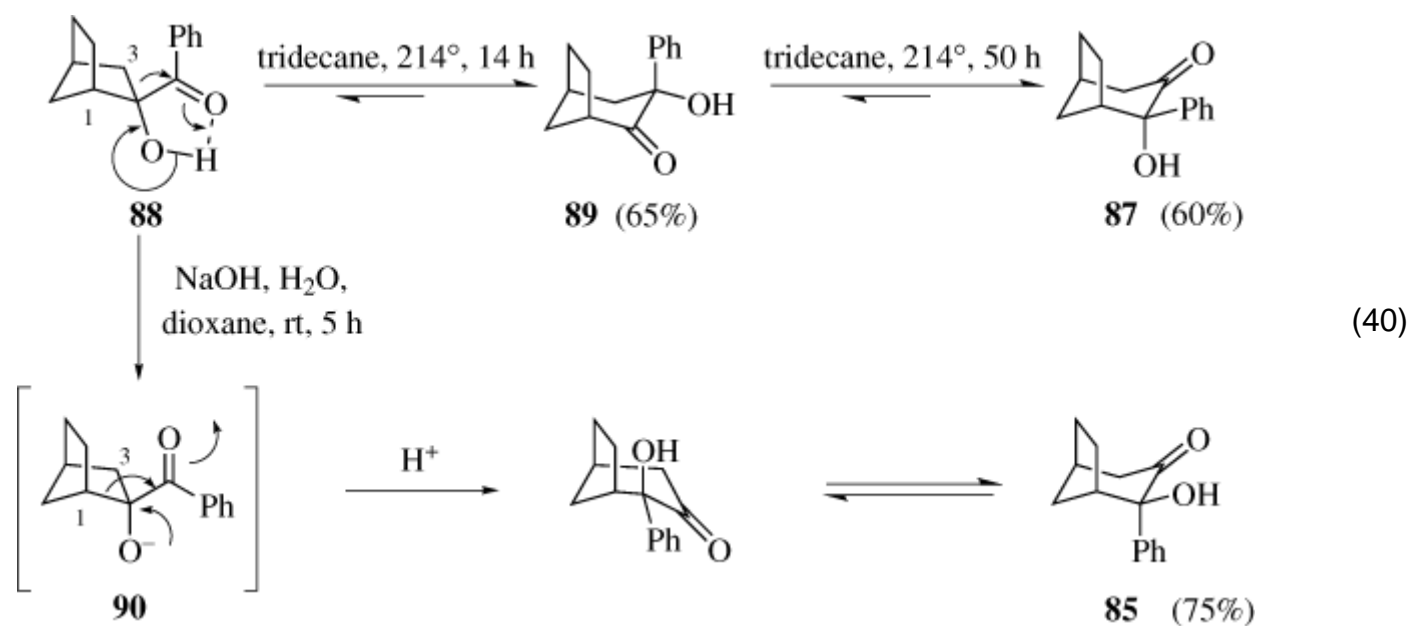


3.3. Bridged α -Ketol Systems

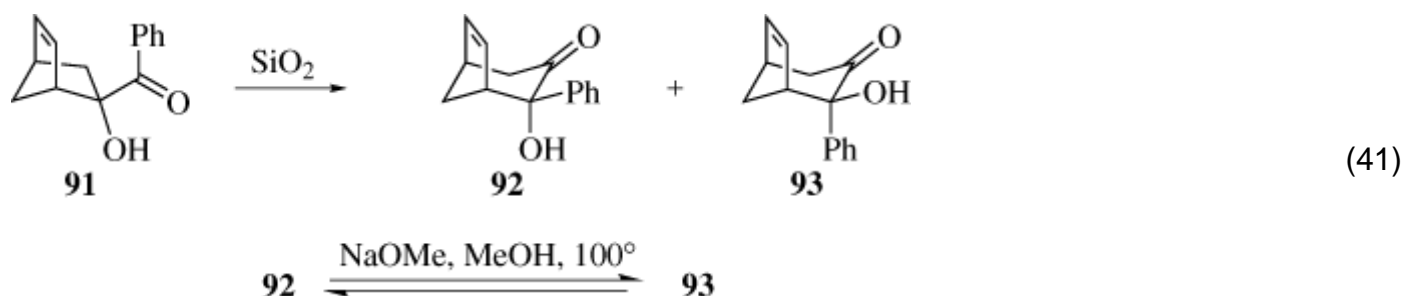
Bridged bicyclics having a vicinal hydroxyl and carbonyl at non-bridgehead positions are particularly prone to ring expansion when 1,2-shifting is accompanied by relief of ring strain. Such systems can also undergo subsequent equilibration in stereo-specifically useful ways. The widely different behavior of the endo and exo norbornanols **84** and **88** under rearrangement conditions is illustrative. (34) When heated neat at 175° for 2 hours, endo isomer **84** is completely transformed into the exo form **85** (Eq. 39). In alkaline medium, norbornanol **84** rearranges instead to α -ketol **87**. These findings have been explained in terms similar to those proposed in the steroid series, namely, reagent control of carbonyl orientation. In the neat thermolysis, the hydroxy and carbonyl are cisoid as in keto carbinol **84** due to hydrogen bonding. In this alignment, hydrogen transfer and alkyl migration can be concerted. By contrast, alkali-promoted deprotonation places a negative charge on the hydroxy oxygen and enhances charge-dipole repulsion, which favors a transoid orientation of the carbonyl as in intermediate **86**. Rearrangement from this conformation leads to product **87**.



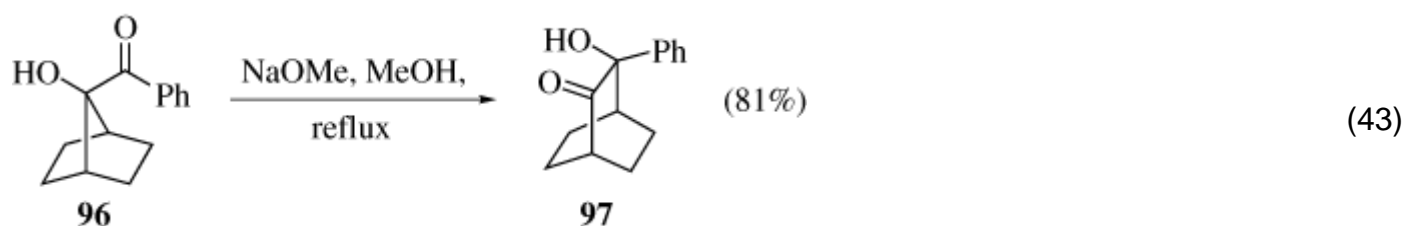
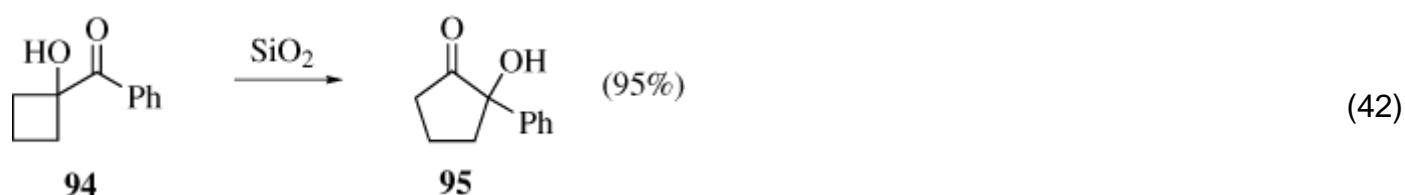
The thermal isomerization of the *exo*-OH ketol **88** involves more complex equilibria. Longer heating periods are required, one consequence of which is that the initially formed α -ketol **89** undergoes further reversible conversion to isomer **87** (Eq. 40). (34) With sodium hydroxide in aqueous dioxane, the rearrangement involves migration of a different ring bond to give α -ketol **85**. The migration of C-1 occurs to the exclusion of C-3 (see **90**) in order to avert serious nonbonded steric interactions between the phenyl group and the ethano bridge.



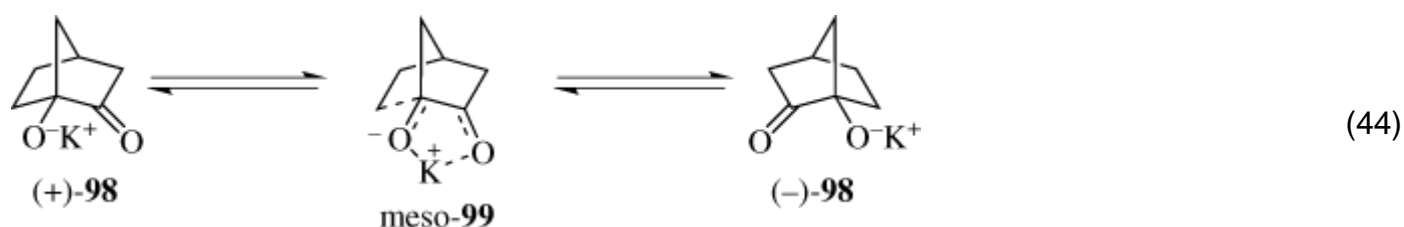
The norbornenyl congener **91** reflects its higher ring strain by undergoing the α -ketol rearrangement during silica gel chromatography (Eq. 41). (32) While the ratio of epimers **92** to **93** depends on the history of the silica gel, heating these mixtures at 100° with 0.5 M sodium methoxide in methanol favors epimer **93** by a ratio of 89:11.



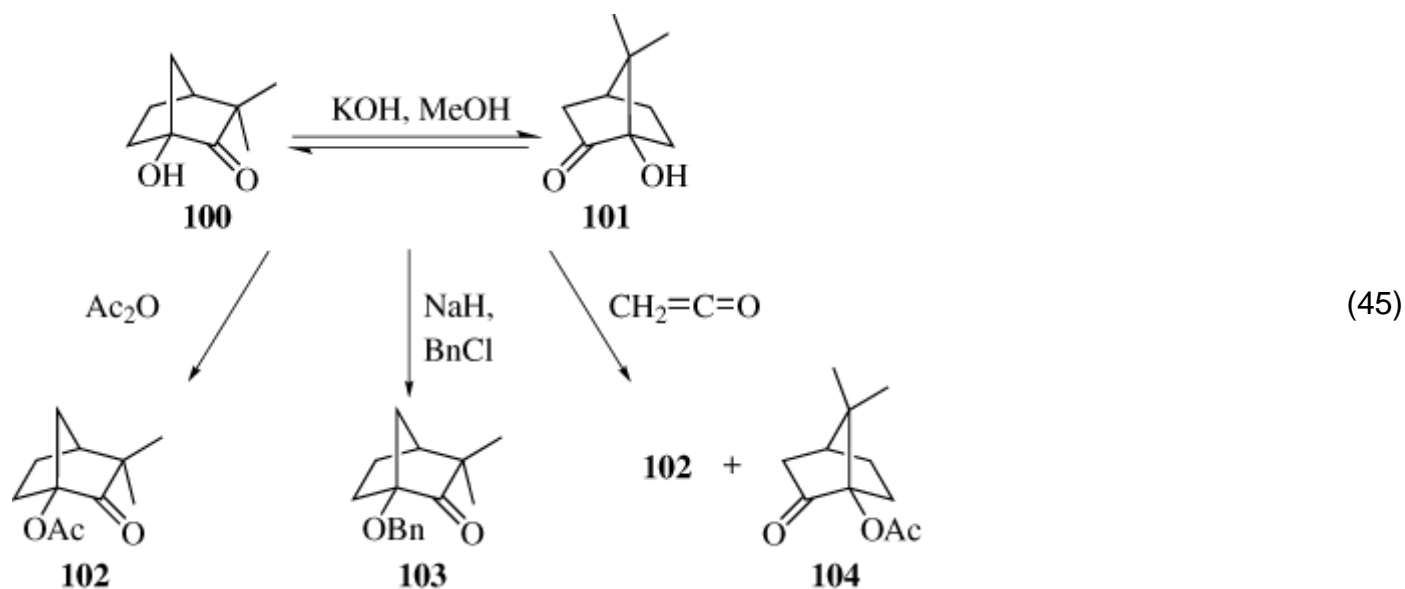
The delicate interrelationship of strain and ease of α -ketol rearrangement has surfaced in other ways. As with norbornenol **91**, silica gel chromatography is sufficient to rearrange the cyclobutyl derivative **94** into cyclopentanone **95** (Eq. 42). (32) On the other hand, α -ketol **96** survives chromatography and is converted into the ring-expanded product **97** only when refluxed with sodium methoxide in methanol (Eq. 43).



Racemic 1-hydroxy-2-norbornanone (**98**) undergoes degenerate α -ketol isomerization on treatment with K_2CO_3 in D_2O at 80° (Eq. 44). (75) After 145 hours, the observed uptake of 3.9 deuterons per molecule is the result of interconversion of the enantiomers (+)-**98** and (-)-**98**, each of which has two exchangeable C-H bonds. The transition state for the rearrangement may be depicted as meso-**99**.

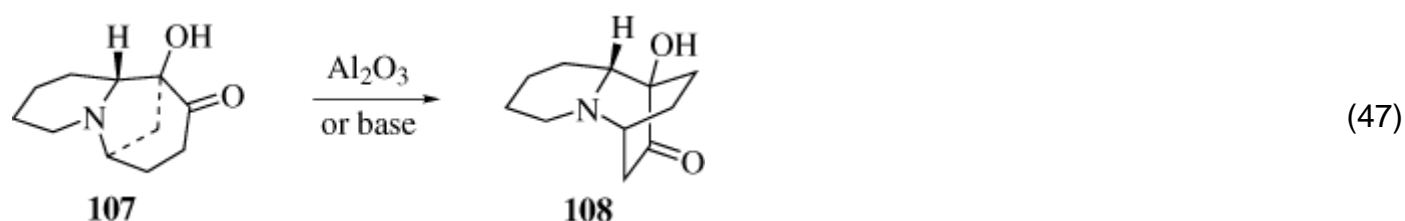
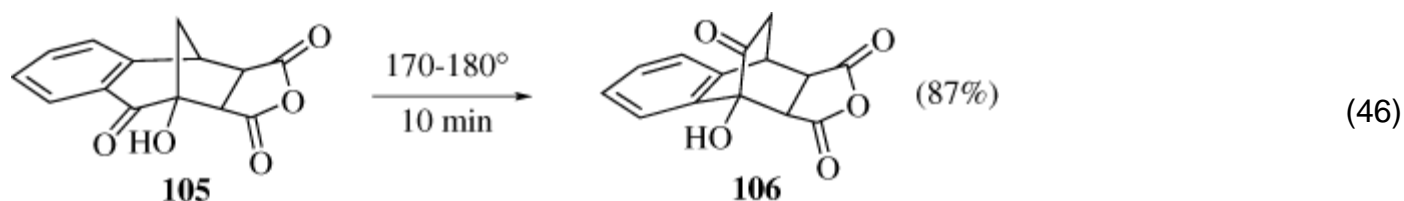


A similar pathway is followed during the base-promoted interconversion of 1-hydroxycamphenilone (**100**) and 1-hydroxycamphor (**101**) (Eq. 45). (76, 77) In alkali at 31° , **101** is favored over **100** by a factor of 2. Acetylation of the mixture with acetic anhydride or *O*-benzylation with benzyl chloride and sodium hydride in dimethylformamide leads predominantly to camphenilone derivatives **102** and **103**, respectively. But treatment of the mixture with ketene in acetone solution gives the isomeric α -acetoxy ketones **102** and **104** in approximately equal amounts.

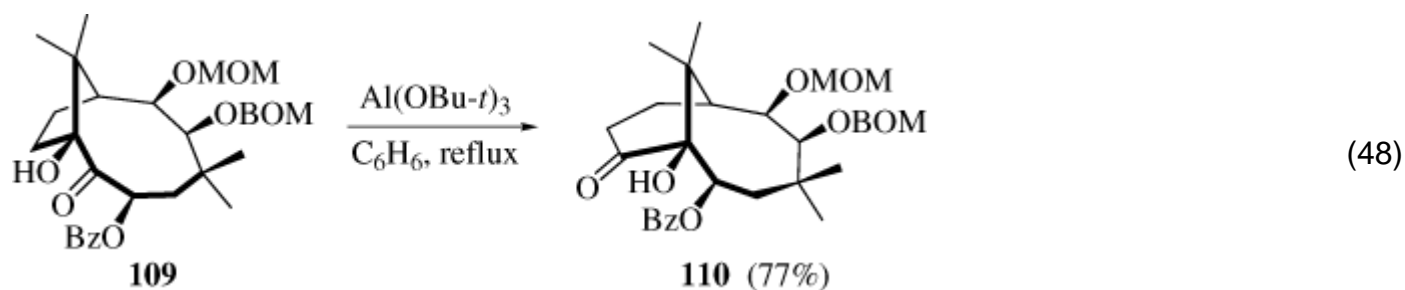


Characteristically, the α -ketol rearrangement of anhydride **105** to **106** occurs thermally and under conditions of acid and base catalysis. (78) Bridge migration takes place rapidly at the melting point of isomer **105** (190°), but more slowly in refluxing acetonitrile (82°) (Eq. 46).

The α -ketol **107** (obtained by degradation of securinine) has been shown to be a sensitive compound, rearranging readily to the more stable isomer **108** during chromatography on alumina or dissolution in an alkaline medium (Eq. 47). (79)



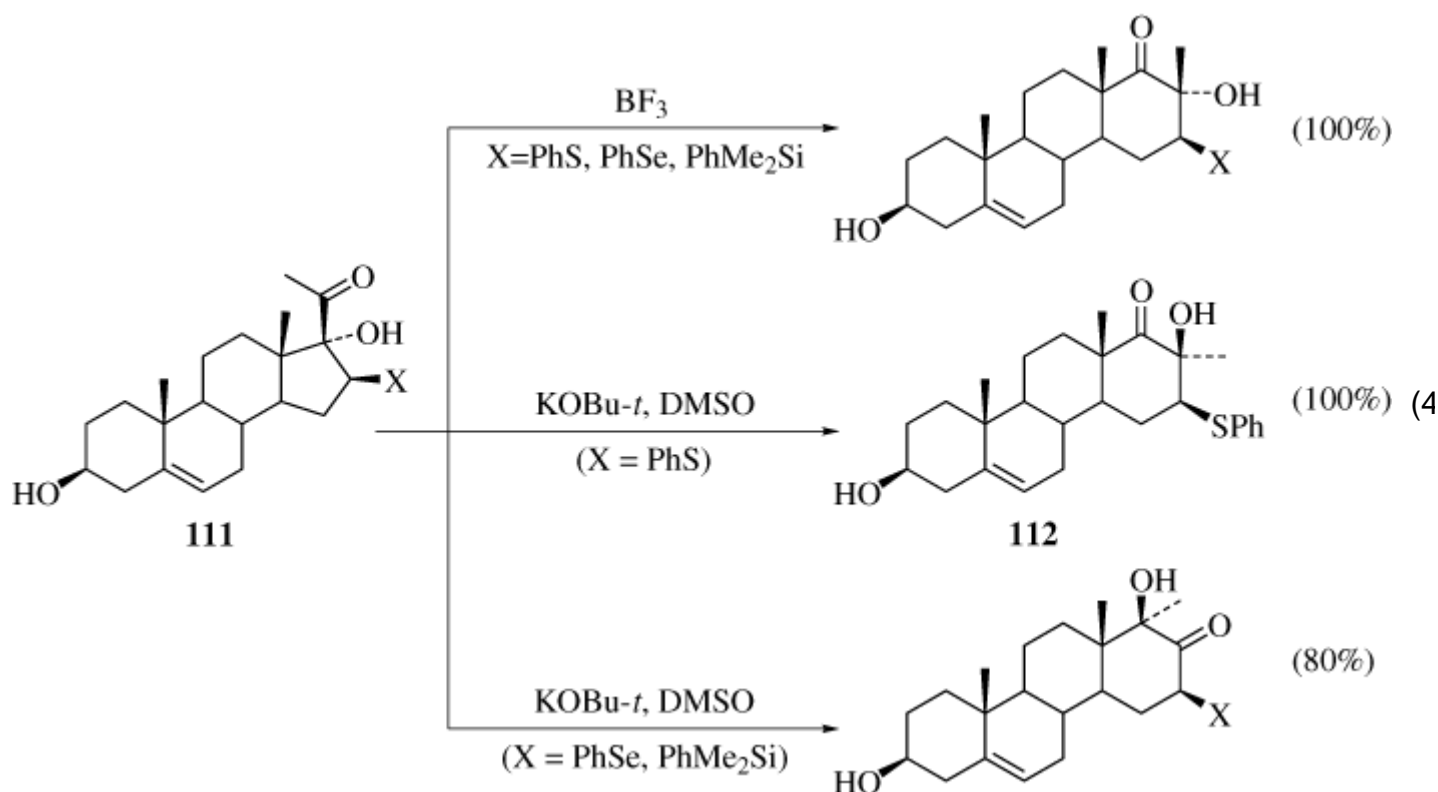
Heating the bridgehead α -ketol **109** with $\text{Al}(\text{O}i\text{Bu})_3$ in benzene isomerizes it unidirectionally to compound **110** (Eq. 48). (80) While coordination of the aluminum atom to the two key oxygen atoms gives rise to a stereoalignment conducive to 1,2-shift of the dimethyl-substituted methano unit, this process is doubtlessly promoted as well by the greater thermodynamic stability of α -ketol **110**. Were the product of ethano bridge migration to be formed, the likelihood is that it would also rearrange to **110**. (5, 6)



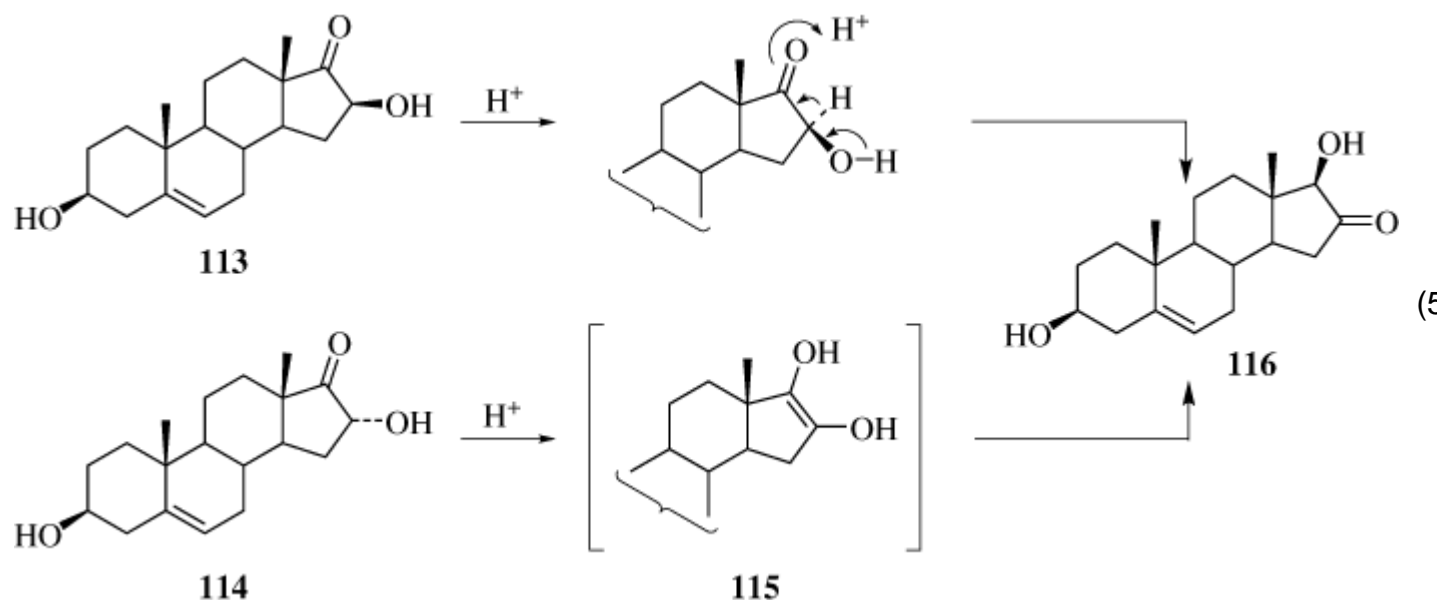
3.4. Steroidal α -Ketols

A great deal has been written about D-homoannulations of 17-hydroxy-20-keto steroids. (1, 2, 4, 81-88) The essence of the mechanistic analysis was previously conveyed in Eqs. 7–9. Thus, the 17 β -OH isomers **11** are initially transformed into stereoisomeric 17 α -methyl-17-ketones **14** or **17** depending on the reaction conditions. (26, 45, 81, 89-97) Alkaline catalysis affords the 17 α -epimer **14** stereospecifically. Lewis acids or heat give the 17 α β -ketones **17** instead. This ring expansion is general in nature and has been broadly applied.

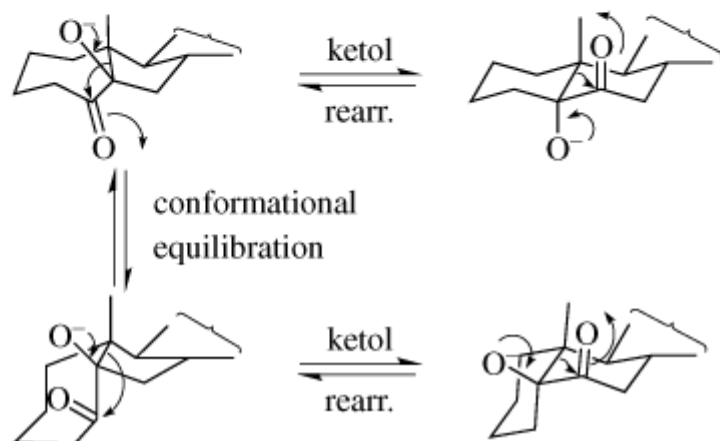
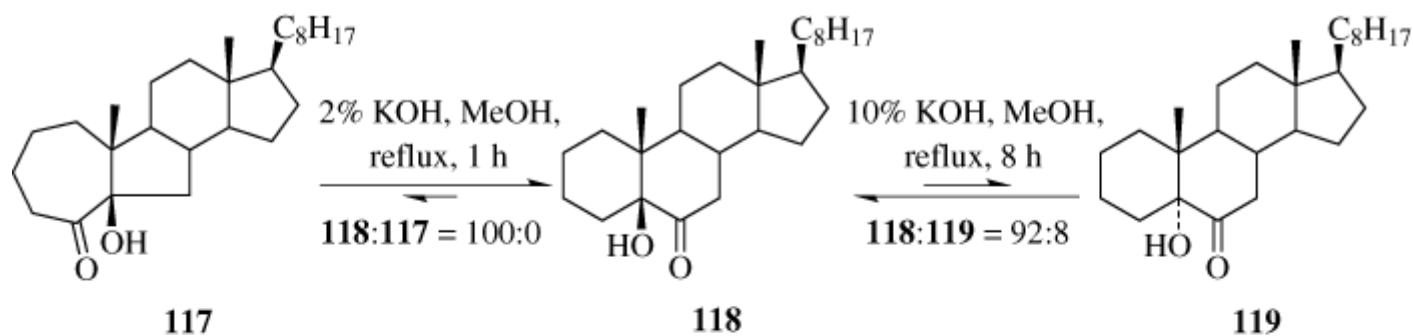
Study of the D-homoannulations of the 17 α -isomers **18** has shown that reagent control persists, but with some drop-off in stereoselectivity. (36, 98-100) Lewis acids uniquely bring about the exceptional migration of C-16, a 1,2-shift exhibited by a large number of variously substituted steroids. (43, 95, 101-104) More recent investigations have included the influence of proximal 16 β -PhS, 16 β -PhSe, and 16 β -PhMe₂Si groups. (105) Under Lewis acid catalysis, none of the three derivatives of steroid **111** exert any anomalous effect on product regiochemistry or stereochemistry (Eq. 49). The phenylseleno and dimethylphenylsilyl substituents also have no influence on the base-catalyzed α -ketol rearrangement; however, the phenylthio group effectively blocks the normal C-13 shift and brings C-16 bond migration into play with formation of D-homo derivative **112** in quantitative yield. Apparently, only S and not Se or Si can effectively stabilize negative charge on the α -carbon at the transition state. The isolation of product **112** holds significance in that it represents the first time that an α -ketol isomer having this D-ring stereochemistry has been generated in other than trace quantities.



Other α -ketol rearrangements in steroids have been reported although explored much less extensively in synthesis. The conversion of 16^{β} - and 16^{α} -hydroxy-17-keto androstanes **113** and **114** to the thermodynamically more stable 17^{β} -hydroxy-16-keto isomer **116** under acidic conditions has been examined by ^{13}C NMR spectroscopy (Eq. 50). (106) The transposition of carbonyl groups occurs via a 1,2-hydride shift in α -keto carbinol **113** and by initial conversion to the enediol **115** followed by reprotonation in the example of steroid **114**. Reasons for the operation of different paths have not been advanced.



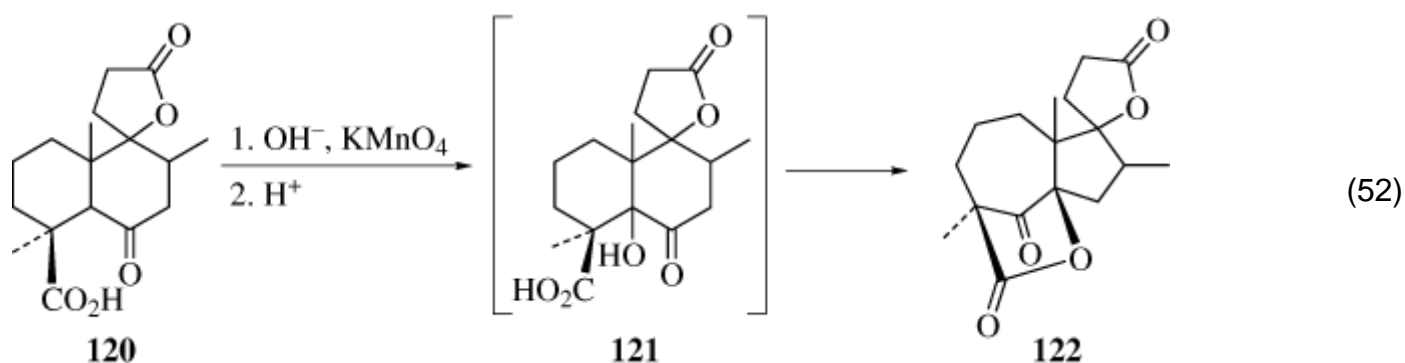
The perhydroazuleno ketol **117** undergoes smooth conversion to 5-hydroxy-cholestan-6-one **118** in the presence of hot 2% methanolic potassium hydroxide for one hour (Eq. 51). (107) Extension of the reaction time to 8 hours in 10% KOH resulted in efficient equilibration with the trans ketol **119**. The cis isomer **118** is favored by a free energy difference of 1.7 kcal/mol. This bias is considerably greater than that observed for the **82**, **83** isomer pair described earlier (Eq. 38). The predominance of the cis isomer in both series can be rationalized in terms of the existence of a stabilizing intramolecular hydrogen bond. The proximal angular methyl in compounds **118** and **119** also likely lessens the intrinsic cis/trans energy difference as observed in simple decalin systems. (74) The mechanistic pathway illustrated in Eq. 51 depicts the alkoxide form of **117** as a key intermediate in this equilibration and addresses the stereo-electronic requirements of the 1,2-alkyl shifts involved.



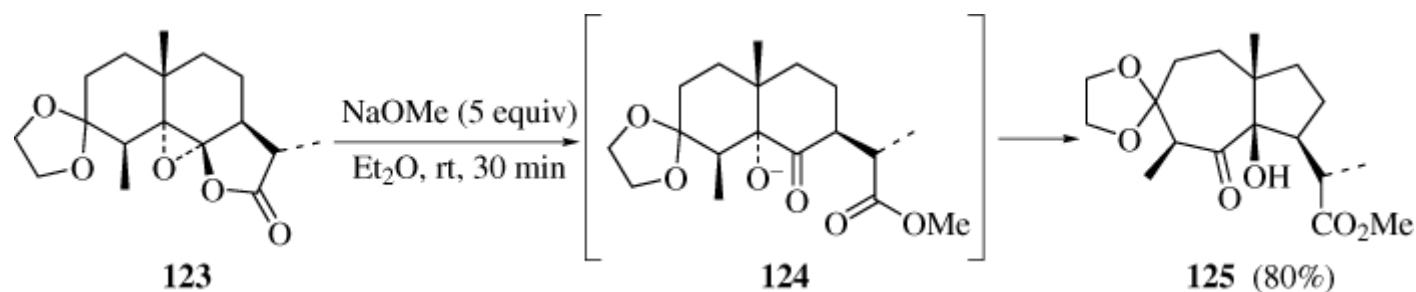
3.5. Complex Polycyclic α -Ketols

The natural product marrubiin is degraded to the keto acid **120**, which then affords keto lactone **122** on treatment with alkaline permanganate. Dilactone **122** seemingly stems from rearrangement of the initially formed α -hydroxy ketone **121** followed by cyclization (Eq. 52). (108) Thus, it is possible to drive isomerizations of the type 7/5 \square 6/6 (see **117** \square **118**) in the reverse direction by intramolecular trapping of the hydroazulenone isomer.

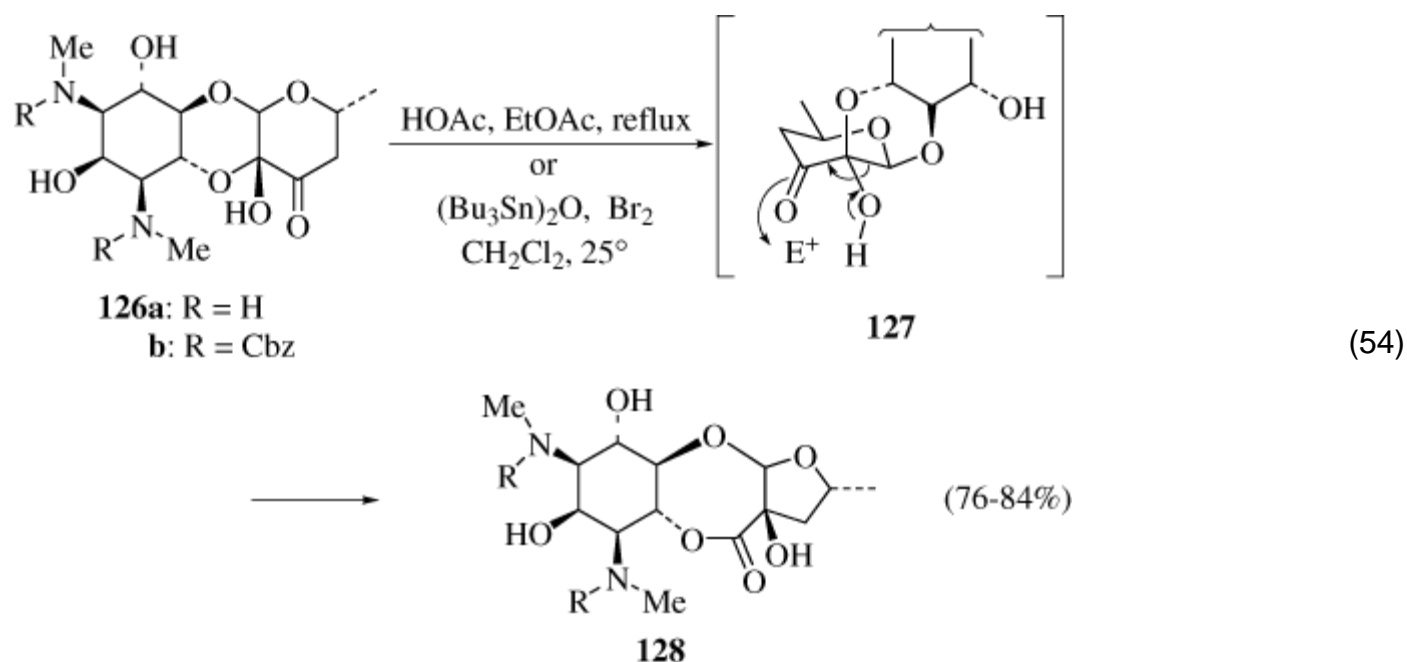
In connection with a reported conversion of the sesquiterpene α -santonin into epoxy lactone **123**, this derivative was subsequently treated with an excess of sodium methoxide in ether at room temperature for 30 minutes. (109) Attack at the lactone carbonyl initiates an interesting reaction cascade involving opening of the oxirane ring



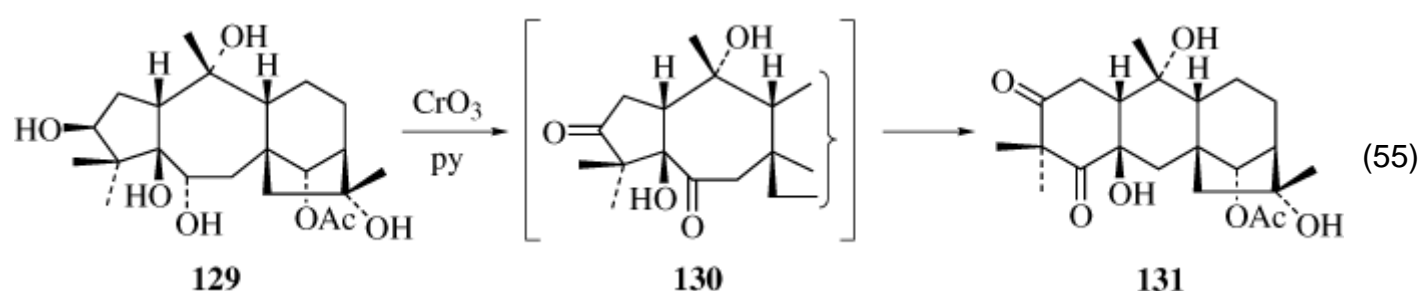
(Eq. 53). The trans arrangement of the alkoxide and carbomethoxy substituents in intermediate **124** precludes them from lactonizing and allows an α -ketol rearrangement to deliver α -ketol **125**. The salviene sesquiterpene framework present in product **125** dominates the equilibrium, a likely reflection of the array of substituents and their stereodisposition.



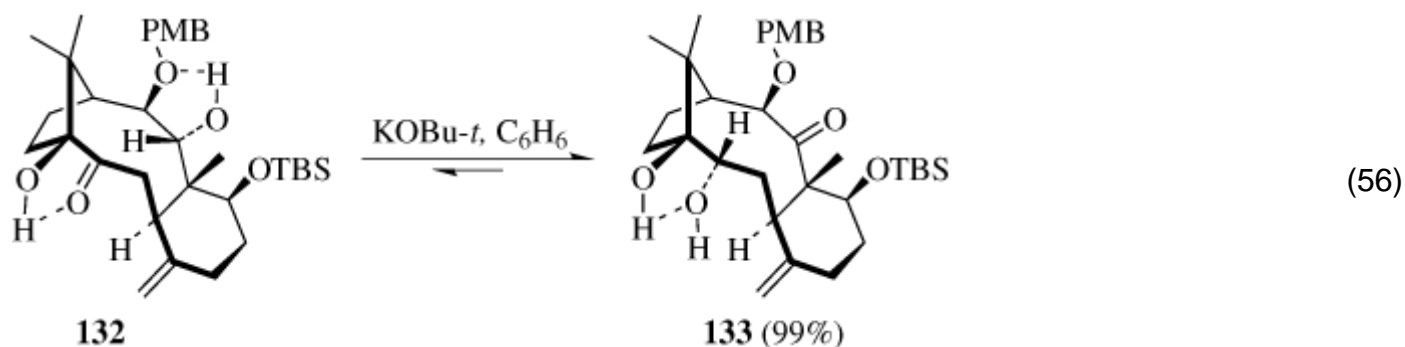
Spectinomycin (**126a**) is an aminocyclitol featuring an α -ketol part structure. Among the many chemical transformations carried out on this antibiotic, rearrangement of its *N*-benzyloxycarbonyl derivative **126b** in hot ethyl acetate containing 10% acetic acid or by treatment with bis(tri-*n*-butyl)tin oxide and bromine in dichloromethane holds particular interest (Eq. 54). (110) Both sets of conditions lead unidirectionally and irreversibly to the α -hydroxy lactone **128** in 76% and 84% yields, respectively. The partial structure **127** shows that the relevant bonds are favorably aligned for skeletal isomerization to hydroxy lactone **128**.



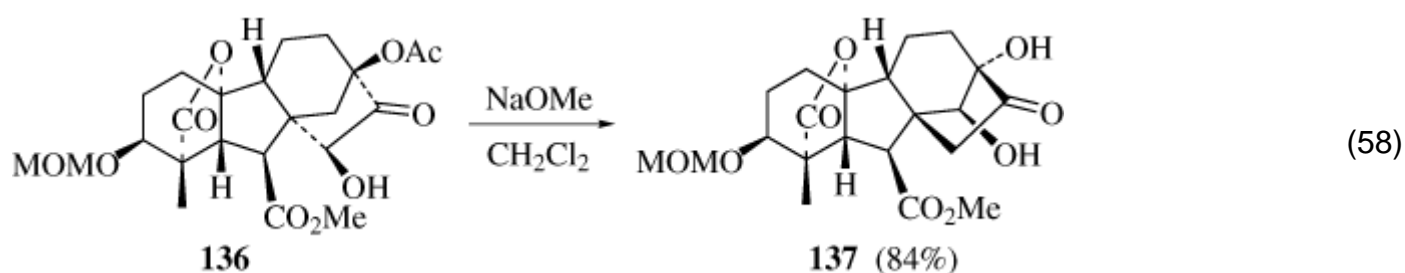
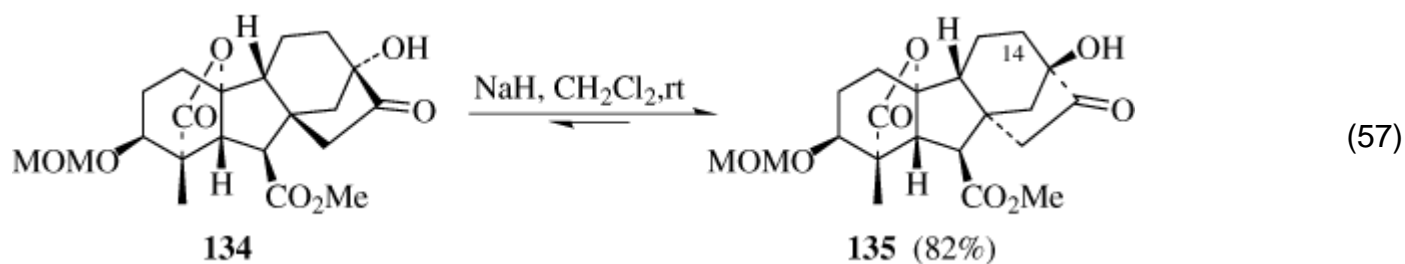
Oxidation of grayanotoxin I **129** with chromium trioxide in pyridine occurs at its two secondary hydroxy sites to give α -ketol **130**, which rearranges immediately to β -diketone **131** (Eq. 55). (111) From the findings outlined in Eqs. 51-53, it is evident that perhydroazulenone-decalone equilibria can favor either ring system and that care must be exercised in attempts at prediction.



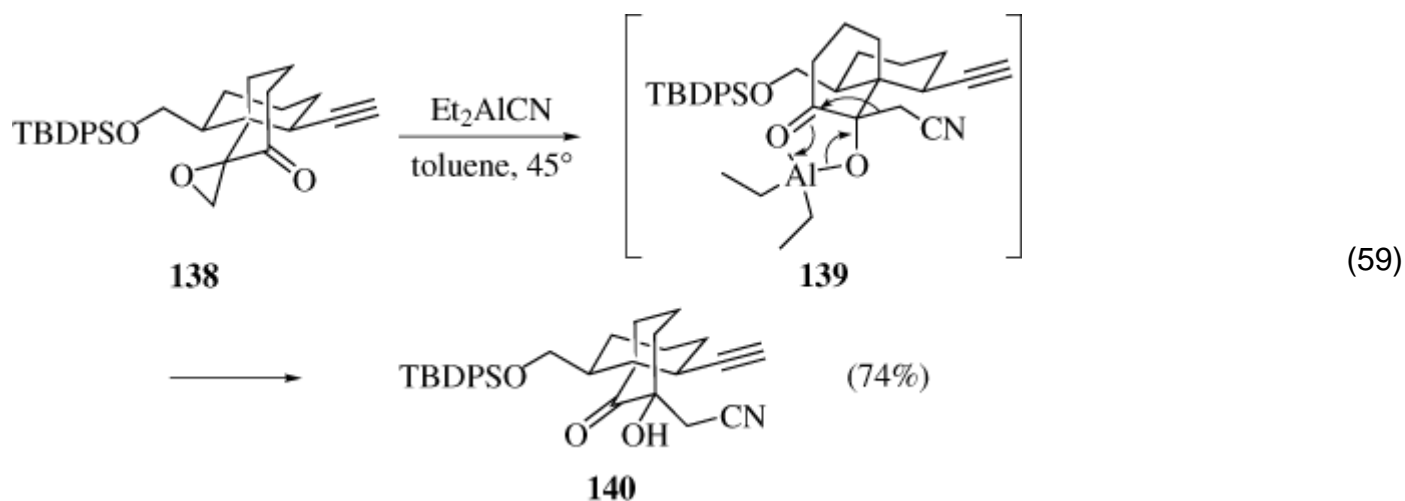
An interesting example of an intercepted α -ketol rearrangement has been reported (Eq. 56). (112) In the case of bridgehead carbinol **132**, exposure to strong base induces the operation of a transannular hydride shift with formation of isomer **133**. No 1,2-bridge migration is observed.



A general protocol developed for the 14-hydroxylation of the gibberellin molecule is predicated on the ability of the α -ketol rearrangement to invert stereochemistry of the five-membered D-ring as in α -ketols **134** and **135** (Eq. 57). (113) Re-equilibration of product **135** with base gives a 1:4 mixture of **134** and **135**, thereby indicating a thermodynamic preference for the latter isomer. In view of this bias, the conversion of the highly functionalized system **136** into **137** in good yield (Eq. 58) is initially surprising. Perhaps the alignment of dipoles associated with the carbonyl unit and both hydroxy groups in ring D of compound **136** destabilizes this particular isomer and upsets the normal equilibrium position.



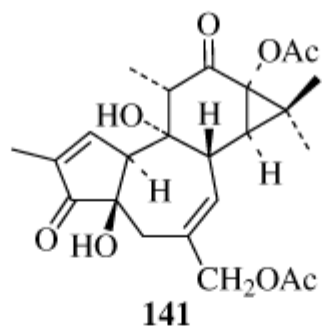
A facile aluminum-mediated 1,2-anionotropic rearrangement can occur when a suitable α -oxido ketone intermediate is generated by nucleophilic epoxide ring opening. Thus, the hydrocyanation of epoxy ketone **138** with diethylaluminum cyanide proceeds regioselectively to the chelated intermediate **139**, with its axial cyanomethyl unit favorably aligned for subsequent 1,2-migration to provide the transposed α -ketol **140** in 74% yield (Eq. 59). (114) The epoxide diastereomer of **138** behaves analogously but less efficiently (48% yield). Consequently, the ease of synfacial alkyl migration depends on configuration within intermediate **139**.



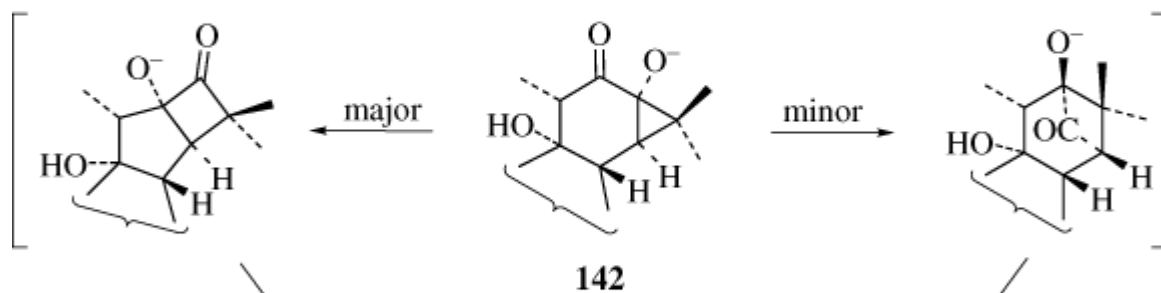
Treatment of 12-desoxy-12-oxophorbol-13,20-diacetate **141** with sodium methoxide in methanol selectively transesterifies the tertiary ester and generates the acyloin anion **142**, setting the stage for two competing α -ketol rearrangements (Eq. 60). (7) In the major pathway, 1,2-shift of the internal cyclopropane bond delivers the cyclobutanes **143a** and **143b** as end products. Migration of the other external cyclopropane bond also competes and ultimately produces hemiacetal **144**, but approximately three times less rapidly.

The isomerization of mursinol **145** to iso-mursinol **146** in methanolic potassium hydroxide is seen to involve an α -ketol rearrangement (Eq. 61). (115) This quantitative transformation demonstrates the substantial thermodynamic preference for the perhydroanthracene carbocyclic framework.

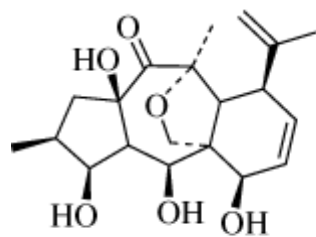
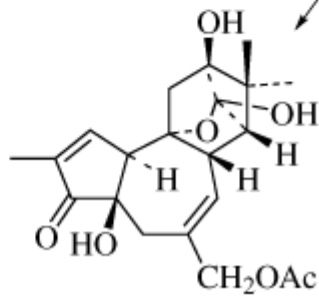
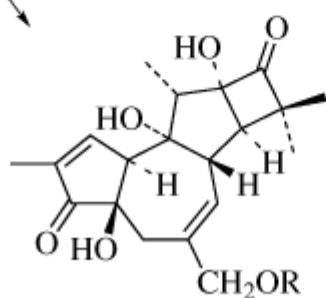
An α -hydroxy ketone rearrangement has been identified as a possible pivotal step in the biosynthesis of the Calebassinine alkaloid family, two members of which are typified by structures **147** and **148**. The supporting experimental fact is that indoline **147**, when treated with potassium hydride and 18-crown-6 in dimethoxyethane at room temperature for one hour, is converted to dihydroquinolone **148** with full stereocontrol (Eq. 62). (116)



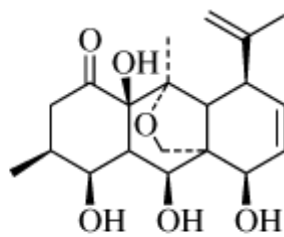
NaOMe, MeOH
100 h, rt



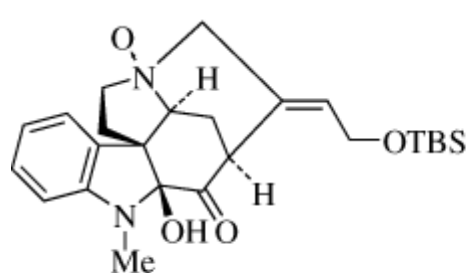
(60)



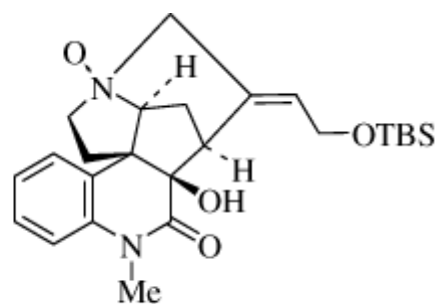
KOH
MeOH



(61)

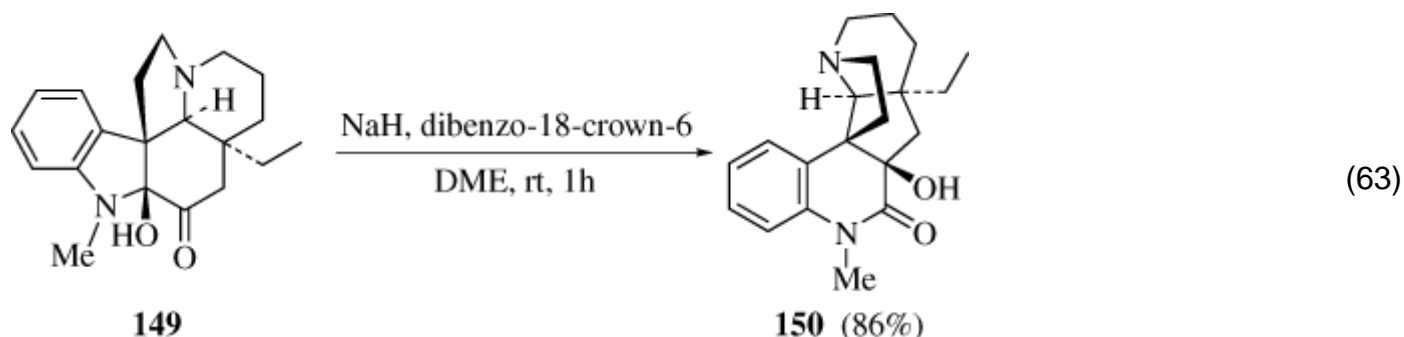


NaH, 18-crown-6
DME, rt, 1 h

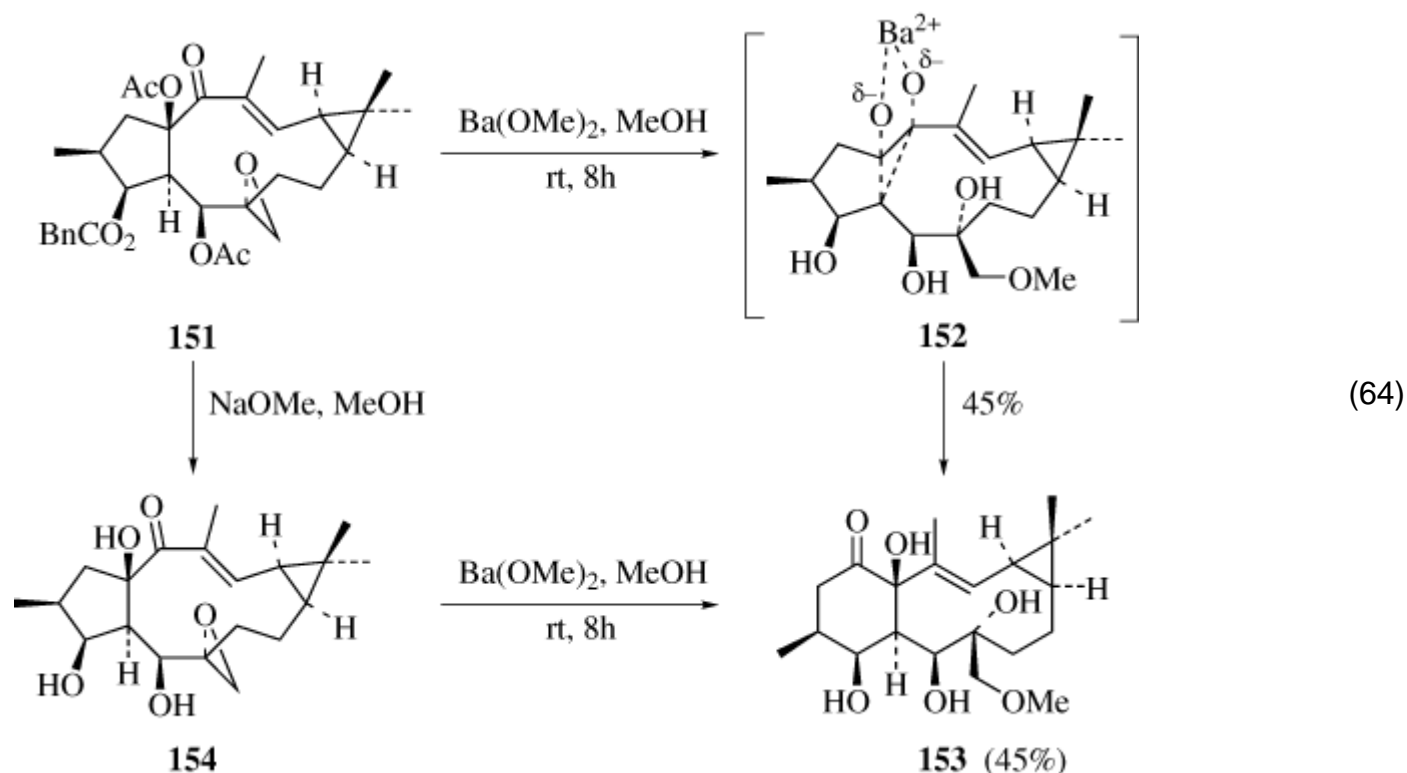


(62)

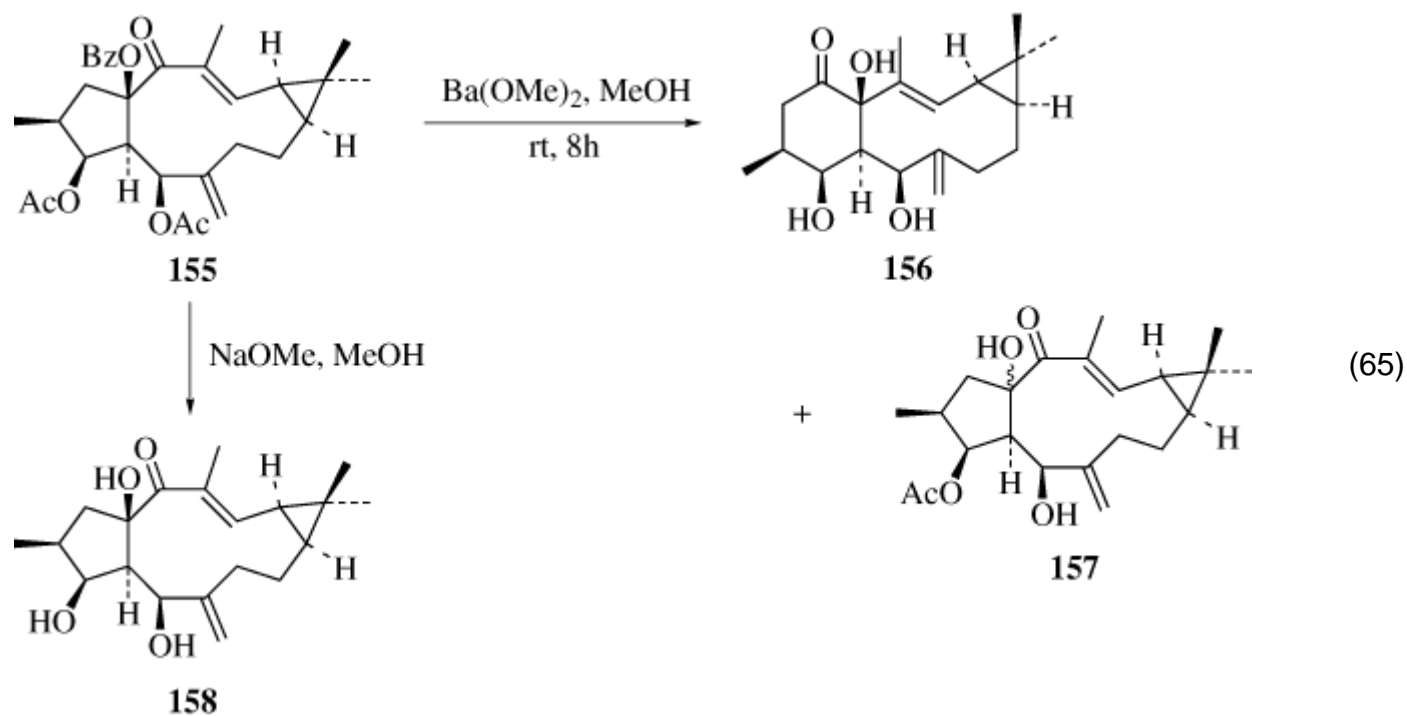
The strategy for interchanging the ring sizes in a 6/5 system had previously been utilized in a synthesis of the Melodinus polycyclic structure as shown in Eq. 63. (117) Thus, under analogous mild conditions, the keto indoline **149**, which is easily prepared from readily available (-)-vincadifformine, rapidly gives the hydroxyquinolone **150**. All attempts to induce the same skeletal change under Lewis acidic conditions led to decomposition.



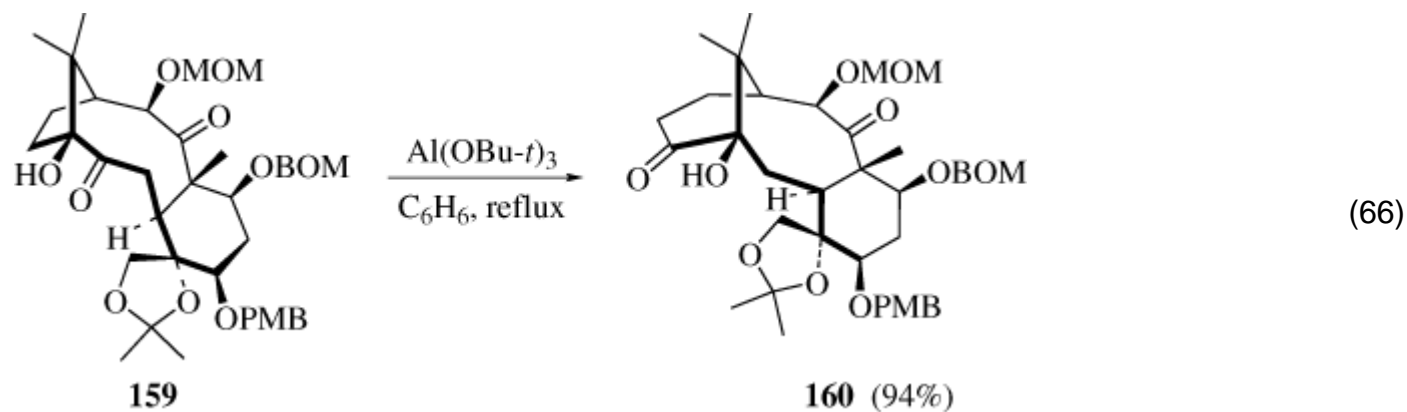
Informative examples of counterion effects have been reported in the anionic rearrangement of epoxyalcohol (**151**) and in the structurally related ester L₃ **155**. (39) Exposure of **151** to nine equivalents of barium methoxide in methanol for eight hours at room temperature gives product **153** in 45% yield. The chelated intermediate **152** is believed to be responsible for inducing stereocontrolled migration of the internal carbon-carbon bond (Eq. 64). When either sodium or potassium bases are used instead in this reaction, only the parent triol **154** is formed. In the presence of barium methoxide, α -ketol **154** gives isomer **153** as the sole product.



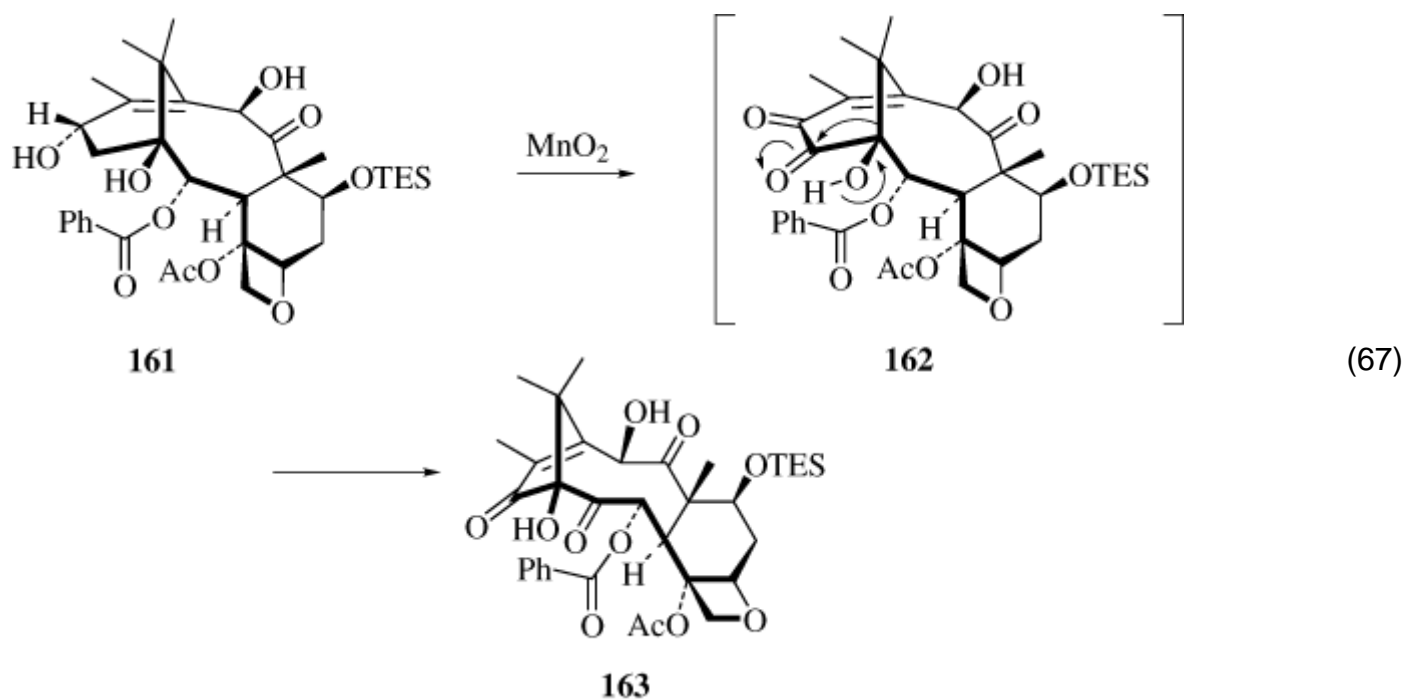
The related triester **155** responds similarly to barium methoxide and affords keto triol **156** and the partially deacylated product **157** (Eq. 65). Methanolic sodium methoxide completely saponifies the starting compound **155** without rearrangement to give keto triol **158**.



α -Ketol rearrangements have featured prominently in the area of taxane chemistry. The efficient aluminum tri-*tert*-butoxide promoted conversion of α -keto carbinol **8** into isomer **10** described earlier (Eq. 6) is typical of several examples. The isotaxane framework can be heavily functionalized as reflected in α -ketol **159** without any apparent adverse effect on the unidirectional course of the isomerization. For example, in Eq. 66 the yield of the derived taxane **160** is 94% (Eq. 66). (42)

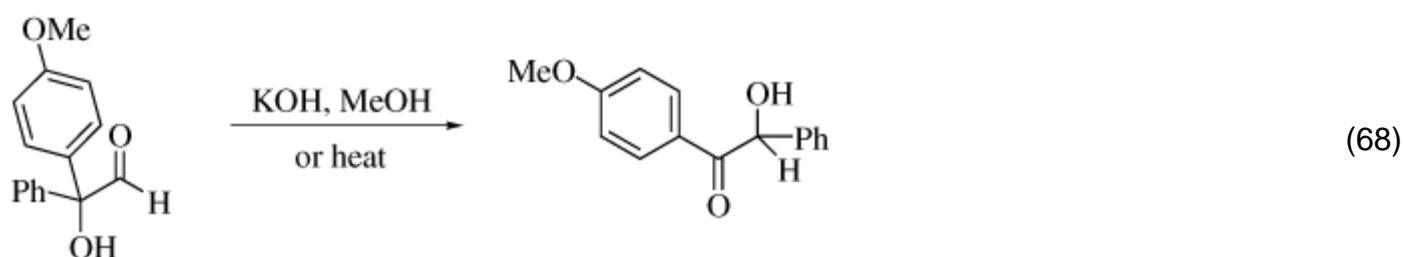


In this context, it is intriguing that manganese dioxide oxidation of compound **161** proceeds smoothly (presumably via the intermediate α -diketone **162**) to the rearranged structure **163** (Eq. 67). (40) Note that the overall skeletal change here is opposite to that in Eq. 6 and Eq. 66. The release of strain accompanying the rearrangement of **162** to **163** likely originates from two contributing factors: the presence of four adjacent trigonal carbons in the anti-Bredt structure **162**; and less nonbonded transannular steric compression in the central nine-membered ring of product **163**. Any possible special role played by the MnO_2 remains to be clarified.

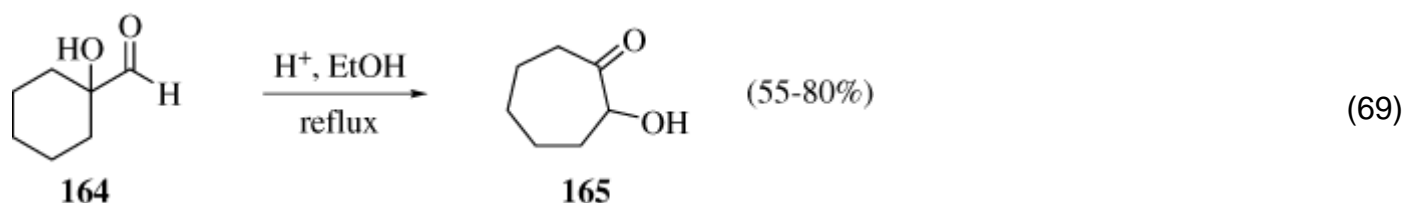


3.6. α -Hydroxy Aldehydes

The thermodynamic advantage gained while progressing from an α -hydroxy aldehyde to an α -hydroxy ketone in acyclic examples free of steric and strain factors forces equilibria unidirectionally to the α -hydroxy ketone isomer. Such conversions are catalyzed by acid (viz. **26** to **27**, Eq. 10), base, or thermally (Eq. 68). (118)

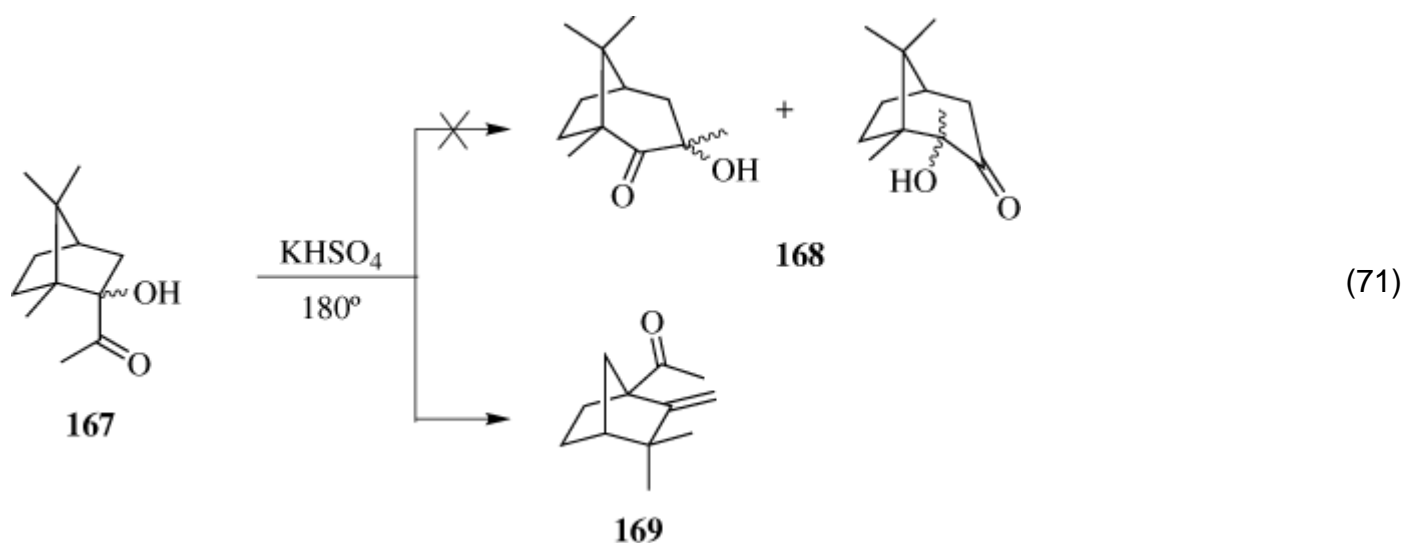
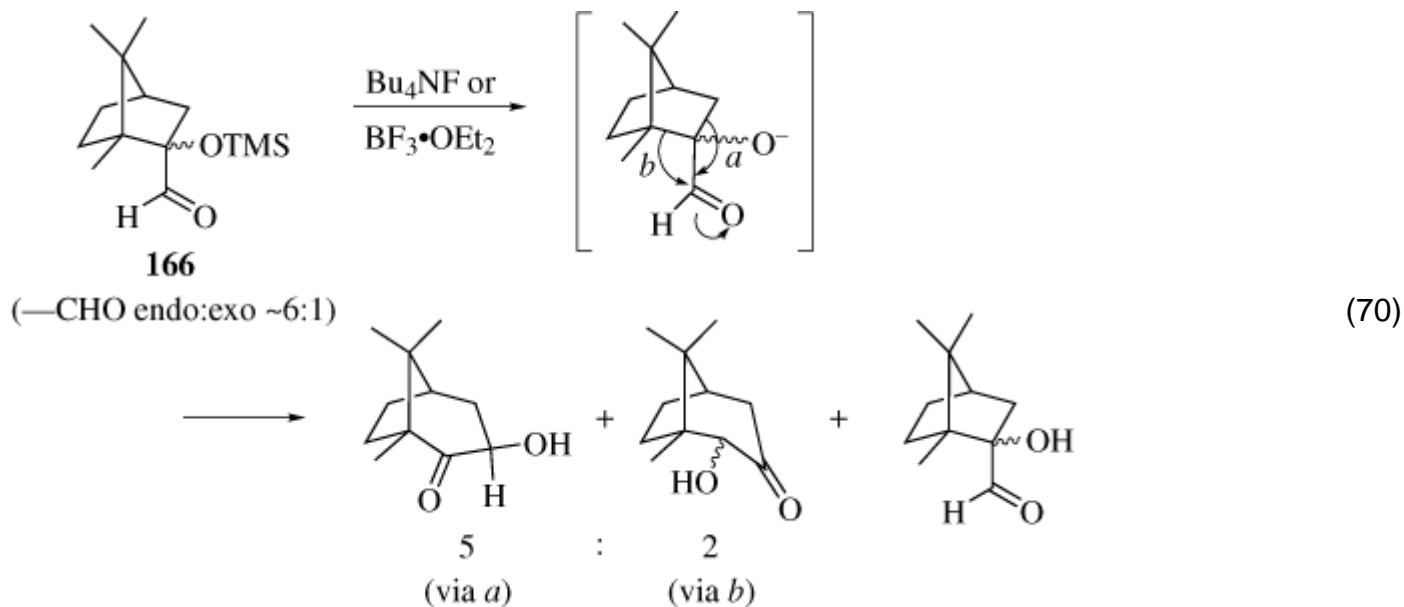


This thermodynamic distinction in a carbocyclic context is highlighted by the ring expansion of α -hydroxy aldehyde **164** to 2-hydroxycycloheptanone **165** in 80% yield (Eq. 69) (119) when compared to the previously discussed ring contraction of α -ketol **71** to exocyclic ketone **72** (Eq. 33). The relative instability of the exocyclic aldehyde resident in compound **164** is presumably at the root of the contrasting thermodynamic preference.



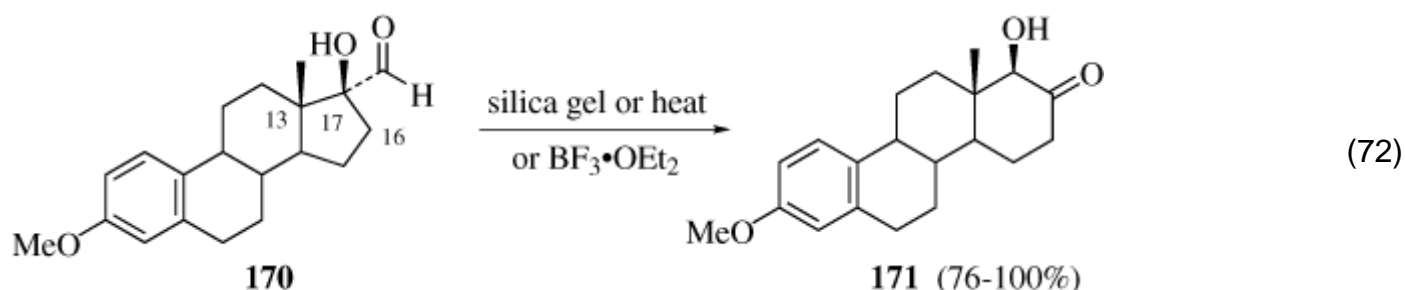
The facile acyloin rearrangement triggered by desilylation of norbornyl aldehyde **166** with either boron trifluoride etherate or tetrabutylammonium fluoride at room temperature leads to the same distribution of three products (Eq. 70). (120) Therefore, neither the presence of a Lewis acid nor

exposure to mildly basic conditions promotes adoption of a dominant stereochemical pathway. The potential for an initial stereodefined rearrangement followed by subsequent equilibration of isomers via an enediol transition structure has been regarded as unlikely due to the mild nature of the reaction conditions. The driving force would seem to derive from relief of ring strain and steric compression. However, a relevant counter-example brings this notion into question (Eq. 71). (121) When the related 2-acetylborneol **167** is vigorously heated in the presence of potassium hydrogen sulfate, the product mixture is composed mainly of the acetylcamphene **169** and is devoid of the possible acyloin products **168**.

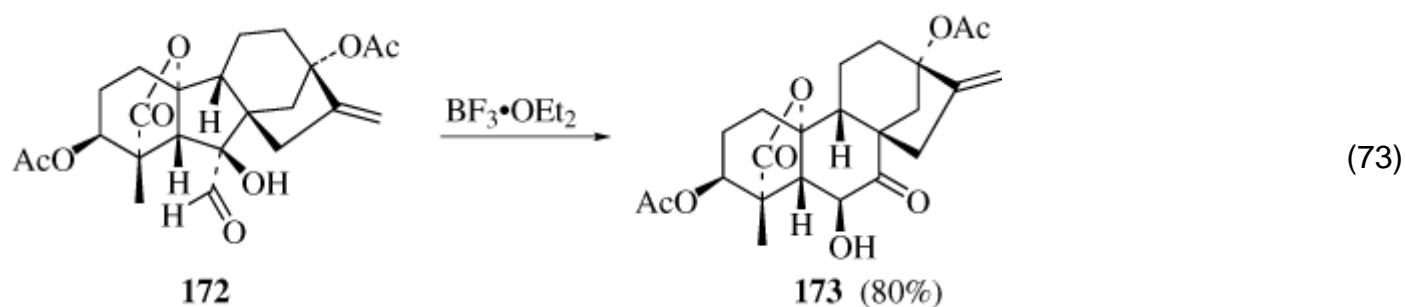


Few examples of the D-homoannulation of 17 β -hydroxy-17 α -formly steroids have been reported in the literature (Eq. 72). (122) Exposure of steroid **170** to silica gel, heat, or a Lewis acid gives the identical D-homoannulated product **171**. The favorable reaction manifold is consistent with a hydrogen bonded or chelated transition structure in which the positive charge developing in the intermediate is preferentially stabilized by migration of the more highly substituted C-13 in preference to the alternative methylene unit (C-16).

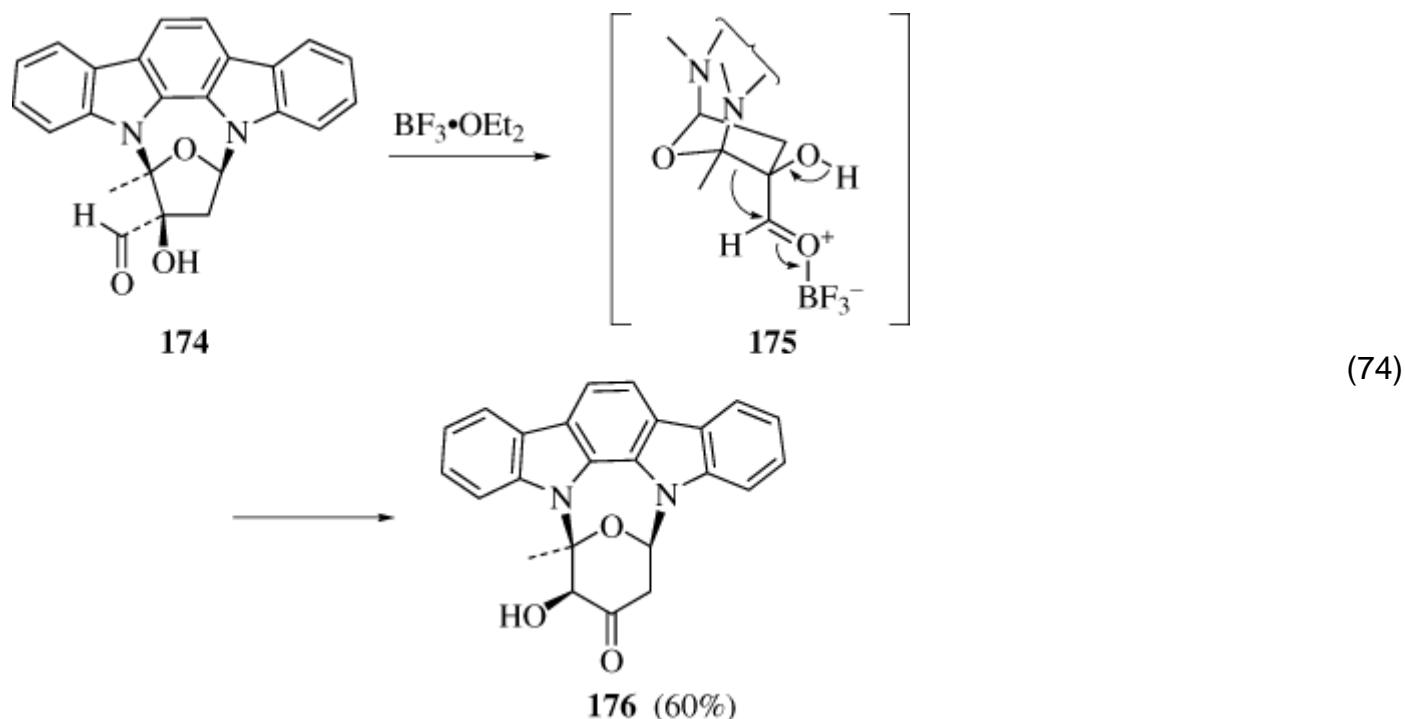
The synthetic utility of α -hydroxy aldehyde rearrangements has recently been exploited in pursuit of more complex target systems. For example, expansion of the gibberellin derivative **172** to the norkaurenoid lactone **173** in the presence of boron trifluoride etherate



proceeds readily and in good yield (80%). Relief of ring strain is implicated as the driving force (Eq. 73). (123)



Another powerful application is incorporated into a total synthesis of (+)-staurosporine and related derivatives. (124-126) Treatment of the highly functionalized furan **174** with boron trifluoride etherate results in stereospecific migration of the more substituted carbon via transition structure **175** to form the ring expanded product **176** (Eq. 74). (124)

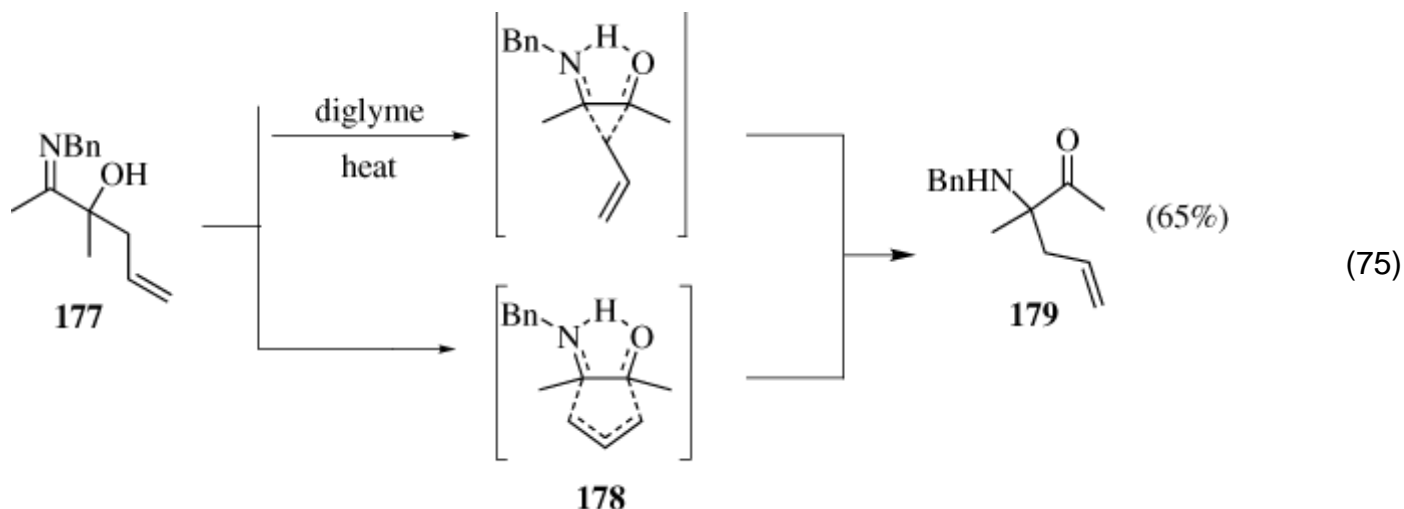


3.7. α -Hydroxy Imines

Although the mechanistic basis of the rearrangements of acyclic hydroxy imines is well founded, their synthetic utility is restricted by the more closely balanced thermodynamic nature of their equilibration to the corresponding amino ketones. (127) The stereospecific thermal conversion of hydroxy imine **28** into a pair of amino ketones (Eq. 12) serves well to support a synchronous

mechanism involving hydroxyl deprotonation by the imine concurrent with carbon skeleton rearrangement. The product composition reflects the ability of either the aryl or methylene substituent to participate in migration. The concerted nature of the mechanism is supported by the propagation of chirality from compound **28** to isomer **29** resulting from a stereospecific migration of the aryl unit. Presumably, migration of the methyl unit also occurs in a stereospecific manner but the achiral nature of the second amino ketone does not allow this behavior to be verified empirically.

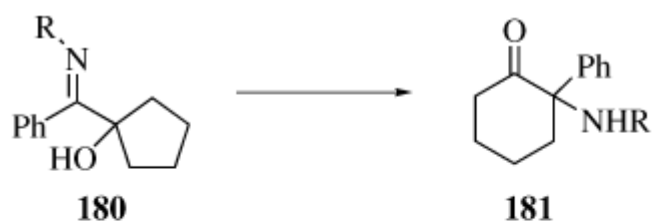
A more utilitarian example of an acyclic α -hydroxy imine rearrangement is illustrated by the conversion of carbinol **177** into ketone **179** (Eq. 75). (127) In this case, a single skeletal rearrangement operates at a synthetically useful level (65%). This example also illustrates the potential for a second rearrangement mechanism to be operative. The participation of allylic substituents in a sigmatropic process, as illustrated in transition state **178**, cannot be ruled out. More complicated examples involving substituted allylic migration components will be addressed below.



Subtleties of the specific system involved often dictate the outcome of a given α -hydroxy imine rearrangement. Factors including ring strain, imine basicity, steric compression in the transition state, the presence or lack of a catalyst, and the thermodynamics inherent in the switch in functionality (from hydroxy imine to amino ketone) have all been implicated. Systematic investigation of these factors has been most thorough in the context of simple monocyclic α -hydroxy imines. (50, 51, 127-133)

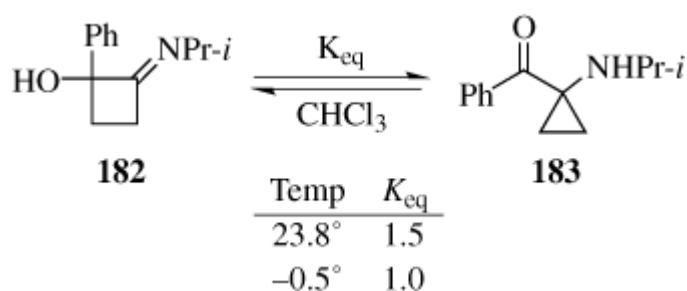
The application of acid catalysis is observed to reduce reaction times and increase product yields by removing the amino ketone from the reaction equilibrium in the form of the corresponding amine salt. The thermal rearrangement of aliphatic imines **180** to amino ketones **181** in the presence or absence of HCl serves to illustrate this feature (Eq. 76). (131)

The interplay of ring strain and other influences is substantially more difficult to define and care must be exercised in making predictive arguments. The facile equilibration of the cyclobutylimine **182** and the cyclopropyl amino ketone **183** is a case in point (Eq. 77). (134, 135) Despite the increase of ring strain in forming cyclopropane **183**, the equilibrium constant for this equilibration at -0.5° is near unity. Therefore, migration of the phenyl substituent offers no thermodynamic advantage to the system and is not observed at these temperatures.



(76)

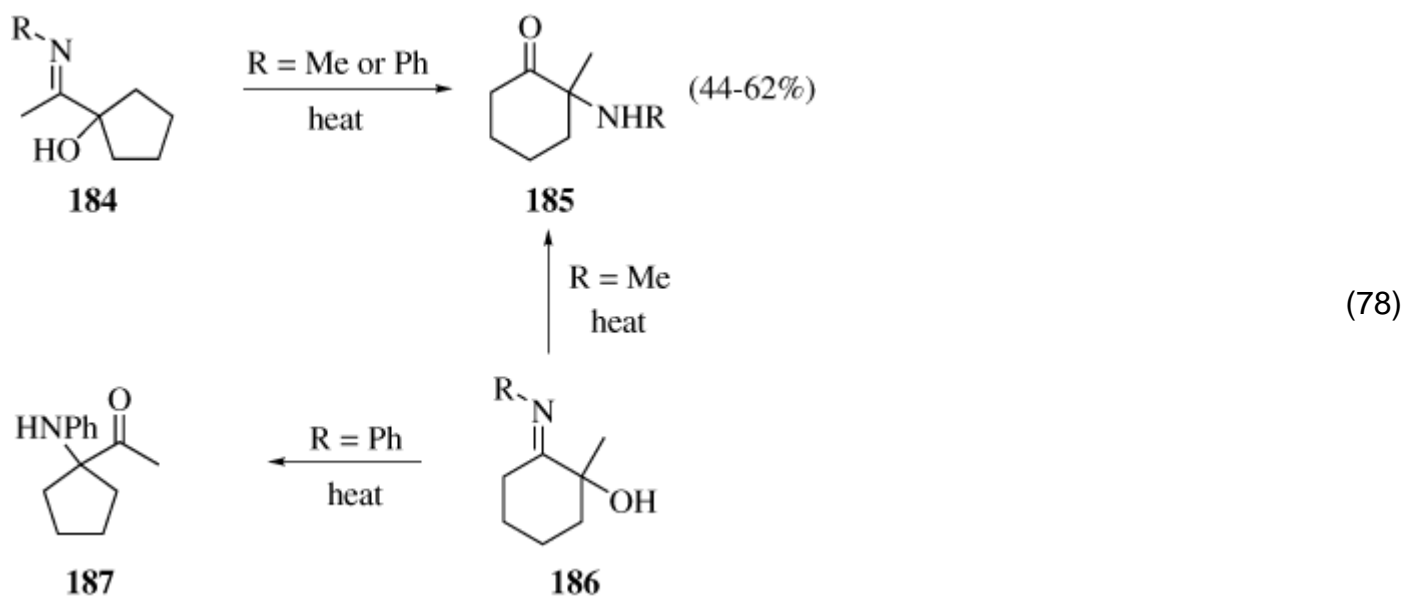
R	Solvent	Catalyst	Temp	Time
Me	<i>o</i> -dichlorobenzene	—	180°	2 h (70%)
Me	<i>o</i> -dichlorobenzene	HCl	180°	0.3 h (95%)
Pr- <i>i</i>	<i>n</i> -decane	—	180°	3 h (75%)
Pr- <i>i</i>	—	HCl	180°	0.1 h (95%)



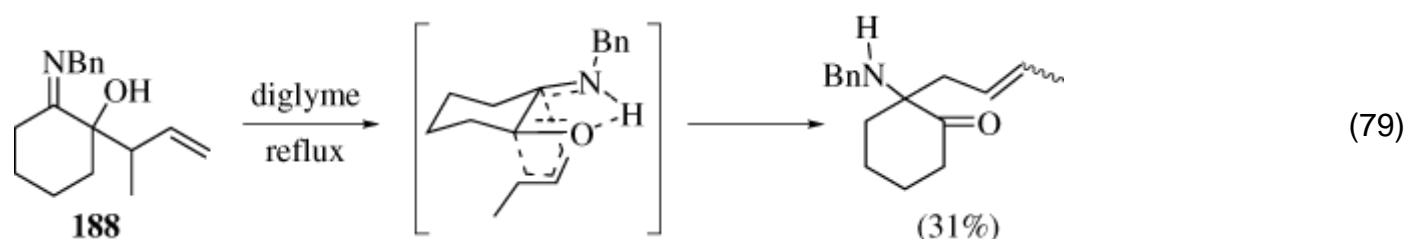
(77)

When compared to a related example in the α -hydroxy ketone series such as the unidirectional transformation of α -keto cyclopropanol **50** to cyclobutanone **51** (Eq. 25), the more balanced thermodynamic nature of α -hydroxy imine rearrangements is made especially apparent.

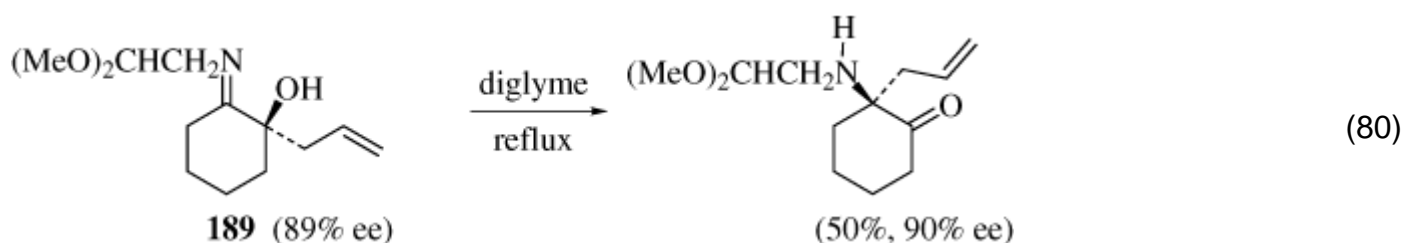
Thermal activation of imino cyclopentanol **184** occurs via the expected manifold to yield the corresponding amino cyclohexanones **185** (Eq. 78). (132) This transformation is likely driven by a combination of ring strain relief and formation of the more stable amino ketones. The influence of the imine substituent is not self-evident here, as a single reaction manifold is available. In contrast, when the six-membered hydroxy imines **186** are involved, two skeletal rearrangements are possible. In the case of the methyl-substituted derivatives, migration of the methyl unit is observed, providing for formation of the more stable amino ketone without ring contraction. However, in the phenyl-substituted case, the energetic penalty of forming the more strained cyclopentane framework is overridden and product **187** is uniquely obtained.



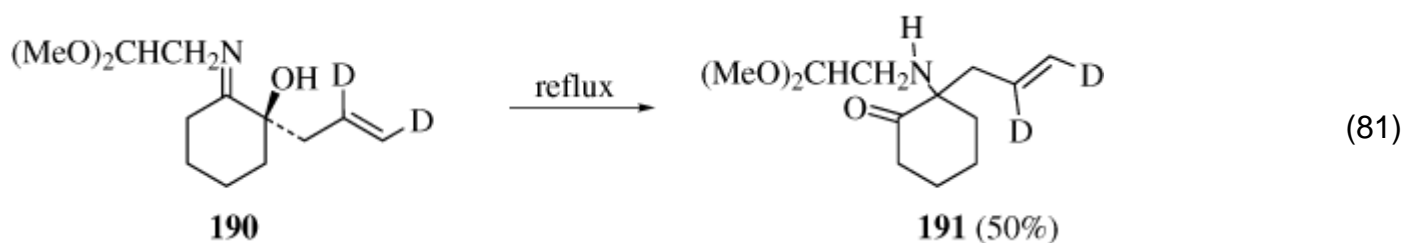
When allylic groups are poised for migration, the potential for a second mechanism via a sigmatropic process exists. An informative example is the complete allylic transposition observed when cyclohexyl imine **188** is heated in diglyme (Eq. 79). (129)



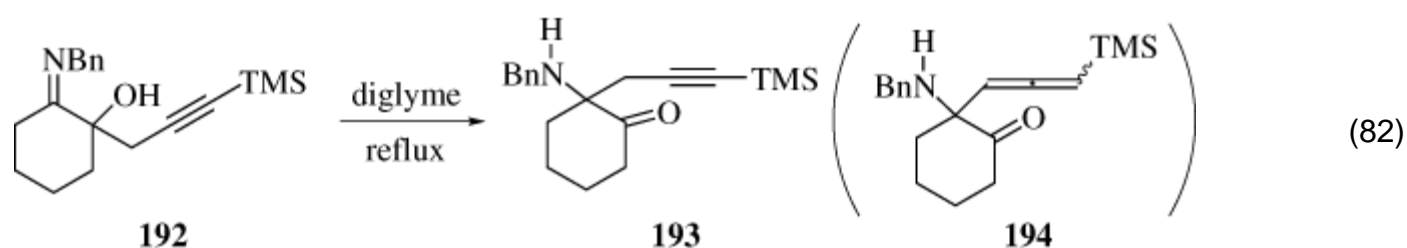
The rearrangement mechanism adopted by systems bearing unfunctionalized allylic groups geminal to the hydroxy functionality cannot be determined by product composition. The mechanisms are complementary and redundant relative to the products obtained and the completeness of the 1,2-chirality transfer process. When an enantio-enriched sample of hydroxy imine **189** is heated in diglyme, the amino ketone product is realized without diminished enantiomeric excess (Eq. 80). (127) Either the alkyl shift mechanism or the sigmatropic mechanism, or both, may be involved here.



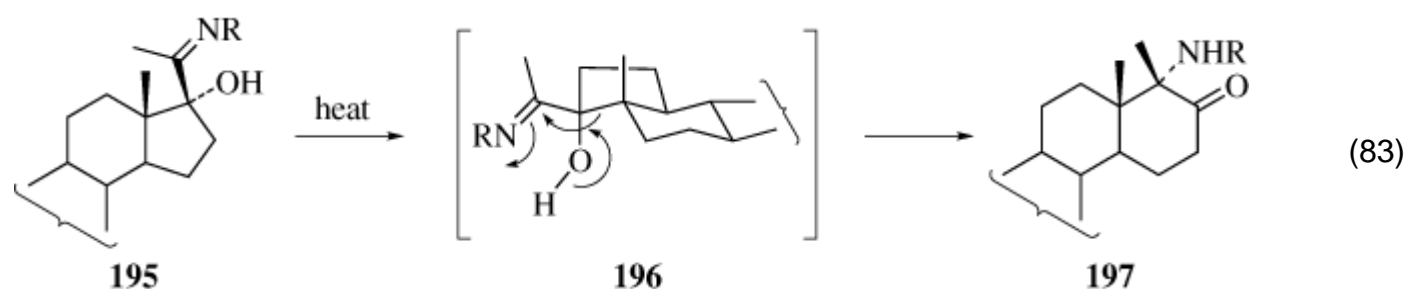
Placement of deuterium labels on the terminal double bond as in compound **190** allows mechanistic insight to be gained. When this α -hydroxy imine is heated in diglyme, the single compound **191** with no evidence of isotopic scrambling is obtained (Eq. 81). (127) In this instance, the alkyl shift mechanism appears to be uniquely operative.



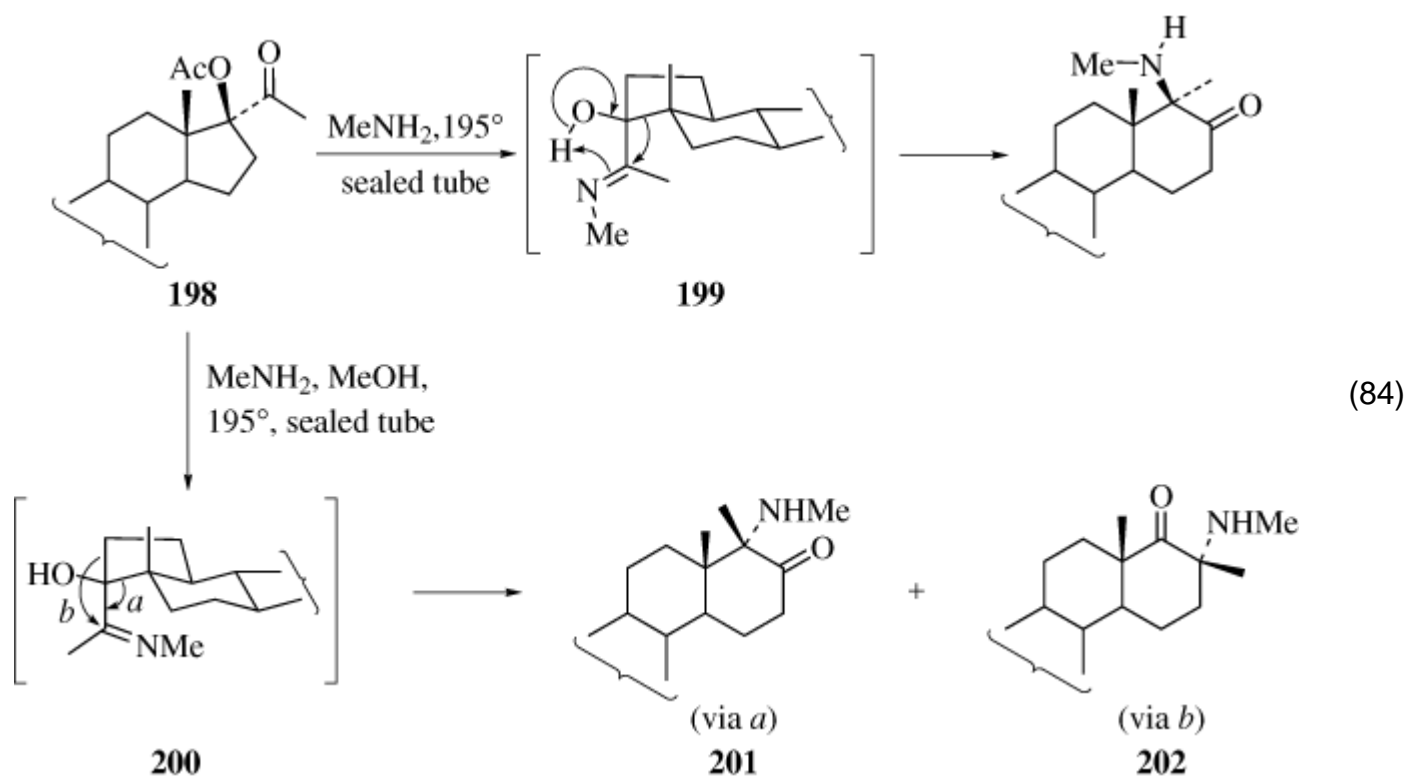
The presence of a propargyl group properly poised for migration likewise opens the possibility for operation of a sigmatropic mechanism. Attempts to perform the α -hydroxy imine rearrangement with precursors bearing unsubstituted propargyl substituents (viz. **192** lacking the TMS group) leads only to decomposition of the starting materials. (**129**) However, once silylated, these substrates undergo smooth conversion into amino ketones. When cyclohexanol **192** is heated in diglyme, cyclohexanone **193** is obtained in 82% yield. The absence of allenic products **194** implies the alkyl shift mechanism to be operative here (Eq. **82**). (**129**)



The α -hydroxy imine rearrangement of stereoisomeric 17-hydroxy-20-imino steroids was investigated in several contexts to broaden understanding of the mechanistic subtleties of the reaction. While many examples support the involvement of an intramolecular cyclic transition state structure, experimentally confirmed anomalies abound. Thus, thermal rearrangement of steroid **195** typically follows the expected reaction course. The *s-cis* geometry is adopted and the most substituted carbon migrates to stabilize the developing positive charge on the imino carbon center in transition state **196**. The D-homoannulation product **197** is formed stereoselectively (Eq. **83**). (**136**, **137**) When R = H or a solvent is employed, the stereoselectivity of the reaction is eroded and diastereomeric mixtures result.



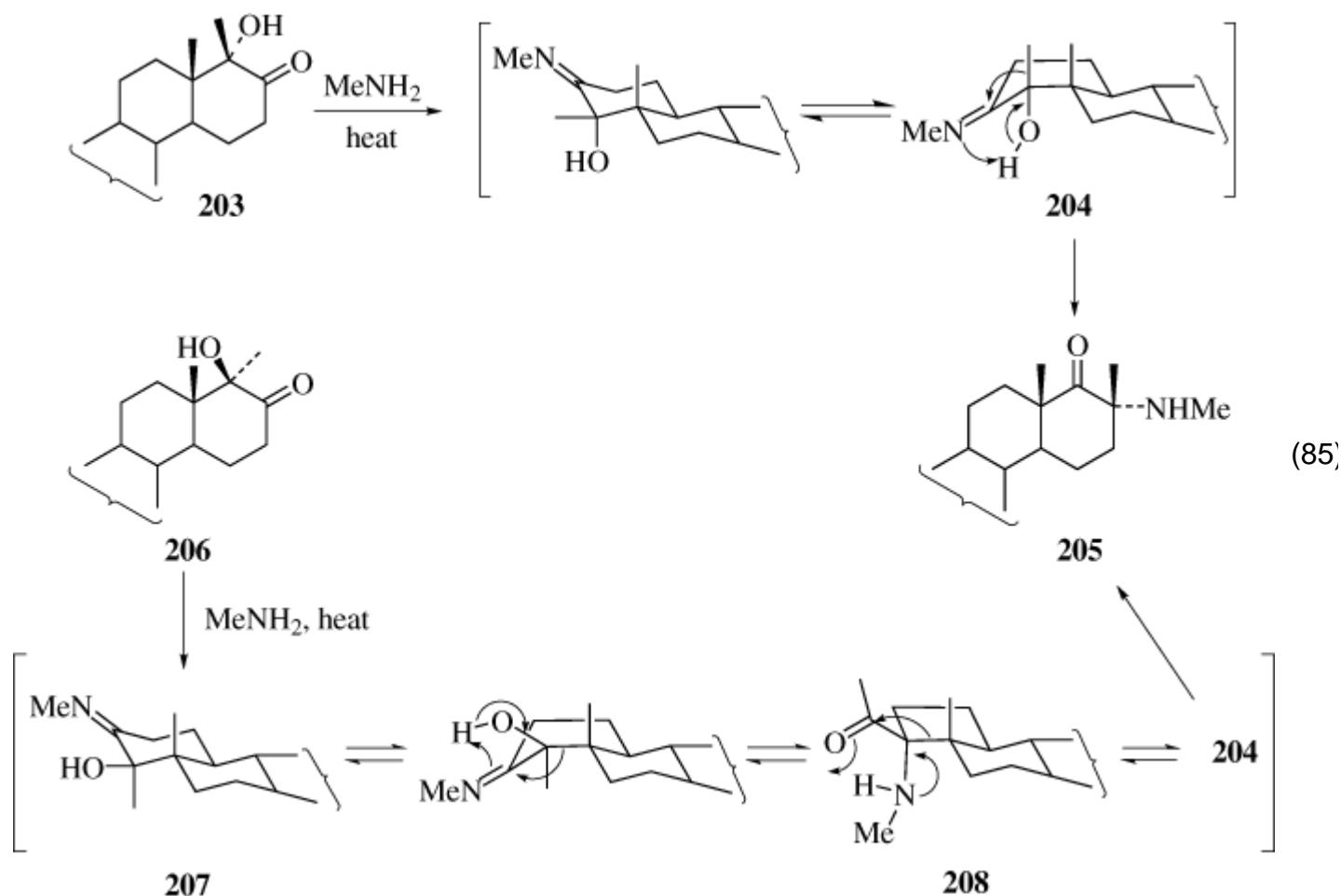
A similar sensitivity to reaction pathway is observed in the 17 β -hydroxy-20-imino series. An illustrative example is the thermal rearrangement of steroid **198** with and without added methanol (Eq. **84**). (**136**) In the absence of methanol, reaction



proceeds stepwise as one might expect: formation of the imine intermediate, subsequent adoption of the *s-cis* reactive conformation **199**, and finally migration of the most electron-rich carbon center. The reaction course is dramatically altered when methanol is present under otherwise identical conditions. In this instance, the preferred transition state geometry appears to be the *s-trans* arrangement **200** and stereoelectronic discrimination between the two possible migrating carbon atoms is notably diminished. Product **202** now dominates the resulting mixture of D-homoannulated products **201** and **202**.

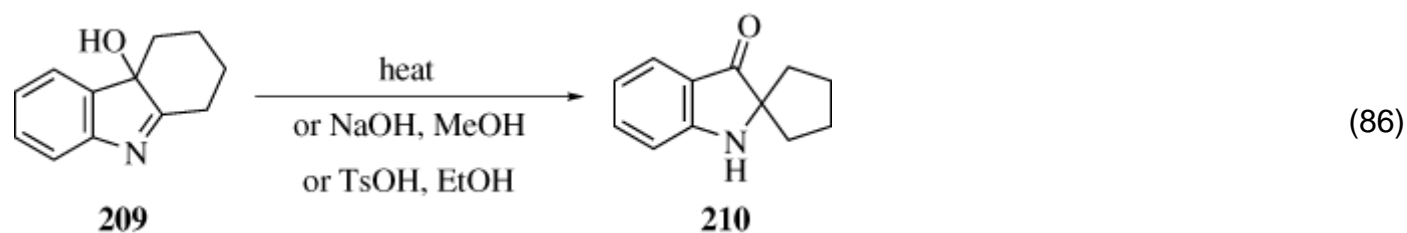
There appears to be no single simple mechanistic accounting of the formation of all the various products from this rearrangement. The researchers responsible for this discovery suggest that the effect of varying the solvent and reagent on product structure may be attributed in part to a change in the rate of imine formation, which in turn, may be caused by a difference in the rate of hydrolysis or aminolysis of the 17β -acetate. (134) Their rationale is that if removal of the 17-acetate occurs only at elevated temperatures, the liberated heat-sensitive α -ketol may rearrange to the D-homo-ketol prior to imine formation. The latter substance could then be transformed into compounds from the isomeric series.

Apparent anomalies also can be found in the rearrangement of D-homoannulated steroids. Heating the epimeric α -hydroxy ketones **203** and **206** with methylamine initiates formation of the single α -amino ketone **205** (Eq. 85). (136) The behavior of **203** appears to follow the predicted course. Thus, adoption of the boat-like transition structure **204** allows access to the reactive *s-cis* conformation. Movement of the α -methyl substituent avoids the introduction of ring strain and steric congestion that



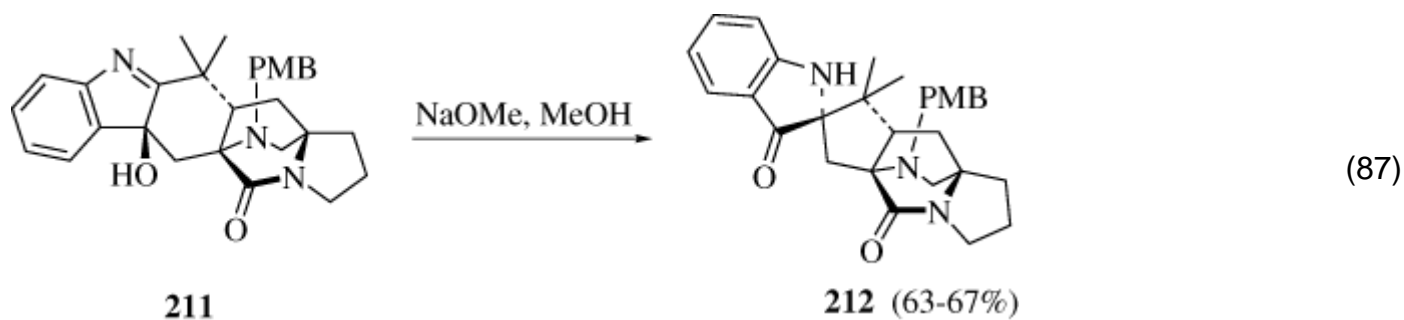
would be incurred should the bridgehead carbon migrate. The product formed by the epimeric α -hydroxy ketone **206** is less easily explained. Its α -hydroxy imine **207** can reside in the *s*-cis conformation where the methyl group is poised for migration (by analogy with transition state **204**). However, the observed formation of α -amino ketone **205** indicates that an alternative mechanism is favored. Other suggestions have been put forward, one of which is detailed in Eq. 85. (135, 136) The thermodynamic impetus favoring the formation of the 17 α -amino-20-keto intermediate **208** is unclear. However, should amino ketone **208** form, equilibration to conformer **204** seems feasible and ultimately would allow formation of the observed product.

Perhaps the most synthetically important variant of the α -hydroxy imine rearrangement is the conversion of hydroxy indolenines to the corresponding spiroindoxyls. The classical conversion, represented by **209** proceeding to **210**, can be realized thermally or via acid or base catalysis (Eq. 86). (138) Kinetic studies indicate that at low acid and base concentrations the reactions are first-order in both the hydroxy indolenine and the acid or base. In the presence of an excess of catalyst, the reaction becomes pseudo first-order in the starting material. Reactions of this type progress to the right by virtue of the stabilized conjugated lactam system resident in the product.

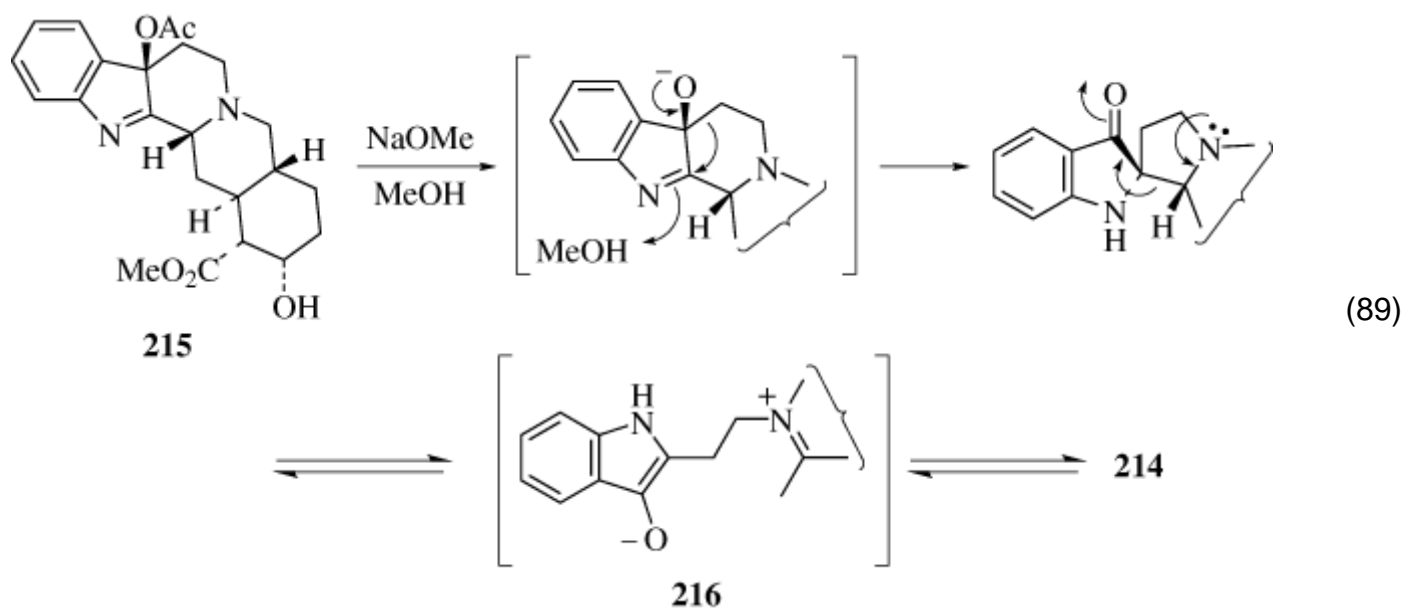
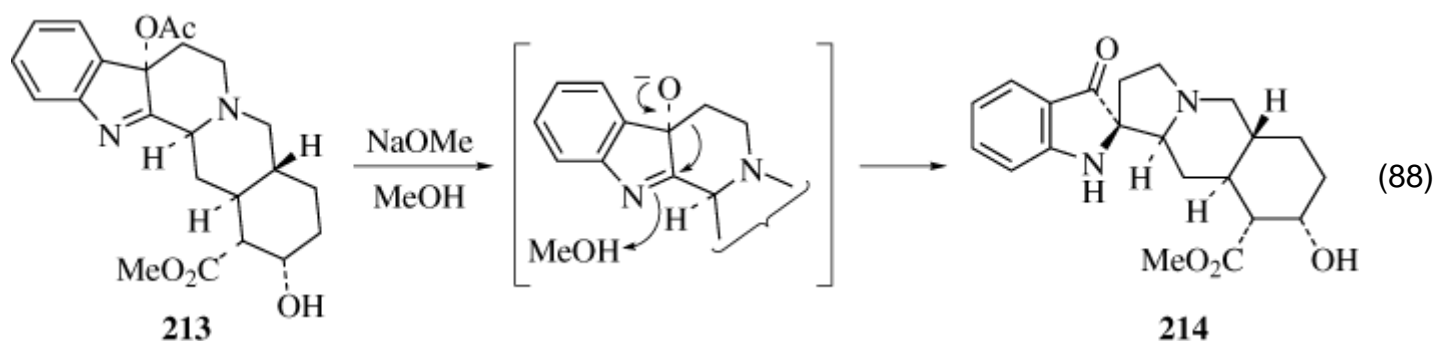


Highly stereospecific α -hydroxy imine rearrangements are also common. The orientation of the hydroxy substituent is seen to direct the configuration of the resulting spiroindoxyl. The

stereospecific conversion of compound **211** into spirane **212**, involved in a synthesis of breviramide A, serves well to illustrate this point (Eq. 87). (139, 140)



An apparent contradiction to the assumed role of the hydroxy functionality as the stereochemical determinant was reported during a study of pseudoindoxyl alkaloids. Exposure of the diastereomeric hydroxy indolenines **213** and **215** to methanolic sodium methoxide leads identically to formation of the single spirolactam **214** (Eqs. 1 and 1). (141) In the case of heterocycle **213**, the hydroxy group appears to be exerting stereochemical influence on the resulting product. In contrast, the explanation advanced for compound **215** focuses instead on the ability of the γ -amino group to participate in formation of the ring-opened enolate-iminium intermediate **216**. Reversible intramolecular cyclization then allows the system to access all four possible diastereomers in reversible fashion. In light of this opportunity to equilibrate to the most stable isomer, **214** dominates the product composition.

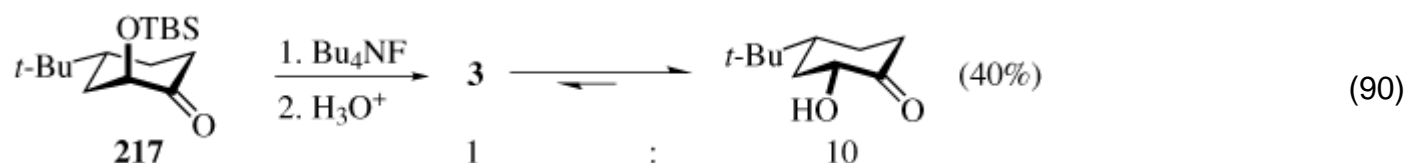


4. Comparison with Other Methods

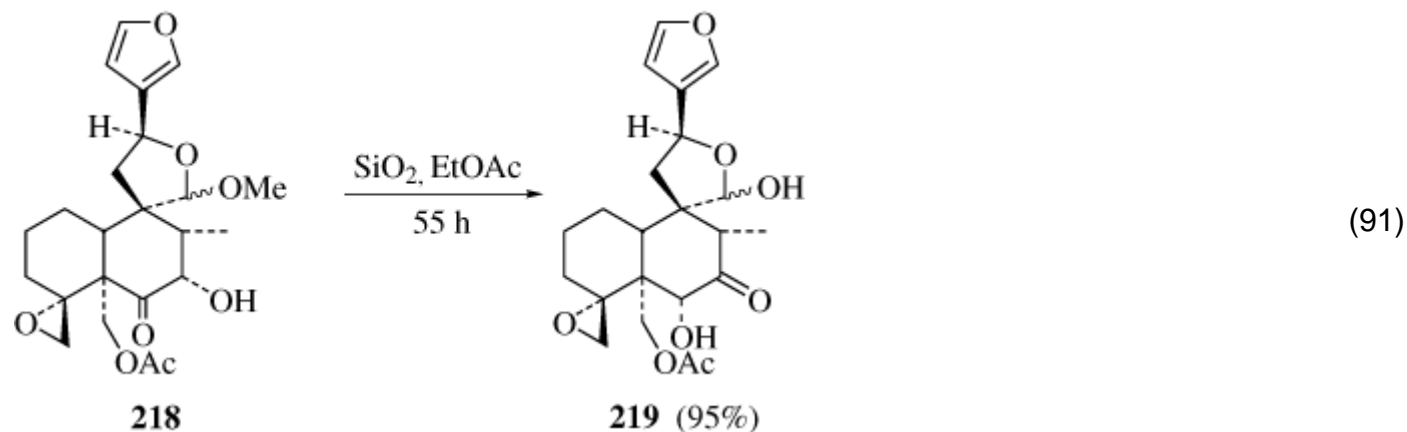
The fascination of organic chemists with rearrangement reactions is one of long standing. Some have been known for many years and have consequently been deployed in many synthetic undertakings. The processes that compare most directly with the subject of this review are those isomerizations that proceed via tautomerization. Alternative methods for obtaining α -hydroxy aldehydes and ketones are presented subsequently.

4.1. Tautomerization Of Secondary α -Ketols

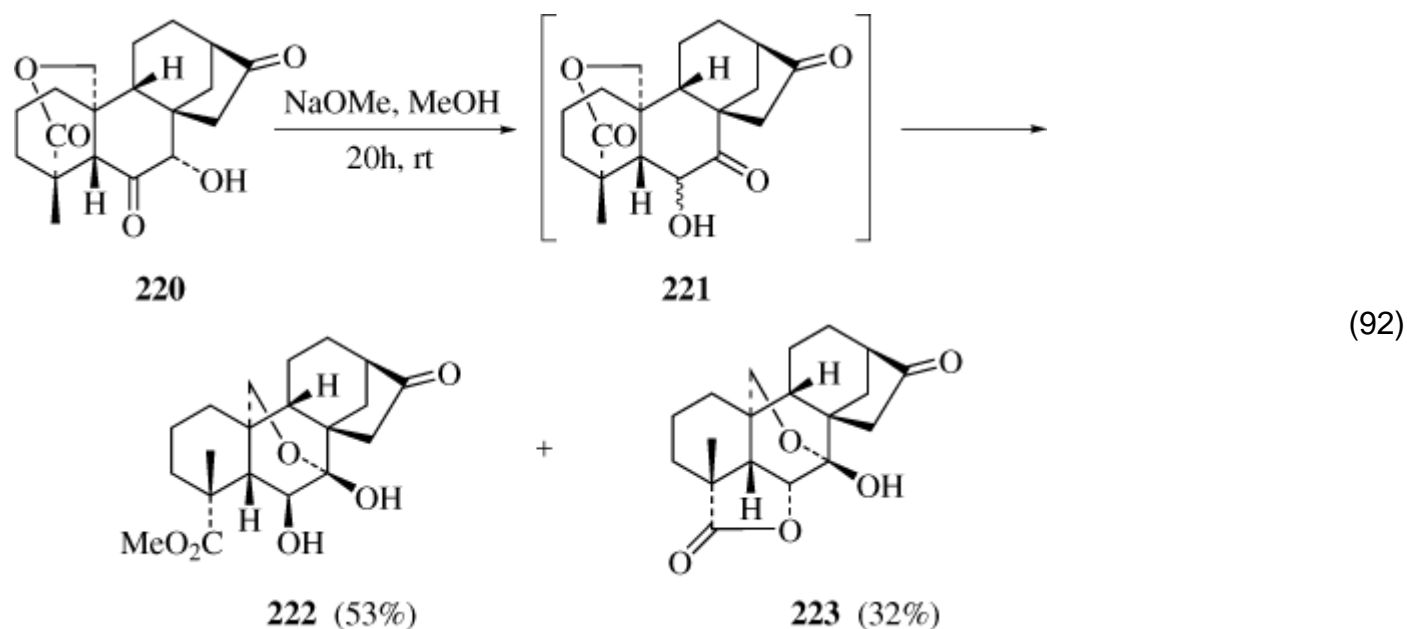
The exposure of secondary α -hydroxy ketones or protected forms thereof to acidic or basic conditions is widely recognized to set the stage for possible thermodynamically-driven repositioning of the functional groups. The fluoride ion induced desilylation of cyclohexanone **217** and subsequent protonation leads via **3** (Eq. 2) chiefly to its epimer (Eq. 90). (20)



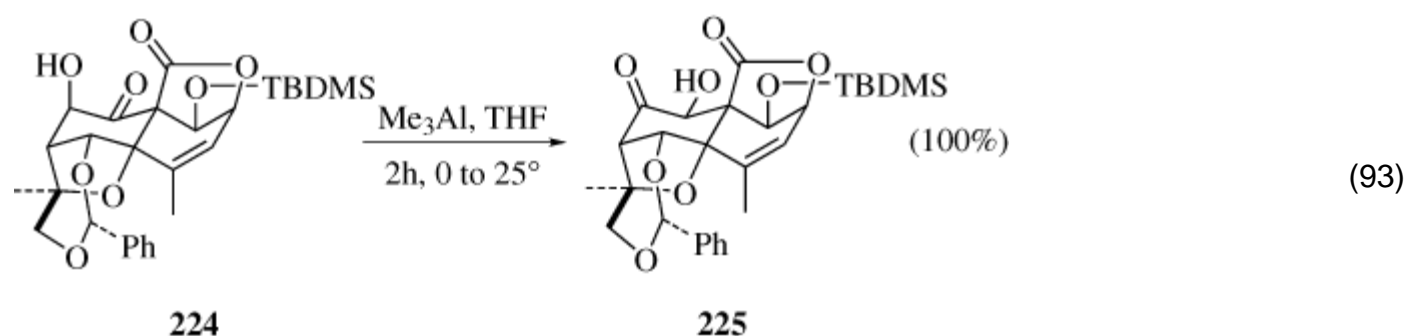
During a study of the reactivity of several naturally occurring neoclerodane diterpenoids, researchers recognized that an α -ketol rearrangement could be induced when α -ketol **218** is simply stirred with silica gel in ethyl acetate solution at 20° (Eq. 91). (142) In the more stable regioisomers **219**, interactions with the methyl group flanking the carbonyl are minimized relative to those in reactant **218**.



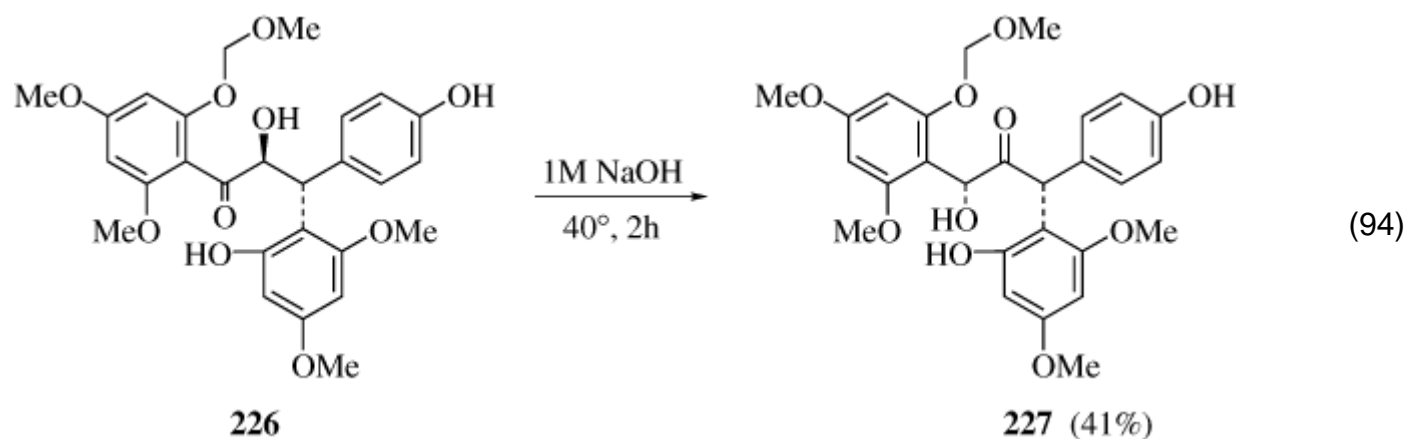
The B-ring expanded gibberellane **220** isomerizes under base catalysis initially to **221**, which then continues on to **222** and **223** (Eq. 92). (48) Evidently, lactone **223** is favored thermodynamically, since it accumulates almost exclusively when a large excess of sodium methoxide is used and remains unchanged when subjected to the reaction conditions.



In connection with a multi-step synthesis of racemic enonyminol, α -ketol **224** was quantitatively transposed to isomer **225** with trimethylaluminum (Eq. 93). (143) This rearrangement disposes the C-9 hydroxy group equatorially, which the investigators required in their route to the target molecule.

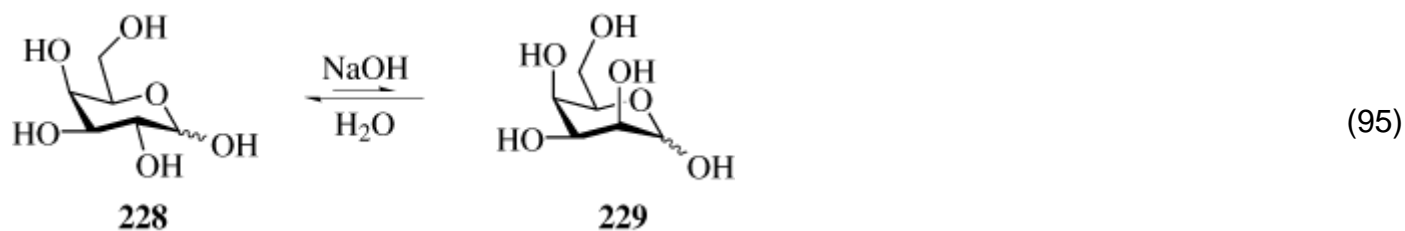


In line with the Favorsky rule mentioned earlier, 3,3-diaryl-2-hydroxypropiophenones typified by **226** are amenable to base-catalyzed α -ketol rearrangement (Eq. 94). (9) The resulting isomeric 1-hydroxy-2-propanones **227** serve as useful intermediates for elaboration of 4-arylflavan-3-ones.

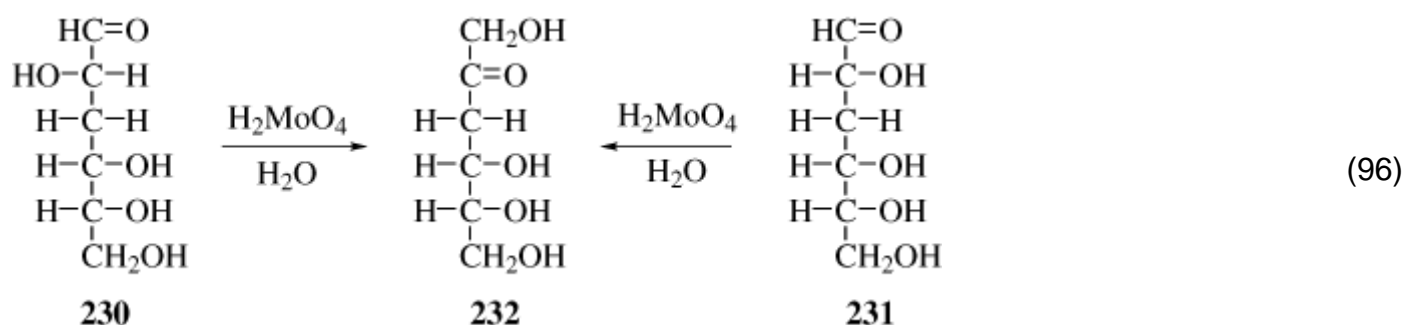


4.2. Rearrangements Involving Carbohydrates

Many reducing sugars are subject to transient conversion into enediols and ready equilibration with isomeric compounds. The first of these rearrangements to be recognized is the venerable Lobry de Bruyn-Albert A van Ekenstein transformation. (22) In actuality, two reactions are included here: epimerization and aldose-ketose interconversion. Sodium and calcium hydroxide are the basic reagents usually utilized, and the interconversion of D-galactose (228) with D-talose (229) is exemplary (Eq. 95). The valuable product 229 is the minor component of this equilibrium because of the thermodynamically destabilizing pair of syn-axial hydroxy groups residing therein. (144)

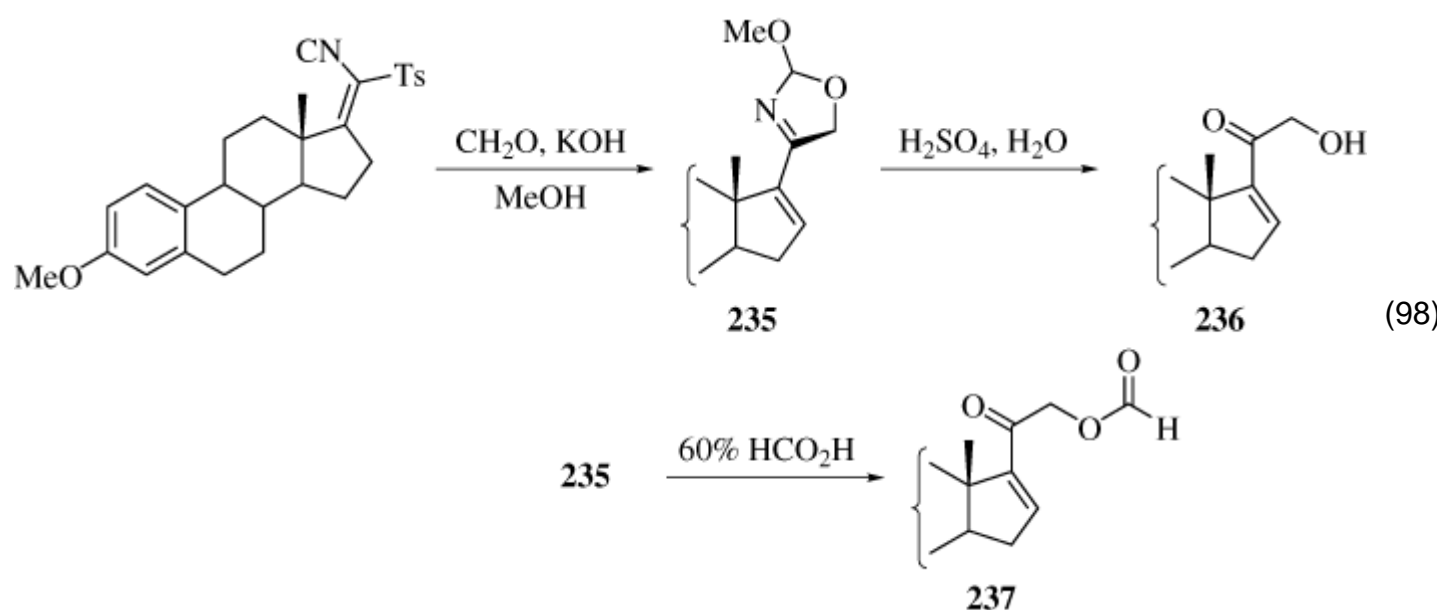
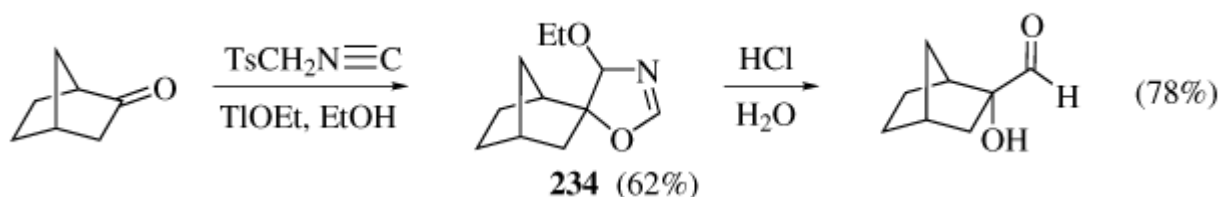
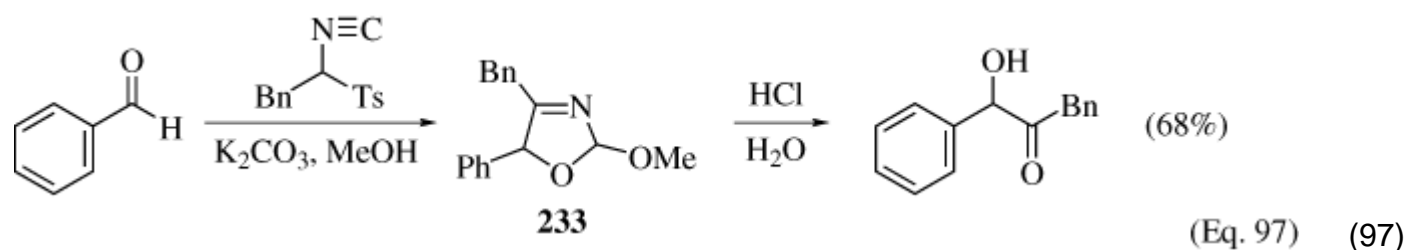


The Bilik reaction consists of the molybdic acid catalyzed interconversion of epimerizable aldoses not shorter than a tetrose. (25) Although complex mixtures are often generated, certain processes such as the irreversible conversion of 3-deoxy-D-arabino-hexose 230 and 3-deoxy-D-erythro-hex-2-ulose 231 into 3-deoxy-D-erythro-hex-2-ulose 232 enjoy synthetic utility (Eq. 96).



4.3. Chain Extension via the Use of Tosyl Isocyanides

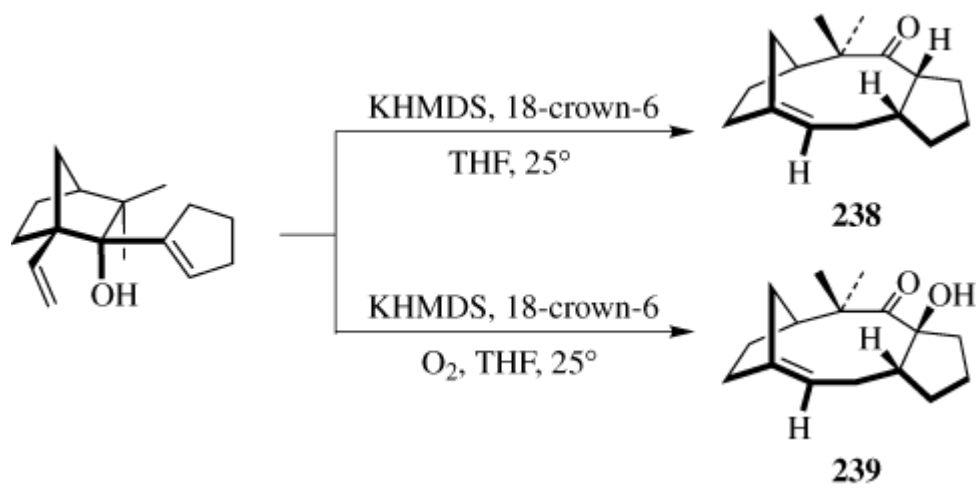
The acidic nature of tosyl isocyanides allows them to be deprotonated under mild basic conditions. In the presence of an aldehyde or ketone, 1,2-addition to the carbonyl group occurs and is followed by intramolecular cyclization to generate an oxazoline. Allylic displacement by solvent ensues. Acid hydrolysis of oxazolines 233 and 234 leads subsequently to formation of an α -hydroxy aldehyde and ketone, respectively (Eq. 97). (145, 146) The most widely used application of this chemistry has focused on introduction of the 17-hydroxyacetyl side chain found in certain corticoid steroids. (147, 148) In this instance, use is made of formaldehyde as the one-carbon homologating agent (Eq. 98). Hydrolysis of oxazoline 235 in aqueous sulfuric acid furnishes α -ketol 236, while partial hydrolysis with 60% formic acid gives keto formate 237, thereby allowing for dihydroxylation of the C16-C17 double bond with potassium permanganate.



4.4. α -Hydroxylation of Enolates, Silyl Enol Ethers, and Silyl Ketene Acetals

The long-standing importance of α -hydroxy carbonyl compounds in synthesis can be gauged by the variety of oxidizing agents that have been developed for the convenient oxidation of enolates and derivatives. A detailed review of this subject is about to become available (149) and should be consulted. The available reagents range from the simple achiral [$^3\text{O}_2$, $^1\text{O}_2$, H_2O_2 , $(\text{Me}_3\text{SiO})_2$, dimethyldioxirane and peracids] to somewhat more exotic counterparts (iodosobenzene and analogs, *N*-sulfonyl oxaziridines, etc). Non-racemic equivalents typified by sugar-derived dioxiranes (149-152) and terpene-derived sulfonylaziridines (149) have been accorded increased attention.

In the lone example given here (Eq. 99), the enolate anion generated by anionic oxy-Cope rearrangement, which is rendered "naked" and highly reactive by virtue of the presence of 18-crown-6 to sequester the potassium ion, is transformed very rapidly into **239** and not **238** if exposed to oxygen. (153)



(99)

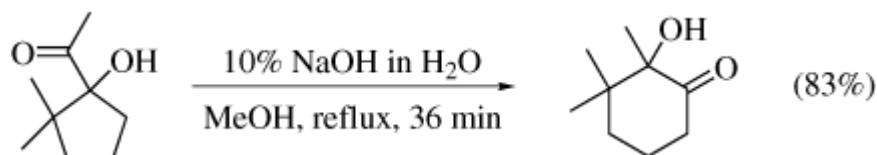
5. Experimental Conditions

The most common experimental procedures for the rearrangement of α -ketols involve simple heating or exposure to a base or an acid. Early studies were carried out with inorganic salts (NiCl₂, PbO, FeCl₃, etc.), but these have largely fallen out of favor. The isomerizations are often sluggish at room temperature and usually require heating in order to proceed at a reasonable rate. The decision to involve a basic or an acidic promoter must be deliberate. All bases do not function similarly. Many examples are known where exposure to hydroxide or methoxide is inadequate. Often, aluminum alkoxides work well. Under these circumstances, however, one needs to be aware that coordination to the aluminum atom is capable of operating, with associated stereoelectronic consequences. The same is true when recourse is made to Lewis acids such as boron trifluoride etherate. When the rearrangement is conducted thermally, intramolecular hydrogen bonding can lead to a conformation-specific enhancement of reactivity. In difficult cases, one's exploration of potentially useful catalysts should not cease prematurely.

As concerns α -hydroxy aldehydes, rearrangement conditions may include treatment with a Lewis acid, a base, or heating. In recent examples involving structurally complex substrates, boron trifluoride etherate has seen considerable synthetic utility. (48, 123-126)

With regard to conditions for the rearrangement of α -hydroxy imines, a similar range of reagents has been effectively employed. Current synthetic applications exist in which thermal rearrangement and exposure to acid or base have found similar synthetic utility for a given substrate. (154, 155) The α -amino ketone products are often isolated in the form of a corresponding acid salt (*i.e.* HCl or HBr).

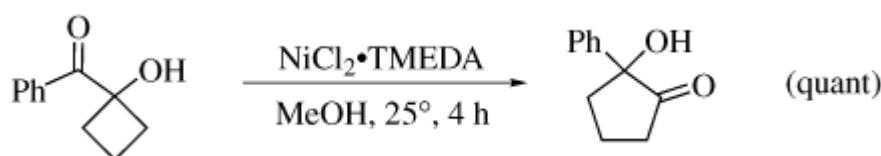
6. Experimental Procedures



6.1.1. 2-Hydroxy-2,3,3-trimethylcyclohexanone (Ring Expansion Promoted by Aqueous Sodium Hydroxide in Methanol) (26)

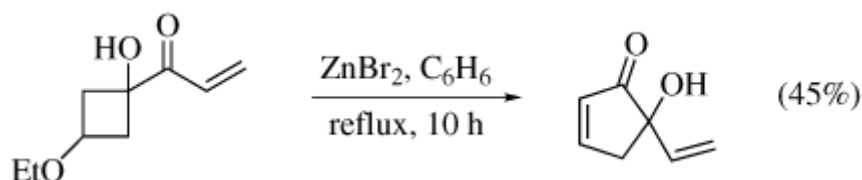
1-Acetyl-2,2-dimethylcyclopentanol (20 mg) in MeOH (2.5 mL) and aqueous 10% KOH (0.5 mL) was heated at the reflux temperature for 36 minutes. Following the addition of water, the product was extracted into CHCl₃ and dried. Solvent evaporation left the isomeric ketol (16.6 mg, 83%) admixed with starting material (3.4 mg, 17%).

The major product exhibited three methyl singlets in the ¹H NMR spectrum (CDCl₃) at δ 1.40, 1.21, and 1.14. Its semicarbazone formed prisms from ethanol, mp 202–204°. Anal. Calcd for C₁₀H₁₉N₃O₂: C, 56.3; H, 9.0; N, 19.7. Found: C, 56.3; H, 9.0; N, 19.8.



6.1.2. 2-Hydroxy-2-phenylcyclopentanone (Ring Expansion Induced by the Nickel Chloride-TMEDA Complex) (37)

A solution of the catalytically active species was prepared by heating nickel(II) chloride (6.5 mg, 0.05 mmol) with TMEDA (0.1 mmol) in anhydrous MeOH (40 mL) at reflux under N₂ for 24 hours. The solution was cooled to 25°, 1-benzoylcyclobutanol (440 mg, 2.5 mmol) was introduced, and stirring was maintained at 25° for 4 hours prior to solvent evaporation and bulb-to-bulb distillation (bp 110° at 0.1 Torr). The product was obtained as a colorless oil in quantitative yield. ¹H NMR (CDCl₃) δ 7.37–7.32 (m, 5H), 3.33 (s, 1H), 2.50–2.35 (m, 3H), 2.26–2.13 (m, 1H), 2.11–1.95 (m, 1H), 1.90–1.70 (m, 1H).

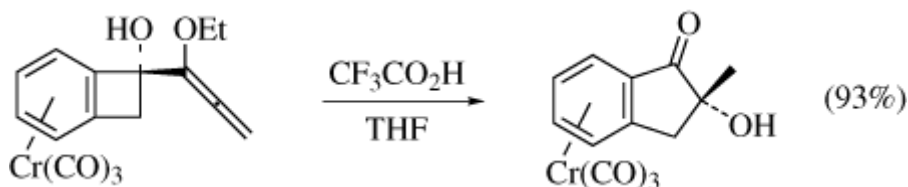


6.1.3. 5-Ethenyl-5-hydroxy-2-cyclopenten-1-one (Zinc Bromide as Catalyst with Concurrent β-Elimination) (31)

Under N₂, a 0.2 M solution of 3-ethoxy-1-(1-oxo-2-propenyl)cyclobutan-1-ol (504 mg, 2.96 mmol) in dry CH₂Cl₂ was added via syringe to 1.9 molar equivalents of anhydrous zinc bromide in a dry round-bottomed flask equipped with a magnetic stirrer. The mixture was stirred at room temperature for 2 hours and heated at gentle reflux for 10 hours. During this time, the mixture became very dark. The progress of reaction was monitored by GLC, and upon consumption of starting material, Et₂O

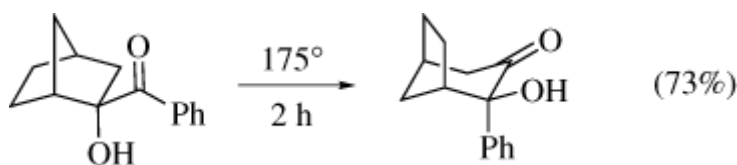
(10 mL/mmol) was added. The organic portion was washed once with an equal volume of 1 N HCl and with saturated NaHCO₃ solution, dried (MgSO₄), filtered, and freed of solvent.

Chromatography of the residue on silica gel (elution with 25% ethyl acetate in hexanes) gave the product as a yellow oil (45%). IR (CH₂Cl₂) 3560, 3450, 3000–2900, 1720, 1595, 1360, 1120 cm⁻¹; ¹H NMR (CDCl₃) δ 7.78 (m, 1H), 6.22 (m, 1H), 5.80 (dd, *J* = 17.2, 10.6 Hz, 1H), 5.40 (d, *J* = 17.2 Hz, 1H), 5.23 (d, *J* = 10.6 Hz, 1H), 2.95 (s, 1H), 2.90 (s, 2H); ¹³C NMR (CDCl₃) δ 207.8, 161.9, 137.1, 130.4, 114.2, 77.3, 42.6. Anal. Calcd for C₇H₈O₂: C, 67.73; H, 6.50. Found: C, 67.62; H, 6.52.



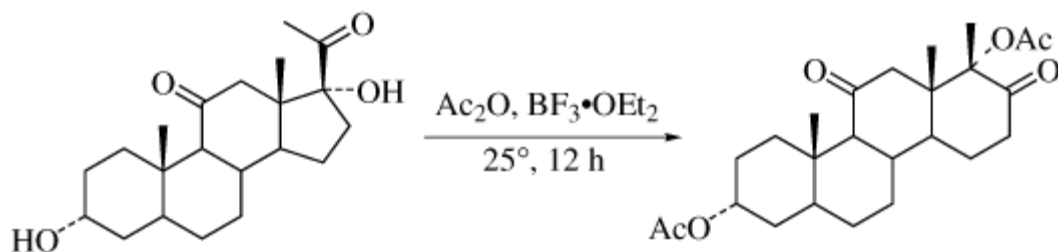
6.1.4. Tricarbonyl (η^6 -2-endo-hydroxy-2-exo-methyl-1-oxobenzocyclopentene) chromium(0) (Hydrolysis/Rearrangement in the Presence of Trifluoroacetic Acid) (28)

Trifluoroacetic acid (250 μ L, 3.27 mmol) was added dropwise to a solution of tricarbonyl [η^6 -1-exo-(1-ethoxyethenyl)-1-endo-hydroxybenzocyclobutene]chromium(0) (175 mg, 0.54 mmol) in 5 mL of THF and 5 mL of water. The color slowly changed from yellow to red. After 3 hours, 20 mL of Et₂O and 20 mL of water were introduced. The organic phase was washed with water, dried, and evaporated. The residue was chromatographed on silica gel (elution with 50% Et₂O in petroleum ether) to provide 149 mg (93%) of product as an orange solid, mp 179°. IR (KBr) 3428, 1972, 1900, 1708, 1524, 1432, 656, 616 cm⁻¹; ¹H NMR (acetone-*d*₆) δ 6.07 (dd, *J* = 6.3, 0.9 Hz, 1H), 6.05 (ddd, *J* = 6.3, 6.3, 0.9 Hz, 1H), 5.79 (dd, *J* = 6.3, 0.9 Hz, 1H), 5.52 (ddd, *J* = 6.3, 6.3, 0.9 Hz, 1H), 4.85 (s, 1H), 3.26 (d, *J* = 17.1 Hz, 1H), 3.10 (d, *J* = 17.1 Hz, 1H), 1.40 (s, 3H); ¹³C NMR (acetone-*d*₆) δ 230.9, 204.4, 120.7, 97.1, 94.0, 90.0, 89.5, 88.3, 74.8, 41.3, 24.1; MS *m/z*: calcd for C₁₃H₁₀CrO₅, 297.9933; found, 297.9927. Anal. Calcd for C₁₃H₁₀CrO₅: C, 52.36; H, 3.38. Found: C, 52.45; H, 3.46.



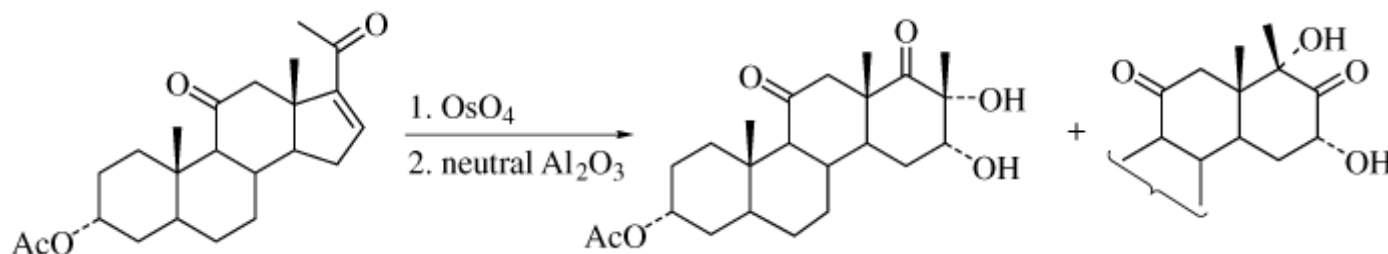
6.1.5. endo-2-Hydroxy-exo-2-phenyl-3-bicyclo[3.2.1]octanone (Thermal Rearrangement) (34)

A 3.02 g (0.014 mmol) sample of *exo*-2-benzoyl-*endo*-2-hydroxy-bicyclo[2.2.1]heptane was heated neat at 175° under an atmosphere of N₂. The rearrangement was followed by IR and found to be complete after 2 hours. The product was recrystallized from hexane to give 2.20 g (73%) of white crystals, mp 58–59°. IR (CCl₄) 3475, 1712 cm⁻¹. Anal. Calcd for C₁₄H₁₆O₂: C, 77.78; H, 7.41. Found: C, 77.63; H, 7.47.



6.1.6. 3 α ,17 α -Diacetoxy-17 β -methyl-D-homoetiocholane-11,17a-dione (Lewis Acid Catalyzed Rearrangement with Acetylation) (100)

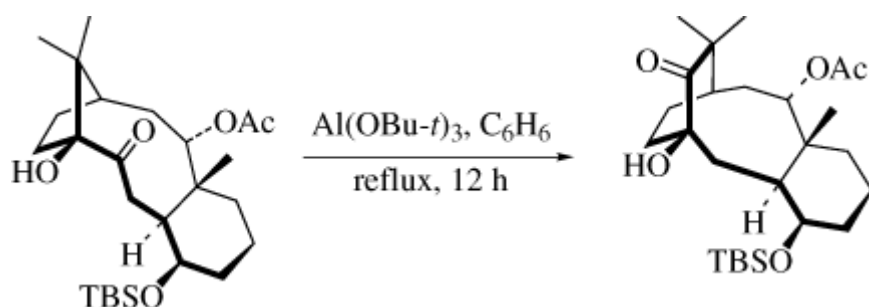
A solution of 3 α ,17 α -dihydroxypregnane-11,20-dione (1.0 g) in CH₃CO₂H (35 mL) containing 2 mL of acetic anhydride and 2 mL of boron trifluoride etherate was allowed to stand overnight at 25°. Addition of water precipitated 1.15 g of white solid, mp 105–145°. Trituration with Et₂O followed by recrystallization from aqueous MeOH gave 0.38 g of the known product, mp 169–171°. Anal. Calcd for C₂₅H₃₆O₆: C, 69.42; H, 8.39. Found: C, 69.62; H, 8.54.



6.1.7. 3 α -Acetoxy-16 α ,17 α -dihydroxy-17 β -methyl-5 β -D-homoandrostane-11,17a-dione and 3 α -Acetoxy-16 α ,17 α -dihydroxy-17a β -methyl-5 β -D-homoandrostane-11,17-dione (Rearrangement on Neutral Alumina) (103)

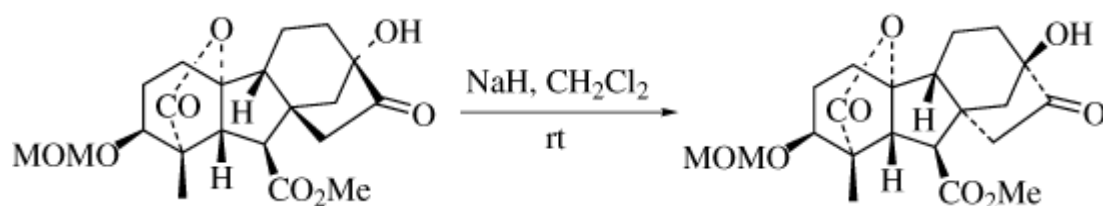
A solution of 20 g of the unsaturated ketone was treated with 19 g of osmium tetroxide in 250 mL of dioxane and allowed to stand for 3 days. At the conclusion of this time, the black osmate ester was decomposed with a stream of hydrogen sulfide in the cold. The precipitate was filtered and the filtrate concentrated at low temperature in vacuo to give 20–22 g of product, which was chromatographed on 600 g of neutral alumina. Fractions eluted with 5% Et₂O in C₆H₆ through 50% Et₂O in C₆H₆ provided 10.6 g (80%) of the 11,17a-dione as dimorphic crystals after crystallization from MeOH-hexane or from Et₂O, mp 172–175° and 196–198°. Both forms exhibited identical infrared spectra. Anal. Calcd for C₂₃H₃₄O₆: C, 67.98; H, 8.37. Found: C, 68.22; H, 8.37.

The fractions from the original chromatography eluted with Et₂O gave 2.8 g (20%) of the 11,17-dione as needles after crystallization from ether, mp 203–205°. Anal. Calcd for C₂₃H₃₄O₆: C, 67.98; H, 8.37. Found: C, 67.84; H, 8.57.



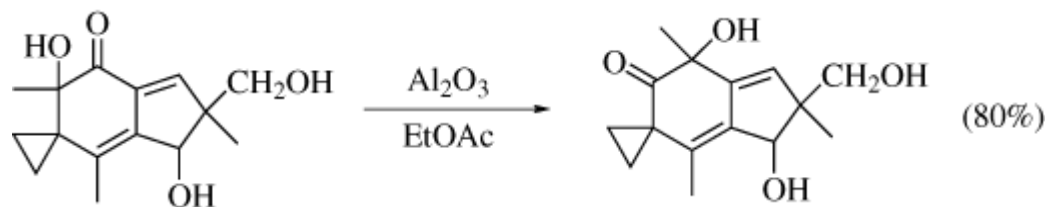
6.1.8. (4R,4aS,6R,9R,11S,11aR)-4-[(*tert*-Butyl)dimethylsiloxy]perhydro-6-hydroxy-8,8,11a-trime: Acetate (Catalysis by Aluminum tri-*tert*-Butoxide) (6)

A solution of the bridged α -ketol (18.3 mg, 3.92×10^{-5} mol) and aluminum tri-*tert*-butoxide (29 mg, 1.18×10^{-4} mol) in dry C₆H₆ was heated at reflux under N₂ for 12 hours while being magnetically stirred. The cooled reaction mixture was diluted with water and EtOAc, and the separated organic phase was washed with 1 M HCl, water, and brine. After drying and solvent evaporation, the residue was chromatographed on silica gel (elution with 12% EtOAc in petroleum ether) to give 17 mg (93%) of product as a colorless solid, mp 164–166°; $[\alpha]_D^{25} -14.1^\circ$ (c 2.7, CHCl₃); IR (CHCl₃) 3540, 1730, 1700, 1250 cm⁻¹; ¹H NMR (C₆D₆) δ 4.92 (d, *J* = 9.6 Hz, 1H), 3.84 (d, *J* = 2.8 Hz, 1H), 3.62 (s, 1H), 2.38 (dd, *J* = 15.4, 7.1 Hz, 1H), 2.16–1.67 (series of m, 10H), 1.65 (s, 3H), 1.53 (m, 2H), 1.35 (s, 3H), 1.36–0.93 (series of m, 3H), 1.15 (s, 3H), 1.06 (s, 3H), 0.94 (s, 9H), 0.08 (s, 3H), 0.02 (s, 3H); ¹³C NMR (C₆D₆) δ 220.6, 168.6, 76.5, 76.2, 76.1, 46.8, 45.6, 40.7, 40.4, 39.9, 37.3, 35.2, 30.8, 30.0, 28.5, 26.7, 26.0, 22.5, 20.5, 19.7, 18.2, 16.1, -4.3, -4.9; HRMS-FAB (*m/z*): [M + H]⁺ calcd for C₂₆H₄₆O₅Si, 467.31; found 467.29.



6.1.9. *ent*-10^β,13-Dihydroxy-3 α -methoxymethoxy-16-oxo-17,20-dinor-8^β,13^β-gibberellane-7,19-dioic Acid Methyl Ester 19,10-Lactone (Use of Sodium Hydride) (113)

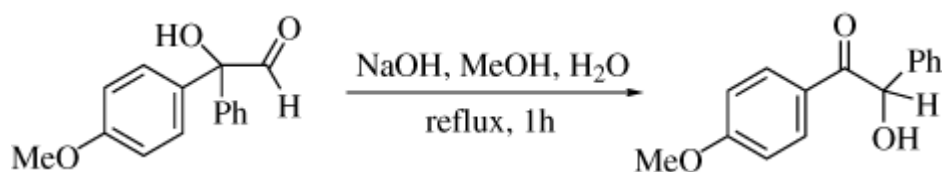
Sodium hydride (68 mg, 60% in mineral oil; washed with hexane) was added to a solution of the α -ketol (340 mg) in CH₂Cl₂ (10 mL) at 25° under N₂. The mixture was kept overnight and quenched with 20% KH₂PO₄ solution (10 mL) at 0°. After washing of the organic layer with brine, drying, solvent evaporation, and chromatography on silica gel (elution with 33% to 50% EtOAc in hexane), the isomerized ketol was obtained as a white solid (280 mg, 82%), mp 159–160°. IR (CHCl₃) 3520, 1770, 1750, 1735 cm⁻¹; ¹H NMR (CDCl₃) δ 4.74 (d, *J* = 6.9 Hz, 1H), 4.63 (d, *J* = 6.9 Hz, 1H), 3.88 (s, 3H), 3.73 (s, 3H), 3.68 (br s, 3H), 3.24 (d, *J* = 6.7 Hz, 1H), 3.06 (dd, *J* = 19.5, 3.8 Hz, 1H), 2.60 (d, *J* = 6.7 Hz, 1H), 2.17 (d, *J* = 19.5 Hz, 1H), 1.21 (s, 3H); ¹³C NMR (CDCl₃) δ 216.1, 177.6, 173.1, 95.8, 91.7, 81.3, 75.8, 55.9, 54.0, 53.3, 52.5, 52.2, 51.0, 47.8, 47.4, 46.3, 34.9, 26.1, 24.5, 17.9, 14.5; HRMS (*m/z*) [M]⁺ calcd for C₂₁H₂₈O₈, 408.1784; found 408.1787. Anal. Calcd for C₂₁H₂₈O₈: C, 61.75; H, 6.91. Found: C, 61.47; H, 6.89.



6.1.10. Isolampterol (Adsorption onto Alumina) (73)

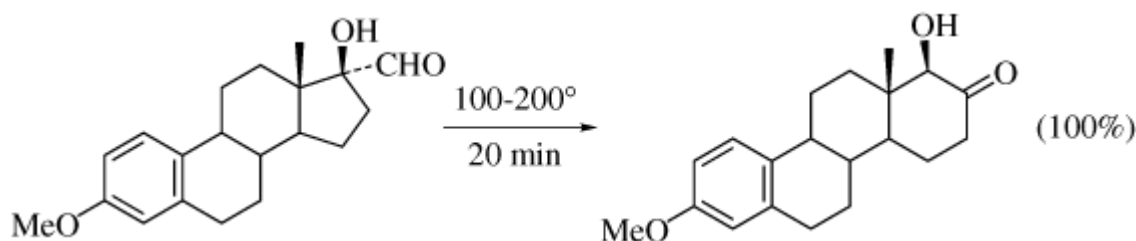
Lampterol (2 g) was dissolved in EtOAc and poured onto a column packed with 100 g of alumina and then developed with the same solvent. After being set aside for 3 days, the column was eluted with MeOH. Removal of the solvent left crystalline isolampterol, which was recrystallized from EtOAc to give pure compound in 80% yield; mp 179–180°. IR (KBr) 3420, 1690, 1645, 1395, 1365,

1018 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 5.70 (s, 1H), 4.60 (s, 1H), 3.39 (br s, 2H), 2.46 (br, 3H), 2.7–1.1 (series of m, 4H), 1.68 (s, 3H), 1.51 (s, 3H), 1.16 (s, 3H); λ_{max} 252 nm ($\log \epsilon$ 4.3); Anal. Calcd for $\text{C}_{15}\text{H}_{20}\text{O}_4$: C, 68.16; H, 7.63. Found: C, 67.84; H, 7.28.



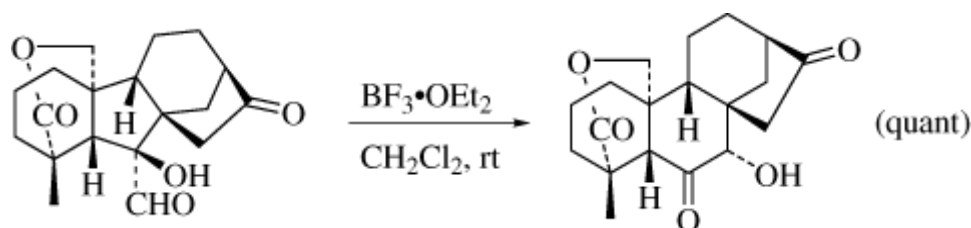
6.1.11. 4-Methoxybenzoic acid (Use of Hot Aqueous Base) (118)

A solution of α -hydroxy-*p*-anisyl phenylacetaldehyde (0.53 g, 2.2 mmol) in 50% aqueous MeOH (40 mL) containing 1.0 g of potassium hydroxide was heated under reflux for 1 hour, diluted with water (40 mL), and cooled. The resulting precipitate, which was filtered and dried, weighed 0.48 g, mp 85–100°. After two recrystallizations from CHCl_3 -petroleum ether, there was obtained 0.25 g (46%) of the known pure product, mp 104–105°.



6.1.12. 17 β -Hydroxy-3-methoxy-D-homoestra-1,3,5(10)-trien-17-one (Thermal D-homoannulation) (107)

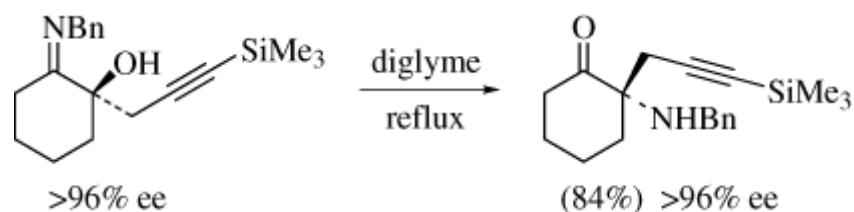
A 13.8 mg sample of the α -hydroxy aldehyde was heated from 100–200° during 20 minutes. The residue was triturated with 1 drop of MeCN and dried to give 13.9 mg of solid, mp 174–180°. Two recrystallizations from MeCN gave pure product as colorless prisms, mp 183–185°. $^1\text{H NMR}$ ($\text{CDCl}_3/\text{D}_2\text{O}$) δ 3.83 (s, 1H), 0.68 (s, 3H). Anal. Calcd for $\text{C}_{20}\text{H}_{26}\text{O}_3$: C, 76.40; H, 8.34. Found: C, 76.62; H, 8.39.



6.1.13. ent-7 α ,20-Dihydroxy-6,16-dioxo-17-norkauran-19-oic Acid 19,20-Lactone (Catalysis by Boron Trifluoride Etherate) (48)

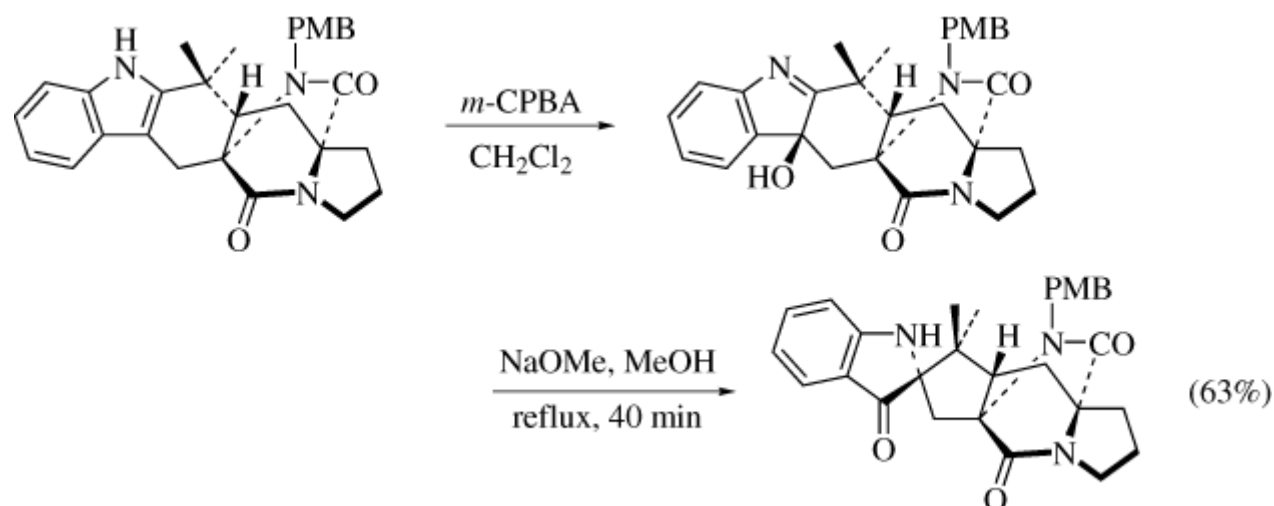
To the hydroxy aldehyde (5 mg, 0.015 mmol) in dry CH_2Cl_2 (1 mL) was added boron trifluoride etherate (2.5 μL , 0.020 mmol), and the mixture was stirred at room temperature for 30 minutes, diluted with EtOAc (5 mL), washed with water (2 mL) and brine (2 mL), dried, and evaporated to give 5 mg (100%) of product as a white solid, mp 186–187°. IR (CHCl_3) 3400–3100, 1730 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 4.83 (d, $J = 12.1$ Hz, 1H), 4.14 (d, $J = 12.1$ Hz, 1H), 3.86 (s, 1H), 3.49 (s, 1H), 2.26 (s, 1H), 1.27 (s, 3H); $^{13}\text{C NMR}$ (CDCl_3) δ 218.5, 210.5, 174.7, 82.5, 73.4, 55.3, 51.6, 51.4, 46.1,

45.0, 43.6, 40.0, 39.0, 35.1, 29.6, 28.4, 22.4, 20.4, 17.6; HRMS (m/z): $[M]^+$ calcd for $C_{19}H_{24}O_5$, 332.1624, found 332.1636.



6.1.14. (-)-2-Benzylamino-2-(3-trimethylsilylprop-2-ynyl)cyclohexanone (α -Hydroxy Imine Rearrangement under Thermal Conditions) (127)

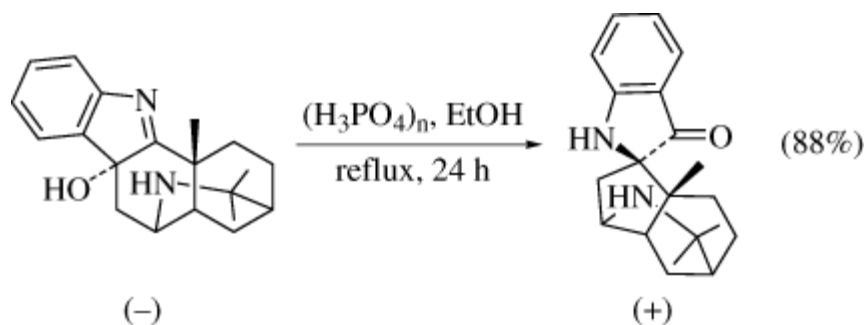
A solution of (-)-2-hydroxy-2-(3-trimethylsilylprop-2-ynyl)cyclohexanone of $> 96\% ee$ (1 mmol) and benzylamine (1.15 mmol) was heated under reflux for 3 hours with azeotropic removal of water by means of a Dean-Stark apparatus. Completion of the imine formation was determined by IR spectroscopy (disappearance of the band at 1710 cm^{-1}). The solution was evaporated to dryness and heated to 50° at 10^{-2} Torr to remove the excess amine. The residue was dissolved in diglyme (3 mL), refluxed for 4 hours, and freed of solvent at 80° and 12 Torr. The residue was taken up in Et_2O and the amino ketone was extracted from the ethereal solution with 0.1 N HCl solution. The aqueous phase was extracted once with Et_2O , basified with saturated NaHCO_3 solution, and extracted twice with Et_2O . The combined organic extracts were washed with water and dried. The residue was purified by flash chromatography on silica gel (elution with 25% Et_2O in petroleum ether) to give the product as a yellow oil (84%). $[\alpha]_D - 86$ (c 1.93, CHCl_3); IR (neat) 3080, 3060, 3025, 2170, 1710, 1605, 1250, 845, 755 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 7.43–7.20 (m, 5H), 3.70 (d, $J = 12\text{ Hz}$, 1H), 3.22 (d, $J = 12\text{ Hz}$, 1H), 3.09 (d, $J = 17\text{ Hz}$, 1H), 3.04–2.90 (m, 1H), 2.30 (d, $J = 17\text{ Hz}$, 1H), 2.31–1.95 (m, 3H), 1.84–1.50 (m, 3H), 0.94 (s, 9H); $^{13}\text{C NMR}$ (CDCl_3) δ 212.6, 140.2, 128.3, 128.2, 127.0, 102.8, 83.2, 64.8, 47.1, 39.1, 38.6, 28.3, 25.1, 20.5, 0.3. Anal. Calcd for $C_{19}H_{27}NOSi$: C, 72.79; H, 8.68; N, 4.47. Found: C, 72.55; H, 8.53; N, 4.58.



6.1.15. Oxidative Rearrangement of Indoles to Spiro Indoxyls under Basic Conditions (140)

To a stirred solution of the hexacyclic indole (10 mg, 0.021 mmol) in THF (1 mL) was added *m*-chloroperbenzoic acid (4.8 mg, 0.028 mmol) at room temperature. After 30 minutes, the mixture was quenched with a drop of methyl sulfide and concentrated under reduced pressure in a cold water bath. The residue was taken up in 1 M sodium methoxide in MeOH (4.5 mL), refluxed for 40 minutes, and cooled to room temperature prior to the addition of 3 N HCl (3 mL). After most of the

alcohol was removed under reduced pressure, the mixture was poured into water, extracted with CH_2Cl_2 , dried, and concentrated under reduced pressure. Preparative thin layer chromatography on silica gel (elution with 20:1 CH_2Cl_2 -MeOH) furnished the product (6.5 mg, 63%), mp 243–246° (from MeOH); $[\alpha]_D - 138.6$ (c 1.32, CHCl_3); IR (KBr) 3350, 1685, 1515, 1385, 1245, 1025, 745 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.51 (d, $J = 7.9$ Hz, 1H), 7.44–7.34 (m, 1H), 7.05 (d, $J = 8.6$ Hz, 2H), 6.85–6.72 (m, 4H), 5.09 (1/2 AB quartet, $J = 15.5$ Hz, 1H), 4.69 (br s, 1H), 4.24 (1/2 AB quartet, $J = 15.5$ Hz, 1H), 3.75 (s, 3H), 3.52–3.37 (m, 2H), 3.23 (dd, $J = 7.8, 10.5$ Hz, 1H), 3.10 (1/2 AB quartet, $J = 16.3$ Hz, 1H), 2.98–2.86 (m, 1H), 2.29 (1/2 AB quartet, $J = 16.3$ Hz, 1H), 2.07–1.85 (m, 4H), 1.76 (dd, $J = 7.8, 12.8$ Hz, 1H), 0.90 (s, 3H), 0.79 (s, 3H).



6.1.16. (+)-Aristolone (Acid-Catalyzed α -Hydroxy Imine Rearrangement) (155)

(–)-Serratoline (1.535 g) was dissolved in EtOH (30 mL), added to a boiling solution of polyphosphoric acid (10.2 g) in EtOH (300 mL), and refluxed for 24 hours under Ar. Most of the solvent was distilled off under reduced pressure and the residue was diluted with crushed ice (160 g), basified to pH 11 through addition of concentrated NH_4OH (150 mL), and extracted with CH_2Cl_2 (3 \times 400 mL). The combined organic layers were dried and evaporated to give 1.61 g of a yellow-green solid. Column chromatographic purification on silica gel (elution with cyclohexane/THF/ Et_3N 100:18:5) furnished (+)-aristolone (1.411 g, 88%) as long yellow needles (from THF/cyclohexane/ Et_3N), mp 224.5–225°; $[\alpha]_D +264$ (c 1.12, CHCl_3); IR (CHCl_3) 3420, 3360, 1691, 1619, 1483, 1469, 1320, 1302, 1100, 1070, 897 cm^{-1} ; ^1H NMR (CDCl_3) δ 7.55 (dddd, $J = 7.7, 1.3, 0.7, 0.6$ Hz, 1H), 7.40 (ddd, $J = 8.2, 7.0, 1.3$ Hz, 1H), 6.77 (dt, $J = 8.2, 0.8$ Hz, 1H), 6.76 (ddd, $J = 7.8, 7.1, 0.8$ Hz, 1H), 4.77 (br s, 1H), 3.69 (ddd, $J = 7.1, 5.4, 1.5$ Hz, 1H), 2.83 (ddd, $J = 14.7, 14.5, 6.1$ Hz, 1H), 2.29 (dd, $J = 15.3, 7.2$ Hz, 1H), 2.15 (dq, $J = 13.6, 3.2$ Hz, 1H), 2.11 (dd, $J = 15.3, 1.6$ Hz, 1H), 1.99 (dm, $J = 14.5$ Hz, 1H), 1.66 (dt, $J = 13.5, 3.0$ Hz, 1H), 1.57 (m, 1H), 1.56 (tdd, $J = 14.5, 6.0, 4.0$ Hz, 1H), 1.32 (dq, $J = 4.0, 3.3$ Hz, 1H), 1.17 (s, 3H), 1.15 (s, 3H), 0.89 (d, $J = 0.8$ Hz, 3H), 0.91 (ddm, $J = 14.6, 6.0$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 202.3, 159.8, 136.9, 124.3, 121.8, 118.3, 111.3, 78.5, 53.1, 52.8, 49.0, 46.0, 45.5, 35.6, 30.0, 28.5, 27.2, 25.0, 23.7, 19.3.

7. Tabular Survey

An attempt has been made to include in the tables all of those examples where the end products are believed to be adequately characterized. The coverage, which extends to mid-2002, does not include the patent literature. All tables are based on the total carbon count of the reactant including protecting groups and the like.

Table 1 has been subdivided into five parts, the first of which (1A) deals with acyclic α -ketols. Many of these examples are of early vintage and no yields are cited. This is because of the equilibrium-based nature of the rearrangement and the original focus on that aspect of the process. Table 1B depicts simple cyclic α -ketols and Table 1C covers the isomerization of bridged α -ketols. Steroidal α -ketols appear in Table 1D. Table 1E covers the rearrangement chemistry of complex polycyclic systems, the majority of which have been examined in connection with recent synthetic undertakings. Assigned to Tables 2 and 3 are the rearrangements of α -hydroxy aldehydes and imines, respectively.

Isolated yields are included in parentheses and a dash indicates that no yield was reported. Reported ratios define the proportion of the starting α -ketol to the product α -ketol. The following abbreviations have been used in the tables:

Ac	acetyl
9-BBN	9-borabicyclononane
Bn	benzyl
BOM	benzyloxymethyl
Bz	benzoyl
Cbz	carbobenzyloxy
de	diastereomeric excess
ee	enantiomeric excess
MOM	methoxymethyl
PMB	<i>p</i> -methoxybenzyl
pybox	2,6-bis[(<i>S</i>)-4-isopropyl(oxazolin-2 \tilde{y} l)]pyridine
TBS	<i>tert</i> -butyldimethylsilyl
TES	triethylsilyl
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMS	trimethylsilyl
TROC	2,2,2-trichloroethoxycarbonyl
Ts	<i>p</i> -toluenesulfonyl

Table 1A. Acyclic α -Ketols

[View PDF](#)

Table 1B. Cyclic α -Ketols

[View PDF](#)

Table 1C. Bridged α -Ketols

[View PDF](#)

Table 1D. Steroidal α -Ketols

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Table 1E. Complex Polycyclic α -Ketols

[View PDF](#)

Table 2. α -Hydroxy Aldehydes

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Table 3. α -Hydroxy Imines

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TABLE 1A. ACYCLIC α -KETOLS

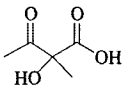
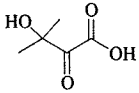
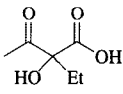
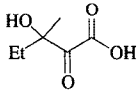
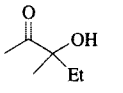
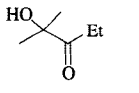
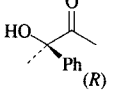
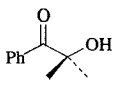
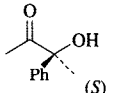
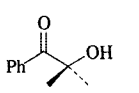
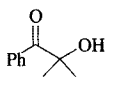
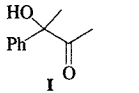
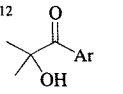
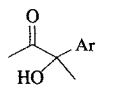
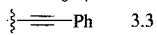
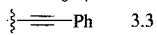
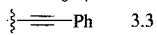
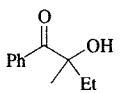
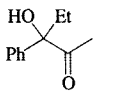
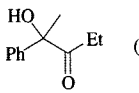
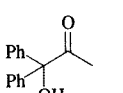
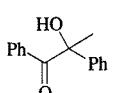
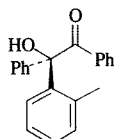
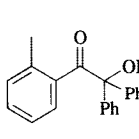
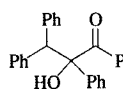
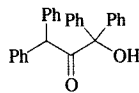
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.													
C ₅ 	Dilute NaOH, H ₂ O	 (—)	156													
C ₆ 	Dilute NaOH, H ₂ O	 (—)	156													
	NiCl ₂ , TMEDA, 130°	 (—)	29													
C ₁₀ 	Biphenyl, 214-252°	 (—)	33													
	Biphenyl, 214-252°	 (—)	33													
	NiCl ₂ , TMEDA, 130°, 12 h	 (88)	29													
	Ni(acac) ₂ , pybox, 130°, 36 h	I (88; 18% ee) (—)	29													
C ₁₀₋₁₂ 	Al(O <i>Bu-t</i>) ₃ (0.1 mol), toluene, 80°	 (—)	<table border="1" data-bbox="1171 1182 1328 1354"> <thead> <tr> <th>Ar</th> <th>K_{eq}</th> </tr> </thead> <tbody> <tr> <td>Ph</td> <td>6.1</td> </tr> <tr> <td><i>p</i>-MeC₆H₄</td> <td>3.9</td> </tr> <tr> <td><i>p</i>-MeOC₆H₄</td> <td>2.1</td> </tr> <tr> <td><i>o</i>-MeC₆H₄</td> <td>0.8</td> </tr> <tr> <td></td> <td>3.3</td> </tr> </tbody> </table>	Ar	K _{eq}	Ph	6.1	<i>p</i> -MeC ₆ H ₄	3.9	<i>p</i> -MeOC ₆ H ₄	2.1	<i>o</i> -MeC ₆ H ₄	0.8		3.3	59, 66
Ar	K _{eq}															
Ph	6.1															
<i>p</i> -MeC ₆ H ₄	3.9															
<i>p</i> -MeOC ₆ H ₄	2.1															
<i>o</i> -MeC ₆ H ₄	0.8															
	3.3															
C ₁₁ 	NiCl ₂ , TMEDA, 130°	 (—) +  (—)	29													
C ₁₅ 	Al(O <i>Bu-t</i>) ₃ , toluene, reflux	 (—)	59													
C ₂₁ 	KOH, MeOH, H ₂ O, reflux, 3 h	 (11)	55													
C ₂₇ 	KOH (1 N), EtOH, reflux, 30 min	 (74)	60													

TABLE 1B. CYCLIC α -KETOLS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.														
C ₆ 	NaOH (0.1 M), 100° or 230°, 5 min	(—)	67														
C ₆₋₁₄ 	NaOH (0.02 M), pyridine (20% aq)	(—)	71														
	\rightleftharpoons	(—)															
R = Me, CHMe ₂ , CMe ₂ Ph																	
C ₇ 	Distillation or NaOH (0.1 M), H ₂ O	(—) K _{eq} = ~1	71														
C ₇₋₁₂ 	Pb(NO ₃) ₂ , KOH, H ₂ O, reflux, 30 min	<table border="1" style="display: inline-table; vertical-align: middle;"> <tr><td>R</td><td></td></tr> <tr><td>Me</td><td>(67)</td></tr> <tr><td>Et</td><td>(50)</td></tr> <tr><td><i>i</i>-Pr</td><td>(52)</td></tr> <tr><td><i>t</i>-Bu</td><td>(59)</td></tr> <tr><td><i>c</i>-C₆H₁₁</td><td>(75)</td></tr> <tr><td>Ph</td><td>(58)</td></tr> </table>	R		Me	(67)	Et	(50)	<i>i</i> -Pr	(52)	<i>t</i> -Bu	(59)	<i>c</i> -C ₆ H ₁₁	(75)	Ph	(58)	30
R																	
Me	(67)																
Et	(50)																
<i>i</i> -Pr	(52)																
<i>t</i> -Bu	(59)																
<i>c</i> -C ₆ H ₁₁	(75)																
Ph	(58)																
C ₇ 	NaOMe, MeO (1:2)	(—)	68														
C ₇₋₁₂ 	KOH, Pb(NO ₃) ₂ , H ₂ O, MeOH	<table border="1" style="display: inline-table; vertical-align: middle;"> <tr><td>R</td><td></td></tr> <tr><td>Me</td><td>(—)</td></tr> <tr><td>Ph</td><td>(—)</td></tr> </table>	R		Me	(—)	Ph	(—)	38								
R																	
Me	(—)																
Ph	(—)																
C ₈ 	BF ₃ ·OEt ₂ , ether	(35)	30														
C ₉ 	SiO ₂	(—)	31														
	ZnBr ₂ , CH ₂ Cl ₂ , heat	(45)	31														
	SiO ₂ , H ₂ O	(35)	31														
	10% KOH, CH ₃ OH, reflux	(83)	26														

TABLE 1B. CYCLIC α -KETOLS (Continued)

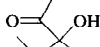
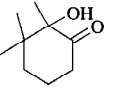
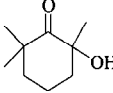
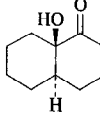
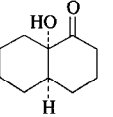
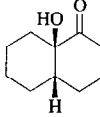
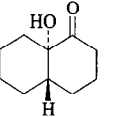
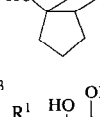
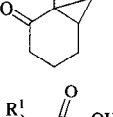
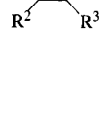
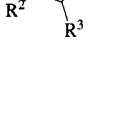
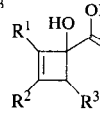
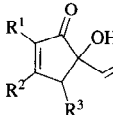






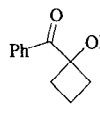
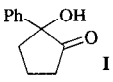
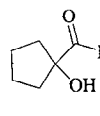
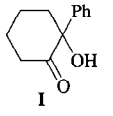
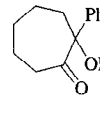
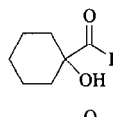

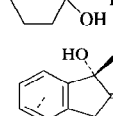


Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																																				
C ₉ 	BF ₃ •OEt ₂ , MeOCH ₂ CH ₂ OMe, 2 days	 (84) +  (16)	26																																				
C ₁₀ 	KOH, CH ₃ OH, reflux, 24.5 h	 I (62:38)	74																																				
	KOH (17%), CH ₃ OH, reflux, 21.5 h	 I (46:54)	74																																				
	KOH (17%), CH ₃ OH, reflux, 21.5 h	 (67:33)	74																																				
	NaOH, H ₂ O	 (—)	69																																				
C ₁₀₋₁₃ 	TFA, THF, H ₂ O	 <table border="1" data-bbox="1111 826 1310 1170"> <thead> <tr> <th>R¹</th> <th>R²</th> <th>R³</th> <th>Yield (%)</th> </tr> </thead> <tbody> <tr> <td>Me</td> <td>Me</td> <td>H</td> <td>76</td> </tr> <tr> <td>Me</td> <td>Me</td> <td>Cl</td> <td>70</td> </tr> <tr> <td>Me</td> <td>Me</td> <td>Me</td> <td>72</td> </tr> <tr> <td>H</td> <td><i>n</i>-Bu</td> <td>H</td> <td>76</td> </tr> <tr> <td>H</td> <td>SiMe₃</td> <td>H</td> <td>62</td> </tr> <tr> <td>H</td> <td>OEt</td> <td>H</td> <td>40</td> </tr> <tr> <td></td> <td></td> <td>H</td> <td>83</td> </tr> <tr> <td></td> <td></td> <td>H</td> <td>92</td> </tr> </tbody> </table>	R ¹	R ²	R ³	Yield (%)	Me	Me	H	76	Me	Me	Cl	70	Me	Me	Me	72	H	<i>n</i> -Bu	H	76	H	SiMe ₃	H	62	H	OEt	H	40			H	83			H	92	31
R ¹	R ²	R ³	Yield (%)																																				
Me	Me	H	76																																				
Me	Me	Cl	70																																				
Me	Me	Me	72																																				
H	<i>n</i> -Bu	H	76																																				
H	SiMe ₃	H	62																																				
H	OEt	H	40																																				
		H	83																																				
		H	92																																				
C ₁₁ 	NiCl ₂ , TMEDA, MeOH, reflux, 4 h NiCl ₂ /pybox, MeOH, reflux, 24 h Silica gel	 I I (100) I (—); 34% ee I (95)	32, 37																																				
C ₁₂ 	KOH or NaOH, ether or KOH, MeOH, reflux NiCl ₂ , TMEDA, MeOH NiCl ₂ /pybox, MeOH NaOMe, MeOH	 I <table border="1" data-bbox="1058 1549 1302 1721"> <thead> <tr> <th>Temp</th> <th>Time</th> <th>I</th> <th>% ee</th> </tr> </thead> <tbody> <tr> <td>—</td> <td>—</td> <td>(—)</td> <td>—</td> </tr> <tr> <td>65°</td> <td>120 h</td> <td>(91)</td> <td>—</td> </tr> <tr> <td>65°</td> <td>120 h</td> <td>(—)</td> <td>34</td> </tr> <tr> <td>100°</td> <td>100 min</td> <td>(—)</td> <td>—</td> </tr> </tbody> </table>	Temp	Time	I	% ee	—	—	(—)	—	65°	120 h	(91)	—	65°	120 h	(—)	34	100°	100 min	(—)	—	27 32, 37 32, 37 32, 37																
Temp	Time	I	% ee																																				
—	—	(—)	—																																				
65°	120 h	(91)	—																																				
65°	120 h	(—)	34																																				
100°	100 min	(—)	—																																				
C ₁₃ 	KOH, Pb(NO ₃) ₂ , H ₂ O, MeOH	 (—)	38																																				
	BF ₃ •OEt ₂ , ether	 (38)	30																																				
	KH, THF, -78 to 20°	 (59, 59% de)	28																																				

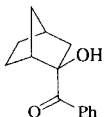
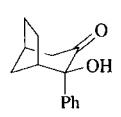
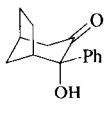
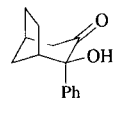
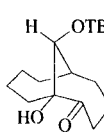
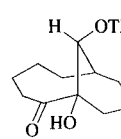
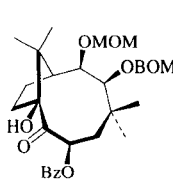
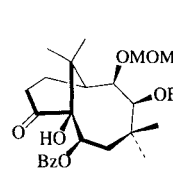
TABLE 1B. CYCLIC α -KETOLS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																																																																														
<p>C₁₃₋₂₆</p>	KOH (5% aq), CHCl ₃	<table border="1"> <thead> <tr> <th>R¹</th> <th>R²</th> <th>R³</th> <th>Temp</th> <th>Time</th> <th>Yield (%)</th> </tr> </thead> <tbody> <tr> <td>Me</td> <td>Ph</td> <td>H</td> <td>65-70°</td> <td>10 min</td> <td>(65)</td> </tr> <tr> <td>Me</td> <td><i>p</i>-C₆H₄CH₃</td> <td>H</td> <td>65-70°</td> <td>10 min</td> <td>(60)</td> </tr> <tr> <td>Me</td> <td><i>p</i>-C₆H₄OCH₃</td> <td>H</td> <td>65-70°</td> <td>10 min</td> <td>(67)</td> </tr> <tr> <td>Me</td> <td>2-furyl</td> <td>H</td> <td>65-70°</td> <td>10 min</td> <td>(60)</td> </tr> <tr> <td>Me</td> <td>Ph</td> <td>Me</td> <td>65°</td> <td>10 min</td> <td>(60)</td> </tr> <tr> <td>Me</td> <td>Ph</td> <td>Bn</td> <td>55-60°</td> <td>5 min</td> <td>(78)</td> </tr> <tr> <td>Me</td> <td><i>p</i>-C₆H₄CH₃</td> <td>Bn</td> <td>55-60°</td> <td>5 min</td> <td>(75)</td> </tr> <tr> <td>Me</td> <td><i>p</i>-C₆H₄OCH₃</td> <td>Bn</td> <td>55-60°</td> <td>5 min</td> <td>(75)</td> </tr> <tr> <td>Me</td> <td>2-furyl</td> <td>Bn</td> <td>30-35°</td> <td>5 min</td> <td>(64)</td> </tr> <tr> <td>Me</td> <td>CH₂CH=CH₂</td> <td>Bn</td> <td>30-35°</td> <td>5 min</td> <td>(60)</td> </tr> <tr> <td><i>i</i>-Pr</td> <td>Ph</td> <td>Bn</td> <td>55-60°</td> <td>5 min</td> <td>(60)</td> </tr> <tr> <td>Ph</td> <td>Ph</td> <td>Bn</td> <td>25-30°</td> <td>5 min</td> <td>(60)</td> </tr> </tbody> </table>	R ¹	R ²	R ³	Temp	Time	Yield (%)	Me	Ph	H	65-70°	10 min	(65)	Me	<i>p</i> -C ₆ H ₄ CH ₃	H	65-70°	10 min	(60)	Me	<i>p</i> -C ₆ H ₄ OCH ₃	H	65-70°	10 min	(67)	Me	2-furyl	H	65-70°	10 min	(60)	Me	Ph	Me	65°	10 min	(60)	Me	Ph	Bn	55-60°	5 min	(78)	Me	<i>p</i> -C ₆ H ₄ CH ₃	Bn	55-60°	5 min	(75)	Me	<i>p</i> -C ₆ H ₄ OCH ₃	Bn	55-60°	5 min	(75)	Me	2-furyl	Bn	30-35°	5 min	(64)	Me	CH ₂ CH=CH ₂	Bn	30-35°	5 min	(60)	<i>i</i> -Pr	Ph	Bn	55-60°	5 min	(60)	Ph	Ph	Bn	25-30°	5 min	(60)	8
R ¹	R ²	R ³	Temp	Time	Yield (%)																																																																												
Me	Ph	H	65-70°	10 min	(65)																																																																												
Me	<i>p</i> -C ₆ H ₄ CH ₃	H	65-70°	10 min	(60)																																																																												
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<i>i</i> -Pr	Ph	Bn	55-60°	5 min	(60)																																																																												
Ph	Ph	Bn	25-30°	5 min	(60)																																																																												
<p>C₁₄</p>	KOBu- <i>t</i> , THF, 0°, O ₂ atm		(—)	72																																																																													
	KH, THF, -78° to 20°		(50) 59% de	28																																																																													
<p>C₁₅</p>	CF ₃ CO ₂ H, THF, H ₂ O, 3 h		(72)	28																																																																													
	Al ₂ O ₃ , ethyl acetate		(80)	73																																																																													
	CF ₃ CO ₂ H, THF, H ₂ O, 3 h		(93)	28																																																																													
<p>C₁₈</p>	KH, THF, -78° to 20°		(43) 10% de	28																																																																													
<p>C₂₁</p>	Et ₃ N·HF		(86)	28																																																																													
<p>C₃₀</p>	HOAc, NaOAc, reflux or (Bu ₃ Sn) ₂ O, Br ₂ , CH ₂ Cl ₂ , 25°		(76) (84)	110																																																																													

TABLE 1C. BRIDGED α -KETOLS

	Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₇		K ₂ CO ₃ , H ₂ O	(100)	75
		K ₂ CO ₃ , D ₂ O, 80°, 145 h	(—)	75
C ₉		KOH, H ₂ O, MeOH	K _{eq} = 2 at 31°	76
		Silica gel	(—) + (—)	32
C ₁₁	or	NaOMe, MeOH	\rightleftharpoons	77
			K _{eq} (39°) = 1.33 in HOCH ₂ CH ₂ OH	
		Alumina or Alkaline medium	(—)	79
C ₁₄		Silica gel	+ (—) ^a	32
		NaOMe, MeOH, 125°, 90 min	(81)	32
		175°, 2 h	I (73)	34
		NaOH, H ₂ O, dioxane, rt, 24 h	I (>90)	34
		214°, 14 h	I (65) + II (28)	34
		214°, 50 h	I (—) + II (60)	34
		NaOMe, MeOH, 65°	(—) \rightleftharpoons (—)	32

TABLE 1C. BRIDGED α -KETOLS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₁₄ 	NaOH, H ₂ O, dioxane, reflux, 8 h	 (75)	34
	NaOH, H ₂ O, dioxane, 62°, 6 days	 (8)	34
C ₁₇ 	Al(OPr- <i>i</i>) ₃ , C ₆ H ₆ , reflux	 (40)	163
C ₃₂ 	Al(OBu- <i>t</i>) ₃ , C ₆ H ₆ , reflux, 2 h	 (77)	80

^a The ratio of the products is variable; they equilibrate with NaOMe/MeOH at 100°.

TABLE 1D. STEROIDAL α -KETOLS

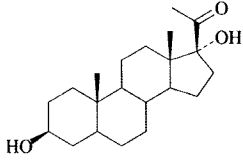
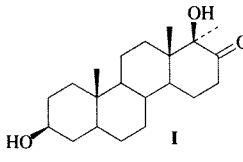
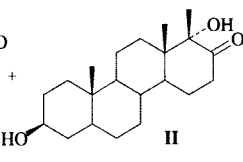
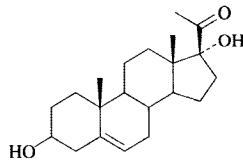
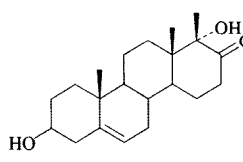
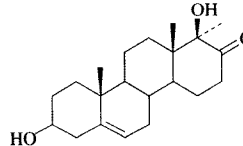
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.					
C ₂₁ 	 I	 II	97					
				KOH (5%), EtOH (50%)	Temp	Time	I	II
				KOH (5%), EtOH (50%)	reflux	10 min	(10)	(0)
				KOH (5%), EtOH (50%)	reflux	20 min	(50)	(trace)
				KOH (5%), EtOH (50%)	reflux	30 min	(70)	(trace)
				KOH (5%), EtOH (50%)	reflux	1 h	(80)	(5)
				KOH (5%), EtOH (50%)	reflux	3 h	(70)	(30)
				KOH (5%), EtOH (50%)	reflux	14 h	(65)	(35)
				KOEt (5%), EtOH	reflux	1 h	(70)	(30)
				KOEt (5%), EtOH	reflux	1.5 h	(65)	(35)
				KOEt (5%), EtOH	reflux	2 h	(65)	(35)
				KOBu- <i>t</i> (0.1 N), <i>t</i> -BuOH	—	15 min	(20)	(80)
				MeOCH ₂ CH ₂ OMe	40°	30 min	(50)	(50)
				MeOCH ₂ CH ₂ OMe	40°	1 h	(50)	(50)
	KOH, MeOH	 I	(—)	93				
	Al ₂ O ₃ , C ₆ H ₆	 II	(—)	93				

TABLE 1D. STEROIDAL α -KETOLS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₂₁ 	Dry FeCl ₃ , silica gel	(60)	35
	Ac ₂ O, H ₂ SO ₄ (cat.), reflux, 3 h	or 157	
	KOH, EtOH, reflux, 4 h	+ 36	
	KOH, MeOH, reflux, 3 h; or 250°, 5 min; or Al(OBu- <i>t</i>) ₃ , acetone, benzene, 100°, 21 h	+ 98	
	Al(OBu- <i>t</i>) ₃ , acetone, benzene, 100°, 21 h	+ 36	
	BF ₃ •OEt ₂ , Ac ₂ O, HOAc, 25°, overnight	(75)	100
	BF ₃ •OEt ₂ , Ac ₂ O, HOAc, 25°, overnight	(35)	100
	Ac ₂ O, reflux, 12 h	I (50)	100
	BF ₃ •OEt ₂ , Ac ₂ O, HOAc, 25°, overnight	(90)	100
	Ac ₂ O, reflux, 12 h	I (90)	100
	LiOBu- <i>t</i> , heptane, MeOCH ₂ CH ₂ OMe, 20°, 30 min	(20)	35
	254°, 1 h	I (16)	35
	Al(OBu- <i>t</i>) ₃ , Me ₂ CO, C ₆ H ₆ , 100°, 20 h	(—)	99

538

539

TABLE 1D. STEROIDAL α -KETOLS (Continued)

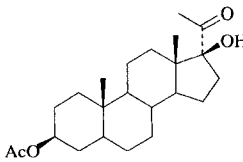
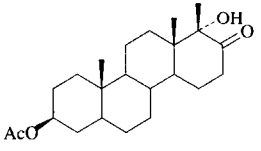
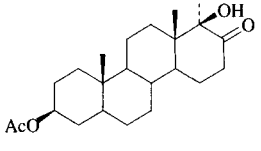
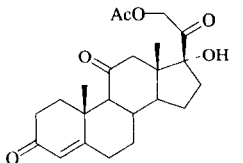
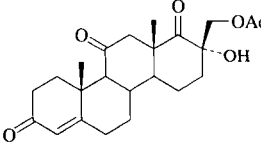
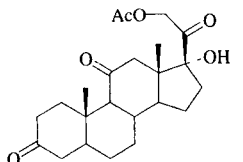
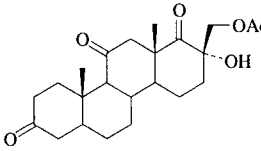
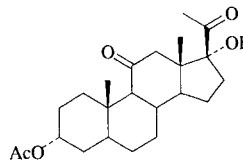
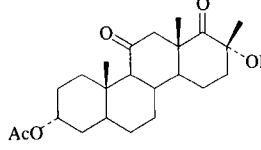
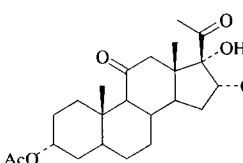
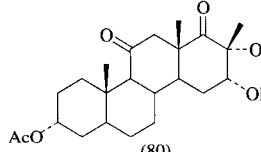
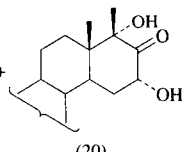
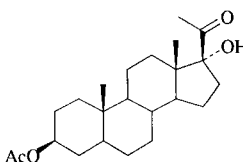
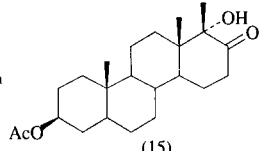
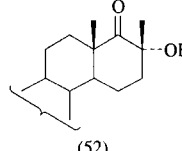
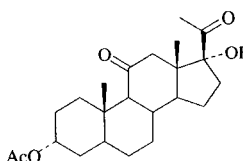
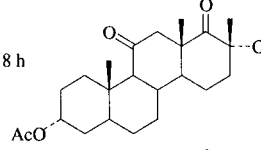
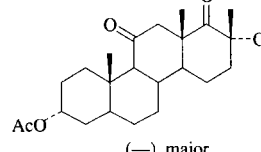
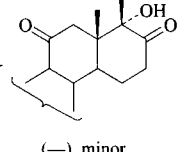
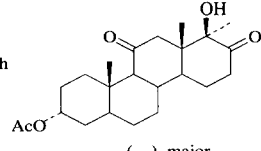
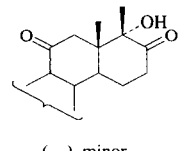
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₂₃ 	1. KOH, MeOH, reflux, 1 h 2. Ac ₂ O, py	 (—)	81
	Neutral Al ₂ O ₃	 (92)	81
	1. Al(OPr- <i>i</i>), cyclohexanone, toluene, dioxane, reflux, 1 h 2. Ac ₂ O, py	 (—)	43
	1. Al(OPr- <i>i</i>), cyclohexanone, toluene, dioxane, reflux, 1 h 2. Ac ₂ O, py	 (—)	43
	1. Al(OPr- <i>i</i>), cyclohexanone, toluene, dioxane, reflux, 1 h 2. Ac ₂ O, py	 (—)	43
	Al ₂ O ₃ , dioxane	 (80) +  (20)	103
	1. Al(OBu- <i>t</i>), C ₆ H ₆ , reflux, 27 h 2. Ac ₂ O, py	 (15) +  (52)	36
	BF ₃ •OEt ₂ , HOAc, Ac ₂ O, rt, 15-18 h	 (—) very major	95
	Al(OBu- <i>t</i>), toluene, reflux, 2 h	 (—) major +  (—) minor	95
	1. 5% KOH, MeOH, reflux, 5-6 h 2. Ac ₂ O, py	 (—) major +  (—) minor	95

TABLE 1D. STEROIDAL α -KETOLS (Continued)

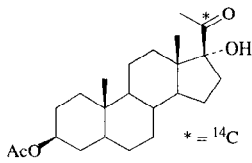
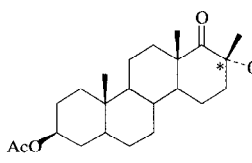
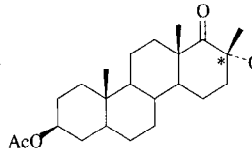
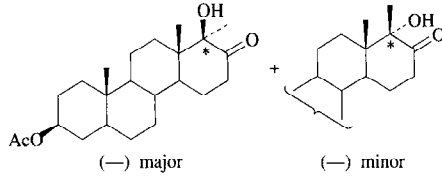
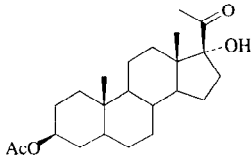
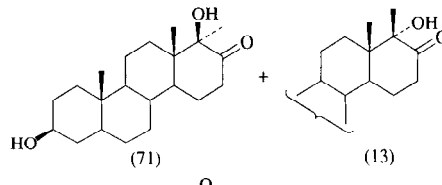
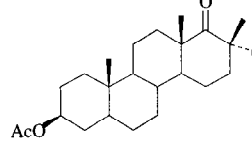
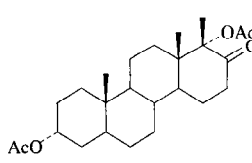
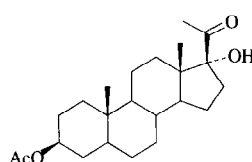
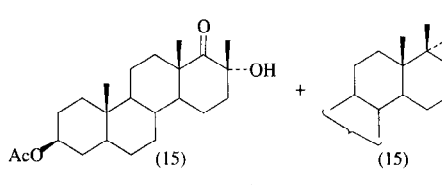
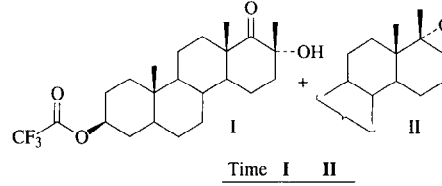
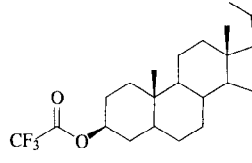
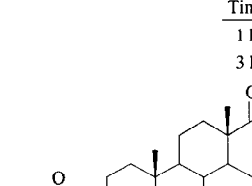
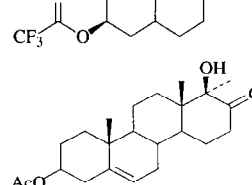
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
 C_{23}	$BF_3 \cdot OEt_2$, HOAc, Ac_2O , rt, overnight	 (95)	101
	1. $Al(OBu-t)_3$, C_6H_6 , reflux, 36 h 2. Ac_2O , py	 (47)	101
	1. KOH, MeOH, reflux, 4 h 2. Ac_2O , py	 (—) major (—) minor	101
	KOH, EtOH, reflux, 4 h	 (71) (13)	36
	$BF_3 \cdot OEt_2$, Ac_2O , HOAc	 (—)	36
	Ac_2O , reflux, 12 h	 (80)	100
	200-225°, 30 min	 (15) (15)	36
	244°	 I II	35
	$BF_3 \cdot OEt_2$, $MeOCH_2CH_2OMe$, 50°, 25 min	 (62)	35
	1. CH_3MgBr , Et_2O , reflux, 3 h 2. Ac_2O , py	 (—)	93

TABLE 1D. STEROIDAL α -KETOLS (Continued)

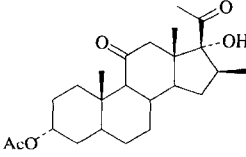
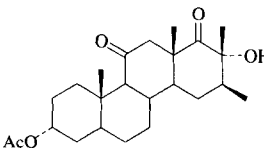
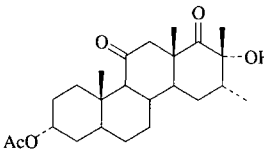
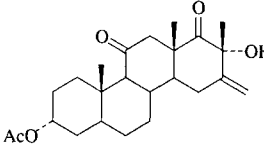
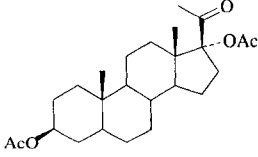
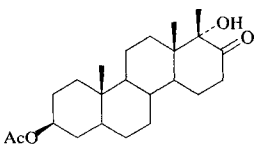
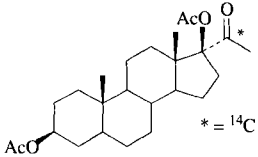
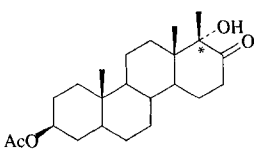
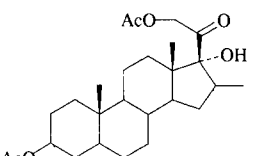
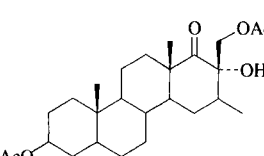
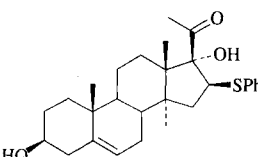
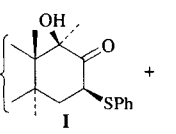
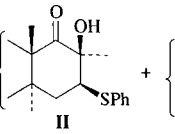
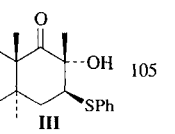
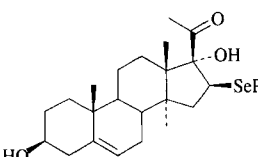
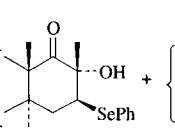
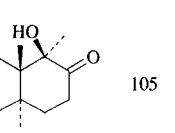
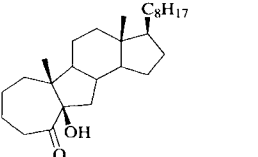
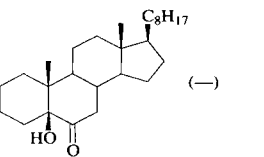
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																				
<p>C₂₄</p> 	200°, 5 min	 (—)	104																				
	BF ₃ •OEt ₂ , Ac ₂ O, HOAc	 (—)	104																				
	Basic Al ₂ O ₃	 (60)	104																				
<p>C₂₅</p> 	1. CH ₃ MgBr, ether, dioxane, reflux, 3 h 2. Ac ₂ O, py	 (—)	93																				
	1. KOH, MeOH, reflux, 1 h 2. Ac ₂ O, py	 * = ¹⁴ C  (92)	101																				
<p>C₂₆</p> 	Dry FeCl ₃ , silica gel	 (>90)	35																				
<p>C₂₇</p> 	KOH, 50% aq EtOH KOBu-t, DMSO BF ₃ •OEt ₂ , THF	 I +  II +  III 105	<table border="1"> <thead> <tr> <th>Temp</th> <th>Time</th> <th>I</th> <th>II</th> <th>III</th> </tr> </thead> <tbody> <tr> <td>reflux</td> <td>20 min</td> <td>(50)</td> <td>(40)</td> <td>(5)</td> </tr> <tr> <td>rt</td> <td>2 min</td> <td>(—)</td> <td>(~100)</td> <td>(—)</td> </tr> <tr> <td>0°</td> <td>2 h</td> <td>(—)</td> <td>(—)</td> <td>(~100)</td> </tr> </tbody> </table>	Temp	Time	I	II	III	reflux	20 min	(50)	(40)	(5)	rt	2 min	(—)	(~100)	(—)	0°	2 h	(—)	(—)	(~100)
		Temp	Time	I	II	III																	
reflux	20 min	(50)	(40)	(5)																			
rt	2 min	(—)	(~100)	(—)																			
0°	2 h	(—)	(—)	(~100)																			
 I +  II +  III 105	<table border="1"> <thead> <tr> <th>Temp</th> <th>Time</th> <th>I</th> <th>II</th> <th>III</th> </tr> </thead> <tbody> <tr> <td>reflux</td> <td>20 min</td> <td>(30)</td> <td>(—)</td> <td>(60)</td> </tr> <tr> <td>rt</td> <td>3 min</td> <td>(80)</td> <td>(—)</td> <td>(—)</td> </tr> <tr> <td>0°</td> <td>70 min</td> <td>(—)</td> <td>(~100)</td> <td>(—)</td> </tr> </tbody> </table>	Temp	Time	I	II	III	reflux	20 min	(30)	(—)	(60)	rt	3 min	(80)	(—)	(—)	0°	70 min	(—)	(~100)	(—)		
Temp	Time	I	II	III																			
reflux	20 min	(30)	(—)	(60)																			
rt	3 min	(80)	(—)	(—)																			
0°	70 min	(—)	(~100)	(—)																			
	KOH (2%), MeOH, reflux	 (—)	107																				

TABLE 1D. STEROIDAL α -KETOLS (Continued)

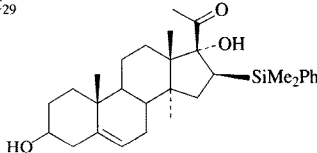
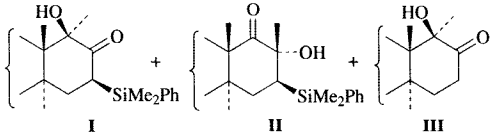
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.															
<p>C₂₉</p> 	<p>KOBu-<i>t</i>, DMSO BF₃•OEt₂, THF</p>	 <table border="1" data-bbox="1038 1249 1326 1333"> <thead> <tr> <th>Temp</th> <th>Time</th> <th>I</th> <th>II</th> <th>III</th> </tr> </thead> <tbody> <tr> <td>rt</td> <td>2 min</td> <td>(50)</td> <td>(0)</td> <td>(45)</td> </tr> <tr> <td>0°</td> <td>30 min</td> <td>(0)</td> <td>(-100)</td> <td>(0)</td> </tr> </tbody> </table>	Temp	Time	I	II	III	rt	2 min	(50)	(0)	(45)	0°	30 min	(0)	(-100)	(0)	105
Temp	Time	I	II	III														
rt	2 min	(50)	(0)	(45)														
0°	30 min	(0)	(-100)	(0)														

TABLE 1E. COMPLEX POLYCYCLIC α -KETOLS

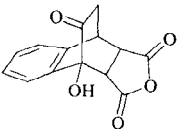
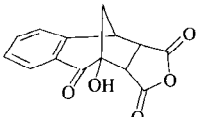
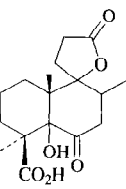
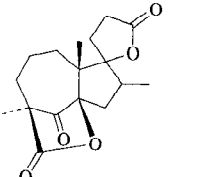
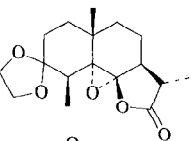
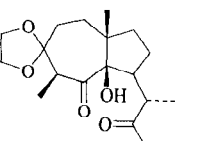
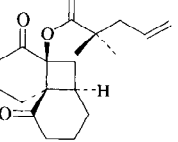
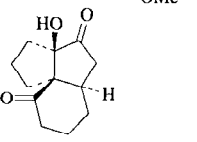
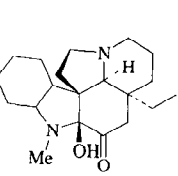
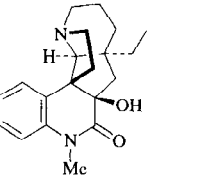
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₁₄ 	170-180°, 10 min	 (87)	78
C ₁₇ 	KOH	 (-)	108
C ₁₉ 	NaOMe, ether	 (80)	109
C ₁₉ 	1. 9-BBN, THF 2. NaOH, H ₂ O ₂ , EtOH	 (96)	70
C ₂₀ 	KH, MeOCH ₂ CH ₂ OMe, dibenzo-18-crown-6, rt	 (86)	117

TABLE 1E. COMPLEX POLYCYCLIC α -KETOLS (Continued)

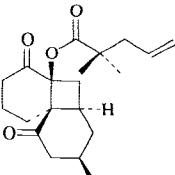
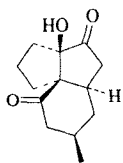
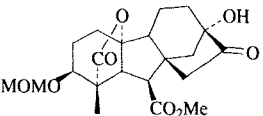
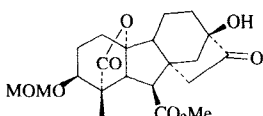
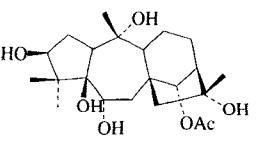
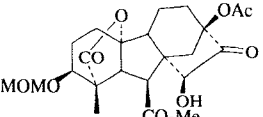
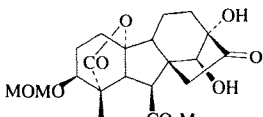
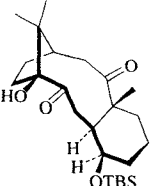
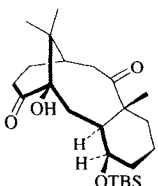
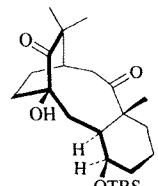
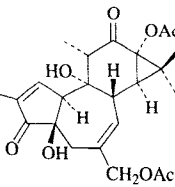
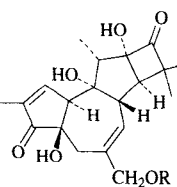
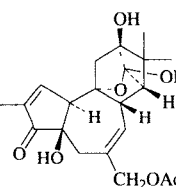
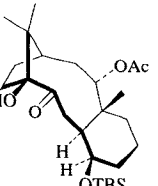
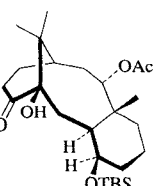
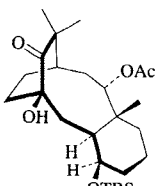
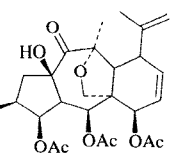
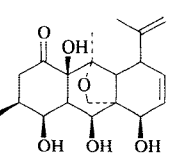
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																				
	1. 9-BBN, THF 2. NaOH, H ₂ O ₂ , EtOH	 (96)	70																				
	NaH, CH ₂ Cl ₂ , 25°, overnight	 (82)	113																				
	CrO ₃ , py	(—)	111																				
	NaOMe, CH ₂ Cl ₂ , 25°	 (>78)	113																				
	Al(OBu- <i>t</i>) ₃	 I +  II	6																				
		<table border="1"> <thead> <tr> <th>Solv</th> <th>Temp</th> <th>Time</th> <th>I</th> <th>II</th> </tr> </thead> <tbody> <tr> <td>C₆H₆</td> <td>25°</td> <td>4 h</td> <td>(54)</td> <td>(35)</td> </tr> <tr> <td>THF</td> <td>25°</td> <td>12 h</td> <td>(46)</td> <td>(37)</td> </tr> <tr> <td>C₆H₆</td> <td>reflux</td> <td>12 h</td> <td>(87)</td> <td>(—)</td> </tr> </tbody> </table>	Solv	Temp	Time	I	II	C ₆ H ₆	25°	4 h	(54)	(35)	THF	25°	12 h	(46)	(37)	C ₆ H ₆	reflux	12 h	(87)	(—)	
Solv	Temp	Time	I	II																			
C ₆ H ₆	25°	4 h	(54)	(35)																			
THF	25°	12 h	(46)	(37)																			
C ₆ H ₆	reflux	12 h	(87)	(—)																			
	NaOMe (6.5 x 10 ⁻⁴ N), MeOH	 +  R = Ac (15); R = H (36) (15)	7																				
	Al(OPr- <i>i</i>) ₃ or Al(OBu- <i>t</i>) ₃	 I +  II	6																				
		<table border="1"> <thead> <tr> <th>Temp</th> <th>Time</th> <th>I</th> <th>II</th> </tr> </thead> <tbody> <tr> <td>50°</td> <td>1 h</td> <td>(42)</td> <td>(38)</td> </tr> <tr> <td>reflux</td> <td>3 h</td> <td>(15)</td> <td>(85)</td> </tr> <tr> <td>reflux</td> <td>12 h</td> <td>(—)</td> <td>(93)</td> </tr> </tbody> </table>	Temp	Time	I	II	50°	1 h	(42)	(38)	reflux	3 h	(15)	(85)	reflux	12 h	(—)	(93)					
Temp	Time	I	II																				
50°	1 h	(42)	(38)																				
reflux	3 h	(15)	(85)																				
reflux	12 h	(—)	(93)																				
	KOH, MeOH	 (100)	115																				

TABLE 1E. COMPLEX POLYCYCLIC α -KETOLS (Continued)

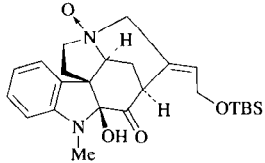
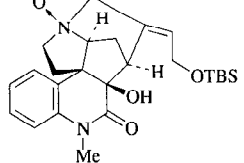
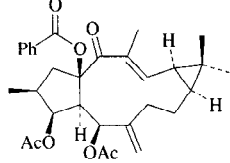
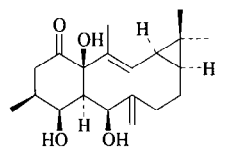
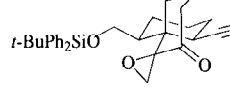
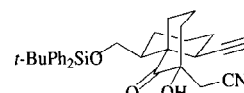
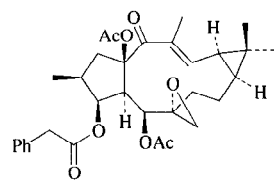
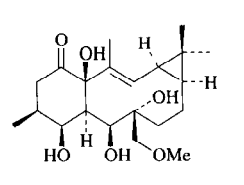
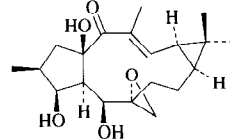
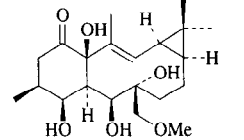
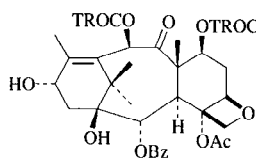
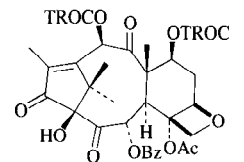
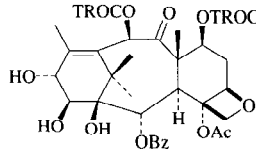
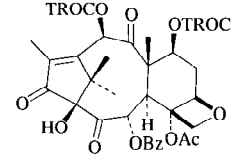
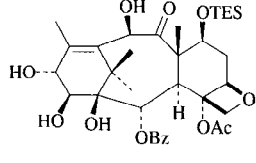
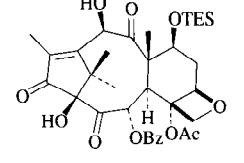
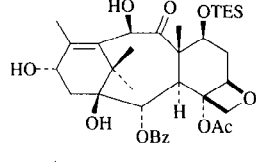
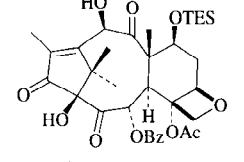
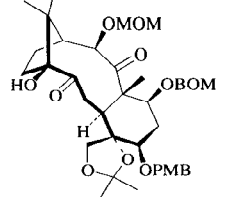
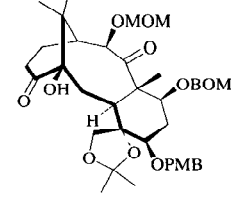
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₃₁ 	KH, 18-crown-6, DME, rt	 (—)	116
	Ba(OMe) ₂ , MeOH, rt	 (—)	39
	Et ₂ AlCN, toluene, 45°	 (74)	114
C ₃₂ 	Ba(OMe) ₂ , MeOH, rt, 8 h	 (45)	39
	Ba(OMe) ₂ , MeOH, rt, 8 h	 (—)	39
C ₃₅ 	MnO ₂	 (41)	40
C ₃₅ 	MnO ₂	 (39)	40
	MnO ₂	 (35)	40
	MnO ₂	 (—)	40
C ₄₀ 	Al(OBu- <i>t</i>) ₃ , C ₆ H ₆ , reflux, 12 h	 (94)	42

TABLE 2. α -HYDROXY ALDEHYDES

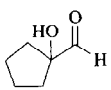
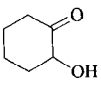
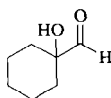
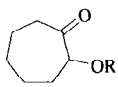
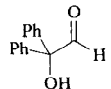
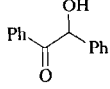
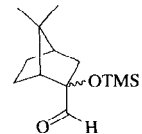
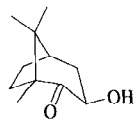
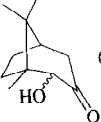
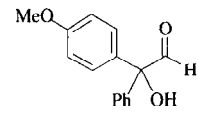
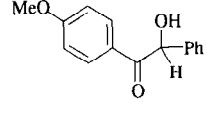
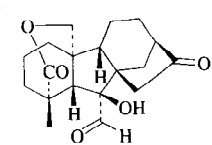
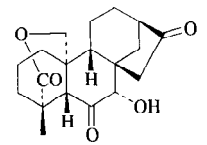
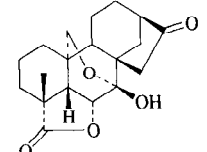
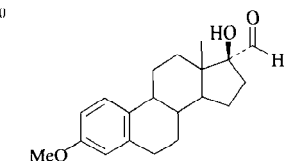
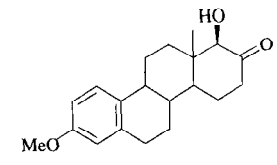
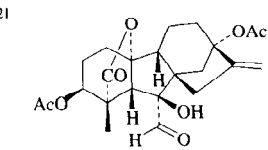
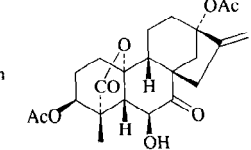
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.												
C ₆ 	EtOH (96%), H ₂ SO ₄ (dilute), sealed tube, 132-140°, 4-5 h	 (80-87)	47												
C ₇ 	H ₂ SO ₄ (dil), sealed tube	 <table border="1" data-bbox="1084 560 1375 646"> <thead> <tr> <th>Solv</th> <th>R</th> <th>Temp</th> <th>Time</th> </tr> </thead> <tbody> <tr> <td>EtOH</td> <td>Et</td> <td>135-148°</td> <td>4-6 h (55-80)</td> </tr> <tr> <td>—</td> <td>H</td> <td>140-148°</td> <td>5-6 h (72-80)</td> </tr> </tbody> </table>	Solv	R	Temp	Time	EtOH	Et	135-148°	4-6 h (55-80)	—	H	140-148°	5-6 h (72-80)	119
Solv	R	Temp	Time												
EtOH	Et	135-148°	4-6 h (55-80)												
—	H	140-148°	5-6 h (72-80)												
C ₁₄ 	H ₂ SO ₄ (cat.), EtOH, sealed tube, 130-140°, 6 h	 (75)	46												
	BF ₃ •OEt ₂ , CH ₂ Cl ₂ , 0° to rt; or Bu ₄ N ⁺ F ⁻	 (16) +  (41)	120												
C ₁₅ 	MeOH (50%), KOH, reflux, 1 h Heat	 (91) (—)	118												
C ₁₉ 	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , rt, 30 min	 (100)	48												
	KH, THF, 0° to rt, 30 min	 (—)	48												
C ₂₀ 	Silica gel Heat (110°) BF ₃ •OEt ₂ , CH ₃ CN, rt	 (91) (100) (76)	122												
C ₂₁ 	BF ₃ •OEt ₂ , CH ₂ Cl ₂ , 20°, 30 min	 (80)	123												

TABLE 2. α -HYDROXY ALDEHYDES (Continued)

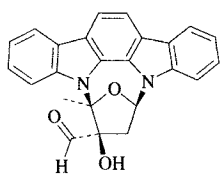
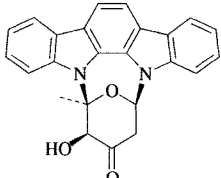
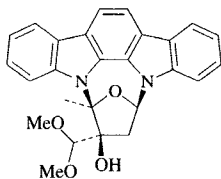
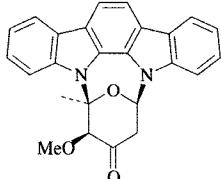
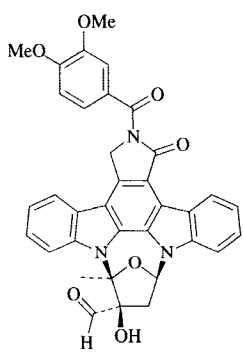
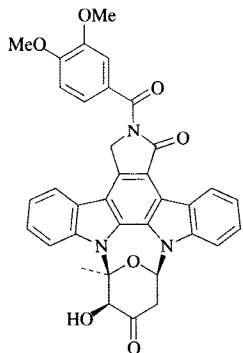
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₂₄ 	BF ₃ •OEt ₂ , rt, 3 h	 (60)	124
C ₂₆ 	BF ₃ •OEt ₂ , ether, 72 h	 (50)	126
C ₃₅ 	BF ₃ •OEt ₂ , ether 25-30°	 (85)	125

TABLE 3. α -HYDROXY IMINES

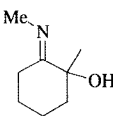
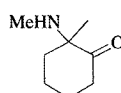
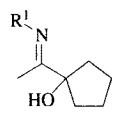
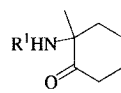
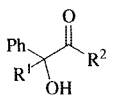
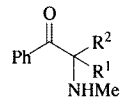
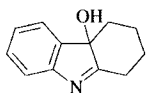
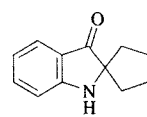
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																				
C ₈ 	Neat Xylene, cat. acetic acid	 <table border="1"> <thead> <tr> <th>Temp</th> <th>Time</th> <th>Yield (%)</th> </tr> </thead> <tbody> <tr> <td>170°</td> <td>10 h</td> <td>(10-15)</td> </tr> <tr> <td>reflux</td> <td>8 h</td> <td>(20)</td> </tr> </tbody> </table>	Temp	Time	Yield (%)	170°	10 h	(10-15)	reflux	8 h	(20)	132											
Temp	Time	Yield (%)																					
170°	10 h	(10-15)																					
reflux	8 h	(20)																					
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C ₁₀₋₁₅ 	MeNH ₂ , 200°, sealed tube, 10 h	 <table border="1"> <thead> <tr> <th>R¹</th> <th>R²</th> <th>Yield (%)</th> </tr> </thead> <tbody> <tr> <td>Et</td> <td>Et</td> <td>(32)</td> </tr> <tr> <td>Me</td> <td>Me</td> <td>(39)</td> </tr> <tr> <td>Ph</td> <td>Me</td> <td>(36)</td> </tr> </tbody> </table>	R ¹	R ²	Yield (%)	Et	Et	(32)	Me	Me	(39)	Ph	Me	(36)	158								
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TABLE 3. α -HYDROXY IMINES (Continued)

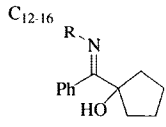
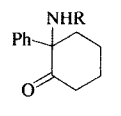
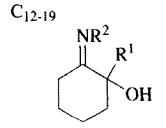
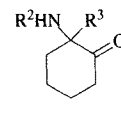
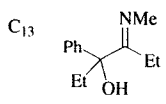
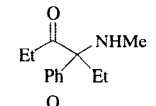
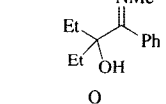
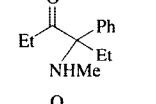
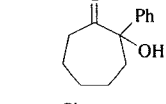
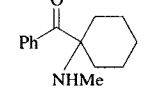
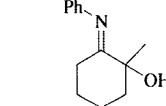
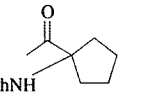
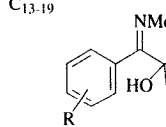
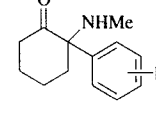
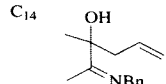
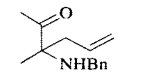
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																																																																																																		
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TABLE 3. α -HYDROXY IMINES (Continued)

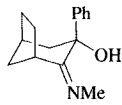
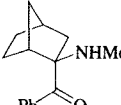
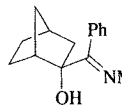
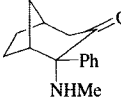
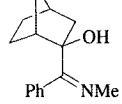
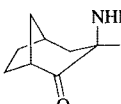
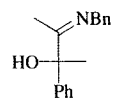
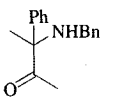
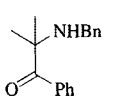
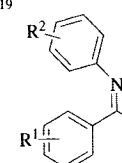
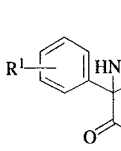
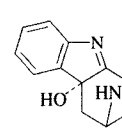
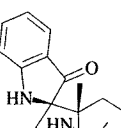
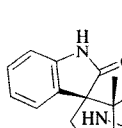
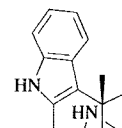
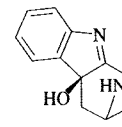
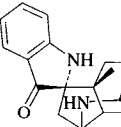


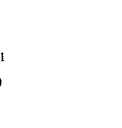
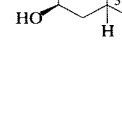
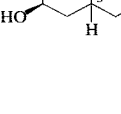
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																											
C ₁₅ 	<i>o</i> -Dichlorobenzene, 185°, 67 h	 (72)	52																											
	<i>o</i> -Dichlorobenzene, 185°, 3 h	 (96)	52																											
	<i>o</i> -Dichlorobenzene, 185°, 14 h	 (86)	52																											
C ₁₇ 	Decalin, reflux, 18 h	 +  (38)	49																											
C ₁₈₋₁₉ 	Decalin, 208 ± 2°	 <table border="1" data-bbox="1180 895 1354 1159"> <thead> <tr> <th>R¹</th> <th>R²</th> <th></th> </tr> </thead> <tbody> <tr> <td>H</td> <td>H</td> <td>(82)</td> </tr> <tr> <td><i>p</i>-OMe</td> <td>H</td> <td>(77)</td> </tr> <tr> <td><i>p</i>-Me</td> <td>H</td> <td>(15)</td> </tr> <tr> <td><i>m</i>-Cl</td> <td>H</td> <td>(20)</td> </tr> <tr> <td>H</td> <td><i>p</i>-OMe</td> <td>(89)</td> </tr> <tr> <td>H</td> <td><i>p</i>-Me</td> <td>(80)</td> </tr> <tr> <td>H</td> <td><i>m</i>-Cl</td> <td>(77)</td> </tr> <tr> <td>H</td> <td><i>p</i>-NO₂</td> <td>(38)</td> </tr> </tbody> </table>	R ¹	R ²		H	H	(82)	<i>p</i> -OMe	H	(77)	<i>p</i> -Me	H	(15)	<i>m</i> -Cl	H	(20)	H	<i>p</i> -OMe	(89)	H	<i>p</i> -Me	(80)	H	<i>m</i> -Cl	(77)	H	<i>p</i> -NO ₂	(38)	50
R ¹	R ²																													
H	H	(82)																												
<i>p</i> -OMe	H	(77)																												
<i>p</i> -Me	H	(15)																												
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H	<i>p</i> -OMe	(89)																												
H	<i>p</i> -Me	(80)																												
H	<i>m</i> -Cl	(77)																												
H	<i>p</i> -NO ₂	(38)																												
C ₂₀ 	(H ₃ PO ₄) _n , EtOH, reflux, 24 h	 I (50-98) +  II (0-15)	154, 155																											
	NaOH, MeOH, reflux, 48 h	I (97) + II (—)	159																											
	O ₂ , CCl ₄ , 72 h	 (20)	155																											
	NaOEt, EtOH, 25°, 22 h	 (86) +  (14)	159																											
C ₂₁ 	Amine, cosolvent, sealed tube, 195°, 10 h	 <table border="1" data-bbox="1145 1951 1414 2077"> <thead> <tr> <th>R¹</th> <th>Amine</th> <th>H₂</th> <th>Cosolvent</th> <th></th> </tr> </thead> <tbody> <tr> <td>Me</td> <td>MeNH₂</td> <td>α</td> <td>—</td> <td>(39)</td> </tr> <tr> <td>Me</td> <td>MeNH₂</td> <td>β</td> <td>—</td> <td>(35)</td> </tr> <tr> <td>Me</td> <td>MeNH₂</td> <td>β</td> <td>MeOH</td> <td>(34)</td> </tr> <tr> <td>H</td> <td>NH₃</td> <td>β</td> <td>MeOH</td> <td>(29)</td> </tr> </tbody> </table>	R ¹	Amine	H ₂	Cosolvent		Me	MeNH ₂	α	—	(39)	Me	MeNH ₂	β	—	(35)	Me	MeNH ₂	β	MeOH	(34)	H	NH ₃	β	MeOH	(29)	136		
R ¹	Amine	H ₂	Cosolvent																											
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Me	MeNH ₂	β	MeOH	(34)																										
H	NH ₃	β	MeOH	(29)																										

TABLE 3. α -HYDROXY IMINES (Continued)

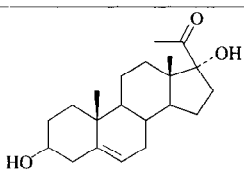
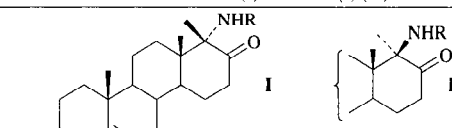
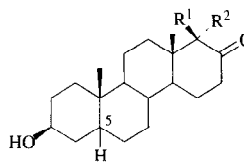
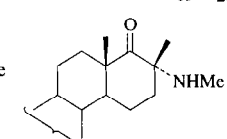
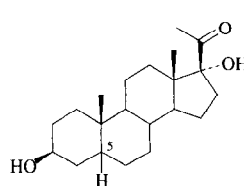
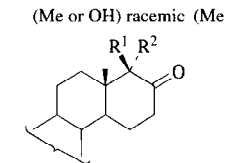
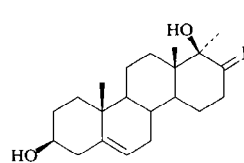
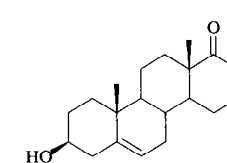
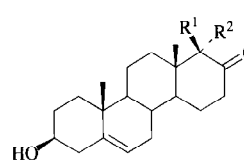
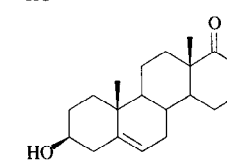
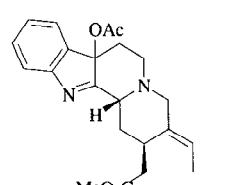
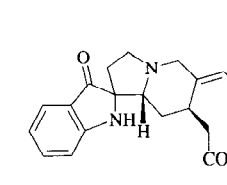
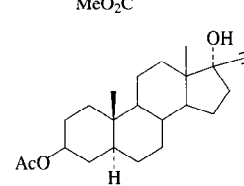
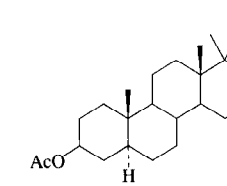
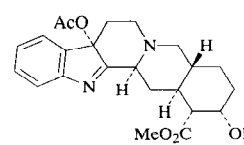
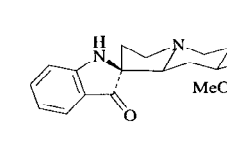
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																																										
	MeNH ₂ , sealed tube	 <table border="1"> <thead> <tr> <th>R</th> <th>Temp</th> <th>I</th> <th>II</th> </tr> </thead> <tbody> <tr> <td>Me</td> <td>200°</td> <td>(77)</td> <td>(0)</td> </tr> <tr> <td>H</td> <td>200°</td> <td>(62)</td> <td>(0)</td> </tr> <tr> <td>H</td> <td>200°</td> <td>(35)</td> <td>(35)</td> </tr> </tbody> </table>	R	Temp	I	II	Me	200°	(77)	(0)	H	200°	(62)	(0)	H	200°	(35)	(35)	160																										
	R		Temp	I	II																																								
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	R ¹		R ²	H ₅	Cosolvent																																								
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	Dowtherm A, 200°, 60-10 h	 (—)	137																																										
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	R ¹		R ²																																										
OH	Me	(—)																																											
Me	OH	(—)																																											
	NaOMe, MeOH, reflux, 1 h	 (17)	161																																										
	HgCl ₂ , aniline, benzene, 60°	 (65)	93																																										
	NaOMe, MeOH, heat	 (—)	141																																										

TABLE 3. α -HYDROXY IMINES (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																																																
C ₂₃ 	NaOMe, MeOH, heat	(—)	141																																																
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C ₂₃₋₂₅ 	Amine, cosolvent, sealed tube 195°, 10 h	I + II	136																																																
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NH ₃	—	NH ₂	CH ₃	β	(29)	(0)																																													
C ₂₅ 	NaOMe, MeOH, heat, 4 h	(11)	141																																																
C ₂₈ 	NaOMe, MeOH	(63)	140																																																
	NaOMe, MeOH	(63-67)	139, 140																																																
C ₂₉ 	NaOMe, MeOH, reflux	(—)	162																																																

8. Acknowledgments

We wish to express our sincere gratitude to Prof. Alex Nickon for his yeomanship editing efforts with an early draft of this review, to Ms. Rebecca Martin for her tireless efforts in typing the entire manuscript and seeing to it that all of the structural formulas conform to *Organic Reactions* guidelines, to Dr. Linda Press of the editorial staff for invaluable guidance and assistance during draft preparation, and to Prof. William Roush for securing reviews of the completed text. J.E.H. is a member of the National Institutes of Health Chemistry/Biology Interface Training Program and received fellowship support from both the NIH and The Ohio State University.

End Notes

† This chapter is dedicated to the memory of Dr. Robert Joyce, whose long time editorial efforts on behalf of *Organic Reactions* are worthy of far greater acclaim.

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Transformation of Glycals into 2,3-Unsaturated Glycosyl Derivatives

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Abstract

Various elimination procedures conducted on appropriate pyranoid and furanoid carbohydrate derivatives, especially on *O*-protected glycosyl halides afford cyclic vinyl ethers which Fischer (inappropriately) named glycals. These are used extensively in general organic synthesis and for the preparation of non-carbohydrate natural products as well as biologically important complex carbohydrates and glycoconjugates. The best known member, tri-*O*-acetyl-D-glucal, is normally made from tetra-*O*-acetyl- α -D-glucopyranosyl bromide, is commercially available, and is used very frequently in this chapter to represent the family in examples of the reactions under discussion.

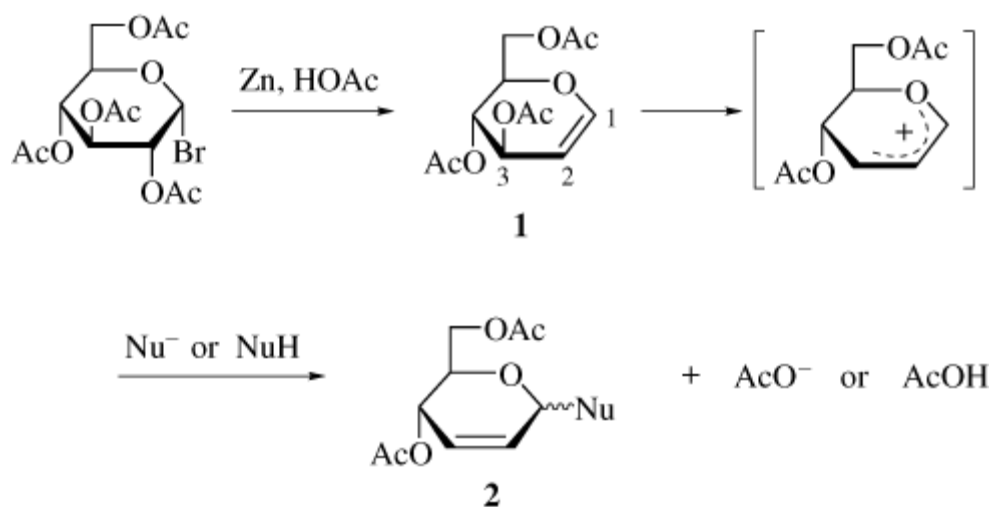
Because of the pronounced region- and stereoselectivities with which their addition reactions can be conducted, glycal derivatives are of major importance in synthesis. They also, however, take part in rearrangement processes that, likewise, have proved useful for synthesis. The principal one involves nucleophilic substitution of the allylic group with allylic rearrangement and results in products having double bonds in the 2, 3 positions and new substituents at the anomeric centers. By far the simplest and most commonly used way to this conversion involves the removal of the allylic substituent of the glycal and the generation of highly resonance-stabilized oxocarbenium ion intermediate. This may then react with nucleophiles at the anomeric center to give products as mixtures of diastereomers. Many examples and variations of this theme are described and form the major part of this chapter, but other ways are also considered

Almost no formal mechanistic studies have been carried out on the reactions in this chapter. Categorization of mechanism required for the treatment of this topic has been done on the basis of conditions used, product identification and largely, chemical intuition.

1. Introduction

Various elimination procedures conducted on appropriate pyranoid and furanoid carbohydrate derivatives, especially on *O*-protected glycosyl halides, afford cyclic vinyl ethers which Fischer (inappropriately, see below) named “glycals”. (1, 2) These are used extensively in general organic synthesis, (3, 4) and for the preparation of non-carbohydrate natural products (5, 6) as well as biologically important complex carbohydrates and glycoconjugates. (7) The best known member, tri-*O*-acetyl-D-glucal (1), is normally made from tetra-*O*-acetyl- α -D-glucopyranosyl bromide, is commercially available, and is taken very frequently in this review to represent the family in exemplifications of the reactions under discussion.

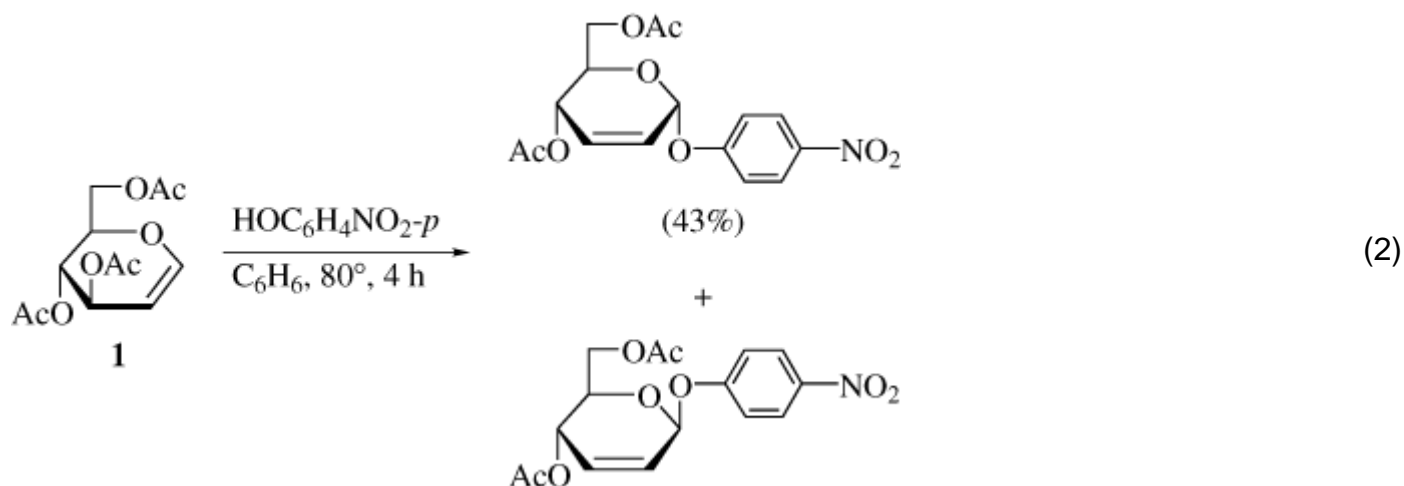
Because of the pronounced regio- and stereoselectivities with which their addition reactions can be conducted, glycal derivatives are of major importance in synthesis. They also, however, take part in rearrangement processes that, likewise, have proved useful for synthetic work. Of these, the principal one involves nucleophilic substitution of the allylic group with allylic rearrangement and results in cyclic products having double bonds in the 2,3-positions and new substituents at the anomeric centers. By far the simplest and most commonly used way of effecting this conversion involves the removal of the allylic substituent of the glycal and the generation of a highly resonance-stabilized oxocarbenium ion intermediate. This may then react with nucleophiles at the anomeric centers to give the products as mixtures of diastereomers (Eq. 1). The transformation is therefore a glycosylation process that allows the bonding of unsaturated sugar moieties through the anomeric C-1 position to a range of *O*-, *S*-, *N*-, and *C*-linked substituents. For convenience these will be termed “aglycons” although this word is usually reserved for the non-carbohydrate parts of *O*-glycosides. Many examples and variations of this simple theme have been described and form the major part of the present review, but other ways of effecting the glycal into 2,3-unsaturated glycosyl derivative conversion are also considered.



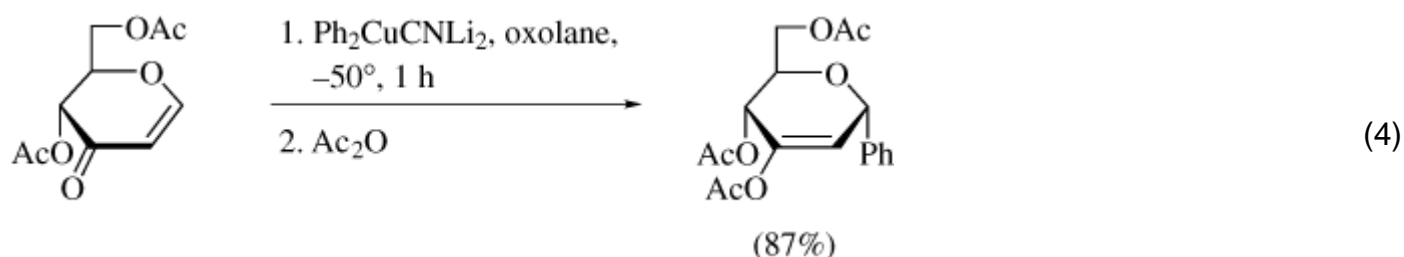
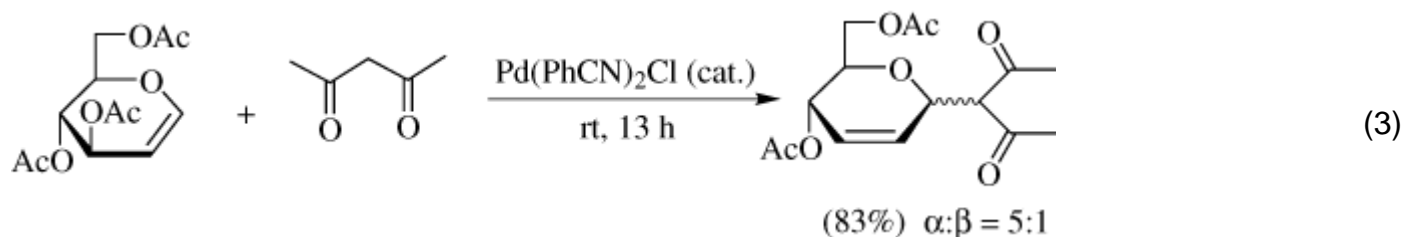
In his seminal paper in which he described the adventitious preparation of tri-*O*-acetyl-D-glucal (1) Emil Fischer also reported that heating the product with water caused it to dissolve and effectively lose one of its acetyl groups. (8) While it took a decade to establish that the main product was the allylic hemiacetal 2 (Eq. 1, Nu = OH), (9) a minor product, formed photochemically from the acyclic form of this hemiacetal, was not identified for more than half a century. (10) This acyclic enal (73) and isomer (74), formed by acetyl migration, become major products as the hydrolysis reaction proceeds (Eq. 51), and are historically notable because they, together with hemiacetal 2 (Nu = OH), are likely to have been the source of the reducing power which Fischer ascribed to glucal and from which he gave it the erroneous “al” suffix. The importance of the masked conjugated enal character of compound 2 (Nu = OH) should not be overlooked in the reactions of glycals and their derivatives. Its presence could account for the occasional finding of saturated products bearing nucleophilic

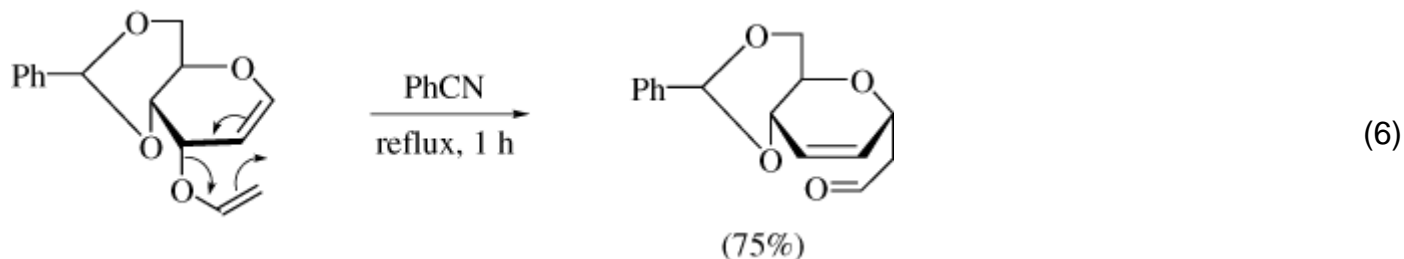
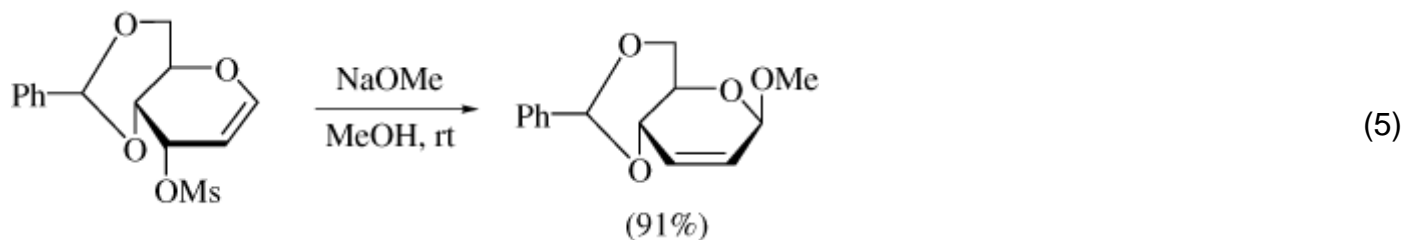
groups at C-1 and C-3 of cyclic 2-deoxyglycopyranosyl compounds instead of the normal allylicly rearranged unsaturated glycosyl derivatives **2**. As will be seen, adventitious water acting catalytically can account for this anomaly (Eq. 67).

The conversion of **1** into **2** (Nu = OH) is the first example of the transformation here reviewed. The second was encountered serendipitously half a century later during an attempted self-catalyzed addition of *p*-nitrophenol to glycal **1** (Eq. 2), (11) and this development led to a new O-glycosylation process (12, 13) and hence to one that utilizes a Lewis acid catalyst and that can be conducted efficiently under mild conditions with equimolar proportions of the nucleophilic reactant (14) to provide precursors of saturated glycosides and disaccharides. (15) Soon afterwards it was established that analogous processes can be applied to the preparation of S- (16), N- (17), and of special significance in synthesis, C- (18) glycosyl compounds.



Other glycal reactions, however, that proceed by entirely different mechanisms, may bring about the same change: some involve addition-elimination (Eq. 3) (19-21) or, very rarely, 1,4-addition (Eq. 4) sequences; (22) some are mechanistically different substitution reactions (Eq. 5); (23) while others are based on sigmatropic rearrangements (Eq. 6). (24) Of all of these other processes only those that involve the addition of palladium species to the glycals and subsequent depalladation have been developed to the point of being generally synthetically useful. (20, 21) Some of the other “non-oxocarbenium” reactions are relatively new and incompletely developed, and some





are limited in their applicability or require uncommon or unstable reagents. Together they therefore do not compare in terms of their general utility with the transformations that proceed via cationic intermediates (Eq. 1, 1 into 2) and that are characterized by their simplicity and effectiveness.

Almost no formal mechanistic studies have been carried out on the reactions covered in this review. The categorization of mechanism required for the treatment of the topic has therefore been done on the basis of the conditions used, product identification, and, largely, chemical intuition. On some occasions appreciable uncertainty regarding mechanism has necessarily been involved. Shorter surveys have appeared on the transformation here under review (2, 25) and its application to the synthesis of *O*-glycosides (18, 26, 27) and *C*-glycosides. (20, 21, 28, 29)

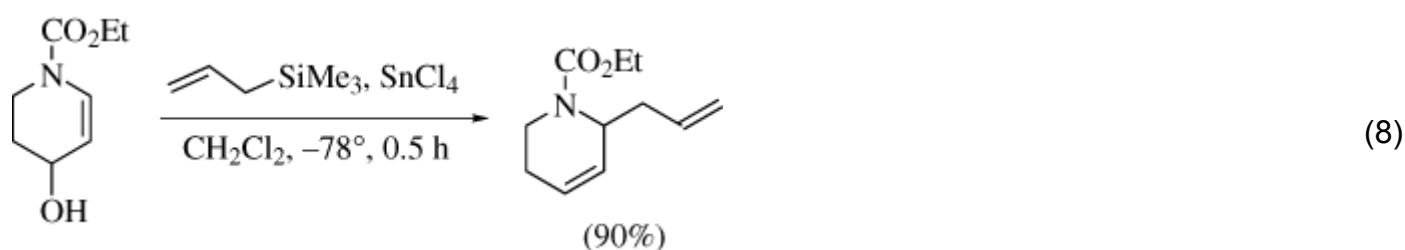
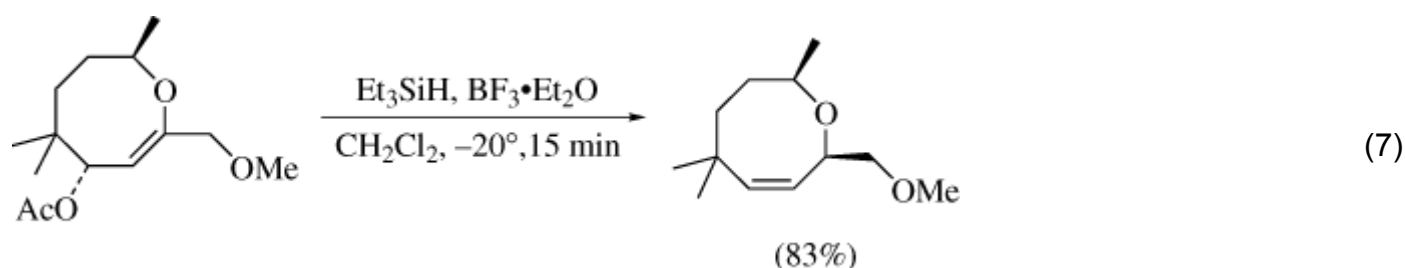
One of us (RJF) wishes to add a personal comment. The direct preparation of 2,3-unsaturated *O*-glycosides from glycol derivatives is commonly called “the Ferrier reaction” (30) — a term I have always carefully avoided because the transformation was first observed by Emil Fischer (8) and because its development depended on the work of the chemists mentioned in the acknowledgements. A different reaction by which functionalized cyclohexanones are efficiently produced on treatment of hex-5-enopyranosyl derivatives with mercury(II) salts in the presence of water (31) has been given the same name (perhaps more legitimately (32)) and confusion has resulted. (30) For these reasons, and the additional one that the present review covers many important conversions beyond those resulting in the production of *O*-glycosides, the title does not refer to a “name reaction.”

2. Mechanisms, Stereochemistry, and Other General Features

2.1. Transformations Involving Oxocarbenium Ions

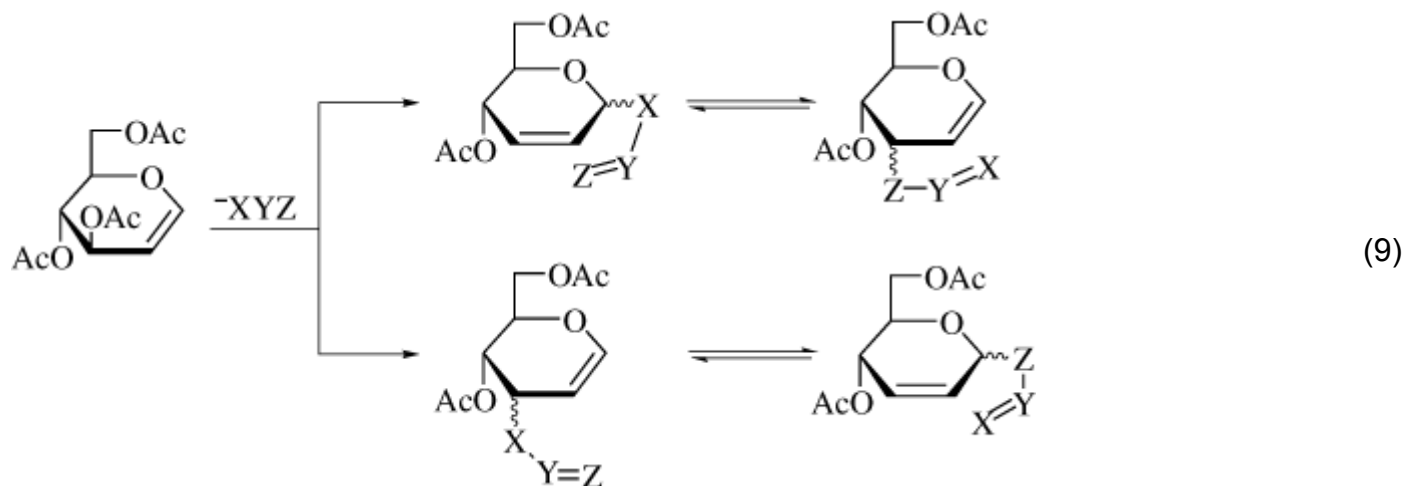
2.1.1. General

In the presence of Lewis acids cyclic enol ethers having leaving groups at the allylic sites readily undergo nucleophilic displacement reactions with allylic rearrangement; an example is given in Eq. 7, (33) and analogous enamines behave similarly (Eq. 8). (34) These are close analogs of the acid-catalyzed transformations of unsaturated carbohydrate compounds which occupy most of this survey. Typically the reactions are conducted with glycal derivatives having acyloxy groups at the allylic positions and with Lewis, and occasionally protonic, acid catalysts to facilitate the departure of these groups with the formation of delocalized oxocarbenium ions. These normally react with O-, S-, N-, and C-nucleophilic species at the anomeric center to give mixtures of diastereomeric products (Eq. 1). Commonly, the last step is reversible and very significant regioselectivity and stereo selectivity are observed, but there are exceptions to these generalizations.

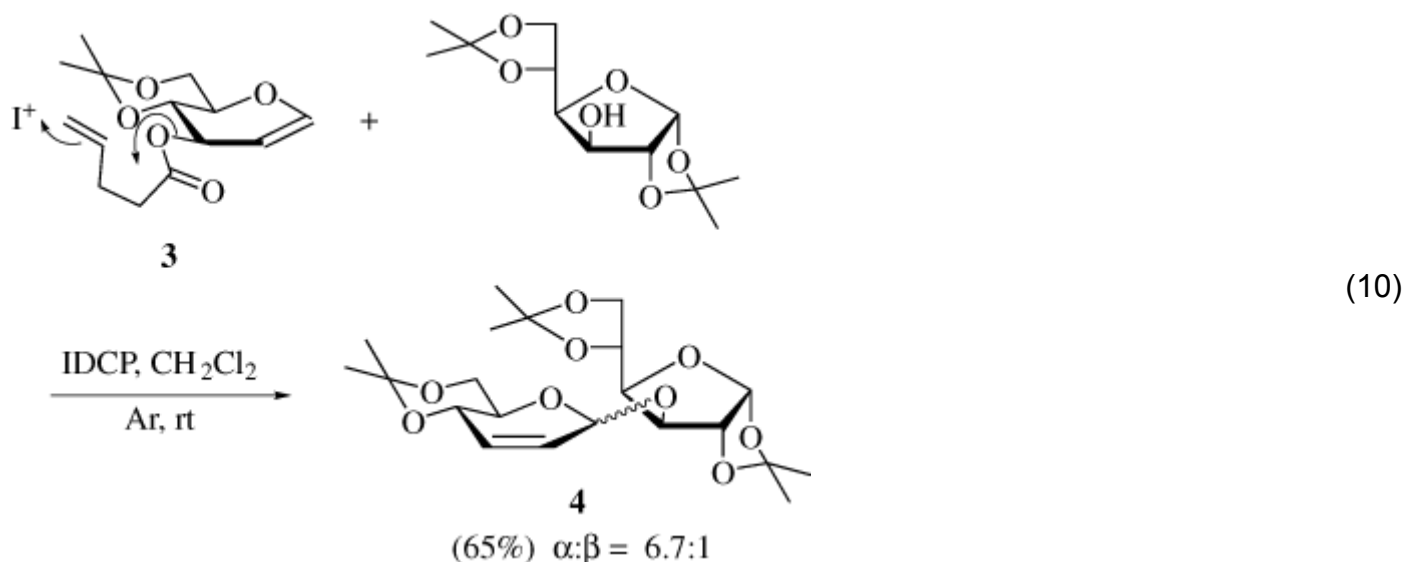


There is proof that ionic intermediates are involved in the reaction, at least under some circumstances, since for example, mixtures of different 2,3-unsaturated *S*-glycosides exchange their aglycons (Nu) under the conditions of their synthesis. (35) Also consistent with the occurrence of ionic intermediates in the reaction is the finding that, from tri-*O*-acetyl-*D*-glucal, the *α*- and *β*-2,3-unsaturated glycosyl products are very commonly formed in the equilibrium ratio of 7:1. In most cases of products formed from this glycal under kinetic control (notably 2,3-unsaturated *C*-glycosides) the *α*-anomers are also favored.

There are further complicating factors. As is discussed under "Regioselectivity", some kinetic products can rearrange to equilibrated mixtures that include high proportions of isomers which are glycols having the nucleophile substituted at C-3. This is especially, but not exclusively, the case when ambident nucleophiles such as azide or thiocyanate are used (Eq. 9).



A variation on the theme outlined in Eq. 1 involves the use of glycal derivatives with substituents at the allylic centers that can be activated as leaving groups under neutral conditions, and therefore the use of acids as catalysts can be avoided. For example, the unsaturated ester **3**, on treatment with iodonium dicollidine perchlorate (IDCP), becomes a glycosylating agent used to make the disaccharide compounds **4** in good yield and α -selectivity (Eq. 10). (36) Further variables of significance in the application of the transformation reaction are the nature and stereochemistry of ring substituents at the homoallylic C-4 position, the presence of substituents at C-2, and the sugar ring size. Appropriate selection of the nucleophiles used leads to the attachment of groups bonded via oxygen, sulfur, nitrogen, fluorine, phosphorus or, importantly, carbon at the anomeric position (or occasionally at C-3) of the unsaturated carbohydrate moieties. Hydrogen may be introduced similarly and, except in this case, the question of the stereochemistry at the new chiral centers in the products is of considerable significance.



Each of the variables applying to the reaction under review is now considered.

2.1.2. Incoming Nucleophiles

Alcohols and phenols are most commonly used as sources of *O*-nucleophilic species, but may be replaced by orthoesters (37) or acetals (14, 38, 39) in which instances hydroxyl-containing by-products of reaction, which are competitive nucleophiles, are not formed concurrently with the 2,3-unsaturated glycosides (Eq. 1; 2, Nu = alkyloxy, aryloxy etc.). Thiols can react similarly, but their trimethylsilyl derivatives may be used with advantage to enhance the regioselectivity of the reaction.

Likewise, *N*-bases are commonly trimethylsilylated, but need not be. Among *C*-nucleophiles used are organometallic compounds, various alkenes, vinyl ethers, vinyl esters, allyl ethers and esters, organosilanes, silyl ketene acetals, and *b*-dicarbonyl compounds. *C*-Aryl glycosides are obtained by use of activated phenols or bromomagnesium phenates. Hydrogen fluoride, dialkyl phosphites, and triethylsilane are, respectively, used in the preparation of 2,3-unsaturated glycosyl fluorides, phosphonates, and hydrides. The last group of products are 1,5-anhydroalditol derivatives.

The issue of intramolecular delivery of nucleophiles is important and is considered together with all the above matters under "Scope and Limitations."

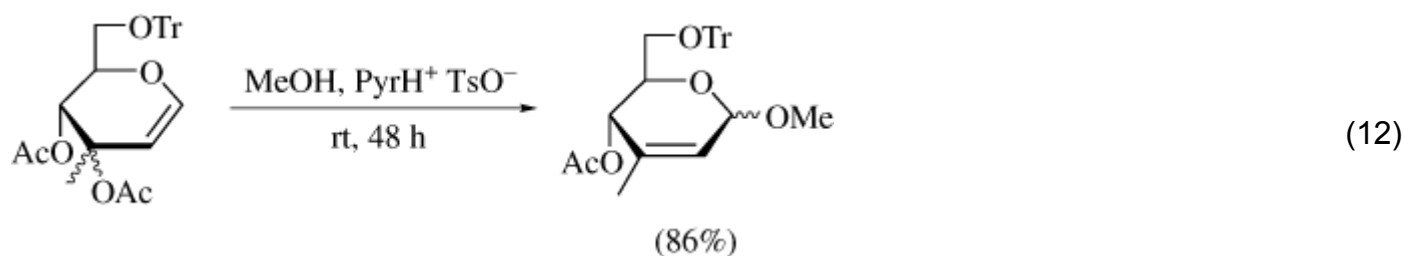
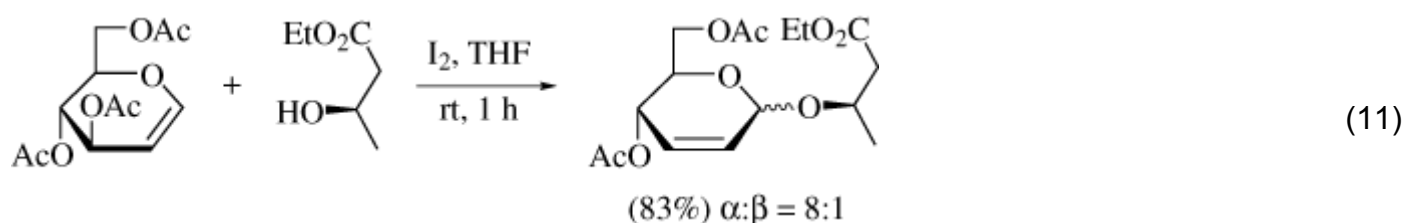
2.1.3. Leaving Groups and Activators

The most common allylic leaving groups used are the carboxylates present in *O*-acetylated and *O*-benzoylated glycals, several of which are commercially available and which, provided sufficiently high temperatures are used, can take part in the rearrangement process with simple alcohols (12) and with phenols (13) to give alkyl or aryl 2,3-unsaturated *O*-glycosides without the need for added catalyst (Eq. 2). To describe these reactions as "uncatalyzed," however, may well be inappropriate since carboxylic acids are usually generated as by-products which may facilitate the removal of the allylic groups, particularly in later stages of the reactions. When glycals with better allylic leaving groups are involved the reactions can proceed without added catalyst and by the S_N2[~] mechanism. (40)

The leaving potential of allylic ester groups can be increased by the introduction of electron-withdrawing substituents; the trichloroacetimidate has been employed for the preparation of 2,3-unsaturated *O*- (40a) and *C*- (40b) glycosides, and the uses of trifluoroacetyl and *p*-nitrobenzoyl esters for making analogous *C*- and *N*-linked analogs are mentioned later (refs. 115 and 211, respectively). The more general and simpler method involves the use of acid catalysts. Frequently, however, it is inappropriate to use protonic acids because they preferentially catalyze additions to the vinyl ether groups of the glycals and lead to saturated 2-deoxyglycosyl derivatives. (12) With heterocyclic bases as nucleophiles protonic acids can promote the allylic rearrangement, and instances have been reported of the production of 2,3-unsaturated pyranosylpurines under the influence of *p*-toluenesulfonic acid, (17, 41) trichloroacetic acid, (42) and trifluoroacetic acid. (43) The first of these acids has also been used to effect the allylic rearrangement of a compound akin to a 3-hydroxyglycal. (44)

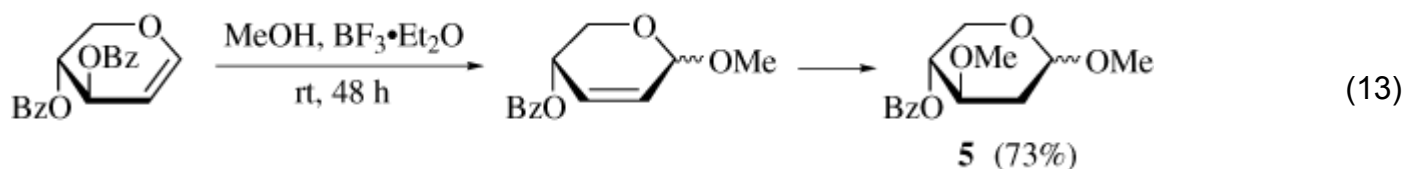
Much more useful are Lewis acids, boron trifluoride etherate being most commonly employed with many glycals. (14) However, yields of products are modest when this catalyst is used with tri-*O*-acetyl-D-galactal (45) and di-*O*-acetyl-L-rhamnal, (46) and with these compounds tin(IV) chloride gives higher yields of 2,3-unsaturated *O*-glycosides. (45, 46) Other Lewis acids have been employed as follows (whether for the synthesis of *O*-, *S*-, *N*-, or *C*-linked 2,3-unsaturated glycosylated products is indicated in parenthesis): FeCl₃ (*O*), (47) (*C*); (48, 49) SbCl₅ (*O*), (50) (*N*); (51) TiCl₄ (*C*); (52-55) (*i*-PrO)₂TiCl₂ (*C*); (56) InCl₃ (*O*), (57) (*C*); (58) SnBr₄ (*O*), (59, 60) (*C*); (61) ZnBr₂ (*C*); (48, 56, 62, 63) LiBF₄ (*O*), (64) (*C*), (65) (*S*); (66) LiClO₄ (*C*); (67, 68) LiClO₄/ TrClO₄ (*N*); (69, 70) TMSOTf (*O*), (71, 72) (*C*); (73-76) Sc(OTf)₃ (*O*), (77) (*C*); (78) Yb(OTf)₃ (*O*), (79) (*N*) (80), (*C*); (81) Montmorillonite (*O*), (82-84) (*C*); (85) DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) (*O*), (86) (*C*), (87) and iodine (*O*), (88-91) (*C*), (92) (*N*). (92) In addition, organoaluminum compounds such as EtAlCl₂, (61) Et₂AlCN. (93) and Me₃Al, (94) which are Lewis acids that also provide nucleophiles, can be employed in the synthesis of 2,3-unsaturated *C*-glycosides, and EtAlCl₂ has been used to catalyze a related displacement of a methanesulfonyloxy group from the homoallylic *C*-4 position of a 3-deoxyglycal to give 2[~],3[~]-cyclopropanucleosides (Eq. 123). Very few comparative studies of these catalysts have been conducted, but "more readily controlled reactions" have been claimed with ZnCl₂, (95) and there are examples in which it is extremely effective while BF₃•Et₂O is not. (96) Likewise FeCl₃ has been described as a "particularly attractive catalyst"; (47) SnBr₄ can lead to satisfactory reaction when the more commonly used catalysts are ineffective, (97) and InCl₃ (57) and Montmorillonite K-10 (84) have been identified as being more effective than some others.

The main feature of iodine lies in the mildness of the conditions under which it operates effectively. Although HI might be a by-product of the reaction induced by iodine, the latter can be used effectively to glycosylate the sensitive ethyl 3-hydroxy-butanoate (Eq. 11) (90) which is decomposed by reagents such as $\text{BF}_3 \cdot \text{Et}_2\text{O}$. Iodine is effective with a wide range of alcohols and, when used with tri-*O*-acetyl-D-glucal, results in yields of anomerically mixed products that are often higher than previously reported, with α,β ratios in the usual range of 7(α 1):1. The yields with phenols are lower at approximately 65% and the ratios are about 10:1. Alcohols subject to very ready elimination, such as many allylic and cyclic benzylic alcohols, and compounds containing basic nitrogen atoms, are amongst the few that do not undergo the glycosylation reaction in the presence of iodine. (90) *O*-Acylated glycols also react in the presence of catalytic proportions of iodine with allyltrimethylsilane, trimethylsilyl cyanide, and trimethylsilyl azide to give 2,3-unsaturated products having allyl, cyano, and azido groups, respectively, at C-1 in high yields and with good α -selectivity. (92) In an example involving a glycal with a quaternary center bearing an acetoxy group at the allylic C-3, pyridinium *p*-toluenesulfonate acts as activator (Eq. 12). (98)

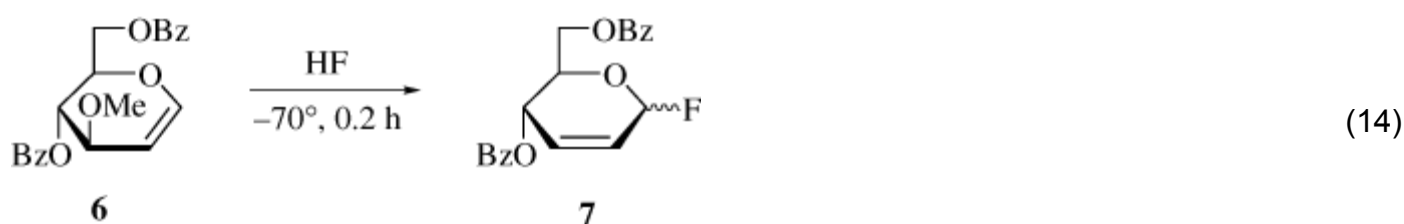


While these activators generally lead to unsaturated products with one introduced nucleophilic group replacing an allylic leaving group (usually with allylic rearrangement), the very occasional report of other reactions has appeared. Thus, whereas treatment of di-*O*-benzoyl-D-xylal with methanol in dichloromethane containing $\text{BF}_3 \cdot \text{Et}_2\text{O}$ initially gives the expected 2,3-unsaturated methyl glycosides, further reaction affords products that have apparently undergone secondary addition of methanol to the double bond, namely saturated methyl

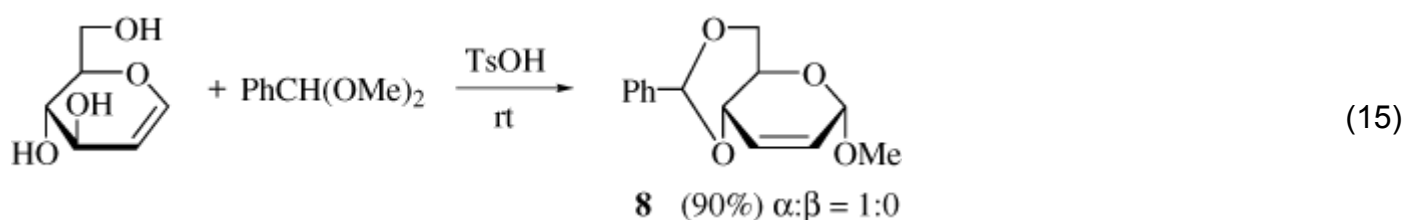
4-*O*-benzoyl-2-deoxy-3-*O*-methylpyranosides **5** (Eq. 13). (99) Other examples of this type of addition product have been reported from the reaction of the methyl uronate analog of triacetylglucal and several α - and β -hydroxycarboxylates. (100) Because of the unusual nature of these results and the specific location at C-3 of the second substituents in the products, it has been suggested (101) that the addition may not occur as indicated above. Rather, initial Michael-like additions occur to α,β -unsaturated aldehydes such as the acyclic form of the 2,3-unsaturated free sugar **2** ($\text{Nu} = \text{OH}$, Eq. 1) derived from the glycal by reaction with water. In some cases the water may be produced by dehydration of the alcohol involved in the reaction, but in any event only trace amounts would be required since the overall hydrolysis, addition, and glycosidation process is catalytic in water. (See "2,3-Unsaturated S-Glycosides and Related Thio-compounds" and Eq. 67 for relevant evidence).



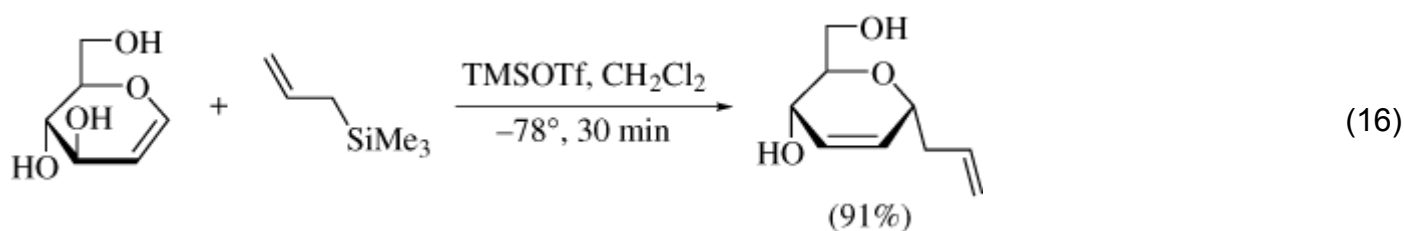
Relatively poor leaving groups at the allylic centers of glycols may also permit allylic displacement reactions to occur. Thus, 4,6-di-*O*-benzoyl-3-*O*-methyl-D-glucal (**6**) affords the 2,3-unsaturated glycosyl fluorides **7** on treatment with hydrogen fluoride at -70° (Eq. 14), (102) and tri-*O*-methyl-D-glucal with 2-[(trimethylsilyl)thio] pyridine in benzene solution in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ gives the analogous unsaturated *S*-pyridyl thioglycosides in good yield. (103) In similar fashion benzyl ether groups can be displaced under the influence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$, (104) and surprisingly, tri-*O*-benzyl-D-glucal in ether solution in the presence of this catalyst rearranges to benzyl 4,6-di-*O*-benzyl-2,3-dideoxy-D-*erythro*-hex-2-enopyranoside in 66% isolated yield. (105) While the allylic benzyloxy group would be most unlikely to have taken part in an intramolecular rearrangement involving a four-membered bicyclic transition state to give the C-1, *O*-linked product, conceivably the aromatic *p*-system could have been involved in an intramolecular benzyloxy migration. In general, however, reactions proceed more effectively when glycols with good leaving groups at C-3 are used; those with 3-*O*-methyl ethers can give low yields of 2,3-unsaturated glycosides. (46)



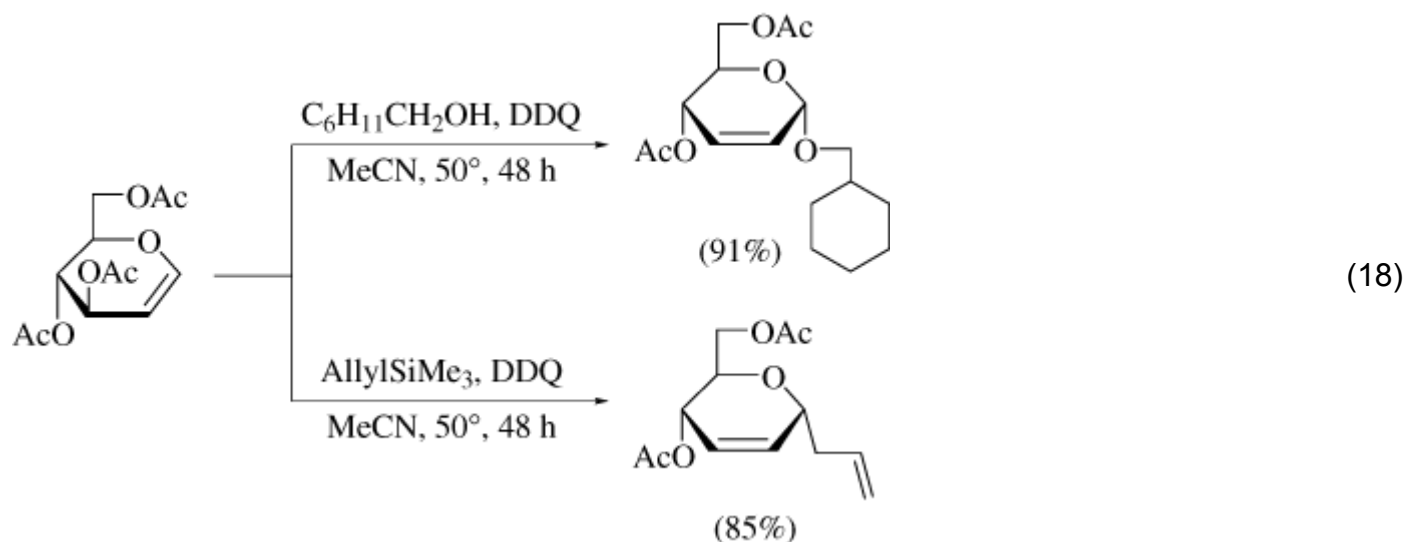
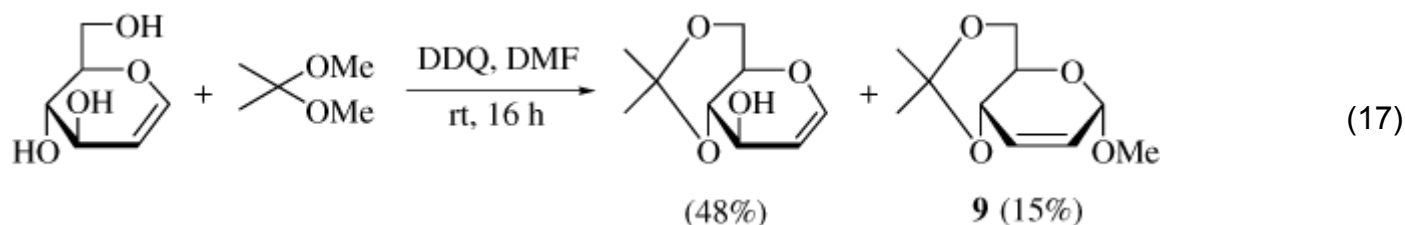
Glycols with unprotected hydroxyl groups at the allylic centers can also take part in the allylic rearrangement process even in the presence of protonic acids. (106) Clearly, when they do, the intermolecular substitution with rearrangement process is favored relative to proton-catalyzed addition. An example is the reaction of D-glucal with benzaldehyde dimethyl acetal in the presence of *p*-toluenesulfonic acid which gives methyl 4,6-*O*-benzylidene-2,3-dideoxy- α -D-*erythro*-hex-2-enopyranoside (**8**) in high yield offering a convenient one-step route to the compound (Eq. 15). (38, 107)



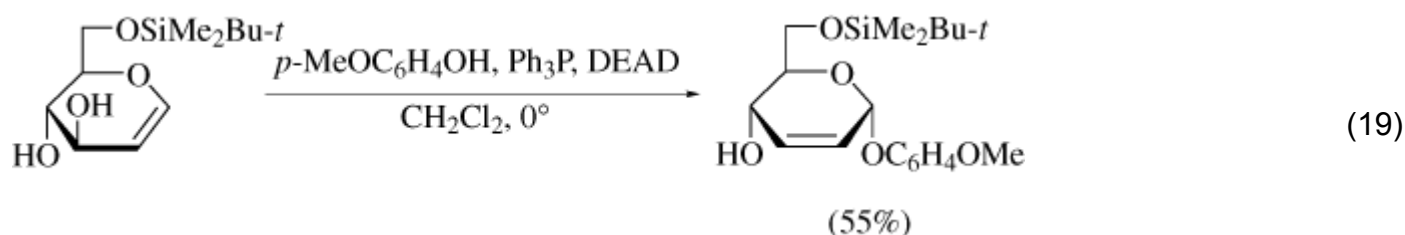
A notable further finding is that unprotected glycols react with high efficiency and almost complete stereoselectivity with allylsilanes to give allyl 2,3-unsaturated α -C-glycosides at low temperatures in dichloromethane/acetonitrile with trimethylsilyl triflate as catalyst (Eq. 16). (73, 74)



The reaction of 3-*O*-unprotected glycal derivatives can otherwise be promoted by several methods that avoid the use of acids as catalysts. DDQ, which acts as a Lewis acid, promotes the formation of the 4,6-*O*-isopropylidene acetal from *D*-glucal by use of 2,2-dimethoxypropane, but in the course of this reaction some of the acetal product reacts further to give the rearranged methyl 2,3-dideoxy-4,6-*O*-isopropylidene- α -*D*-erythro-hex-2-enopyranoside **9** (Eq. 17). (108) The use of DDQ is more effective with derivatives having ester groups at C-3, and *O*-acetylated glycals can be efficiently converted into 2,3-unsaturated *O*-glycosides (**86**) and *C*-glycosides (**87**) with the same catalyst (Eq. 18).

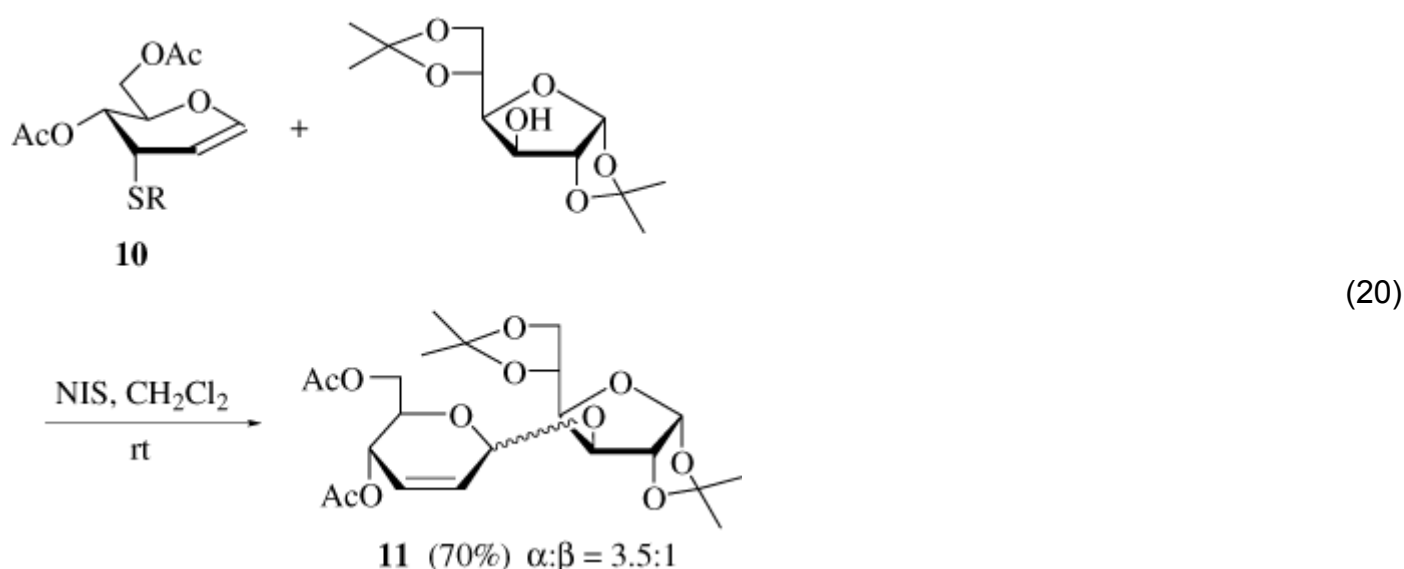


The Mitsunobu reaction can be applied effectively to activate allylic hydroxyl groups of glycals and give *O*-aryl glycosides (Eq. 19), (109) whereas a normal, Lewis acid catalyzed reaction may lead to *C*-glycosides by isomerization of the first-formed *O*-linked products (cf. Eq. 59). Only the α -anomers of the glycosides formed from *L*-rhamnol are produced under Mitsunobu conditions, but *L*-fucal reacts to give mixed anomers. (109) On the other hand, 4,6-di-*O*-benzyl-*D*-galactal with *p*-cresol or pent-4-enoic acid under Mitsunobu conditions affords mainly the *D*-gual products of S_N2 displacement at C-3, (110) showing that these reactions do not proceed by way of the usual oxocarbenium ion intermediate. It appears, therefore, that the Mitsunobu reaction of glycals with unsubstituted C-3 hydroxyl groups is mechanistically delicately poised.



A further elegant method for activating the allylic hydroxyl groups under neutral conditions has been developed during studies of the application of pent-4-enyl and pent-4-enoyl groups in carbohydrate chemistry. The latter are successful when used to generate the leaving groups of glycal glycosyl donors when the normal Lewis acid dependent procedures fail. (36) Thus, whereas tri-*O*-acetyl-D-glucal, under normal coupling conditions involving $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as catalyst, does not give the expected disaccharide derivative with 1,2:5,6-di-*O*-isopropylidene-D-glucose, the 3-*O*-pent-4-enoyl analog **3** affords 65% of the anomers **4** (a,b, 6.7:1) (Eq. 10). (36) Iodonium dicollidine perchlorate (IDCP) is used to activate the leaving group electrophilically, the iodine-containing intermediate formed from **3** collapsing as indicated to give the required oxocarbenium ion with 4-(iodomethyl)butanolactone as byproduct. This method of disaccharide synthesis has some appreciable advantages over the standard procedure and has led to a new approach to the classical problem of sucrose synthesis. (36, 111) 4,6-Di-*O*-benzyl-3-*O*-pentenoyl-D-galactal and -D-glucal can act as glycosyl donors and therefore, respectively, provide a further approach to the synthesis of 2,3-dideoxy- α -D-*threo*- and -*erythro*-hex-2-enopyranosides. (36)

In the course of the above work attention was directed to the leaving properties of allylic phenylthio groups, the 3-(phenylthio)-D-allal derivative **10** (R = Ph) giving disaccharides **11** in 70% yield (a,b = 3.5:1) on treatment with di-isopropylidene-glucose in the presence of *N*-iodosuccinimide as electrophilic activator (Eq. 20). (36)



In like manner the 2-pyridylthio compound **10** (R = 2-pyridyl), on activation with $\text{Pd}(\text{MeCN})_2\text{Cl}_2$ and silver triflate in CH_2Cl_2 at room temperature, reacts readily with primary and secondary alcohols to give 2,3-unsaturated glycosides in yields of 60–80%. It and its C-3 epimer both give the α - and β -*O*-glycosides in the same ratio (9:1), indicating that a common oxocarbenium ion is involved. (112)

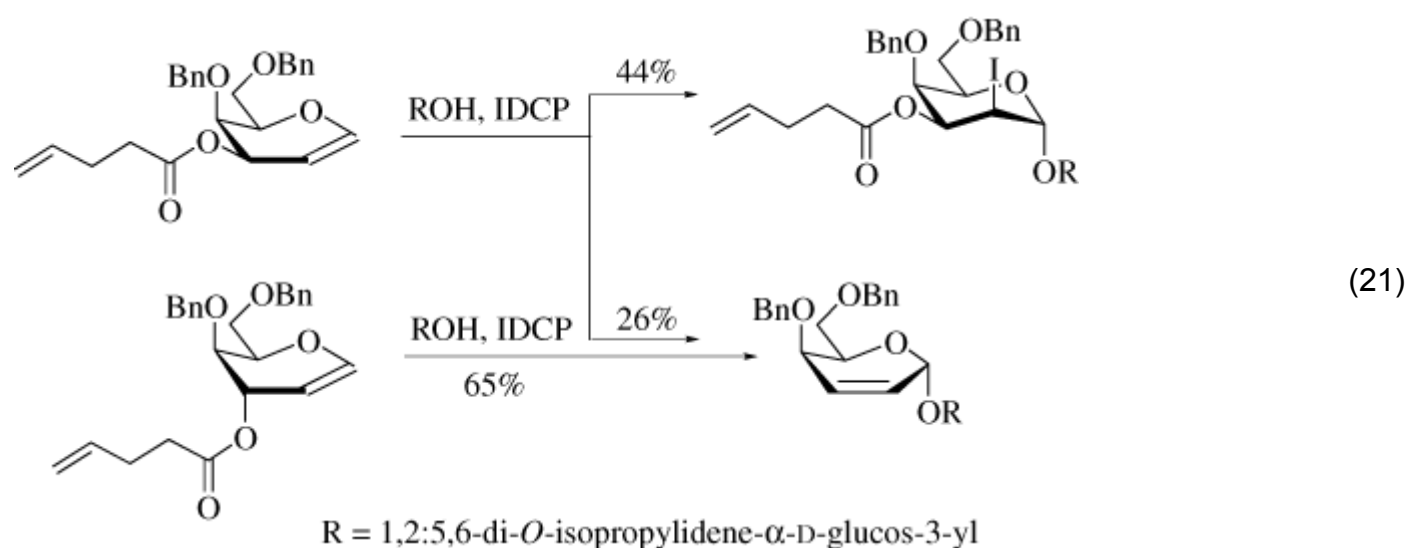
The tributylstannyl group can be displaced from C-3 of glycal derivatives by carbon free radicals such as (ethoxycarbonyl)methyl in an unusual approach to 2,3-unsaturated C-glycosides. (113)

2.1.4. Configuration at the Allylic Center of the Glycals

Because of the relatively high natural abundance of D-hexoses with the R("b")-configuration at C-3, and the consequent ready availability of the corresponding glycals (notably D-glucal and D-galactal) and their derivatives, the allylic rearrangement reaction has been carried out predominantly with these epimers. The D-allal derivative **10**, (R = 2-pyridyl) with a "3a" substituent, however, represents an exception; when activated under neutral conditions it reacts to give 2,3-unsaturated glycosidic products as expected, and more readily than does the D-glucal analog. (112) This is not however

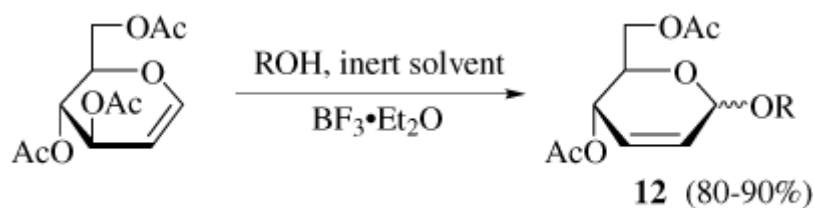
always so since, for example, 3-*O*-acetyl-4,6-*O*-benzylidene-*D*-allal (114) does not react under standard (BF₃•Et₂O) conditions with ethanol to give the expected unsaturated ethyl glycosides; instead a complex mixture of products is obtained. (36) Likewise, the 3-*O*-trifluoroacetyl analog is more unstable than the *D*-glucal-based isomer. (115) Most probably these findings are related to favored *trans*-diaxial eliminations of acetic acid or trifluoroacetic acid, respectively, which can occur with the allal derivatives, the eliminations being subject to acid catalysis.

In further examples of reactions occurring under neutral conditions epimeric pairs of 3-pentenoyl glycal derivatives, such as *D*-allal/*D*-glucal and *D*-gulal/*D*-galactal esters, appear to react in “orthodox” manner to give *D*-*erythro*- and *D*-*threo*-2,3-unsaturated disaccharide compounds, respectively, when coupled with other sugar derivatives following activation with IDCP (Eq. 10). (36) Indications are that compounds with pseudo-axial leaving groups (particularly the above gulal compounds) undergo substitution/rearrangement more readily than the 3-epimers as expected on the basis of the “vinylogous anomeric effect,” which favors the departure of allylic leaving groups of glycal derivatives when they are pseudo-axial and anti-periplanar to an unshared electron pair on the ring oxygen atom (Eq. 21). (116)

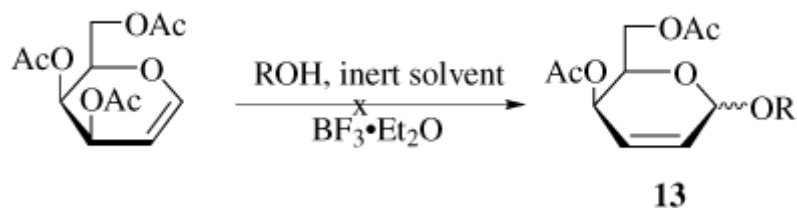


2.1.5. Configuration at the Homoallylic Center of the Glycals

The relative orientation of groups at the homoallylic C-4 position of pyranoid glycals, which may provide anchimeric assistance to the departure of the allylic leaving groups, can affect the substitution reactions appreciably. Thus, under conditions in which the normal BF₃-catalyzed reaction gives high yields of *erythro*-glycosides 12 from tri-*O*-acetyl-*D*-glucal, the *threo*-analogs 13 are not obtained satisfactorily from tri-*O*-acetyl-*D*-galactal which has *cis*-related C-3, C-4 ester groups (Eq. 22), (117) the difference being so significant that the ethyl α -*threo*-glycoside has been prepared for synthetic work from the readily available *erythro*-analog by carrying out a Mitsunobu inversion at C-4 rather than directly from tri-*O*-acetyl-*D*-galactal as starting material. (118)

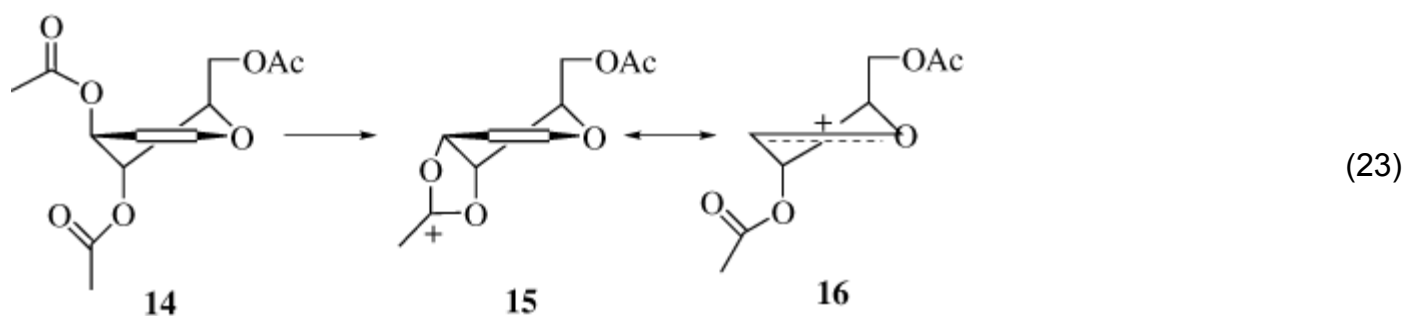


(22)



A striking example of the significance of this stereochemical factor is offered by the reactions of tri-*O*-acetyl-D-glucal and -galactal with phenols in refluxing chlorobenzene containing 5% acetic acid. Whereas the former gives aryl 2,3-unsaturated *O*-glycosides exclusively, the latter undergoes addition to afford 75–80% of aryl 2-deoxygalactosides. (119) Similar observations have been made on the relevant reactions of nucleoside bases with glycal derivatives. (120) In further exemplifications of the same phenomenon the efficient conversion of acetylated glycals into 2,3-unsaturated glycosyl fluorides by treatment in CH₂Cl₂ with pyridinium poly(hydrogen fluoride) is observed only for compounds with trans-related ester groups at C-3, C-4. (121) Also with acetic acid (117) or with ethanol, (45, 117) under conditions in which tri-*O*-acetyl-D-glucal gives 2,3-unsaturated glycosyl compounds efficiently, the galactal ester affords mixtures containing products of addition and isomerization.

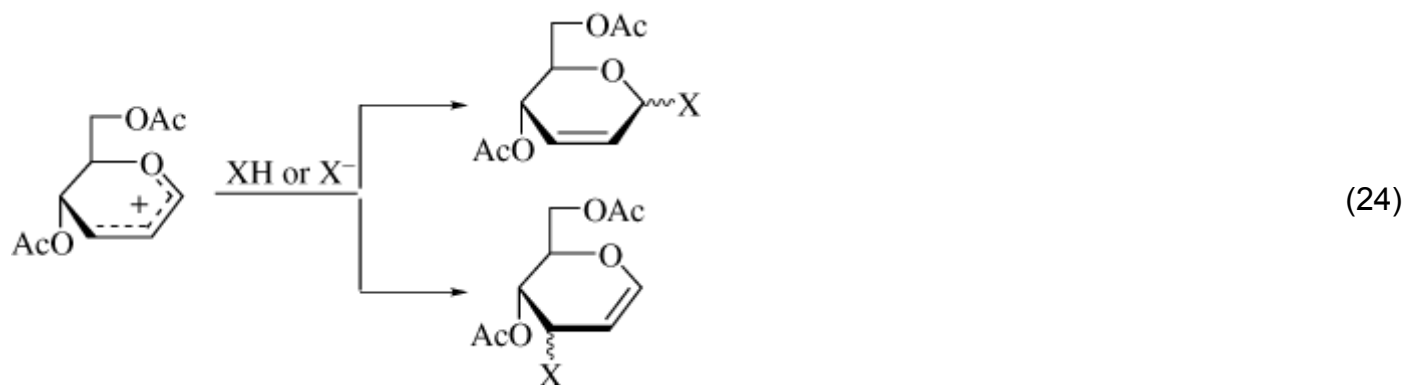
The hypothesis that neighboring group participation is involved in the ejection of the allylic group and establishment of the dioxocarbenium ion from tri-*O*-acetyl-D-glucal (122) seems sound, this being the more probable since the latter is deemed to react in the conformation **14** to lead to the delocalized cyclic reaction intermediate (15/16) (Eq. 23). (116) It is clear, however, that all D-glucal derivatives do not require such neighbouring group participation to take part in the substitution/rearrangement reaction since derivatives with groups at C-4 that cannot participate can be active. (36, 105) Problems with the conversion of tri-*O*-acetyl-D-galactal into 2,3-unsaturated-*O*-glycosides can be solved simply by change of the Lewis acid catalyst to SnCl₄ or to LiBF₄ in MeCN, but in the latter case the yields are only moderate. (64) With SnCl₄ the allylic rearrangement process is specifically promoted, and simple primary alcohols are converted into the α-unsaturated glycosides in high yield. With secondary alcohols and phenols yields are in the 60% region. (45) SnCl₄ can also be a superior catalyst with glycals that have trans-related groups at C-3, C-4. Thus di-*O*-acetyl-L-rhamnol gives only modest proportions (40–55%) of 2,3-unsaturated glycosides when BF₃·Et₂O is used as catalyst, whereas with SnCl₄ the yield is approximately doubled. (46) It appears, therefore, that the latter catalyst is more effective than is BF₃ in coordinating with allylic ester groups to enhance their leaving group properties. Consistent with this, the rate of the rearrangement reaction of tri-*O*-acetyl-D-glucal with ethanol in CH₂Cl₂ is appreciably higher with SnCl₄ than with BF₃·Et₂O when the catalysts are used in equimolar proportions under otherwise identical conditions. (123)



Montmorillonite K-10 may also be used as a mild and efficient catalyst for conducting the rearrangement reactions of galactal derivatives with phenols or alcohols; (82, 124) otherwise 4,6-di-*O*-benzyl-3-*O*-pentenoyl-D-galactal and -gual can be effective starting materials for making 2,3-unsaturated-D-*threo*-hex-2-enopyranosyl compounds. (36)

2.1.6. Regioselectivity

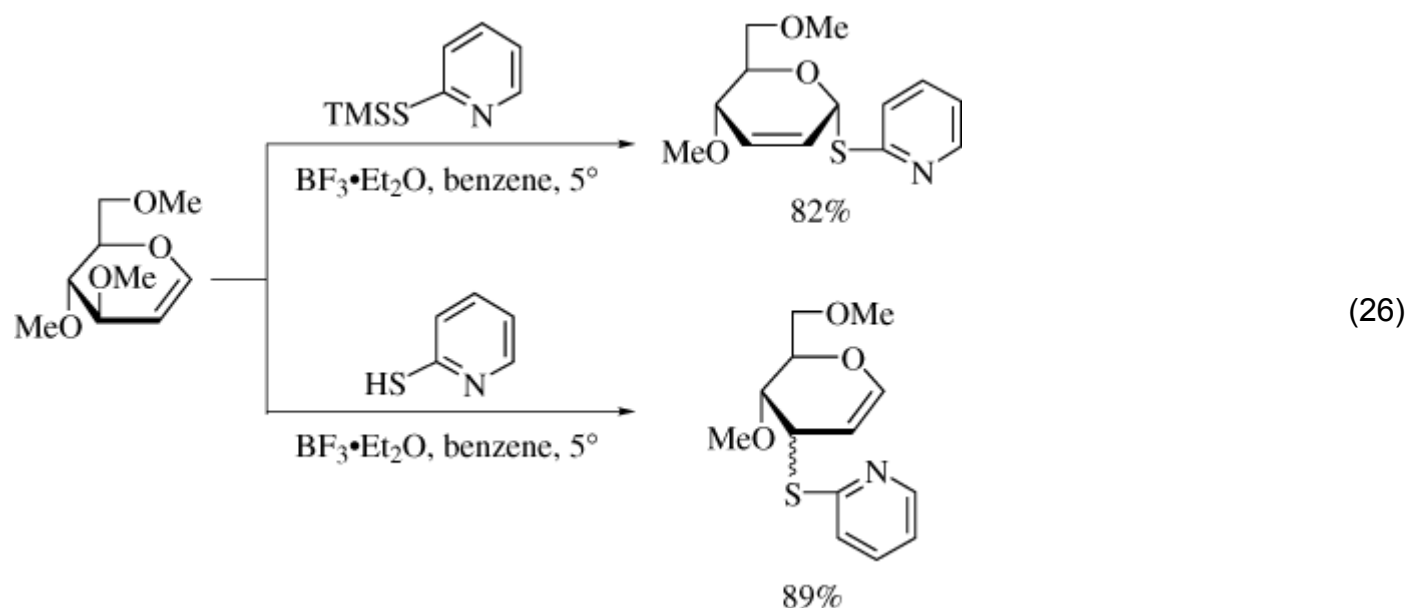
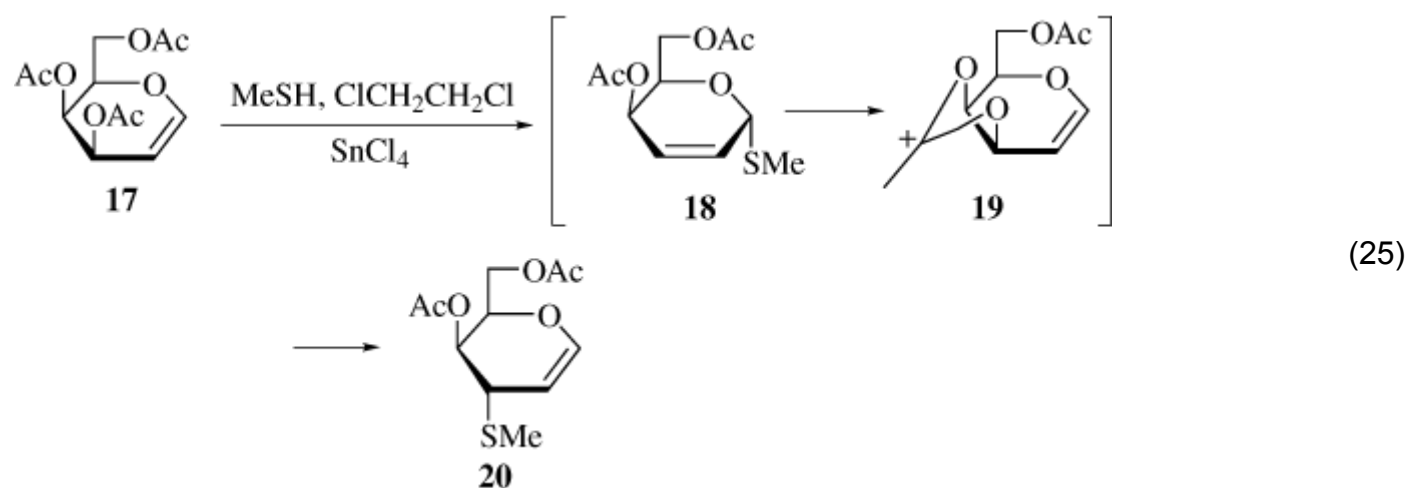
To this point this survey has not dealt with the possibility that the oxocarbenium intermediates in the acid-catalyzed rearrangements of glycols can bond to nucleophiles not just at C-1 but, alternatively, via C-3 (Eq. 24). To a major extent this neglect is because the general features discussed so far have related to cases with alcohols or phenols as nucleophiles which attack virtually only at the anomeric center to give *O*-glycosides. The very occasional reference to glycol derivatives affording saturated alkyl 3-*O*-alkyl-2-deoxyglycosides (Eq. 13) cannot be taken as evidence of initial formation of 3-*O*-alkylglycols, and more likely suggests the intermediacy of 2,3-unsaturated aldehydes (see "Leaving Groups and Activators"). On the other hand, *S*- and *N*-nucleophiles can give products derived by attack at C-3 in major proportions, and there has been the occasional report of the generation of C-3 branched-chain glycol derivatives having been produced by the use of



C-nucleophiles. While the reactions leading to 3-substituted glycols directly from glycol derivatives do not fall under the general title of this review, they will be dealt with briefly because of their close interrelationships with the main processes under consideration.

It has been pointed out (35) that the above-mentioned regioselectivities correlate with the hard nature of *O*-nucleophiles and the softer character of *N*- and *S*-, and to a lesser extent, *C*-nucleophiles according to the Pearson classification. (125, 126) The latter group (*N*- and *S*-compounds in particular) therefore tend to lead to 3-substituted glycols under equilibrium conditions. For example, the reaction of tri-*O*-acetyl-D-galactal (17) with methanethiol in the presence of SnCl₄ finally gives the gualal derivative 20 almost exclusively, but significant proportions of the kinetic product 18 are formed during the early stages of the reaction. (35) This may suggest the glycol D-*lyxo*-3,4-acetoxonium ion 19 is an intermediate in the isomerization process (Eq. 25). An interesting variation of the use of thiols has employed their trimethylsilyl derivatives to enhance their nucleophilicity and their hardness, and in consequence regioselective reactions at C-1 can occur. With the corresponding free thiols under the same conditions the 3-substituted glycol isomers

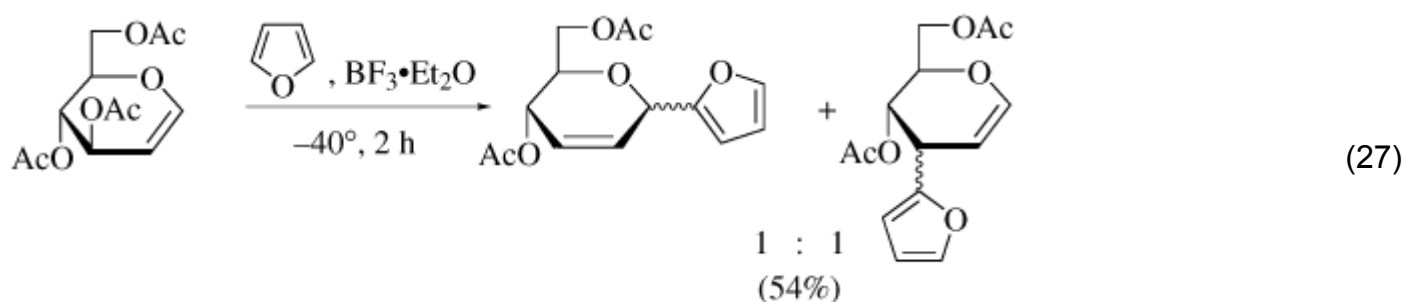
prevail (Eq. 26). (103)



Various *N*-nucleophiles also initially attack the cyclic oxocarbenium ions derived from glycols at C-1, and rearrangements of the first products then occur to afford the C-3 *N*-bonded glycol isomers. These nucleophiles therefore resemble the thiols noted above.

Given the relatively soft nature of *C*-nucleophiles it is unexpected that the most common products derived by their use result from attack on the oxocarbenium ions at the relatively hard anomeric center. This apparent anomaly has been explained by invoking kinetic factors and the greater chemical stability of the first-formed *C*-glycosides. (125) Products derived by bonding of the nucleophiles to C-3 can, however, be encountered under normal circumstances involving acid catalysts, but it is not known whether they are formed by isomerization of *C*-glycosidic precursors as could happen in specific instances. Furan (Eq. 27), (127) methyl dicyanoacetate, (128) and copper/zinc species, for example $\text{NC}(\text{CH}_2)_3\text{Cu}(\text{CN})\text{ZnI}$, (129) all react with triacetylglucal in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to give mixed products including glycol derivatives with branching groups bonded to C-3. With the copper/zinc reagent the branched glycol derivative with the glucal configuration is formed specifically. (129) From di-*O*-acetyl-D-rhamnal with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as catalyst, again equal proportions of 1,2-unsaturated and 2,3-unsaturated isomeric products are formed (50% in total), with the epimers having retained configuration predominating strongly. The same distribution of products results from the reaction of the glycol isomer 1,4-di-*O*-acetyl-2,3,6-trideoxy-L-*erythro*-hex-2-ene under the same conditions, and while this

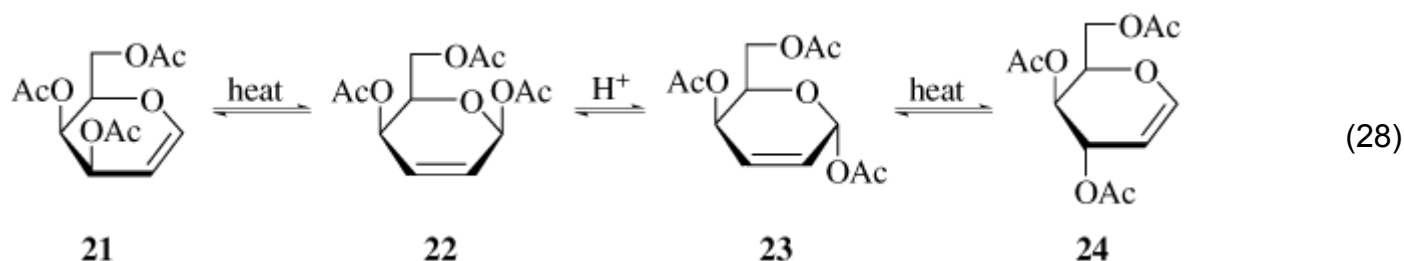
evidence indicates that a common allylic carbenium ion is involved, and that the products are formed under kinetic control, it does not rule out the possibility that product isomerizations occur. It is noteworthy that the less reactive organozinc Reformatsky C-nucleophiles lead to 2,3-unsaturated C-glycosides on reaction with glycal derivatives in the presence of Lewis acids (see Table 5).



In summary, under acidic conditions, reactions of glycal derivatives with nucleophiles which lead to C-O bonding give 2,3-unsaturated glycosyl derivatives, and the same applies in the few cases recorded of reactions leading to C-F and C-P bond formation. In contrast, nucleophiles leading to new C-N and C-S bonds give mixtures of 2,3-unsaturated glycosyl products and 3-substituted glycals with the latter predominating at equilibrium. Most reactions involving C-nucleophiles give 2,3-unsaturated C-glycosides, but there are several reports of the formation of glycal products having branched chains at C-3.

To a considerable extent these findings correlate with the hard-soft generalizations, but the issue of hydride reduction requires separate consideration. Hydride is a soft nucleophile and would consequently be expected to react at C-3. Consistent with this, tri-*O*-acetyl-D-glucal reacts with diphenylsilane in THF in the presence of ZnCl₂ and a Pd(0) catalyst by direct reductive loss of the allylic acetoxy group. (130) On the other hand, triethylsilane in inert solvents containing BF₃·Et₂O leads to hydride introduction at C-1 and the production of 2,3-unsaturated 1,5-anhydroalditols ("glycosyl hydrides") (Eq. 93). It is not clear what the mechanisms of these reductions are, but an indication comes from the finding that alkyl 4,6-di-*O*-acetyl- α -D-*erythro*-hex-2-enopyranosides which react with LiAlH₄ to give 4,6-di-*O*-acetyl-3-deoxy-D-glucal do so following coordination of the aluminum to O-1 and subsequent directed attack of hydride at C-3 (130) (cf. Eq. 122).

It should be noted that several 2,3-unsaturated glycosyl derivatives and their 3-substituted glycal isomers can interconvert by [3,3]-sigmatropic processes to facilitate the production of thermodynamic products from precursors formed under kinetic control (Eq. 9). This can account, for example, for the production of tri-*O*-acetyl-D-gulal (24) from its C-3 epimer, tri-*O*-acetyl-D-galactal (21), on heating in acetic acid, since these isomers can equilibrate thermally with the 2,3-unsaturated α - and β -glycosyl acetates 23 and 22, which, in turn, can anomerize under acidic conditions (Eq. 28). (131) The possibility of sigmatropic isomerization makes it difficult to define specific mechanisms for the reaction of glycal esters with, for instance, azide ions or purines and pyrimidines. Not only are the initial products subject to thermal rearrangement, but so are the carbohydrate starting materials.



2.1.7. Diastereoselectivity at the Anomeric Center

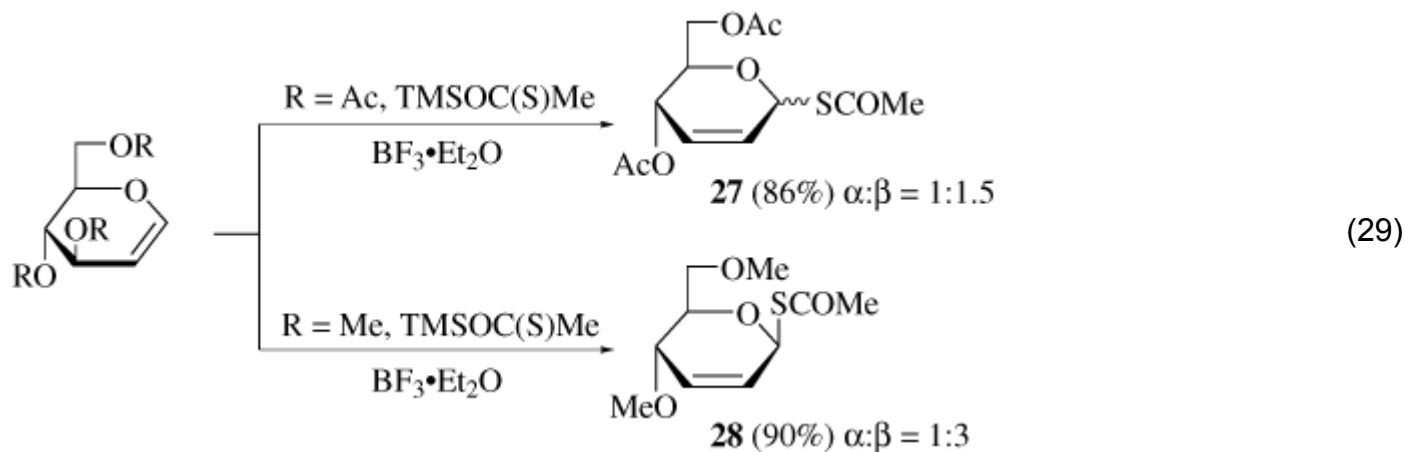
Although the question of the configurations at the anomeric centers of 2,3-unsaturated glycosyl products formed by the reaction under consideration is complex, and may depend upon many variables such as the substrates (hexose- and pentose-based glycols giving markedly different results, see below), the leaving groups, the nucleophiles, the catalysts, the reaction conditions, the mechanism of the reactions, and whether the products are formed under kinetic or thermodynamic control, some generalizations can be made. In its reaction with alcohols and phenols in the presence of Lewis acids tri-*O*-acetyl-D-glucal gives predominantly 2,3-unsaturated *a*-glycosides with the anomeric *a,b* ratios usually being in the range (7 *a* 2):1. Because of the reversibility of the reactions under most conditions used, these represent equilibrium figures. At low temperatures, however, highly stereoselective formation of *a* products has been observed in the synthesis of both *O*- (59, 100) and *C*- (74) glycosides. On the other hand, the *a,b* ratio can be reduced to about 2:1 for reactions involving secondary carbohydrate alcohols as acceptors. (97)

When the reaction of tri-*O*-acetyl-D-glucal with methanol is conducted at high temperatures without catalysts the *a,b* ratio of the unsaturated glycosides formed is 1.5:1, and while it is tempting to take this as the kinetic ratio no such assumption is safe since acetic acid, which could have catalyzed some *b* to *a* anomerization, is generated during the reaction. (12) Few other data point to the generation of *b*-glycosides under kinetic control from this glycal. See, however, the section "2,3-Unsaturated Glycosyl Phosphonates."

An interesting stereochemical point emerges from the analogous acid-catalyzed reaction of alcohols with tri-*O*-acetyl-D-galactal for which the corresponding equilibrium ratios of products are significantly larger than 7:1. In an extreme case this glycal gives 2,3-unsaturated *a*-glycosides "almost totally" on treatment with simple alcohols in the presence of SnCl₄. (45) This is somewhat surprising since inversion at C-4 of the main products **25** derived from tri-*O*-acetyl-D-glucal might not be expected to affect the energies of the C-4 epimers **25** and **26** relative to their respective *b*-anomers to any appreciable extent. It is therefore suggested that the anti-arrangement of the allylic substituents in the *a*-D-threo-glycosides **26** may be particularly stable, because both are pseudo-axial and therefore favored by the allylic (132) and the vinylogous anomeric (116) effects. That is, configuration **26** may be stabilized by a "double allylic effect." This conclusion is consistent with the finding, from energetics calculations, that, for acyclic allylic alcohols and ethers, the lowest energy rotamers have the oxygen-bonded substituents over the double bonds. (133, 134) It is noteworthy also that axial *O*-bonded substituents at C-4 on pyranoid rings stabilize oxocarbenium ions at C-1 by through-space effects, (135) which suggests that this observed factor could also result to some extent from a transannular anomeric effect. The observation that *a*-selectivity seems also to be greater in the formation of 2,3-unsaturated *C*-glycosides from tri-*O*-acetyl-D-galactal, which is unlikely to be reversible, suggests that the formation of the *C*-glycosidic analogs of **26** is also relatively favored kinetically.

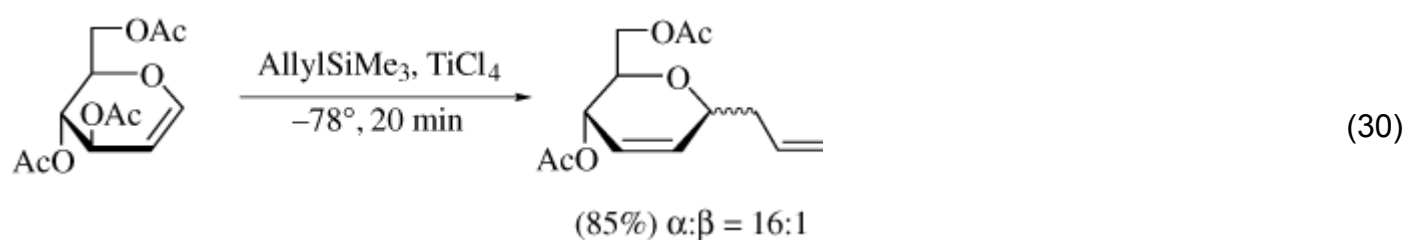


While thiols react with the oxocarbenium ions produced from most glycal derivatives at C-3 as well as at the anomeric position, the thioglycosides produced in the latter process have predominantly the *a*-configuration with quasi-axial sulfur bonded substituents. (103) However, when tri-*O*-acetyl-D-glucal is treated with trimethylsilyl thionoacetate and BF₃·Et₂O the glycosyl thioacetates **27** are produced with the *a,b* ratio a surprising 1:1.5 (Eq. 29), and when this reaction is repeated with

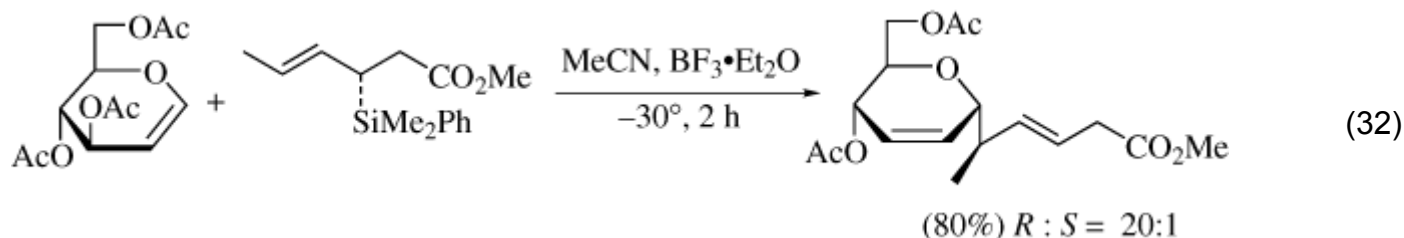
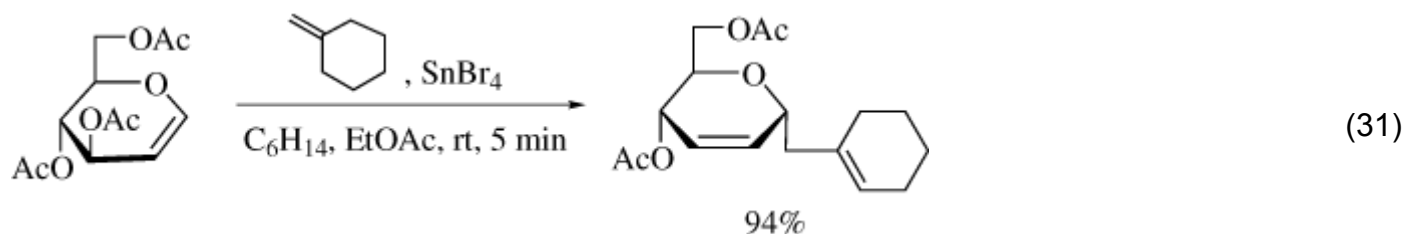


tri-*O*-methyl-*D*-glucal, compound **28** represents 75% of the product mixture. (103) These unusual results may indicate that the silicon of the nucleophilic reagent is involved to a degree in coordination with the allylic leaving groups during the approach by the nucleophile to C-1 and that, of the two leaving groups, methoxy coordinates better.

As with *O*-nucleophiles high diastereoselectivity in favor of a products is also commonly observed in the rearrangement reaction of glucal derivatives with carbon nucleophiles under the influence of Lewis acids. For example, the allyl *C*-glycosides are obtained in 85% yield with an α,β ratio of 16:1 from tri-*O*-acetyl-*D*-glucal with allyltrimethylsilane and TiCl_4 as catalyst (Eq. 30). (52) When tri-*O*-acetyl-*D*-allal, epimeric at C-3 with the glucal isomer, is employed, the same products are obtained in 95% yield, but the anomeric ratio is now 6:1 which indicates that, to some degree, the nucleophile takes part in bond forming at C-1 before a free oxocarbenium ion has been generated, i.e. there is an element of the anti- $\text{S}_{\text{N}}2^{\sim}$ to the reaction mechanism. Tri-*O*-acetyl-*D*-galactal also undergoes very efficient reaction with allyltrimethylsilane and, as with *O*-nucleophiles, gives a higher α,β ratio (30:1) than is obtained with tri-*O*-acetyl-*D*-glucal. Notably, by use of trimethylsilyl triflate as activator, and unsubstituted glycals or their acetates in dichloromethane/acetonitrile as solvents at -78° , several allyl α -*C*-glycosides have been made with anomeric selectivities greater than 99:1. (73, 74) Most surprisingly, the unprotected glycals are more effective glycosyl donors than their acetates under these conditions, and both *D*-glucal and *D*-galactal react with almost complete stereoselectivity.



Various alkenes, from which tertiary carbocations can be formed on reaction with electrophiles such as the glycal-derived oxocarbenium ions, may also be used to generate *C*-glycosides with high yields and stereoselectivities; in several instances complete α -stereoselectivity is observed from various acetylated glycals (Eq. 31). (61) In many cases of this kind, and with substituted allylsilanes, new chiral centers are generated in the noncarbohydrate moieties, and the stereoselectivities gained at these centers in the reactions involving the silanes can be high (Eq. 32) and dependent on stereochemical features of the reactants and, less obviously, on the catalysts used. (136, 137)



The situation regarding the anomeric configurations of the unsaturated glycosyl cyanides obtainable directly from tri-*O*-acetyl-*D*-glucal merits comment. Reaction with trimethylsilyl cyanide in nitromethane at room temperature with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as catalyst gives 57 and 42% of the 2,3-unsaturated *a*- and *b*-cyanides, respectively, and by use of sodium cyanide under the same conditions 41 and 27% yields are obtained. (138) On the other hand, trimethylsilyl cyanide used with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in dichloromethane at room temperature gives the *a*-anomer in 79% yield as the only product. (125) These results may suggest that, under kinetic control, the *a*-product is slightly favored, whereas in dichloromethane with acid catalysis it is strongly favored as the thermodynamic product. A similar situation occurs when the Lewis acid Et_2AlCN is employed in benzene. At room temperature the *a*- and *b*-glycosyl cyanides are formed in the ratio 3:2, (93) but when the reaction is conducted in this solvent under reflux the *a*-compound dominates clearly (9:1), (24) which suggests that the *b*-anomer can isomerize under the higher temperature conditions.

In summary, it can be concluded that most of the acid-catalyzed reactions of hexose-derived glycols give 2,3-unsaturated *C*-glycosides with good *a*-selectivity. Since most *C*-glycosides are chemically more stable than *O*-, *S*-, and *N*-linked analogs, they are less likely to rearrange under the conditions of their synthesis, and the observed products are therefore more likely to be those formed under kinetic control. In some instances this point has been experimentally confirmed, and therefore the selectivity observed can be ascribed to a kinetic effect which favors axial attack at the anomeric center (139) and accounts for the *a*-selectivity exhibited, for instance, by tri-*O*-acetyl-*D*-glucal and -*D*-galactal and for the *b*-selectivity of di-*O*-acetyl-*D*-xylal. In this last case the oxocarbenium ion can be expected to react in the $^5\text{H}_4$ half chair conformation (cf. Eq. 23, 16) with the *C*-4 acetoxy group pseudo-axial and impeding nucleophilic attack at *C*-1 from the *a*-face. *C*-Glycosides that can anomerize, for example those with diacylmethyl substituents as the aglycons, are produced from these acetylated glycols under either Pd or BF_3 catalysis with the same anomers predominating. (19) This, however, appears still to be for kinetic reasons because *D*-glucal-derived compounds having (benzoyl)methyl aglycons equilibrate in basic conditions to give mainly 2,3-unsaturated-*b*-*D*-erythro-*C*-hexosides. (140) Presumably this occurs by deprotonation at the active methylene sites and ring opening of the derived anions.

Activated aromatic compounds, anisole for example, react with tri-*O*-acetyl-*D*-glucal in the presence of Lewis acids to give mainly the *b*-linked aryl *C*-glycosides because, presumably, anomerization can occur readily by way of stable ring-opened *C*-1 carbenium ions to form the true thermodynamic products. (141)

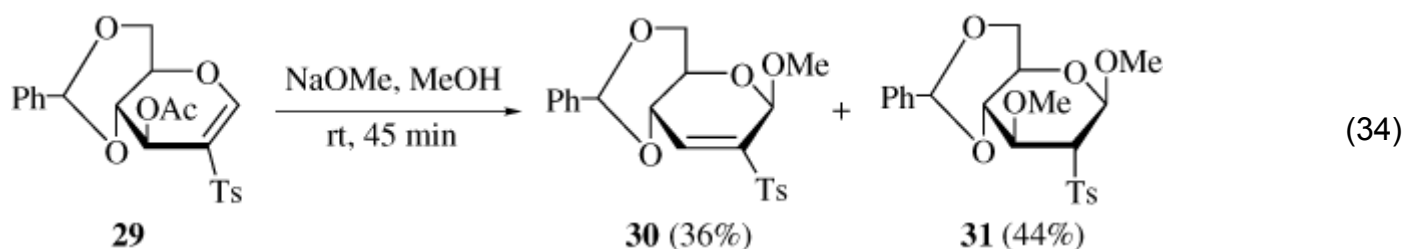
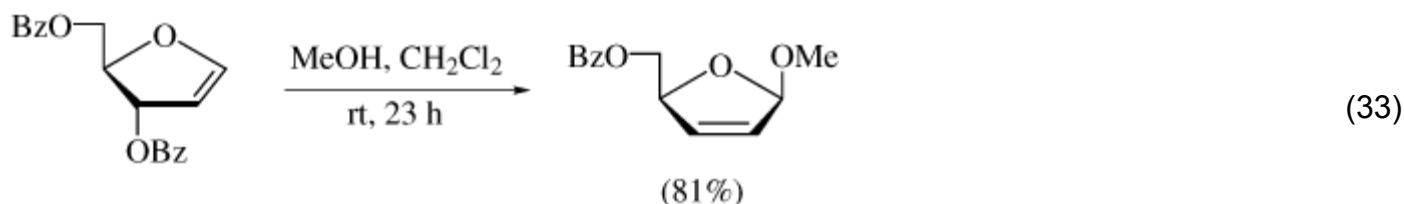
As indicated above, the ratios of anomers of 2,3-unsaturated compounds derived from the pentose-based glycols are quite different from those found with the hexose glycols. In general

b-compounds are strongly favored (Tables 2, 5), and it may be that reports that indicate the opposite are mistaken. Throughout the development of understanding of the reaction under review the question of assignment of product anomeric configuration has been problematical, and errors have been made— particularly before reliable information and analytical methods became available.

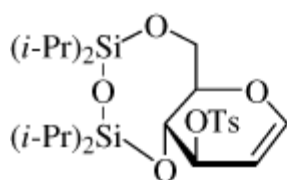
2.2. Reactions Proceeding by Other Nucleophilic Substitution Mechanisms

Mechanistic categorization of the substitution reactions undergone by glycols, other than those that proceed by initial loss of the allylic substituents to give oxocarbenium ions, is not easy. In no cases have the mechanisms been rigorously determined, and some are impossible to identify from the data available. Particularly this is the case for reactions that involve organometallic reagents that may act as Lewis acids as well as providing the required nucleophiles. Reactions that use organometallic compounds together with Lewis acids and Mitsunobu reactions have been mentioned in the section “Transformations Involving Oxocarbenium Ions”— but, especially in the latter case, with no assurance that this assignment is mechanistically sound. Indeed, some evidence for S_N2 displacements under Mitsunobu conditions is given under “Scope and Limitations, 2,3-Unsaturated Glycosyl Carboxylates” and “2,3-Unsaturated O-Glycosides.” An additional difficulty relates to the possibility that incorrect configurational assignments may have been given to some of the unsaturated products. Until definitive methods such as X-ray crystallographic and nOe NMR experiments were applied to establish configurations it was no easy matter to make the assignments, and errors appeared in the literature. Some, but perhaps not all, have been corrected.

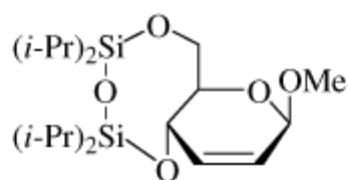
Some reactions, especially those that do not depend on acidic conditions, are very likely to follow the S_N2^{\sim} path. Examples are the spontaneous formation of 2,3-unsaturated O-glycosides when furanoid glycol esters are dissolved in organic solvents containing alcohols (Eq. 33), (142, 143) and the conversion of the sulfonyl derivative **29** into the mono- and dimethoxy products **30** and **31** on treatment with sodium methoxide in methanol (Eq. 34). (144) That these are b-glycosides is in keeping with the former product having been formed by the commonly occurring syn- S_N2^{\sim} process (145) and hence the dimethoxy derivative **31** in a Michael-like addition step. (144)



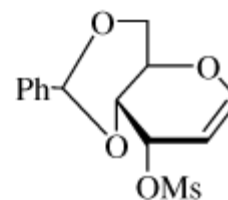
When the C-3 epimer of compound **29** is subjected to the same reaction the main product (60%) is the a-anomer of unsaturated glycoside **30**, again in keeping with the reaction being syn- S_N2^{\sim} in character. Furthermore, when compound **29** and its C-3 epimer are reduced with sodium borodeuteride, the products are those derived by attack of deuteride at C-1 to initiate syn- S_N2^{\sim} processes. (144) Also consistent with this, the reactive tosylate **32** is converted mainly into the b-glycoside **33** in 90% yield (a:b = 1:10) on treatment with methanol. (146) However, with sodium methoxide in methanol, the presumed allal mesylate **34**, made from the corresponding alcohol but not isolated and characterized, is reported to give the unsaturated glycoside with the b-configuration (Eq. 5) which suggests the displacement has involved the anti-stereochemistry. (23)



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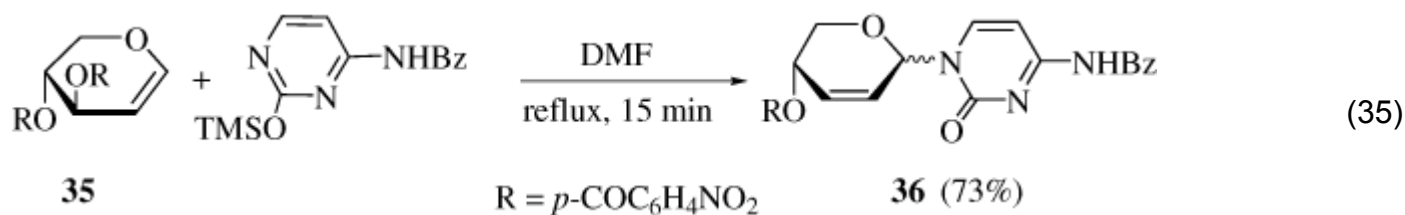


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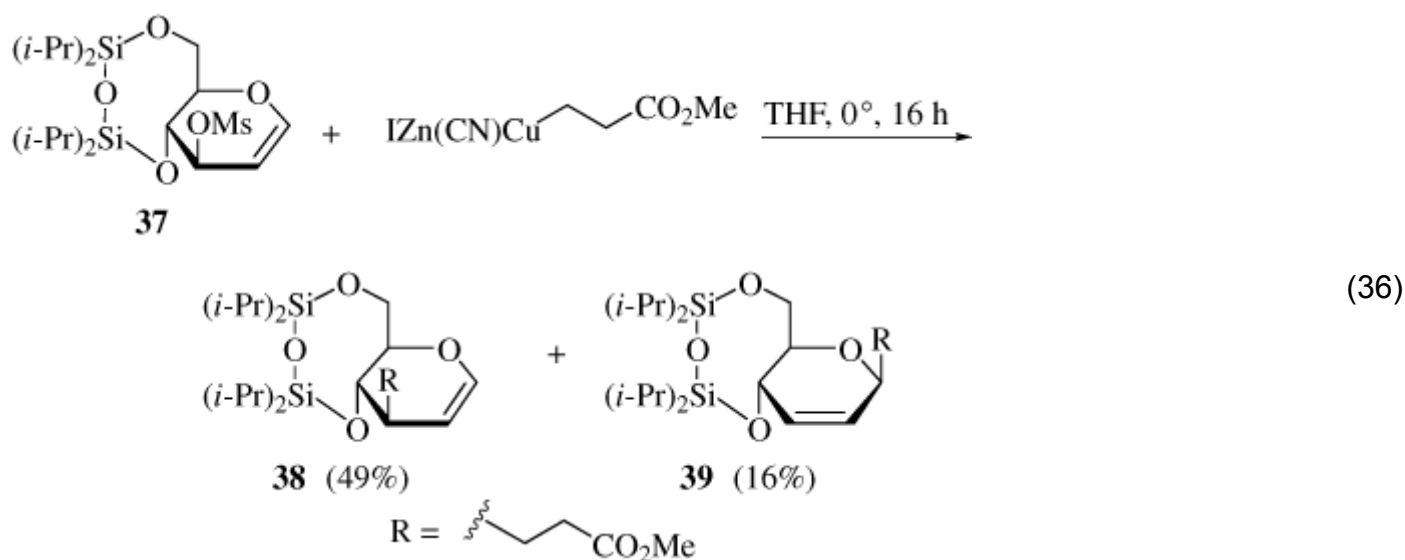


34

An intentional effort to exploit the S_N2^{\sim} pathway for the preparation of b-linked 2,3-unsaturated nucleoside derivatives met with partial success. Treatment of the active glycosyl donor 3,4-di-*O*-*p*-nitrobenzoyl-D-xylal (**35**) with 4-*N*-benzoyl-*O*-(trimethylsilyl)cytosine without added catalyst gives the 2,3-unsaturated nucleosides **36** (a:b = 1:1) in good yield and no products with the base bonded to C-3 (Eq. **35**). (**40**)

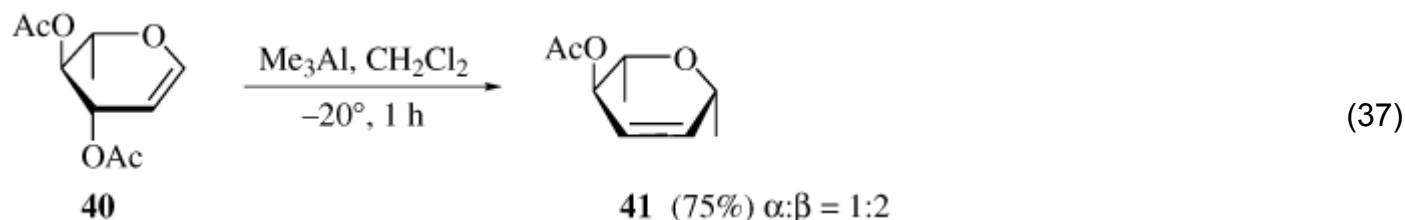


Examples have been given under “Regioselectivity” in the section “Transformations Involving Oxocarbenium Ions” that indicate that a few C-nucleophiles react under these conditions at C-3. Some reactions conducted with organometallic reagents without added Lewis acids also give this type of product, but their specific mechanisms are not established. For example, the mesyl analog **37** of compound **32**, on treatment with the zinc copper reagent IZn(CN)CuCH₂CH₂CO₂Me, gives the C-3- and C-1-bonded products **38** and **39** with the former predominating (Eq. **36**), (**146**) but whether they are formed concurrently from an oxocarbenium ion or by S_N1 and syn- S_N2^{\sim} processes, respectively, as suggested by their structures, is unknown. Similarly, the D-allal mesylate **34**, on reaction with MeMgI, affords the 3-*C*-methyl-D-glucal in modest yield as the main product, but now with inversion of configuration as if an S_N2 process were involved. (**23**) In addition, the anomeric 2,3-unsaturated methyl C-glycosides are formed, the minor being the α -anomer which would be the product of syn- S_N2^{\sim} displacement. However, when compound **34** is treated with allylmagnesium chloride, the major product is now the 2,3-unsaturated allyl b-*C*-glycoside (73% yield) with only small proportions of the 3-*C*-allyl isomer being present. The main differences between the results obtained with these methyl and allyl Grignard reagents suggest that, with the latter reagent, the 3-*C*-substituted kinetic product is able to rearrange by the electrocyclic Cope reaction, thereby complicating even further the characterization of the reaction mechanisms involved.



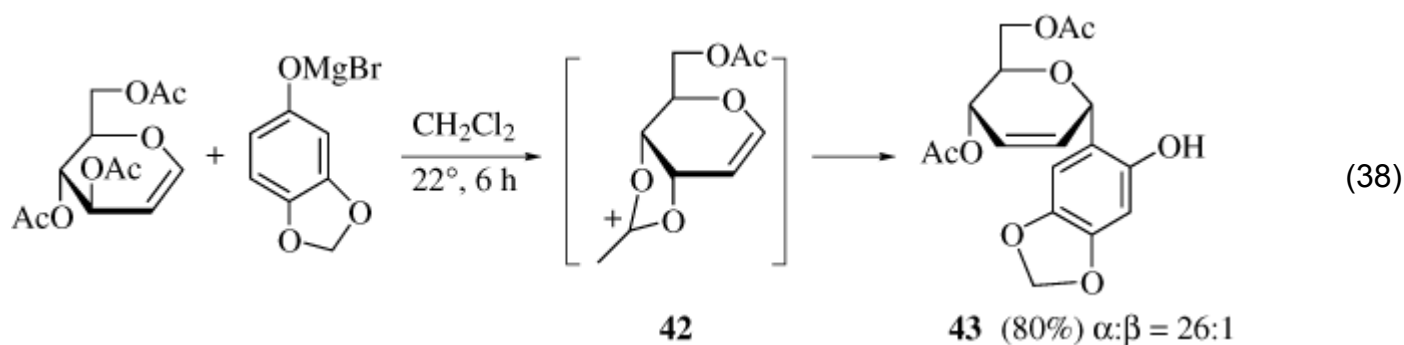
An example of what appears to be a syn- S_N2^{\sim} displacement from a 3-*O*-benzylfuranoid glycal with arylmagnesium bromides is illustrated in Eq. 101, (147) and the corresponding 3,5-di-*O*-acetylglycal, on treatment with an organozinc reagent, likewise gives the product of syn- S_N2^{\sim} displacement. (148) In Table 8 the conversion of 3,4,6-tri-*O*-benzyl-2-*C*-formyl-*D*-glucal into 2-*C*-formyl-2,3-unsaturated α -*C*-glycosides, which apparently involves anti displacement, is listed. (149)

Reaction of glycal derivatives with trialkylaluminums leads efficiently to 2,3-unsaturated alkyl *C*-glycosides (Eq. 37). In the illustrated example the main β -product **41**, derived in 50% yield together with the α -anomer (25%) from di-*O*-acetyl-*L*-rhamnol (**40**), appears to have been formed by a syn- S_N2^{\sim} displacement. However, several 4-deoxyglycal derivatives give the products seemingly derived by anti displacements with very high selectivity. (94)



The question of the mechanisms of reactions of this type is further complicated by observations made on treatment of glycal esters with various metal phenates that may act as Lewis acids. Whereas titanium and aluminum salts of activated phenols give 2,3-unsaturated aryl *O*-glycosides, use of bromomagnesium analogs results in the formation of aryl *C*-glycosidic isomers (Eq. 38). (150) Compound **43** is produced in 77% yield with only 3% of the β -anomer which represents higher selectivity than is exhibited in reactions that proceed by way of oxocarbenium ions. Therefore an anti- S_N2^{\sim} mechanism seems an alternative. However, when the reaction is applied to tri-*O*-acetyl-*D*-galactal, the *C*-4 epimer of the glucal ester, the reactivity is low and only 12% of the *C*-4 epimer of compound **43** is produced. This observation duplicates strikingly the findings made with the oxocarbenium-based reactions, and suggests that the trans-related acetoxy group at *C*-4 of tri-*O*-acetyl-*D*-glucal facilitates the cleavage of the *C*-3—*O* bond. Conceivably, therefore, the reaction illustrated in Eq. 38 could proceed by way of ion **42**, perhaps produced with the aid of coordination of the *C*-3 acetoxy group to the magnesium ion. Ion **42** could undergo reaction with the phenate at the ortho-position of the aromatic ring to give the α -linked product **43** in a syn- S_N2^{\sim} step. Such a mixed mechanism reconciles the observations and allows for the more usual syn

stereochemistry of the nucleophilic displacement.



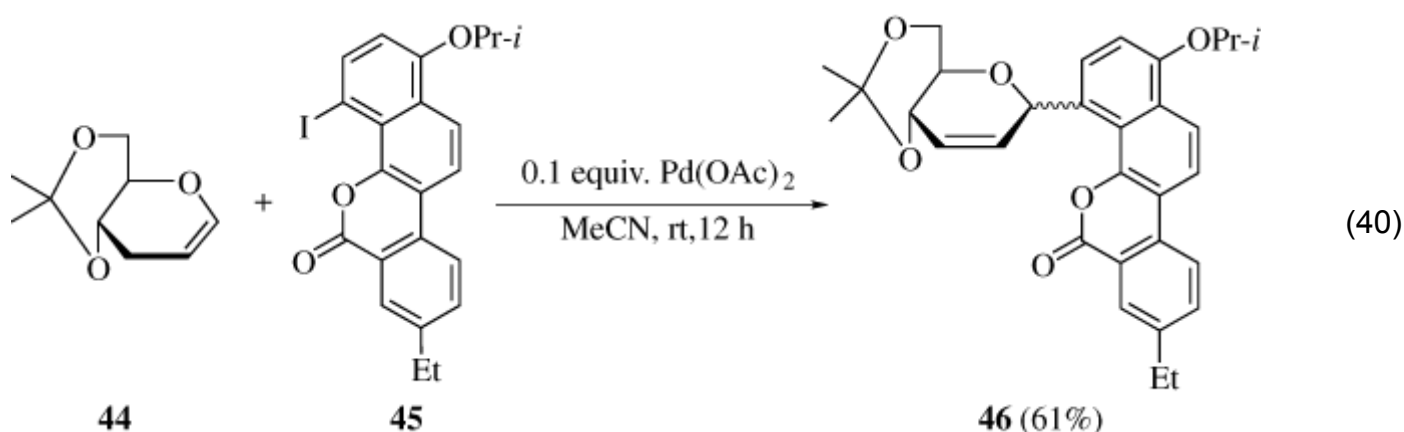
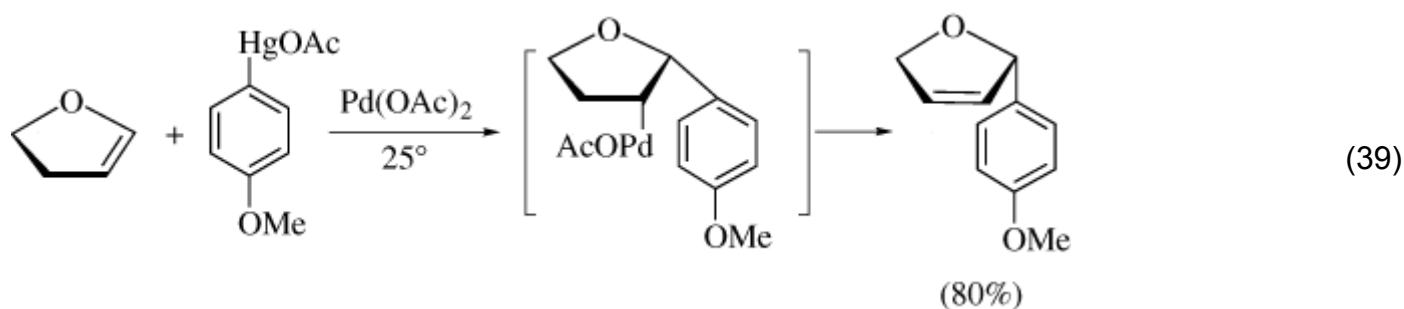
Radical reactions that are relevant to the present review occur with glycols having 3-deoxy-3-tributylstannyl groups; the latter are made from 2,3-unsaturated glycosyl sulfones by treatment with tributyltin hydride under ultraviolet light. With ethyl iodoacetate, under the same radical-inducing conditions, they give 2,3-unsaturated C-glycosides with (ethoxycarbonyl)methyl aglycons. (113)

2.3. Addition-Elimination Reactions

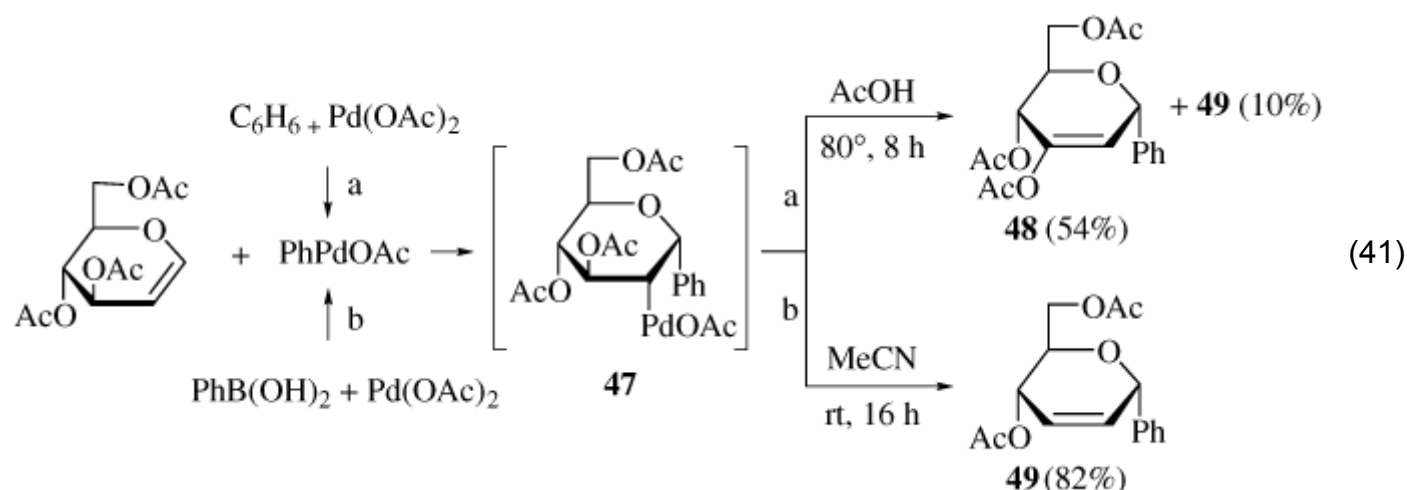
2.3.1. Palladium-Based Reactions

2.3.1.1. General

Treatment of vinyl ethers with organopalladium reagents, made by transmetalation from organomercury or organotin analogs (20, 21) or arylboronic acids, (151) or by oxidative addition of Pd(0) to vinyl iodides or triflates using palladium acetate, (20, 21) leads to the type of transformation under review (Eq. 39). (21) In most examples the reactions are catalytic in palladium. Initially regioselective *syn*-1,2-addition to the alkene occurs via *p*-complexes and hence *s*-adducts that decompose by elimination of “palladium hydride” species. Consistent with this, when 3-deoxyglycol 44 is treated with aryl iodide 45 in the presence of palladium acetate it gives the aryl glycosides 46 with an *a,b* ratio of 9:1 (Eq. 40). (152)

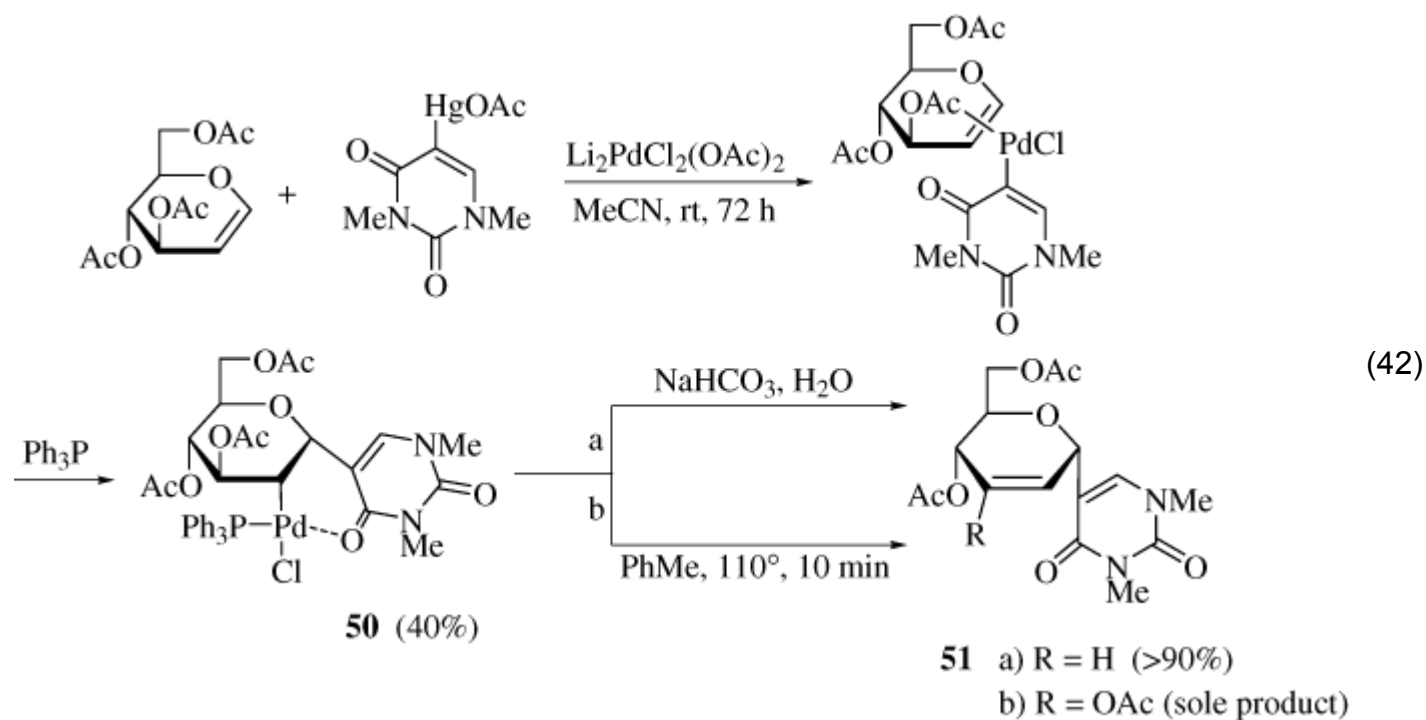


Importantly, glycal derivatives having oxygen-bonded groups at C-3 also take part, and Eq. 41 illustrates the reactions that occur with substituted or unsubstituted aromatic hydrocarbons under palladium mediation. As indicated by path a, benzene and palladium acetate in acetic acid at elevated temperatures give the arylpalladium species which adds specifically from the a-side of the double bond of tri-O-acetyl-D-glucal to give adduct **47**. This spontaneously undergoes syn-elimination of the elements of HPdOAc to afford the main 3-substituted product **48** (54%), whereas anti-elimination of Pd(OAc)₂ gives the minor alkene **49** (10%). (153, 154) A greatly improved route to the latter product involves the generation of the arylpalladium reagent at room temperature from the corresponding arylboronic acid (Eq. 41, path b). The addition step is catalytic in palladium and can be applied with substituted arylboronic acids, although electron-withdrawing substituents reduce the yields. (151)

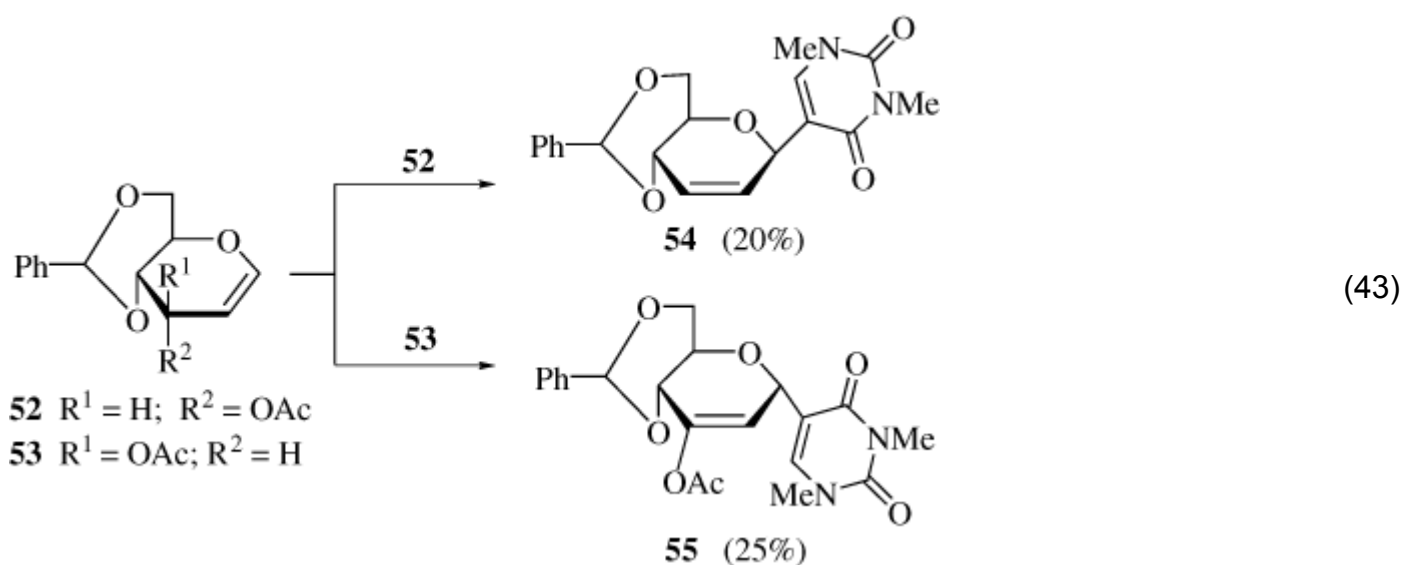


A further example of control of this type of reaction involves different treatments of isolated s-bonded adducts. In the case illustrated in Eq. 42 addition of tri-phenylphosphine permits the isolation of the initial adduct as the stable complex **50** which, on reaction with aqueous bicarbonate, gives the alkene **51** (R = H) in nearly quantitative yield. Alternatively, brief heating of complex **50** in toluene affords the enol acetate **51** (R = OAc) as the sole product. (155)

Product formation can also be controlled by use of conformation restricting factors. For example, 3-O-acetyl-4,6-benzylidene-D-allal (**52**), on treatment with the relevant pyrimidine mercurial derivative activated with palladium acetate followed by bicarbonate, affords the 2,3-dideoxy-b-2-ene **54** as the main product, whereas the



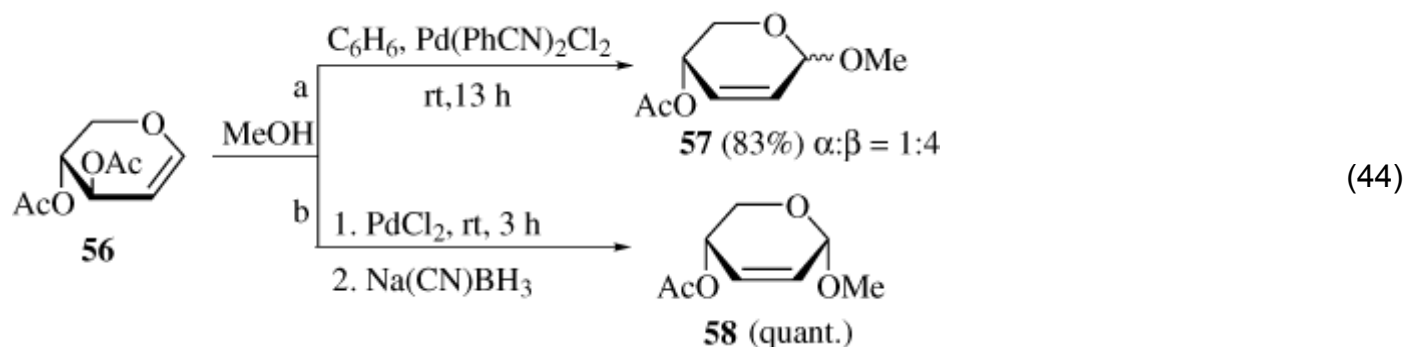
glucal epimer **53** leads to the α -C-glycoside **55** with the C-3 acetoxy group retained. In both cases the yields are modest (Eq. 43). (156)



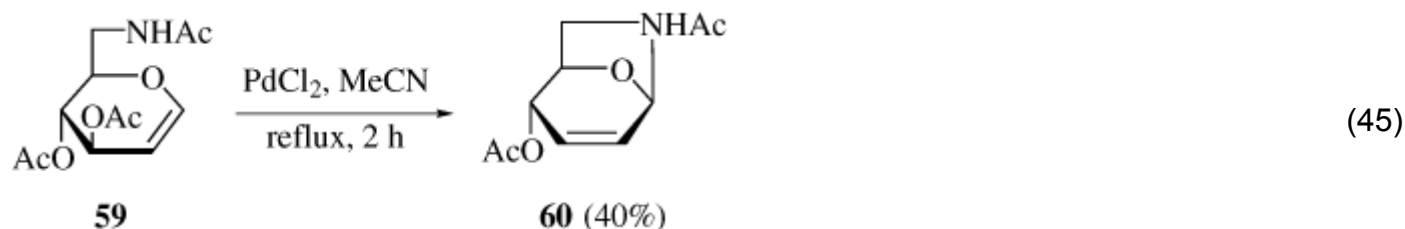
2.3.1.2. Incoming Nucleophilic Groups

The palladium-based approach is most often applied with aromatic and heterocyclic C-nucleophilic species, but compounds with activated methylene groups can also be used (19) as can trimethylsilyl cyanide (157) (see "2,3-Unsaturated C-Glycosides"). A new mechanistic point has to be considered, however, with the active methylene compounds since the mixtures of C-glycosides formed are surprisingly like those obtained by reaction of the glycals with the same active methylene compounds in the presence of Lewis acids. For example, with pentane-2,4-dione and Pd(PhCN)₂Cl₂ as activator, tri-O-acetyl-D-glucal gives the 2,3-unsaturated-3[~]-linked C-glycosides in a similar yield (83%) and in the same a,b ratio (5:1) as are observed when BF₃·Et₂O is used as catalyst (Eq. 3). With the C-4 epimer, tri-O-acetyl-D-galactal, the corresponding yields are again similar but, in this case, only the α -anomer is formed with each promoter. (19) It is difficult to account for this; the products have apparently not equilibrated because, under equilibrating conditions, b-anomers predominate in the case of 2,3-unsaturated C-glycosides having active hydrogen atoms attached to the bonded carbon atom of the aglycons. (140)

Reaction of glycal derivatives with Pd(II) compounds can also lead to 2,3-unsaturated O-glycosides, but the specific products available by this approach are subject to subtle variations. For example, on treatment with methanol (2 equivalents) in benzene in the presence of Pd(PhCN)₂Cl₂, di-O-acetyl-D-xylal (**56**) gives the methyl α - and β -2,3-dideoxy-D-glycero-pent-2-enopyranosides **57** in the ratio 1:4 (Eq. 44, path a). (19) When, however, palladium chloride is used with the alcohol as solvent (path b) and the adduct is reduced with sodium cyanoborohydride, the only product is the methyl α -glycoside **58**. (158) Moreover, closely related reactions can give 3,4-unsaturated O-glycosides (see “Regioselectivity”, below). In an unusual example the use of Pd(MeCN)₂Cl₂ and copper(II) triflate has been preferred to the Lewis acid catalyzed procedure for the preparation of isopropyl 4,6-di-O-acetyl-2,3-dideoxy- α -D-erythro-hex-2-enopyranoside from tri-O-acetyl-D-glucal. A quantitative yield is reported, whereas with BF₃·Et₂O complications arise because of “polymerization and other unwanted side reactions.” (159)

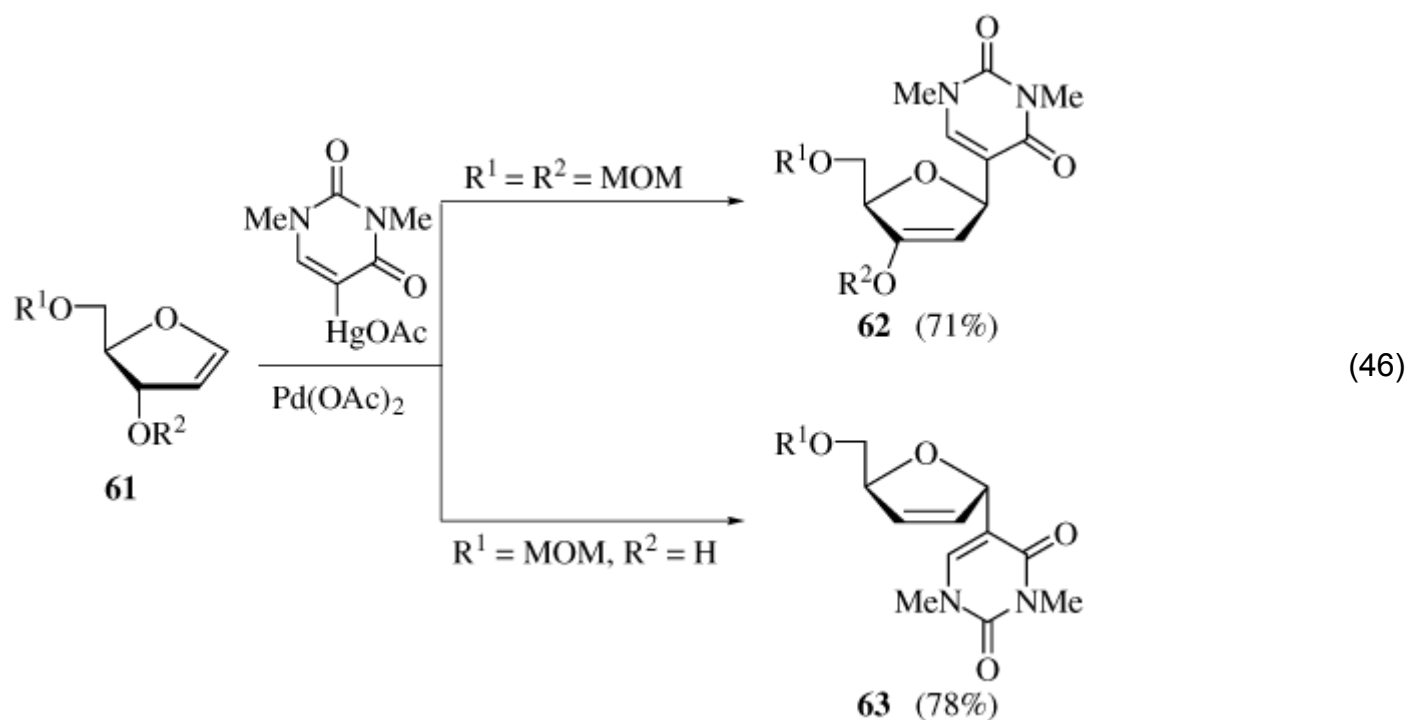


Palladium-promoted reactions involving *N*-nucleophiles that lead to C-N bonded products are rare, but one example is the intramolecular transformation of the 6-acetamido-6-deoxyglucal derivative **59** into the bicyclic imino compound **60** (Eq. 45). (160)



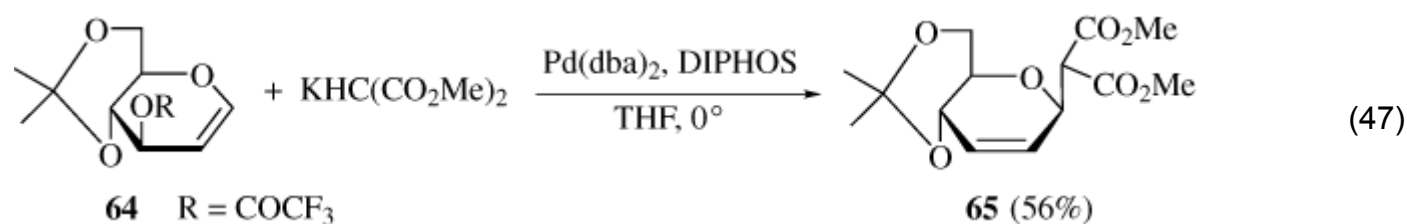
2.3.1.3. Leaving Groups

As indicated above, hydride or acyloxy groups can be removed from the allylic positions of glycal derivatives during palladium-promoted transformations. When there is a hydroxyl group at this center it has a dominating influence on the reactions that occur (Eq. 46). (20) When both hydroxyl groups of compounds **61** are *O*-substituted, and mercurated pyrimidine is introduced together with palladium acetate, complex formation occurs from the *b*-direction, *syn*-“palladium hydride” elimination follows, and good yields of 3-substituted, unsaturated *b*-C-nucleoside analogs such as **62** are obtained. On the other hand, when the hydroxyl group at C-3 of compounds **61** is free and that at C-5 is substituted, addition takes place from



the *a*-face of the molecule and *syn*-elimination of “palladium hydroxide” leads to *a*-2,3-dideoxy-unsaturated compounds such as **63**. This latter process, therefore, is akin to the acid-catalyzed allylic substitution reaction under review.

The electron-rich double bonds of glycols do not form (*p*-allyl)palladium(II) complexes and therefore, for example, tri-*O*-acetyl-*D*-glucal does not react with Pd(0) species under conditions in which aliphatic allylic acetates undergo reaction. The 3-trifluoroacetate analog **64**, however, with potassium dimethyl malonate in the presence of (1,5-diphenylpent-1,4-dien-3-one)₂-Pd(0) [Pd(*dba*)₂] and Ph₂PCH₂CH₂PPh₂ (DIPHOS or *dppe*) gives the *C*-glycoside **65** (Eq. 47). (115) Since the reaction does not proceed in the absence of the palladium derivative the possibilities that the product is formed via an oxocarbenium ion or by an S_N2[~] mechanism are minimized.



2.3.1.4. Configurations at the Allylic and Homoallylic Centers

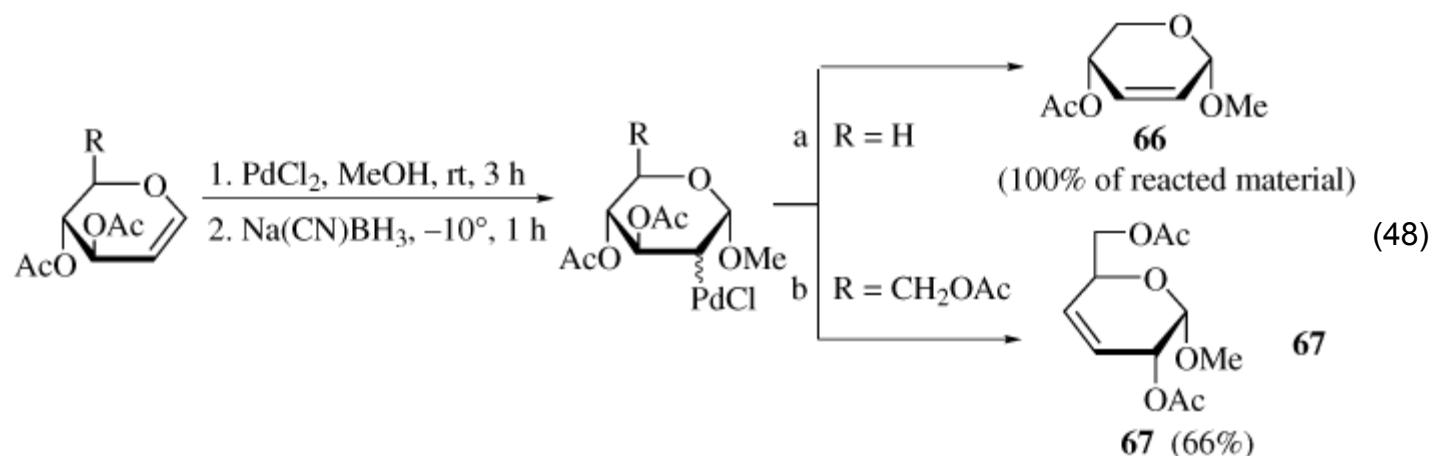
As has been indicated above, the groups at C-3 of glycols control the direction of initial *syn*-additions, and allal (e.g. **52**) and glucal (e.g. **53**) derivatives give adducts formed on the *b*- and *a*-sides of the double bonds, respectively (Eq. 43).

The influence of the configuration of the groups at C-4 of glycols on palladium-promoted transformations is normally minor. Thus, in its reaction with pentane-2,4-dione, tri-*O*-acetyl-*D*-glucal gives the *a*- and *b*-*C*-glycosides in the ratio 5:1 (Eq. 3), whereas the galactal ester gives only the *a*-product. (19) Somewhat similarly, products **48** and **49** are formed from tri-*O*-acetyl-*D*-glucal in the ratio 5:1 (Eq. 41, path a), whereas only the 4-epimer of the former results from the same reaction applied to tri-*O*-acetyl-*D*-galactal. (153, 154)

2.3.1.5. Regioselectivity

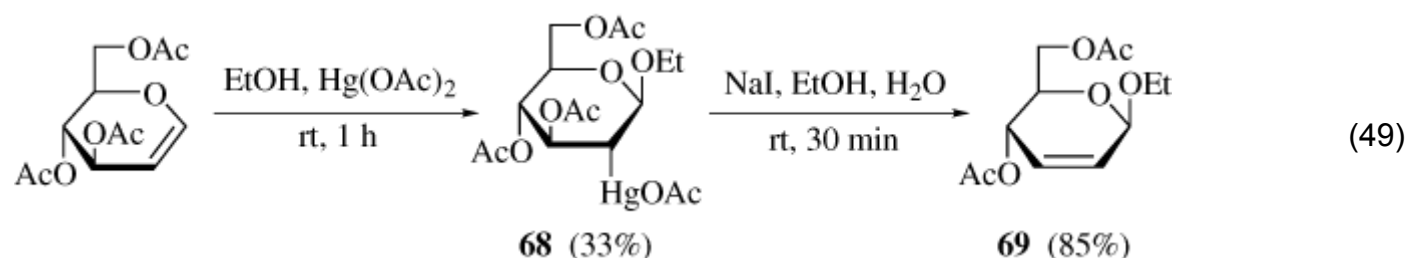
A feature of the palladium-promoted transformation reaction is that, under some circumstances, the

main products are 3,4-unsaturated glycosides. Di-*O*-acetyl-D-xylal in methanol, treated with palladium chloride, gives adducts that, on reduction with sodium cyanoborohydride, undergo elimination to afford the unsaturated glycoside **66** (Eq. 48, path a). When, however, tri-*O*-acetyl-D-glucal is subjected to these reactions, the hexoside analog of glycoside **66** represents only 14% of the reaction products, the remainder being the rearranged isomer **67** (Eq. 48, path b). (158) In this latter case the initial adduct is reduced to afford a Pd(O) complex that allylically rearranges to give an isomeric complex from which alkene **67** is derived. That this rearrangement is dependent on the nature of the substituents at C-5 of the glycal is suggested by the finding that the same reactions carried out with di-*O*-acetyl-D-xylal (**56**) gives no 3,4-alkene (Eq. 44, path b). Furthermore, the corresponding glycals with CH₂OH and CH₂CN groups at C-5 give, respectively, the 3,4- and 2,3-alkenes as sole products. This further indicates that coordinating groups bonded to C-5 stabilize the intermediates that lead to the rearranged 3,4-unsaturated products. (158)

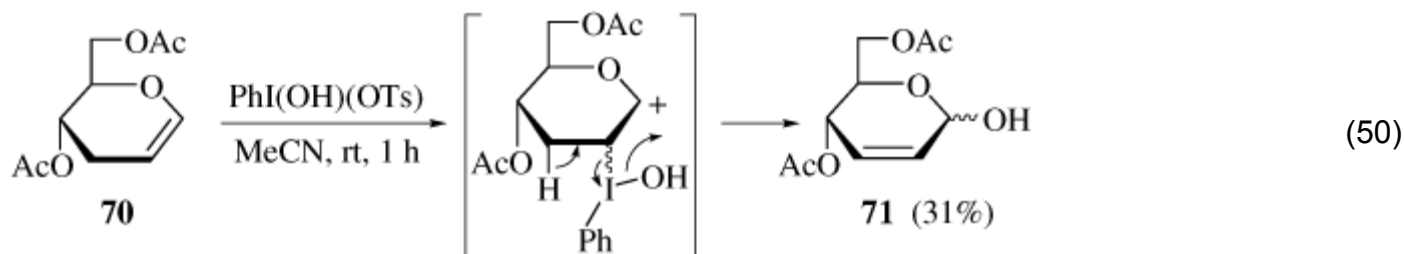


2.3.2. Other Addition-Elimination Reactions

Mercury(II) salts can be used to bring about the glycal conversion reaction by two-step addition-elimination procedures. For example, tri-*O*-acetyl-D-glucal, treated with mercury(II) acetate in ethanol, gives the crystalline ethyl 2-acetoxymercuri-2-deoxy-β-D-glucoside adduct **68** which, on reaction with sodium iodide in aqueous ethanol, affords the 2,3-unsaturated β-product **69** (Eq. 49). (161) This process, therefore, is complementary to the acid-catalyzed approach for making 2,3-unsaturated *O*-glycosides in giving the thermodynamically unfavored anomers. When the mercuriation reaction is conducted in acidic aqueous media the adducts collapse to the E-forms of the acyclic enals (see "Scope and Limitations, 2,3-Unsaturated Free Sugars".) (162)



An entirely different type of reaction, which apparently proceeds by an addition-elimination process, causes the oxidative transformation of the 3-deoxyglycal derivative **70** into the unsaturated free sugar compound **71** (Eq. 50). (163) By a related azidonation process such compounds give 2,3-unsaturated glycosyl azides as well as 3-azido-3-deoxyglycals on treatment with (PhIO)_n/TMSN₃ in dichloromethane. (164)



2.4. A 1,4-Addition Reaction

The introduction of a carbonyl group at C-3 of a glycal allows a modified form of the transformation reaction under review that involves trapping of intermediate enolates. In the reaction illustrated in Eq. 4, Michael-like addition to the enone of nucleophilic phenyl is followed by trapping of the intermediate enolate with acetic anhydride in a 1,4-addition process. An alternative highly efficient synthesis of the 3-O-substituted C-glycoside **48** (Eq. 41) results. (22)

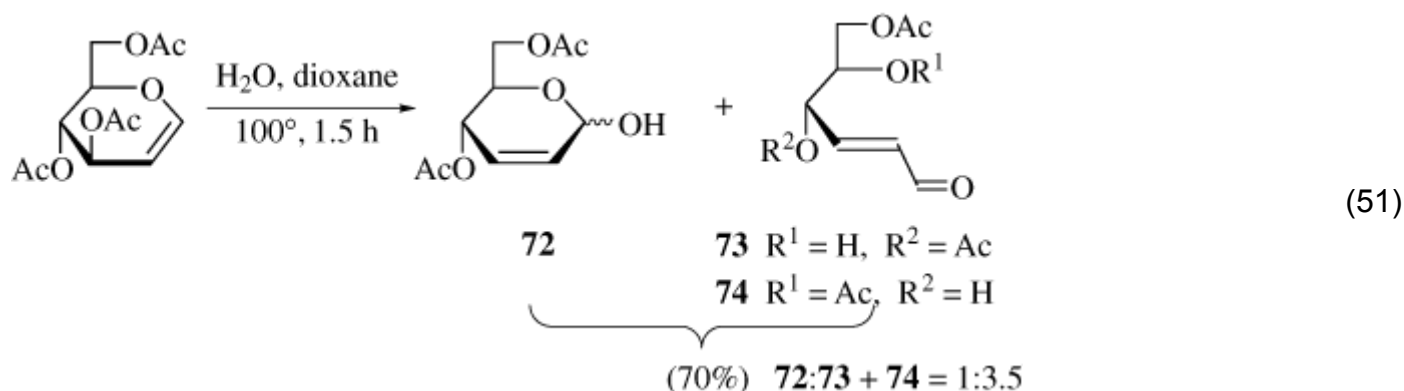
2.5. Electrocyclic Reactions

Thermal [3.3]-sigmatropic isomerizations can offer very satisfactory means of carrying out the transformations under review (Eq. 9), and glycal derivatives with such groups as acyloxy, azido, and vinyl ether at the allylic C-3 position all take part in the reaction. A notable feature is that stereochemical integrity can be maintained throughout the process. All reactions are, in principle, reversible; where the positions of the equilibria lie depend very much on the specifics of the different examples. These reactions are discussed under "Scope and Limitations, Intramolecular Applications."

3. Scope and Limitations

3.1. 2,3-Unsaturated Free Sugars

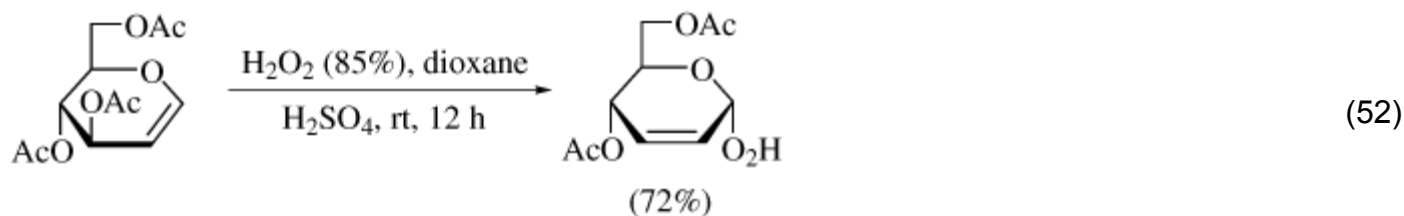
Fischer's early work showed that, in hot water, tri-*O*-acetyl-D-glucal undergoes the substitution with allylic rearrangement reaction [Eq. 1, **1** into **2** (Nu = OH)]. Extensions of this work have, however, revealed that isomerization about the double bond of the acyclic form of the hemiacetal product and some migration of the acetyl group from O-4 to O-5 also occur. As well as the unsaturated free sugar **72**, therefore, compounds **73** and **74** are produced (Eq. 51). (165) When the reaction is continued the E-aldehydes accumulate to become the major products present to the extent of about 60%. Tri-*O*-acetyl-D-galactal reacts less satisfactorily with water and lower yields of the corresponding aldehydes are obtained. (165) Later kinetic and thermodynamic studies of this reaction applied to tri-*O*-acetyl-D-glucal (166) and di-*O*-acetyl-D-xylal (167) confirmed the major significance of the enals in later stages of the reactions and indicated the presence of several other products formed concurrently. In the dark, or in the presence of hydroquinone, formation of enals is suppressed. (10)



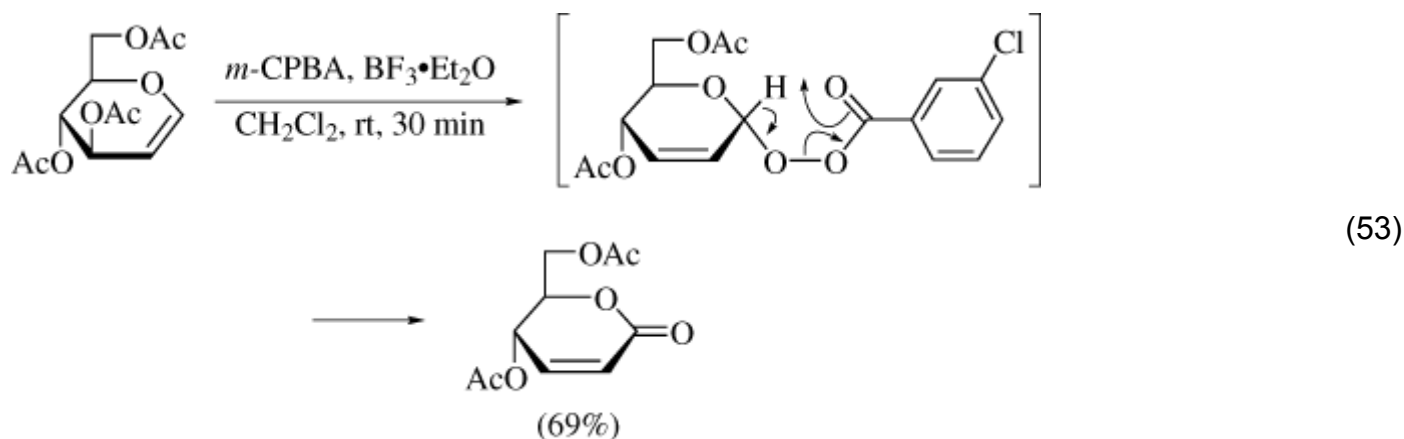
A very suitable, alternative means of producing E-enals such as **73** involves treatment of acetylated glycols in aqueous dioxane containing sulfuric acid and catalytic amounts of mercury(II) sulfate. (162) Under these conditions, rather than the enals being formed by displacement processes, it seems that addition/elimination steps are responsible (cf. Eq. 49). Compounds of this kind can give rise to unexpected further products of reaction. Thus, in the course of the condensation of tri-*O*-acetyl-D-glucal with 4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enose in toluene with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as catalyst, about 10% of the products consist of the E-enal **73** substituted at O-5 with a 2,3-unsaturated glycosyl moiety, and formed apparently by competitive reaction of the hydroxyl group at C-5 of **73** with the glycal. As expected, however, the main product (33%) is the 1- α , 1- α linked, symmetrical diunsaturated dimer. (168)

3.2. 2,3-Unsaturated Glycosyl Peroxides

Hydrogen peroxide also takes part in the reaction under review. tri-*O*-acetyl-D-glucal in dioxane containing sulfuric acid reacts to give the α -linked hydroperoxide as an oil in 72% yield (Eq. 52). (169) With aqueous hydrogen peroxide in the presence of molybdenum trioxide the yield is 52% ($a:b = 2:1$), and the α -anomer is obtained crystalline after flash chromatography. (170) Tri-*O*-acetyl-D-galactal gives a much poorer yield. Similarly, whereas tri-*O*-benzyl-D-glucal gives 45% of the 2,3-unsaturated α -hydroperoxide, tri-*O*-benzyl-D-galactal fails to give any of the analogous product, undergoing addition reactions instead. (170) Lewis acids such as $\text{BF}_3 \cdot \text{Et}_2\text{O}$ or SnCl_4 may also be used in the preparation of glycosyl hydroperoxides. (171)

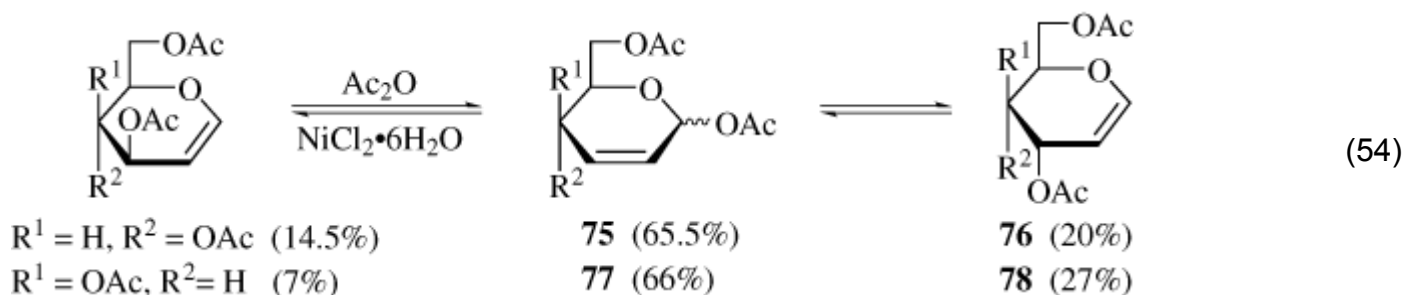


Related reactions occur when glycol esters are treated with equimolar amounts of *m*-chloroperoxybenzoic acid in dichloromethane containing $\text{BF}_3 \cdot \text{Et}_2\text{O}$, but the initially formed peroxides spontaneously decompose to afford the 2,3-unsaturated aldonolactones in good yields (Eq. 53). (172)



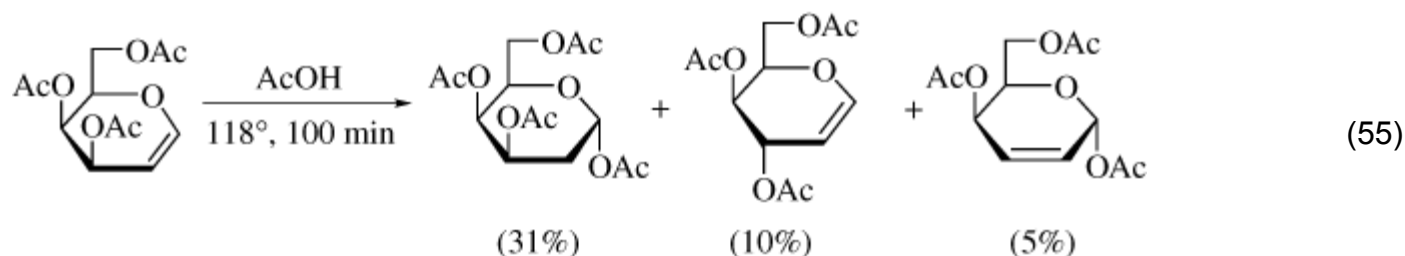
3.3. 2,3-Unsaturated Glycosyl Carboxylates

Heating with acetic anhydride converts tri-*O*-acetyl-D-glucal and -galactal into the isomeric 2,3-unsaturated glycosyl acetates; the reactions are catalyzed by heptamolybdate ion. (173) There is more to the isomerizations than this, however, since these glycols in boiling acetic anhydride with added metal salts, e.g. $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$, give not just the 2,3-unsaturated glycosyl esters but also the C-3 epimers of the starting compounds (tri-*O*-acetyl-D-allal and -gual, respectively; Eq. 54). (131) The proportions of the products derived from tri-*O*-acetylglucal are the same as those recorded earlier for the mixture obtained by treating it in benzene containing $\text{BF}_3 \cdot \text{Et}_2\text{O}$, and also by thermal rearrangement. (122) This suggests that equilibrium is attained by sigmatropic isomerization to the 2,3-unsaturated compound **75** (b), anomerization to **75** (a), and reverse sigmatropic rearrangement of the allal ester **76**. In the same way, tri-*O*-acetyl-D-galactal can equilibrate with isomers **77** and **78**. The required interconversion of the 2,3-unsaturated a- and b-compounds under acidic conditions should not be difficult given their allylic and acetal-like natures.

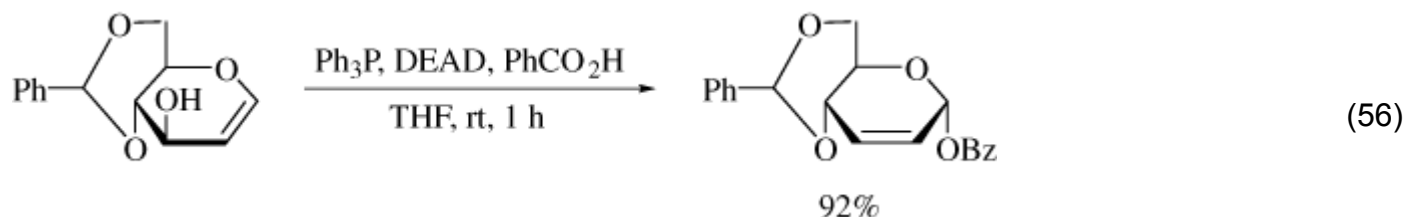


Carboxylic acids, with or without catalysts, cause the allylic rearrangement reaction to occur, but now the possibility of additions to give 2-deoxyglycosyl esters also arises. The situation with the

glucal ester, however, is not complex; the equilibrium mixture indicated in Eq. 54 is established in refluxing acetic acid within 30 minutes without the formation of saturated compounds. (174) As is to be expected (see “Transformations Involving Oxocarbenium Ions, Configuration at the Homoallylic Center of the Glycals”), tri-*O*-acetylglactal is much less amenable to the isomerization process. It reacts more slowly, and mixed products derived by addition, isomerization, and elimination are formed (Eq. 55). (117) In the experiment illustrated a full product analysis was not possible, and the yields shown indicate only the proportions of the samples isolated. It is to be expected that some of the starting material would have remained, and higher proportions of the illustrated unsaturated products than are indicated would have been present. Additionally, a diene, provisionally identified as a pyran derivative formed by an elimination reaction, is also produced.



As an alternative to thermal or acid-catalyzed reactions, the Mitsunobu procedure can be used to produce 2,3-unsaturated glycosyl carboxylates (Eq. 56). However, whereas the illustrated *D*-glucal derivative reacts very specifically, under the same conditions the epimeric *D*-allal compound gives the illustrated product in only 36% yield together with 3-*O*-benzoyl-4,6-*O*-benzylidene-*D*-glucal, formed apparently by S_N2 displacement at C-3, and also products of addition and starting material. (175) Clearly, in this reaction of these epimeric glycals, a common ionic intermediate is not involved and S_N2^{\sim} displacements, if they occur, are favored only by the glucal derivative, the difference in reactivities perhaps being a consequence of the propensity of the allal isomer to undergo diaxial conjugate elimination. Applied to 4,6-di-*O*-benzoyl-*D*-galactal the reaction again gives mixed products, in this case the tribenzoate formed by S_N2^{\sim} displacement at C-3 and the 2,3-unsaturated α -glycosyl benzoate, in 27% and 31% yields, respectively. (176) As concluded previously (see “Transformations Involving Oxocarbenium Ions, Leaving Groups and Activators”) the Mitsunobu reaction applied to glycals having unprotected hydroxyl groups at C-3 appears to be mechanistically delicately poised.

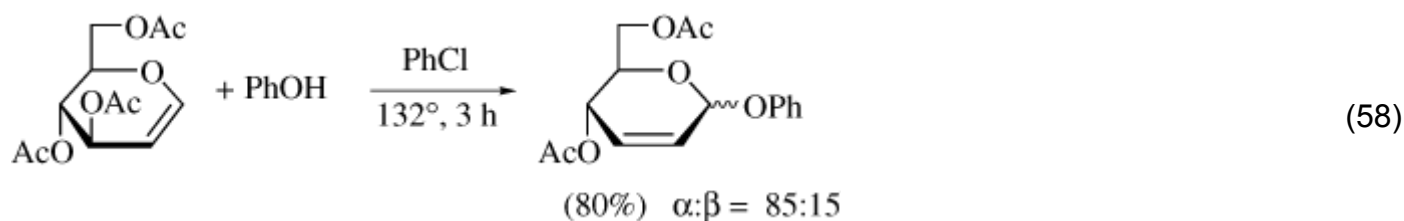


3.4. 2,3-Unsaturated *O*-Glycosides

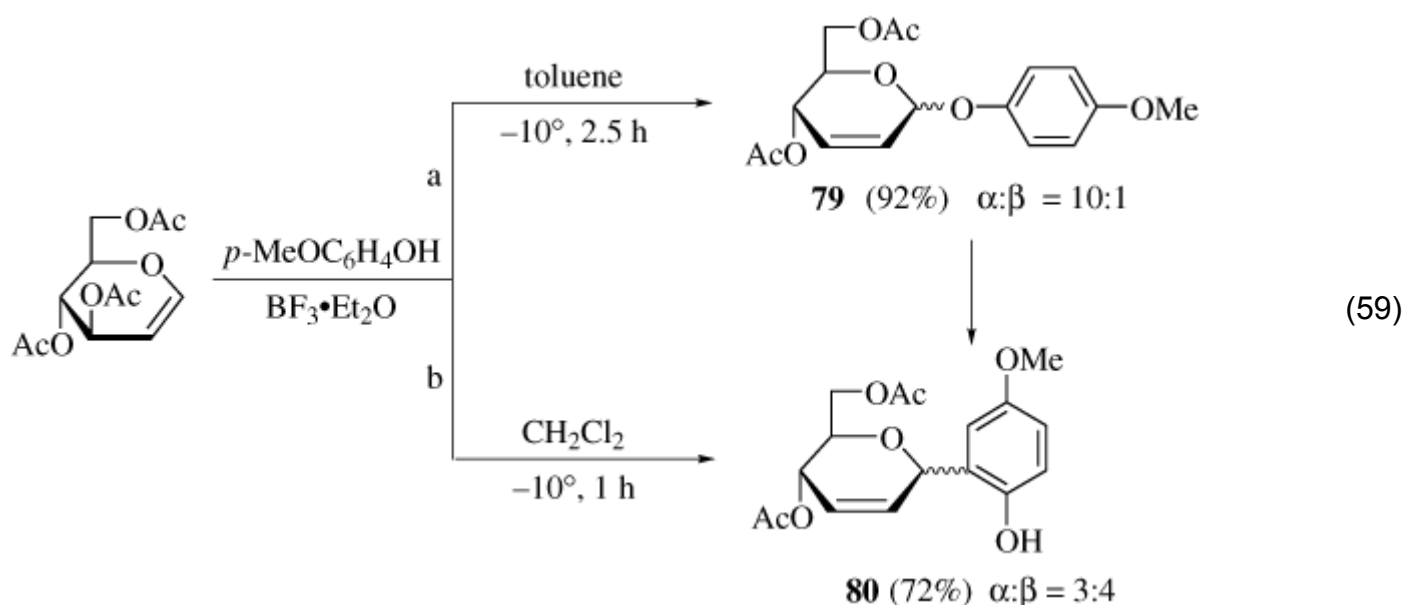
Most reactions resulting in the formation of C-1–O bonds have been carried out with alcohols or phenols and lead to 2,3-unsaturated *O*-glycosides. Many of these products have simple alkyl aglycons, and most frequently have been made with the aid of $BF_3 \cdot Et_2O$ as catalyst. Yields quoted are commonly near 80–90% for products derived from primary alcohols and somewhat less for those from secondary alcohols; the *t*-butyl glycoside derived from di-*O*-acetyl-*L*-rhamninal is obtained in 50% yield ($SnCl_4$ catalyst) (Eq. 57), (46) and that from tri-*O*-acetyl-*D*-glucal in 73% yield (I_2 catalyst). (90) *D*-Galactal triacetate does not react with these efficiencies unless particular catalysts, e.g. $SnCl_4$, are used. (45)



Phenols take part in the rearrangement reaction, under thermal, acid-catalyzed, or Mitsunobu conditions. Whereas heating together of tri-*O*-acetyl-D-glucal and *p*-nitrophenol at 80° in benzene for 4 hours efficiently gives mixed anomers of the allylically rearranged glycosides (Eq. 2), (11) less acidic phenols require harsher conditions. Thus for the analogous reaction of this substrate with phenol itself to proceed in a comparable time a 50° increase in temperature is required (Eq. 58). (13) Similar results are reported for several substituted phenols. (119, 124, 177) Pure α -anomers can be isolated directly in approximately 40% yields in the cases of the glycosides derived from tri-*O*-acetyl-D-glucal with *m*- and *p*-nitrophenol and *p*-*tert*-butylphenol, and from di-*O*-acetyl-L-rhamnal with *p*-*tert*-butylphenol. (178)

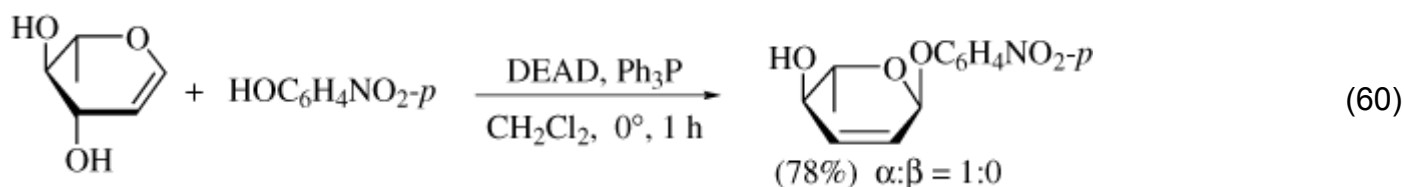


As with alcohols, the rearrangements carried out with phenols can be acid catalyzed, (14) and yields above 90% of 2,3-unsaturated *O*-glycosides **79** have been achieved at sub-zero temperatures with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.05 equivalents) as catalyst in toluene as solvent (Eq. 59, path a). (179, 180) For the reaction illustrated a quantitative yield and an α , β ratio of 15:1 have been recorded following the use of $\text{Sc}(\text{OTf})_3$ in $\text{MeCN} - \text{H}_2\text{O}$ (9:1). (77) Also, as with alcohols, tri-*O*-acetyl-D-galactal reacts much less specifically with phenols than does tri-*O*-acetyl-D-glucal, (117) but again the problem can be overcome by use of SnCl_4 as catalyst. Recorded yields, however, are only 43% for the phenyl and 57% for the *p*-bromophenyl α -compounds under these conditions. In this series, no β -glycosides are detected. (45)

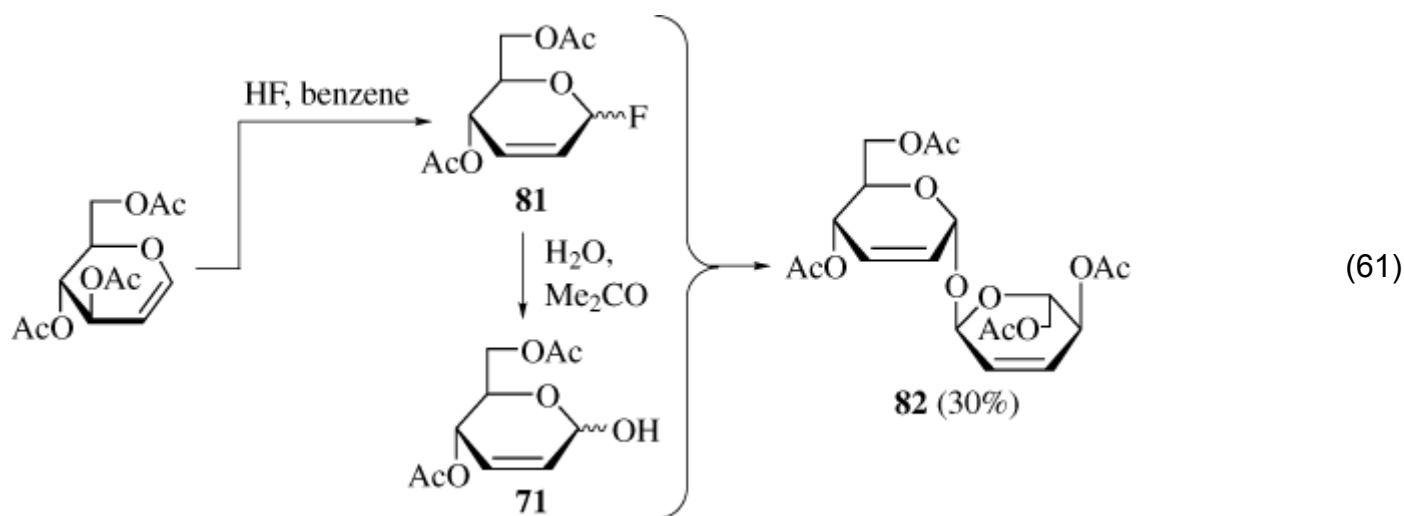


The conditions for making 2,3-unsaturated O-glycosides bearing aromatic aglycons with activating substituents have to be controlled because these products readily isomerize in the presence of acid catalysts to aryl C-glycosides. Thus when tri-O-acetyl-D-glucal is treated with *p*-methoxyphenol, but now in CH₂Cl₂ with added BF₃·Et₂O (0.2 equivalents), the C-glycosides **80** are obtained exclusively (Eq. 59, path b; cf. Eq. 89). (180) These compounds can also be made from the O-linked isomers as starting materials.

A different approach to unsaturated aryl O-glycosides, which avoids complications associated with the use of acidic catalysts and which can be applied with O-unsubstituted glycols, employs the Mitsunobu reaction (Eq. 60). (109) Other examples also result in the formation of α-products only, adding to the suspicion that the mechanism of the displacement process is different from that operating in the more common Lewis acid catalyzed reactions, and may involve specific S_N2[~] processes. In the analogous reaction of L-fucal (6-deoxy-L-galactal), however, mixed anomers are formed, and the details of these displacements have therefore yet to be defined. (109) An additional mild means of making aryl 2,3-unsaturated glycoside derivatives involves the use of iodine in THF at room temperature. (90) With tri-O-acetyl-D-glucal activated and deactivated phenols take part in the reaction to give yields of about 60–75% and α,b ratios in the range 10:1–15:1, that is, somewhat higher than those usually reported for the analogous reactions catalyzed by common Lewis acids.



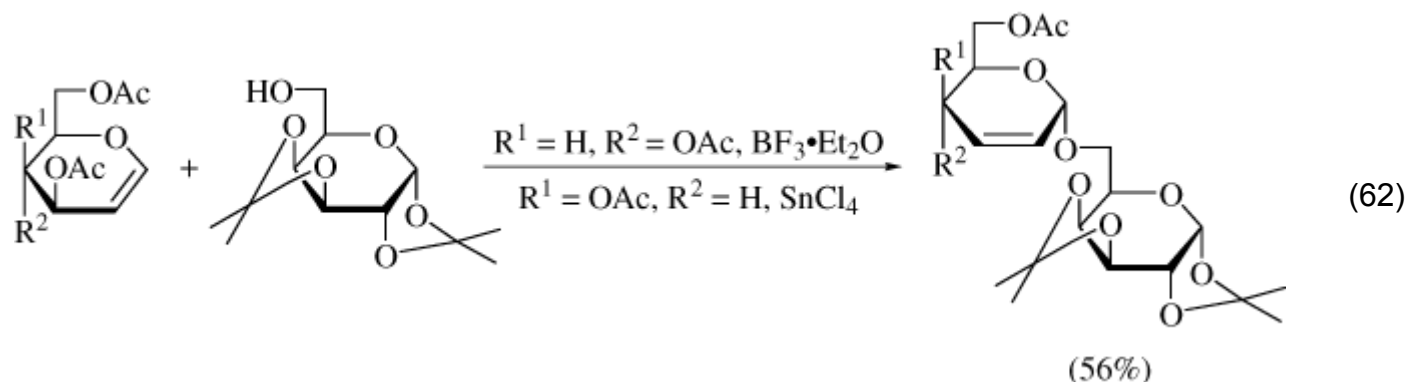
Hydroxylated sugar compounds are amongst the most significant of the many complex alcohols that have been glycosylated with glycal derivatives because their use represents a novel approach to the synthesis of di- or higher saccharides. The reaction of tri-O-acetyl-D-glucal with hydrogen fluoride in benzene at room temperature, followed by aqueous treatment, gives a mixture from which the crystalline compound **82** is obtained in 30% yield (Eq. 61). (181) With the anomeric centers linked



by an oxygen atom this product is therefore a derivative of a non-reducing disaccharide, and most probably it is derived by reaction of the intermediate fluoride **81** with its hydrolysis product **71**. It was later made formally in 44% yield by BF₃-catalyzed reaction of tri-O-acetyl-D-glucal with alcohol **71** (Eq. 61), was characterized as the α,α-compound and used to make two diamino-dideoxy derivatives of α-D-mannopyranosyl α-D-mannopyranoside. (182) An analogous pentose-based diunsaturated analog of disaccharide **82**, again formed directly from an analogous glycosyl fluoride,

has been described. (183)

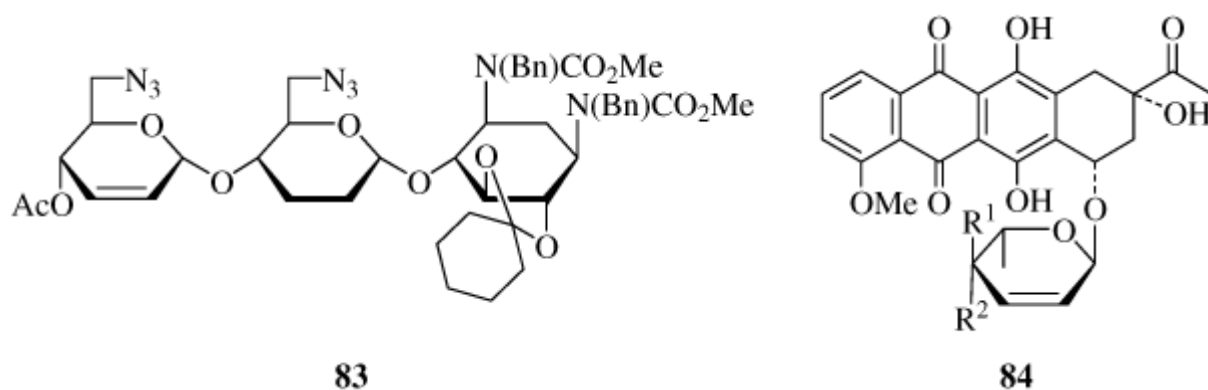
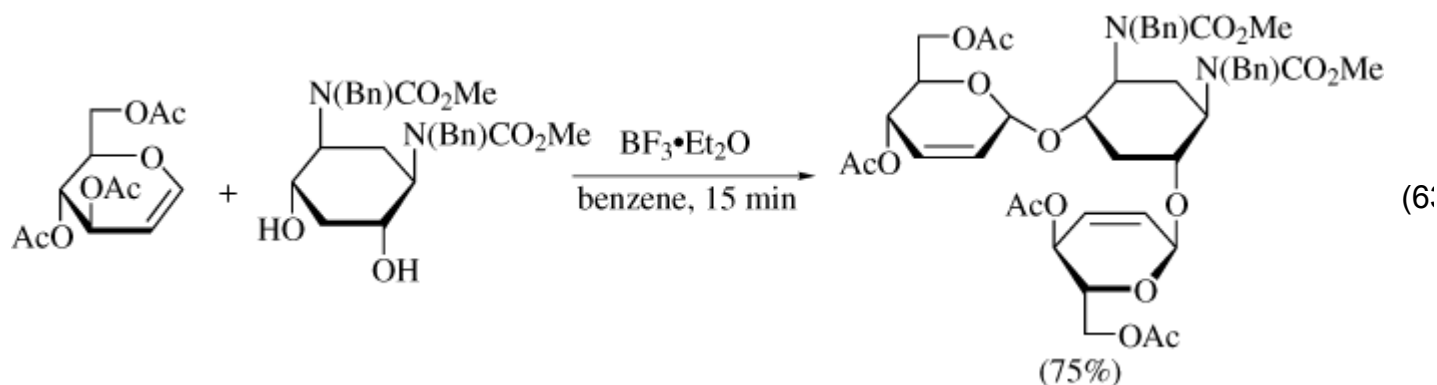
Application of the normal procedure for coupling tri-*O*-acetyl-D-glucal to 1,2:3,4-di-*O*-isopropylidene-D-galactose with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as catalyst affords the expected disaccharide derivative in 56% yield, (14) and the C-4 epimer is made with the same efficiency by use of tri-*O*-acetyl-D-galactal with SnCl_4 as catalyst (Eq. 62). (45) Further applications of the reaction have involved several sugar secondary alcohols; yields are in the 60 to 10% range, and carbohydrate functional groups found to be compatible with the Lewis acid promoted reaction are glycosides, epoxides, acetals, halogens, acyl and sulfonyl esters, and alkyl and benzyl ethers. (184-188) See also Table 2.



However, not all potential secondary alcohol acceptors react satisfactorily under normal conditions, and in such cases milder, neutral methods are recommended. An important development in this area depends upon the pent-4-enoyl ester procedure. By its use D-glucal, D-allal, and D-galactal derivatives carrying this group at C-3 are successfully condensed with 1,2:5,6-di-*O*-isopropylidene-D-glucose (Eq. 10) which does not react satisfactorily with tri-*O*-acetyl-D-glucal in the presence of BF_3 . More significantly, because of its sensitivity and the presence of a tertiary anomeric hydroxyl group, the reaction also succeeds with 1,3,4,6-tetra-*O*-acetyl-D-fructose, and the products open a new synthetic approach to sucrose-like disaccharides. (36, 111)

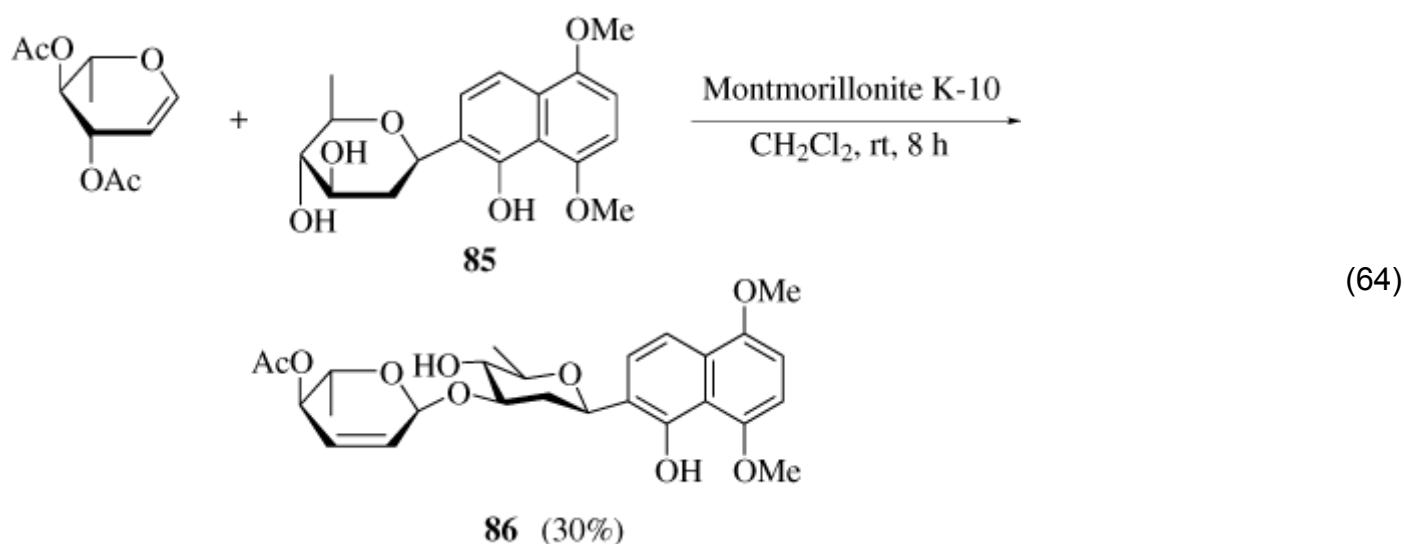
Many examples have been recorded of the substitution with rearrangement reaction with functionalized aliphatic alcohols including those bearing halogen atoms, alkene, alkydiene, and alkyne functions and trimethylsilyl, phenylthio, phenylselenyl, carbonyl, phosphonyl, and carboxylate ester and even carborane groups (Table 2). The products have been employed for many purposes often utilizing functionality in the aglycons together with that of the double bonds in the carbohydrate moieties.

Eq. 63 illustrates a rare disubstitution; the yield is similar to that often recorded for couplings to simple secondary alcohols. (189) Compound 83, which is made by two sequential applications of the allylic substitution reaction, (190) can be converted into saturated compounds of relevance to aminoglycoside antibiotic chemistry. Even though it is a tetraol, daunomycinone, when treated with di-*O*-acetyl-L-rhamnol or -L-fucal under $\text{BF}_3 \cdot \text{Et}_2\text{O}$ catalysis, affords anthracyclines 84 ($\text{R}^1 = \text{OAc}, \text{R}^2 = \text{H}$ and $\text{R}^1 = \text{H}, \text{R}^2 = \text{OAc}$) in 67 and 15% yields, respectively, in a further application of the rearrangement reaction in medicinal chemistry. (191) It is noteworthy that in the latter case the C-4 acetoxy group, which is *cis*-related to the leaving group of the glycal diacetate, cannot offer anchimeric assistance to its departure and, at least with BF_3 as catalyst, the rearrangement is impeded. Furthermore favorable, competitive *trans*-elimination of acetic acid from C-3, C-4 is possible with the fucal diacetate.



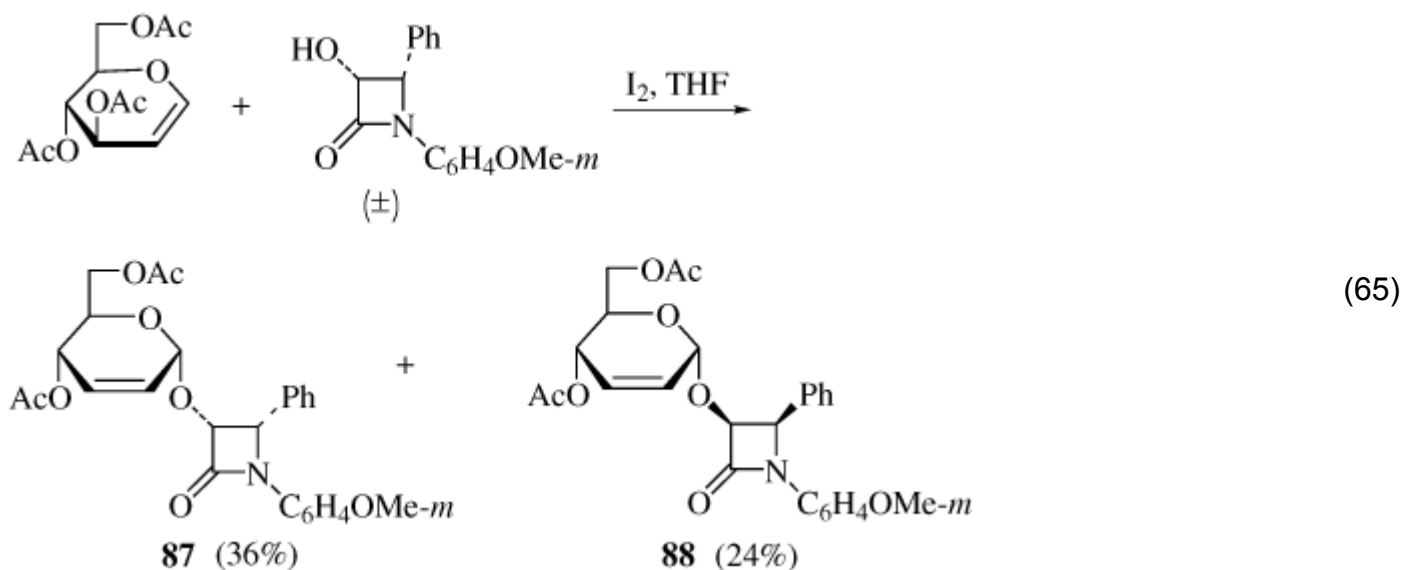
Seldom is the substitution reaction carried out in a selective manner, but compound **86** is obtained in 30% yield from the reaction of di-*O*-acetyl-L-rhamninal with triol **85**, and concurrently the 3-linked β -anomer (15%) and the 4-linked α -isomer (18%) are formed (Eq. 64). (192) As is to be expected, with diols involving primary and secondary hydroxy functions, the former react preferentially. (97)

The reaction illustrated in Eq. 65 that leads to the diastereomeric α -linked compounds **87** and **88** is unusual in that it is promoted by iodine in THF at room temperature. Whether it proceeds by way of the oxocarbenium ion as intermediate is not known; the iodine is apparently not consumed in the reaction. Chromatographic separation of the products and mild hydrolysis of their glycosidic bonds affords the enantiomeric 3-hydroxy-2-azetidinones; that obtained from glycoside **88** was required for the partial synthesis of taxol^Z (**89**) Very surprisingly, whereas di-*O*-acetyl-L-rhamninal can be used in like manner for the resolution of the enantiomeric



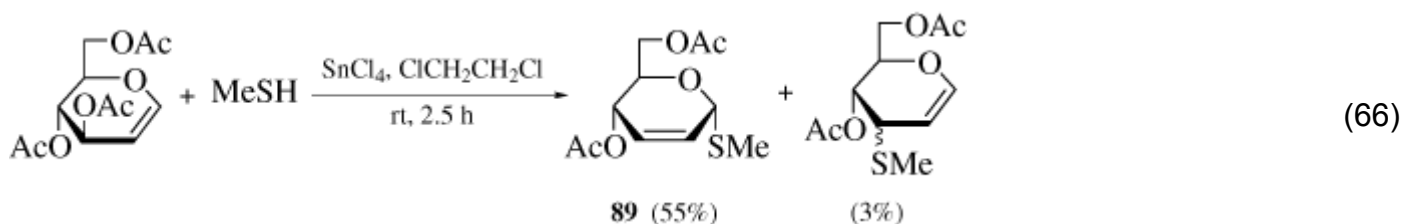
trans-isomers of the hydroxyazetidinones, tri-*O*-acetyl-D-glucal does not react with these compounds under the conditions used. (91) This approach has been extended to the synthesis of

enantiomerically pure β -lactams having 1-hydroxyethyl substituents in place of the hydroxy group on the four-membered ring. (193)

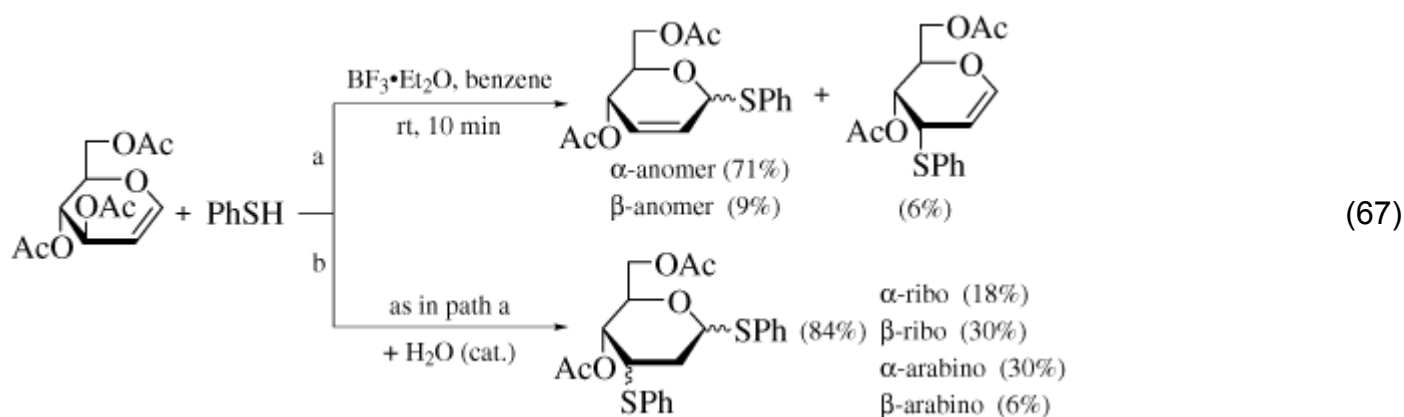


3.5. 2,3-Unsaturated S-Glycosides and Related Thio Compounds

The Lewis acid catalyzed reaction of thiols with glycal esters does not parallel exactly that of alcohols and phenols. tri-*O*-acetyl-D-glucal with methanethiol in the presence of SnCl_4 , under mild conditions, gives the three products indicated in Eq. 66. From tri-*O*-acetyl-D-galactal the corresponding α -thioglycoside (41%) and the 3-thioglycal derivative (17%) are obtained. These observations, however, indicate the nature and distribution of the kinetic products; at equilibrium quite different ratios are observed, the 3-thioglycals then being favored to the extent of more than 10:1. (35) That the isomerizations occur by reverse formation of oxocarbenium ions was elegantly shown by treating a mixture of the 2,3-unsaturated *S*-hexyl and *D*-threo-analogs of compound 89 in CH_2Cl_2 with SnCl_4 and finding that they were converted into a mixture largely consisting of *D*-glucal, *D*-allal, and *D*-gulal derivatives with *S*-methyl and *S*-hexyl groups at C-3. The alcohol and thiol reactions with glycals are therefore quite different, and from this came the proposal that the differences correlate with the respective hard/soft characters of the nucleophiles. (35)

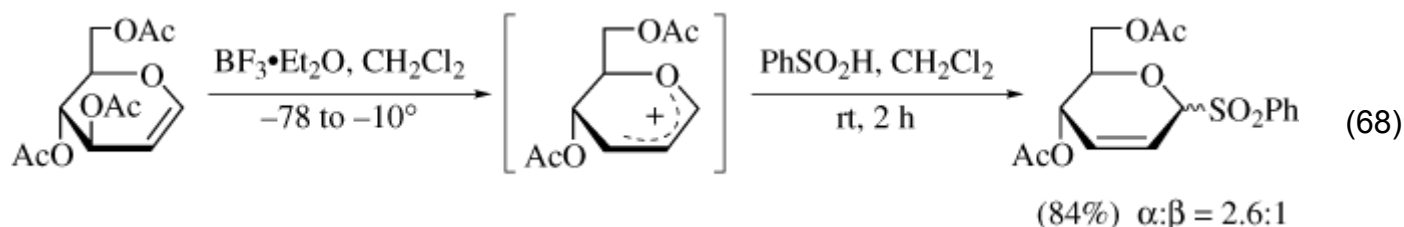


tri-*O*-acetyl-D-glucal, on treatment with thiophenol and a Lewis acid under controlled conditions, gives the products shown in Eq. 67 (path a). (194, 195) One report, however, indicates that the products are saturated 2-deoxy-1,3-dithio compounds, (103) and this observation is reproducible when catalytic proportions of water are added to the reaction mixture (Eq. 67, path b). (101) Apparently this spurious result is the consequence of the acid-catalyzed reaction of water with the normal oxocarbenium ions and the formation of the enals 72 (acyclic tautomer) and 73 (Eq. 51) which undergo Michael-like addition of the thiols followed by thiolysis at the anomeric centers (see "Transformations Involving Oxocarbenium Ions; Leaving Groups and Activators"). Tri-*O*-acetyl-D-galactal in dichloromethane containing thiophenol with SnCl_4 can be converted almost quantitatively into the 2,3-unsaturated phenylthio α -glycoside. (196)



To modify these reactions so that the 2,3-unsaturated thioglycosidic products are formed exclusively, the use of (trimethylsilyl)thiols is recommended (Eq. 26). This generalization extends to the preparation of 2,3-unsaturated glycosyl thioacetates, although in this case the reaction surprisingly is reported to favor the formation of b-esters (Eq. 29). (103) The synthesis of such thioacetates from di-*O*-acetyl-*L*-rhamnal and -*L*-fucal by use of thioacetic acid or its potassium salt in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ has also been reported. (197) In the course of this work thioacetic acid was shown to add in Michael-like fashion to the unsaturated aldehydes of the kind available from acylated glycols on reaction with water (Eq. 51) giving saturated 2-deoxy products with the nucleophile bonded at C-3 (cf. Eq. 67, path b).

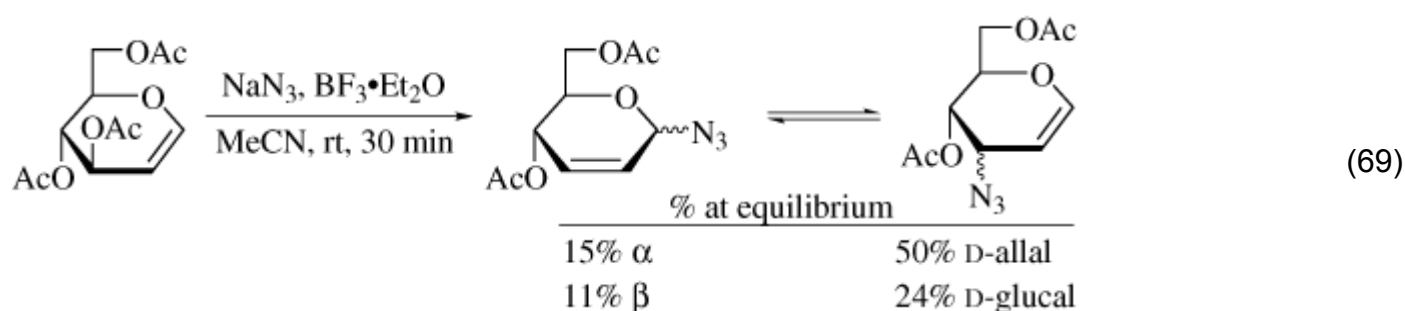
An unusual and efficient way of making 2,3-unsaturated glycosyl sulfones involves the use of tri-*O*-acetyl-*D*-glucal and benzenesulfinic acid (Eq. 68). In this reaction the glycal ester is pretreated with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ at -78° , presumably to generate the oxocarbenium intermediate, prior to addition of the acid in what appears to be a novel modification of the usual procedure. (198) In a slight modification of this approach to 2,3-unsaturated glycosyl sulfones the tetrabutylammonium salt of the sulfinic acid is used. (113)



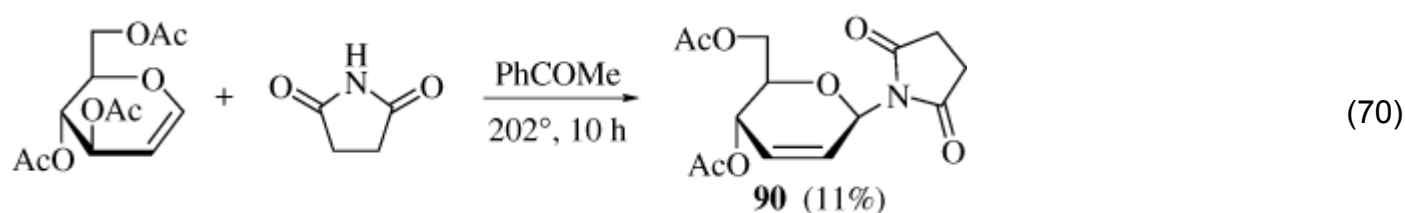
3.6. 2,3-Unsaturated Glycosyl Azides and *N*-Glycosides

On heating with sodium azide in aprotic solvents in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ various glycal derivatives give 2,3-unsaturated glycosyl azides. These are, however, invariably accompanied by 3-azido-3-deoxyglycals since the azide ion is a soft nucleophile. The reactions appear to involve the usual cyclic oxocarbenium ions which are initially attacked at C-1 to afford the unsaturated glycosyl azides, and these isomerize to the more stable 3-substituted glycals –but whether intramolecularly by [3.3]-sigmatropic processes or following reionization is not known. At equilibrium the major product derived from tri-*O*-acetyl-*D*-glucal is the 3-azido-*D*-allal derivative, the *D*-glucal epimer, and the *a*- and *b*-unsaturated glycosyl azides being present in smaller proportions (Eq. 69). Yields up to 95% of the same products in the same proportions are obtained when tri-*O*-acetyl-*D*-allal is used as starting material. (199, 200) Similar observations have been made with 3,4-di-*O*-acetyl-6-deoxy-*D*- (201) and *L*- (202-204) glucal, tri-*O*-benzoyl- (205) and tri-*O*-benzyl- (206) *D*-glucal, but when 4,6-*O*-benzylidene-*D*-glucal-3-esters are used only the epimeric 3-azido-3-deoxy-*D*-glycals are produced, with the allal isomer again dominating. (205, 206) The hard/soft principle has also been used to account for this variation. (205) Tri-*O*-acetyl-*D*-galactal affords the 3-azido-*D*-gual derivative

together with the 2,3-unsaturated α -glycosyl azide in the ratio 3:1, (199) again demonstrating that the isomers of these configurations are highly unfavored in this series. Trimethylsilyl azide may also be used together with Lewis acids to give, from tri-*O*-acetyl-D-glucal for example, the mixed products indicated in Eq. 69. In this case, higher proportions of the α -glycosyl azide are recorded, which perhaps indicates that the equilibration process was incomplete when the product analysis was conducted. (80) The same reagent, together with SbCl_5 , has also been used in combinatorial approaches to glycosyl azides and 3-azido-3-deoxyglycosides. (50)

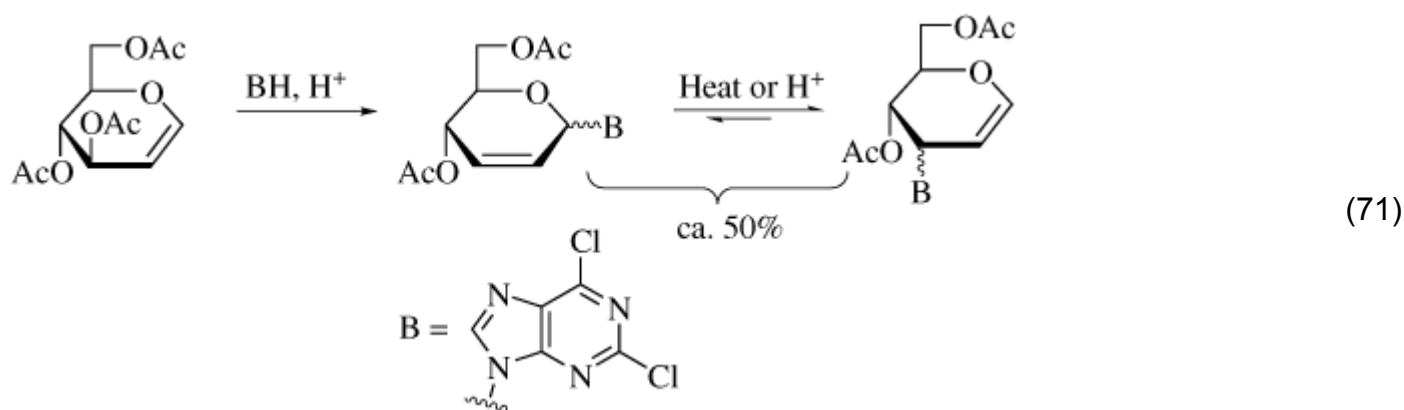


Little relevant work has been conducted with simple amines or amides. While they may be incompatible with acylated glycals and acid catalysts, it would appear probable that they would take part in the substitution with rearrangement reaction if heated appropriately with glycal ethers or used in conjunction with non-acidic activating systems. A rare example is demonstrated by the heating of tri-*O*-acetyl-D-glucal and succinimide in equivalent proportions at high temperature which affords the crystalline β -glycosylamine derivative **90** in low yield as the only identified product (Eq. 70). (207) A related example is given in the "Intramolecular Applications" section.

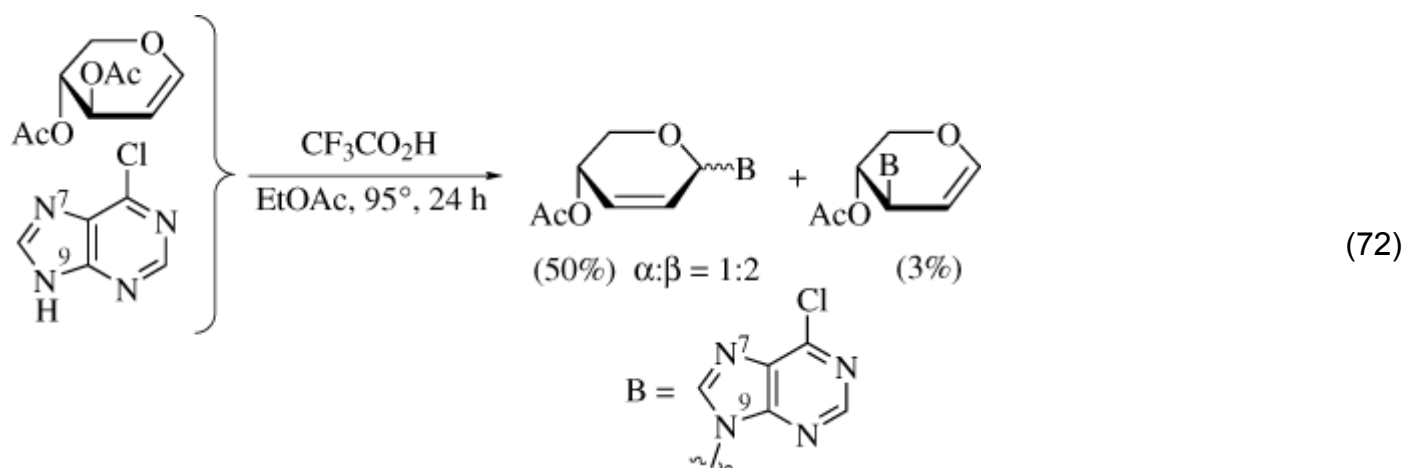


Several aromatic *N*-heterocyclic compounds have been used successfully in glycal to 2,3-unsaturated glycosylamine transformations and, surprisingly, protonic acids can be employed as catalysts despite their propensity to promote addition reactions with glycal derivatives. Particular attention has been given to purine and pyrimidine derivatives because of their significance in natural nucleosides and because of the biological activities of some of the naturally occurring and synthetic 2,3-unsaturated pyranosyl nucleosides and their addition products. First experiments with glycal esters and bases of this category in the presence of protonic acids afforded "normal" 2,3-unsaturated products with C-1 linked to a nitrogen atom, but as with the azido products, these are formed under kinetic control and rearrange mainly to 3-substituted glycals under equilibrating conditions. (207)

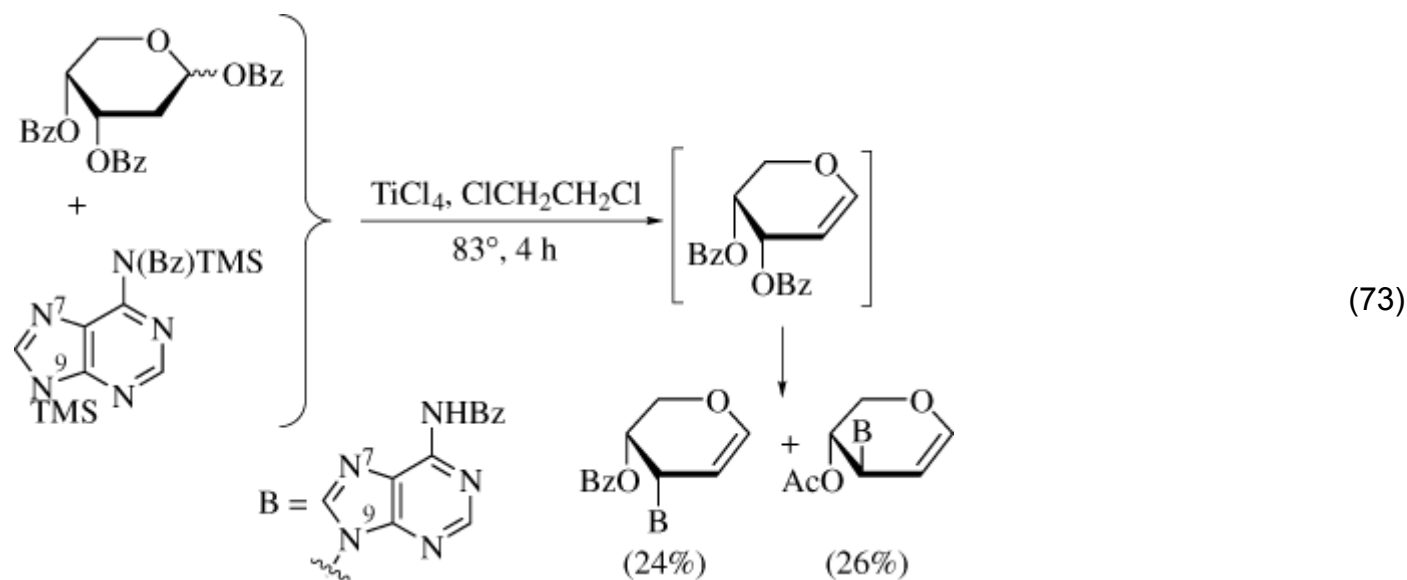
tri-*O*-acetyl-D-glucal heated with 2,6-dichloropurine in boiling nitromethane containing small amounts of *p*-toluenesulfonic acid or mercury(II) cyanide, or fused together in the presence of the latter catalyst, give mainly the anomeric unsaturated nucleosides, whereas heating in nitrobenzene leads to the 3-substituted glycal isomers. The yields are satisfactory and the kinetic products are convertible into the thermodynamic ones (Eq. 71). (207) However, heating of a 2,3-unsaturated α -*N*-glycosylated base, formed under kinetic control, in nitrobenzene from which all acid has been carefully removed, does not cause the isomerization to occur, which suggests that it is not thermal but proceeds by way of the oxocarbenium ion. (208)



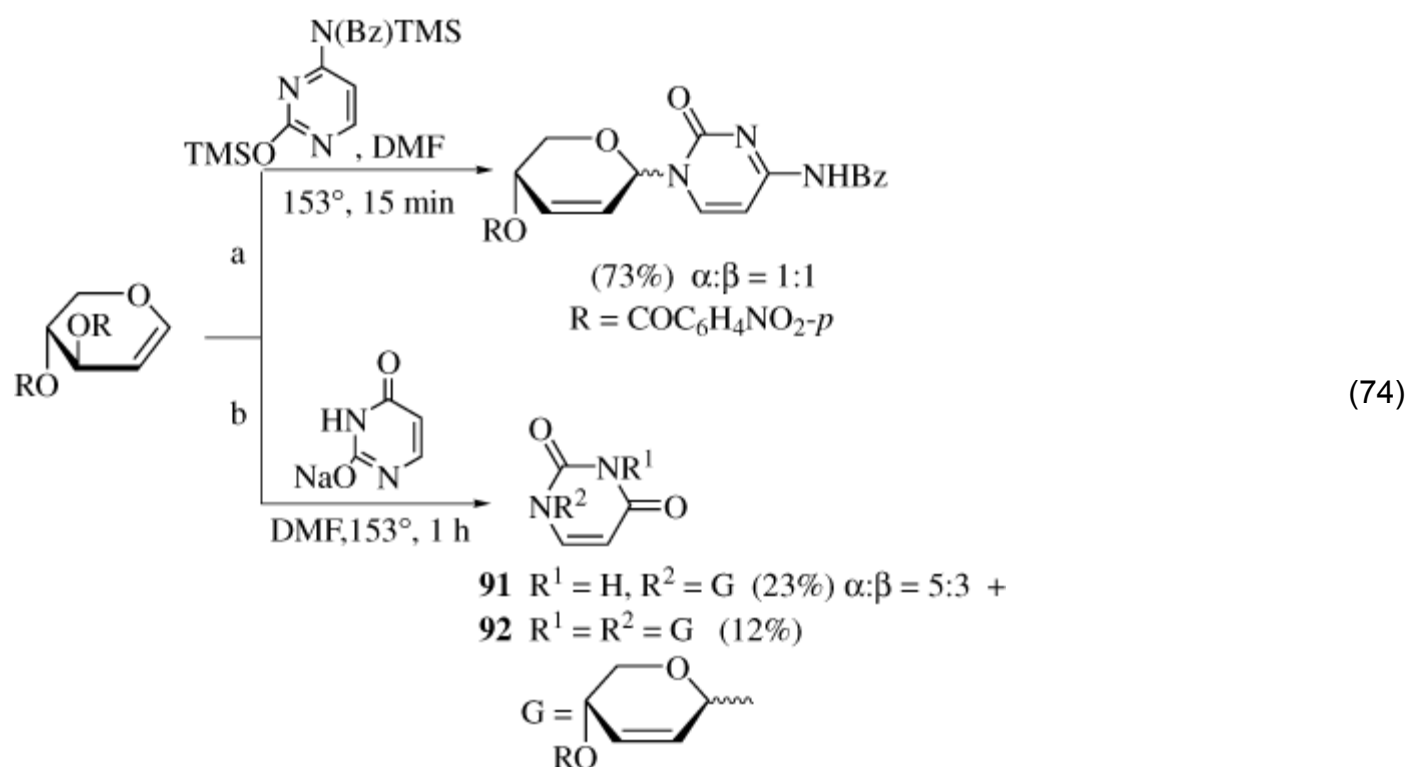
In closely related reactions of 6-chloropurine with 3,4-di-O-acetyl-D-xylal and -L-arabinal, and catalyzed by trifluoroacetic acid, similar sets of mixed 9-linked products are obtained (Eq. 72) but, in addition, further isomers linked through N-7 of the heterocyclic base are encountered. 2-Deoxynucleosides, produced by acid-catalyzed addition to the latter glycal, in which anchimeric assistance cannot facilitate the substitution with allylic transformation process, are also formed. (209)



The types of mixed products indicated in Eq. 71 may also be made from saturated precursors, but it appears very probable that glycols are involved as intermediates. Reaction of 1,3,4-tri-O-benzoyl-2-deoxy-*a,b*-D-erythro-pentose with trimethylsilylated *N*-6-benzoyladenine in refluxing 1,2-dichloroethane containing TiCl_4 gives the D-erythro and D-threo glycols having the base linked via N-9 to C-3 (Eq. 73). Also, small proportions of the saturated 2-deoxy-b-nucleoside are formed. Presumably the initial reaction involves acid-catalyzed elimination of benzoic acid or HCl to give the glycal and is followed by a substitution step probably to afford initial 2,3-unsaturated nucleosides which rearrange to the final 3-substituted glycols. Most surprisingly, when this reaction is conducted with SnCl_4 as catalyst, the main products are the anomeric saturated 2-deoxynucleosides formed conceivably via the corresponding saturated glycosyl chlorides. (210)

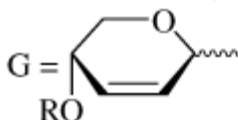


In an effort to suppress the formation of the 3-substituted glycols in reactions of this type studies were conducted with 3,4-di-*O*-(*p*-nitrobenzoyl)-*D*-xylal which, with its good allylic leaving group, reacts in the absence of an acid catalyst. Several purine and pyrimidine bases and their trimethylsilyl derivatives or sodium salts react in hot DMF and give yields between 22 and 76% of the 2,3-unsaturated nucleosides with α,β ratios between 1:2 and 2:1. Only with trimethylsilylated *N*-benzoylcytosine (Eq. 74, path a) is any 3-substituted glycol derivative formed, and then only in 3% yield together with 73% of the unsaturated glycosylamine derivatives shown. This procedure therefore largely provides means of avoiding the rearrangement of the kinetic products to their thermodynamic isomers. (40, 211) A mild alternative method for making 2,3-unsaturated nucleosides without the 3-substituted glycol isomers involves the use of trimethylsilylated purines or pyrimidines and acetylated glycols in 1,2-dichloroethane at room temperature with added trityl perchlorate and sometimes lithium perchlorate. (69, 70) From the reaction of the sodium salt of uracil with 3,4-di-*O*-(*p*-nitrobenzoyl)-*D*-xylal, the very unusual isomeric products **92**, each having 2,3-unsaturated glycosyl moieties bonded to both nitrogen atoms of the base, are isolated in addition to the normal products **91** (Eq. 74, path b). (40)

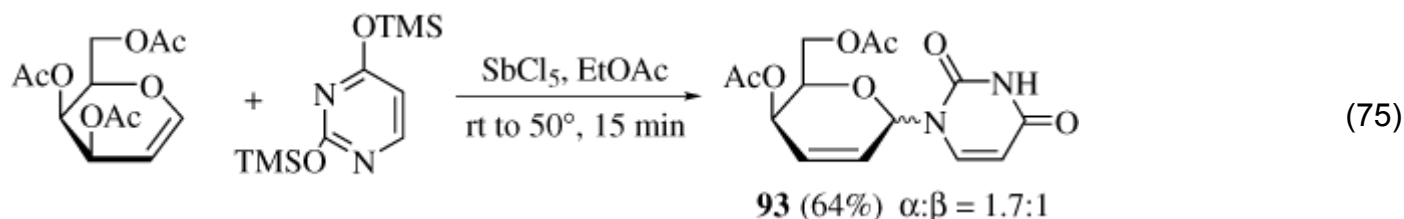


91 $R^1 = H, R^2 = G$ (23%) $\alpha:\beta = 5:3$ +

92 $R^1 = R^2 = G$ (12%)

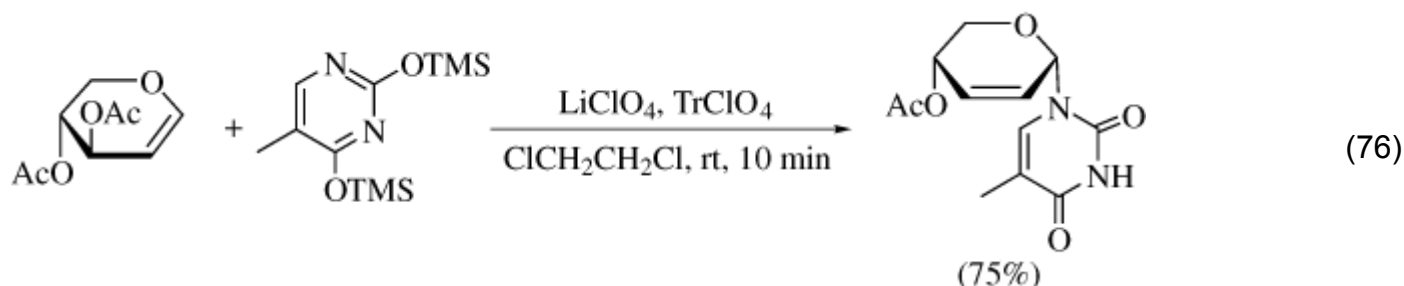


The β -anomer of compound **93**, required for the synthesis of the antibiotic blasticidin S, is a further example of a pyrimidine nucleoside made by the substitution reaction with rearrangement (Eq. **75**). (51) In this reaction trace amounts of a 3-uracylglycal derivative are also formed, but the production of these isomers in reactions involving pyrimidine bases apparently is inhibited relative to their formation when purine derivatives are involved. Thus, whereas trimethylsilylated *N*-benzoylcytosine (a pyrimidine derivative) reacts with di-*O*-acetyl-D-xylal and -L-arabinal in 1,2-dichloroethane containing SnCl_4 to give the 2,3-unsaturated nucleoside anomers, the



N-benzoyladenine analog (a purine derivative) affords mainly the epimeric 3-substituted glycols. (212)

It can be concluded that understanding of the reactions undergone by glycols with heterocyclic bases is incomplete and complex. One subtlety is illustrated by the finding that, despite the possible complexities, the acid-catalyzed reaction of di-*O*-acetyl-D-xylal with bis(trimethylsilyl)thymine affords the α -linked nucleoside as the only observed product (Eq. **76**). It is not certain that the $\text{S}_{\text{N}}2^{\sim}$ mechanism under kinetic control can be assumed for the reaction, as was proposed. (70) A further complexity relates to the reactions of benzotriazoles with tri-*O*-acetyl-D-glucal and tri-*O*-acetyl-D-galactal. Whereas the former glycal takes part in the allylic rearrangement reaction when applied in the presence of strong acids to give the 2,3-unsaturated *N*-1-linked glycosylamines, the latter undergoes addition reactions under the same conditions. (120) This again illustrates the relative ease with which glycal esters with trans-related groups at C-3 and C-4 take part in the allylic rearrangement process (see "Transformations Involving Oxocarbenium Ions; Configuration at the Homoallylic Center of the Glycols").

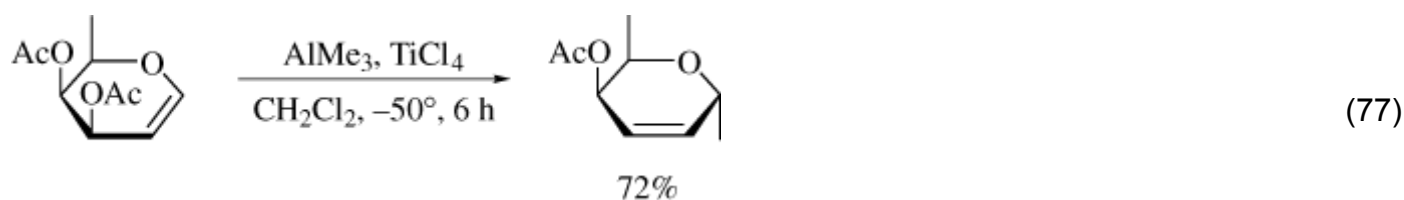


3.7. 2,3-Unsaturated C-Glycosides

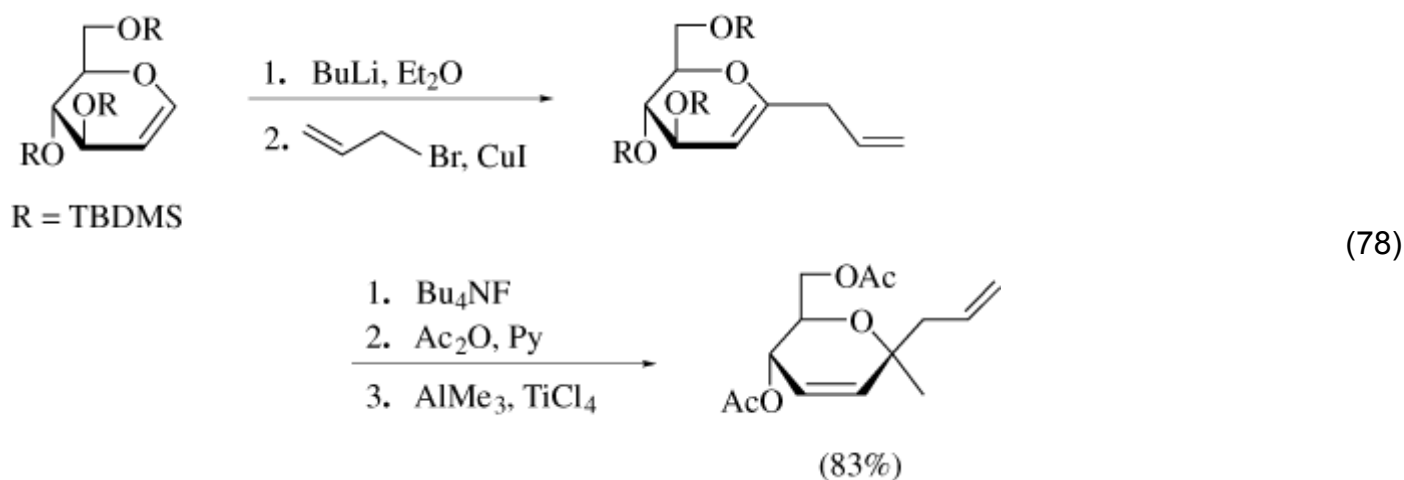
A range of *C*-nucleophilic carbon species takes part in the allylic substitution reaction. In consequence, good methods are available for making di- and tetrahydropyranyl and -furanly compounds with *C*-linked substituents adjacent to the hetero atoms, many of which are related to natural products. Nucleophiles that are suitable include: *C*-metalated species, cyanides, alkenes, various *O*- and *C*-silylated compounds, enol ethers and esters, activated aromatic derivatives, and β -dicarbonyl compounds.

A direct *C*-alkylation procedure involves the use of trialkylaluminums in the presence of TiCl_4 (Eq. **77**). (53) As is commonly the case with glycols having trans-related groups at C-3,C-4, less selective reaction than that illustrated in Eq. **77** occurs with di-*O*-acetyl-L-rhamnal

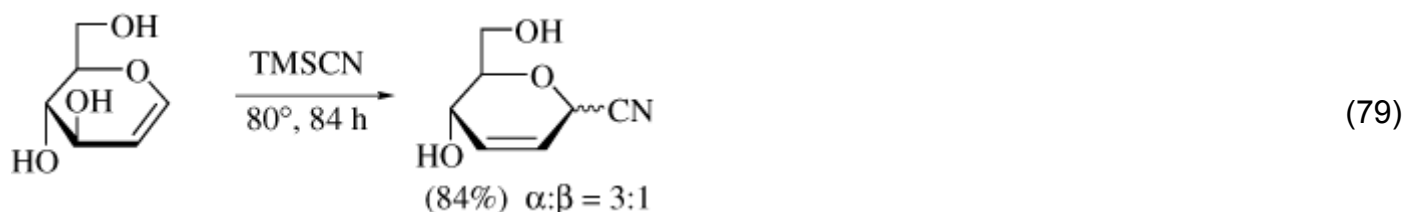
(di-*O*-acetyl-6-deoxy-*L*-glucal) from which the *a*- and *b*-*C*-glycosides are formed in the ratio 4:5 and in the combined yield of 89%. (53) A range of alkyl and alkynyl groups can be introduced by this approach, (94) and it can be applied to glycols already bearing *C*-bonded substituents at *C*-1 and thus used to



provide (surprisingly, but advantageously) a stereospecific means of obtaining geminally disubstituted compounds bearing different *C*-1 substituents required for natural product syntheses (e.g. Eq. 78). (54)



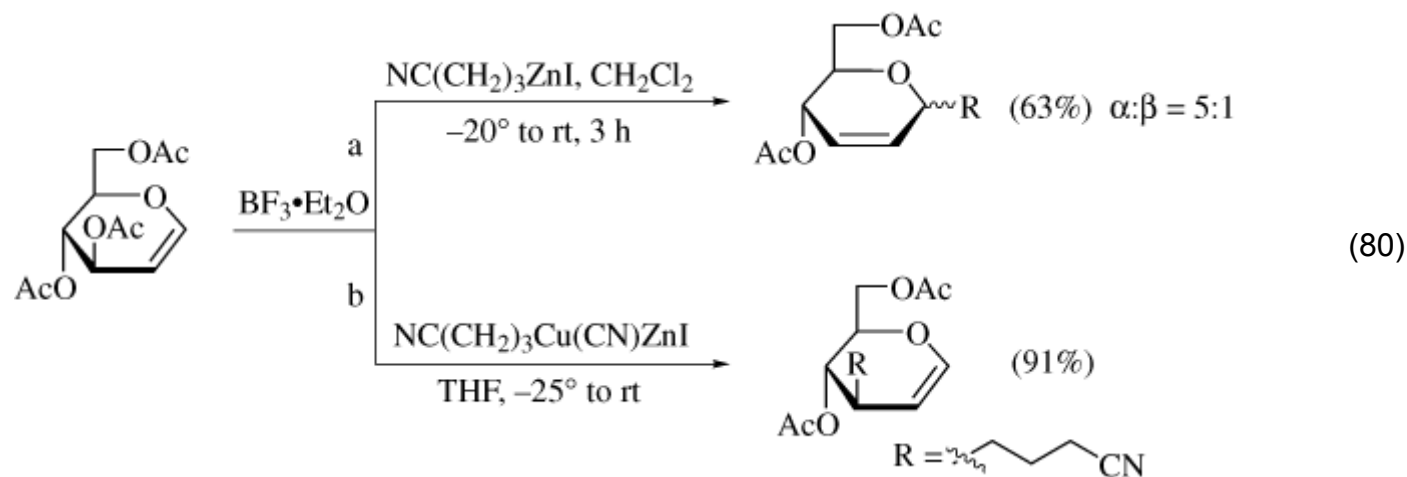
Organoaluminum compounds have also been used to introduce the cyano group. tri-*O*-acetyl-*D*-glucal reacts in benzene solution at room temperature with Et_2AlCN to give the 2,3-unsaturated glycosyl cyanides in 75% yield with an *a*,*b* ratio of 3:2; 3-cyano products are not observed. (93) In refluxing benzene the same products are formed, but with the anomeric ratio now 9:1, which allows efficient production of the crystalline *a*-compound, and suggests that the formation of the *b*-anomer is kinetically favored. (24) Conceivably it is the allylic effect (132) that favors the axial *a*-isomer at equilibrium. Trimethylsilyl cyanide, used in inert solvents at room temperature with $\text{BF}_3 \cdot \text{Et}_2\text{O}$, is also a suitable reagent for introducing the cyano group and making the *a*-isomer. (125, 138) Notably, tri-*O*-acetyl-*D*-glucal and glucal itself (Eq. 79) react on heating with the silyl cyanide, without solvent or catalyst, to give the unsaturated *C*-glycosides in what appears to be approximately the kinetically controlled ratio. (213) In the presence of palladium acetate the reaction proceeds at room temperature, apparently via the *O*-silylated glycal. (157)



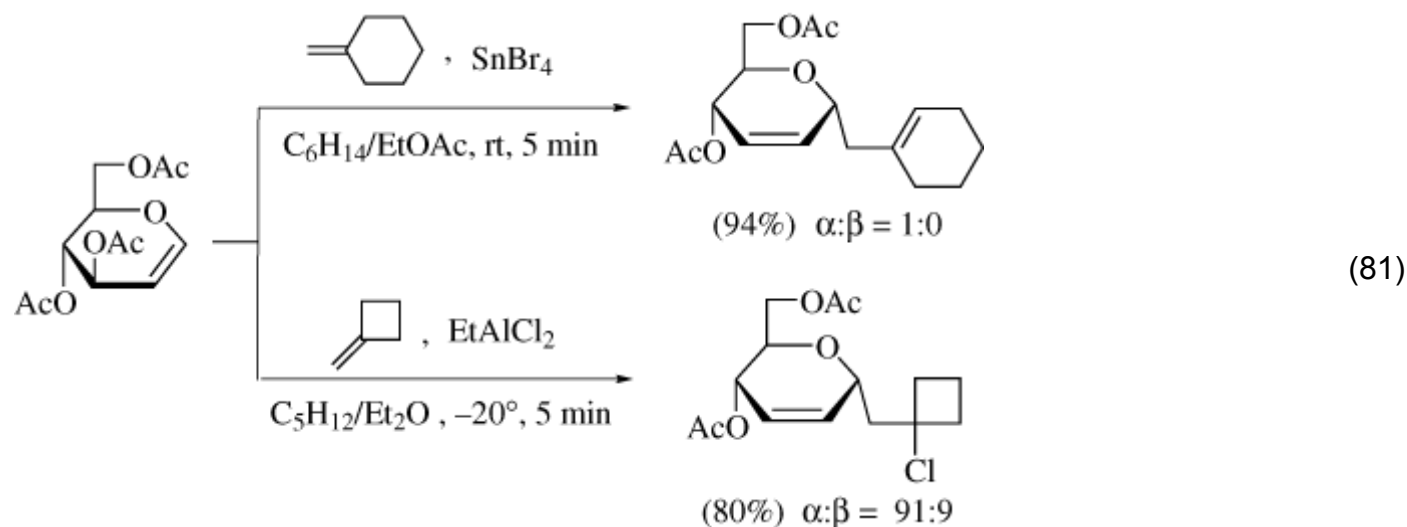
Several organozinc derivatives of the Reformatsky type, and including (cyanopropyl)zinc iodide (148), have been used effectively in the presence of Lewis acids in CH_2Cl_2 to produce

2,3-unsaturated C-glycosidic compounds from O-protected glycals (Eq. 80, path a). (146, 148, 214-216) Zinc/copper analogs in THF, on the other hand, favor the production of C-3-substituted glycals (Eq. 80, path b), formed presumably via the 3,4-acetoxonium ion. (129)

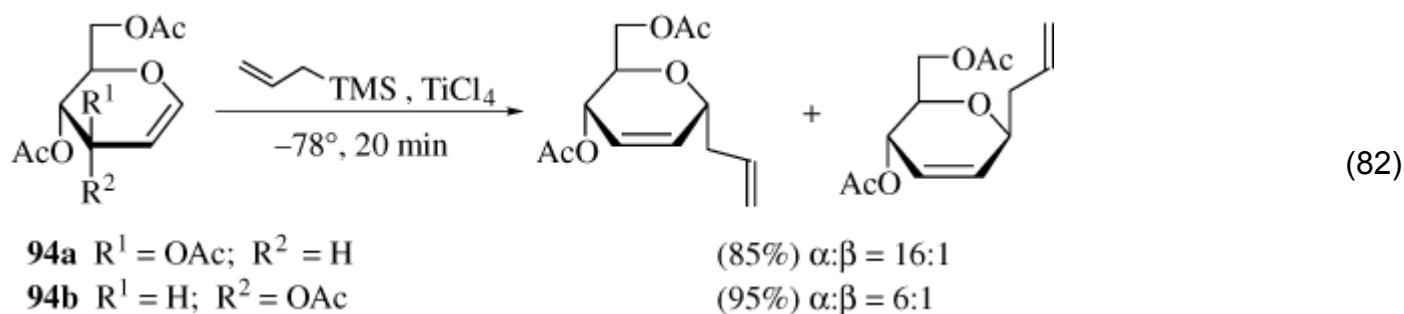
Electrophilic addition of the oxocarbenium ions available from glycal derivatives to alkenes also provides an efficient route to C-glycosidic products, often with surprising efficiency and selectivity. (61) Most suitable alkenes are those that lead to tertiary carbocation intermediates, and the ionic adducts first formed can lose a proton



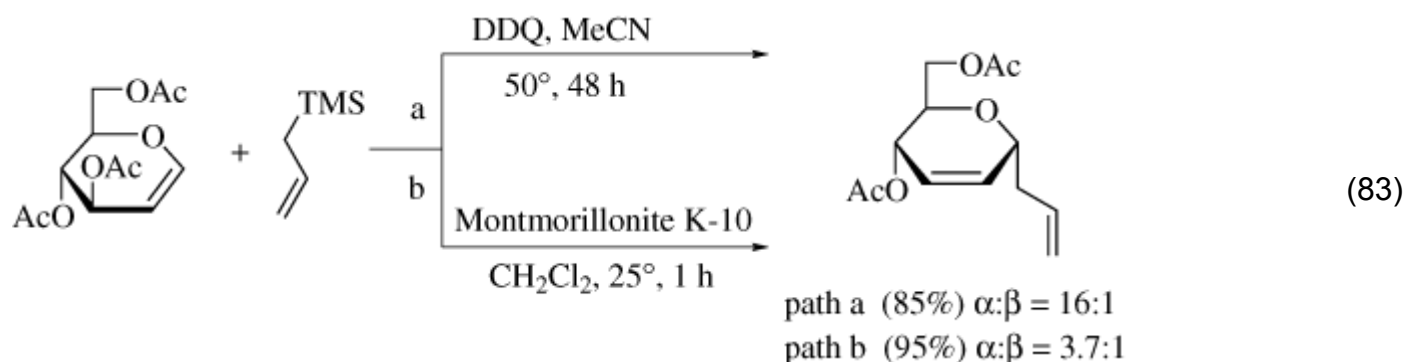
or bond to a nucleophile depending upon reaction conditions. Respective examples are given in Eq. 81. (61)



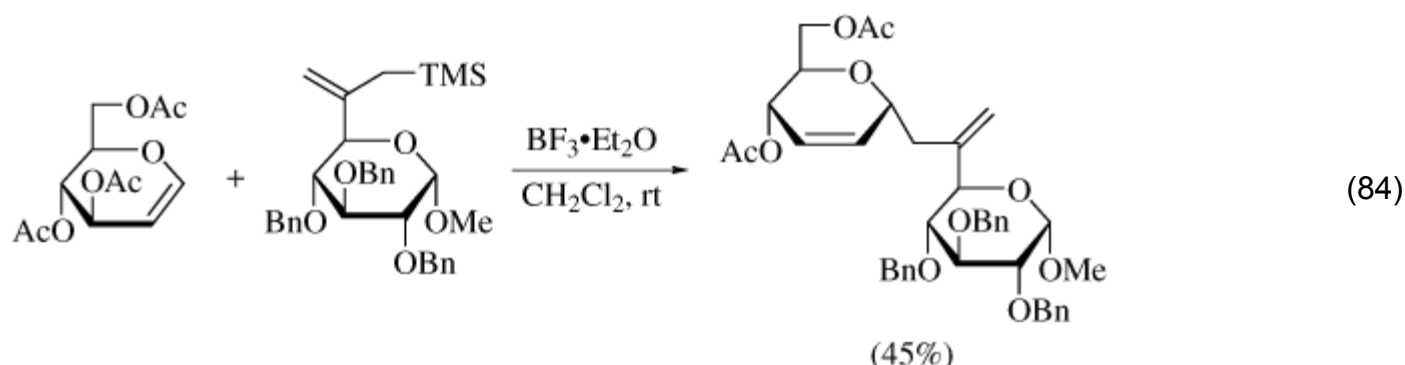
Other types of alkenes from which stable intermediates are derived behave similarly. The silicon atom of allyltrimethylsilane stabilizes a carbenium ion at the central allyl carbon atom and is displaced rapidly from the intermediates formed on reaction of the silane with electrophiles. (217) Applications to C-glycoside synthesis are shown in Eq. 82, (52) and the reaction has been repeated with many catalysts (Table 5). That the glycal epimers (94a) and (94b) give products with somewhat different anomeric ratios indicates that the reactive intermediates are like the oxocarbenium ion, but that the leaving groups are not dissociated entirely from C-3 when interaction with the silane occurs. Also, the products have not equilibrated fully, if at all, under the conditions of their synthesis. The a,b ratio of the C-glycosides derived in this way from tri-O-acetyl-D-galactal is 30:1, (52) which is consistent with the relatively high proportions of a-O-glycoside anomers formed from this glycal.



For this reaction trimethylsilyl triflate in dichloromethane/acetonitrile at low temperatures gives higher conversion efficiencies and α,β ratios than do other catalysts. Remarkably, these conditions are also more effective when applied to *O*-unprotected glycols than to their acetates; the product yields are higher, and the α,β ratios are in excess of 99:1 for *D*-glucal (Eq. 16), *D*-galactal, *D*-fucal, and *L*-rhamnol. (73, 74) The reaction between *O*-acylated glycols and allyltrimethylsilane can also be promoted by DDQ (Eq. 83, path a) (87) and by Montmorillonite K-10 (Eq. 83, path b). (85) In the latter case a higher proportion of β -anomer is obtained, conceivably suggesting a reverse kinetic anomeric effect may be in operation.



2-Substituted allyltrimethylsilanes lead to diastereomeric mixtures with some asymmetric induction in the aglycons, (59, 137) and related compounds with a carbohydrate substituent *C*-linked at *C*-2 of the allyl moiety afford *C*-bonded disaccharide derivatives. An example is shown in Eq. 84. (218)

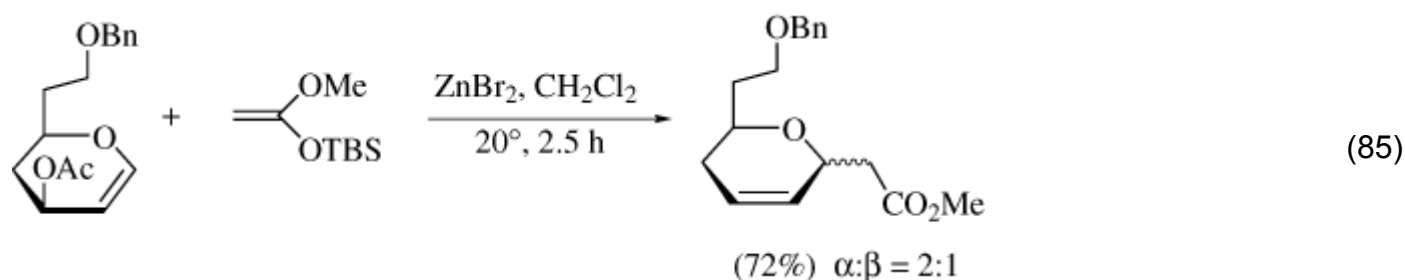


Alkynylsilanes also react with electrophiles under the influence of Lewis acids; (217) tri-*O*-acetyl-*D*-glucal gives the crystalline silylated alkyne **95** ($R = \text{SiMe}_3$) in 75% yield on reaction with bis(trimethylsilyl)acetylene. (129) The reaction is versatile with respect to the silylated alkyne used; analogs of **95** with $R = \text{SPh}, \text{C}\equiv\text{CSiMe}_3, \text{CH}=\text{CHCl}$, and $\text{CH}=\text{CHC}\equiv\text{CSiMe}_3$ (219) and others (220) have been reported. The second of these offers access to a compound consisting of two

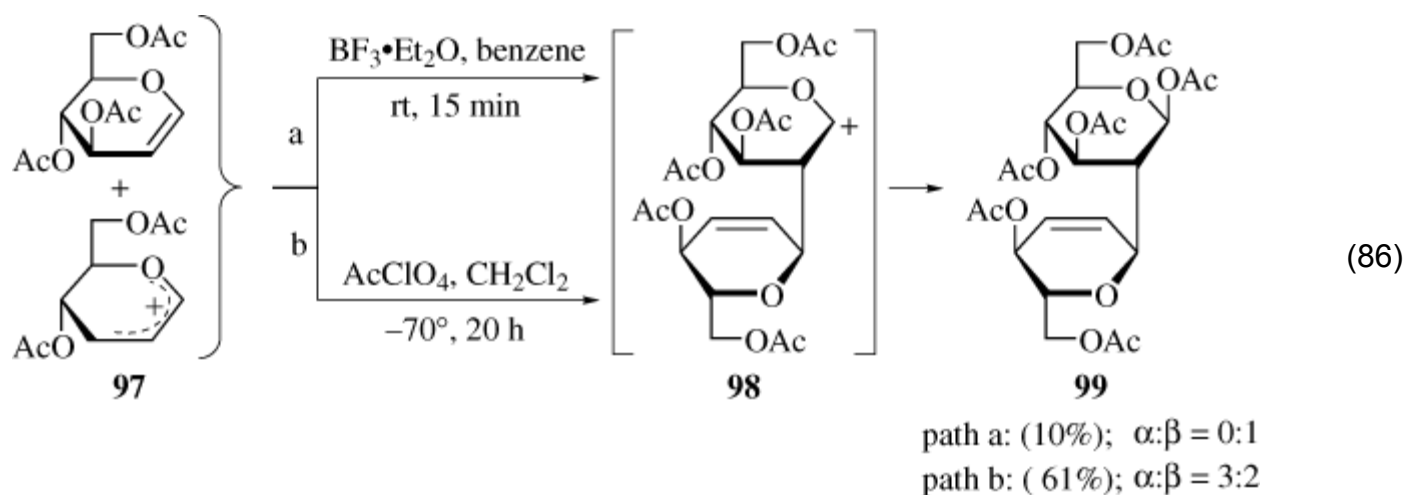
unsaturated sugar units linked via the anomeric centers by a conjugated diacetylene bridge, and the latter affords an analog with an yne-ene-yne linkage. Alkyne **95** (R = H) is formed in 75% yield by fluoride ion catalyzed cleavage of the trimethylsilyl compound. (221)



Vinyl and substituted vinyl ethers and esters are further nucleophilic species that react with glycal-based electrophiles. For example, carbonyl compounds **96** (R = H, Me, Ph) are obtained by condensation of tri-*O*-acetyl-D-glucal with the enol acetates or enol silyl ethers derived from acetaldehyde, acetone, and acetophenone, respectively. Good yields with anomeric selectivities >4:1 in favor of the illustrated products are obtained when $\text{BF}_3 \cdot \text{Et}_2\text{O}$ is the catalyst. (49, 140, 222) A modification uses the mixed ketene acetal 1-methoxyvinyl *tert*-butyldimethylsilyl ether and results in the formation of products with (methoxycarbonyl)methyl substituents at C-1 (Eq. 85). (56)

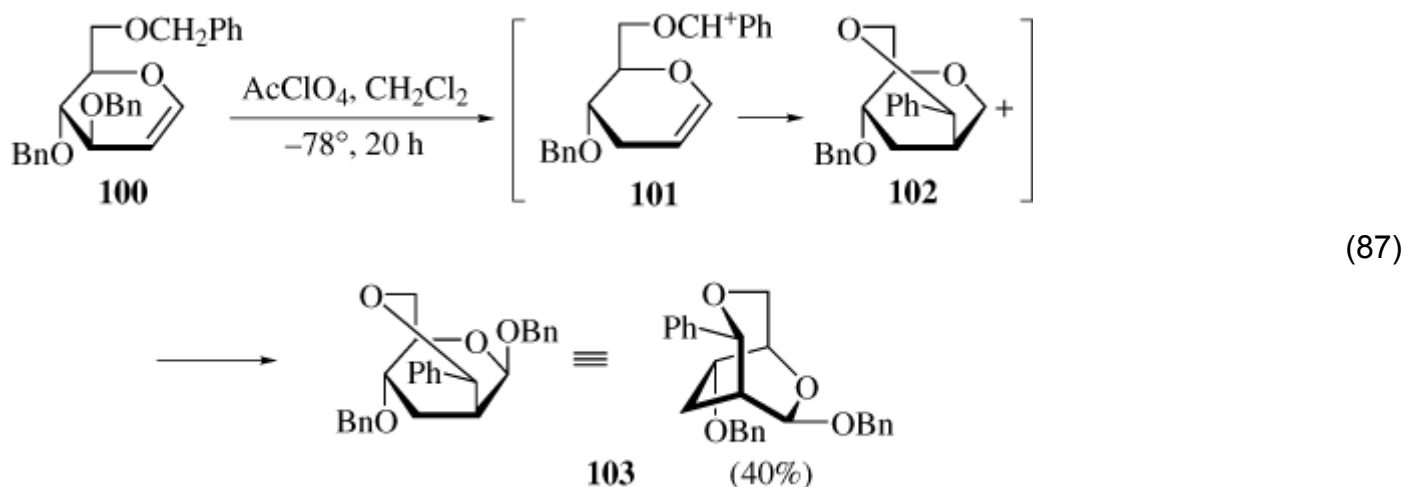


The above-mentioned reaction of the oxocarbenium ions derivable from glycals with vinyl ethers raises the issue of the possible in situ reaction of these ions with the vinyl ether functions of the glycals from which they are derived. This type of process does occur. For example, cyclic oxocarbenium ion **97**, derived from tri-*O*-acetyl-D-glucal, adds electrophilically to the electron-rich C-2 of the vinyl ether moiety of the unionized starting material to give the dimeric glycosyl carbenium ion **98**. Rather than lose a proton to afford a 2-substituted glycal, this ion reacts at C-1 with the acetate ion initially liberated to afford a crystalline mixture of products (40%) from which the stable, highly crystalline β -anomer **99** is obtained in 10% yield (Eq. 86, path a). (122)

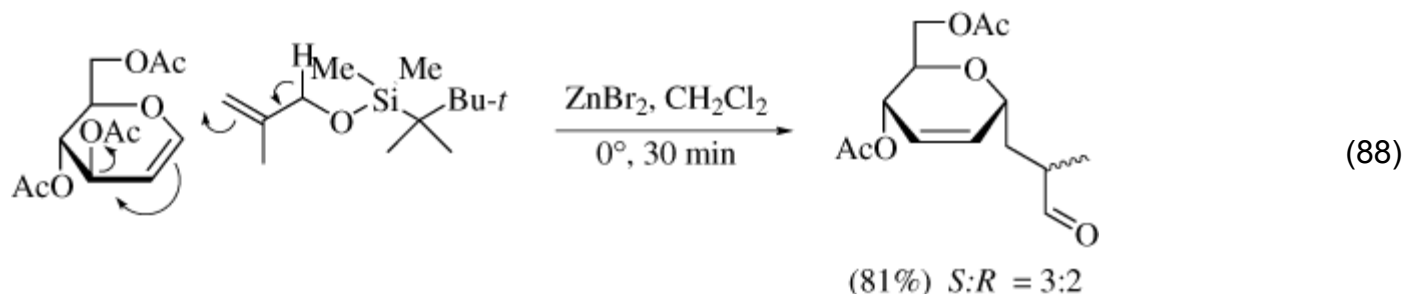


C-Linked disaccharide derivatives of this type can be formed whenever glycal esters are used in the presence of Lewis acids, and they have been observed as by-products in the reactions of: di-*O*-acetyl-L-rhamnal with sodium azide in acetonitrile in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$; (203) tri-*O*-acetyl-D-glucal with the hydroxy compound 4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enose (derived from the glycal) in benzene with the same catalyst; (182) and of tri-*O*-benzoyl-D-galactal with anhydrous HF. (223) Exclusive formation of C-linked dimers is observed in the reactions of tri-*O*-acetyl-D-glucal, -D-galactal, and di-*O*-acetyl-D-xylal, and -L-rhamnal by themselves in inert solvents at 0° with $\text{BF}_3 \cdot \text{Et}_2\text{O}$; (128, 224) on treatment of tri-*O*-acetyl-D-glucal in ether with iodine; (225) and on mixing tri-*O*-acetyl-D-glucal and chlorosulfonyl isocyanate in ether (226) or without solvent. (227) The yields in these last reactions are moderate and some products isolated are mixtures of epimers at the anomeric centers of the saturated rings. Significantly improved yields have been achieved by use of acetyl perchlorate (0.02 equivalents) as catalyst in CH_2Cl_2 at -78° as follows: tri-*O*-acetyl-D-glucal, 61% dimers (a,b 3:2) (Eq. 86, path b); tri-*O*-acetyl-D-galactal, 77% dimer (a,b 1:0); di-*O*-acetyl-D-xylal, 21% dimer (a,b 1:0); 3-*O*-acetyl-6-*O*-benzyl-4-deoxy-D-glucal, 59% dimers (a,b 16:1). (228)

Tri-*O*-benzyl-D-glucal (100) reacts quite differently in the presence of acetyl perchlorate. Initially, normal loss of the allylic substituent gives the C-3 carbenium ion, but hydride shift (established by isotopic labeling studies) from the methylene group of the C-6 benzyl ether to C-3 now occurs to give ion 101 which adds electrophilically to the double bond. The resulting anomeric carbocation 102 bonds to the benzyloxy group initially cleaved to give the bicyclic branched-chain product 103 (Eq. 87). (229, 230) It is relevant to note that glycal ether 100 undergoes allylic isomerization to benzyl 4,6-di-*O*-benzyl-2,3-dideoxy-D-*erythro*-hex-2-enopyranoside with Lewis acids, (105) but whether this product (especially the b-anomer) is an intermediate in the formation of the tricyclic compound 103 is not clear.

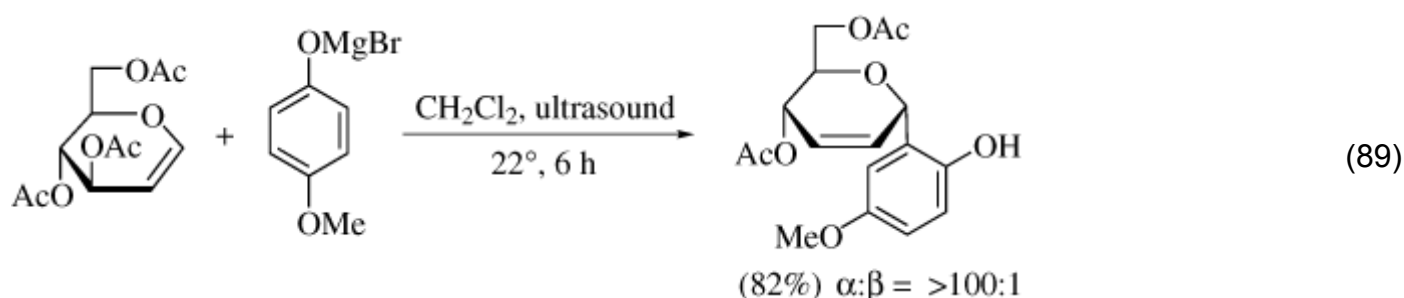


Reaction of allyl silyl ethers with glycals provides an efficient route to unsaturated C-glycosides having carbonyl functions at C-3 of the aglycons. An example which indicates the general nature of the reaction is illustrated in Eq. 88. (48) Analogous ketonic products are also obtainable in this way, and can likewise be made from di-*O*-acetyl-D-xylal, but then the efficiency drops to about 60%. (62)



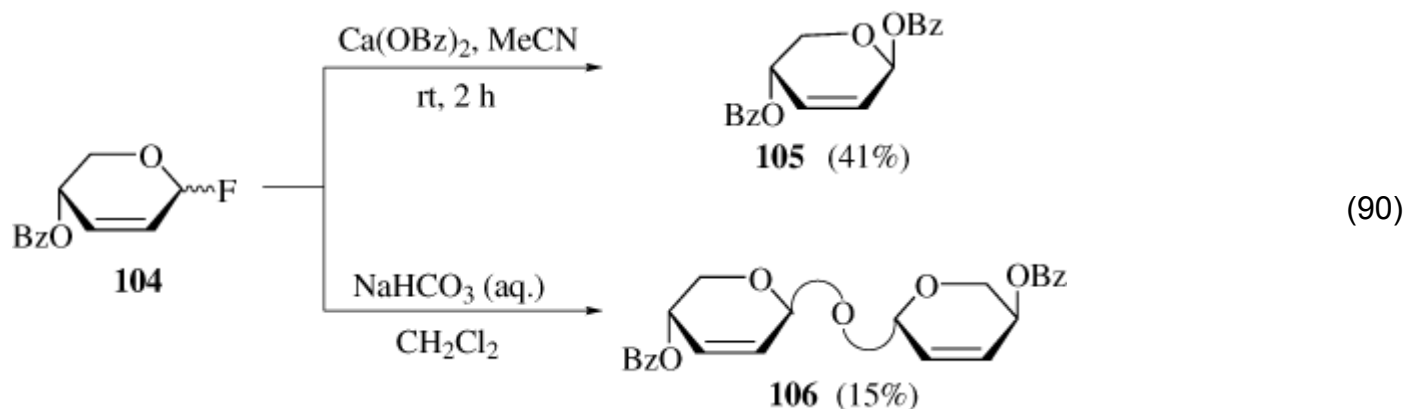
Phenols react with acetylated glycols thermally or under Lewis acid catalysis to give 2,3-unsaturated O-glycosides with good yields and high α -selectivity (see “Scope and Limitations; 2,3-Unsaturated O-Glycosides”). When activating groups are present on the aromatic rings, however, these products readily isomerize to give C-glycosides. In the case of tri-O-acetyl-D-glucal, the β -C-linked compounds predominate (α , β ratio ca. 3:4 independent of the anomeric configuration of the O-glycoside used) (Eq. 59). For the conversion of the O-linked compound **79**, and the analogs with hydrogen or nitro in place of the methoxy group, into the C-linked glycosides such as **80**, the reaction rates and the yields correlate strongly with the electron-donating characteristics of the substituents. (177)

A related way of making 2,3-unsaturated C-aryl glycosides involves treatment of the acetylated glycols with bromomagnesium phenates in ether/ CH₂Cl₂ at room temperature under ultrasonication (Eq. 89). (150) Surprisingly, the α , β ratios of the products derived from tri-O-acetyl-D-glucal are unusually high (>20:1), sometimes indicating close to complete diastereoselectivity. Other routes to aryl compounds involve the use of arylpalladium (Eq. 41) or arylzinc (216) reagents.

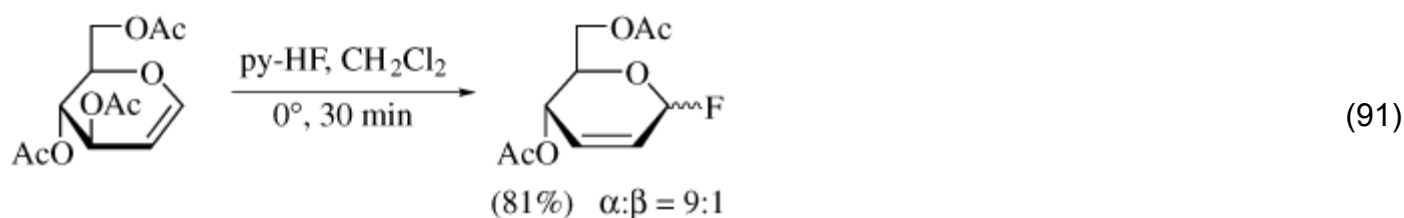


3.8. 2,3-Unsaturated Glycosyl Halides

Whereas reactions of tri-O-acetyl- or tri-O-benzoyl-D-glucal with hydrogen bromide and hydrogen chloride usually lead to the 2-deoxyglycosyl halides by addition reactions, a saturated solution of hydrogen fluoride in benzene at 0° causes the formation of the 4,6-di-O-acyl-2,3-unsaturated glycosyl fluorides as relatively unstable syrups, although they can be subjected to rapid chromatographic purification with partial success. (121) These acetylated fluorides can react with their products of partial hydrolysis to give unsaturated, C-1,C-1-linked disaccharide derivatives such as **82** (Eq. 61), and with other alcohols to give 2,3-unsaturated glycosides. (102, 181) In similar fashion the very reactive pent-2-enopyranosyl fluorides **104** can be made from each of the corresponding C-3 epimeric glycol dibenzoates and can be converted into the 1,4-dibenzoate **105** and the disaccharide **106** (Eq. 90). (183)



A later development which claims to give the 2,3-unsaturated glycosyl fluorides in forms that are more suitable for use as synthetic intermediates employs the more accessible pyridinium poly(hydrogen fluoride) (py-HF) at 0° in dichloromethane (Eq. 91). However, competing reactions interfere in the cases of glycal esters having cis-related substituents at C-3 and C-4 of glycal esters. (121)

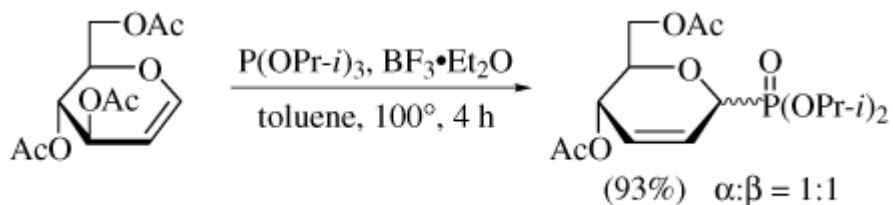


2-Acyloxy-2,3-unsaturated glycosyl chlorides have been reported as products of reaction of 2-hydroxyglycal esters with HCl. (231) They were identified by ¹H NMR spectroscopy and converted directly into the corresponding glycosyl esters suggesting they are very reactive compounds.

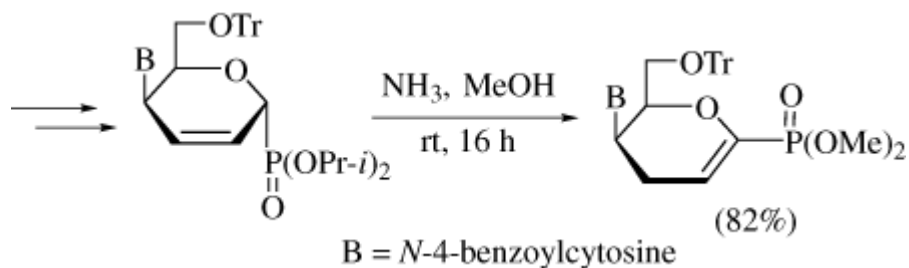
3.9. 2,3-Unsaturated Glycosyl Phosphonates

Glycal esters react with dialkyl phosphites in the presence of BF₃•Et₂O to give the corresponding 2,3-unsaturated glycosyl phosphonates. (232) Since the products derived from tri-O-acetyl-D-glucal or -allal have the same α,β ratio (1:2), a common oxocarbenium ion intermediate can be proposed for the reactions, and the preponderance of the β-anomer suggests that a reverse kinetic anomeric effect (233) is in operation. The corresponding anomeric ratios of the 4-epimers derived from tri-O-acetyl-D-galactal or -gural is 1:3. Pentose-based glycal esters behave in like manner. (232)

The 2,3-unsaturated diisopropyl phosphonates shown in Eq. 92 can be made in 93% yield by use of triisopropyl phosphite, and the 6-trityl ethers, prepared following de-O-acetylation with K₂CO₃ in methanol, can then be separated to afford the α- and β-anomers in 39 and 46% yields, respectively. (234) Analogous phosphonates are obtained from tri-O-acetyl-L-glucal and di-O-acetyl-L-rhamnal, and in each series the O-bonded substituents at C-4 of the products can be replaced by nucleoside bases to yield nucleotide analogs some of which have antiviral activity (Eq. 92). (234) A feature of the chemistry of the 2,3-unsaturated glycosyl phosphonates is that, particularly with the α-anomers, prototropic rearrangement occurs under basic conditions



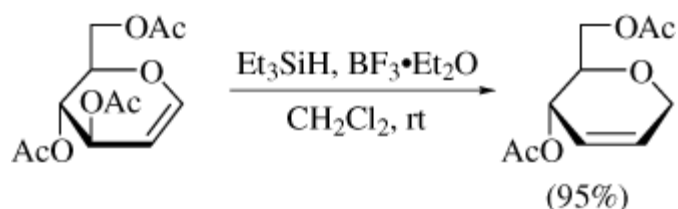
(92)



to give the isomeric 3-deoxyglycal 1-phosphonates, presumably following proton abstraction from the anomeric position (Eq. 92). Closely related work has led to the synthesis of nucleotide analogs based on 2,3-dideoxy-1,2-unsaturated glycosyl phosphonates having nucleoside bases substituted at C-6. (235)

3.10. 2,3-Unsaturated Glycosyl Hydrides (2,3-Unsaturated 1,5-Anhydroalditols)

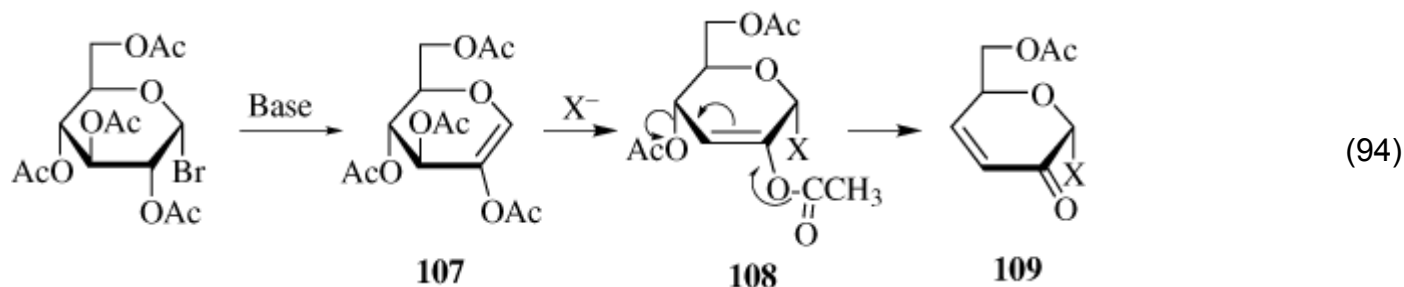
A novel method of preparing chiral dihydro- and tetrahydropyran derivatives is based on the reductive rearrangement undergone by *O*-substituted glycols when treated with triethylsilane in an inert solvent in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (Eq. 93). (236) The products are 2,3-unsaturated 1,5-anhydroalditol derivatives (cf. Eq. 7), and those of hydride attack at C-3 are not observed, which is surprising given the hard/soft nucleophilic substitution generalization developed for glycal rearrangements. On the other hand, tri-*O*-acetyl-D-glucal reacts with diphenylsilane in THF in the presence of ZnCl_2 and a Pd(0) catalyst to give the 3-deoxyglycal by hydride attack at C-3. (130) The reverse reaction by which a 3-deoxyglycal is obtained from a 2,3-unsaturated glycoside is illustrated later in Eq. 122.



(93)

3.11. Applications to Glycals with Substituents at C-2

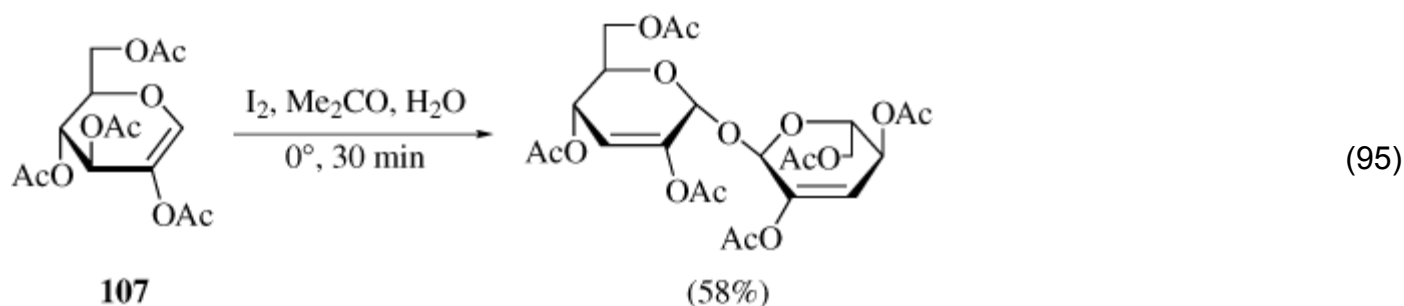
When *O*-acylated glycosyl halides are induced to lose hydrogen halide from C-2, C-1, they give stable compounds trivially termed "2-hydroxyglycal esters" (e.g. 107, Eq. 94). (1, 2, 27) In general, these 2-acyloxyglycals react in similar manner to their glycal analogs under conditions in which the allylic substitution with allylic rearrangement reaction occurs (107 into 108, X = *O*-, *S*-, *N*-, *C*-, *Cl*-, *F*-bonded groups), but there are reports of glycal esters undergoing relevant reactions when their 2-acyloxy analogs do not. (75) There is a strong tendency for the unsaturated glycosyl compounds 108 to lose the elements of acid anhydride (perhaps in a concerted manner) to produce enones 109 under a range of conditions (Eq. 94).



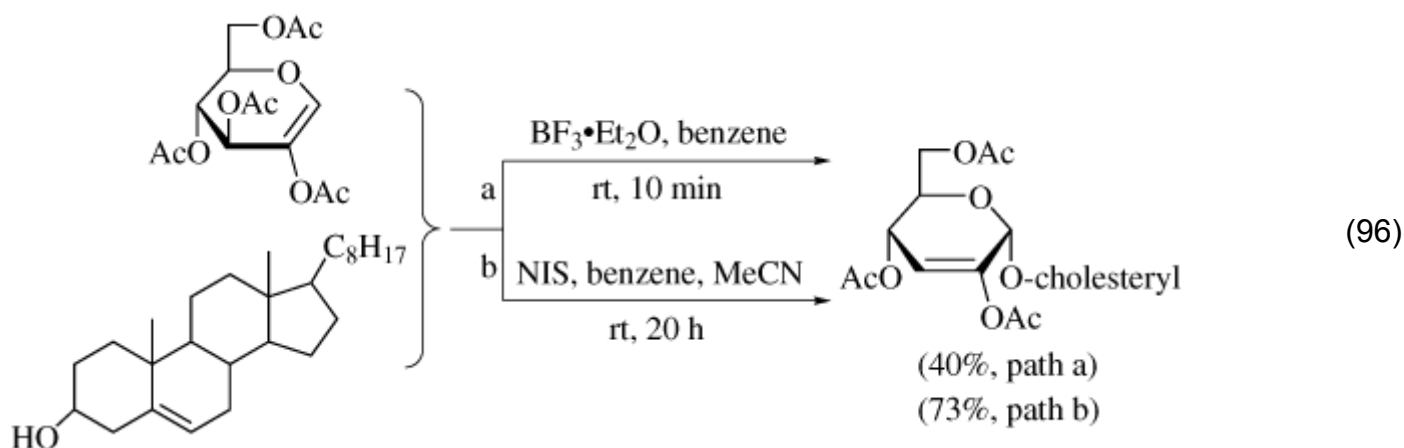
Heating of compound **107** in acetic acid causes complete rearrangement to the α -2,3-unsaturated glycosyl acetate **108** (X = OAc) and its β -anomer in the ratio 3.3:1, (237, 238) and this isomerization can also be conducted at room temperature in inert solvents in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$. (238) However, when such treatment is prolonged, the first product reacts further to give the enone **109** (X = OAc) and its β -anomer in the ratio 6:1 (Eq. 94). (239) In interesting contrast, heating in boiling nitrobenzene for 75 minutes converts compound **107** into the β -anomer of **108** (X = OAc) (75%) by a sigmatropic process. (238)

With the 4-epimer ("tetra-O-acetyl-2-hydroxy-D-galactal") of compound **107**, the major product formed by heating in acetic acid is the α -anomer of the 2,3-unsaturated tetraacetate, which is isolated directly in 58% yield, or 67% when methanesulfonic acid is used to catalyze the reaction. (240) However this isomerization is appreciably slower than for the D-arabino-isomer **107** (with its C-4 acetoxy group able to participate in the displacement process), no β -anomer is formed, and small proportions of penta-O-acetyl-D-galactose are produced by a competing addition process. (238) Enone **109** (X = OAc), together with its β -anomer, also result from extended reaction of tetra-O-acetyl-2-hydroxy-D-galactal in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$. (239) However, under thermal conditions this glycol derivative is much more stable than its 4-epimer **107**. (238)

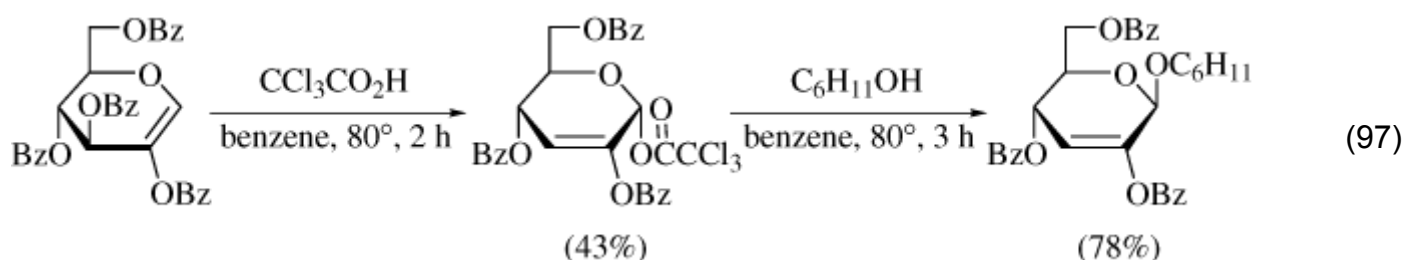
Controlled partial hydrolysis of compound **107** by use of iodine as catalyst results in coupling of the initial hydroxy product **108** (X = OH) with the unreacted starting material to give the expected dimer (Eq. 95) (79) by a process that duplicates that shown by glycol esters that are unsubstituted at C-2 (Eqs. 61 and 90).



Stable O-glycosides (**108**, X = OR), derived from many alcohols including cholesterol (Eq. 96, path a), (241) *tert*-butanol, (242) and methyl 2,3-anhydro-6-bromo-6-deoxy- α -D-allopyranoside (**187**) can be made by the normal method involving $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as catalyst. The same type of products can also be prepared with very high α -selectivity by use of *N*-iodosuccinimide in acetonitrile and primary, secondary, or tertiary alcohols (Eq. 96, path b). (243) The finding that triethylamine inhibits this reaction favors the possibility that it proceeds by acid-catalyzed allylic rearrangement, but this does not necessarily exclude addition-elimination mechanistic options. A



method of making alkyl 2,4,6-tri-*O*-benzoyl-3-deoxy-*b*-*D*-*erythro*-hex-2-enopyranosides involves uncatalyzed alcoholysis of the corresponding 2,3-unsaturated glycosyl α -trichloroacetate (Eq. 97). (241)

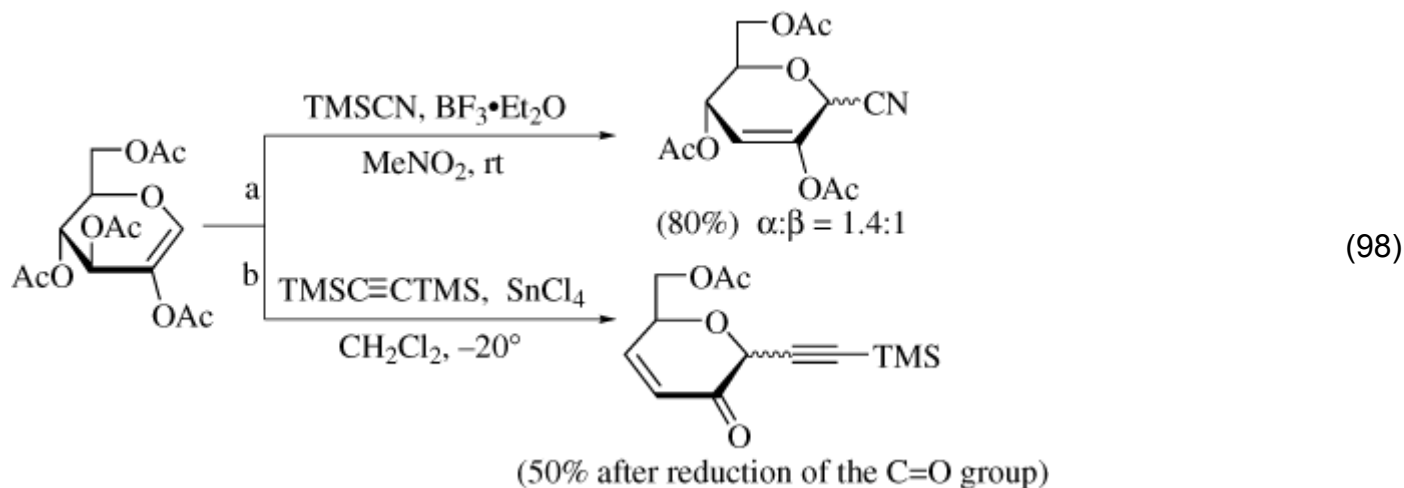


Anomer **108** [X = OCH(Me)CN] can be made together with the *b*-isomer (40% each) by ultraviolet irradiation of glycol derivative **107** in lactonitrile under nitrogen. However, the reaction occurs in the dark with lactonitrile that has been irradiated previously, which indicates that light generates acid and this catalyzes the process. (244)

Reaction of hydroxyglycol esters with purine bases in the presence of protonic acid catalysts gives access to (3~deoxyhex-2~enopyranosyl)purine nucleoside derivatives, for example **108** (X = theophyllin-7-yl). (245, 246) Yields are moderately good and, unlike in the glycol series, no 3-linked products appear to be formed. Likewise, compound **107** is converted in high yield into the corresponding glycosyl azide **108** (X = N₃) and its *b*-anomer (a,*b* ratio 2–5:1) on treatment with trimethylsilyl azide in acetonitrile containing a Lewis acid. With Yb(OTf)₃ the azides are produced almost quantitatively, whereas other catalysts [notably Sc(OTf)₃] cause the concurrent formation of significant proportions of enone **109** (X = N₃) and its *b*-anomer. (80)

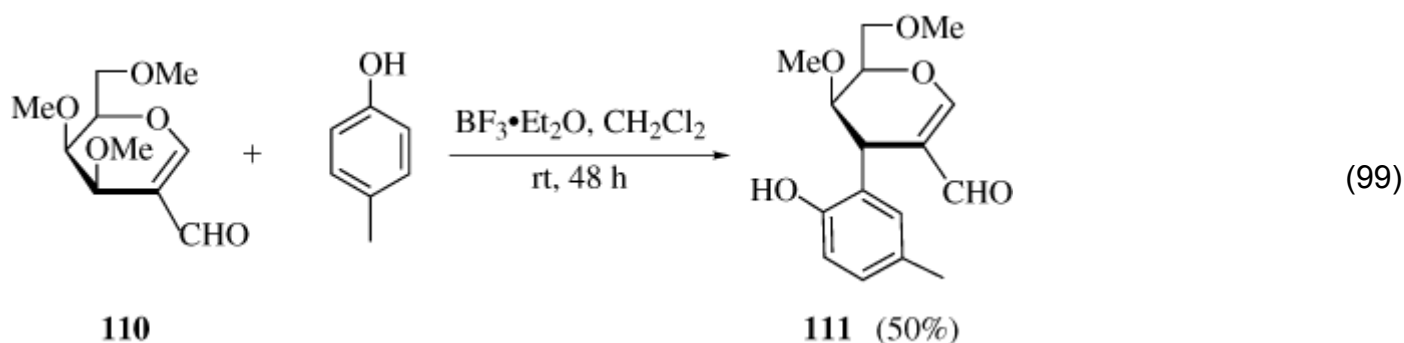
Treatment of compound **107** with hydrogen halides in benzene gives access to the reactive unsaturated glycosyl halides **108** (X = Cl, (231) F, (247)), the latter, on warming, readily affording the enone **109** (X = F). (248)

C-Glycosides are also obtainable in the 2-hydroxyglycol series (Eq. 98, path a), (138) however trimethylsilyl allyl ethers, (249) C-silylated alkynes (Eq. 98, path b), (219, 220, 250) and aromatic hydrocarbons (251) can give products that readily degrade to enones.



The occasional mention has been made in the literature of glycal derivatives with substituents other than acyloxy groups at C-2, and when these control the nucleophilic addition, novel products can be formed. Thus reaction of tosyl derivative **29** with sodium methoxide in methanol gives the monomethoxy and dimethoxy compounds **30** and **31** (Eq. 34). Presumably attack by methoxide occurs initially at C-1 to give a stabilized anion at C-2 which ejects the acetoxyl group from C-3 to afford alkene **30**. Michael-like addition then gives the saturated product **31**. (144)

In a related situation the reaction of the 2-C-formylglycal **110** with phenols and a Lewis acid catalyst gives 3-C-arylglycal products such as **111** of apparent direct nucleophilic displacement (Eq. 99). (252) It seems more probable, however, that the reaction involves the initial formation, by either unimolecular or S_N2^{\sim} processes, of the 2,3-unsaturated α -O-glycoside which then undergoes Claisen rearrangement (cf. Eq. 115). 3,4,6-Tri-O-benzyl-2-deoxy-2-C-formyl-D-glucal, treated with organocopper reagents, gives alkyl or aryl 2-C-formyl-2,3-unsaturated α -C-glycoside derivatives in 60–70% yields. (149)



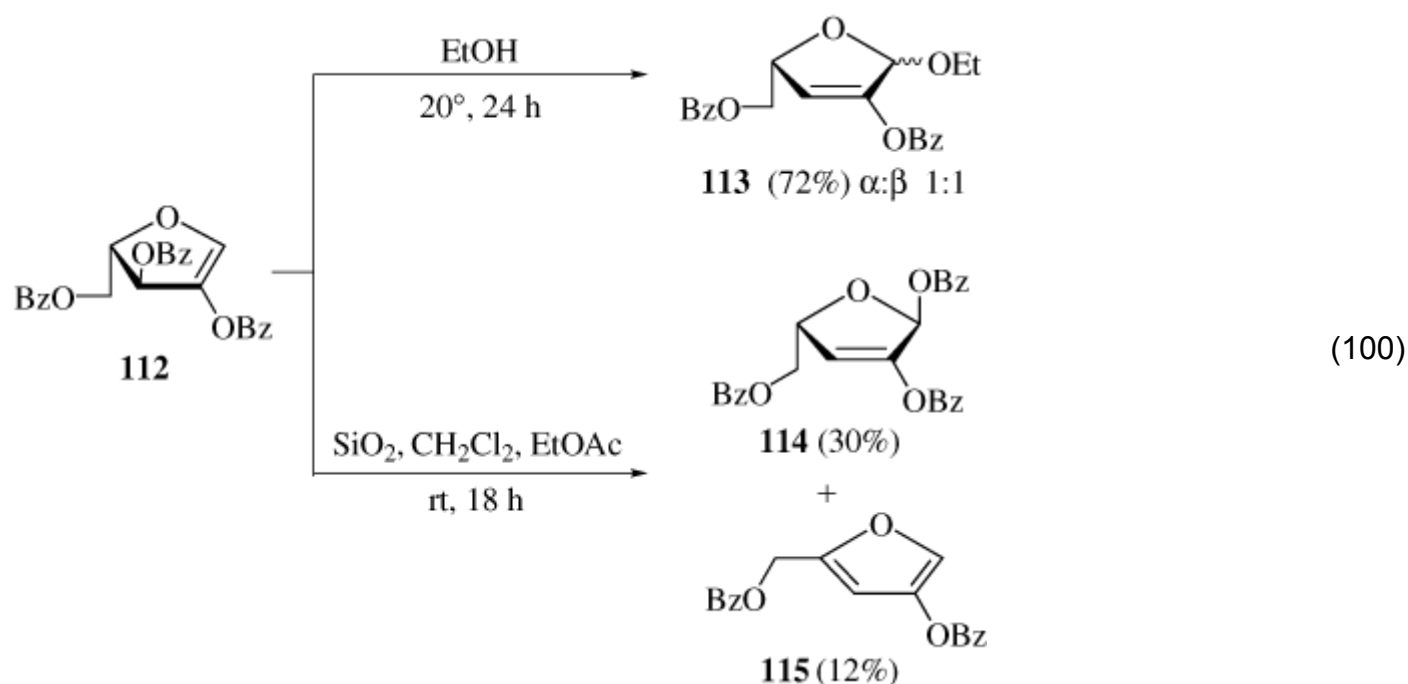
3.12. Applications to Furanoid Glycal Derivatives

While the general rearrangement reaction under review has been applied very extensively with glycal derivatives of the dihydropyran kind, the same does not hold for dihydrofuran analogs despite the significance in natural products of furanoid glycosides of the O-, C-, and, particularly, N-linked types. To a major extent this can be attributed to the greatly enhanced chemical sensitivity of 5-membered glycal derivatives which, being largely planar, are prone to elimination processes to afford furans. They are therefore relatively difficult to prepare and to manipulate chemically. There are, nevertheless, several reports of the application of the substitution reaction with allylic rearrangement to the preparation of 2,3-unsaturated furanoid O-, N-, and C-glycosides which, for the same reason, can also be fragile compounds.

An early example indicated the great sensitivity of glycals of this series since the furanoid glycal of

Eq. 33, made by NaI treatment of the corresponding 2-*O*-*p*-nitrobenzenesulfonyl- β -D-ribofuranosyl bromide, spontaneously reacts at room temperature in methanol/ CH₂Cl₂ (3:1) to lose benzoic acid and give the crystalline methyl glycoside (142) later shown by independent synthesis to be the β -anomer. (143)

In similar fashion, the furanoid “2-hydroxyglycal” ester 112, on dissolution in ethanol at room temperature, affords the ethyl glycosides 113; over silica gel at room temperature it rearranges to the 2,3-unsaturated isomer 114 and concurrently loses benzoic acid to give the furan 115 (Eq. 100). For the quantitative conversion of compound 112 into furan 115 toluenesulfonic acid in benzene at 60° can be used. (253) By comparison with the facile conversion of 112 into 114, the D-glucose-derived pyranoid analog of the former tribenzoate requires heating in boiling nitrobenzene (210°) for 15 minutes to cause it to undergo analogous thermal isomerization. (238) The absence of silica gel in this experiment is unlikely to invalidate this comparison which is consistent with the normal relatively high reactivity of furanoid compounds compared with pyranoid analogs.



An unusual reaction whereby 1,2-unsaturated ribofuranoid nucleosides are converted directly into the 2,3-unsaturated 1,4-aldonolactone dimethyl acetals (254) is referred to at the end of the section “Scope and Limitations, Variations of the Reaction”.

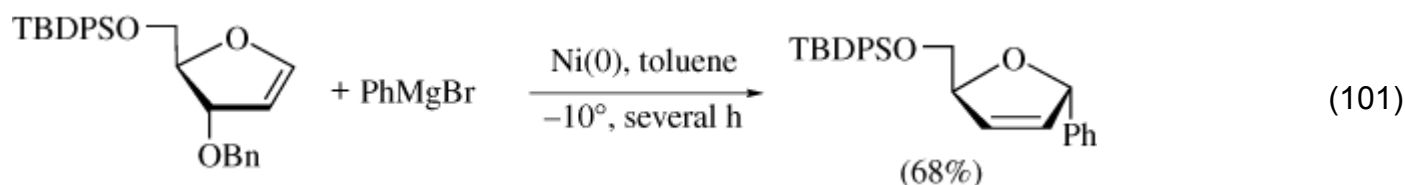
While it does not appear that the preparation of *N*-linked furanoid nucleoside derivatives by this approach has been reported, a relevant intramolecular procedure is noted in the following section (Eq. 105).

Significant headway has been made in the preparation of 2,3-unsaturated furanoid C-glycosides which, lacking good leaving groups at the anomeric centers, are chemically more robust than their *O*-, *S*-, and *N*-linked analogs. In particular, several intramolecular processes have proved suitable for their synthesis as indicated in the following section (e.g. Eqs. 109, 111).

For the direct intermolecular synthesis of furanoid C-glycosides palladium-promoted reactions can be useful. When both hydroxyl groups of compounds 61 (Eq. 46) are *O*-substituted, and mercurated pyrimidine is used together with palladium acetate, complex formation occurs from the β -direction, *syn*-“palladium hydride” elimination follows, and good yields of unsaturated β -C-nucleoside analogs such as 62 are obtained. (20) On the other hand, when the hydroxyl group at C-3 of compound 61 is free and that at C-5 is substituted, addition takes place from the α -face of the molecule (trans to the

large ring substituent), and syn-elimination of “palladium hydroxide” leads to α -2,3-dideoxy-unsaturated compounds such as **63**. This latter process, therefore, is akin to the acid-catalyzed allylic substitution reaction under review and can be applied with simple or complex aryl or heterocyclic compounds that can be activated by mercuration or stannylation. Stoichiometric proportions of a suitable palladium(II) compound are required to effect transmetalation. Otherwise, iodoaromatic derivatives with catalytic amounts of Pd(OAc)₂ may be used. (20)

A different direct approach to furanoid 2,3-unsaturated aryl C-glycosides involves treatment of ether-protected glycols with Grignard reagents in the presence of Ni(0) (Eq. 101). (147) Analogous pyranoid glycols do not react in this manner, but undergo sugar ring-opening reactions under these conditions. (147)

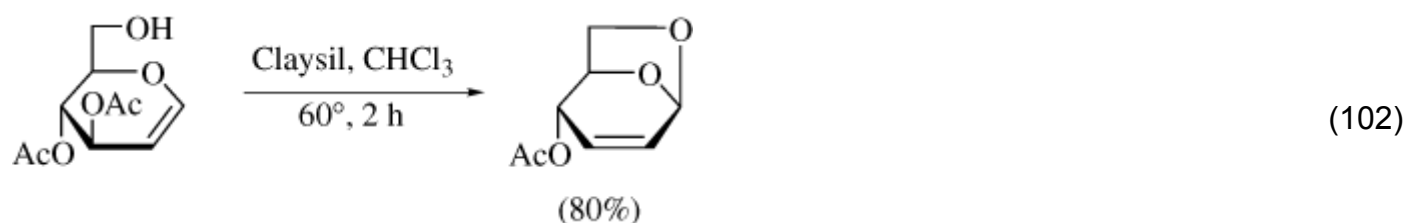


Other relevant examples of reactions involving furanoid compounds are provided later in Eqs. 119, 128, and 138.

3.13. Intramolecular Applications

Several examples have been reported of the allylic substitution reaction occurring within glycol derivatives that contain both nucleophilic groups able to attack the anomeric center and appropriate leaving functions in the allylic position. In this way an alternative means of producing 2,3-unsaturated compounds with O-, N-, or C-linked anomeric substituents is provided, and this approach has been of particular significance in the synthesis of C-glycosides. Commonly the leaving groups and the nucleophilic centers are both contained within the allylic O-3 substituents, in which cases sigmatropic processes can effect the rearrangements in manners that confer the appreciable advantage of stereospecificity.

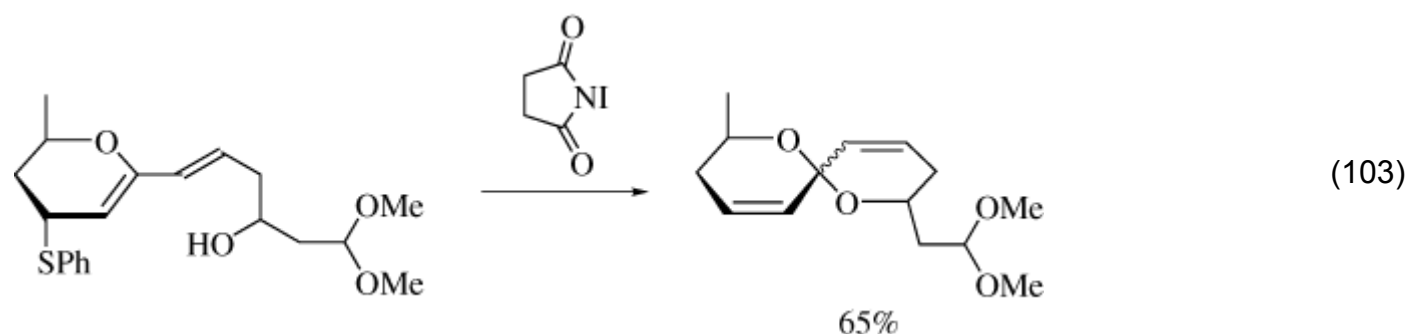
The simplest intramolecular example occurs when D-glucal, and derivatives that have free hydroxy or O-silylated groups at C-6, are treated under dehydrating conditions. With a silver-Montmorillonite K-10 catalyst (Claysil) this type of reaction proceeds to give the corresponding 2,3-unsaturated 1,6-anhydrohexoses in about 80% yield (Eq. 102). (82) Otherwise these cyclizations may be promoted by use of Lewis acids (104) or simply by dehydration by use of anhydrous copper sulfate. (255)



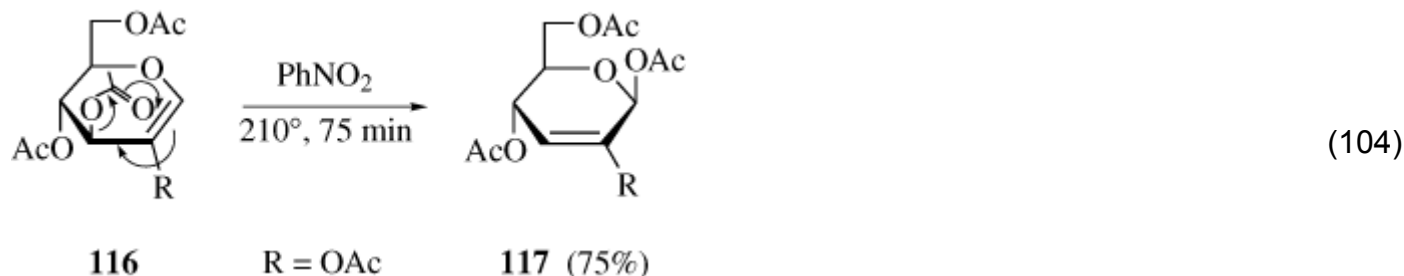
A similar reaction occurs when 6-acetamido-3,4-di-O-acetyl-6-deoxy-D-glucal is treated in MeCN with Pd(MeCN)₂Cl₂. The nitrogen atom bonds to C-1 and displaces the C-3 acetoxy group with allylic migration to give compound **60** in 40% yield (Eq. 45). (160)

An example of a related reaction involving a nucleophilic oxygen atom in the aglycon of a C-glycosidic glycol, and activation of the allylic thio group with *N*-iodosuccinimide, and which results in the formation of spirobicyclic products, is illustrated in Eq. 103. (256) For other spirobicyclic

products see Eq. 112.

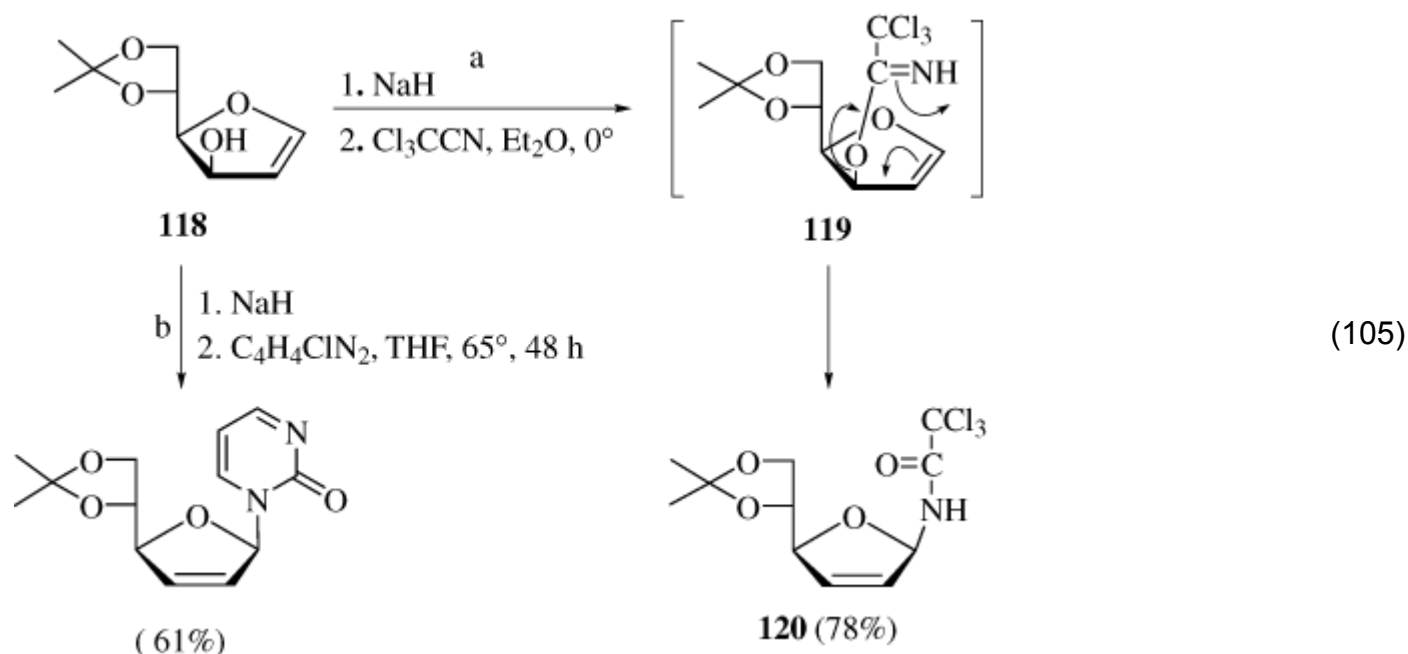


The simplest sigmatropic reactions in which common glycal derivatives take part are the thermal rearrangements illustrated in Eq. 104. However, tri-*O*-acetyl-*D*-galactal and its 2-acetoxy derivative, the C-4 epimers of substrates **116** ($R = H, OAc$), are thermally stable under these neutral conditions which suggests that the ester groups at C-4 must be trans to the allylic leaving groups to afford the anchimeric assistance necessary for the reaction to proceed. (238) From tri-*O*-acetyl-*D*-glucal the first formed *b*-product (**117**, $R = H$) anomerizes to some extent and, in addition, some of the C-3 epimer (tri-*O*-acetyl-*D*-allal) of the starting material is formed, conceivably, by thermal retro-rearrangement of the 2,3-unsaturated α -glycosyl acetate. (122) The apparent complexity of this reaction suggests that an acid catalyst enables the observed anomerization and hence retro-rearrangement to occur (cf. Eq. 28). Glycal benzoates take part in these rearrangements significantly more readily than do acetates, (238) and *O*-benzoylated furanosyl glycals are particularly prone to give their thermodynamically preferred 2,3-unsaturated isomers (Eq. 100). (253)



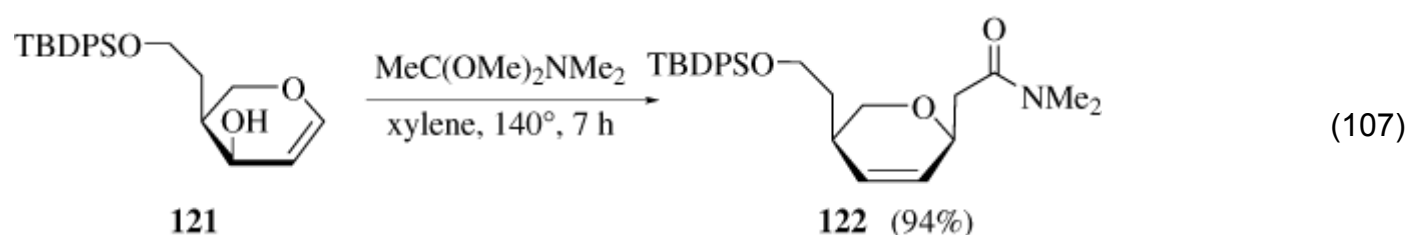
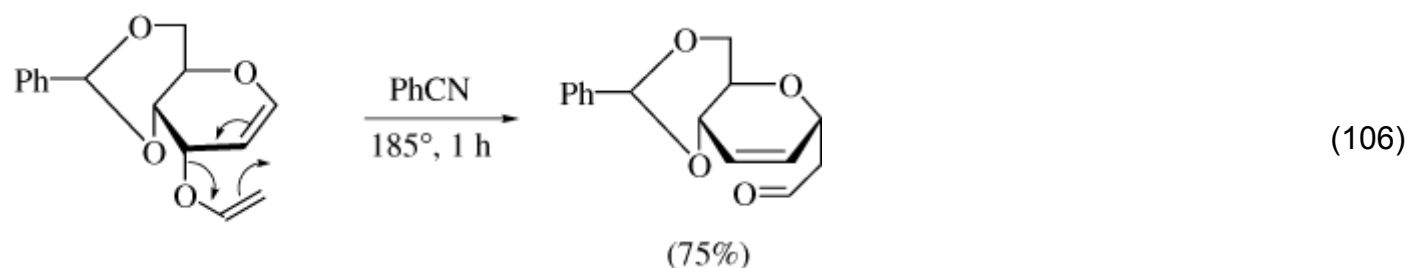
The rearrangement of acetylated glycals, and the anomerizations of the products, are catalyzed by Lewis acids, and it is a simple matter to convert glycal esters, especially those with trans-related groups at C-3 and C-4, into mixtures containing mainly their 2,3-unsaturated glycosyl ester isomers (Eq. 54). Likewise, tetra-*O*-acetyl-2-hydroxy-*D*-glucal (**116**, $R = OAc$), on heating in acetic acid with or without an acid catalyst, is converted into compound **117** (Eq. 104, $R = OAc$) (10%) and its *a*-anomer (55%). (237) However, the *b*-anomer is obtained in 75% yield simply by heating in the absence of an acid (Eq. 104). (238)

Procedures that involve sigmatropic rearrangements of specifically 3-*O*-substituted glycals have been used in the synthesis of furanosylamine derivatives. Reaction of glycal **118** with sodium hydride followed by trichloroacetonitrile does not result in the expected 3-trichloroacetimidate **119**; instead the product **120** of [3.3]-sigmatropic rearrangement of the latter is isolated (Eq. 105, path a). (257) Likewise, the *N*-glycosylpyrimidine made as indicated in Eq. 105, path b, is produced from the same starting material and 2-chloropyrimidine, the key step being an aza-Claisen rearrangement. (257)



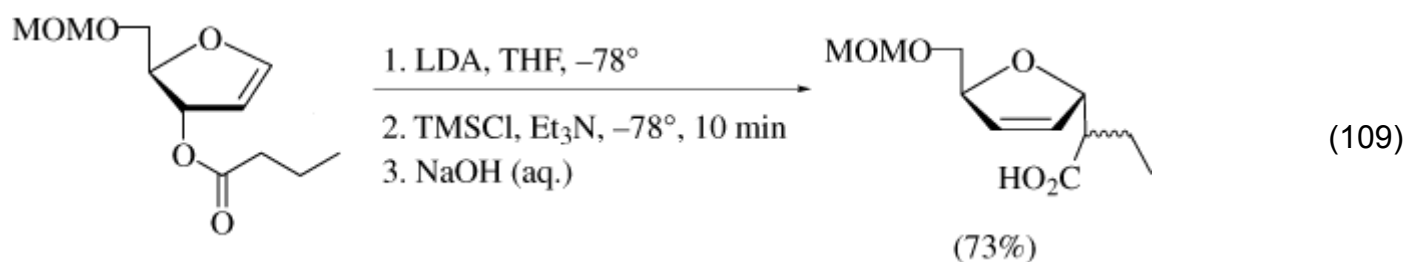
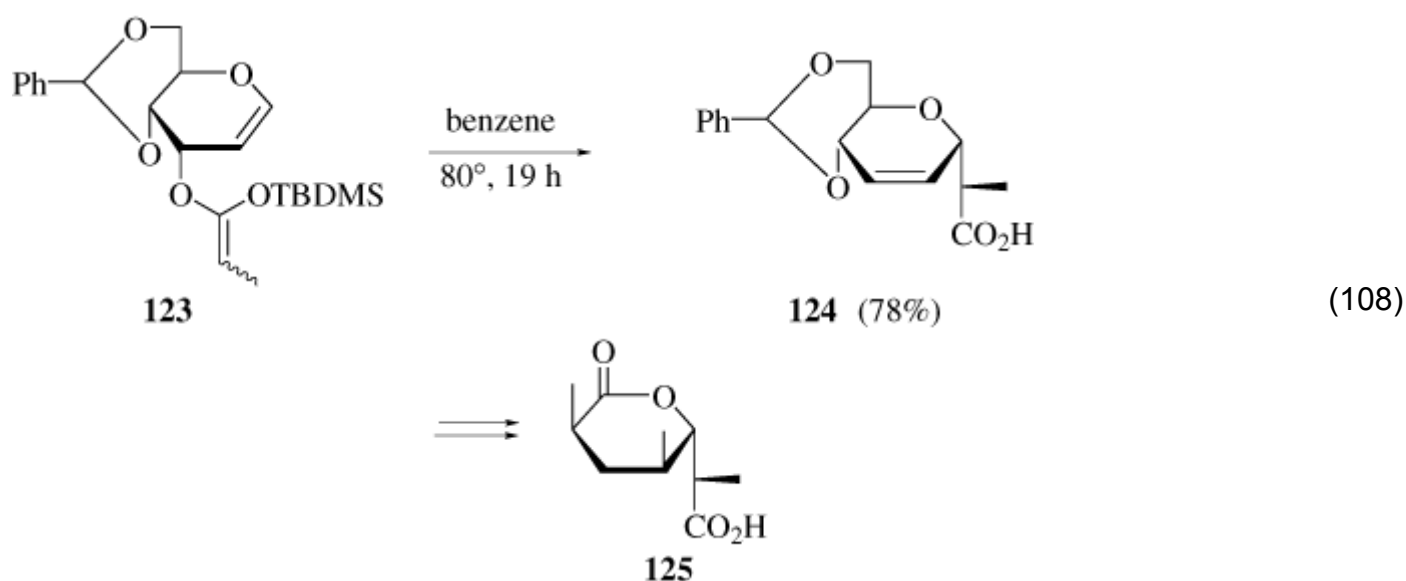
Glycal derivatives containing appropriate unsaturated nitrogen-containing allylic groups, for example 3-azidoglycals (Eq. 69) or C-3'-linked purine or pyrimidine nucleoside analogs (Eq. 71), can reversibly undergo [3.3]-sigmatropic rearrangements to give 2,3-unsaturated isomers with *N*-bonded substituents at C-1. This can make it difficult to identify the pathways by which particular compounds of these types are derived.

Potentially the simplest way of making 2,3-unsaturated C-glycosides by intramolecular procedures involves the Claisen rearrangement of 3-O-vinylglycals (Eq. 106). (24) However, while the thermal step to give the aldehyde proceeds satisfactorily, the overall approach is limited by the mediocre yield (50%) of the transvinylation reaction used to make the required vinyl ether. In similar manner, the branched-chain glycal **121**, itself made by application of the Eschenmoser variation of the Claisen rearrangement reaction, has been converted into the doubly C-substituted dihydropyran **122** by a second application of that reaction (Eq. 107). The product was required for studies aimed at the synthesis of pseudomonic acids. (258)

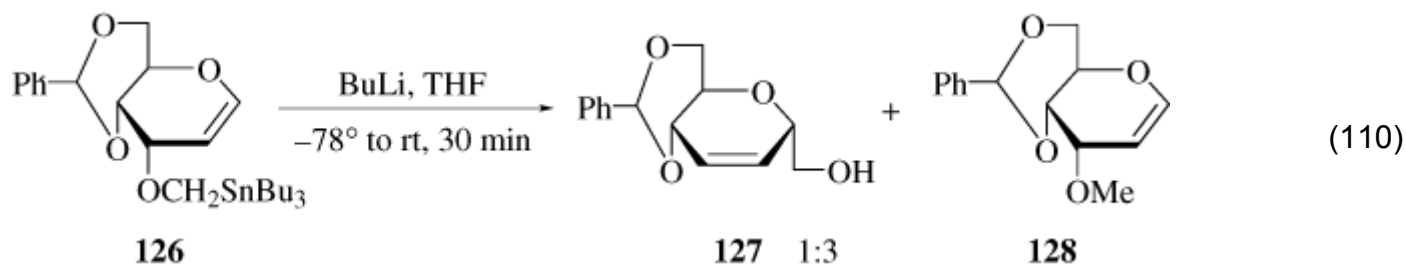


In related work extensive relevant use has been made of Ireland's ester enolate modification of the

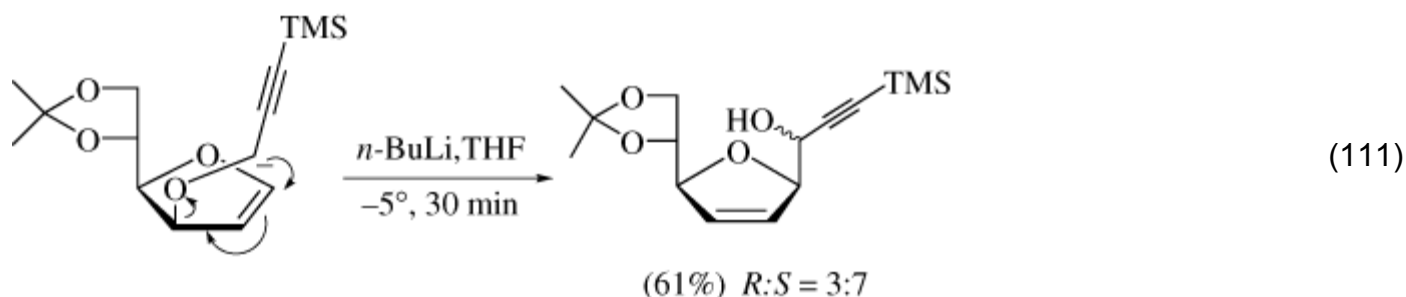
Claisen rearrangement. Heating of the silyl ketene acetals **123** gives mainly acid **124** from which the Prelog-Djerassi lactone **125** is obtained (Eq. 108). (259) Several related applications have been used in the production of bioactive pyranoid C-glycosides (**116**, **260**, **261**) and C-linked disaccharides, (**261**, **262**) and analogous 2,5-dihydrofurans bearing functionalized carbon substituents with defined configurations at both positions adjacent to the ring oxygen atoms can be made from furanoid glycols (Eq. 109). (**263**, **264**)



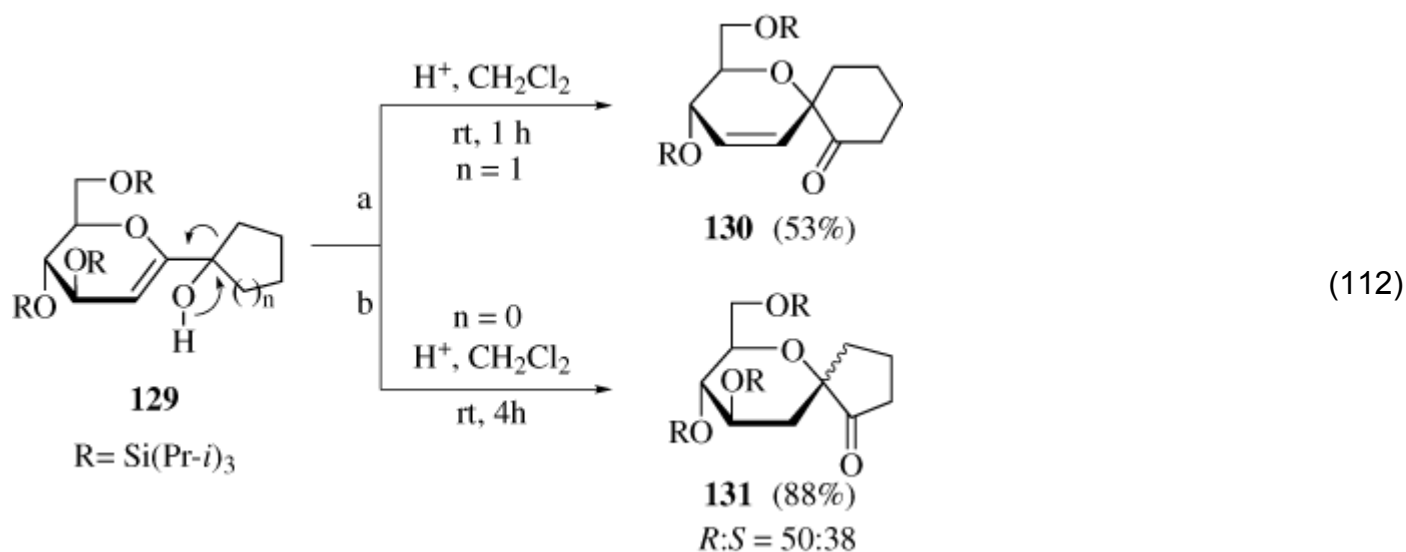
The carbanion produced on lithiation of the (tri-*n*-butylstannyl)methyl ether **126** of 4,6-O-benzylidene-D-allal undergoes [2,3]-sigmatropic rearrangement to give the unsaturated C-glycoside **127**, but only as a minor product, the major being the methyl ether **128** formed from the anionic intermediate by proton abstraction (Eq. 110). (24) A related [2,3]-Wittig rearrangement, however, occurs with better efficiency when 3-trimethylsilylpropargyl ethers of furanoid glycols are treated with *n*-BuLi (Eq. 111). (**265**)



An entirely different type of rearrangement to afford spirocyclic products such as **130** and **131** occurs when glycols bearing cyclic tertiary alcohol C-1 substituents are treated in an inert solvent with camphorsulfonic acid. (**266**) In the case of compound

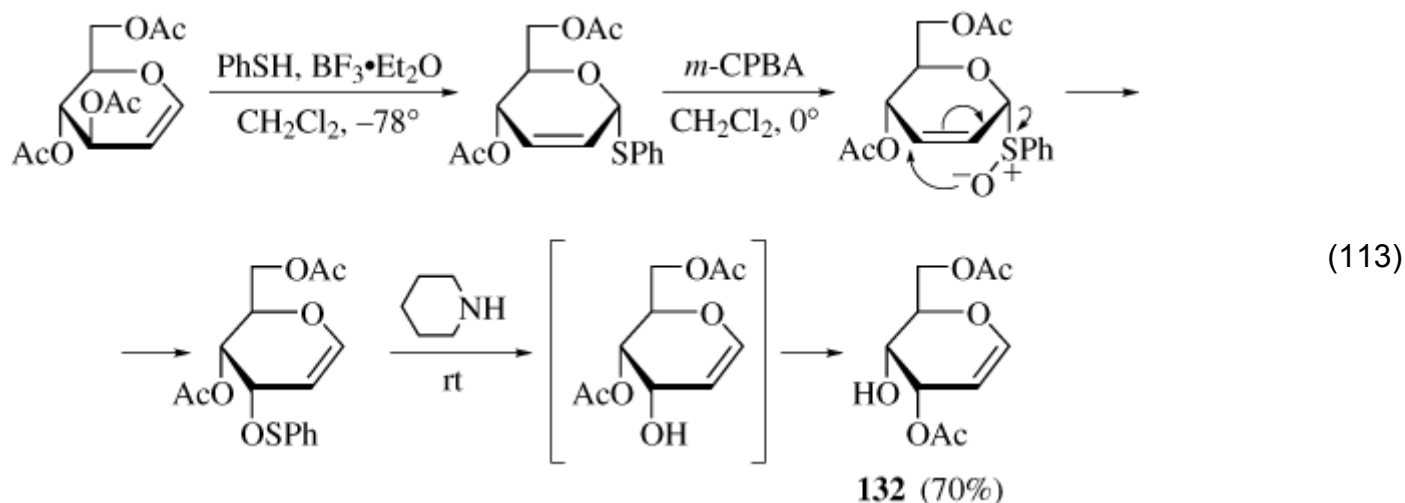


129 ($n = 1$) it appears that reaction is initiated by protonation at the allylic glycal oxygen atom and that normal displacement with allylic rearrangement occurs via the derived 2,3-unsaturated C-1 carbocation (Eq. 112, path a). With the cyclobutyl derivative **129** ($n = 0$), however, protonation at C-2 seems to trigger the reaction by establishing a saturated pyranoid C-1 carbocation that induces the cyclobutyl ring expansion (Eq. 112, path b). (267)

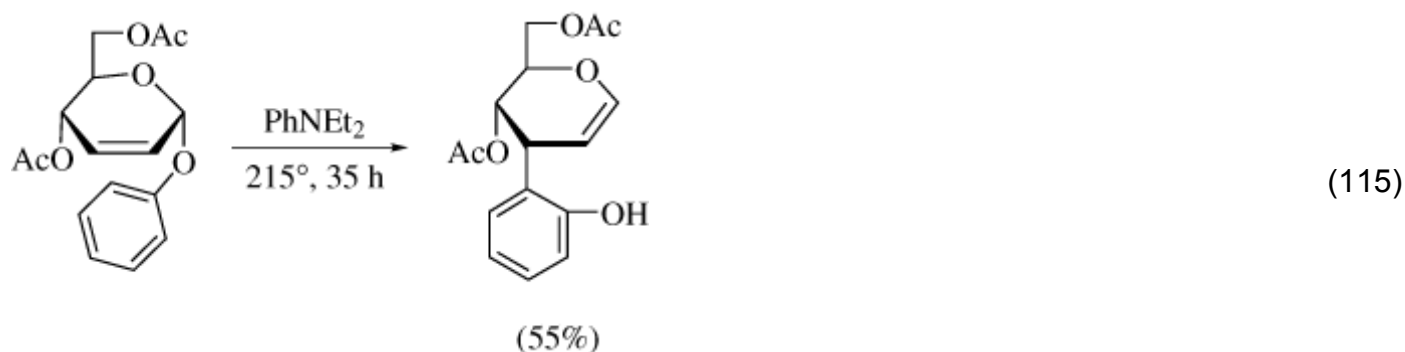
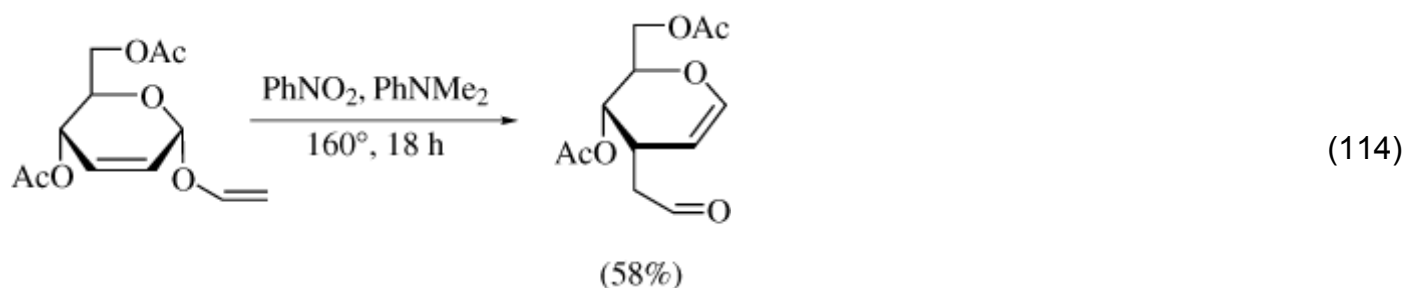


3.14. The Reaction in Reverse

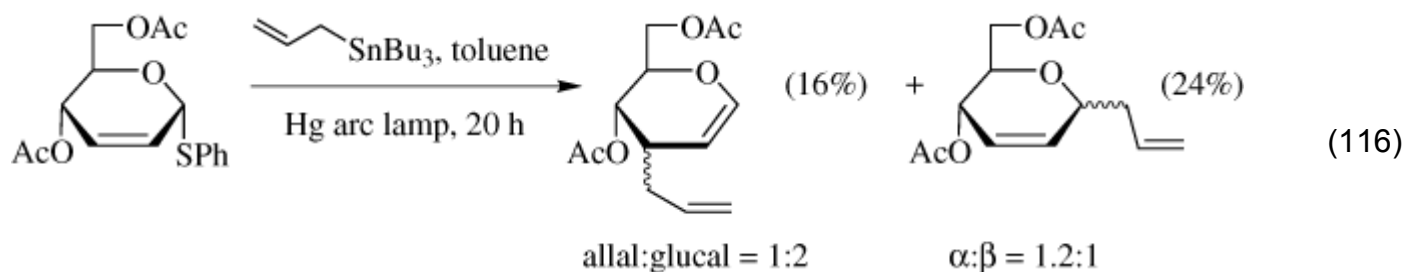
Although both kinetic and thermodynamic factors commonly favor the conversion of glycols into 2,3-unsaturated glycosyl compounds, there are some circumstances in which the former can be produced from the latter. A notable application of the reverse reaction affords a simple method of obtaining D-allal and D-gulal derivatives from the more readily available acetylated D-glucal and D-galactal, respectively, via 2,3-unsaturated *S*-phenyl thioglycosides made by the transformation under review. These are oxidized to the allylic sulfoxides which isomerize by [2,3]-sigmatropic processes to allylic sulfenate esters; treatment with piperidine then affords the corresponding alcohols. (194) When the sequence is applied to tri-*O*-acetyl-D-glucal the product isolated is 3,6-di-*O*-acetyl-D-allal (**132**) (Eq. 113), acetyl migration from *O*-4 to *O*-3 occurring during the final hydrolysis step. 4,6-*O*-isopropylidene-D-allal is obtained in 87% yield from the 4,6-*O*-isopropylidene analog of the thioglycoside shown in Eq. 113. (268) From tri-*O*-acetyl-D-galactal, 4,6-di-*O*-acetyl-D-gulal is produced (60% overall), which suggests that the acetyl migration in the illustrated case occurs during the cleavage of the sulfenate ester. This approach has also been used to prepare 6-deoxy-D-gulal (269) and -allal (270) and a 6-deoxy-4-thio-D-allal derivative. (271) The relevant thermal rearrangement of 2,3-unsaturated thioglycosides to 3-thioglycols under the conditions of their synthesis is referred to in the section "2,3-Unsaturated *S*-Glycosides and Related Thio Compounds." A similar but radical-dependent allylic transformation occurs when a D-glucal-derived 2,3-unsaturated 1-phenylsulfenate is treated with tributyltin hydride in toluene under photoinitiation, mixed 3-deoxy-3-tributylstannylglycols (allal: glucal = 4:1) being produced in 65% yield. (113)



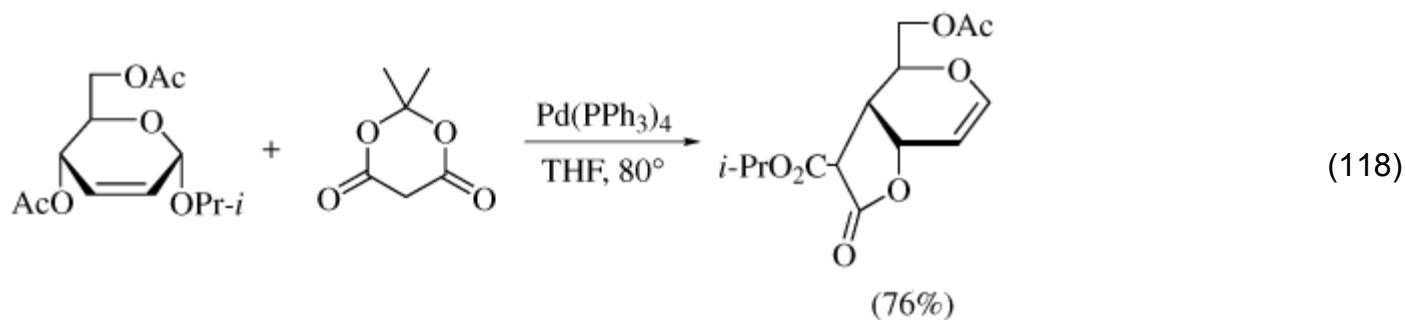
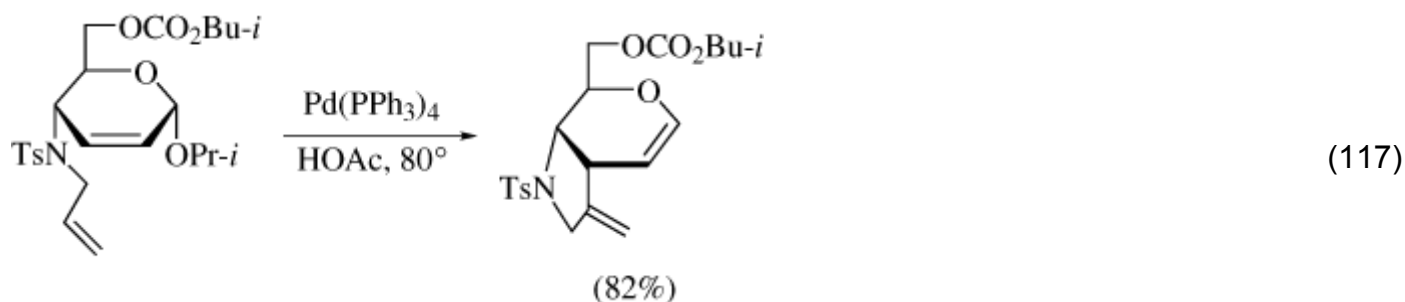
Vinyl glycosides of 2,3-unsaturated sugars rearrange thermally to 3-deoxy-3-*C*-(formylmethyl)glycals (Eq. 114). (272, 273) Aromatic analogs isomerize similarly to the more stable 3-*C*-linked glycal compounds (Eq. 115), and rearrangement of the *b*-isomer of the illustrated glycoside occurs much more readily; heating of the latter at 160° gives 78% of the 3-*C*-aryl-3-deoxy-*D*-glucal derivative in 30 minutes (see also Eq. 99). (274) The occurrence of other 3-*C*-substituted glycals in the products of heating glycal derivatives with phenols and related compounds probably also results from isomerizations of 2,3-unsaturated aryl glycosides. Thus the formation of 4,6-di-*O*-acetyl-3-deoxy-*D*-allal with a *C*-*C*-linked *tert*-butylbenzoquinone substituent at *C*-3 by the reaction of tri-*O*-acetyl-*D*-glucal with *tert*-butyl-1,4-benzoquinone probably can be accounted for in this way, the first formed *C*-3-linked hydroquinone derivative being subsequently oxidized. (275) A free radical means of making glycals with



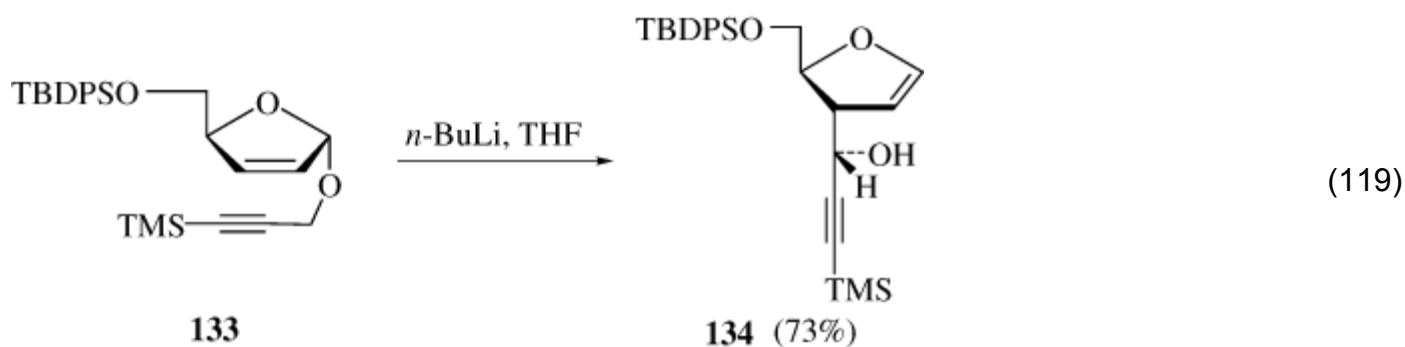
C-*C*-bonded substituents at *C*-3 starting from 2,3-unsaturated *S*-phenyl thioglycosides involves treatment with allyltri-*n*-butylstannane under a medium pressure mercury arc lamp. Mixed products are obtained in modest yields (Eq. 116). (276) Related results are obtained on cross coupling a glucal-based 2,3-unsaturated (*S*-benzothiazol-2-yl)-1-thioglycoside with organocopper reagents, the main products being 3-alkyl- or 3-aryl-3-deoxyallal derivatives. (277)



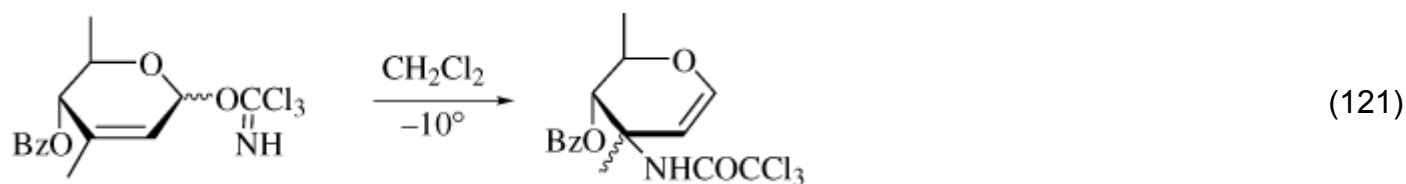
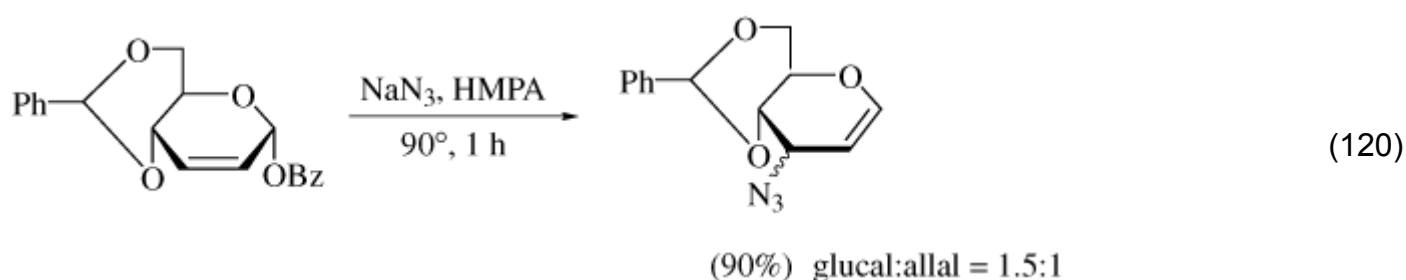
A different cyclization occurs when alkyl 2,3-unsaturated glycosides bearing 4-*N*-allylamino-4-deoxy substituents are treated with Pd(0) reagents (Eq. 117). (278) In analogous fashion, similar treatment of 4-*O*-allyl derivatives of 2,3-unsaturated glycosides results in bicyclic glycal products having a C-linked substituent at C-3. (279, 280) By a related process an allal derivative with a branching malonic acid substituent at C-4 and lactone ring closed to O-3 is obtained by treatment of isopropyl 4,6-di-*O*-acetyl-2,3-dideoxy- α -D-erythro-hex-2-enopyranoside with excess of Meldrum's acid in the presence of catalytic amounts of Pd(PPh₃)₄ (Eq. 118). Apparently the acid is introduced at C-4 of a palladium complex to give an intermediate that decomposes by loss of acetone, lactone ring formation and, surprisingly, also with migration of the aglycon unit. (159)



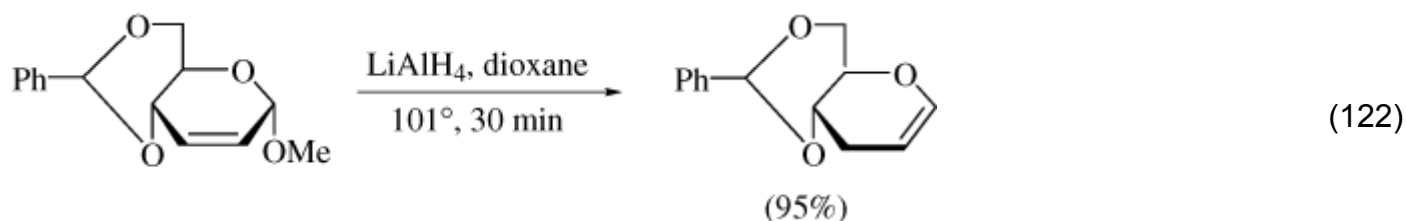
In the opposite sense of the reaction illustrated in Eq. 111, the carbanion derived from the propargylic glycoside **133** undergoes [2,3]-Wittig rearrangement to give the branched-chain glycal **134** with the *S*-configuration at the new alcohol center (Eq. 119). (281)



Cyclic oxocarbenium ion intermediates present in the acid-catalyzed allylic substitution reactions of glycol esters can also be obtained from 2,3-unsaturated glycosyl compounds. Therefore reactions of 2,3-unsaturated glycosides under conditions in which the C-1 substituents are substituted by nitrogen-containing reagents can result in 3-*N*-substituted glycols in keeping with the propensity for *N*-nucleophiles to give such products from glycols under thermodynamic conditions. As examples, ethyl 4,6-di-*O*-acetyl-2,3-dideoxy- α -D-erythro-hex-2-enopyranoside reacts with chlorosulfonyl isocyanate to give 4,6-di-*O*-acetyl-3-deoxy-3-(ethoxycarbonyl)amino-D-glucal amongst other products. (282) Also, heating of an analogous 2,3-unsaturated glycosyl benzoate with sodium azide gives the 3-azidoglycal epimers in high yield (Eq. 120). (205) A related intramolecular example of the formation of 3-amino-3-deoxyglycal compounds is illustrated in Eq. 121; the trichloroacetimidates rapidly rearrange under the mild conditions of their synthesis. (283)



A reductive process which illustrates the allylic rearrangement reaction operating in the opposite sense is the conversion of 2,3-unsaturated *O*-glycoside derivatives by treatment with LiAlH_4 in ether or dioxane (Eq. 122). (130, 284) That this reaction results in delivery of hydride at C-3 within a complex involving the oxygen atom of the methoxy group is shown by the finding that both in the illustrated case and in the case of the corresponding methyl β -glycoside the incoming hydride bonds to the side of the pyranoid ring from which the alkoxy group leaves. Starting materials with the α -threo-configuration, however, either do not react or give products derived from complexes involving O-4 as well as O-1. (285) Later studies have led to the conclusion that only if the substituents on C-1 and C-4 of the starting materials are cis-related does this reaction occur satisfactorily. (286) This reductive process is therefore the reciprocal of that resulting from reaction of triethylsilane in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ with either ethyl 4,6-di-*O*-acetyl-2,3-dideoxy- α -D-erythro-hex-2-enopyranoside or tri-*O*-acetyl-D-glucal, which gives the products of hydride attack at C-1 of the oxocarbenium ion intermediates (Eq. 93). (236)

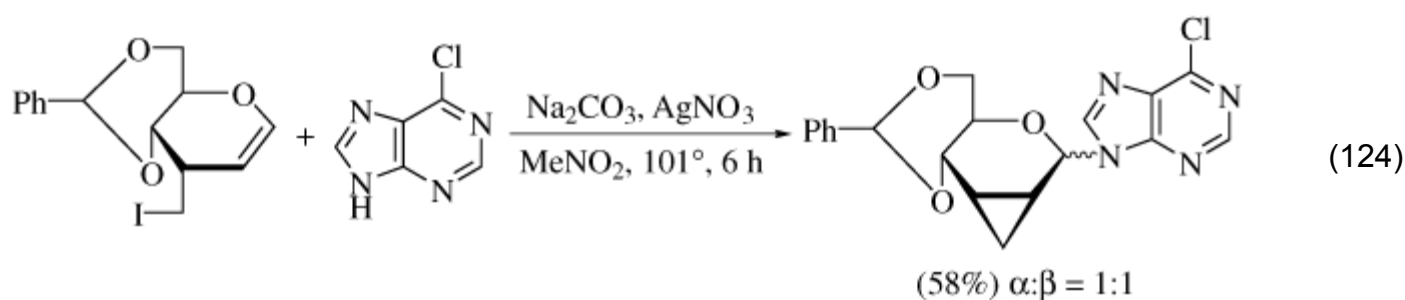
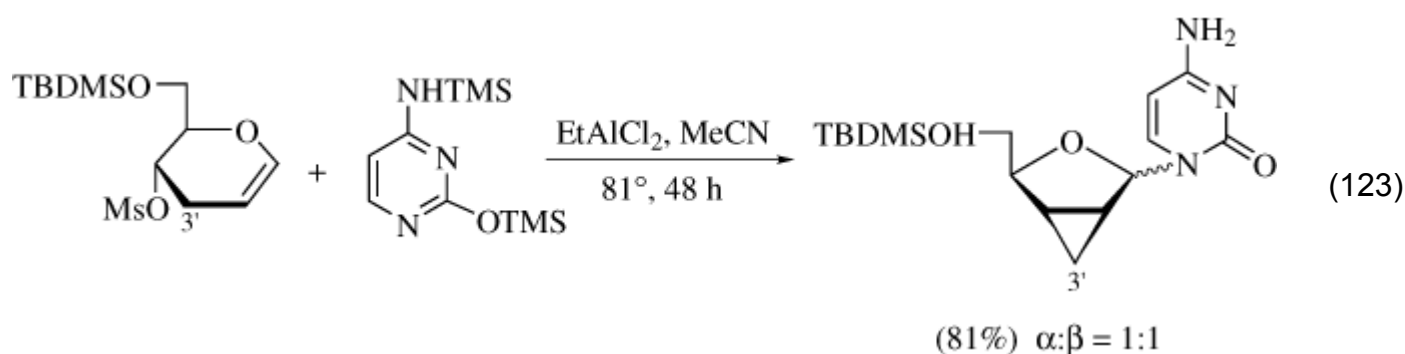


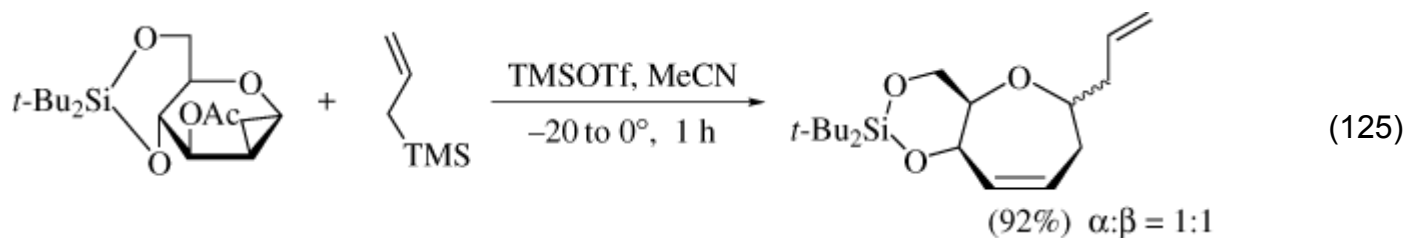
In appropriate situations simple prototropic shifts can cause the allylic isomerization to occur in the opposite direction. For example, 2,3-unsaturated C-formyl glycosides readily rearrange to the conjugated 3-deoxy-1-C-formylglycal isomers. (24) In similar fashion 2,3-unsaturated glycosyl phosphonates give analogous 3-deoxyglycal 1-phosphonates under basic conditions (Eq. 92), (234) but this type of isomerization is apparently not reported for the corresponding unsaturated glycosyl cyanides. Also following prototropic shifts 3-deoxy-3-*p*-tolylsulfonyl- and 3-deoxy-3-nitroglycals are produced under basic conditions from the isomeric 2,3-unsaturated compounds having a methylene group at C-1. (287) These transformations are facilitated by the ring oxygen atom and are consistent with the conversion of allyl ethers into prop-1-enyl ethers under basic conditions.

3.15. Variations of the Reaction

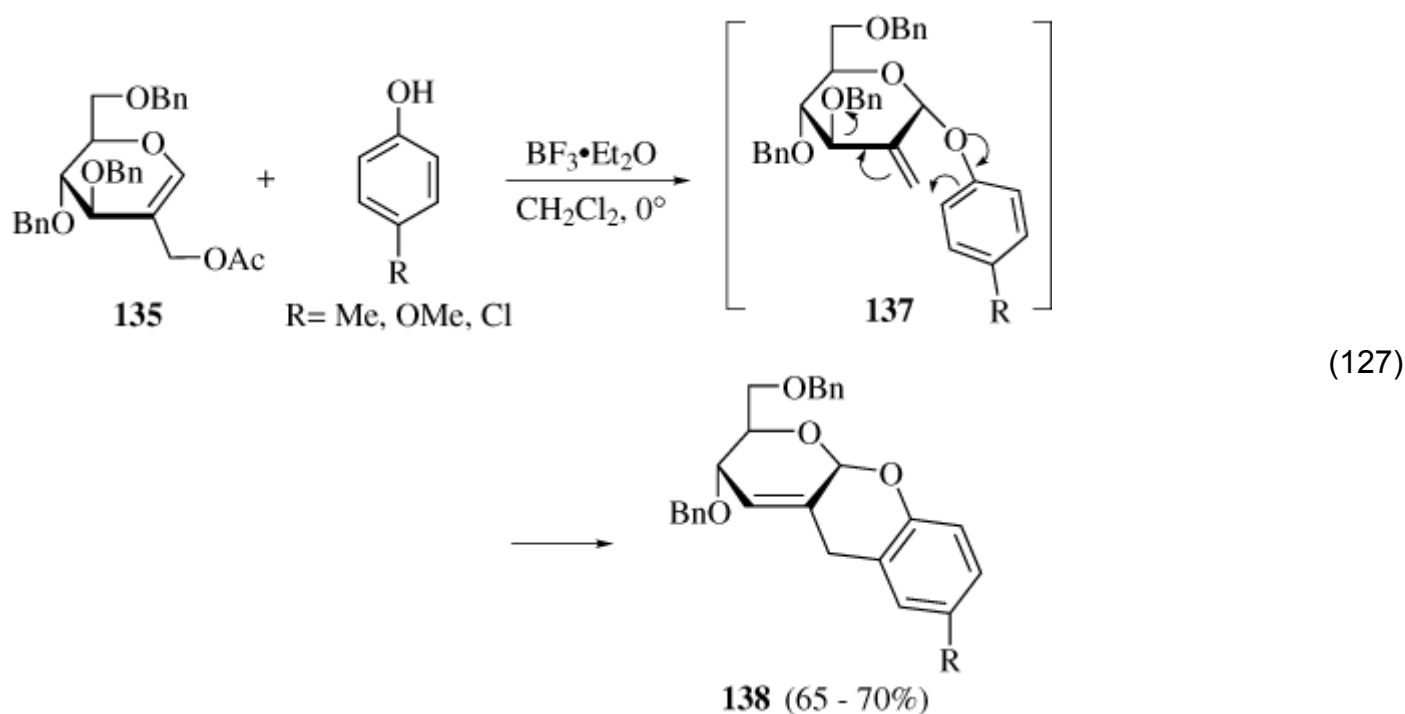
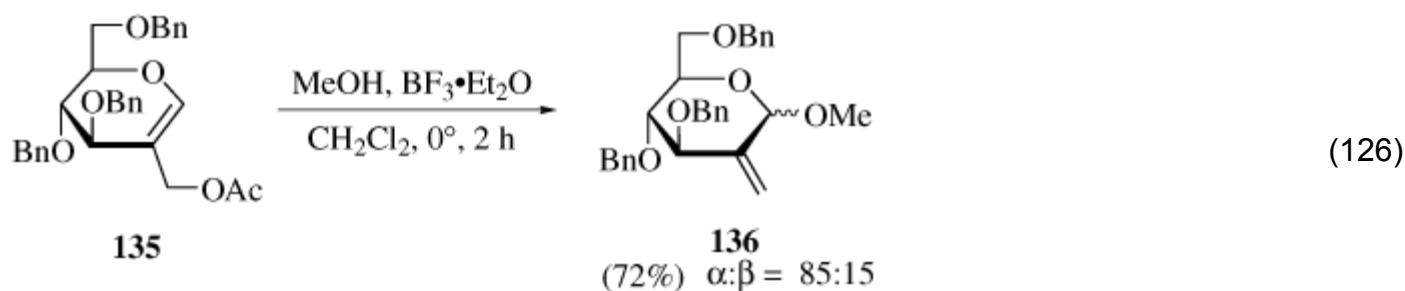
Most of the variations of the rearrangement reaction described to this point have been simple and have pertained to particular features of the process outlined in Eq. 1 (1 into 2). There are several more extensive variations one of which involves aza analogs of glycals; it may be applicable in the very active field of iminoalditol chemistry. A prototype is illustrated in Eq. 8; (34) the major product, which gives access to the *Streptomyces* metabolite streptazolin, has the allyl substituent on the carbon atom adjacent to the hetero atom, as is consistent with findings made with the preparation of C-allyl unsaturated glycosides from glycal derivatives. However, reaction of the enamide of Eq. 8 with ethanol or thiophenol in the presence of an acid catalyst gives mainly products of displacement of the hydroxy group without allylic rearrangement, and this does not parallel the behaviour of glycals.

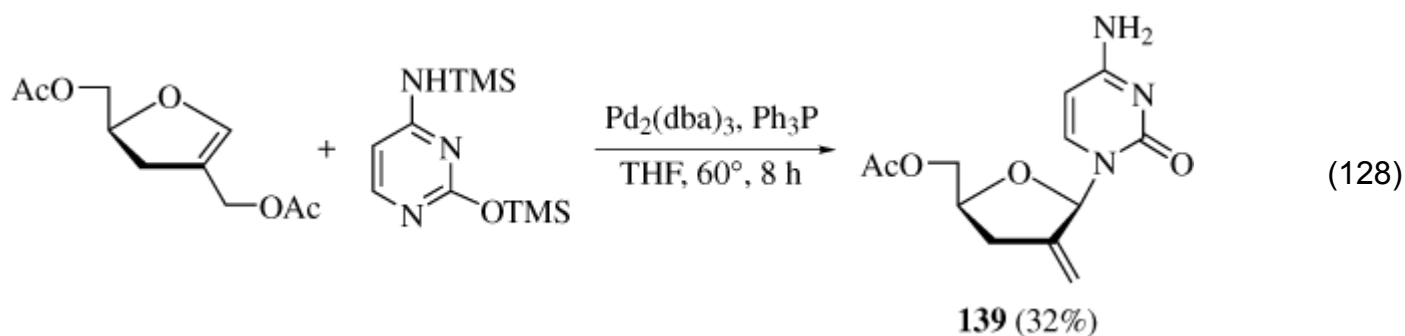
Eq. 123 illustrates the reaction of a glycal with its leaving group in the homoallylic C-4 position, (288) and the related conversion shown in Eq. 124, which leads to a cyclopropapyranoid rather than -furanoid nucleoside, has also been described. (289) In Eq. 125 a reaction that mimics the allylic substitution process is illustrated, but the electrons of the sugar-derived moiety that migrate originate from a cyclopropane ring rather than a double bond. (290) The consequence is expansion of the sugar ring as opposed to the contraction illustrated in Eq. 123 addition to the allyl group, hydrogen, azido, alkoxy, arylthio, cyano, and other C-bonded groups can be introduced into the 7-membered ring in this way. (290)



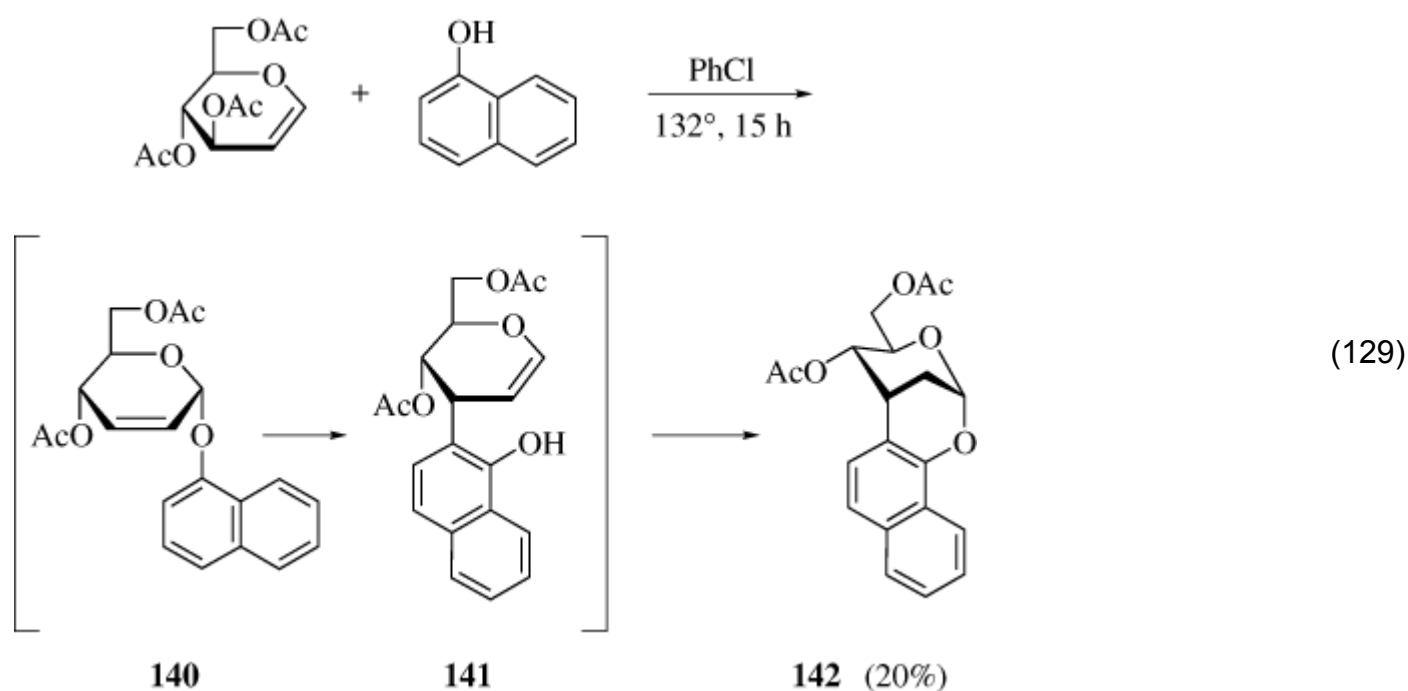


A further variation of the reaction uses the branched-chain glycal **135** which, in the presence of methanol and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as catalyst, loses the allylic ester group (rather than the allylic benzyloxy group) to give the exomethylene glycosides **136** as the main products (Eq. 126). (291) This reaction applied to the 3,4,6-tri-O-methyl analog of compound **135** gives, together with methyl 2,3,4-tri-O-benzyl- α -D-glucopyranoside, the α -linked disaccharide analog of compounds **136** in 75% yield. (292) With phenols the benzylated compound **135** gives the expected products **137**, but these react further under the reaction conditions to give pyranobenzopyrans **138** by electrophilic substitution in the aromatic rings and acid-catalyzed displacement of the allylic benzyloxy substituent as indicated in Eq. 127. (293) Although the reaction intermediates of this process cannot be isolated, they can be synthesized independently by the Mitsunobu method (109) and shown to react as expected. (293) In a closely related case a 3-deoxyribofuranoid analog of allylic acetate **135**, treated separately with silylated thymine and cytosine in the presence of a palladium catalyst, gives 3'-deoxyribonucleosides with an exo-methylene group at C-2'. With the latter base compound **139** is produced (Eq. 128). (294)

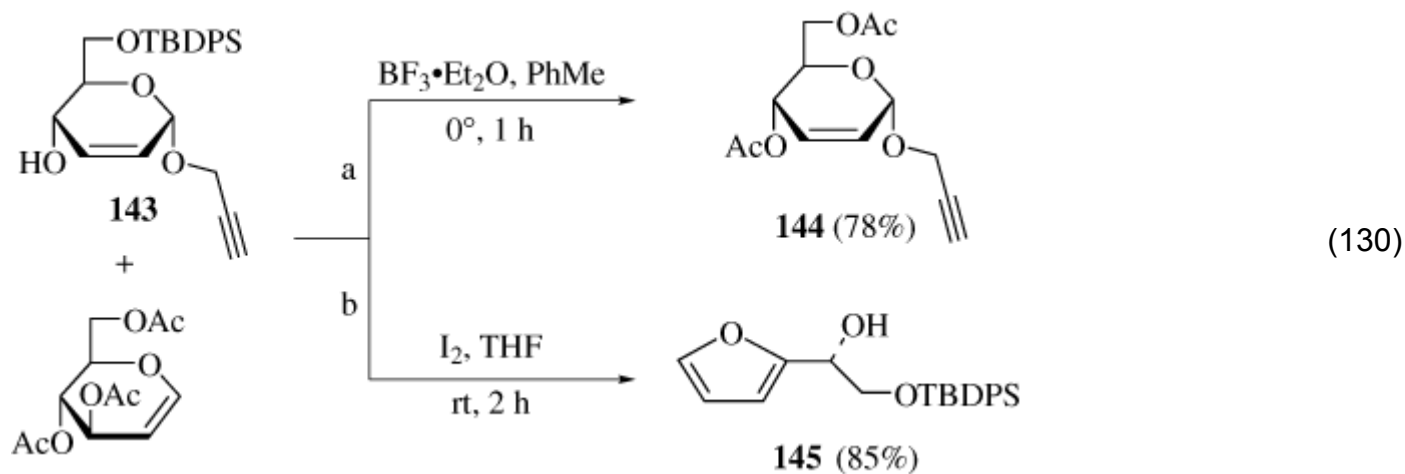




Heating of tri-*O*-acetyl-D-glucal with *o*-naphthol in chlorobenzene leads to compound **142** as the only isolated product. This can be rationalized by invoking a Claisen rearrangement occurring within the initial, expected *o*-glycoside **140** to give the C-3 linked glycal **141** (cf. Eq. 115) which undergoes intramolecular addition (Eq. 129). (178) The **140** into **141** step represents a further example of the reverse reaction.



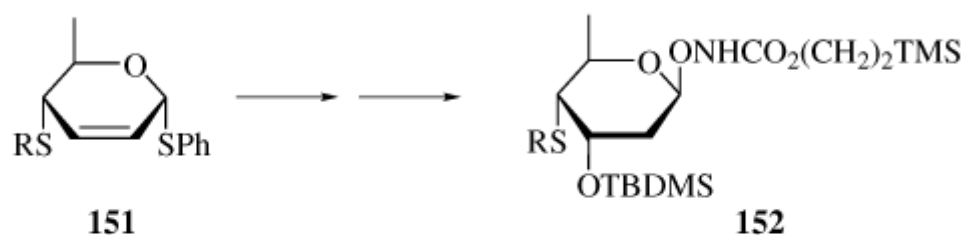
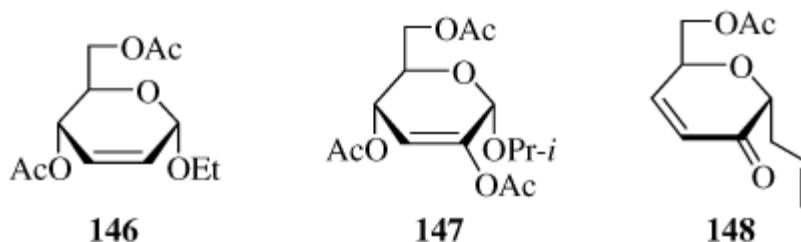
Two variations of the reaction of a different kind, encountered during attempts to make an *O*-linked disaccharide derivative from tri-*O*-acetylglucal under normal conditions involving the use of Lewis acid catalysts, are illustrated in Eq. 130. (295) In the first case (path a) the expected glycosyl acceptor alcohol **143**, as proposed by the authors, undergoes desilylation followed by trans-acetylation from the glycal to give diacetate **144**. It seems more probable, however, especially as the process is very efficient, that *O*-1 of the alcohol **143** acts as the nucleophile in a standard allylic transformation reaction, but whether it does so while still bonded within **143** or after elimination of propargyl alcohol from it is not clear. In the second anomalous reaction (Eq. 130, path b) compound **143** reacts by coordination of *O*-1 with iodine and attack by *O*-4 at C-1 with formation of the furanoid ring of compound **145**. It is not known at what stage in the overall reaction the propargylic alcohol is eliminated. Worthy of note is the observation that the apparently high Lewis base (nucleophilic) character of *O*-1 of **143** is deemed to have been the cause of the anomalous behaviour in both cases. In neither of these reactions were other components of the final mixtures identified.



A further variation, of which there is only one report, involves the reaction of 1',2'-unsaturated ribofuranoid nucleosides in methanol in the presence of a dialkyl malonate and ceric ammonium nitrate as catalyst. Rather than leading to C-2'-branched-chain products by addition, the reaction yields the dimethyl acetals of 2,3-unsaturated 1,4-aldonolactones. Normal displacement of the oxygen-bonded substituent from C-3 apparently occurs together, however, with methanolytic removal of the bases. (254)

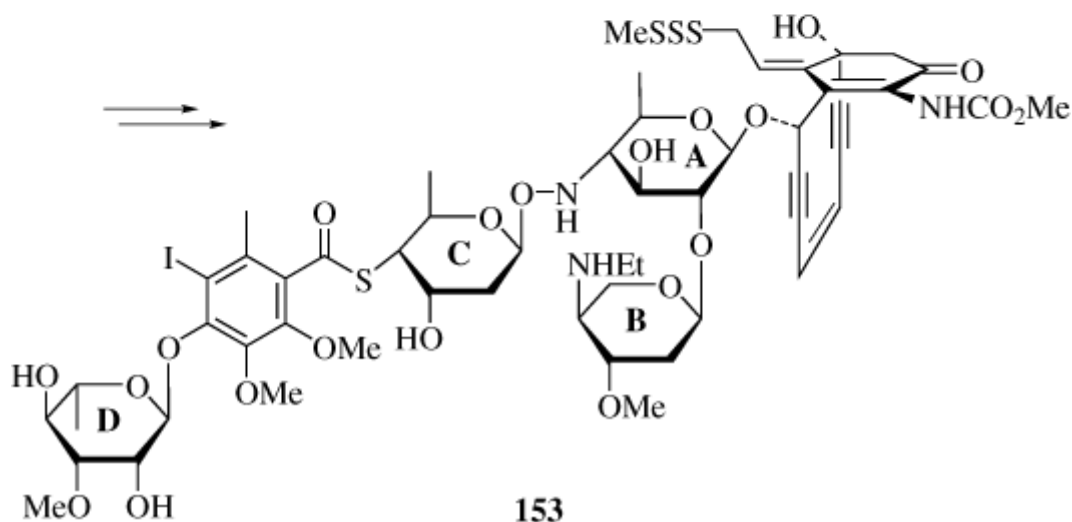
4. Applications to Synthesis

Some of the simpler compounds readily available by application of the reactions under review, e.g. **146**, (**14**) **147**, (**296**) and **148** (**297**) and their variants, are basic synthons for innumerable pyranoid products, both obvious and less so. For example, compounds **149** and **151** have been used as starting materials for the preparation of the glycosylating agents **150** and **152**, respectively, used to introduce the monosaccharide components D and C of the enediyne antibiotic calicheamicin g_1^1 (**153**, Eq. **131**). (7) For the synthesis of trichloroacetimidate **150** dihydroxylation followed by selective *O*-methylation of the L-rhamninal-based glycoside **149** were the key steps. For the preparation of intermediate **152** the unsaturated *S*-phenyl 1-thioglycoside **151** was obtained from D-galactal by application of the allylic substitution reaction followed by thiolation with inversion at C-4. Use of the [2.3]-sigmatropic rearrangement of the derived phenylsulfoxide then resulted in a 4-thio-D-allal compound (cf. Eq. **113**). From this, compound **152** was made and coupled with the aromatic moiety of the final product by *S*-arylation, and to monosaccharide A component by way of the unusual hydroxylamino linkage.

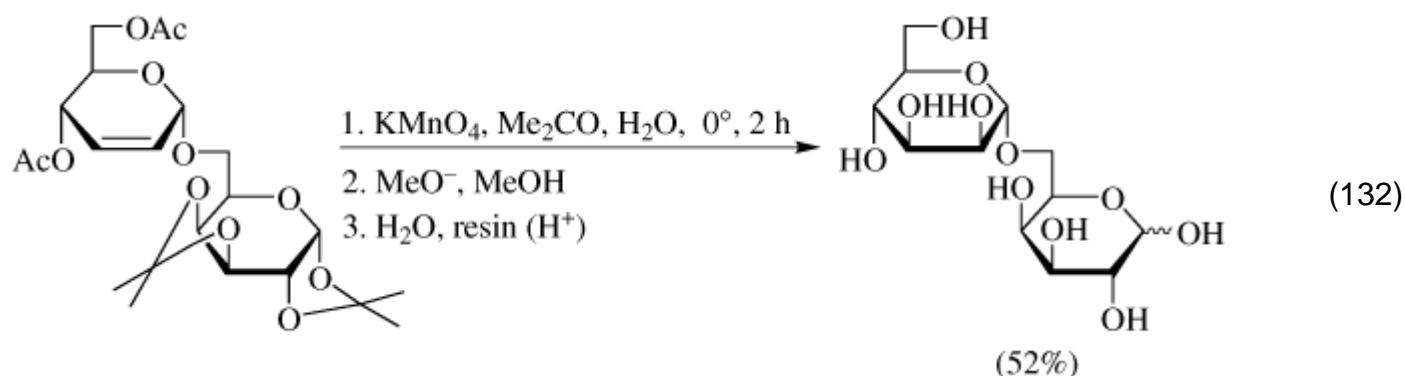


R = dinitrophenyl

(131)

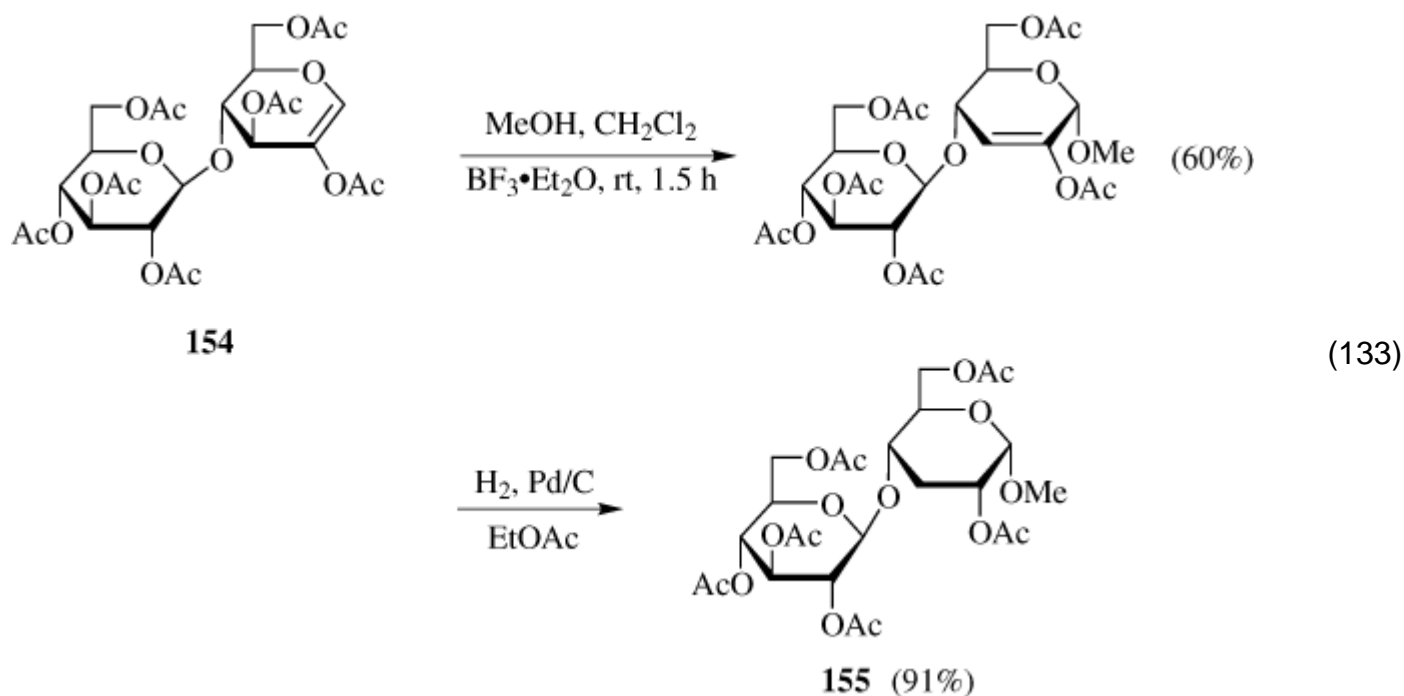


Manipulation of the double bonds of 2,3-unsaturated glycosides can provide means of access to natural and unusual glycosides, disaccharides, and analogs, but this approach to such compounds is surprisingly little used. Thus glycosides (15, 298) and disaccharides (15, 299) containing the biologically important α -D-mannopyranosyl unit are available by cis-hydroxylation of 2,3-dideoxy- α -D-*erythro*-hex-2-enopyranosides. For example, 6-O- α -D-mannopyranosyl-D-galactose (Eq. 132) (15) and 5'-O- α -D-mannopyranosyl ribofuranosyl nucleosides (299) have been made by this approach, and likewise, tri-O-acetyl-L-rhamnal has provided access to 6-deoxy- α -L-talopyranosides and -gulopyranosides by way of 2,3-unsaturated glycosides. (300) Epoxidation of 2,3-unsaturated glycosides derived from D-glucal can lead to α -D-altropyranosyl analogs including disaccharides. (15)

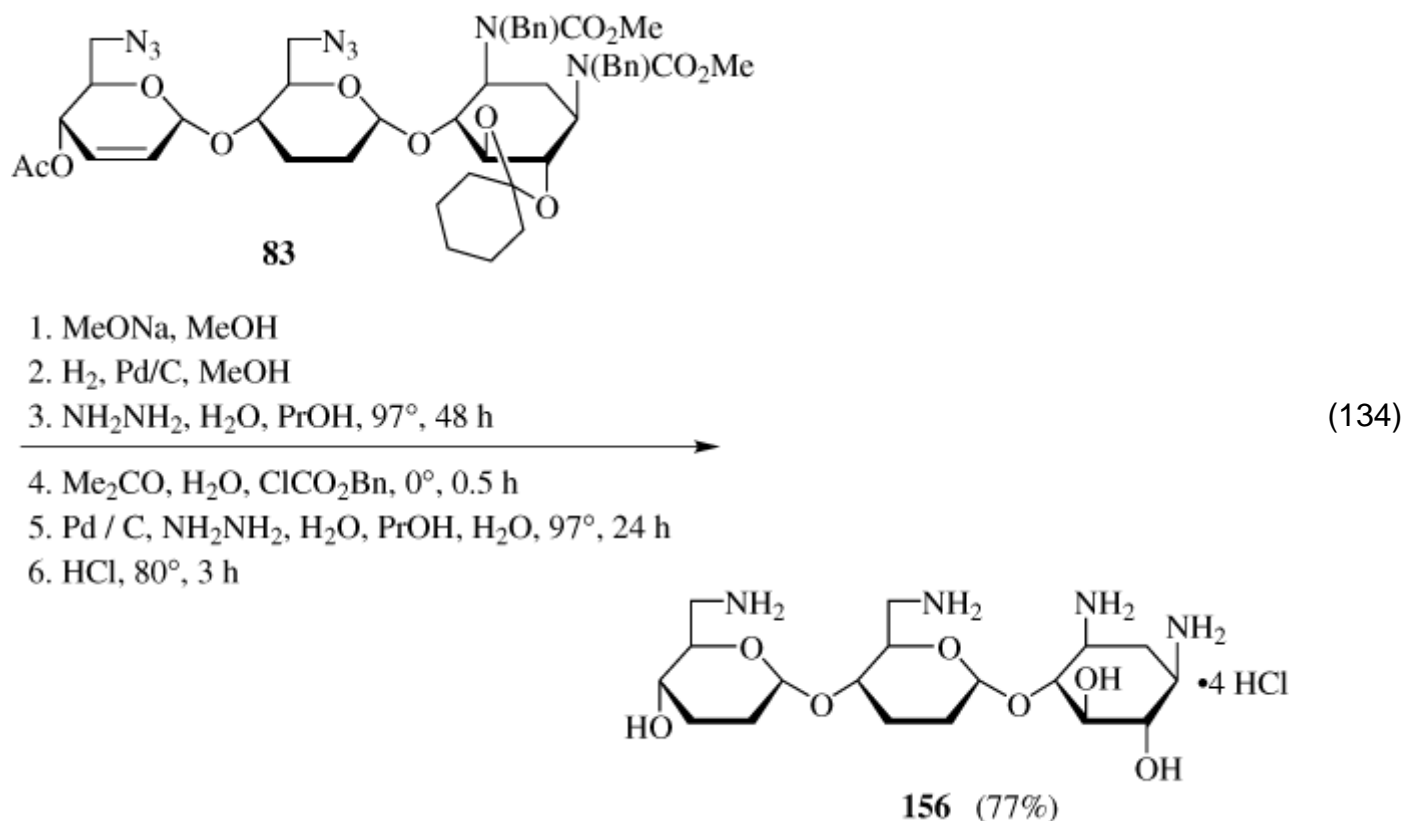


An ingenious cis-hydroxylation of a steroidal 6-deoxy- α -L-*erythro*-hex-2-enopyranoside can be effected by way of a 2-bromo-2-deoxy-3-hydroxy adduct, the bromine atom of which is displaced with inversion of configuration. By this procedure cholestanyl 6-deoxy- α -L-allopyranoside has been made. (301) A further hetero-addition reaction to have been applied is hydroxyamination by which 2,3-unsaturated glycosides derived from tri-O-acetyl-D-glucal can be converted into mixtures of 2-amino-2-deoxy- and 3-amino-3-deoxy- α -D-mannopyranosides. (302) By this approach non-reducing disaccharides containing these amino sugars have been made. (182)

Otherwise, di- or higher saccharides can be manipulated in the reducing units to afford their glycol or hydroxyglycol derivatives, and these can be utilized by way of allylically rearranged derivatives. Eq. 133 illustrates the synthesis of the 3-deoxycellobiosyl glycoside 155 via the hydroxyglycol derivative 154. (303)



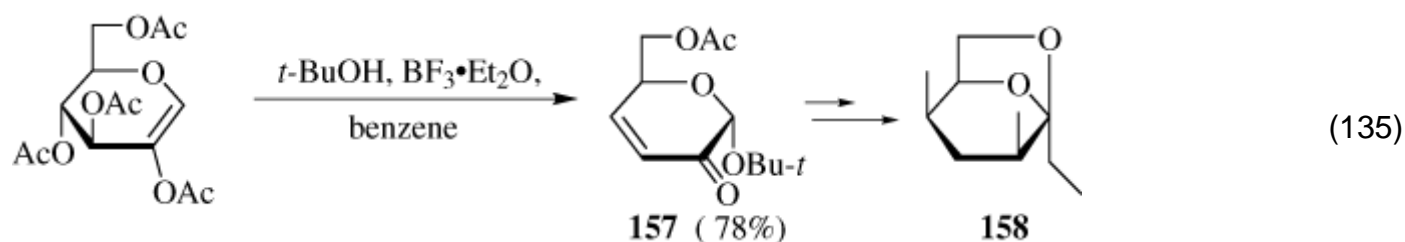
One of the very few iterative applications of the allylic substitution reaction reported is the synthesis of the 2,3:2',3'-tetra-deoxydisaccharide-substituted inosamine derivative **83** from which the apramycin analog **156** is obtainable (Eq. 134). (190) Likewise, examples of the introduction of more than one unsaturated moiety into an acceptor compound are rare; a diglycosylation of a diaminocyclohexane diol has however been carried out in connection with work in the aminoglycoside antibiotic field (Eq. 63). (189)



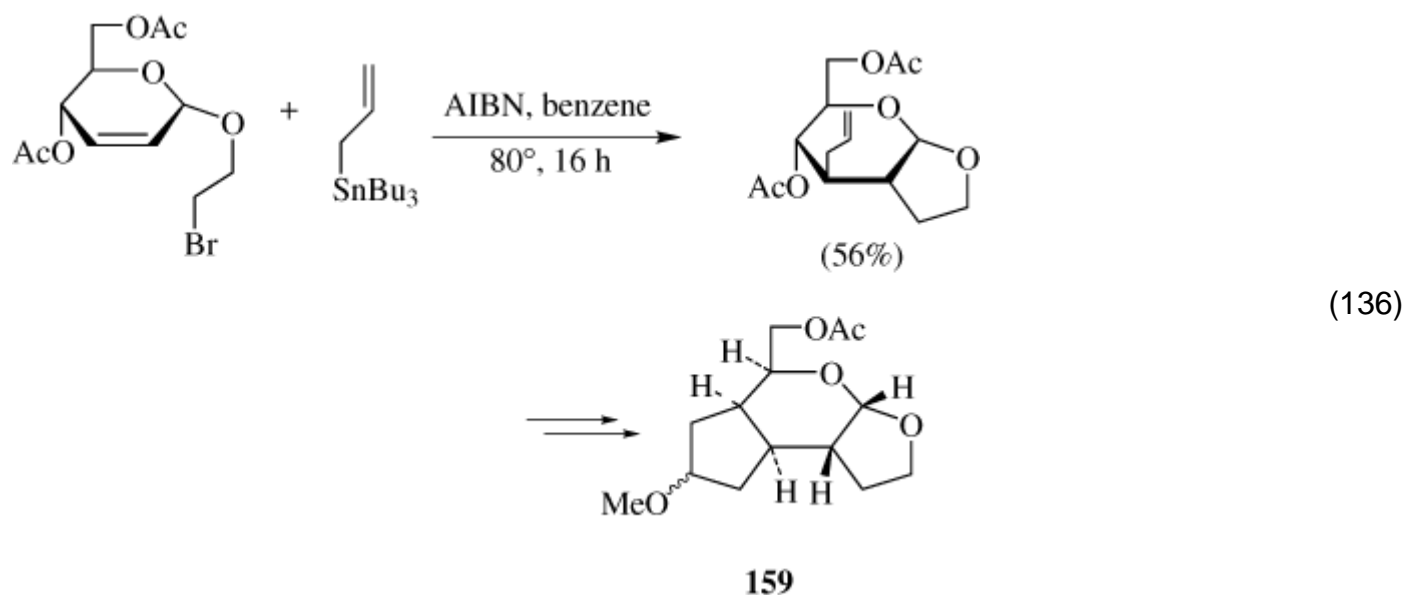
Of at least as much significance as their use in carbohydrate synthesis is the application of the allylic substitution reaction to the provision of suitable compounds for the synthesis of

non-carbohydrates. For example, enone **157** was prepared from tetra-*O*-acetyl-2-hydroxy-D-glucal for use in the synthesis of multistriatin **158** (Eq. 135). (242)

A free radical addition to the double bond of a 2,3-unsaturated glycosyl derivative is the key step in the synthesis of tricyclic compound **159** (Eq. 136). (304)

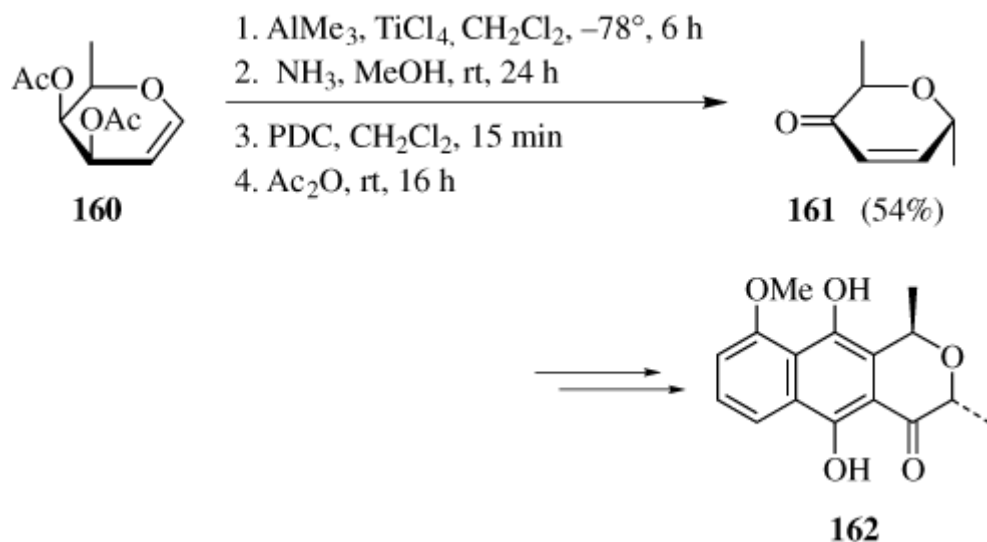


2,3-Unsaturated C-glycosides are of very great significance in the formation of non-carbohydrate compounds from carbohydrates. A simple but elegant example is the synthesis of (–)-hongconin (**162**), a Chinese plant product which exhibits antianginal activity, outlined in Eq. 137. Addition of a lithiated cyanophthalide to



enone **161**, derived from di-*O*-acetyl-6-deoxy-D-galactal (**160**) affords the product in few steps and efficiently. (53)

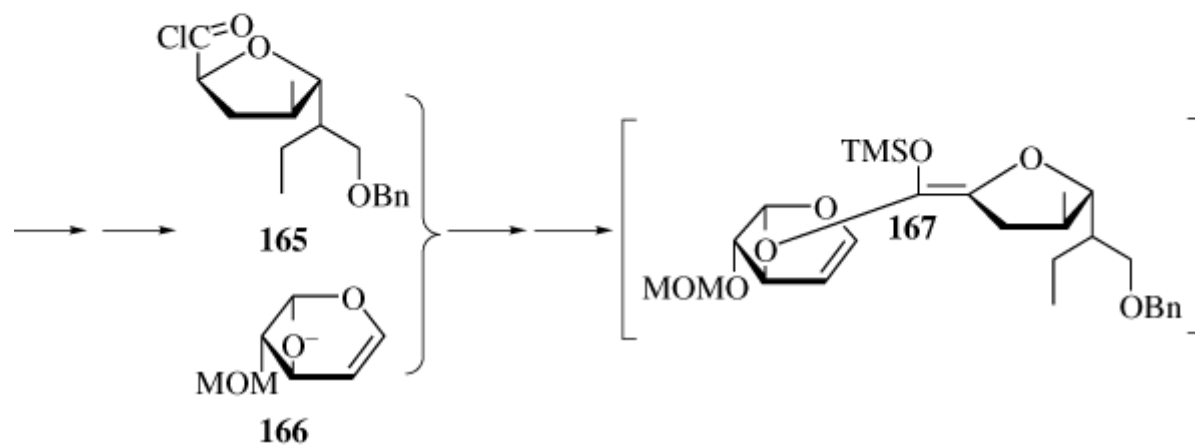
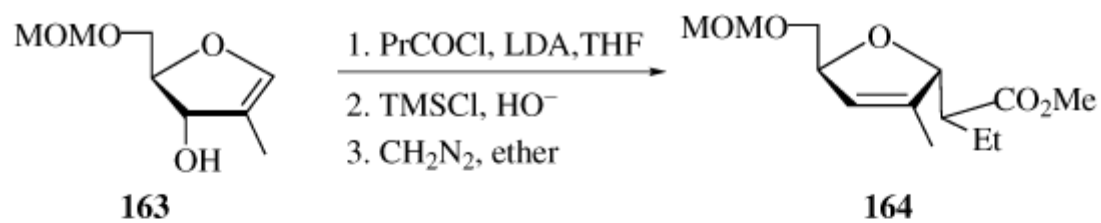
Two applications of ester enolate Claisen rearrangements to the synthesis of the complex natural ionophoric antibiotic lasalocid A (**170**) are shown in Eq. 138. (305) Conversion of glycal **163** into its butanoyl ester, followed by silylation of the ester enolate form and [3.3]-sigmatropic rearrangement gives the allylically rearranged dihydrofuran **164**. By standard methods this is converted into the acyl chloride **165**, which is condensed with the anion **166** of 4-*O*-methoxymethyl-L-gulal to give a disaccharide-like ester from which the silyl enol derivative **167** is produced. This spontaneously undergoes Claisen rearrangement to the acid **168** which has been used to prepare the compound **169** and hence the target compound **170** by aldol coupling with a 4-aryl-2-methylbutanal derivative. (305)



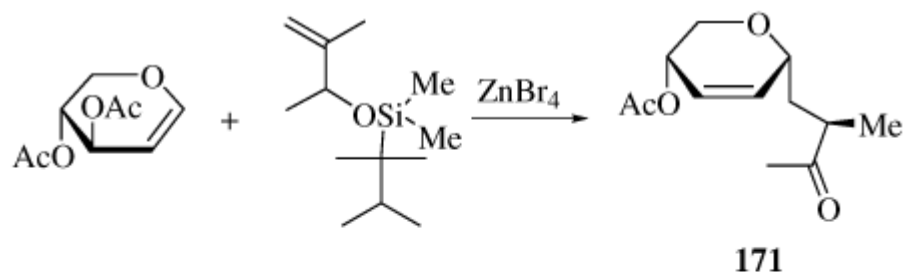
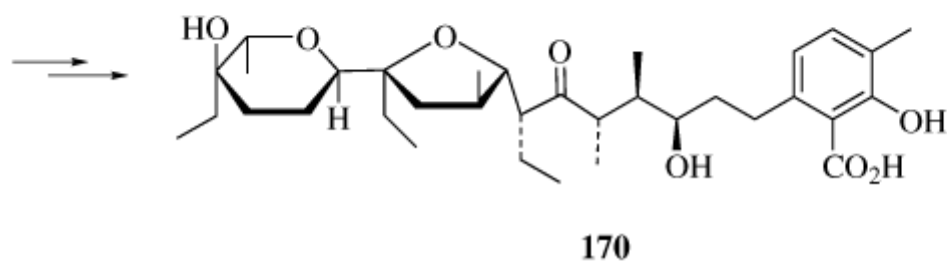
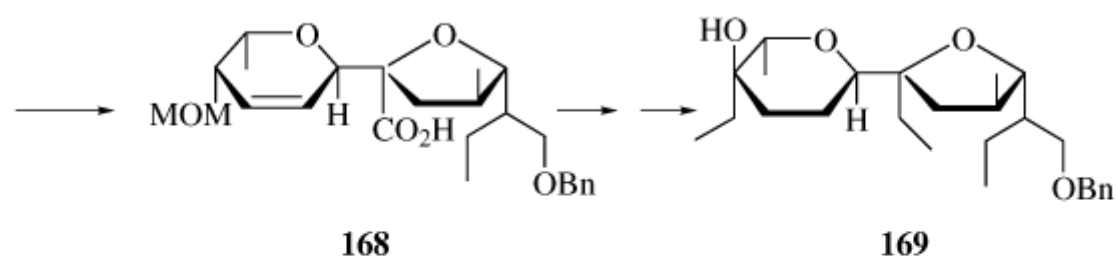
(137)

Intramolecular Diels-Alder reactions represent a further powerful means by which the alkenes formed by the reaction under review can be utilized in synthesis (Eq. 139). The conversion of di-O-acetyl-D-xylal into compound **171** is illustrated, and the side chain is elaborated by coupling with crotonaldehyde. Thermal cyclization of product **172** gives the tricyclic compound **173** as a single diastereomer. (62)

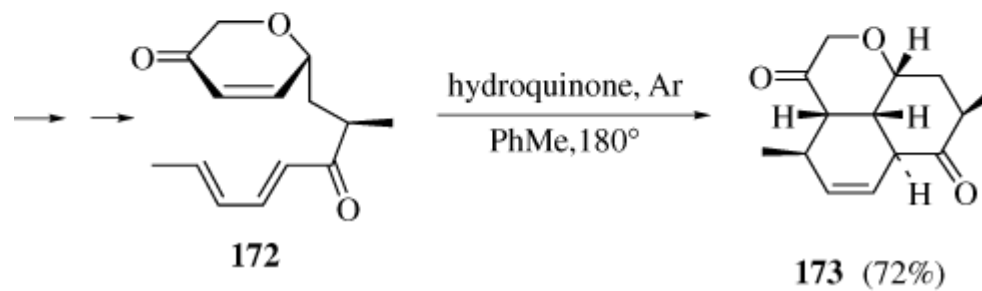
In summary, the reaction under review affords a means of glycosylating a range of nucleophilic species, and the unsaturated carbohydrate moieties so introduced



(138)



(139)



and/or the aglycons can then be manipulated extensively. A large number of O-glycosides have been made from alcohols ranging from the simple to the complex, the latter exemplified by racemic hydroxy-b-lactams which were subsequently resolved; (91) alcohols containing carboranes of interest for ^{10}B neutron capture cancer therapy; (306) an alcohol containing a C_{60} component; (307) anthracyclines to open new routes to the anthracycline antibiotics; (191) and streptamine derivatives for the production of aminoglycoside antibiotics. (189) The use of sugar alcohols as nucleophiles is of particular significance since it leads to higher saccharides.

Unsaturated thioglycosides made by use of the reaction have potential as glycosylating agents that can be activated under neutral conditions. The synthesis of nucleoside analogs is mostly limited to pyranoid derivatives because of the relative lability of furanoid glycols. Exceptions that appear to be potentially valuable for the preparation of natural nucleosides are illustrated in Eq. 105.

A major feature of the reaction is its applicability to the formation of 2,3-unsaturated furanoid and pyranoid C-glycosides both of which are of appreciable value in synthetic work aimed at complex, non-carbohydrate natural products. Intramolecular processes have been of particular value with compounds of this category.

5. Comparison with Other Methods of Making Glycosides, Nucleosides, etc.

The main reaction under consideration, i.e. that involving the intermediacy of unsaturated glycosyl oxocarbenium ions, is a versatile glycosylation procedure by which modified sugar moieties may be bonded to alcohols and phenols, thiols, nitrogen bases through their hetero atoms, and a wide range of compounds via C-C links. To a much lesser extent it is used to make 2,3-unsaturated glycosyl phosphonates and some halides. In one sense it is more limited than conventional glycosylation methods in that the products contain incomplete sugar units which must undergo specific refunctionalization before normal glycosides are obtained. On the other hand, the glycal-based approach is more versatile in that the unsaturated functionality of the products offers wide scope for the application of addition reactions of different kinds as is exemplified in the preceding section. In this way the reaction is unique and is applicable outside the field of carbohydrate chemistry. Its use within the field has been largely limited to work involving non-carbohydrate aglycons, and its potential in oligosaccharide synthesis has yet to be fully exploited.

In an extensive review of the topic of *O*-glycosylation in natural product synthesis (308) it was pointed out that no good general method of *O*-glycosylation exists. The most common procedures involving the use of glycosyl halides, esters, and imidates or various 1-hydroxy or 1,2-anhydro compounds (as well as other glycosides, notably thioglycosides and 4-pentenyl glycosides) all have their limitations. Specific types of glycosides, for example β -mannopyranosides, require specific approaches and, in this respect, the rearrangement process under review may have undeveloped potential since *O*-, *S*-, *N*-, or *C*-linked α -D-mannopyranosides can be produced with high selectivity from the unsaturated α -glycosides directly available from tri-*O*-acetyl-D-glucal. While these are not the most difficult compounds to make by standard glycosylation procedures, there may be potential for approaching the synthesis of specific complex poly- α -mannoses, which are of great biological importance, by way of polyunsaturated oligosaccharides subject to hydroxylation at a late stage in the synthesis.

The α,β selectivity of the glycal *O*-glycosidation reaction using tri-*O*-acetyl-D-glucal is usually near 7:1 in favor of the α -anomer which is not as high as is desirable nor as can be obtained by standard glycosylation methods. This limitation, however, may be ameliorated by use of low temperatures. (59, 60, 100) It is possible to make unsaturated *O*- and *S*-furanosides by way of furanoid glycals, but the chemical fragility of both the starting materials and products makes this approach to saturated furanosides unattractive compared with other methods involving saturated furanoid glycosylating agents. (309) The same applies to the preparation of furanosyl nucleosides although the reaction illustrated in Eq. 105 seems to have potential.

Because of the very extensive range of methods available for making *C*-glycosides (28, 29) it is difficult to make comparisons, but several of the glycal-based methods are efficient and easy to apply. Furthermore, their double bonds provide opportunities for structural adaptation and elaboration. The finding that unsubstituted glycals can be converted into aryl and allyl 2,3-unsaturated *C*-glycosides with almost complete efficiency and selectivity (74) appears to hold particular promise. Also, the stereo-specific means of generating a *C*-linkage at the anomeric center by intramolecular transfer from a C-3 vinyl ether or related unsaturated function in a glycal is very attractive. It can be concluded that the relatively stable unsaturated *C*-glycosidic products derivable directly from furanoid and pyranoid glycals have had appreciable use and retain wide potential as synthons in non-carbohydrate natural product synthesis.

6. Experimental Conditions

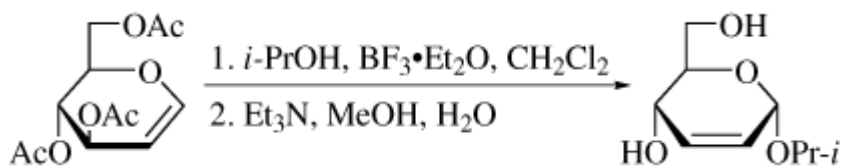
The acid-catalyzed rearrangement processes used to prepare 2,3-unsaturated *O*-glycosides are normally straightforward and simple to apply: the reaction is initiated by addition of the catalyst to a solution of the glycal and alcohol, usually with the latter in slight molar excess, in a solvent such as benzene, dichloromethane, or acetonitrile and at room temperature or below. (14) Reactions proceed faster in acetonitrile, but in it, a,b ratios of products can be lower. (47) The matter of the presence of water in the solvents is worthy of note because, in some circumstances, traces can divert the reaction completely and give saturated products (Eq. 67). (101) On the other hand, tri-*O*-acetyl-D-glucal reacts with *p*-methoxyphenol in aqueous acetonitrile (10% H₂O) with scandium triflate as catalyst to give the 2,3-unsaturated aryl α -*O*-glycoside in near quantitative yield. (77) Normally, however, water should be excluded. It is advisable to monitor the reactions either polarimetrically or by thin layer chromatography.

By use of elevated temperatures the reactions involving alcohols (12) or phenols (13, 177) can proceed without the use of catalysts. They can also be conducted without solvents in sealed tubes, and in these conditions, the use of microwave ovens reduces reaction times for the synthesis of *O*-glycosides to a few minutes. (310, 311)

The normal sequence of mixing of the components usually leads to efficient glycosylations and apparently avoids potential problems associated with the self-condensation reactions that glycal derivatives can undergo in the presence of the Lewis acid catalysts commonly used (Eq. 86). (122) In one example which leads to a 2,3-unsaturated thioglycoside derivative, however, BF₃•Et₂O is added to a solution of tri-*O*-acetyl-D-glucal in dichloromethane at -78° under argon, and the mixture is warmed to 10° at which point the nucleophile, benzenesulfonic acid, is added. A high yield of the 2,3-unsaturated glycosyl sulfone is produced, which is not the case if the pretreatment of the glycal with the catalyst is omitted. (198) It appears that this may represent a special case, but it does show that the glycal remained available to the nucleophile after the pretreatment with catalyst — conceivably in an activated form such as the oxocarbenium ion — and suggests such pretreatment could be advantageous in instances that present difficulties.

For the preparation of *S*- and *C*-glycosides similar conditions to those employed for *O*-glycosides are usually used but, particularly for the *C*-linked products, an extensive range of Lewis acid and organometallic catalysts have been found to be suitable, and frequently reactions are conducted at reduced temperatures. Trimethylsilyl cyanide at 80° converts glycals, both *O*-substituted and unsubstituted, into 2,3-unsaturated glycosyl cyanides without either solvent or catalyst. (213) In the case of *N*-glycosides formed by use of purine or pyrimidine derivatives, protonic acids have been employed, and glycals having good leaving groups at the allylic positions can undergo uncatalyzed condensations with *N*-heterocyclic bases to give 2,3-unsaturated nucleoside derivatives. (40)

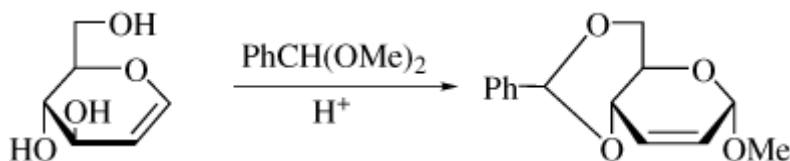
7. Experimental Procedures



7.1.1. Isopropyl 2,3-Dideoxy- α -D-erythro-hex-2-enopyranoside (Reaction of a Glucal Ester and a Simple Alcohol with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as Catalyst, Followed by Deacetylation) (312)

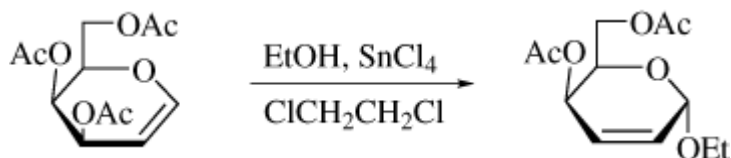
$\text{BF}_3 \cdot \text{Et}_2\text{O}$ (70 mL, 0.57 mol) was added dropwise with stirring under nitrogen over 15 minutes at room temperature to tri-O-acetyl-D-glucal (100 g, 0.36 mol) and 2-propanol (115 mL, 1.7 mol) in CH_2Cl_2 (450 mL). After a further 15 minutes the mixture was poured into ice-cold NaHCO_3 (500 g) in water (3 g/L) with stirring, and stirring was continued for 45 minutes. The organic phase was separated, washed with H_2O , passed through a column containing Na_2SO_4 and silica gel, and concentrated to leave a syrup. This was dissolved in MeOH (2 g/L) and stirred with water (240 mL) and Et_3N (250 mL) at 50° for 14 hours. The mixture was evaporated to dryness in vacuo to leave a white solid which was crystallized by trituration with Et_2O and hexane to give crude crystals which, on recrystallization (Et_2O /hexane) gave the title diol (56 g, 81%), mp $95.5\text{--}97.5^\circ$, $[\alpha]_{\text{D}} + 75.3^\circ$

($c = 1.1$, CHCl_3). $^1\text{H NMR}$ (CDCl_3) δ 1.18 (d, $J = 6$ Hz, 3H), 1.24 (d, $J = 6$ Hz, 3H), 1.50 (1H), 1.82 (brd, $J = 5$ Hz, 1H), 3.6–4.1 (4H), 4.20 (brt, $J = 6$ Hz, 1H), 5.08 (t, $J = 1$ Hz, 1H), 5.71 (ddd, $J = 10, 3, 2$ Hz, 1H), 5.95 (d, $J = 10$ Hz, 1H). Anal. Calcd for $\text{C}_9\text{H}_{16}\text{O}_4$: C, 57.43; H, 8.57. Found: C, 57.44; H, 8.54.



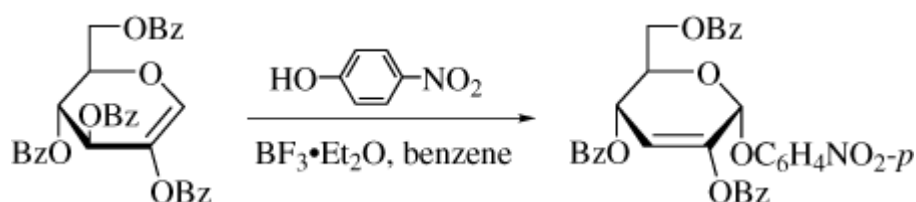
7.1.2. Methyl 4,6-O-Benzylidene-2,3-dideoxy- α -D-erythro-hex-2-enopyranoside (Reaction of D-Glucal and a Dimethyl Acetal with a Protonic Acid as Catalyst) (107)

D-Glucal (0.30 g, 2.0 mmol) was stirred in benzaldehyde dimethylacetal (5 mL, 30 mmol) and *p*-toluenesulfonic acid (0.03 g, 0.18 mmol) was added. The stirring was continued at room temperature for 15 minutes, hexane (8 mL) was added and the solution was heated under reflux until the methanol had been removed by azeotropic distillation (Dean-Stark apparatus). After cooling, excess saturated aqueous NaHCO_3 was added and the volatile liquids were removed under reduced pressure. Water (5×10 mL) was added and successively removed under reduced pressure. The residue was extracted with CH_2Cl_2 (3×30 mL) and the combined extracts were washed with water (2×15 mL) and dried (Na_2SO_4) and the solvent was removed in vacuo to give the title acetal (0.45 g, 90%), mp 117° , $[\alpha]_{\text{D}} + 120^\circ$ ($c = 1.1$, CHCl_3). $^1\text{H NMR}$ [60 MHz, $\text{Py}(\text{D}_5)$] δ 4.30 (m, 1H), 4.30 (m, 1H), 4.95 (ddd, $J = <0.3, 1.5, 2.2$ Hz, 1H), 5.77 (dt, $J = 2.2, 10$ Hz, 1H), 6.20 (dd, $J = <0.3, 10$ Hz, 1H). (313) Anal. Calcd for $\text{C}_{14}\text{H}_{16}\text{O}_4$: C, 67.7; H, 6.50. Found: C, 67.9; H, 6.37. (314)



7.1.3. Ethyl 4,6-Di-O-acetyl-2,3-dideoxy- α -D-threo-hex-2-enopyranoside (Reaction of a Galactal Ester and a Simple Alcohol with SnCl_4 as Catalyst) (45)

Tri-O-acetyl-D-galactal (0.27 g, 1 mmol) and ethanol (0.092 g, 1 mmol) in 1,2-dichloroethane (10 mL) were treated with 1,2-dichloroethane (1 mL) containing SnCl_4 (0.075 g, 0.3 mmol). After 1 hour at room temperature, triethylamine and chloroform (50 mL) were added to the yellow-brown solution and the mixture was washed with water (2 x), dried (MgSO_4) and concentrated. The oily residue was passed through a column of silica gel (10 g) to give the title compound (0.237 g, 92%), bp $140^\circ/0.6$ mm, mp $19.5\text{--}20.5^\circ$, $[\alpha]_D - 171^\circ$ ($c = 1$, CH_2Cl_2). ^1H NMR (100 MHz, CDCl_3) δ 1.7, 1.8 (2 s, 6H), 4.3 (m, 3H), 4.85 (d, $J = 2.7$ Hz, 1H), 4.95 (m, 1H), 5.77 (ddd, $J = 0.9, 2.7, 10.0$ Hz, 1H), 5.98 (dd, $J = 5.4, 10.0$ Hz, 1H). Anal. Calcd for $\text{C}_{12}\text{H}_{18}\text{O}_6$: C, 55.8; H, 7.0. Found: C, 55.6; H, 7.2.



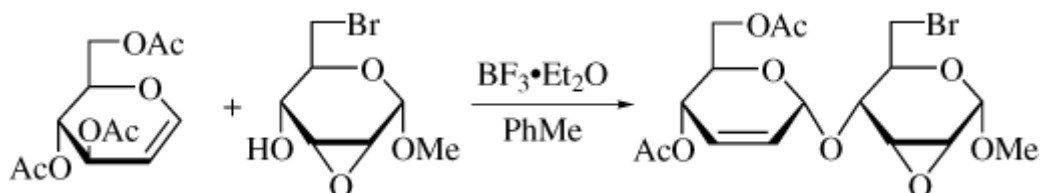
7.1.4. *p*-Nitrophenyl 2,4,6-Tri-O-benzoyl-3-deoxy- α -D-erythro-hex-2-enopyranoside (Reaction of a Hydroxyglycal Ester and a Phenol with $\text{BF}_3\text{Et}_2\text{O}$ as Catalyst) (241)

1,5-Anhydro-2,3,4,6-tetra-O-benzoyl-D-arabino-hex-1-enitol (0.58 g, 1 mmol) and *p*-nitrophenol (0.14 g, 1 mmol) were dissolved in benzene (10 mL) and $\text{BF}_3\text{Et}_2\text{O}$ (0.5 mL, 2.7 mmol) was added with stirring. After 15 minutes at room temperature anhydrous Na_2CO_3 was added, and after stirring for 2 hours, the solids and solvent were removed by filtration and distillation. Crystallization of the residue from ethanol gave the title glycoside (0.42 g, 71%), mp $187\text{--}188^\circ$, $[\alpha]_D + 164^\circ$ ($c = 1.0$, CHCl_3). ^1H NMR (60 MHz, CDCl_3) δ 5.98 (dd, $J = 1.5, 9$ Hz, 1H), 6.13 (s, 1H), 6.30 (d, $J = 1.5$ Hz, 1H). Anal. Calcd for $\text{C}_{33}\text{H}_{25}\text{NO}_{10}$: C, 66.6; H, 4.2; N, 2.35. Found: C, 66.6; H, 4.4; N, 2.35.



7.1.5. 4-O-Acetyl-1,6-anhydro-2,3-dideoxy- β -D-erythro-hex-2-enopyranose (Intramolecular Substitution with Allylic Rearrangement with $\text{BF}_3\text{Et}_2\text{O}$ as Catalyst) (104)

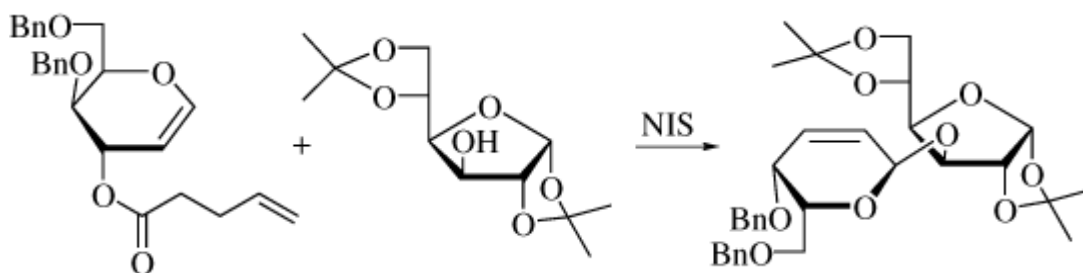
3,4-Di-O-acetyl-D-glucal (2.3 g, 10 mmol) in dry CH_2Cl_2 (35 mL) at 0° was treated with $\text{BF}_3\text{Et}_2\text{O}$ (0.12 mL, 1 mmol) and the solution was brought to room temperature over 1 hour. K_2CO_3 (1 g) was added, the mixture was stirred for 30 minutes, diluted with CH_2Cl_2 (200 mL), washed with water, dried (Na_2SO_4) and the solvent was evaporated. The residue was passed through a short column of SiO_2 (40 g) with hexane — EtOAc (4:1) to give the title compound (1.45 g, 85%) as a syrup, $[\alpha]_D + 190^\circ$ ($c = 1$, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ 3.45 (dd, $J = 1.6, 8.0$ Hz, 1H), 3.92 (dd, $J = 6.5, 8.0$ Hz, 1H), 4.65–4.9 (m, 2H), 5.5 (dd, $J = 0.8, 3.4$ Hz, 1H), 5.71 (dddd, $J = 0.8, 1.7, 4.5, 9.5$ Hz, 1H), 6.15 (ddd, $J = 0.9, 3.4, 9.5$ Hz, 1H). Anal. Calcd for $\text{C}_8\text{H}_{10}\text{O}_4$: C, 56.5; H, 5.9. Found: C, 56.1; H, 5.8.



7.1.6. Methyl

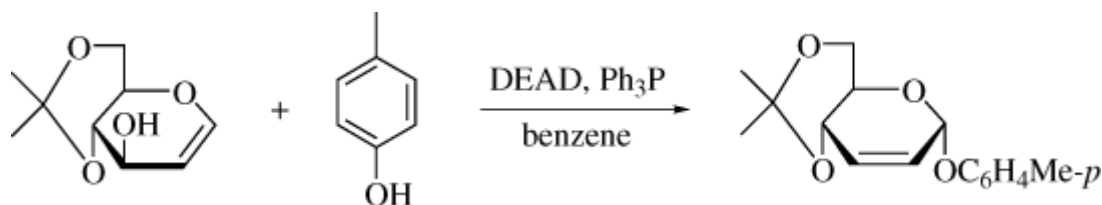
4-O-(4,6-Di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranosyl)-2,3-anhydro-6-bromo-6-deoxy (Reaction of a Glucal Ester and a Carbohydrate Alcohol with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as Catalyst) (187)

To tri-O-acetyl-D-glucal (5.52 g, 20.2 mmol) and methyl 2,3-anhydro-6-bromo-6-deoxy-α-D-allopyranoside (4.34 g, 18.2 mmol) in toluene (250 mL) was added at room temperature $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.15 mL, 45%, 0.4 mmol) and the solution was left for 1.5 hours. Na_2CO_3 was added and the mixture was stirred for 1 hour and filtered. The filtrate was taken to dryness and the residue was crystallized from ether to give the title disaccharide (5.8 g, 71%), mp 148–149°, $[\alpha]_{\text{D}} + 162.9^\circ$ (c , 0.9, CHCl_3). ^1H NMR (270 MHz, CDCl_3) δ 2.11 (s, 6H), 3.50 (s, 3H), 3.57 (dd, J = 5.6, 11 Hz, 1H), 3.59 (m, 2H), 3.70 (dd, J = 2.4, 11 Hz, 1H), 3.95 (ddd, J = 2.4, 5.6, 9.2 Hz, 1H), 4.06 (ddd, J = 1.0, 6.7, 9.7 Hz, 1H), 4.15 (dd, J = 0.7, 9.2 Hz, 1H), 4.25 (m, 1H), 4.27 (m, 1H), 4.96 (d, J = 1 Hz, 1H), 5.34 (ddd, J = 1.5, 1.5, 9.7 Hz, 1H), 5.43 (m, J = 1.2, 2.8, 1.5 Hz, 1H), 5.85 (ddd, J = 1.9, 2.8, 10.3 Hz, 1H), 5.94 (dt, J = 1.2, 1.5, 10.3 Hz, 1H). Anal. Calcd for $\text{C}_{17}\text{H}_{23}\text{BrO}_9$: C, 45.25; H, 5.14; Br, 17.71. Found: C, 45.47; H, 5.18; Br, 17.92.



7.1.7. 3-O-(4,6-Di-O-benzyl-2,3-dideoxy-α-D-threo-hex-2-enopyranosyl)-1,2:5,6-di-O-isopropylidene [A Displacement Reaction Dependent on Activation of a 3-O-(4-pentenyl)] (36)

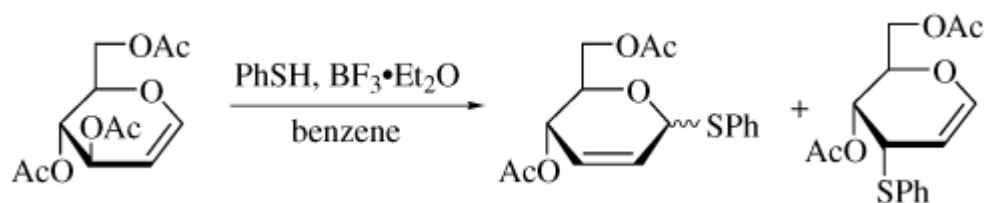
4,6-Di-O-benzyl-3-O-(4-pentenyl)-D-gulal (1 equivalent) and 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (1.1 equivalent) were azeotropically dried with toluene and kept under vacuum for 1 hour. The resulting mixture was dissolved in CH_2Cl_2 (1 mL/10 mmol) under argon and powdered molecular sieves were added. *N*-Iodosuccinimide (1.6 equivalents) was added and when the reaction was complete (TLC) the solution was diluted with CH_2Cl_2 and the solids were removed by filtration. The filtrate was washed with aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (10%), saturated aqueous NaHCO_3 , saturated aqueous NaCl , and water, dried and the residue was purified by flash chromatography. The title compound (65%) was obtained as an oil, $[\alpha]_{\text{D}} - 103.9^\circ$ (c = 0.6, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ 1.12 (s, 3H), 1.29 (s, 3H), 1.37 (s, 3H), 1.43 (s, 3H), 3.67 (dd, J = 2.7, 5.2 Hz, 1H), 3.75 (d, J = 5.9 Hz, 2H), 3.93 (dd, J = 5.4, 8.4 Hz, 1H), 4.05 (dd, J = 5.7, 8.4 Hz, 1H), 4.08 (d, J = 2.7 Hz, 1H), 4.19 (m, 2H), 4.27 (d, J = 2.7 Hz, 1H), 4.55 (m, 4H), 4.77 (d, J = 3.6 Hz, 1H), 5.27 (d, J = 3.0 Hz, 1H), 5.80 (d, J = 3.6 Hz, 1H), 5.94 (dd, J = 3.0, 10.2 Hz, 1H), 6.09 (dd, J = 5.2, 10.2 Hz, 1H). Anal. Calcd for $\text{C}_{32}\text{H}_{40}\text{O}_9$: C, 67.6; H, 7.1. Found: C, 67.7; H, 7.2.



7.1.8. *p*-Tolyl 2,3-Dideoxy-4,6-O-isopropylidene- α -D-erythro-hex-2-enopyranoside (Reaction of a glycal Having an Unprotected Allylic Hydroxyl Group under Mitsunobu Conditions) (110)

DEAD (0.57 g, 3.3 mmol) in benzene (2 mL) was added dropwise with stirring over 10 minutes to a solution of 4,6-O-isopropylidene-D-glucal (0.56 g, 3 mmol), triphenylphosphine (0.78 g, 3 mmol), and *p*-cresol (0.32 g, 3 mmol) in dry benzene (10 mL). Stirring was continued for 5 hours. The precipitated diethyl hydrazinedicarboxylate was removed by filtration, the filtrate was washed with NaOH (20%, aqueous), then with water and dried, filtered and the solvent was evaporated. Column chromatography (SiO₂, hexane-ethyl acetate 9:1) gave the title glycoside and its β -anomer (0.66 g, 80%, α , β 4:1). Preparative HPLC by use of the Shimadzu LC 8A instrument (MeOH, H₂O 8:2)

afforded a sample of the pure α -compound, mp 121°, $[\alpha]_D + 133.3^\circ$ ($c = 0.17$, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 1.40 (s, 3H), 1.50 (s, 3H), 2.28 (s, 3H), 3.73–3.90 (m, 3H), 4.25 (d, $J = 7.3$ Hz, 1H), 5.60 (br s, 1H), 5.83 (dt, $J = 2.4, 10.2$ Hz, 1H), 6.12 (d, $J = 10.2$ Hz, 1H), 6.93 (d, $J = 9.2$ Hz, 2H), 7.08 (d, $J = 9.2$ Hz, 2H). HRMS: $[M + H]^+$ calcd for C₁₆H₂₀O₄, 276.13616; found, 276.13149.



7.1.9. Phenyl 4,6-Di-O-acetyl-2,3-dideoxy-1-thio- α -D-erythro-hex-2-enopyranoside (and Isomers) (Reaction of a Glucal Ester and Thiophenol with BF₃·Et₂O as Catalyst) (195)

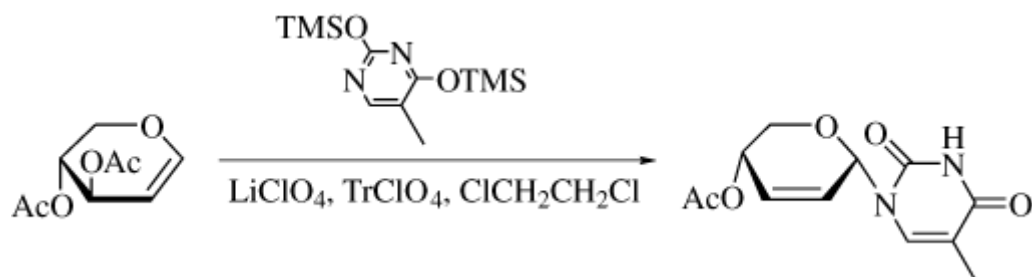
Thiophenol (10 mL, 98 mmol) and BF₃·Et₂O (0.5 mL, 4 mmol) were added in turn to a stirred solution of tri-O-acetyl-D-glucal (21.8 g, 80 mmol) in benzene (50 mL) at 20°. Stirring was continued for 10 minutes and the solution was washed with aqueous Na₂CO₃, followed by water, and was then dried (MgSO₄). Removal of the solvent gave a syrup which solidified. A portion (1.02 g) was separated by radial chromatography to give (in the order of elution)

4,6-di-O-acetyl-1,5-anhydro-2-deoxy-3-S-phenyl-3-thio-D-ribo-hex-1-enitol (57 mg, 6%), mp 79–80°, $[\alpha]_D + 279^\circ$ ($c = 1$, CHCl₃), phenyl

4,6-di-O-acetyl-2,3-dideoxy-1-thio- α -D-erythro-hex-2-enopyranoside (0.69 g, 71%), mp 64.5–66°, $[\alpha]_D + 366^\circ$ ($c = 1$, CHCl₃) and phenyl

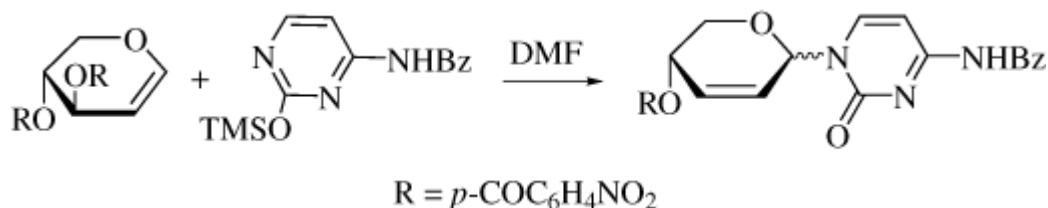
4,6-di-O-acetyl-2,3-dideoxy-1-thio- β -D-erythro-hex-2-enopyranoside (88 mg, 9%), $[\alpha]_D + 104^\circ$ ($c = 1$,

CHCl₃). For the title α -glycoside: ¹H NMR (200 MHz in CDCl₃) δ 4.22 (dd, $J = 2.7, 12.1$ Hz, 1H), 4.31 (dd, $J = 5.6, 12.1$ Hz, 1H), 4.48 (ddd, $J = 2.7, 5.6, 9.5$ Hz, 1H), 5.39 (dt, $J = 1.9, 9.5$ Hz, 1H), 5.77 (dt, $J = 1.8, 3.2$ Hz, 1H), 5.87 (dt, $J = 1.8, 10.1$ Hz, 1H), 6.08 (ddd, $J = 1.9, 3.2, 10.1$ Hz, 1H). Anal. Calcd for C₁₆H₁₈O₅S : C, 59.6; H, 5.6; S, 9.9. Found: C, 59.6; H, 5.6; S, 10.0. The remaining partly crystalline product was placed on an unglazed porcelain tile to give the α -glycoside (16.1 g, 65%) after crystallization from CH₂Cl₂ and light petroleum.



7.1.10. 1-(4-O-Acetyl-2,3-dideoxy- α -D-glycero-pent-2-enopyranosyl)thymine (Reaction of a Xylal Ester and a Silylated Pyrimidine with Lithium Perchlorate and Trityl Perchlorate as Catalysts) (70)

To a solution of bis(trimethylsilyloxy)thymine (0.175 g, 1.4 mmol) and di-O-acetyl-D-xylal (0.20 g, 1 mmol) in 1,2-dichloroethane (10 mL) were added lithium perchlorate (0.106 g, 0.5 mmol) and trityl perchlorate (0.342 g, 1 mmol) and the mixture was stirred for 10 minutes at room temperature and neutralized with aqueous NaHCO_3 , washed with water, dried, and concentrated. Flash chromatography on silica gel 60 F₂₅₄ (230–400 mesh) with ether gave the title compound (0.20 g, 75%), mp 175°, $[\alpha]_D + 175^\circ$ ($c = 0.1$, MeOH). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 1.9 (s, 3H), 2.1 (s, 3H), 3.81 (dd, $J = 6.4, 11.9$ Hz, 1H), 4.15 (dd, $J = 4.8, 11.8$ Hz, 1H), 5.36 (m, 1H), 5.88 (dd, $J = 1.8, 10.3$ Hz, 1H), 6.34 (dd, $J = 2.7, 10$ Hz, 1H), 6.41 (d, $J = 2$ Hz, 1H), 7.04 (s, 1H), 8.35 (brs, 1H). Anal. Calcd for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_5$: C, 54.1; H, 5.3; N, 10.5. Found: C, 53.8; H, 5.2; N, 10.4.



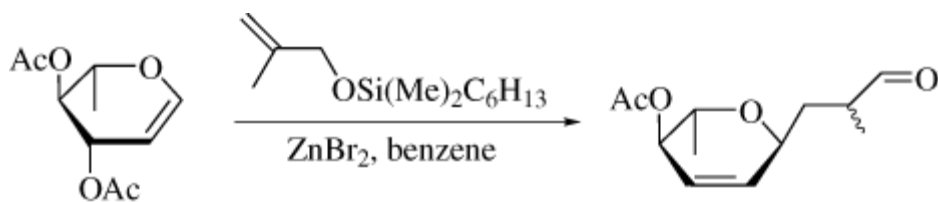
7.1.11. 1-[4-O-(*p*-Nitrobenzoyl)-2,3-dideoxy- α,β -D-glycero-pent-2-enopyranosyl]- N^4 -benzoylcytosine (A Substitution Reaction of a Xylal Ester under Neutral Conditions) (40)

N^4 -Benzoylcytosine (6.3 g, 29.3 mmol) in hexamethyldisilazane (70 mL) and a catalytic amount of $(\text{NH}_4)_2\text{SO}_4$ were heated at boiling point overnight. After cooling to room temperature DMF (200 mL) was added and the volatiles were evaporated. DMF (200 mL) was added to the solid residue and the mixture was heated to 190°. 3,4-Bis-O-(*p*-nitrobenzoyl)-D-xylal (12 g, 29 mmol) was added and after 15 minutes heating was discontinued. Cooling to room temperature gave a precipitate (1.1 g) that was removed by filtration, and the DMF was removed by evaporation. Addition of CHCl_3 (300 mL) to the residue caused precipitation of the title compound (*b*-anomer). Some uracil nucleoside also precipitated at this point and was discarded. The organic solution was washed with saturated aqueous NaHCO_3 and then water, then dried and evaporated to dryness to give a dark brown syrup. Flash chromatography (gradient EtOAc/toluene 3:1 to 4:1 to EtOAc) gave more of the *b*-title compound (total 5.22 g, 39%) and the *a*-anomer (4.62 g, 34%).

b-Anomer: mp 250° (dec.) (from dioxane-MeOH). $^1\text{H NMR}$ (200, 360 or 500 MHz, $\text{DMSO}-d_6$) δ 4.04 (dd, $J = 2.9, 13.6$ Hz, 1H), 4.15 (dd, $J = 3.3, 13.6$ Hz, 1H), 5.51 (q, $J = 3.7$ Hz, 1H), 6.27 (dd, $J = 2.9, 10.3$ Hz, 1H), 6.58–6.49 (m, 1.5H), 6.60 (dd, $J = 1.4, 4.3$ Hz, 0.5H), 8.42–7.5 (m, 11H), 11.40 (s, 1H). HRMS: $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{19}\text{N}_4\text{O}_7$, 463.1254; found, 463.1238.

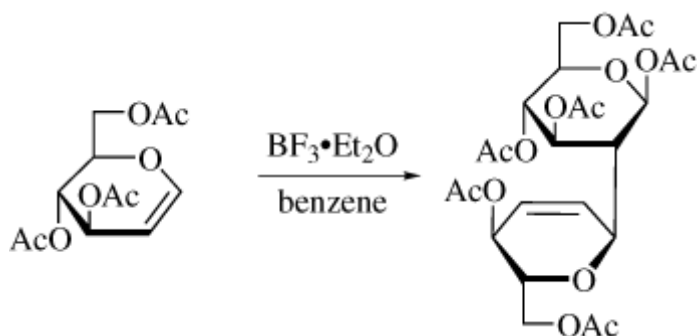
a-Anomer: mp 171–172° (from dioxane-MeOH). $^1\text{H NMR}$ (200, 360, 500 MHz, $\text{DMSO}-d_6$) δ 4.20 (2 d, $J = 1.9, 2.7, 13.2$ Hz, 2H), 5.42 (br m, $J = 10.9$ Hz, 1H), 6.25 (dd, $J = 11.3$ Hz, 1H), 6.59–6.44

(m, 2H), 7.39–8.44 (3 m, 11H), 11.38 (s, 1H). HRMS: $[M + H]^+$ calcd. for $C_{23}H_{19}N_4O_7$, 463.1254; found, 463.1249.



7.1.12. 7-O-Acetyl-4,8-anhydro-2-C-methyl-2,3,5,6,9-pentadeoxy-L-*allo/altro*-non-5-enose (Reaction of a Rhamnol Ester and an Allyl Silyl Ether with $ZnBr_2$ as Catalyst) (48)

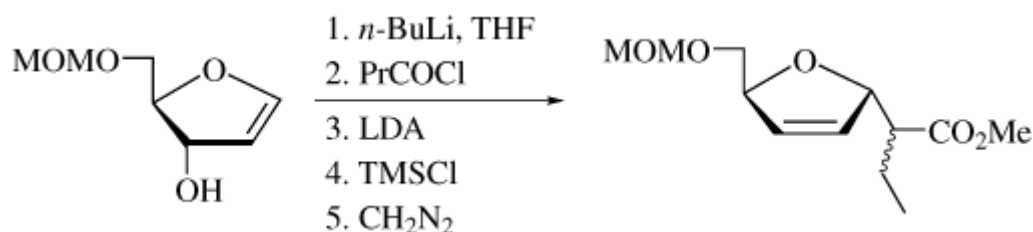
A solution of di-O-acetyl-L-rhamnol (8.56 g, 40 mmol) and 1-[(thexyldimethylsilyloxy)-2-methyl-2-propene] (10.26 g, 45 mmol) in CH_2Cl_2 (20 mL) was added dropwise at 0° over 2 hours to CH_2Cl_2 (25 mL) and $ZnBr_2$ (4.5 g, 40 mmol). The resulting brown suspension was stirred for 30 minutes and poured into saturated aqueous Na_2HPO_4 (25 mL) and ether (50 mL). The organic layer was separated, and the aqueous phase washed successively with saturated aqueous $NaHCO_3$ (25 mL) and $NaCl$ (25 mL) and dried ($MgSO_4$). Removal of the solvent and flash chromatography (pentane/ether, 9:1) gave the title compounds (7.93 g, 82%), $[a]_D - 88^\circ$ ($c = 0.1$, $CHCl_3$). 1H NMR (300 MHz, $CDCl_3$) δ 1.15 (d, $J = 7$ Hz, 3H), 1.2 (d, $J = 7$ Hz, 3H), 1.42 (ddd, $J = 3.3, 7.4, 14.3$ Hz, 1H), 2.08 (s, 3H), 2.15 (ddd, $J = 6.0, 10.3, 14.3$ Hz, 1H), 2.6 (m, 1H), 3.83 (dq, $J = 5.4, 7$ Hz, 1H), 4.25 (m, 1H), 4.9 (m, 1H), 5.77–5.87 (m, 2H), 9.67 (d, $J = 1.7$ Hz, 1H). The 2,4-dinitrophenyl-hydrazone had mp 138° . Anal. Calcd for $C_{18}H_{22}N_4O_7$: C, 53.20; H, 5.42; N, 13.79. Found: C, 53.64; H, 5.47; N, 13.78.



7.1.13. 1,3,4,6-Tetra-O-acetyl-2-C-(4,6-di-O-acetyl-2,3-dideoxy- α -D-erythro-hex-2-enopyranosyl) (Dimerization of Tri-O-acetyl-D-glucal with $BF_3 \cdot Et_2O$ or $AcClO_4$ as Catalyst) (122, 228)

tri-O-acetyl-D-glucal (10 g, 37 mmol) in dry benzene (100 mL) was treated with $BF_3 \cdot Et_2O$ (2.0 mL), which caused the immediate development of a red-brown color that changed to deep purple after 15 minutes. Na_2CO_3 (10 g) was then added and during the subsequent stirring the color was discharged. Filtration and evaporation of the solvent gave a syrup which on trituration with methanol deposited a crystalline solid (4.0 g, 40%), mp 180 – 193° . Fractional crystallization from ethyl acetate afforded the pure title compound (1.0 g, 10%), mp 205 – 206° , $[a]_D + 88^\circ$ ($c = 1$, $CHCl_3$). 1H NMR (100 MHz, $CDCl_3$) δ 2.15 (ddd, $J = 1.6, 9.5, 11.0$ Hz, 1H), 4.38 (ddd, $J = 1.2, 1.6, 2.0$ Hz, 1H), 4.70 (ddd, $J = 0.3, 1.7, 5.2$ Hz, 1H), 4.92 (t, $J = 9.5$ Hz, 1H), 5.38 (br t, $J = 9.1, 11.0$ Hz, 1H), 5.76 (ddd, $J = 2.0, 5.2, 10.6$ Hz, 1H), 5.84 (d, $J = 9.5$ Hz, 1H), 5.94 (dd, $J = 0.3, 10.6$ Hz, 1H). Anal. Calcd for $C_{24}H_{32}O_{14}$: C, 52.9; H, 5.9. Found: C, 52.6; H, 6.0. (122)

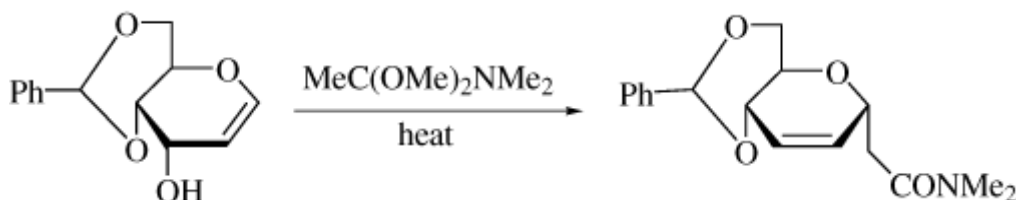
Use of acetyl perchlorate in CH_2Cl_2 at -76° for 20 hours results in the isolation of the title compound together with its C-1 α -anomer (61%, a:b = 3:2). (228)



7.1.14. Methyl

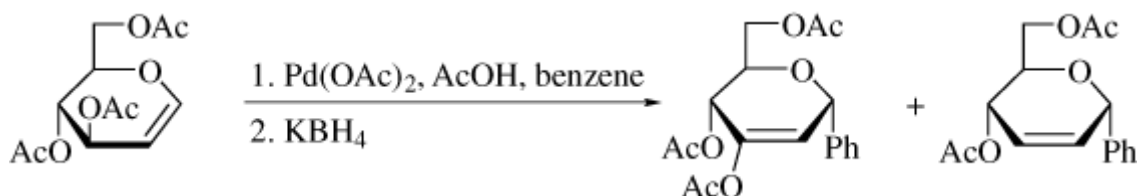
3,6-Anhydro-2,4,5-trideoxy-2-C-ethyl-7-O-methoxymethyl-D,L-xylo/lyxo-hept-4-enonates (C-Furanosides by Silyl Enol Ester Claisen Rearrangement) (263)

n-Butyllithium in hexane (0.35 mL, 2.41 M, 0.84 mmol) followed after 5 minutes by butanoyl chloride (87 μ L, 0.84 mmol) were added to a stirred solution of 1,4-anhydro-2-deoxy-5-methoxymethyl-D,L-*erythro*-pent-1-enitol (138 mg, 0.70 mmol) in dry THF (2.8 mL) at -78° under argon. After 5 minutes at 0° the mixture was added under argon to a stirred solution of LDA (0.94 mmol) in dry THF at -78° . After a further 10 minutes the mixture was treated with TMSCl (0.24 mL, 1.4 mmol) and Et₃N (0.06 mL). After a further 10 minutes at -78° and 1 hour at room temperature the mixture was diluted with aqueous NaOH (10 mL, 0.5 M) and washed with ether (2 mL). The organic phase was extracted with the same alkaline solution (3 \times 10 mL) and the combined aqueous extracts were washed with ether (20 mL) and acidified to pH 2. Ether extraction and drying of the extract (MgSO₄) gave the distereomeric acids (118 mg, 73%) which were treated with CH₂N₂ in ether. The resulting title methyl esters were chromatographed on SiO₂ (ether-petroleum ether, 1:1.5) to give an oil. ¹H NMR δ 0.89 (t, *J* = 6 Hz, 3H), 1.52 (m, 2H), 3.33 (s, 3H), 3.53 (d, *J* = 5 Hz, 2H), 3.72 (s, 3H), 4.62 (s, 2H), 5.92 (m, 2H). Anal. Calcd for C₁₂H₂₀O₅: C, 59.0; H, 8.25. Found: C, 58.9; H, 8.2.



7.1.15. 3,7-Anhydro-6,8-O-benzylidene-2,4,5-trideoxy-N,N-dimethyl-D-arabino-oct-4-enonamide (C-Pyranosides by Thermal Eschenmoser Rearrangement) (24)

4,6-*O*-Benzylidene-D-allal (2.34 g, 10.0 mmol) and *N,N*-dimethylacetamide dimethyl acetal (3.0 g, 20 mmol) were heated in dry refluxing xylene (200 mL) under argon for 2 hours with a CaCl₂-filled Soxhlet extractor as a methanol trap. Evaporation of the solvent gave the title compound (3.0 g, 85%) in crystalline form, mp 108.5–109° (from petroleum ether), [α]_D + 56.0° (*c* = 0.85, MeOH). ¹H NMR (220 MHz, CDCl₃) δ 2.52 (dd, *J* = 5.5, 14.5 Hz, 1H), 2.85 (dd, *J* = 7.5, 14.5 Hz, 1H), 2.90, 2.95 (2 s, 6H), 3.53 (m, 1H), 3.80 (t, *J* = 10 Hz, 1H), 4.84 (m, 1H), 5.54 (s, 1H), 5.78 (dt, *J* = 2, 2, 10, Hz, 1H), 6.03 (br d, 1H), 7.3–7.5 (m, 5H). Anal. Calcd for C₁₇H₂₁NO₄: C, 67.3; H, 6.9; N, 4.6. Found: C, 67.3; H, 6.9; N, 4.6.



7.1.16. (3,4,6-Tri-O-acetyl-2-deoxy- α -D-erythro-hex-2-enopyranosyl)benzene and (4,6-Di-O-acetyl-2,3-dideoxy- α -D-erythro-hex-2-enopyranosyl)benzene (Reaction of a Glucal Ester and Benzene with Pd(OAc)₂ as Activator) (153, 154)

tri-O-acetyl-D-glucal (0.82 g, 3 mmol) was dissolved in acetic acid (24 mL) and benzene (45 mL), Pd(OAc)₂ (0.93 g, 3 mmol) was added, and the mixture was kept at 80° for 8 hours. The palladium was removed by filtration and the solvent was removed under reduced pressure to give a residue that was dissolved in THF (50 mL) and water (10 mL). After cooling to 0°, KBH₄ (0.10 g) was added with stirring and after 30 minutes the mixture was again filtered. The THF was removed from the filtrate and the aqueous solution was extracted with CHCl₃ (100 mL). The organic phase was washed with water to neutral pH and dried (MgSO₄), and the solvent was removed under reduced pressure. Flash chromatography on silica gel H60 (ether-light petroleum 4:1) gave (4,6-di-O-acetyl-2,3-dideoxy- α -D-erythro-hex-2-enopyranosyl)benzene (87 mg, 10%), [a]_D + 3.3° (*c* = 1.34, CHCl₃). ¹H NMR (250 MHz in CDCl₃) δ 3.86 (ddd, *J* = 3, 6, 7.5 Hz, 1H), 4.12 (dd, *J* = 3, 12 Hz, 1H), 4.26 (dd, *J* = 6, 12 Hz, 1H), 5.32 (m, *J* = 1.5, 7.5 Hz, 1H), 5.34 (s, 1H), 5.99 (d, *J* = 9 Hz, 1H), 6.18 (m, *J* = 1.5, 9 Hz, 1H). Anal. Calcd for C₁₆H₁₈O₅: C, 66.2; H, 6.25. Found: C, 66.2; H, 6.2. This was followed by (3,4,6-tri-O-acetyl-2-deoxy- α -D-erythro-hex-2-enopyranosyl)benzene (0.56 g, 54%), [a]_D + 69° (*c* = 1.7, CHCl₃). ¹H NMR (250 MHz, CDCl₃) δ 4.05–4.5 (m, 3H), 5.47 (m, 1H), 5.47 (m, 1H), 5.92 (d, *J* = 2.5 Hz, 1H). Anal. Calcd for C₁₈H₂₀O₇: C, 62.1; H, 5.8. Found: C, 61.8, H, 5.6.

8. Tabular Survey

The survey provided in the following nine tables identifies the great majority of 2,3-unsaturated glycosyl compounds that have been made by the general reaction under review. Products having hydroxy, carboxylate, and hydroperoxy groups at the anomeric center are listed in Table 1; Tables 2, 3, 4, 5 deal with analogous O-, S-, N-, and C- bonded glycosidic compounds; glycosyl halides and phosphonates are treated in Tables 6 and 7. While this system would have allowed the listing of all relevant compounds, it was decided that compounds derived from two sets of “particular” glycals –those with substituents at C-2, and those with furanoid rings –merit separate treatment, and they are contained in Tables 8 and 9, respectively. When this “mixed” categorizing system has led to ambiguity, as for example with 2-substituted C-glycosides or furanoid nucleoside derivatives, the “special nature” factor has been given precedence, and these compounds are listed in Tables 8 and 9, respectively, rather than in 5 and 4.

In all the Tables the examples are listed on the basis of the glycals involved, and by application of the following parameters in sequence: 1. increasing glycal carbon number; 2. increasing glycal hydrogen number; 3. alphabetical order of glycals [arabinal, xylal; allal, galactal, glucal, gulal; L-rhamnol (6-deoxy-L-glucal) being taken to be a derivative of the parent glycal]; 4. increasing carbon count of all glycal substituents; 5. increasing total carbon count of the acceptor species; and 6. D-compounds take precedence over their L-enantiomers.

Reaction yields are frequently recorded, but it has not been possible to do this systematically since those that appear in the literature may refer to pure compounds, to purified mixtures of specified compounds (often isomers), or to unpurified mixtures. Almost all of the reactions under consideration give mixtures of a- and b-anomers, and the important matter of the recording of their ratios also raises difficulties. Sometimes the literature contains data relating to the mixtures produced, sometimes to specific anomers isolated, and sometimes it is assumed that major anomers are formed exclusively when there is every chance that this is not so.

Notwithstanding these issues, the data supplied regarding yields and anomeric ratios may offer useful guidance. Occasionally with the latter, however, this may not be so since the identification of the anomeric configurations of specific reaction products of the type under consideration was not easy before reliable analytical methods became available, and mistakes were made. It is therefore possible that the earlier literature, and hence the Tables, may contain occasional erroneous anomeric assignments. Especially this appears to be so with the C-glycosides made from pentose-based glycal derivatives. On the first two pages of Table 5 there are several examples of reactions that appear to be strongly a-selective while apparently similar processes are stated to give mainly b-products. Configurational assignment errors may account for these.

The literature has been covered through 2001 with some references to 2002 papers, and the great majority of relevant reported reaction products are listed, as are different reaction conditions employed in their production. Occasionally, however, when extensive lists of closely related compounds are described in papers, or when novel catalysts are applied to make known products, expediency has required that some selectivity be applied. The Tables therefore do not include all reported examples of the application of the reactions under review.

The following abbreviations are used in the Tables:

Ac	acetyl
AIBN	2,2-azo(bis)isobutyronitrile
Ar	aryl
Bn	benzyl
BOC	<i>tert</i> -butoxycarbonyl
Bu	butyl

<i>t</i> -Bu	<i>tert</i> -butyl
Bz	benzoyl
<i>c</i> -C ₆ H ₁₁	cyclohexyl
CAN	cerium(IV) ammonium nitrate
Cbz	benzyloxycarbonyl
CSA	camphorsulfonic acid
dba	dibenzylideneacetone
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIBALH	diisobutylaluminum hydride
DIPHOS	bis(1,2-diphenylphosphino)ethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dppe	bis(1,2-diphenylphosphino)ethane
Et	ethyl
Fmoc	9-fluorenylmethylcarbonyl
<i>hν</i>	light radiation
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoric triamide
IDCP	iodonium dicollidine perchlorate
LDA	lithium diisopropylamide
<i>m</i> -CPBA	<i>m</i> -chloroperoxybenzoic acid
Me	methyl
MOM	methoxymethyl
Ms	methanesulfonyl
MS	Molecular Sieves
NBS	<i>N</i> -bromosuccinimide
NIS	<i>N</i> -iodosuccinimide
Ph	phenyl
Phth	phthaloyl
Piv	pivaloyl
PMB	<i>p</i> -methoxybenzyl
Pr	propyl
<i>i</i> -Pr	isopropyl
Py	pyridine
TBDMS	<i>tert</i> -butyldimethylsilyl
TBDPS	<i>tert</i> -butyldiphenylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
Tr	triphenylmethyl
tr	trace
TS	<i>p</i> -toluenesulfonyl

Table 1. 2,3-Unsaturated Free Sugars(*Z* and *E*), Glycosyl Peroxides, and Glycosyl Carboxylates

[View PDF](#)

Table 2. 2,3-Unsaturated *O*-Glycosides

[View PDF](#)

Table 3. 2,3-Unsaturated *S*-Glycosides and Related Compounds

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Table 4. 2,3-Unsaturated Glycosyl Azides and *N*-Glycosides

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Table 5. 2,3-Unsaturated *C*-Glycosides

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Table 6. 2,3-Unsaturated Glycosyl Halides

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Table 7. 2,3-Unsaturated Glycosyl Phosphonates

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Table 8. 2-Substituted 2,3-Unsaturated Glycosyl Compounds

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Table 9. 2,3-Unsaturated Furanoid Glycosyl Compounds

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TABLE 1. 2,3-UNSATURATED FREE SUGARS (Z AND E), GLYCOSYL PEROXIDES, AND GLYCOSYL CARBOXYLATES

Glycal	Nucleophile	Reaction Conditions	Product(s)	$\alpha:\beta$, Yield(s) (%)	Refs.		
	H ₂ O	HgSO ₄ (cat.), H ₂ SO ₄ , H ₂ O, dioxane, rt, 3 h		— (88)	162		
	EtCO ₂ H BzOH	EtCO ₂ H, MeC(OEt) ₃ , C ₆ H ₆ , 80° PPh ₃ , DEAD, THF, rt, 1 h		R COEt 1:0 (50) Bz >1:1 (36)	315 175		
	H ₂ O	HgSO ₄ (cat.), H ₂ SO ₄ , dioxane, H ₂ O, rt, 3 h		— (82)	162		
	Ac ₂ O	(NH ₄) ₆ Mo ₇ O ₂₄ •4H ₂ O, 110°, 15 min		R OAc 1:0 (65)	173		
	AcOH	118°, 100 min		OAc — (5)	117		
	H ₂ O ₂	MoO ₃ , H ₂ O ₂ (45%), rt		O ₂ H 20:1 (12)	170		
	<i>m</i> -ClC ₆ H ₄ CO ₃ H	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , -10° to rt, 30 min		— (81)	172		
	H ₂ O	80°, 4 h		— (—)	197		
	AcOH	DEAD, Ph ₃ P, C ₆ H ₆ , rt, 8 h		— (80)	110		
	OH ⁻	PhI(OH)OTs, MeCN, N ₂ , rt, 75 min		— (31)	163		
	R ¹ CO ₂ Me	H ₂ O ₂	HCO ₂ H, dioxane, 0°, 12 h	R ² O ₂ H 1:0 (76)	169		
	R ¹ CH ₂ OAc	Intramolecular	BF ₃ •Et ₂ O, benzene, rt, 2 h	OAc 5:1 (60)	122		
	R ¹ CH ₂ OAc	Intramolecular	PhNO ₂ , 210°, 75 min	OAc 3:1 (—)	122		
	R ¹ CH ₂ OAc	Ac ₂ O	NiCl ₂ •6H ₂ O, 120°, 1 h	OAc — (65)	131		
	R ¹ CH ₂ OAc	Ac ₂ O	(NH ₄) ₆ Mo ₇ O ₂₄ •4H ₂ O, 110°, 15 min	OAc — (65)	173		
	R ¹ CH ₂ OAc	H ₂ O ₂	MoO ₃ , H ₂ O ₂ (45%), rt	O ₂ H 2:1 (52)	170		
	R ¹ CH ₂ OAc	H ₂ O ₂	H ₂ SO ₄ , dioxane, 0°, 12 h	O ₂ H 1:0 (72)	169		
	R ¹ CH ₂ OAc	H ₂ O	Dioxane, reflux	OH — (—)	10		
	R ¹ CH ₂ OAc	H ₂ O	HgSO ₄ (cat.), H ₂ SO ₄ , H ₂ O, dioxane, rt, 3 h	R OAc — (>90)	162		
	CH ₂ NHAc	H ₂ O	HgSO ₄ (cat.), H ₂ SO ₄ , H ₂ O, dioxane, rt, 3 h	NHAc — (95)	160		
	R ¹ OAc	R ² OAc	<i>m</i> -ClC ₆ H ₄ CO ₃ H	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , -10° to rt, 30 min		— (69)	172
	R ¹ OAc	R ² OTs	<i>m</i> -ClC ₆ H ₄ CO ₃ H	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , -10° to rt, 30 min		— (78)	172
	R ¹ OBz	R ² OBz	<i>m</i> -ClC ₆ H ₄ CO ₃ H	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , -10° to rt, 30 min		— (74)	172
	R ¹ = R ² = OBn	H ₂ O ₂	MoO ₃ , H ₂ O ₂ (65%), rt		4:1 (60)	170	
	BzOH	PPh ₃ , DEAD, THF, rt, 1 h		1:0 (92)	175		

TABLE 1. 2,3-UNSATURATED FREE SUGARS (*Z* AND *E*), GLYCOSYL PEROXIDES, AND GLYCOSYL CARBOXYLATES (*Continued*)

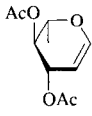
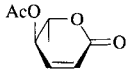
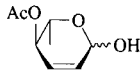
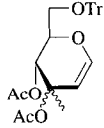
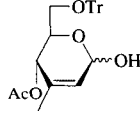
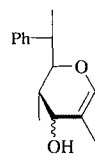
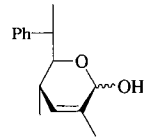
Glycal	Nucleophile	Reaction Conditions	Product(s)	α : β , Yield(s) (%) Refs.
	<i>m</i> -ClC ₆ H ₄ CO ₃ H	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , -10° to rt, 30 min		— (89) 172
	H ₂ O	H ₂ O, 80°, 4 h		— (—) 197
	H ₂ O	Dioxane, hydroquinone, dark, 100°, 20 min		— (—) 98
^C ₁₅ 	H ₂ O	HCl, dioxane, reflux		— (—) 316

TABLE 2. 2,3-UNSATURATED *O*-GLYCOSIDES


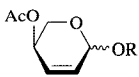


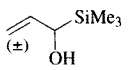


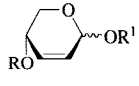
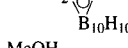

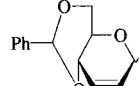
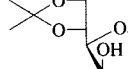
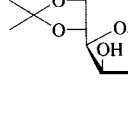
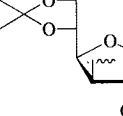
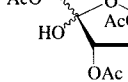
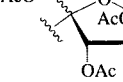
Glycal	Nucleophile	Reaction Conditions	Product(s)	$\alpha:\beta$, Yield(s) (%) Refs.		
	HOCH ₂ P(O)(OPr- <i>i</i>) ₂	TMSOTf, MeCN		$\frac{R}{CH_2P(O)(OPr-i)_2}$ 1:3 (65) 71, 72		
		I ₂ , THF			1:2.2 (70) 277	
		BF ₃ •Et ₂ O, MeCN, -30°, 3 h		1:8 (45) 318		
	R = Ac	MeOH		$\frac{R^1}{Me}$ 1:0 (98) 158		
		HOCH ₂ P(O)(OPr- <i>i</i>) ₂		TMSOTf, MeCN	$\frac{R^1}{CH_2P(O)(OPr-i)_2}$ 1:3 (72) 71, 72	
		HOCH ₂ CH ₂ CN		BF ₃ •Et ₂ O, CH ₂ Cl ₂ , -30°	$\frac{R^1}{CH_2CH_2CN}$ 1:3 (81) 59	
		HOCH ₂ C(CH ₃)=CH		BF ₃ •Et ₂ O, C ₆ H ₆	$\frac{R^1}{CH_2C(CH_3)=CH}$ 9:1 (90) 306	
				BF ₃ •Et ₂ O, CH ₂ Cl ₂ , rt, 10 min	$\frac{R^1}{B_{10}H_{10}}$ 1:1.7 (85) 99	
	R = Bz	MeOH		R ¹ = Me 0:1 (91) 23		
	R = Ms	MeO ⁻		MeONa, MeOH, rt		
	R = 			IDCP, CH ₂ Cl ₂ , Ar, rt		4:1 (57) 36
		IDCP, CH ₂ Cl ₂ , rt			8:1 (32) 36	

TABLE 2. 2,3-UNSATURATED O-GLYCOSIDES (Continued)

Glycol	Nucleophile	Reaction Conditions	Product(s)	α : β , Yield(s) (%)	Refs.
		Pd(MeCN) ₂ Cl ₂ , AgOTf, CH ₂ Cl ₂ , rt, MS, 28 min		16:1 (72)	112
R = Ph		IDCP, CH ₂ Cl ₂ , Ar, rt		3.3:1 (63)	36
		NIS, CH ₂ Cl ₂ , Ar, rt		3.5:1 (70)	36
	Cholestanol	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , 0°, 40 min		1:0 (86)	301
	Intramolecular	H ₂ SO ₄ , THF, 65°, 1 h		— (40)	319
	Intramolecular	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , 0° to rt, 1 h		— (81-82)	104
	Intramolecular	Montmorillonite, CHCl ₃ , 50°, 15 h		— (80-85)	82
	MeOH EtOH <i>i</i> -PrOH <i>t</i> -BuOH <i>p</i> -BrC ₆ H ₄ OH <i>p</i> -O ₂ NC ₆ H ₄ OH PhOH C ₆ H ₁₁ OH BnOH C ₆ H ₁₁ CH ₂ OH	SnCl ₄ , ClCH ₂ CH ₂ Cl, rt, 1 h SnCl ₄ , ClCH ₂ CH ₂ Cl, rt, 1 h SnCl ₄ , ClCH ₂ CH ₂ Cl, rt, 1 h SnCl ₄ , ClCH ₂ CH ₂ Cl, rt, 1 h SnCl ₄ , ClCH ₂ CH ₂ Cl, rt, 1 h C ₆ H ₆ , 79°, 4 h SnCl ₄ , ClCH ₂ CH ₂ Cl, rt, 1 h SnCl ₄ , ClCH ₂ CH ₂ Cl, rt, 1 h SnCl ₄ , ClCH ₂ CH ₂ Cl, rt, 1 h DDQ, MeCN, 50°, 48 h		1:0 (80) 45 1:0 (92) 45 1:0 (58) 45 1:0 (60) 45 1:0 (57) 45 1:0 (9) 117 1:0 (43) 45 1:0 (66) 45 1:0 (82) 45 8.4:1 (72) 86	
		SnCl ₄ , ClCH ₂ CH ₂ Cl, rt, 1 h		10:1 (56)	45
		IDCP, CH ₂ Cl ₂ , rt		1:0 (26)	36
	MeOH	AG 50W-X8, MeCN, 64°, 20 h		— (—)	320
	HOC ₆ H ₄ NO _{2-p}	DEAD, Ph ₃ P, CH ₂ Cl ₂ , 0°, 1 h		1:2 (50)	109

TABLE 2. 2,3-UNSATURATED O-GLYCOSIDES (Continued)

Glycal	Nucleophile	Reaction Conditions	Product(s)	$\alpha:\beta$, Yield(s) (%)	Refs.
		$\text{BF}_3 \cdot \text{Et}_2\text{O}$, C_6H_6 , -10° , 30 min		1:0 (15)	191
	Intramolecular	CuSO_4 (anhydr.), THF, 65° , 6 h		— (42)	255
	MeOH	TsOH, $\text{PhCH}(\text{OMe})_2$, rt		— (90)	107
		CSA, DMF, rt, 2 d		— (36)	36
		DEAD, Ph_3P , C_6H_6 , rt, 10 h		2.3:1 (65)	110
	$\text{HOC}_6\text{H}_4\text{OMe-}p$	DEAD, Ph_3P , C_6H_6 , rt, 5 h		5.5:1 (78)	110
		DEAD, Ph_3P , C_6H_6 , rt, 48 h		9:1 (55)	110
	Intramolecular	Montmorillonite, CHCl_3 , 50° , 8 h		— (80-85)	82
	Intramolecular	$\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , 0° , 1 h		— (85)	104
	$\text{HC}(\text{OMe})_3$	$\text{BF}_3 \cdot \text{Et}_2\text{O}$, rt, 4 h		1:0 (45)	37
	$\text{HC}(\text{OMe})_3$	$\text{BF}_3 \cdot \text{Et}_2\text{O}$, rt, 6 h		1:0 (86)	37
		$\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , N_2 , -5° , 1.5 h		1:0 (—)	190
	MeOH	ZnCl_2 , CH_2Cl_2 , rt, 50 min		4:1 (75)	95
	$\text{HO}(\text{CH}_2)_2\text{CN}$	$\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , -40°		1:0 (80)	59
	BnOH	SnCl_4		— (95)	321
	HO-CCl_3	$\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , -78° , 12 h		5:1 (69)	322
		$\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , -40 to -20° , 1 h		1:0 (80)	60
		$\text{BF}_3 \cdot \text{Et}_2\text{O}$, -35° , 10 min		1:0 (92)	100
		SnBr_4 , CH_2Cl_2 , -45 to -25° , 1 h		1:0 (28)	60

TABLE 2. 2,3-UNSATURATED *O*-GLYCOSIDES (Continued)

Glycal	Nucleophile	Reaction Conditions	Product(s)	α : β , Yield(s) (%)	Refs.
	MeOH	180°, N ₂ , 4 h		R Me	1.5:1 (80) 12
	MeOH	BF ₃ •Et ₂ O, rt		Me	— (82) 14
	MeOH	I ₂ , THF, rt, 0.5 h		Me	6:1 (87) 90
	MeOH	SnCl ₄ , -78°, 10 min		Me	6:1 (83) 323
	HOCH ₂ CF ₃	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , rt, 30 min		CH ₂ CF ₃	1:0 (90) 324
	HOCH ₂ CO ₂ Et	I ₂ , THF, rt		CH ₂ CO ₂ Et	1:0 (—) 89
	HOCH ₂ CO ₂ Bn	BF ₃ •Et ₂ O		CH ₂ CO ₂ Bn	1:0 (30) 325
	HO(CH ₂) ₂ SPh	BF ₃ •Et ₂ O, C ₆ H ₆ , rt, 8 min		(CH ₂) ₂ SPh	4.6:1 (92) 326
	HOCH ₂ CH(Ph)Cl	BF ₃ •Et ₂ O, C ₆ H ₆ , rt, 8 min		CH ₂ CH(Ph)Cl	6:1 (88) 326
	HO(CH ₂) ₂ Br	BF ₃ •Et ₂ O, C ₆ H ₆ , N ₂ , rt, 30 min		(CH ₂) ₂ Br	1:0 (76) 304
	HO(CH ₂) ₂ SiMe ₃	BF ₃ •Et ₂ O, C ₆ H ₆ , rt		(CH ₂) ₂ SiMe ₃	9:1 (86) 327
	(HO(CH ₂) ₂) ₂ NFmoc	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , -45°		(HO(CH ₂) ₂) ₂ NFmoc + 	— (15) 59 — (72) 59
	HO(CH ₂) ₂ SePh	BF ₃ •Et ₂ O, C ₆ H ₆ , rt, 15 min		(CH ₂) ₂ SePh	1:0 (85) 273
	EtOH	EtOH, 180°, N ₂ , 4 h		Et	— (35) 12
	EtOH	BF ₃ •Et ₂ O, C ₆ H ₆ , rt, 25 min		Et	8:1 (70) 14
	EtOH	SnCl ₄ , Cl(CH ₂) ₂ Cl		Et	— (94) 45
	HOCH ₂ C≡CH	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , rt		CH ₂ C≡CH	10:1 (100) 326, 328
	HO(CH ₂) ₂ CN	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , -20°		(CH ₂) ₂ CN	1:0 (91) 59
	HOCH(CH ₃)CN	<i>h</i> ν , N ₂ , 27 h		CH(CH ₃)CN	1:1.3 (84) 244
		BF ₃ •Et ₂ O, C ₆ H ₆ , rt, 8 min			— (96) 326
	BF ₃ •Et ₂ O, MeCN, 0°, 10 min			10:1 (85) 329	
	BF ₃ •Et ₂ O, MeCN, -30°, 3 h			15:1 (60) 317	
HO(CH ₂) _n	BF ₃ •Et ₂ O, C ₆ H ₆			— (70-90) 306	
n = 1-3, R = H, Me					
	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , -25 to -5°			1:0 (91) 59	
	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , -30°, 5 h			1:0 (82) 100	
	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , -25 to -10°, 1 h			1:0 (90) 60	
	BF ₃ •Et ₂ O, C ₆ H ₆			— (—) 330	
	I ₂ , THF, rt, 1 h			6:1 (98) 90	
	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , -25 to -10°, 1 h			1:0 (85) 60	
	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , -30°			1:0 (35) 59 (48)	
<i>n</i> -PrOH	BF ₃ •Et ₂ O, C ₆ H ₆ , rt, 25 min		<i>n</i> -Pr	— (80) 14	
<i>i</i> -PrOH	BF ₃ •Et ₂ O, C ₆ H ₆ , rt, 25 min		<i>i</i> -Pr	— (65) 14	
<i>i</i> -PrOH	I ₂ , THF, rt, 1 h		<i>i</i> -Pr	8:1 (97) 90	
<i>i</i> -PrOH	Pd(MeCN) ₂ Cl ₂ , Cu(OTf) ₂ , 40°		<i>i</i> -Pr	— (—) 159	
	Montmorillonite K-10, CH ₂ Cl ₂ , 45°, 1.5 h			— (82) 84	
	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , rt			10:1 (43) 328	

TABLE 2. 2,3-UNSATURATED *O*-GLYCOSIDES (Continued)

Glycal	Nucleophile	Reaction Conditions	Product(s)	α : β , Yield(s) (%)	Refs.
		BF ₃ •Et ₂ O, CH ₂ Cl ₂ , rt		25:1 (49)	328
		BF ₃ •Et ₂ O, C ₆ H ₆ , rt, 45 min		1:0 (31)	331
		BF ₃ •Et ₂ O, C ₆ H ₆ , rt, 45 min		1:0 (46)	331
		BF ₃ •Et ₂ O, CH ₂ Cl ₂ , -35°, 15 min		1:0 (84)	100
		BF ₃ •Et ₂ O, MeCN, -30°		— (—)	332
		BF ₃ •Et ₂ O, CH ₂ Cl ₂ , N ₂ , rt, 2 h		19:1 (75)	333
		I ₂ , THF, rt, 1 h		8:1 (83)	90
		I ₂ , THF, rt, 1 h		7:1 (88)	90
		BF ₃ •Et ₂ O, CH ₂ Cl ₂ , -30°		1:0 (89)	59
		BF ₃ •Et ₂ O, C ₆ H ₆ , rt		1:0 (26)	334
		BF ₃ •Et ₂ O, C ₆ H ₆ , rt		— (—)	334
		BF ₃ •Et ₂ O, C ₆ H ₆ , rt, 8 min		9:1 (83)	326
		I ₂ , THF, rt, 1 h		6:1 (75)	90
		Sc(OTf) ₃ , CH ₂ Cl ₂ , 25°, 1.5 h		7:1 (95)	77
		BF ₃ •Et ₂ O, MeCN, Ar, -30°, 3.5 h		1:1 (60)	335
		BF ₃ •Et ₂ O, C ₆ H ₆ , rt, 8 min		5:1 (80)	326
	<i>n</i> -BuOH	BF ₃ •Et ₂ O, C ₆ H ₆ , rt, 25 min	<i>n</i> -Bu	— (80)	14
	<i>n</i> -BuOH	FeCl ₃ , MeCN, 82°, 5 min	<i>n</i> -Bu	4:1 (90)	47
	<i>i</i> -BuOH	BF ₃ •Et ₂ O, C ₆ H ₆ , rt, 25 min	<i>i</i> -Bu	— (80)	14
	<i>t</i> -BuOH	I ₂ , THF, rt, 2 h	<i>t</i> -Bu	6:1 (73)	90
		BF ₃ •Et ₂ O, PhMe, rt, 1.5 min		3:1 (—)	184
		BF ₃ •Et ₂ O, MeCN, -30°		1:0 (—)	332
		BF ₃ •Et ₂ O, MeCN, -30°		1:0 (—)	332
		BF ₃ •Et ₂ O, CH ₂ Cl ₂ , 0°, 1 h		— (100)	336
		BF ₃ •Et ₂ O, CH ₂ Cl ₂ , CaSO ₄ , rt, 4 h		1:0 (32)	272

TABLE 2. 2,3-UNSATURATED *O*-GLYCOSIDES (Continued)

Glycal	Nucleophile	Reaction Conditions	Product(s)	$\alpha:\beta$, Yield(s) (%)	Refs.
		BF ₃ •Et ₂ O, CH ₂ Cl ₂ , 0°, 1 h		11:1 (94)	36
		BF ₃ •Et ₂ O, C ₆ H ₆ , rt		1:0 (—)	334
		Sc(OTf) ₃ , CH ₂ Cl ₂ , 25°, 2 h		7:1 (90)	77
		BF ₃ •Et ₂ O, C ₆ H ₆ , -45°, 30 min		1:0 (72)	59
				1:0 (15)	
		BF ₃ •Et ₂ O, C ₆ H ₆ , -30°		1:0 (45)	59
				1:0 (25)	
		BF ₃ •Et ₂ O, PhMe, rt, 3 h		1:0 (60)	336a
		BF ₃ •Et ₂ O, C ₆ H ₆ , -30°		1:0 (75)	59
		BF ₃ •Et ₂ O, MeCN, -30°		1:0 (—)	332
	HOC ₆ H ₄ Cl- <i>o</i>	BF ₃ •Et ₂ O, C ₆ H ₆ , rt, 8 min	C ₆ H ₄ Cl- <i>o</i>	10:1 (46)	325
	HOC ₆ H ₄ F- <i>p</i>	Sc(OTf) ₃ , CH ₂ Cl ₂ , 25°, 1 h	C ₆ H ₄ F- <i>p</i>	12:1 (92)	77
	HOC ₆ H ₄ NO ₂ - <i>o</i>	PhCl, 132°, 15 h	C ₆ H ₄ NO ₂ - <i>o</i>	— (56)	178
	HOC ₆ H ₄ NO ₂ - <i>p</i>	I ₂ , THF, rt, 24 h	C ₆ H ₄ NO ₂ - <i>p</i>	10:1 (59)	90
	HOC ₆ H ₄ NO ₂ - <i>p</i>	C ₆ H ₆ , 79°, 4 h	C ₆ H ₄ NO ₂ - <i>p</i>	1:0 (43)	11
	HOC ₆ H ₄ NO ₂ - <i>p</i>	BF ₃ •Et ₂ O, C ₆ H ₆ , rt, 12 min	C ₆ H ₄ NO ₂ - <i>p</i>	— (36)	14
	HOC ₆ H ₄ OMe- <i>o</i>	I ₂ , THF, rt, 3 h	C ₆ H ₄ OMe- <i>o</i>	15:1 (75)	90
	HOC ₆ H ₄ OMe- <i>p</i>	PhCl, 132°, 5 h	C ₆ H ₄ OMe- <i>p</i>	4:1 (78)	177
	HOC ₆ H ₄ OMe- <i>p</i>	BF ₃ •Et ₂ O, PhMe, -10°, 2.5 h	C ₆ H ₄ OMe- <i>p</i>	10:1 (92)	179, 180
	HOC ₆ H ₄ OMe- <i>p</i>	I ₂ , THF, rt, 3 h	C ₆ H ₄ OMe- <i>p</i>	15:1 (75)	90
	HOC ₆ H ₄ OMe- <i>p</i>	Sc(OTf) ₃ , MeCN-H ₂ O (9:1), 25°, 0.5 h	C ₆ H ₄ OMe- <i>p</i>	1:0 (95)	77
	PhOH	PhCl, reflux, 3 h	Ph	5.7:1 (77)	13, 337
	PhOH	BF ₃ •Et ₂ O, PhMe, -20°, 10 h	Ph	10:1 (59)	179, 180
	PhOH	I ₂ , THF, rt, 4 h	Ph	10:1 (65)	90
		BF ₃ •Et ₂ O, acetone, rt		1:0 (85)	299
		BF ₃ •Et ₂ O, PhMe, rt, 1.5 h		1:0 (58)	184

TABLE 2. 2,3-UNSATURATED O-GLYCOSIDES (Continued)

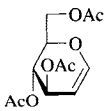
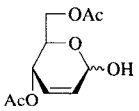
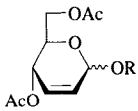
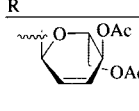
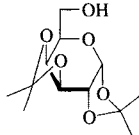
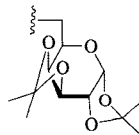
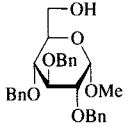
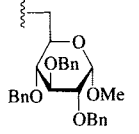
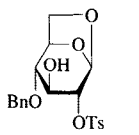
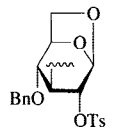
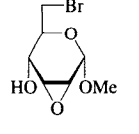
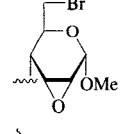
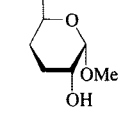
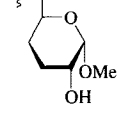
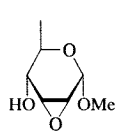
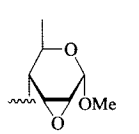
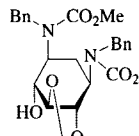
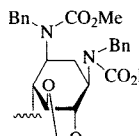
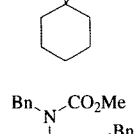
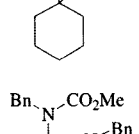
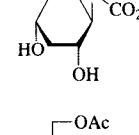
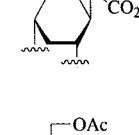
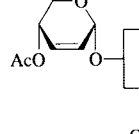
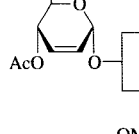
Glycol	Nucleophile	Reaction Conditions	Product(s)	$\alpha:\beta$	Yield(s) (%)	Refs.	
		$\text{BF}_3 \cdot \text{Et}_2\text{O}$, C_6H_6 , 10 to 20°, 20 min			1:0	(44)	182
		$\text{BF}_3 \cdot \text{Et}_2\text{O}$, C_6H_6 , rt, 15 min			8:1	(56)	14
		$\text{Yb}(\text{OTf})_3$, CH_2Cl_2 , rt, 18 h			1:0	(89)	79
		$\text{BF}_3 \cdot \text{Et}_2\text{O}$, PhMe , rt, 1.5 h			1:0	(57)	184
		$\text{BF}_3 \cdot \text{Et}_2\text{O}$, PhMe , rt, 1.5 h			1:0	(54)	187
		$\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , -10°, 20 min			6:1	(40)	97
		$\text{BF}_3 \cdot \text{Et}_2\text{O}$, PhMe , rt, 2 h			1:0	(71)	187
		$\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , -5°, 2 h			1:0	(75)	190
		$\text{BF}_3 \cdot \text{Et}_2\text{O}$, C_6H_6 , rt, 15 min			1:0	(75)	189
		$\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , -45 to -20°, 1 h			1:0	(—)	60
		180°			—	(82)	338

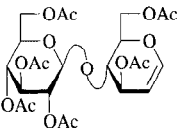
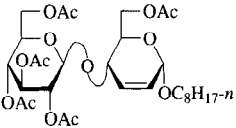
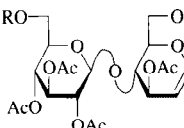
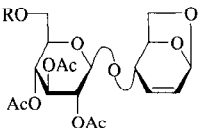
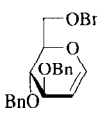
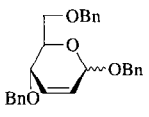
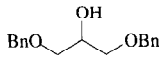
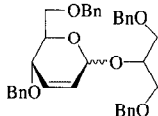
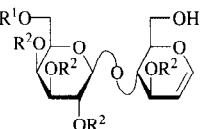
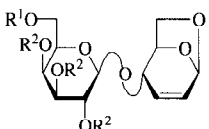
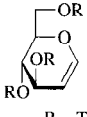
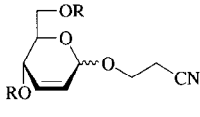

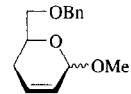
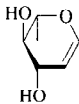
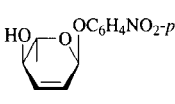
TABLE 2. 2,3-UNSATURATED O-GLYCOSIDES (Continued)

Glycol	Nucleophile	Reaction Conditions	Product(s)	α : β	Yield(s) (%)	Refs.	
	HOCH ₂ C ₆ H ₄ 1- <i>o</i>	BF ₃ •Et ₂ O, C ₆ H ₆ , rt		1:0	(—)	339	
	HOCH ₂ C ₆ H ₄ NO ₂ - <i>o</i>	InCl ₃ , CH ₂ Cl ₂ , rt, 15 min		7:1	(80)	57	
	BnOH	I ₂ , THF, rt, 1 h		7:1	(94)	90	
	BnOH	BF ₃ •Et ₂ O, C ₆ H ₆ , rt, 1 h		9:1	(93)	340	
	BnOH	Yb(OTf) ₃ , CH ₂ Cl ₂ , rt, 3 h		10.5:1	(94)	79	
	C ₆ H ₁₁ CH ₂ OH	DDQ, MeCN, 50°, 48 h		5.6:1	(91)	86	
		BF ₃ •Et ₂ O, CH ₂ Cl ₂ , rt, 3.5 h		4:1	(84)	341	
		BF ₃ •Et ₂ O, C ₆ H ₆ , rt, 8 min		6:1	(88)	326	
		BF ₃ •Et ₂ O, C ₆ H ₆ , rt, 8 min		1:0	(—)	334	
		I ₂ , THF, rt		1:0	(60)	89	
				+ diastereomer (1.5:1)			
		BF ₃ •Et ₂ O, C ₆ H ₆ , rt, 75 min		1:0	(76)	342	
		I ₂ , THF, rt, 2 h		6:1	(95)	90	
	Ar = <i>p</i> -O ₂ NC ₆ H ₄						
		PhCl, 132°, 10 h		1.8:1	(50)	177	
HO-C ₆ H ₄ (Bu- <i>t</i>)- <i>p</i>	PhCl, 132°, 15 h		C ₆ H ₄ (Bu- <i>t</i>)- <i>p</i>	1:0	(60)	178	
	I ₂ , THF, rt, 2 h		6:1	(85)	90		
HO-(CH ₂) ₁₀ -OH	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , -20°			—	(45)	59	
				—	(24)		
	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , -30°			1:0	(47)	59	
	I ₂ , THF, rt, 3 h			5:1	(93)	90	
Cholesterol	BF ₃ •Et ₂ O, C ₆ H ₆ , rt, 12 min		Cholesteryl	—	(50)	14	
Cholesterol	FeCl ₃ , MeCN, 82°, 1 h		Cholesteryl	4:1	(95)	47	
	TsOH, CH ₂ Cl ₂ , rt			4:1	(62)	307	

TABLE 2. 2,3-UNSATURATED *O*-GLYCOSIDES (Continued)

Glycol	Nucleophile	Reaction Conditions	Product(s)	α : β , Yield(s) (%)	Refs.
	$\text{HOC}_6\text{H}_4\text{NO}_2\text{-}p$ $\text{HOC}_6\text{H}_4\text{OMe-}p$	DEAD, Ph_3P , CH_2Cl_2 , 0° , 1 h DEAD, Ph_3P , CH_2Cl_2 , 0° , 1 h		1:0 (68) 1:0 (55)	109 109
		IDCP, CH_2Cl_2 , Ar, rt		6.7:1 (65)	36
		$\text{Pd}(\text{MeCN})_2\text{Cl}_2$, AgOTf, CH_2Cl_2 , MS, rt, 90 min		9:1 (62)	112
	$\text{HC}(\text{OMe})_3$	$\text{BF}_3 \cdot \text{Et}_2\text{O}$, 50° , 2 h		— (68)	37
	MeOH	—		1:10 (90)	146
	Intramolecular Intramolecular	Montmorillonite, Ag^+ , CHCl_3 , 50° , 15 h $\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , 0° to rt, 1 h		— (80-85)	82
		$\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , -20 to -10°		1:0 (86)	60
	$\text{HO}(\text{CH}_2)_2\text{CN}$	$\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , -35°	$(\text{CH}_2)_2\text{CN}$	1:0 (90)	59
	$n\text{-C}_9\text{H}_{19}\text{OH}$	$\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , -35°	$n\text{-C}_9\text{H}_{19}$	1:0 (55)	59
	Cholesterol	I_2 , THF, reflux, 12 h	Cholesteryl	8:1 (52)	90
		$\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , -20 to -10°		1:0 (75)	60
	$\text{HOC}_6\text{H}_4\text{NHAc-}p$	I_2 , THF, reflux, 12 h	$\text{C}_6\text{H}_4\text{NHAc-}p$	8:1 (>45)	90
	$n\text{-C}_8\text{H}_{17}\text{OH}$	$\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , -20 to -10° , 40 min	$n\text{-C}_8\text{H}_{17}$	1:0 (85)	59
	Cholesterol	I_2 , THF, reflux, 12 h	Cholesteryl	8:1 (58)	90

TABLE 2. 2,3-UNSATURATED *O*-GLYCOSIDES (Continued)

Glycal	Nucleophile	Reaction Conditions	Product(s)	$\alpha:\beta$, Yield(s) (%) Refs.
	$n\text{-C}_8\text{H}_{17}\text{OH}$	$\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , -20 to 0° , 1 h		1:0 (55) 59
 R = TBDMS	Intramolecular	Montmorillonite, CHCl_3 , 50° , 15 h		— (80) 82
	None	$\text{BF}_3 \cdot \text{Et}_2\text{O}$, Et_2O , rt, 2 h		— (66) 105
		$\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , -20°		1:0 (65) 60
 R ¹ = TBDMS R ² = Bn, Bz	Intramolecular	Montmorillonite, Ag^+ , CHCl_3 , 50° , 15 h		— (80-85) 82
 R = TBDMS	$\text{HOCH}_2\text{CH}_2\text{CN}$	SnBr_4 , CH_2Cl_2 , -45 to 0° , 40 min		1:0 (38) 59
	MeOH	HCl, MeOH		— (—) 343
	$\text{HOOC}_6\text{H}_4\text{NO}_2\text{-}p$	DEAD, Ph_3P , CH_2Cl_2 , 0° , 1 h		1:0 (78) 109

678

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TABLE 2. 2,3-UNSATURATED O-GLYCOSIDES (Continued)

Glycol	Nucleophile	Reaction Conditions	Product(s)	$\alpha:\beta$, Yield(s) (%) Refs.
	MeOH	SnCl ₄ , CH ₂ Cl ₂ , 2°, 20 min		R Me 5.6:1 (90) 46
	MeOH	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , rt, 20 min		Me 10:1 (55) 344
	MeOH	PdCl ₂ , MeOH, rt, 3-5 h		Me 1:0 (100) 158
	MeOH	ZnCl ₂ , CH ₂ Cl ₂ , rt, 16 h		Me 4:1 (81) 345
	EtOH	BF ₃ •Et ₂ O, C ₆ H ₆ , 15 min		Et 1:0 (55) 346
	EtOH	SnCl ₄ , CH ₂ Cl ₂ , 25°, 20 min		Et 5.9:1 (82) 46
	HC≡CCH ₂ OH	DDQ, MeCN, 50°, 48 h		CH ₂ C≡CH 5.5:1 (86) 86
	<i>i</i> -Pr•OH	DDQ, MeCN, 50°, 24 h		<i>i</i> -Pr 2.1:1 (81) 86
	<i>i</i> -PrOH	DDQ, MeCN, 50°, 24 h		<i>i</i> -Pr 11:1 (75) 46
	<i>t</i> -BuOH	SnCl ₄ , CH ₂ Cl ₂ , 25°, 20 min		<i>t</i> -Bu β (tr) (50) 46
		Montmorillonite K-10, CH ₂ Cl ₂ , 40°, 1 h		5:1 (84) 83
		BF ₃ •Et ₂ O, PhMe, rt, 1 h		1:0 (46) 188
	<i>c</i> -C ₆ H ₁₁ OH	DDQ, MeCN, 50°, 24 h		<i>c</i> -C ₆ H ₁₁ 6.2:1 (87) 86
	HOC ₆ H ₄ OMe- <i>p</i>	BF ₃ •Et ₂ O, PhMe, -10°, 5 h		C ₆ H ₄ OMe- <i>p</i> 10:1 (97) 179, 180
	PhOH	BF ₃ •Et ₂ O, PhMe, -10°, 5 h		Ph 20:1 (57) 179, 180
	BnOH	SnCl ₄ , CH ₂ Cl ₂ , 25°, 20 min		Bn 5.3:1 (85) 46
	BnOH	SnCl ₄ , CH ₂ Cl ₂ , -60 to -35°, 1 h		Bn 13:1 (75) 300
	BnOH	BF ₃ •Et ₂ O, C ₆ H ₆ , rt		Bn 5:1 (88) 347
	<i>c</i> -C ₆ H ₁₁ CH ₂ OH	DDQ, MeCN, 50°, 24 h		CH ₂ C ₆ H ₁₁ - <i>c</i> 4.8:1 (88) 86
	<i>n</i> -C ₈ H ₁₇ OH	DDQ, MeCN, 50°, 24 h		<i>n</i> -C ₈ H ₁₇ 5.1:1 (83) 86
		I ₂ , THF, rt, 30 h		1:0 (50) 91 + diastereomer (1:1)
	HOC ₆ H ₄ (Bu- <i>t</i>)- <i>p</i>	PhCl, 132°, 15 h		C ₆ H ₄ (Bu- <i>t</i>)- <i>p</i> 1:0 (50) 178
		Montmorillonite K-10, CH ₂ Cl ₂ , 22°, 8 h		1:0 (30) 192 Ar =
		BF ₃ •Et ₂ O, C ₆ H ₆ , 5°, 10 min		1:0 (67) 191
	MeOH	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , rt, 15 min		6.6:1 (92) 99
		Pd(MeCN)Cl ₂ , AgOTf, CH ₂ Cl ₂ , MS, rt, 1 h		R = 16:1 (81) 112, 348

TABLE 2. 2,3-UNSATURATED *O*-GLYCOSIDES (Continued)

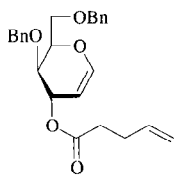
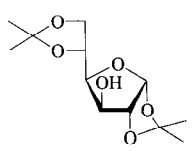
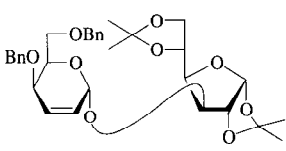
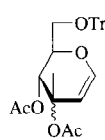
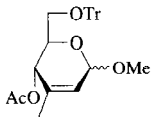
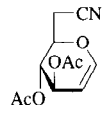
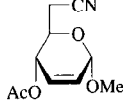
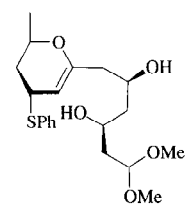
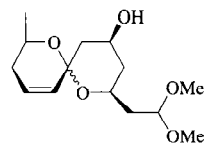
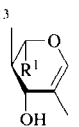
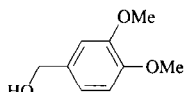
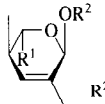
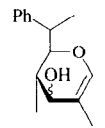
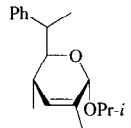
Glycal	Nucleophile	Reaction Conditions	Product(s)	$\alpha:\beta$, Yield(s) (%)	Refs.
		IDCP, CH ₂ Cl ₂ , Ar, rt		1:0 (65)	36
<p>C₇</p> 	MeOH	PyH ⁺ OTs ⁻ , rt, 48 h		— (86)	98
	MeOH	PdCl ₂ , MeOH, rt, 3.5 h		1:0 (80)	158
<p>C₁₂</p> 	Intramolecular	NIS, CH ₂ Cl ₂ , Ar, rt		3:1 (56)	36, 256
<p>C₁₃</p> 		TsOH, C ₆ H ₆ , rt, 1 h	 R ² = CH ₂ C ₆ H ₃ (OMe) ₂ -3,4	1:0 (78)	44
<p>C₁₅</p> 	<i>i</i> -PrOH	TsOH, 0°		1:0 (96)	316

TABLE 3. 2,3-UNSATURATED S-GLYCOSIDES AND RELATED COMPOUNDS

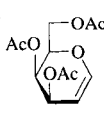
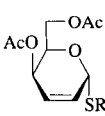
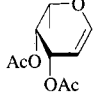
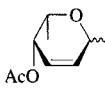
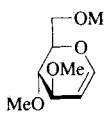
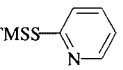
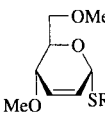
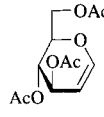
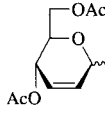
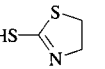
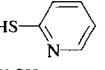
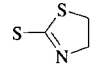
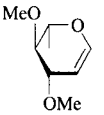
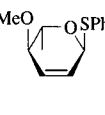
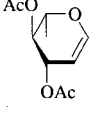
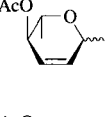
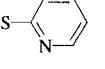
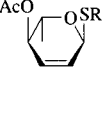
Glycol	Nucleophile	Reaction Conditions	Product(s)	$\alpha:\beta$, Yield(s) (%) Refs.	
	MeSH	SnCl ₄ , CH ₂ Cl ₂ , rt, 12 h		R	
	PhSH	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , -78°		Me	1:0 (41) 35
	PhSH	SnCl ₄ , CH ₂ Cl ₂ , -20° to rt		Ph	— (—) 194
	<i>n</i> -C ₆ H ₁₃ SH	SnCl ₄ , CH ₂ Cl ₂ , -20° to rt		Ph	— (96) 196
				<i>n</i> -C ₆ H ₁₃	1:0 (43) 35
	AcSH	BF ₃ •Et ₂ O		— (—) 197	
	TMSS- 	BF ₃ •Et ₂ O, C ₆ H ₆ , 5°, 5 min		R	
	TMSSPh	BF ₃ •Et ₂ O, C ₆ H ₆ , 5°, 5 min		Ph	1:0 (82) 103
	MeSH	SnCl ₄ , Cl(CH ₂) ₂ Cl, rt, 2.5 h		R	
	TMSOC(=S)Me	BF ₃ •Et ₂ O, C ₆ H ₆ , 80°		SMe	1:0 (55) 35
	HS- 	BF ₃ •Et ₂ O, Cl(CH ₂) ₂ Cl, 20°, 4 d		S	1:1.5 (86) 103
	HS- 	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , rt, 1 h		S- 	1:0 (63) 349
	PhSH	BF ₃ •Et ₂ O, C ₆ H ₆		SPh	1:0 (92) 103
	<i>n</i> -C ₆ H ₁₃ SH	SnCl ₄ , Cl(CH ₂) ₂ Cl, rt, 3 h		SC ₆ H _{13-<i>n</i>}	8:1 (80) 195
	<i>c</i> -C ₆ H ₁₁ SH	LiBF ₄ , MeCN, rt, 7 h		SC ₆ H _{11-<i>c</i>}	1:0 (41) 35
PhSO ₂ H	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , Ar, rt, 2 h	S(O ₂)Ph	9:1 (72) 66		
				1:1 (46) 198	
	TMSSPh	BF ₃ •Et ₂ O, C ₆ H ₆ , 5°, 5 min		1:0 (64) 103	
	AcSH	BF ₃ •Et ₂ O		— (—) 103	
	HS- 	BF ₃ •Et ₂ O, C ₆ H ₆ , 5°, 5 min		R	
	PhSH	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , -78°		Ph	1:0 (83) 103
				1:0 (71) 194	

TABLE 4. 2,3-UNSATURATED GLYCOSYL AZIDES AND N-GLYCOSIDES

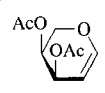
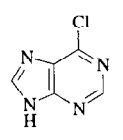
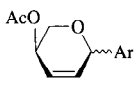
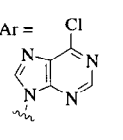
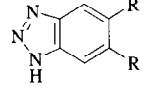
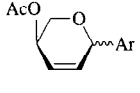
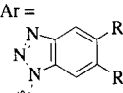
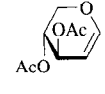
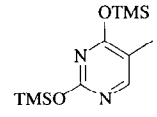
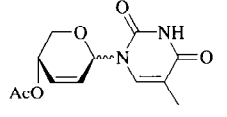
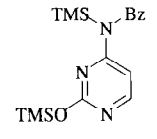
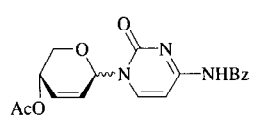
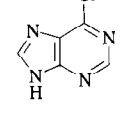
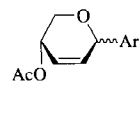
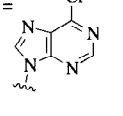
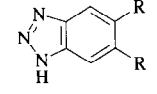
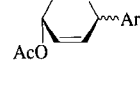
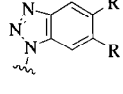
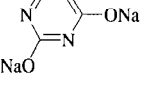
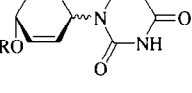

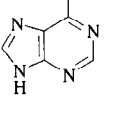
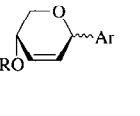
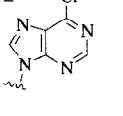
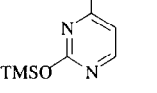
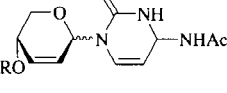
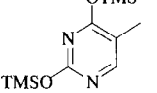
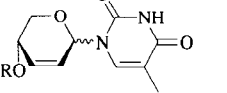
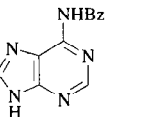
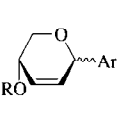
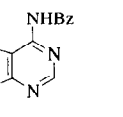
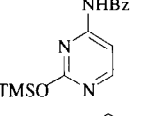
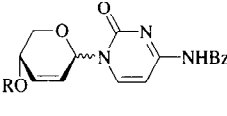
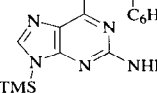
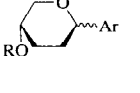
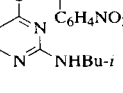
Glycal	Nucleophile	Reaction Conditions	Product(s)	$\alpha:\beta$, Yield(s) (%)	Refs.
C ₅ 		CF ₃ CO ₂ H, EtOAc, 95°, 24 h	 Ar = 	1:1.5 (20)	209
	 R = Cl, H, Me	CF ₃ CO ₂ H, EtOAc, 100°, 24 h	 Ar = 	— (—)	350
		LiClO ₄ , TrClO ₄ , Cl(CH ₂) ₂ Cl, rt, 10 min		1:0 (75)	70
		—		— (40)	351
		CF ₃ CO ₂ H, EtOAc, 95°, 24 h	 Ar = 	1:2 (50)	209
	 R = Cl, H, Me	CF ₃ CO ₂ H, EtOAc, 110°, 24 h	 Ar = 	— (16) — (45) — (11)	43, 350 43, 350 43, 350
		DMF, 190°, 1 h		3:5 (23)	40, 211
 R = COC ₆ H ₄ NO ₂ -p		DMF, 190°, 10 min	 Ar = 	1:1 (57)	40, 211
		DMF, 110°, 5 min		1:1 (52)	40, 211
		DMF, 110°, 7 h		1:1 (48)	40, 211
		DMF, 190°, 10 min	 Ar = 	1:1 (60)	40, 211
		DMF, 190°, 15 min		1:1 (73)	40, 211
		DMF, 190°, 40 min	 Ar = 	2:1 (76)	40, 211

TABLE 4. 2,3-UNSATURATED GLYCOSYL AZIDES AND N-GLYCOSIDES (Continued)

Glycol	Nucleophile	Reaction Conditions	Product(s)	$\alpha:\beta$, Yield(s) (%)	Refs.
		SbCl ₅ , EtOAc, rt, 15 min		1.6:1 (64)	51
		TsOH, 140°, 30 min		1:0 (12)	245
		DEAD, Ph ₃ P, C ₆ H ₆ , rt, 10 h		1.8:1 (70)	110
	Intramolecular	Pd(MeCN) ₂ Cl ₂ , MeCN, 81°, 2 h		— (40)	160
	TMSN ₃	SnCl ₄ , MeCN, 0°		4:1 (25)	138
	TMSN ₃	Sc(OTf) ₃ , CH ₂ Cl ₂ , rt, 4.5 h		2.3:1 (88)	78
		PhCOMe, 202°, 10 h		— (11)	207
		$\frac{R}{Me}$ LiClO ₄ , TrClO ₄ , Cl(CH ₂) ₂ Cl, N ₂ , MS, rt, 3 h		1:1.1 (63)	69
		N(Me)Bn TMSOTf, MeCN, 0°, 1 h		1:1.1 (67)	352
		LiClO ₄ , Cl(CH ₂) ₂ Cl, N ₂ , MS, rt, 3 h		0:1 (56)	69
		TrClO ₄ , Cl(CH ₂) ₂ Cl, N ₂ , rt, 5 min		1:1 (61)	69
		$\frac{R^1}{Cl} \quad \frac{R^2}{H}$ MeNO ₂ , TsOH, 101°, 9 h		— (60)	207
		SMe H TsOH, 120°, 2.5 h, low pressure		— (~5)	353
		NHAc H TsOH, 140°, 2 h, low pressure		— (~5)	353
		H H CF ₃ CO ₂ H, EtOAc, 90°, 2-4 d		2:1 (28)	120
		H TMS LiTrClO ₄ , TrClO ₄ , Cl(CH ₂) ₂ Cl, N ₂ , rt, 5 min		1.2:1 (76)	69
		$\frac{R}{H}$ TsOH, 120°, 3 h		— (42)	17
	TMS	LiTrClO ₄ , TrClO ₄ , Cl(CH ₂) ₂ Cl, N ₂ , rt, 5 min		1:1 (61)	69
		$\frac{R}{Cl}$ CF ₃ CO ₂ H, EtOAc, 90°, 2-4 d		1.3:1 (40)	120, 208
	H	CF ₃ CO ₂ H, EtOAc, 90°, 2-4 d		1:1 (20)	120, 208
	Me	CF ₃ CO ₂ H, EtOAc, 90°, 2-4 d		1:1 (12)	120, 208

TABLE 4. 2,3-UNSATURATED GLYCOSYL AZIDES AND *N*-GLYCOSIDES (Continued)

Glycal	Nucleophile	Reaction Conditions	Product(s)	$\alpha:\beta$, Yield(s) (%)	Refs.
	TMSN ₃	(PhIO) _n , CH ₂ Cl ₂ , -20°		3:1 (50)	164
	NaN ₃	HMPA, N ₂ , 90°, 65 h		— (17)	205
	TMSN ₃	Sc(OTf) ₃ , CH ₂ Cl ₂ , rt, 8 h	I	2.3:1 (85)	78
		LiClO ₄ , TrClO ₄ , Cl(CH ₂) ₂ Cl, N ₂ , MS, rt, 3 h		1.1:1 (81)	69
		LiClO ₄ , TrClO ₄ , Cl(CH ₂) ₂ Cl, N ₂ , MS, rt, 3 h		1:1.2 (63)	69
	"	TMSOTf, MeCN, 0°, 1.5 h	I	1:1.5 (52)	354
		$\frac{R}{\text{NHBz}}$ LiClO ₄ , TrClO ₄ , Cl(CH ₂) ₂ Cl, N ₂ , MS, rt, 3 h		1.2:1 (61)	69
	Cl	LiClO ₄ , TrClO ₄ , Cl(CH ₂) ₂ Cl, N ₂ , MS, rt, 3 h		1.2:1 (70)	69
	$\frac{R}{\text{H}}$ TMS	TsOH, 140°, 15 min TrClO ₄ , Cl(CH ₂) ₂ Cl, N ₂ , rt, 5 min		1:0 (23)	245
	TMS			1.2:1 (72)	69
	NaN ₃	DMF, 140°, 2.5 h		5:1 (24)	204
	PhI(N ₃) ₂ ^a	CH ₂ Cl ₂ , -20° to rt		1:1 (37)	355

^a WARNING: this reagent is explosive and should be handled with appropriate precautions.

TABLE 5. 2,3-UNSATURATED C-GLYCOSIDES

Glycal	Nucleophile	Reaction Conditions	Product(s)	$\alpha:\beta$, Yield(s) (%)	Refs.
		$\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , -78 to -60°, 1 h		1:38 (96)	357
		$\text{Li}_2\text{Pd}(\text{OAc})_2\text{Cl}_2$, MeCN , 25°, 12 h		1:0 (20)	356
		$\text{Pd}(\text{PhCN})_2\text{Cl}_2$, rt, 13 h $\text{BF}_3 \cdot \text{Et}_2\text{O}$, rt, 15 min		1:4 (65) 19 1:7 (55) 19	
	Et_2Zn	$\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , -20° to rt, 1 h		12:1 (53)	215
	$\text{TMS}-\text{C}\equiv\text{C}-\text{TMS}$	TiCl_4 , CH_2Cl_2 , -40 to -15°, 2 h		<1:19 (97)	55
	$\text{TMS}-\text{CH}=\text{CH}_2$	$\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , -40 to -15°, 2 h		1:19 (95)	55
	$\text{TMS}-\text{C}\equiv\text{C}-\text{R}$	TiCl_4 , CH_2Cl_2 , -20°, 2 h		<1:19 (54)	55
	$\text{TMS}-\text{C}\equiv\text{C}-\text{R}$	SnCl_4 , CH_2Cl_2 , -20°, 2 h		<1:19 (83)	55
	Et_2AlCN	C_6H_6 , rt, 1-4 h		1.5:1 (88)	93
	Et_2Zn	$\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , -20° to rt, 1 h		24:1 (80)	215
	$\text{TMS}-\text{C}\equiv\text{C}-\text{TMS}$	TiCl_4 , CH_2Cl_2 , -40 to -15°, 2 h		<1:19 (73)	55
	$\text{TMS}-\text{C}\equiv\text{C}-\text{SPh}$	$\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , 0°, 15 min		<1:19 (88)	55
	$\text{TMS}-\text{CH}=\text{CH}_2$	$\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , -40 to -15°, 2 h		<1:19 (99)	55
	$\text{TMS}-\text{C}\equiv\text{C}-\text{H}$	TiCl_4 , CH_2Cl_2 , -40 to -15°, 2 h		<1:19 (99)	55
		ZnBr_2 , CH_2Cl_2 , 0°, 1 h		1:0 (96)	48
		$\text{Pd}(\text{PhCN})_2\text{Cl}_2$, rt, 13 h $\text{BF}_3 \cdot \text{Et}_2\text{O}$, rt, 15 min		1:4 (65) 19 1:7 (55) 19	
		$\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , -20 to 0°, 1 h		1:6 (65)	55
	AcClO_4	CH_2Cl_2 , -78°, 20 h		1:0 (21)	228
		ZnBr_2 , CH_2Cl_2 , 0°, 1 h		1:0 (>80)	62, 63

TABLE 5. 2,3-UNSATURATED C-GLYCOSIDES (Continued)

Glycol	Nucleophile	Reaction Conditions	Product(s)	$\alpha:\beta$, Yield(s) (%)	Refs.
		TiCl ₄ , CH ₂ Cl ₂ , -20°, 2 h		<1:19 (87)	55
		SnCl ₄ , CH ₂ Cl ₂ , -20°, 40 min		<1:19 (96)	55
		SnCl ₄ , CH ₂ Cl ₂ , -20°, 2 h		0:1 (40)	358
	Intramolecular	C ₆ H ₆ , 65°, 1 h		— (>59)	116
	TMSCN	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , 0°, 0.5 h		— (76)	359
	Ph ₂ Cu(CN)Li ₂	1. THF, Ar, CuCN, PhLi -50°, 10 min 2. Ac ₂ O, -25°		1:0 (87)	22
	Ph ₂ Cu(CN)Li ₂	1. THF, Ar, CuCN, PhLi -50°, 10 min 2. Ac ₂ O, -25°		1:0 (87)	22
	TMS-protected propene	TiCl ₄ , CH ₂ Cl ₂ , -78°, 20 min		6:1 (95)	52
		BF ₃ •Et ₂ O, C ₆ H ₆ , rt		5:1 (81)	19
		Pd(PhCN) ₂ Cl ₂ , rt, 13 h		5:1 (62)	19
	Intramolecular	MeC(OMe) ₂ NMe ₂ , xylene, 140°, 6 h		1:0 (85)	24
R^1 H	MeMgI	THF, 0°, 30 min		1:2.5 (21)	23
Ms		THF, 0°, 30 min		0:1 (73)	23
Ms		THF, 0°, 30 min		0:1 (77)	23
	Intramolecular	PhCN, 180°, 2 h		1:0 (75)	24
	Intramolecular	1. C ₆ H ₆ , 80°, 19 h 2. CH ₂ N ₂ , Et ₂ O		9:1 (78)	259

TABLE 5. 2,3-UNSATURATED C-GLYCOSIDES (Continued)

Glycal	Nucleophile	Reaction Conditions	Product(s)	α : β , Yield(s) (%)	Refs.
		TMSOTf, CH ₂ Cl ₂ :MeCN (2:1), -78°, 1 h		>99:1 (90)	73, 74
	Et ₂ Zn	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , -20° to rt, 1 h		1:0 (73)	215
	BrZn-CH ₂ -CO ₂ Bu- <i>t</i>	Me ₃ SiOTf, CH ₂ Cl ₂ , 0°, 1 h		2:1 (16)	218
		SnCl ₄ , CH ₂ Cl ₂ , -20°, 30 min		1:0 (82)	360
		TiCl ₄ , CH ₂ Cl ₂ , -78°, 20 min		30:1 (93)	52
		DDQ, MeCN, 70°, 48 h	I	>99:1 (76)	87
		TMSOTf, CH ₂ Cl ₂ :MeCN (2:1), -78°, 3 h	I	>99:1 (19)	73, 74
		CH ₂ Cl ₂ , Montmorillonite, 25°, 3 h	I	18:1 (84)	85
		LiBF ₄ , MeCN, 82°, 4.5 h	I	20:1 (90)	65
		BF ₃ •Et ₂ O, MeCN, -30°, 10 min		1:0 (76)	136
		TMSOTf, CH ₂ Cl ₂ , 25°, 2 h		1:4.3 (64)	75
		Pd(PhCN) ₂ Cl ₂ , rt, 13 h	I	1:0 (59)	19
		BF ₃ •Et ₂ O, MeCN, -30°, 2 h		1:0 (99)	137
				1:0 (72)	137
		AcClO ₄ , CH ₂ Cl ₂ , -78°, 20 h		1:0 (77)	228
		BF ₃ •Et ₂ O, PhMe, 0°, 5 min	I	1:0 (44)	224
		CH ₂ Cl ₂ , rt, 6 h, ultrasonics		100:1 (12)	150
		BF ₃ •Et ₂ O, C ₆ H ₆ , rt		1:0 (81)	19
		Pd(PhCN) ₂ Cl ₂ , rt, 13 h	I	1:0 (65)	19
	PhB(OH) ₂	Pd(OAc) ₂ , MeCN, rt		1:0 (80)	151

TABLE 5. 2,3-UNSATURATED C-GLYCOSIDES (Continued)

Glycal	Nucleophile	Reaction Conditions	Product(s)	$\alpha:\beta$, Yield(s) (%)	Refs.
	C ₆ H ₆	Pd(OAc) ₂ , AcOH, 120°, 2 h		1:0 (51)	153
	MeOC ₆ H ₄ F- <i>p</i>	Pd(OAc) ₂ , AcOH, 120°, 2 h		1:0 (59)	153
	MeOC ₆ H ₄ NO ₂ - <i>p</i>	Pd(OAc) ₂ , AcOH, 120°, 2 h		1:0 (25)	153
	MeOC ₆ H ₄ OMe- <i>m</i>	Pd(OAc) ₂ , AcOH, 120°, 1.5 h		1:0 (67)	153
	MeOC ₆ H ₄ OMe- <i>p</i>	Pd(OAc) ₂ , Cu(OAc) ₂ ·H ₂ O, AcOH, 120°, 2 h		1:0 (43)	153
	TMSCN	Pd(OAc) ₂ , MeCN, 80°, 24 h		3:1 (99)	157
	TMSCN	80°, 84 h	I	2.8:1 (84)	213
		TMSOTf, CH ₂ Cl ₂ :MeCN (2:1), -78°, 30 min		>99:1 (91)	73, 74
		Pd(dba) ₂ /dppe, THF, rt		0:1 (56)	111
		Pd(dba) ₂ /dppe, THF, DMF, MeCN, rt, 2 h		0:1 (63)	111
	NaCN	BF ₃ ·Et ₂ O, MeCN, -15°		1.5:1 (68)	138
	TMSCN	BF ₃ ·Et ₂ O, CH ₂ Cl ₂ , rt, 5 min	I	1:0 (79)	125, 138
	TMSCN	Pd(OAc) ₂ , MeCN, 20°, 3 h	I	1.4:1 (95)	157
	TMSCN	80°, 13 h	I	1.4:1 (95)	213
	TMSCN	Se(OTf) ₃ , CH ₂ Cl ₂ , rt, 4 h	I	1.5:1 (90)	78
	Et ₂ AlCN	C ₆ H ₆ , 80°	I	1:0 (90)	24, 93

TABLE 5. 2,3-UNSATURATED C-GLYCOSIDES (Continued)

Glycal	Nucleophile	Reaction Conditions	Product(s)	α : β , Yield(s) (%)	Refs.
	Et ₂ Zn	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , -20° to rt, 1 h		R Et	3.2:1 (95) 215
		FeCl ₃ , Ac ₂ O, CH ₂ Cl ₂		CH ₂ CH(OAc) ₂	8:1 (83) 49
		LiClO ₄ , Et ₂ O, 0°, 1 h		CH ₂ CO ₂ Et	3:1 (61) 68
		BF ₃ •Et ₂ O, CF ₃ SiMe ₃ , Bu ₄ N ⁺ Ph ₃ SnF ₂ ⁻ , -40° to rt			4:1 (60) 361
	BrZnCH ₂ CO ₂ Bu- <i>t</i>	TMSOTf, CH ₂ Cl ₂ , 0°, 1 h		CH ₂ CO ₂ Bu- <i>t</i>	1:2 (49) 214
	IZnCH ₂ CO ₂ Bu- <i>t</i>	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , -20° to rt, 3-8 h		CH ₂ CO ₂ Bu- <i>t</i>	4:1 (29) 215
	TMS—≡—TMS	TiCl ₄ , CH ₂ Cl ₂ , -20°, 15 h			1:0 (75) 127, 219
	TMS—≡—SPh	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , 0°, 1 h			1:0 (84) 219
	TMS—≡	SnCl ₄ , CH ₂ Cl ₂ , -20°, 30 min			1:0 (82) 360
	TMS—≡	TMSOTf, MeCN, 0°			1:0 (83) 362
		BF ₃ •Et ₂ O, CH ₂ Cl ₂ , rt, 0.5 h			16:1 (85) 49
	TMS—CH=CH ₂	TiCl ₄ , CH ₂ Cl ₂ , -78°, 20 min			16:1 (85) 52
	TMS—CH=CH ₂	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , -50°, 1 h			6:1 (100) 127
	TMS—CH=CH ₂	DDQ, MeCN, 50°, 48 h			16:1 (85) 87
	TMS—CH=CH ₂	TMSOTf, CH ₂ Cl ₂ :MeCN (2:1), -78°, 30 min			37:1 (63) 73, 74
	TMS—CH=CH ₂	CH ₂ Cl ₂ , Montmorillonite, 25°, 1 h			3.6:1 (95) 85
		BF ₃ •Et ₂ O, CH ₂ Cl ₂ , -40°, 2 h			1:0 (27) 127
IZn—CH ₂ CH ₂ CH ₂ CN		BF ₃ •Et ₂ O, CH ₂ Cl ₂ , -20° to rt, 3-8 h			5:1 (63) 215
		Pd(PhCN) ₂ Cl ₂ , rt, 13 h			4:1 (85) 19
IZn—CH ₂ CH ₂ CH ₂ CO ₂ Et		BF ₃ •Et ₂ O, CH ₂ Cl ₂ , -20° to rt, 3-8 h			5:1 (87) 215
		BF ₃ •Et ₂ O, MeCN, -30°, 10 min			8:1 (58) 136
TMS—≡—CH=CHCl		SnCl ₄ , CH ₂ Cl ₂ , 0°, 1 h			1:0 (81) 219
		Li ₂ Pd(OAc) ₂ Cl ₂ , MeCN, 25°, 12 h			— (20) 356
		TMSOTf, CH ₂ Cl ₂ , 25°, 2 h			1:4 (68) 75
IZn—CH ₂ CH ₂ CH ₂ —		BF ₃ •Et ₂ O, THF, 0 to 30°, ultrasonics			9:1 (50) 146
	R ¹				$\frac{S}{R}$
	H	ZnBr ₂ , CH ₂ Cl ₂ , 0°, 1 h			3:2 1:0 (82) 48
	Me	ZnBr ₂ , CH ₂ Cl ₂ , 0°, 1 h			1:1 1:0 (57) 48

TABLE 5. 2,3-UNSATURATED C-GLYCOSIDES (Continued)

Glycal	Nucleophile	Reaction Conditions	Product(s)	$\alpha:\beta$, Yield(s) (%) Refs.
		$\text{BF}_3 \cdot \text{Et}_2\text{O}$, MeCN, rt, 20 min		1:0 (63) 61
		$\text{Pd}(\text{PhCN})_2\text{Cl}_2$, rt, 13 h $\text{BF}_3 \cdot \text{Et}_2\text{O}$, C_6H_6 , rt		5:1 (83) 19 5:1 (73) 19
		EtAlCl_2 , CH_2Cl_2 , -20° , 5 min		10:1 (80) 61
		R^1 OH OAc SO_2Ph		1:0 (90) 61 1:0 (60) 61 1:0 (94) 61
	PhB(OH) ₂	$\text{Pd}(\text{OAc})_2$, MeCN, rt	Ph	1:0 (82) 151
	PhOC _n H _{2n+1} n = 6, 8, 10, 12	SnCl_4 , CH_2Cl_2 , rt, 2 h	$\text{C}_6\text{H}_4\text{OC}_n\text{H}_{2n+1}-p$	1:8 (30) 363
	HOC ₆ H ₄ OMe- <i>p</i>	$\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , -10° , 1 h	2-HOC ₆ H ₃ OMe-5	3:4 (72) 179, 180
		CH_2Cl_2 , rt, 6 h, ultrasonics		
	R^1 R^2 R^3			
	H H <i>t</i> -Bu			>100:1 (71) 150
	H —OCH ₂ O—			27:1 (80) 150
	H H H			26:1 (63) 150
	H H OMe			>100:1 (82) 150
	H OMe H			21:1 (69) 150
	<i>t</i> -Bu H OMe			60:1 (66) 150
	PhOMe	SnCl_4 , $\text{Cl}(\text{CH}_2)_2\text{Cl}$	$\text{C}_6\text{H}_4\text{OMe}-p$	0:1 (—) 141
		SnCl_4 , CH_2Cl_2 , 0° , 1.25 h		1:0 (79) 219, 221
		$\text{BF}_3 \cdot \text{Et}_2\text{O}$, MeCN, -30° , 2 h		1:0 (80) 137
		$\text{BF}_3 \cdot \text{Et}_2\text{O}$, C_6H_6 , rt, 15 min		1:0 (10) 122 (OAc) 0:1
I		AcClO_4 , CH_2Cl_2 , -78° , 20 h	II	1:0 (61) 228 (OAc) 1.5:1
		$\text{BF}_3 \cdot \text{Et}_2\text{O}$, CF_3TMS , $\text{Bu}_4\text{N}^+\text{Ph}_3\text{SnF}_2^-$, -4° to rt		4:1 (75) 361
		$\text{Yb}(\text{OTf})_3$, CH_2Cl_2 , rt, 12 h		5:1 (88) 81
	BnZnBr	TMSOTf, CH_2Cl_2 , -20° to rt, 3-8 h	Bn	1.7:1 (57) 215
	$\text{IC}_6\text{H}_4\text{CH}_2\text{ZnBr}-p$	$\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , 30 to 0° , 0.5 h	$\text{CH}_2\text{C}_6\text{H}_4-l-p$	3.5:1 (75) 148
		SnBr_4 , CH_2Cl_2 , rt, 5 min		1:0 (85) 61

TABLE 5. 2,3-UNSATURATED C-GLYCOSIDES (Continued)

Glycal	Nucleophile	Reaction Conditions	Product(s)	$\alpha:\beta$, Yield(s) (%)	Refs.
	 R ¹ = H, <i>t</i> -Bu	SnBr ₄ , CH ₂ Cl ₂ , rt, 5 min		1:0 (94)	61
		BF ₃ •Et ₂ O, C ₆ H ₆ , rt		— (82)	19
	Ph-C(=O)-TMS	BF ₃ •Et ₂ O, CF ₃ TMS, Bu ₄ N ⁺ Ph ₃ SnF ₂ ⁻ , -40° to rt		3:1 (60)	361
	BnCH ₂ ZnI	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , -20° to rt, 3-8 h	CH ₂ Bn	7:1 (53)	215
		BF ₃ •Et ₂ O, CH ₂ Cl ₂		4:1 (60)	364
		BF ₃ •Et ₂ O, CH ₂ Cl ₂ , -40 to 0°, 0.5 h		4:1 (99)	140
		BF ₃ •Et ₂ O, CH ₂ Cl ₂ , rt		1:0 (37)	218
	C ₈ H ₁₇ -C(=O)-TMS	BF ₃ •Et ₂ O, CF ₃ TMS, Bu ₄ N ⁺ Ph ₃ SnF ₂ ⁻ , -40° to rt		4:1 (63)	361
		SnCl ₄ , CH ₂ Cl ₂ , -22°, 75 min		1:1 (94)	365
	R ¹ =	SnCl ₄ , CH ₂ Cl ₂ , 0°, 3 h		3.4:1 (71)	219, 221
		SnCl ₄ , CH ₂ Cl ₂ , 0°, 15 min		1:0 (78)	221
C ₆ H ₆		Pd(OAc) ₂ , AcOH, 80°, 8 h		R:Ph OAc:1:0 (54) H:1:0 (10)	153, 154, 156
PhOMe		Pd(OAc) ₂ , AcOH, 120°, 2 h		OAc:1:0 (41)	153
MeOC ₆ H ₄ OMe- <i>m</i>		Pd(OAc) ₂ , Cu(OAc) ₂ •H ₂ O, AcOH, 90°, 10 h		OAc:1:0 (36)	153

TABLE 5. 2,3-UNSATURATED C-GLYCOSIDES (Continued)

Glycal	Nucleophile	Reaction Conditions	Product(s)	$\alpha:\beta$, Yield(s) (%)	Refs.
	R = Ac	TMSOTf, CH ₂ Cl ₂ , -40 to 0°, 8 h		88:1 (91)	76
	R =	Intramolecular		0:1 (86)	262, 366
	TMS	BF ₃ •Et ₂ O		20:1 (88)	367
	TMSO	BF ₃ •Et ₂ O	I R = CH ₂ CH=CH ₂ I R = CH ₂ COPh	5:1 (80)	367
	Et ₂ Zn	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , -20° to rt, 1 h		2:1 (81)	215
	R ¹	Et ₂ Zn		4.1:1 (87)	215
	R ¹	TMSOTf, CH ₂ Cl ₂ , 25°, 2 h		1:1.6 (98)	75
	R ¹	Intramolecular	CH ₂ CO ₂ TBDMS	0:1 (55)	116
	TBDMSO	LiClO ₄ , EtOAc		1:0 (90)	67
	TBDMSOC ₆ H ₄ Br- <i>o</i>	<i>t</i> -BuLi, ZnCl ₂ , Et ₂ O, -70 to 25°		>10:1 (82)	216
		Pd(OAc) ₂ , MeCN, rt, 12 h		8:1 (64)	152
		Pd(OAc) ₂ , NaOAc, Bu ₃ N, I DMF, rt, 6 d		9:1 (61)	152
	TMS	TiCl ₄ , CH ₂ Cl ₂ , -78°, 20 min		1:0 (99)	52
		AcClO ₄ , CH ₂ Cl ₂ , -78°, 20 h		1:0 (59)	228
	Intramolecular	C ₆ H ₆ , 60°, 2 h	RO	— (>40)	116

TABLE 5. 2,3-UNSATURATED C-GLYCOSIDES (Continued)

Glycal	Nucleophile	Reaction Conditions	Product(s)	$\alpha:\beta$, Yield(s) (%)	Refs.
	TMS-CH=CH ₂	TMSOTf, CH ₂ Cl ₂ :MeCN (2:1), -78°, 2 h		99:1 (66)	73, 74
	AlMe ₃	TiCl ₄ , CH ₂ Cl ₂ , -78°		1:0 (72)	53
	TMSCN	BF ₃ ·Et ₂ O, MeCN, 0°, 45 min		R CN	9:1 (80) 224
	Et ₂ AlCN	C ₆ H ₆ , rt, 1-4 h		CN	1.5:1 (90) 93
	TMS-CH=CH ₂	DDQ, MeCN, 70°, 48 h			> 99:1 (74) 87
	TMS-CH=CH ₂	CH ₂ Cl ₂ , montmorillonite, 25°, 3 h			67:1 (80) 85
	TMS-CH=CH ₂	TMSOTf, CH ₂ Cl ₂ :MeCN (2:1), -78°, 2 h			99:1 (20) 73, 74
	TBDMSO MeO	LiCo(B ₉ C ₂ H ₁₁) ₂ , ClCH ₂ CH ₂ Cl, rt, 5 h		1.5:1 (84)	368
	TMS-CH=CH ₂	TMSOTf, CH ₂ Cl ₂ , -78°, 30 min		99:1 (94)	73, 74
	Intramolecular	1. <i>n</i> -BuLi, THF, -78° 2. EtCOCl 3. LDA, THF 4. TBDMSCl, 35°, 2 h		0:1 (79)	263, 264
	AlMe ₃	TiCl ₄ , CH ₂ Cl ₂ , -78°		R Me	4:5 (89) 53
	TMSCN	BF ₃ ·Et ₂ O, MeCN, 0°, 45 min		CN	1:1.6 (76) 369
	Et ₂ AlCN	C ₆ H ₆ , rt, 1-4 h		CN	1.5:1 (90) 93
	Et ₂ Zn	BF ₃ ·Et ₂ O, CH ₂ Cl ₂ , -20° to rt, 1 h		Et	1.5:1 (71) 215
	BrZnCH ₂ CO ₂ Bu- <i>t</i>	TMSOTf, CH ₂ Cl ₂ , 0°, 1 h		CH ₂ CO ₂ Bu- <i>t</i>	2:1 (48) 214
			BF ₃ ·Et ₂ O, PhMe, -78° to rt, 1.5 h		CH ₂ CO ₂ Me
	TMS-CH=CH ₂	DDQ, MeCN, 50°, 48 h			15:1 (90) 87
	TMS-CH=CH ₂	CH ₂ Cl ₂ , Montmorillonite, 25°, 1 h			4.2:1 (97) 85
	TMS-CH=CH ₂	CH ₂ Cl ₂ , TMSOTf, -78°, 30 min			10:1 (95) 73, 74
			BF ₃ ·Et ₂ O, CH ₂ Cl ₂		
		TMSOTf, CH ₂ Cl ₂ , 25°, 2 h			1:1.1 (91) 75
		EtAlCl ₂ , C ₃ H ₁₂ , Et ₂ O, -20°, 5 min			6:1 (90) 61

TABLE 5. 2,3-UNSATURATED C-GLYCOSIDES (Continued)

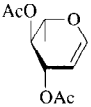
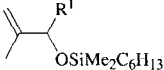
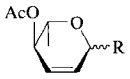


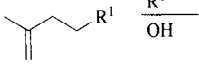
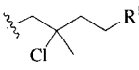

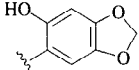

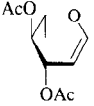
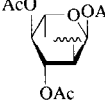


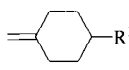
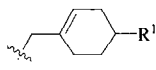
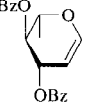
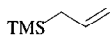
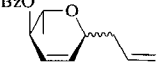
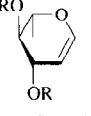
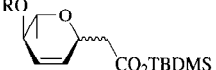
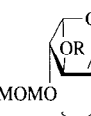
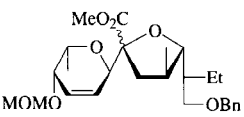

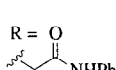
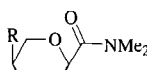

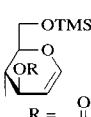
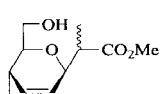
Glycal	Nucleophile	Reaction Conditions	Product(s)	$\alpha:\beta$, Yield(s) (%)	Refs.	
		ZnBr ₂ , CH ₂ Cl ₂ , 0°, 1 h		$\frac{R^1}{H}$ 3:2 1:0 (82) 48 $\frac{R^1}{Me}$ 1:1 1:0 (61) 48		
		BF ₃ ·Et ₂ O ₂ , C ₆ H ₁₄ , EtOAc, -25°, 20 min			1:0 (63) 61	
		OH	TiCl ₄ , C ₆ H ₁₄ , EtOAc, 0°, 3-15 min		1:0 (79) 61	
		OBz	TiCl ₄ , C ₆ H ₁₄ , EtOAc, 0°, 3-15 min		1:0 (70) 61	
		SO ₂ Ph	TiCl ₄ , C ₆ H ₁₄ , EtOAc, 0°, 3-15 min		1:0 (89) 61	
		BrMgO- 	CH ₂ Cl ₂ , rt, 6 h, ultrasonics		8:1 (77) 150	
		Me ₂ Al-C≡C-Bu	CH ₂ Cl ₂ , hexane, -2° to rt, 0.5-1 h		2.1:1 (80) 94	
			AcClO ₄ , CH ₂ Cl ₂ , -78°, 20 h		1:0 (44) 228	
			SnBr ₄ , C ₃ H ₁₂ , Et ₂ O, rt, 5 min		12:1 (80) 61	
		$\frac{R^1}{H}$ <i>t</i> -Bu	H		6:1 (90) 61	
EtAlCl ₂ , C ₃ H ₁₂ , EtOAc, -20°, 5 min			7:1 (93) 61			
	TMS- 	DDQ, MeCN, 50°, 48 h		10:1 (77) 87		
	Intramolecular	C ₆ H ₆ , 60°, 1 h		1:0 (>53) 116		
	Intramolecular	1. LiN(<i>Pr</i> -) ₂ , THF 2. TMSCl 3. CH ₂ N ₂		1:0 (67) 305		
	Intramolecular	R = 		1:0 (87) 372		
		R = CH ₂ OTBDPS	MeC(OMe) ₂ NMe ₂ , xylene, 140°		1:0 (94) 258	
	Intramolecular	1. LDA, THF, -50°, 1 h 2. TMSCl, Et ₃ N, 50°, 4 h 3. Bu ₄ NF 4. CH ₂ N ₂		0:1 (67) 260		

TABLE 5. 2,3-UNSATURATED C-GLYCOSIDES (Continued)

Glycol	Nucleophile	Reaction Conditions	Product(s)	$\alpha:\beta$, Yield(s) (%)	Refs.
	Intramolecular	1. TBDMSCl, LiHMDS 2. C ₆ H ₆ , 80° 3. LiAlH ₄		1:0 (87)	373
	Intramolecular	1. LiHMDS, TMSCl, Py, -78 to 20° 2. CH ₂ N ₂		0:1 (85)	261
	AlMe ₃ TMSCN AlEt ₃ TMS- TMS-	TiCl ₄ , CH ₂ Cl ₂ , -78° TiCl ₄ , CH ₂ Cl ₂ , -78° TiCl ₄ , CH ₂ Cl ₂ , -78° TiCl ₄ , CH ₂ Cl ₂ , -78° TiCl ₄ , CH ₂ Cl ₂ , -78°		<u>R</u> Me CN Et	— (92) 54 — (82) 54 — (82) 54 — (79) 54 — (75) 54
	TBDMSO- TBDMSO-	Cl ₂ Ti(OPr- <i>i</i>), PhMe, -42° ZnBr ₂ , CH ₂ Cl ₂ , rt, 2.5 h		<u>R</u> CH ₂ CHO CH ₂ CO ₂ Me	32:1 (80) 56 2:1 (72) 56
	AlMe ₃ Et ₃ SiH	TiCl ₄ , CH ₂ Cl ₂ , -78° TiCl ₄ , CH ₂ Cl ₂ , -78°		<u>R</u> Me H	— (83) 54 — (92) 54
i) ₃ group at C2, an OSi(Pr- <i>i</i>) ₃ group at C3, and a hydroxyl group at C5."/>	—	(53) 266, 267			
	Intramolecular	CSA, CH ₂ Cl ₂ , rt, 30 h		—	(81) 266, 267
	(R ¹) ₂ R ² Al <u>R¹</u> <u>R²</u> Me Me Pr Pr <i>i</i> -Bu <i>i</i> -Bu Et Bu-	CH ₂ Cl ₂ , hexane, -20° to rt, 0.5-1 h		25:1 (96) 94 7:1 (93) 94 15:1 (74) 94 1:0 (85) 94	
	(R ¹) ₂ R ² Al <u>R¹</u> <u>R²</u> Me Me Me Bu- Me TMS-	CH ₂ Cl ₂ , hexane, -20° to rt, 0.5-1 h		99:1 (91) 94 1:0 (84) 94 1:0 (66) 94	

TABLE 5. 2,3-UNSATURATED C-GLYCOSIDES (Continued)

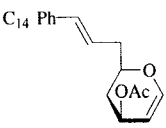
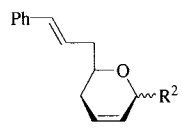
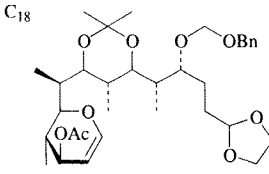
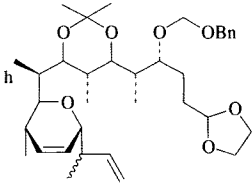
Glycal	Nucleophile	Reaction Conditions	Product(s)	$\alpha:\beta$, Yield(s) (%) Refs.						
<p>C₁₄</p> 	<p>(R¹)₂R²Al</p> <table border="0"> <tr> <td>R¹</td> <td>R²</td> </tr> <tr> <td>Me</td> <td>Me</td> </tr> <tr> <td>Et</td> <td>Bu-C≡C-</td> </tr> </table>	R ¹	R ²	Me	Me	Et	Bu-C≡C-	<p>CH₂Cl₂, hexane, -20° to rt, 0.5-1 h</p>		<p>10:1 (52) 94 1:0 (55) 94</p>
R ¹	R ²									
Me	Me									
Et	Bu-C≡C-									
<p>C₁₈</p> 	<p>TMS-CH=CH-CH₃</p>	<p>ZnBr₂, MeNO₂, -10°, 0.5 h</p>		<p>— (77) 44</p>						

TABLE 6. 2,3-UNSATURATED GLYCOSYL HALIDES


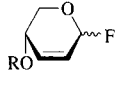
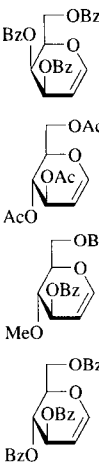
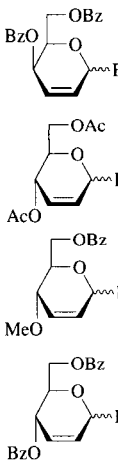
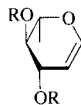
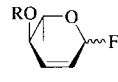
Glycal	Nucleophile	Reaction Conditions	Product(s)	$\alpha:\beta$, Yield(s) (%)	Refs.
 R = Ac R = Bz	F ⁻	Py-HF, CH ₂ Cl ₂ , 0°, 5 min		4:1 (80)	121
	F ⁻	HF in C ₆ H ₆ , 0°, 15 min		4:1 (80)	183
	F ⁻	Py-HF, CH ₂ Cl ₂ , 0°, 5 min		4:1 (80)	121
 BzO OAc AcO MeO BzO	F ⁻	HF, -70°, 15 min		—	(—) 223
	F ⁻	Py-HF, CH ₂ Cl ₂ , 0°, 30 min		9:1 (81)	121
	F ⁻	HF in C ₆ H ₆ , 0°, 30 min		—	(—) 181
	F ⁻	HF, C ₆ H ₆ , -70°, 15 min		—	(100) 374
	F ⁻	Py-HF, CH ₂ Cl ₂ , 0°, 15 min		7:1 (75)	121
	F ⁻	HF in C ₆ H ₆ , 0°, 30 min		—	(90) 181
 R = Ac R = Bz	F ⁻	Py-HF, CH ₂ Cl ₂ , 0°, 30 min		12:1 (79)	121
	F ⁻	HF in C ₆ H ₆ , 0°, 10 min		—	(100) 374

TABLE 7. 2,3-UNSATURATED GLYCOSYL PHOSPHONATES

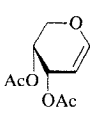

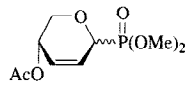


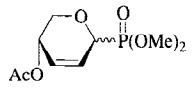
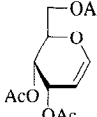

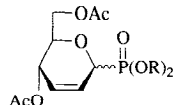


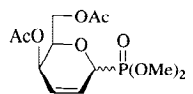
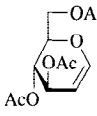

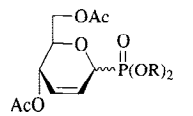
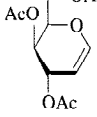

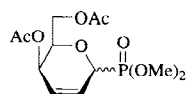


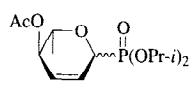
Glycal	Nucleophile	Reaction Conditions	Product(s)	$\alpha:\beta$, Yield(s) (%) Refs.
C ₅ 		BF ₃ •Et ₂ O, C ₆ H ₆ , 60°, 1.5 h		1:1.9 (74) 232
		BF ₃ •Et ₂ O, C ₆ H ₆ , 60°, 1.5 h		1:1.9 (74) 232
C ₆ 		<u>R</u> Me Et	BF ₃ •Et ₂ O, C ₆ H ₆ , 60°, 2 h BF ₃ •Et ₂ O, C ₆ H ₆ , 60°, 2 h	 1:1.9 (57) 232 1:1.4 (34) 232
		BF ₃ •Et ₂ O, C ₆ H ₆ , 60°, 2 h		1:3 (68) 232
		<u>R</u> Me Et Pr- <i>i</i>	BF ₃ •Et ₂ O, C ₆ H ₆ , 60°, 4 h BF ₃ •Et ₂ O, C ₆ H ₆ , 60°, 4 h BF ₃ •Et ₂ O, C ₆ H ₆ , 60°, 4 h	 1:1.9 (57) 232 1:1.4 (34) 232 1:1.2 (93) 234
		BF ₃ •Et ₂ O, C ₆ H ₆ , 60°, 2 h		1:3 (68) 232
		BF ₃ •Et ₂ O, PhMe, 100°, 4 h		— (91) 234

TABLE 8. 2-SUBSTITUTED 2,3-UNSATURATED GLYCOSYL COMPOUNDS

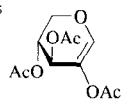
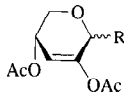
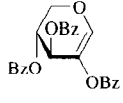
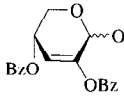
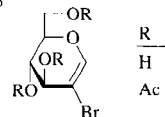
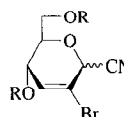
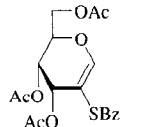
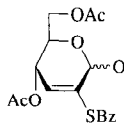
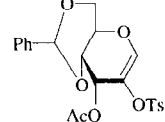
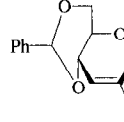
Glycal	Nucleophile	Reaction Conditions	Product(s)	$\alpha:\beta$, Yield(s) (%) Refs.	
	HCl	HCl, C ₆ H ₆ , 30 min		0:1 (100) 231	
	AcOH	118°, 1 h		1:3 (90) 240	
	Theophylline	TsOH, 140°, low pressure, 20 min		— (—) 245	
	Intramolecular	PhNO ₂ , 210°, 75 min		OAc 0:1 (75) 238	
	Intramolecular	BF ₃ •Et ₂ O, C ₆ H ₆ , rt, 5 min		OAc 0:1 (66) 238	
	AcOH	118°, 1 h		1:5 (90) 240	
	CCl ₃ CO ₂ H	BF ₃ •Et ₂ O, C ₆ H ₆ , reflux, 1.5 h		CCl ₃ CO 1:0 (18) 241	
	Intramolecular	PhNO ₂ , 210°, 15 min		Bz 0:1 (80) 238	
		ClC ₆ H ₄ CO ₂ H- <i>m</i>		BF ₃ •Et ₂ O, CH ₂ Cl ₂ , -10° to rt, 30 min	— (78) 172
	R		>49:1 (90) 157		
	H			4:1 (72) 213	
	Ac				
	TMSCN		Pd(OAc) ₂ , MeCN, 80°, 96 h		
	Ac ₂ O	H ₂ SO ₄ , -18°, 24 h		— (—) 375	
	MeO ⁻	MeOH, rt, 45 min		— (60) 144	

TABLE 8. 2-SUBSTITUTED 2,3-UNSATURATED GLYCOSYL COMPOUNDS (Continued)

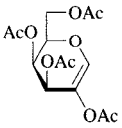
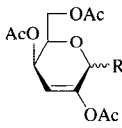


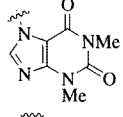
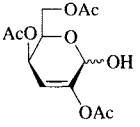
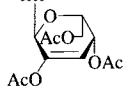
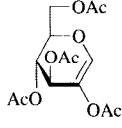
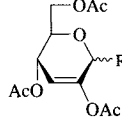






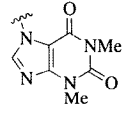
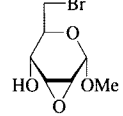
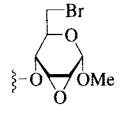
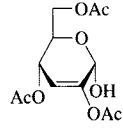
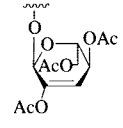
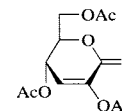
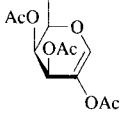
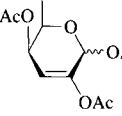
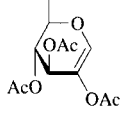
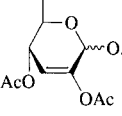
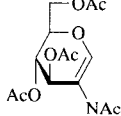

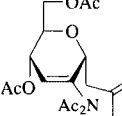
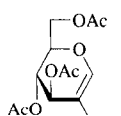
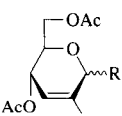
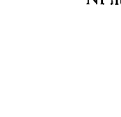
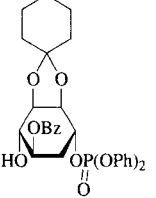

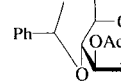
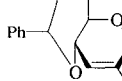
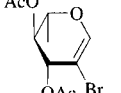
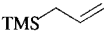
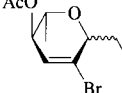
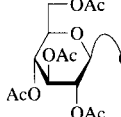
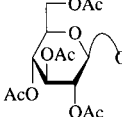
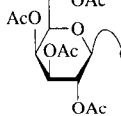
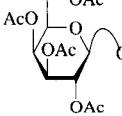
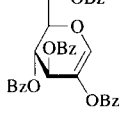
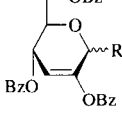






















Glycol	Nucleophile	Reaction Conditions	Product(s)	α,β , Yield(s) (%)	Refs.		
	TMSCN	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , rt, 30 min		R			
	AcOH	118°, 7 h		CN	1:1 (73)	125	
	AcOH	AcOH, MsOH, 100°, 4 h		OAc	1:0 (55)	240	
				OAc	1:0 (94)	240	
		BF ₃ •Et ₂ O, CH ₂ Cl ₂ , rt, 0.5 h		1:0 (51)	49		
	Theophylline	TsOH, 150°, 15 min		1:0 (41)	245, 246		
		1. BF ₃ •Et ₂ O, CH ₂ Cl ₂ , rt, 5 min 2. H ₂ O, rt, 5 min		1:0 (58)	88		
	Cholesterol	NIS, MeCN, benzene, rt, 24 h	O-Cholesteryl	1:0 (23)	234		
	Intramolecular	BF ₃ •Et ₂ O, C ₆ H ₆ , rt, 2.5 h	OAc	— (60)	238		
	HCl	C ₆ H ₆ , 3 h		R			
	HF	-70°, 3 h		Cl	1:0 (100)	231	
	HF	C ₆ H ₆ , 5°		F	7:1 (98)	247	
	MeOH	BF ₃ •Et ₂ O, C ₆ H ₆ , rt, 40 min		F	— (100)	248	
	TMSCN	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , rt, 30 min		OMe	— (100)	241	
	TMSN ₃	Yb(OTf) ₃ , MeCN, 26°, 33 h		CN	1:1 (78)	125, 138	
	Intramolecular	BF ₃ •Et ₂ O, C ₆ H ₆ , rt, 2 h		N ₃	2:1 (95)	80	
	Intramolecular	PhNO ₂ , 210°, 75 min		OAc	1:0 (60)	238	
	AcOH	118°, 3 h		OAc	0:1 (75)	238	
	Ac ₂ O	118°, 3 h		OAc	5.5:1 (65)	237	
	EtOH	ZnCl ₂ , 24°, 10 min		OAc	1:0 (80)	376	
	EtOH	BF ₃ •Et ₂ O, C ₆ H ₆ , rt, 1 h		OEt	1:0 (100)	241	
	EtOH	NIS, MeCN, 0°, rt, 2.5 h		OEt	1:0 (92)	234	
				<i>hν</i> , N ₂ , 27 h		1:1 (80)	244
				BF ₃ •Et ₂ O, CH ₂ Cl ₂ , rt		16:1 (94)	329
		BF ₃ •Et ₂ O, CH ₂ Cl ₂ , rt, 0.5 h		1:0 (71)	49		
	<i>i</i> -PrOH	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , rt	OPr- <i>i</i>	1:0 (63)	296		
	<i>i</i> -PrOH	NIS, MeCN, 0°, rt, 2.5 h	OPr- <i>i</i>	1:0 (91)	234		
	<i>t</i> -BuOH	NIS, MeCN, 0°, rt, 60 h	OBu- <i>t</i>	1:0 (66)	234		
	<i>t</i> -BuOH	BF ₃ •Et ₂ O, C ₆ H ₆ , rt	OBu- <i>t</i>	1:0 (84)	242		
	Theophylline	TsOH, 140°, low pressure, 20 min		1:0 (42)	245, 246		
	HOC ₆ H ₄ OMe- <i>p</i>	BF ₃ •Et ₂ O, C ₆ H ₆	OC ₆ H ₄ OMe- <i>p</i>	1:0 (49)	377		
		BF ₃ •Et ₂ O, PhMe, rt, 12 h		4:1 (59)	187		
		I ₂ , Me ₂ CO-H ₂ O		1:0 (58)	88		
	Cholesterol	BF ₃ •Et ₂ O, C ₆ H ₆ , rt, 0.7-2 h	O-Cholesteryl	1:0 (40)	241		
	Cholesterol	I ₂ , THF, reflux, 4 h	O-Cholesteryl	6:1 (62)	90		
	Cholesterol	NIS, MeCN, 0°, rt, 20 h	O-Cholesteryl	— (73)	234		
	Cholestanol	BF ₃ •Et ₂ O, C ₆ H ₆ , rt, 0.2 h	O-Cholestanyl	1:0 (76)	241		
	CIC ₆ H ₄ CO ₃ H- <i>m</i>	BF ₃ •Et ₂ O, CH ₂ Cl ₂ , -10° to rt, 30 min		— (67)	172		

TABLE 8. 2-SUBSTITUTED 2,3-UNSATURATED GLYCOSYL COMPOUNDS (Continued)

Glycol	Nucleophile	Reaction Conditions	Product(s)	$\alpha:\beta$, Yield(s) (%)	Refs.
	AcOH	MsOH, AcOH, 96°, 2 h		1:0 (57)	240
	Intramolecular	PhNO ₂ , 210°, 40 min		1:3 (60)	238
		BF ₃ •Et ₂ O, CH ₂ Cl ₂ , rt, 0.5 h		— (61)	49
	<i>i</i> -PrOH	BF ₃ •Et ₂ O, MeCN, MS, rt, 15 min		1:0 (75)	378
		BF ₃ •Et ₂ O, MeCN, MS, rt, 15 min		1:0 (94)	378
	MeO ⁻	MeOH, rt, 45 min		— (36)	144
		BF ₃ •Et ₂ O, CH ₂ Cl ₂ , 0 to 20°		4:1 (95)	379
	MeOH	BF ₃ •Et ₂ O, MeOH, CH ₂ Cl ₂ , rt, 1.5 h		1:0 (60)	303
	AcOH	BF ₃ •Et ₂ O, rt, 1 h		19:1 (100)	380
	MeOH	BF ₃ •Et ₂ O, C ₆ H ₆ , 50-60°, 4 h		1:0 (72)	241
	CCl ₃ CO ₂ H	C ₆ H ₆ , 79°, 2 h		1:0 (43)	241
	EtOH	BF ₃ •Et ₂ O, C ₆ H ₆ , 50-60°, 3 h		1:0 (61)	241
	AcOH	118°, 3 h		5:1 (76)	237
	<i>i</i> -PrOH	NIS, MeCN, rt, 20 h		1:0 (49)	234
	<i>n</i> -PrOH	BF ₃ •Et ₂ O, C ₆ H ₆ , 50-60°, 2 h		— (100)	241
	<i>c</i> -C ₆ H ₁₁ OH	BF ₃ •Et ₂ O, C ₆ H ₆ , 50-60°, 2 h		1:0 (41)	241
	HOC ₆ H ₄ NO ₂ - <i>p</i>	BF ₃ •Et ₂ O, C ₆ H ₆ , 50-60°, 0.25-4 h		1:0 (71)	241
	Intramolecular	PhNO ₂ , 210°, 15 min		0:1 (79)	238
	Intramolecular	BF ₃ •Et ₂ O, C ₆ H ₆ , rt, 35 min		4:1 (100)	238
	Cholesterol	BF ₃ •Et ₂ O, C ₆ H ₆ , 50-60°, 0.25 h		1:0 (71)	241
	Theophylline	TsOH, 150°, 35 min		3:1 (80)	246

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TABLE 8. 2-SUBSTITUTED 2,3-UNSATURATED GLYCOSYL COMPOUNDS (Continued)

Glycal	Nucleophile	Reaction Conditions	Product(s)	$\alpha:\beta$, Yield(s) (%)	Refs.
	$\text{ClC}_6\text{H}_4\text{CO}_3\text{H-}m$	$\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , -10° to rt, 30 min		— (91)	172
C_7^a 	$\begin{matrix} \text{R}^1 & \text{R}^2 \\ \text{Me} & \text{CH}_2\text{OAc} \end{matrix}$	LiClO_4 , CH_2Cl_2 , rt, 2 h		1:0 (75)	292
	Bn CH_2OAc	MeOH	$\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , 0° , 2 h	6:1 (72)	291
	Bn CHO	$n\text{-BuCu}$	$\text{BF}_3 \cdot \text{Et}_2\text{O}$, Et_2O , -78° , 1 h	1:0 (70)	149
$\text{C}_{13}, \text{C}_{15}^b$					

^a See the entries included in Table 5, p. 712.^b See the entries included in Table 2, p. 683.

TABLE 9. 2,3-UNSATURATED FURANOID GLYCOSYL COMPOUNDS

Glycal	Nucleophile	Reaction Conditions	Product(s)	$\alpha:\beta$, Yield(s) (%)	Refs.
		Pd(OAc) ₂ , NaHCO ₃ , MeCN, rt, 42 h; 65°, 1 h		$\frac{R}{OH}$ 0:1 (45) 381 + H 1:0 (29) 381	
	Intramolecular	1. <i>n</i> -BuLi, THF, -78° 2. PrCOCl 3. LDA, THF 4. TMSCl, 35°, 15 min 5. H ₃ O ⁺		4:1 (73) 263	
		Pd(OAc) ₂ , (<i>i</i> -Pr) ₂ NEt, MeCN, rt, 3 d		1:0 (78) 382	
		Pd(OAc) ₂ , NaHCO ₃ , MeCN, rt, 24 h; 55°, 1.5 h		— (77) 381	
		Pd(OAc) ₂ , NaHCO ₃ , MeCN, rt, 24 h		— (71) 382	

TABLE 9. 2,3-UNSATURATED FURANOID GLYCOSYL COMPOUNDS (Continued)

Glycal	Nucleophile	Reaction Conditions	Product(s)	$\alpha:\beta$, Yield(s) (%)	Refs.
	$\text{IC}_6\text{H}_4\text{CH}_2\text{ZnBr-}p$	$\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 -30 to 0°, 30 min		1:0 (34)	148
	MeOH	CAN, $\text{CH}_2(\text{CO}_2\text{Pr-}i)_2$		— (70)	254
		$\text{Pd}(\text{OAc})_2$, $(i\text{-Pr})_2\text{NEt}$, MeCN, rt, 2 days; 75°, 2 h		— (33)	382
	$\text{MeOC}_6\text{H}_4\text{R}^1\text{-}p$	$\frac{\text{R}^1}{\text{HgOAc}}$ $\text{Pd}(\text{OAc})_2$, NaHCO ₃ , MeCN, rt, 18 h SnBu_3 $\text{Pd}(\text{OAc})_2$, NaHCO ₃ , MeCN, rt, 18 h	 I $\text{R}^2 = \text{C}_6\text{H}_4\text{OMe-}p$	— (57)	383
		$\text{Pd}(\text{OAc})_2$, NaHCO ₃ , MeCN, rt, 18 h		— (96)	383
		$\text{Pd}(\text{OAc})_2$, NaHCO ₃ , MeCN, rt, 24 h		— (92)	382
		$\text{Pd}(\text{OAc})_2$, MeCN, rt, 24 h		— (66)	383
	MeOH	CH_2Cl_2 , rt, 5 min		— (81)	142
		$\text{Pd}(\text{OAc})_2$, NaHCO ₃ , MeCN, rt, 24 h		— (45)	381
		$\text{Pd}(\text{OAc})_2$, MeCN, rt, 5 min		— (84)	384
	PhMgBr	Ni(O), PhMe, -10°, 5 h		1:0 (68)	147

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TABLE 9. 2,3-UNSATURATED FURANOID GLYCOSYL COMPOUNDS (Continued)

Glycal	Nucleophile	Reaction Conditions	Product(s)	$\alpha:\beta$, Yield(s) (%)	Refs.
	Intramolecular	CH ₂ Cl ₂ /EtOAc (9:1), SiO ₂ , rt, 18 h		$\frac{R^2}{Bz}$ 0:1 (30)	253
	EtOH	20°, 24 h		Et 1:1:1 (72)	253
	Intramolecular	BuLi, THF, -5°, 30 min		0:1 (18)	265
	Intramolecular	1. <i>n</i> -PrCOCl 2. LDA, THF 3. TMSCl 4. CH ₂ N ₂ , Et ₂ O		1:0 (60)	305
	Intramolecular	1. BuLi, THF, Ar, -78° 2. EtCOCl, 0° 3. LDA, THF 4. TMSCl, Et ₃ N, -78° to rt		$\frac{R^2}{CO_2H}$ 0:1 (52)	263
	Intramolecular	Et ₂ O, 0°, spontaneous		0:1 (78)	257
		TMSOTf, CH ₂ Cl ₂ , 25°, 2 h		1:1 (61)	75
	Intramolecular	THF, 65°, 2 d		0:1 (61)	257
	Intramolecular	<i>n</i> -BuLi, THF, -5°, 30 min		0:1 (61)	265
	Intramolecular	<i>n</i> -BuLi, THF, -5°, 30 min		0:1 (30)	265
	Intramolecular	<i>n</i> -BuLi, THF, -5°, 30 min		<i>R:S</i> 1:9 (OH) 0:1 (40)	265
		Pd(OAc) ₂ , NaHCO ₃ , MeCN, rt, 2 h		— (56)	382
		Pd(OAc) ₂ , NaHCO ₃ , MeCN, rt, 2 h		— (88)	382

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The chance discovery by Ann Ryan of an unexpected substitution reaction that occurs with allylic rearrangement when tri-*O*-acetyl-D-glucal is heated with *p*-nitrophenol, and its skillful exploitation by her, Nagendra Prasad, George Sankey, David Ciment, Mitree Ponpipom, and John Hurford under the supervision of one of us (RJF) at Birkbeck College, University of London, in the late 1950s and the 1960s form the basis from which several of the extensive set of reactions described in this review grew. The contributions of these people, who worked with great commitment and apparent enjoyment but with no appreciation that their contributions would lead to the many developments and applications described here, are acknowledged with great pleasure. While their achievements led to simple routes to 2,3-unsaturated compounds with *O*- and *N*-linked groups at C-1 of pyranoid and furanoid derivatives, these were extended and expanded to include methods for the synthesis of *S*- and particularly *C*-linked analogs by many other chemists.

There is another rather different and important acknowledgment to be made because Ann Ryan's discovery was the second observation of the substitution with allylic rearrangement reaction in question. As will be related, the first was recorded by the founding father of carbohydrate chemistry, Emil Fischer, 50 years earlier.

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α -Hydroxylation of Enolates and Silyl Enol Ethers

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Abstract

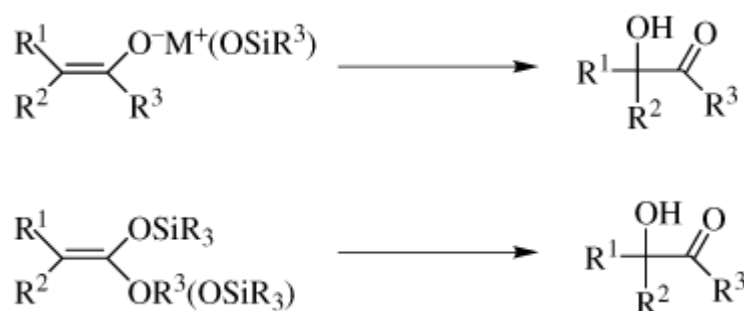
The autoxidation of enolizable carbonyl compounds was reported as early as 1871, and the accelerating action of base is well documented. The products of these reactions, however, were usually mixtures of compounds resulting from decomposition of the unstable α -hydroperoxy intermediates. It was not recognized until the 1960s that these intermediates can be reduced to α -hydroxy compounds with zinc dust. This observation laid the foundation for what has become one of the simplest and most widely used strategies for introducing a hydroxyl group adjacent to a carbonyl group, namely the oxidation of metal enolates. The α -hydroxy carbonyl array not only occurs in many biologically active molecules, but also serves as an important building block for synthesis.

While the oxygenation of enolates still play an important role in the synthesis of α -hydroxy carbonyl compounds, a variety of new, more convenient oxidizing agents, including chiral nonracemic ones, have been introduced. In addition, silyl enol ethers and silyl ketene acetals can serve as educts for α -hydroxycarbonyl compounds. This chapter covers the literature of α -hydroxylation of metal enolates and silyl enol ethers up to the end of 2000. Nitriles and aza-enolates are included. The related α -alkoxylation, α -acyloxylation, and α -sulfonyloxylation of metal enolates are briefly discussed.

1. Introduction

The autoxidation of enolizable carbonyl compounds was reported as early as 1871, (1) and the accelerating action of base is well documented. (2, 3) The products of these reactions, however, were usually mixtures of compounds resulting from decomposition of the unstable α -hydroperoxy intermediates. (2-4) It was not recognized until the 1960's that these intermediates can be reduced to α -hydroxy compounds with zinc dust. (5, 6) This observation laid the foundation of what has become one of the simplest and most widely used strategies for introducing a hydroxy group adjacent to a carbonyl group, namely the oxidation of metal enolates. The α -hydroxy carbonyl array not only occurs in many biologically active molecules, but also serves as an important building block for synthesis. (7-13)

While the oxygenation of enolates with oxygen still plays an important role in the synthesis of α -hydroxy carbonyl compounds, a variety of new, more convenient oxidizing reagents, including chiral nonracemic ones, have been introduced. In addition, silyl enol ethers and silyl ketene acetals can serve as educts for α -hydroxy carbonyl compounds.



This chapter covers the literature of the α -hydroxylation of metal enolates and silyl enol ethers up to the end of 2000. Although they are not strictly enolates, nitrile anions and aza-enolates are also included. Several reviews on this subject have appeared. (2, 8, 12-17) The related α -alkoxylation, α -acyloxylation, and α -sulfonyloxylation of metal enolates and silyl enol ethers are briefly discussed in this chapter; the α -oxygenation of carbonyl compounds via enols, alkyl enol ethers, and vinyl esters is excluded but pertinent references are given in the section on Comparison With Other Methods.

2. Reagents and Mechanisms

2.1. Preparation of Enolates

For reviews on the generation of enolates and other pertinent literature, see references 18-22 23, (ester enolates), 24 (asymmetric enolates), and 25 (boron enolates). See also the literature cited in ref. 26. The most commonly used bases are lithium diisopropylamide (LDA), the alkali salts of hexamethyldisilazane (LiHMDS, NaHMDS, KHMDS), and potassium *tert*-butoxide (KO*Bu-t*). Other bases include the alkali hydrides (LiH, (27) NaH, KH), lithium dimethyl (28) and diethylamide, (29-31) lithium 2,2,6,6-tetramethylpiperidide (LTMP), (32, 33) lithium cyclohexylisopropylamide (LICA), (34-37) triphenylmethyl lithium, (38) *n*-butyllithium, (39-42) *tert*-butyllithium, (43) magnesium diisopropylamide, (44) and trimethyl- and triethylaluminum. (45) Weaker bases can be used for β -dicarbonyl compounds (see the relevant section in Scope and Limitations).

2.2. Preparation of Silyl Enol Ethers and Silyl Ketene Acetals

Reviews on the generation of silyl enol ethers are found in references 16 and 46-48. For the synthesis of silyl ketene acetals see references 49 to 51.

2.3. Oxidants

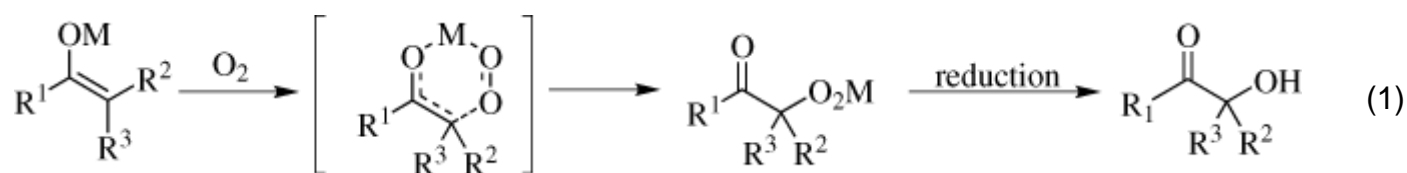
A variety of oxidizing reagents have been explored for the α -hydroxylation of metal enolates and enol silyl ethers. These can be grouped into six categories: oxygen, peroxy reagents, hypervalent iodine reagents, metal oxides, *N*-sulfonyloxaziridines, and miscellaneous reagents. Other reagents are also available for the α -alkoxylation, α -acyloxylation, and α -sulfonyloxylation of enolates and derivatives, and these are briefly discussed in the section on Related Reactions. References to the preparation and commercial availability of the oxidants employed in the hydroxylation of enolates and silyl enol ethers are given in the section on Experimental Conditions.

Mechanisms of the α -hydroxylations are highly dependent on the structure of the oxidizing reagent, the substrate, and the reaction conditions.

2.3.1. Oxygen

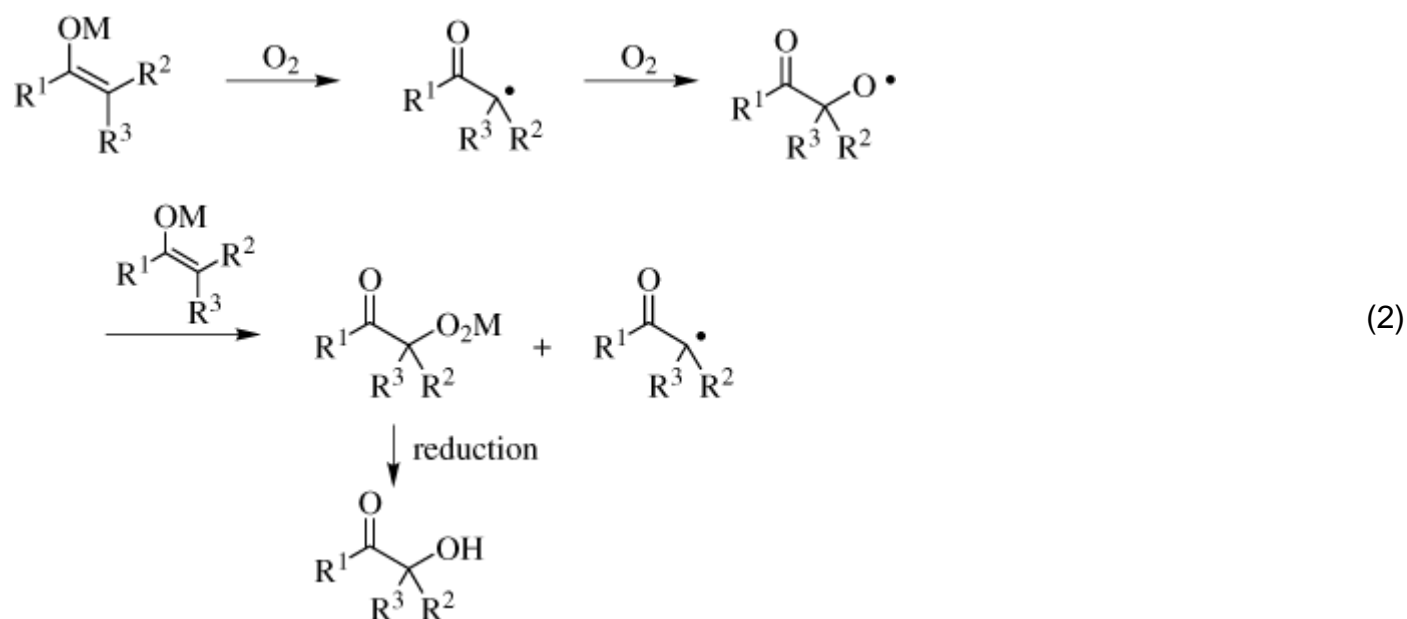
2.3.1.1. Molecular (Triplet) Oxygen

Molecular (triplet) oxygen ($^3\text{O}_2$) reacts with enolates to give α -hydroperoxycarbonyl intermediates, which in many cases can be isolated; (5, 6, 52) reduction then affords α -hydroxy carbonyl products. (5, 6, 12, 13, 53-56) The reaction can be done in a stepwise fashion using zinc dust as the reducing agent, but is more conveniently carried out in a one-pot procedure using a trialkyl phosphite as the in situ reductant. Hexamethylphosphorous triamide has been used occasionally as the in situ reductant as well. (39) Two mechanistic rationales have been advanced for this transformation. The first involves direct oxygenation by electrophilic addition of oxygen to the enolate via a six-membered transition state (Eq. 1). Alternatively, oxidation may proceed by a radical-chain mechanism involving single-electron transfer from the enolate to oxygen generating an α -keto radical. The latter then reacts with oxygen to give an α -hydroperoxy radical which in turn attacks the enolate affording the α -hydroperoxide with regeneration of the α -keto radical (Eq. 2). Yields are usually best when the α -carbon is disubstituted, thus precluding the possibility of over-oxidation. However, acceptable yields have been reported for a number of systems where the α -carbon bears only one substituent. (54, 57-61)



A related reaction is the oxidation of ketones with potassium superoxide with, or without, added

oxygen. (62) The first step involves enolate formation by potassium superoxide with simultaneous release of oxygen which then effects the oxidation. Oxidative cleavage can take place instead. (63)

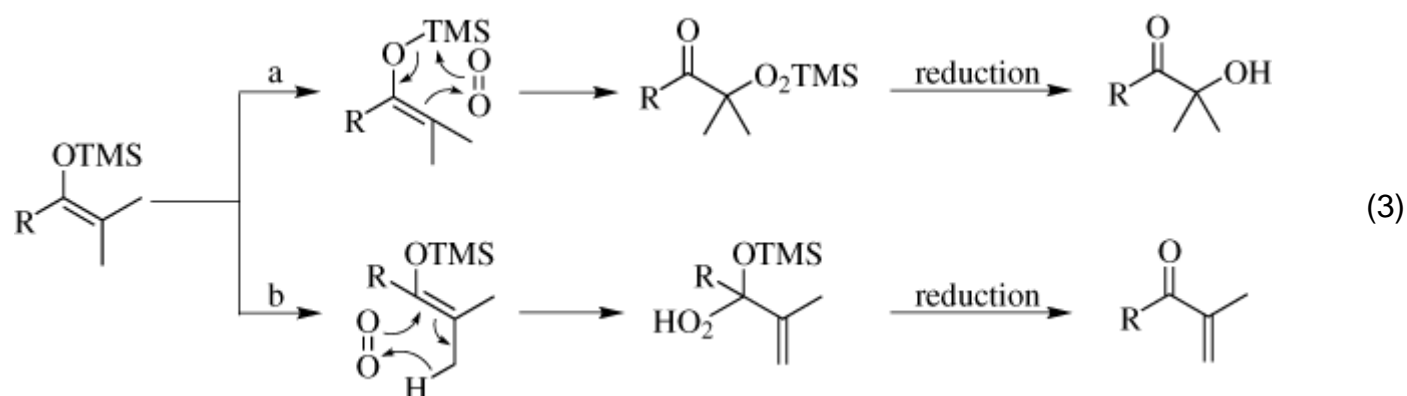


In some instances, α -hydroxy carbonyl compounds are formed in the absence of a reducing agent. For example, the isopropoxy ligands in titanium enolates can serve this function by a Meerwein-Ponndorf mechanism, (57) or the α -hydroperoxy carbonyl intermediate can act as the oxidizing agent (57, 64) (see also Eq. 43).

Using transition metal catalysts such as bis(3-methyl-2,4-pentadionato) cobalt(II) [Co(mac)₂] (65, 66) or Ni(mac)₂, (67) silyl enol ethers are oxidized by oxygen to α -hydroxy carbonyl products. Reaction of oxygen with certain ketone silyl enol ethers in the presence of triphenylphosphine and tris(dimethylamino)sulfonium (trimethylsilyl) difluoride (TAS-F) gives α -ketols. (68)

2.3.1.2. Singlet Oxygen

Singlet oxygen (¹O₂) reacts with silyl enol ethers to give α -silylperoxy carbonyl compounds by a silyl ene mechanism (path a, Eq. 3). (69-80) A competing side reaction involving a normal ene reaction (path b) results in formation of α,β -unsaturated ketones. Reaction of 1- and 2-silyloxy-1,3-dienes with singlet oxygen gives Diels-Alder addition products. (81) Triphenyl phosphite ozonide, an adduct of ozone with triphenyl phosphite, can be used as a source of singlet oxygen in these reactions. (82) Reduction of the intermediate peroxides gives hydroxy enones. This type of reaction can also occur with silyloxystyrenes. (83)



Singlet oxygen reacts with enolates of some β -dicarbonyl compounds to give α -hydroxy products. (84)

2.3.1.3. Ozone

Ozone (O_3) reacts with certain silyl enol ethers to give α -silyloxy carbonyl compounds. (85)

2.3.2. Peroxy Reagents

2.3.2.1. Hydrogen Peroxide

Hydrogen peroxide α -hydroxylates boron enolates of isoxazolines. (86) A few examples of the hydrogen peroxide oxidation of enolates derived from β -dicarbonyl compounds are known. (87-89) Concentrated hydrogen peroxide (98%) is sometimes required for satisfactory yields. Silyl enol ethers are hydroxylated by hydrogen peroxide (30–35%) in the presence of catalytic amounts of methyltrioxorhenium ($MeReO_3$) (90) or cetylpyridinium peroxotungstophosphate ($[C_5H_5N(CH_2)_{15}Me]_3^{+3}\{PO_4[W(O)(O_2)_2]_4\}^{-3}$). (91) The $MeReO_3$ -catalyzed reaction has also been applied to silyl ketene acetals; the urea/hydrogen peroxide complex is used as an anhydrous source of the oxidant in this case. (92)

2.3.2.2. *tert*-butyl Hydroperoxide (*t*-BuO₂H)

This reagent reacts with silyl enol ethers in the presence of $CuCl$ to give α -hydroxy carbonyl products after desilylation. (93) Use of $MoO_2(acac)_2$ as the catalyst results in cleavage of the carbon-carbon double bond. (94) Its lithium salt has also been used to α -hydroxylate a variety of enolates. (64)

2.3.2.3. Potassium Peroxymonosulfate

This reagent, which is commercially available as the mixture $2 KHSO_5 + KHSO_4 + K_2SO_4$ (Oxone[™], Caroate[™]), has been used to convert steroid 1-siloxy-1,3-dienes into γ -hydroxy enones. (95) It is also the oxidant of choice for the generation of dioxiranes from ketones (see below).

2.3.2.4. Aryl Peroxides $[Ar(CO_2)_2]$

These peroxides aryloxyolate enolates of ketones, (96) lactones, (38), β -diketones, (97) β -keto esters, (98) and malonic esters (99-102) as well as enamine anions (45, 103) and silyl enol ethers. (104) The main products in the latter reaction are α -silyloxy ketones.

2.3.2.5. *p*-Nitrophenylsulfonyl Peroxide

This oxidizing agent α -sulfonyloxyates silyl enol ethers (105, 106) and alkyl trialkylsilyl ketene acetals. (107, 108)

2.3.2.6. Bis(trimethylsilyl) Peroxide $[(TMSO)_2]$

This reagent reacts with enolates to give α -silyloxy carbonyl compounds which are readily converted into the α -hydroxy products by desilylation. (49) It also reacts with the dianions of carboxylic acids to give α -hydroxy acids. (109)

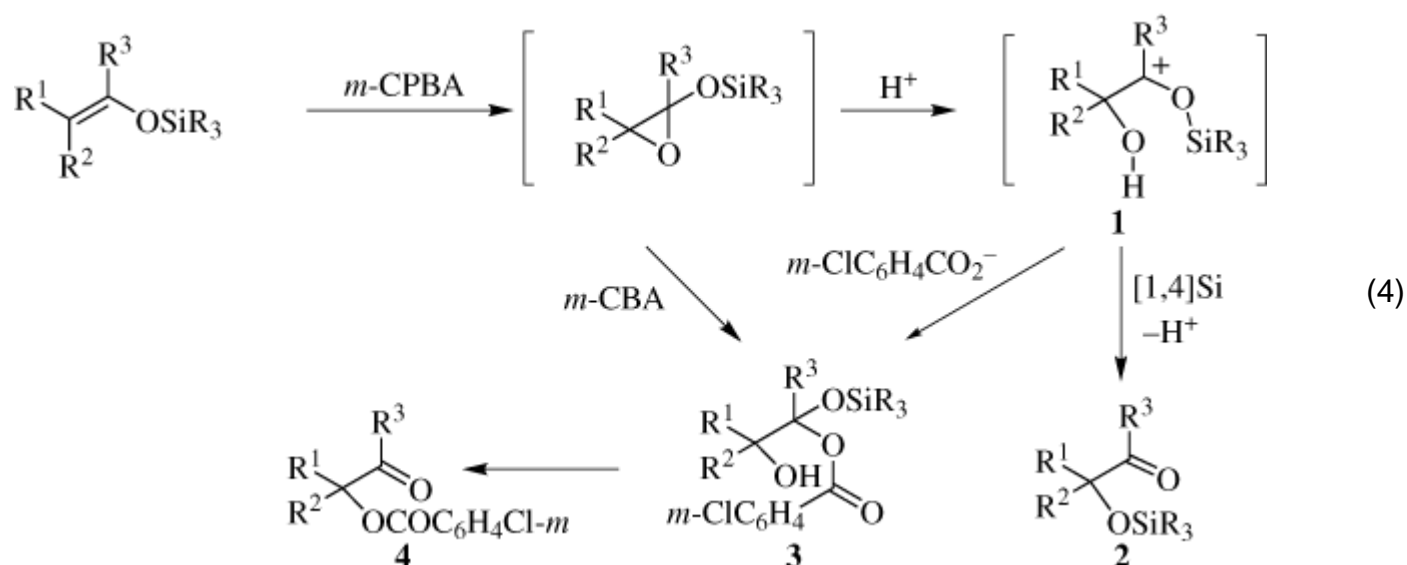
2.3.2.7. Dioxiranes

Dimethyldioxirane (DMDO) reacts with enolates to give α -hydroxy carbonyl compounds. (110-113) This reagent also reacts with silyl enol ethers to afford α -silyloxy epoxides which can often be isolated because of the non-acidic nature of DMDO. (114-116) Rearrangement of these intermediates leads to α -hydroxy carbonyl compounds. A potential side reaction is aldol condensation of the α -ketol with acetone, the reduction product of DMDO and the solvent from which DMDO is generated. (111) In situ generated sugar-derived dioxiranes are used in the asymmetric synthesis of α -hydroxy ketones from silyl enol ethers. (117, 118)

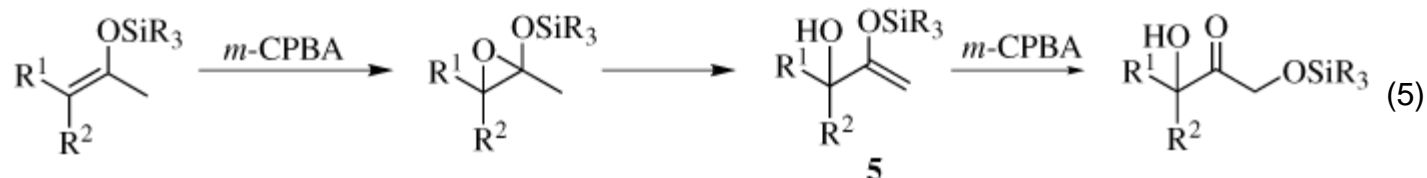
2.3.2.8. *m*-chloroperoxybenzoic Acid (*m*-CPBA)

This oxidant is widely used for the oxidation of silyl enol ethers to α -hydroxy carbonyl compounds, (119-123) the transformation is often referred to as the Rubottom oxidation. Reaction with aldehyde-

and ketone-derived silyl enol ethers affords α -hydroxy aldehydes and α -hydroxy ketones, respectively. (123) With alkyl silyl ketene acetals *m*-CPBA produces α -hydroxy esters (124) and with ketene bis(trimethylsilyl) acetals α -hydroxy carboxylic acids. (125) The intermediate epoxides have been isolated in some cases (126-128) and even characterized by X-ray analysis. (127) Depending on the structure of the silyl enol ether and the reaction conditions, the resulting epoxide can undergo several different kinds of rearrangements to give the α -oxygenated products. The most common is silyl migration to give α -silyloxycarbonyl compounds **2** (Eq. 4). This pathway, which may involve a tight ion pair or an oxacarbenium ion **1**, is usually favored in less polar solvents such as methylene chloride and hexane. The ketones **2** can often be isolated, especially with *tert*-butyldimethylsilyl enol ethers. Evidence for ion **1** has been obtained in the case of silyl enol ethers derived from aldehydes ($R^3 = H$). (123) The intermediate cation **1** can be trapped by *m*-chlorobenzoic anion to give compound **3** which has been isolated as well. (123) This intermediate can also be formed by direct ring opening of the epoxide by *m*-chlorobenzoic acid (*m*-CBA). (123, 129) Ester **3** can undergo acyl migration and silanol elimination to give α -acyloxy carbonyl products **4**. This process is favored in more polar solvents. (129, 130) Reaction of alkyl silyl and bis(silyl) ketene acetals with *m*-CPBA proceeds by a similar mechanism. (124, 125)



Oxidation of ketone silyl enol ethers that are disubstituted in the α -position with two equivalents of *m*-CPBA in the presence of potassium bicarbonate gives α,α' -dihydroxylated ketones after acidic workup. (131) The mechanism of this abnormal reaction is believed to involve rearrangement of the intermediate epoxide to the allylic alcohol **5** (Eq. 5).



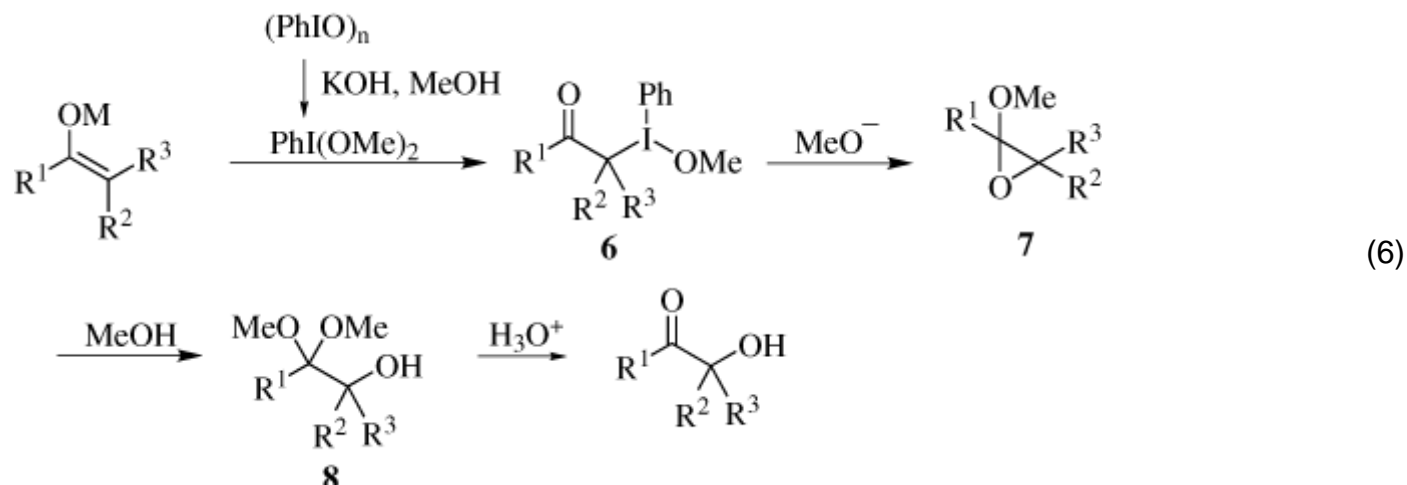
Peracetic acid (132, 133) and perbenzoic acid (134, 135) have also been used to hydroxylate silyl enol ethers.

2.3.3. Hypervalent Iodine Reagents (136)

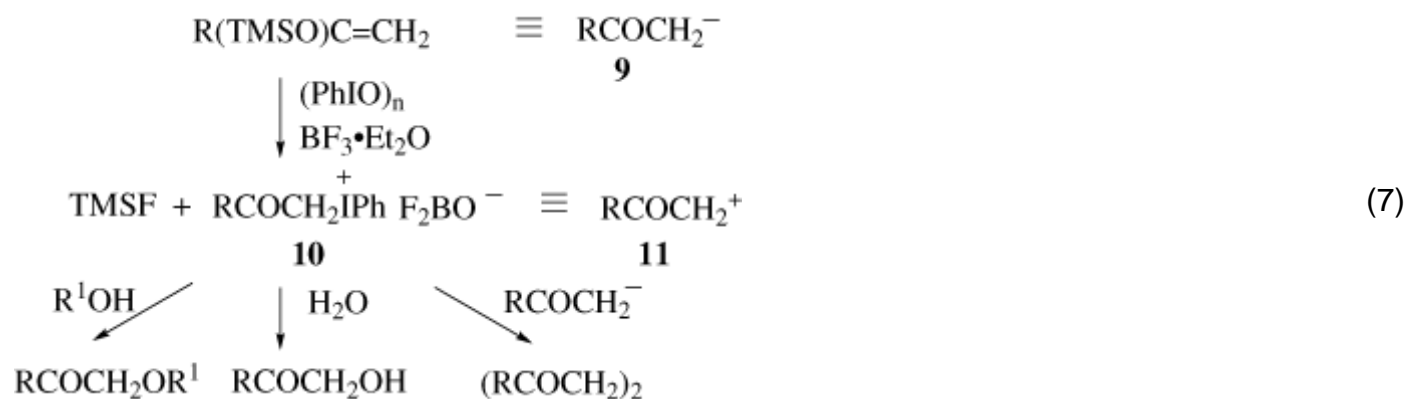
2.3.3.1. Iodosobenzene [(PhIO)_n]

Iodosobenzene reacts with ketones in methanol in the presence of potassium hydroxide to give α -hydroxy dimethyl ketals which upon acidic hydrolysis give α -hydroxy ketones. (137-139) The first step involves generation of the enolate followed by reaction with PhI(OMe)₂, formed in situ from

iodosobenzene, to give intermediate **6** (Eq. 6). Attack of methoxide on the carbonyl group followed by intramolecular reductive elimination of PhI gives the epoxide **7**. Ring opening affords the α -hydroxy acetal **8**



which can be isolated under basic conditions. The mechanism is supported by ^{18}O labeling. (137) In the presence of boron trifluoride etherate and water, iodosobenzene reacts with silyl enol ethers to give α -hydroxy carbonyl compounds directly. (140, 141) The initial formation of intermediate **10** can be viewed as an *umpolung* of the carbanion **9** into the carbocation **11**. In the presence of alcohols, α -alkoxy ketones are formed; (142) dimerization occurs when no nucleophile is present (143, 144) (Eq. 7). In the presence of bis(salicylidene)-1,2-diamine ("salen") manganese(III) complexes as catalysts, $(\text{PhIO})_n$ oxidizes ketone silyl enol ethers to α -hydroxy and α -silyloxy ketones. (145, 146) Non-racemic products are obtained when chiral (salen) manganese(III) complexes are employed. (145)



2.3.3.2. Iodobenzene Diacetate [PhI(OAc)₂]

The reaction of iodobenzene diacetate parallels that of iodosobenzene. (137) The presence of internal alcoholic or phenolic hydroxyl groups often results in intramolecular alkoxylation when stereoelectronically allowed. Certain sterically hindered ketones do not react. Iodobenzene diacetate also reacts with esters to give α -hydroxy acids or esters. (138)

2.3.3.3. *o*-Iodosylbenzoic Acid

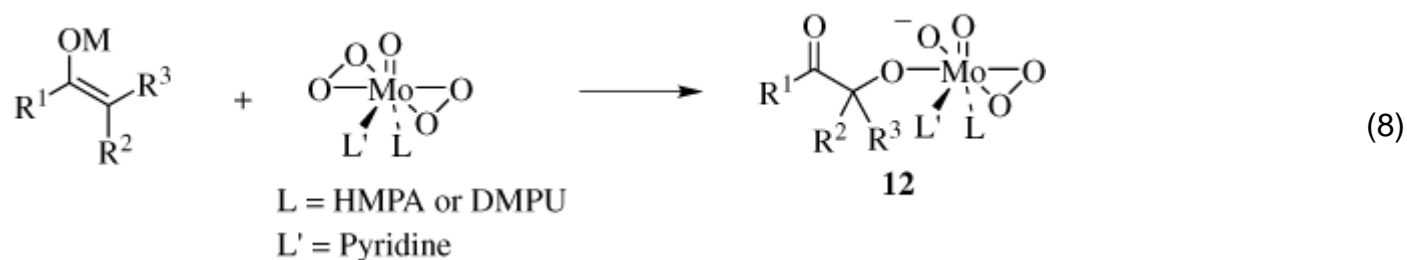
This reagent reacts with ketone enolates in a manner similar to $(\text{PhIO})_n$. The advantage of using this reagent is that the by-product, *o*-iodobenzoic acid, can be removed easily by extraction into aqueous base.

Hypervalent iodine compounds in most cases are not suitable for the α -hydroxylation of β -dicarbonyl compounds because iodonium ylids are formed instead. (147-150)

2.3.4. Metal Oxides and Related Reagents

2.3.4.1. Oxodiperoxymolybdenum (Pyridine) Hexamethylphosphoric Triamide (MoOPH) and Oxodiperoxymolybdenum (Pyridine) 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (MoOPD)

Both of these reagents oxidize a variety of enolates to the corresponding α -hydroxy carbonyl compounds. (40, 151, 152) The latter, although somewhat less reactive, is a safer alternative to the former because it employs the less toxic 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (*N,N*-dimethylpropyleneurea, DMPU). α -Hydroxylations with MoOPD are also generally cleaner; in most cases, the yields are slightly lower than those obtained with MoOPH. The mechanism most likely involves O-O cleavage to form intermediate **12** (Eq. 8). (8, 40, 152) Both peroxy bridges can participate in the reaction since in some cases α -hydroxylation takes place with less than stoichiometric amounts of the reagent. (8)



2.3.4.2. Osmium Tetroxide (OsO₄)

Reaction of the OsO₄/*N*-methylmorpholine *N*-oxide catalytic system with silyl enol ethers gives α -hydroxy aldehydes (153) and ketones. (126, 154-157) Osmium tetroxide catalyzed asymmetric dihydroxylation of ketone silyl enol ethers affords α -hydroxy ketones in enantiomerically enriched forms. (158-160)

2.3.4.3. Tetra(acyloxy) Lead Derivatives [Pb(OCOR)₄]

These lead derivatives acyloxylate silyl enol ethers, (161-163) and (bis)silyl ketene acetals. (164, 165)

2.3.4.4. Chromyl Chloride (CrO₂Cl₂)

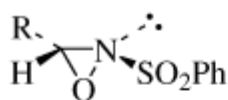
Chromyl chloride reacts with silyl enol ethers to give α -hydroxy ketones. (166)

2.3.4.5. Silver(I) Oxide and Silver(II) Oxide

Both of these oxides react with α,β -unsaturated dicarbonyl compounds in the presence of sodium hydroxide to give γ -hydroxy products. (167)

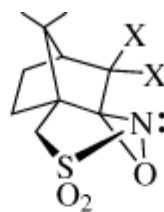
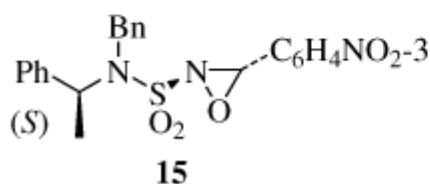
2.3.5. *N*-Sulfonyloxaziridines

With their bulky and strongly electronegative sulfonyl groups *N*-sulfonyloxaziridines are chemoselective, electrophilic oxygen transfer reagents. (168, 169) This class includes the racemic *trans*-2-(phenylsulfonyl)-3-phenyloxaziridine (PSPO, **14**; often referred to as the Davis reagent), 3-(*p*-nitrophenyl)-2-(phenylsulfonyl)oxaziridine (NPSO, **14**), the chiral non-racemic sulfamyl analog **15**, as well as the chiral non-racemic (+)- and (-)-(camphorylsulfonyl)oxaziridines (CSO, **16**, X " H), (+)- and (-)-[(8,8-dichlorocamphoryl)sulfonyl]oxaziridines (DCCSO, **16**, X " Cl), and (+)- and (-)-[(8,8-dimethoxycamphoryl)sulfonyl] oxaziridines (DMCSO, **16**, X " OMe). These reagents hydroxylate metal enolates at very low temperatures. Many analogs have been prepared but they seem to offer only marginal advantage in some cases; their structures and reactions with 1-phenyl-1-propanone are listed in Table 2A and with 2-methyl-1-tetralone in Table 2B (see also under C7 in Table 9B). The corresponding reagent derived from fenchone is much less reactive. (170) Theoretical (171, 172) and experimental (173) studies suggest an S_N2 mechanism for the transfer of oxygen from *N*-sulfonyloxaziridines to nucleophiles. The aminal **18** then fragments into sulfonyl imine and alkoxide (Eq. 9). (174)

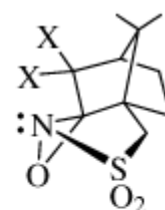


R = Ph: PSPO (\pm)-**13**

R = 4-O₂NC₆H₄: NPSO (\pm)-**14**



(+)-**16**

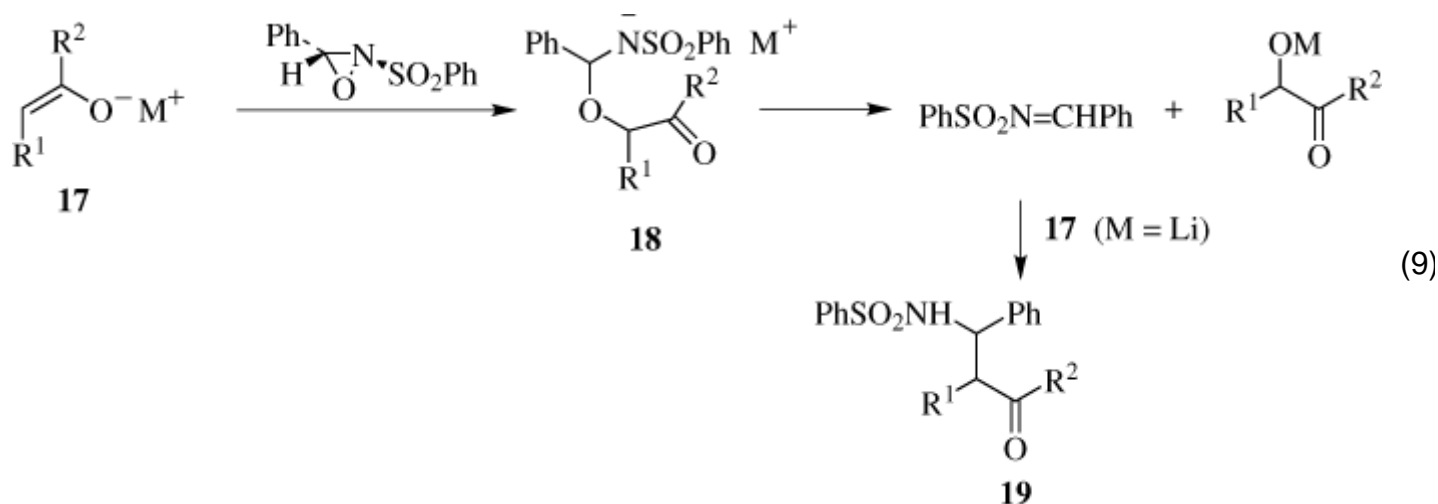


(-)-**16**

X = H: CSO

X = Cl: DCCSO

X = OMe: DMCSO



Although there is no direct evidence implicating intermediate **18** in the hydroxylation of enolates, such evidence exists for the oxidation of carbanions with PSPO. (174, 175) In oxidations of lithium enolates (**17**, M = Li) with PSPO, the iminoaldol **19** is formed as a by-product. (174-177) Sodium and potassium enolates or CSO and its derivatives do not give this side reaction. (178) The (camphorylsulfonyl) oxaziridines are not sufficiently reactive to oxidize silyl enol ethers. PSPO, NPSO, and analog **15** can be used but relatively high reaction temperatures (refluxing chloroform) are required. (179, 180) The more reactive oxaziridinium salts, generated in situ from ketiminium salts and potassium peroxymonosulfate, α -hydroxylate silyl enol ethers at room temperature. (180a)

2.3.6. Miscellaneous Reagents

2.3.6.1. Benzeneseleninic Anhydride [(PhSeO)₂O]

This reagent hydroxylates ketone enolates. (181-183)

2.3.6.2. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)

DDQ aryloxyates silyl enol ethers. (184)

2.3.6.3. Sodium Hypochlorite

This reagent, in combination with 4-phenylpyridine *N*-oxide and (salen)Mn(III) complexes, asymmetrically hydroxylates silyl enol ethers. (146)

2.3.6.4. Alkyl Hypochlorites (ROCl)

These hypochlorites, in combination with a transition metal catalyst, alkoxyate silyl enol ethers. (185)

2.3.6.5. Methyl Hypofluorite (MeOF)

This reagent is generated in situ from elemental fluorine and methanol, and is used to methoxyate silyl enol ethers. (186) The **HOF/MeCN** complex, generated in situ from fluorine and aqueous

acetonitrile, α -hydroxylates silyl enol ethers. (187)

2.3.6.6. Iodine

Iodine α -hydroxylates enolates of β -acylamino esters; (188) in combination with silver salts of carboxylic acids, it acyloxylates silyl enol ethers. (189)

2.3.6.7. Ferrocenium Hexafluorophosphate

This reagent oxidizes ester enolates to α -radicals that can be trapped with 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO). (190)

2.3.6.8. Electrochemical Oxidation

Electrochemical oxidation of aldehydes or ketones in methanol under basic conditions gives α -hydroxy dimethyl acetals and ketals, respectively. (191)

2.4. Functional Group Compatibility

The following list of functional groups that are compatible with the various oxidants was compiled from the tables. Absence of a functional group does not necessarily mean that it is incompatible. Protected functional groups are not included. Because of the large number of examples, references to substrates with isolated double bonds are not listed.

2.4.1. Oxygen/Base

isolated and conjugated double bonds, (192-195) secondary (58) and phenolic (196) hydroxyls, dihydrofurans, (167) phenyl thioethers, (197) dithioketals, (198-200) and CONH₂. (201, 202)

2.4.2. *m*-CPBA

isolated double bonds, dienes, (203-205) diene molybdenum complexes, (206) α,β -unsaturated carbonyl compounds, (131, 132, 207, 208) vinyl esters, (209) epoxides, (210-212) dihydrofurans, (213) acetals and ketals, (126, 129, 214, 215)-N(TMS)₂, (216)-NMeAr, (217) and azides. (130) Tertiary amines are oxidized to *N*-oxides.

2.4.3. Hypervalent Iodine Reagents

isolated double bonds, α,β -unsaturated carbonyl compounds (218) (with alcoholic base, Michael adducts are formed), secondary hydroxyls, (218-220) epoxides, (221) secondary and tertiary amines, (219, 222-225) *N*-unsubstituted aziridines, (221) aromatic NH₂, (222) thioethers, (226) stable radicals, (223) ferrocenes, (227) and aryl chromium complexes. (228)

2.4.4. MoOPH and MoOPD Reagents

isolated double bonds, dienes, (229) enynes, (230) primary (231) and tertiary (232, 233) hydroxyls, epoxides, (229, 234, 235) dihydrofurans, (167) tertiary amines, (236, 237) and thioethers. (197)

2.4.5. *N*-Sulfonyloxaziridines

isolated double bonds, dienes, (193, 238) vinyl chlorides, (239) vinyl ethers, (240) α,β -unsaturated carbonyl compounds, (241, 242) secondary hydroxyls, (98, 243) epoxides, (210) oxetanes, (244, 245) ketals, (246) secondary (247) and tertiary (248) amines, aromatic NH₂, (216) and -SnBu₃. (249)

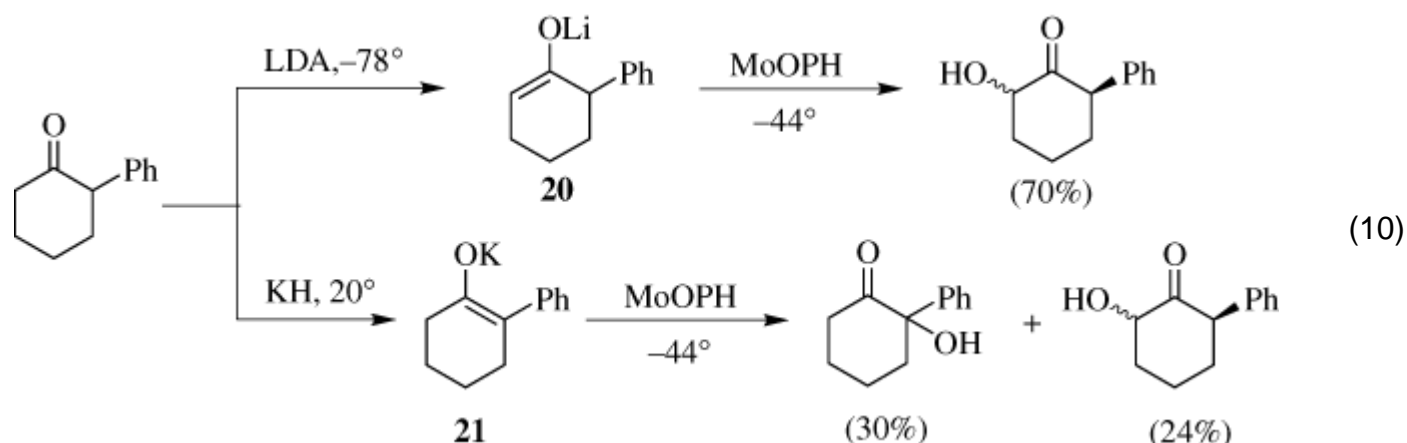
3. Selectivity

3.1. Regioselectivity

3.1.1. Enolates

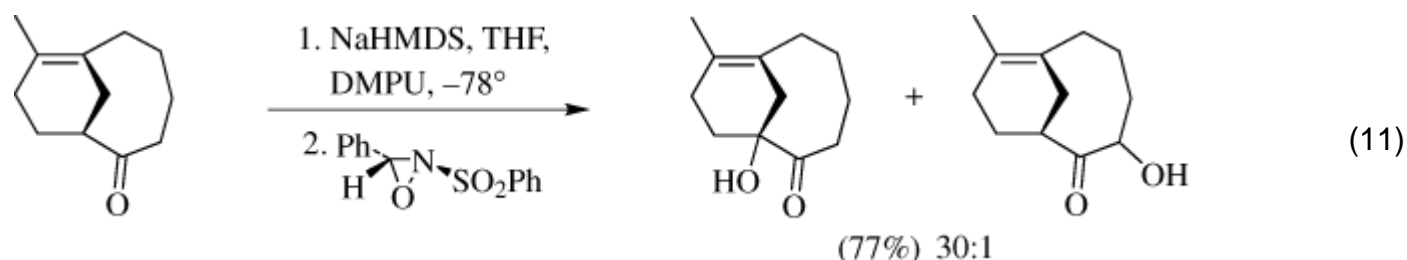
Unsymmetrical ketones with both α - and α' -protons may give a mixture of α - and α' -hydroxylated products upon oxidation. The regioselectivity of the hydroxylation reaction is influenced by the structure of the carbonyl substrate, the way in which the enolate is generated, and, to a lesser extent, the hydroxylating reagent.

When the α - and α' -substitution pattern of a ketone is sufficiently different, selective generation of one regioisomeric enolate can often be realized by means of kinetic or thermodynamic control. For example, treatment of 2-phenylcyclohexanone with LDA at -78° gives the kinetic enolate **20** which upon hydroxylation affords 2-hydroxy-6-phenylcyclohexanone (Eq. 10). (40, 151) When potassium hydride is used at higher temperatures, the more stable enolate **21** is formed as evidenced by trapping with acetic anhydride. However, oxidation gives a mixture of both regioisomers, probably because of the presence of small equilibrium concentrations of the more reactive enolate **20**. (40, 151)



In contrast to normal aliphatic ketones, deprotonation of bicyclo[5.3.1]undecenone gives the more highly substituted bridgehead enolate under conditions of kinetic control. (250) Hydroxylation of this enolate affords the corresponding α -hydroxy ketone in a ratio of 30:1 in favor of the bridgehead hydroxy derivative (Eq. 11).

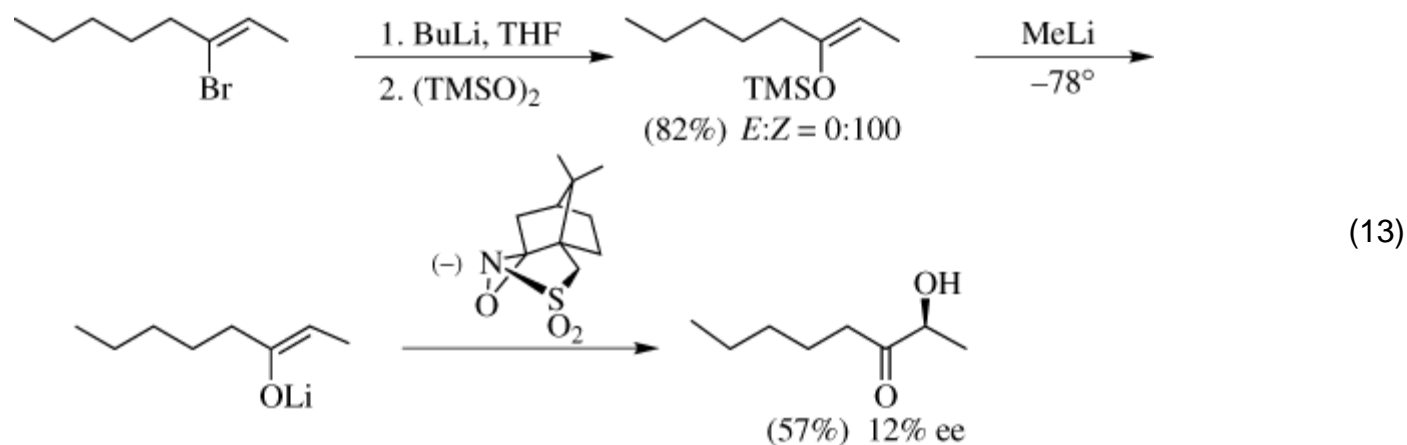
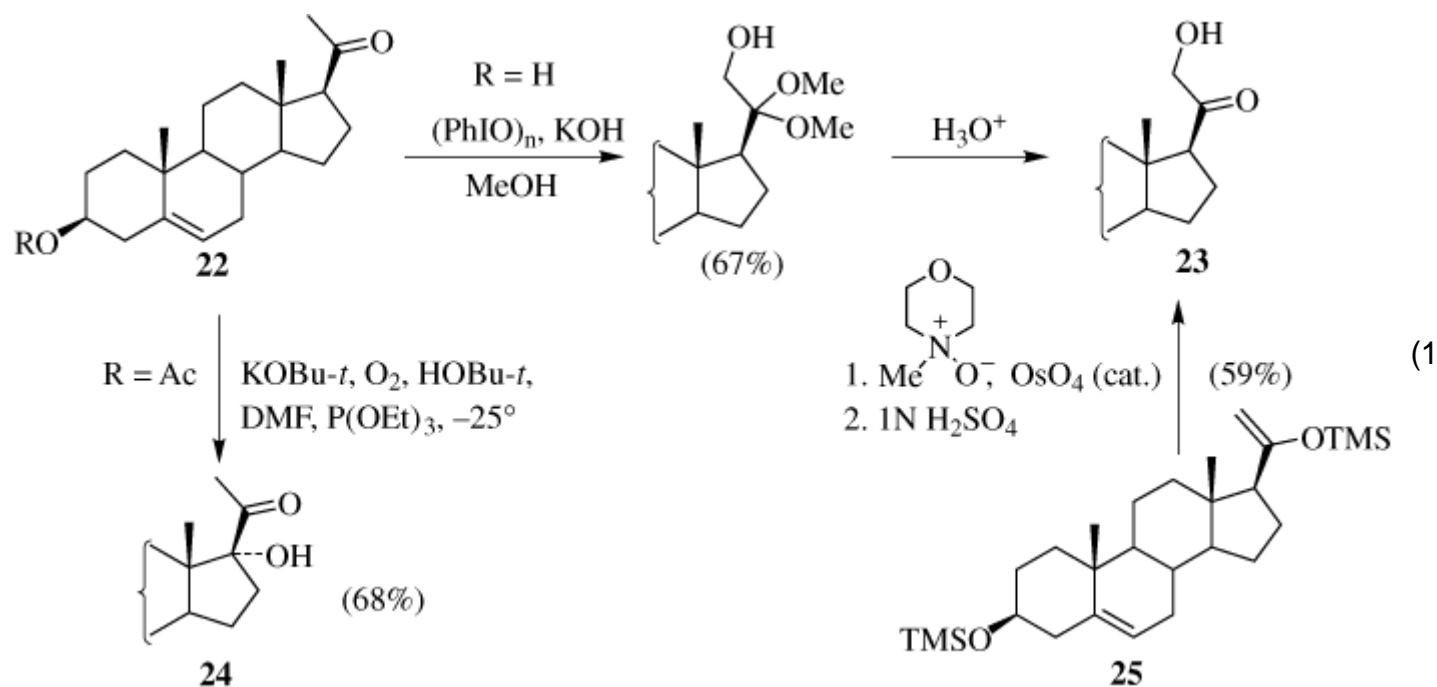
Regioselective formation of both α - and α' -hydroxy ketones from a single unsymmetric ketone substrate is often possible by choice of a proper hydroxylation strategy. Hypervalent iodine reagents hydroxylate the less substituted enolate. Thus



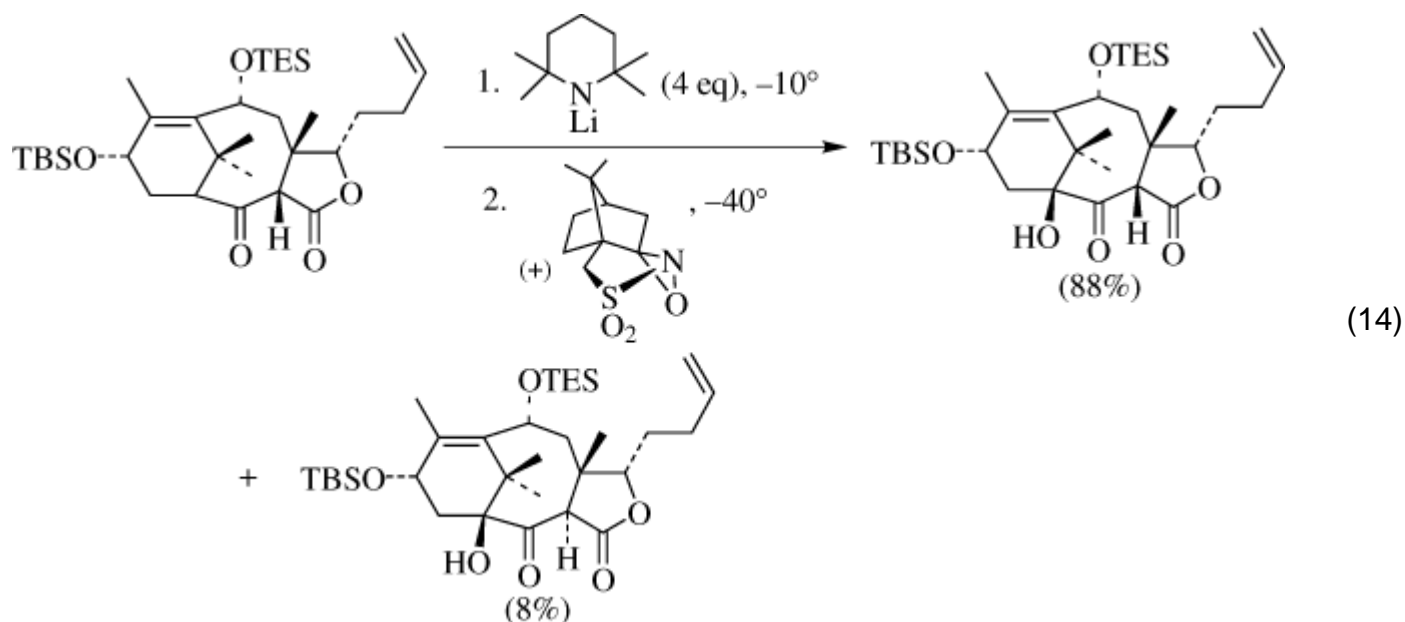
reaction of ketone **22** with $(\text{PhIO})_n$ followed by acid hydrolysis gives hydroxy ketone **23** which can also be obtained by the osmium tetroxide catalyzed hydroxylation of silyl enol ether **25** (Eq. 12). (154, 251) In a related system use of the MoOPH reagent also causes hydroxylation of the methyl rather than the methine group. (252) On the other hand, oxygenation of the enolate of ketone **22** produces the regioisomer **24**. (55) In general, oxygenation in the presence of potassium

tert-butoxide results in generation of the thermodynamically more stable enolate and consequently hydroxylation at the more substituted carbon.

In another approach the enolate is generated regioselectively from a silyl enol ether which in turn is obtained by oxidation of a vinyl anion (Eq. 13). (26)



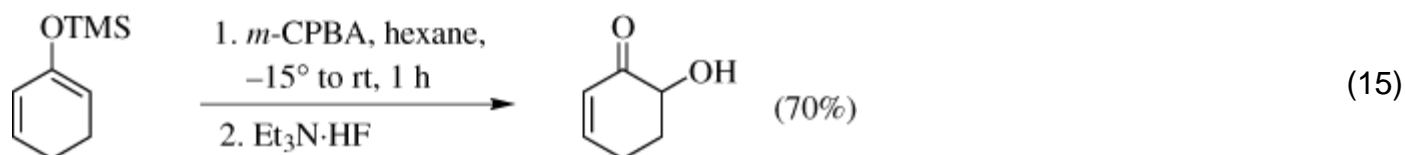
Oxidation of the enolates generated from β -dicarbonyl compounds with an equivalent amount of a base usually results in α -hydroxylation. When an excess of strong base is used, the dianion is formed and hydroxylation affords the γ -hydroxy product; epimerization of the α -hydrogen is a minor side reaction in the example given in Eq. 14. (32)



The regiochemical problems encountered with enols of α,β -unsaturated carbonyl compounds are discussed in the Scope and Limitations section.

3.1.2. Silyl Enol Ethers

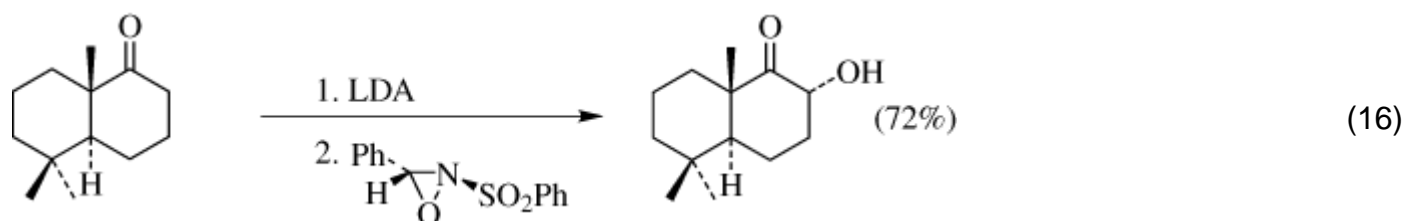
Methods exist for the regioselective preparation of silyl enol ethers from ketones; the location of the double bond then determines the direction of hydroxylation. Among the few examples of 1-silyloxydienes subjected to the hydroxylation reaction both α - and γ -products have been observed (see Table 17A); 2-silyloxydienes usually afford α -hydroxy enones (Eq. 15). (93, 253, 254)



3.2. Diastereoselectivity and Enantioselectivity

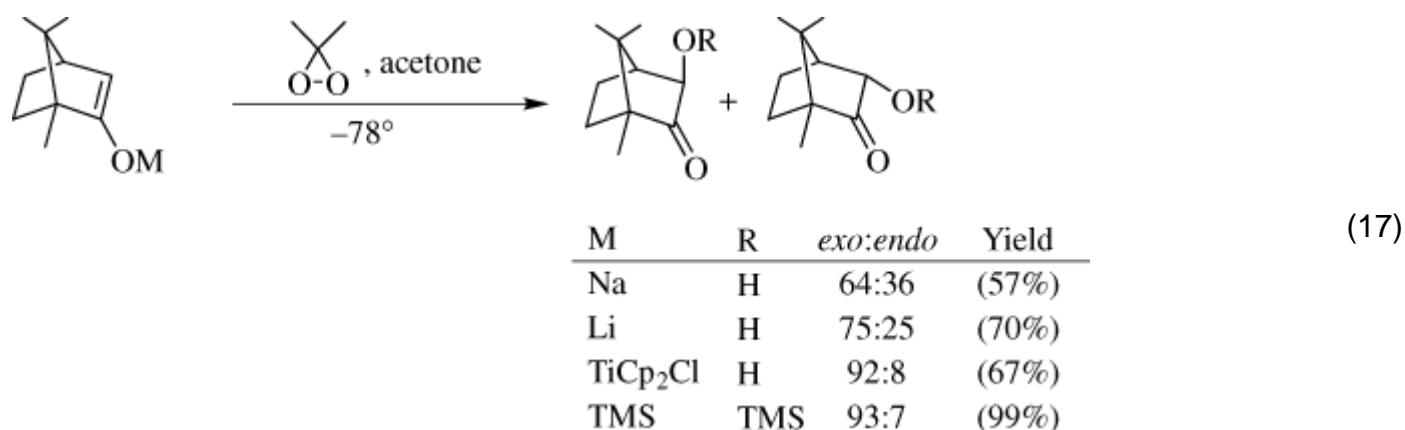
3.2.1. Enolates

The diastereoselectivity in the α -hydroxylation of enolates is governed by their structures, the hydroxylating reagent, and the reaction conditions. The major product can generally be predicted to be the one that results from approach of the oxidant from the sterically less hindered face (Eq. 16). (255) Exceptions, however, have been reported. (256)

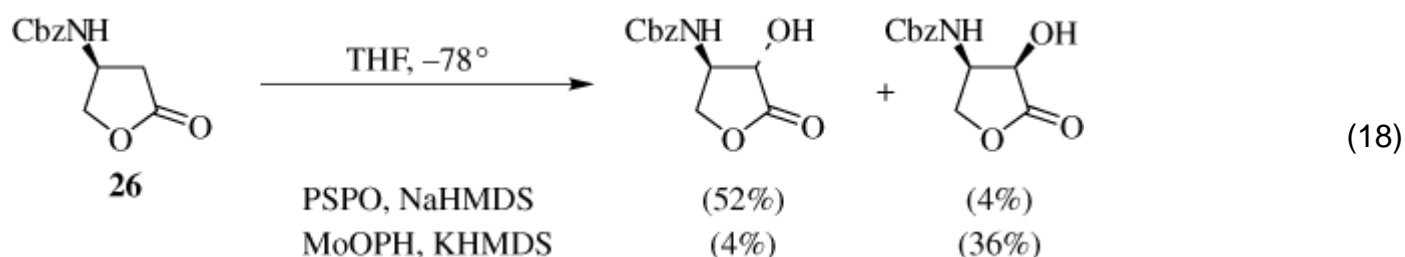


The diastereoselectivity can often be optimized by selecting an appropriate enolate metal ion. This is exemplified by the α -hydroxylation of camphor with dimethyldioxirane (Eq. 17); (110, 111) steric effects due to the variation of the size of the counter ion aggregate are believed to account for the

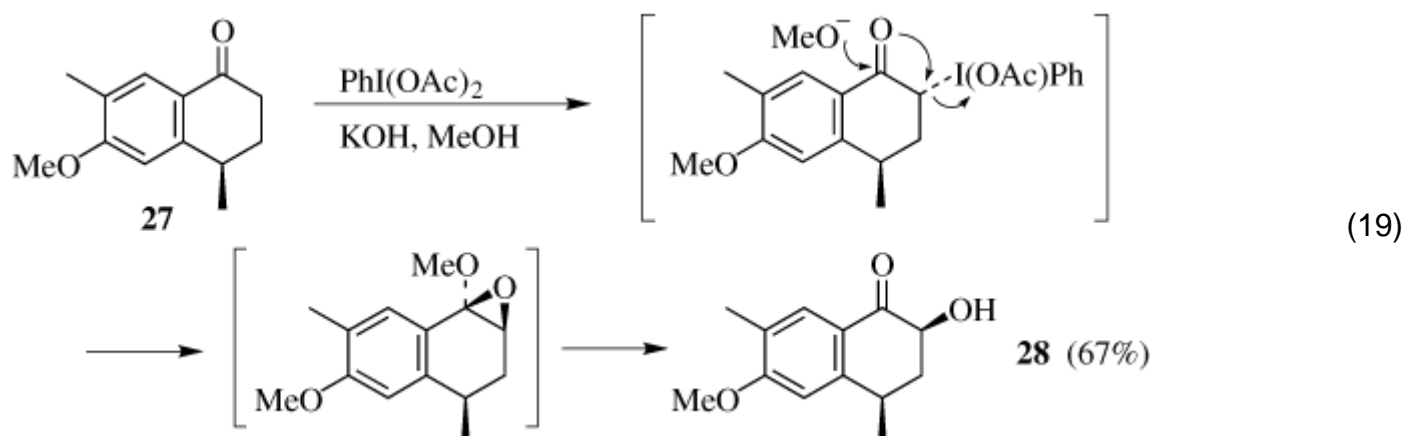
observed results. The most efficient method in this case is the hydroxylation of the silyl enol ether.



The oxidizing reagent also influences the diastereoselectivity of the enolate hydroxylation. For example, oxidation of the sodium enolate of lactone **26** with PSPO affords the *trans*-hydroxy lactone as the major product whereas MoOPH gives predominantly the *cis* isomer with the potassium enolate (Eq. 18). (257) The unusual *cis*-selectivity obtained with MoOPH can be explained in terms of its initial coordination with the carbamate anion (N or O) followed by intramolecular delivery of oxygen (cf. also Eq. 33).

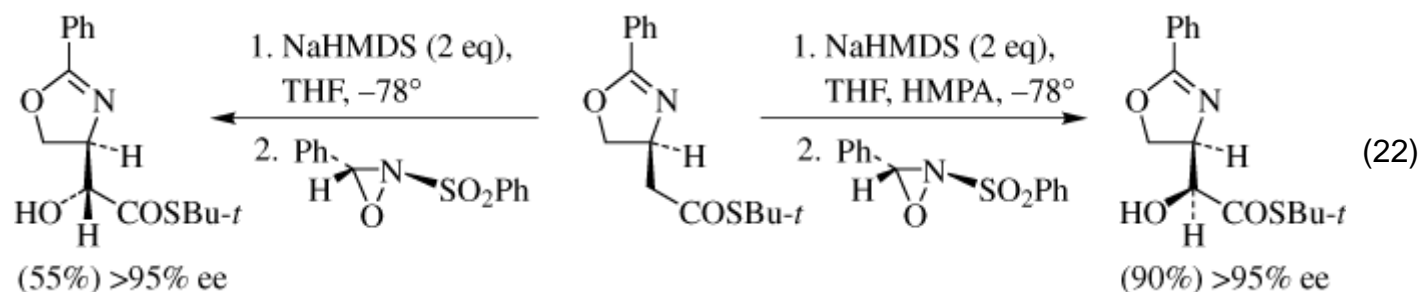
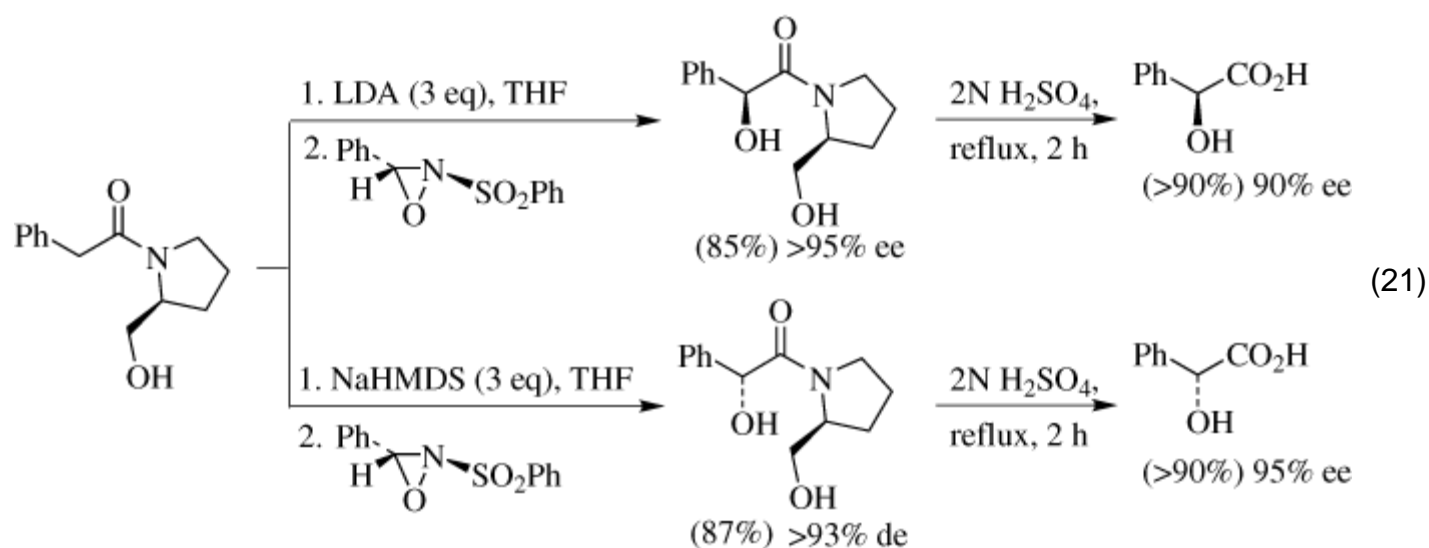
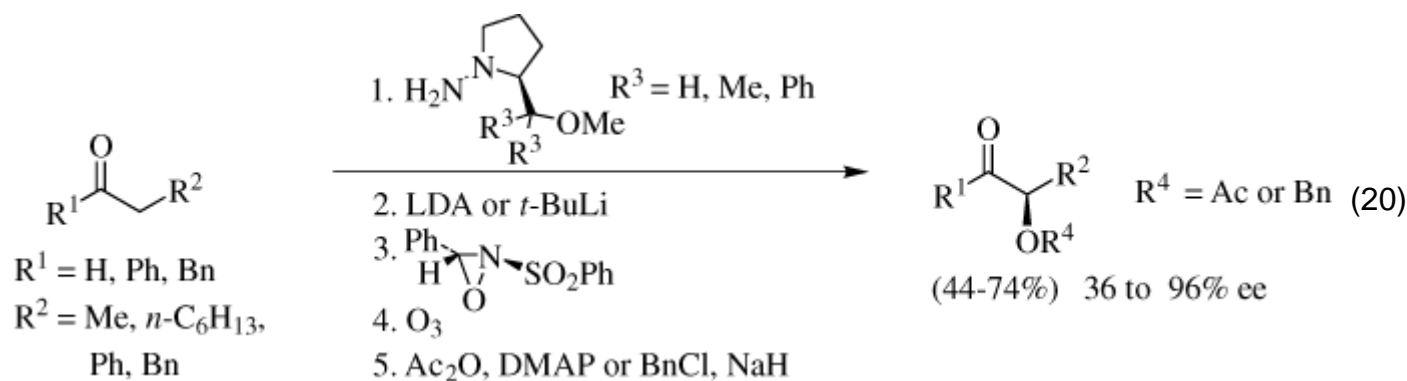


In contrast to other hydroxylating agents, hypervalent iodine reagents afford α -ketols with the α -hydroxy group attached to the more sterically hindered face of the enolate. The mechanism is shown in Eq. 19. (228) Attack of PhI(OAc)₂ on tetralone **27** occurs from the less hindered side; the subsequent methoxide-induced epoxide

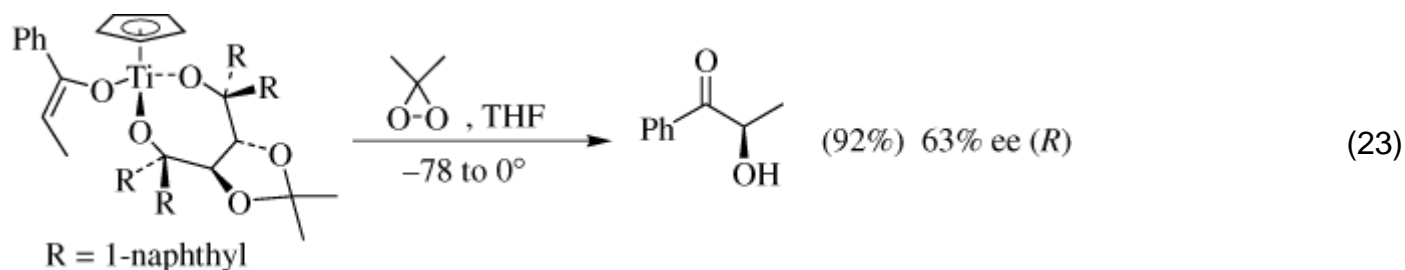


formation proceeds with inversion to give ketone **28** after hydrolysis. The corresponding 1,3-*trans* isomer is obtained in 64% yield from the same precursor **27** by reaction of its silyl enol ether with *m*-CPBA. (228)

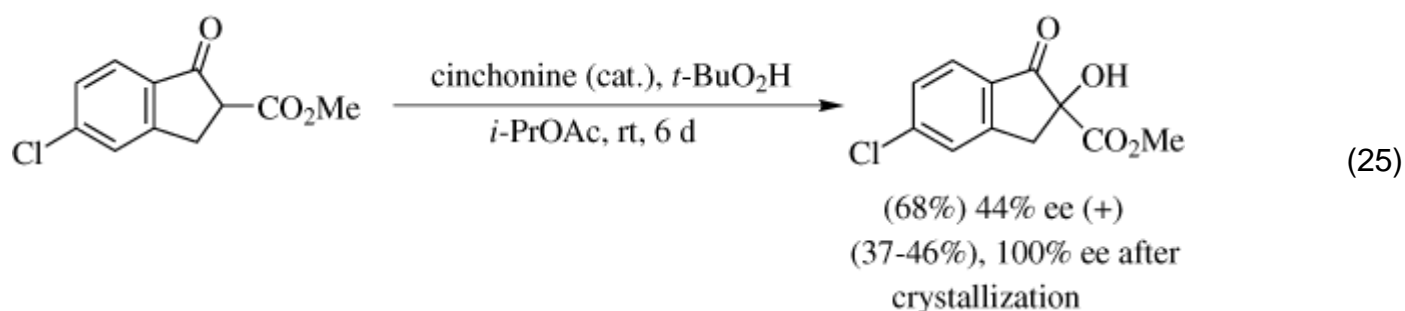
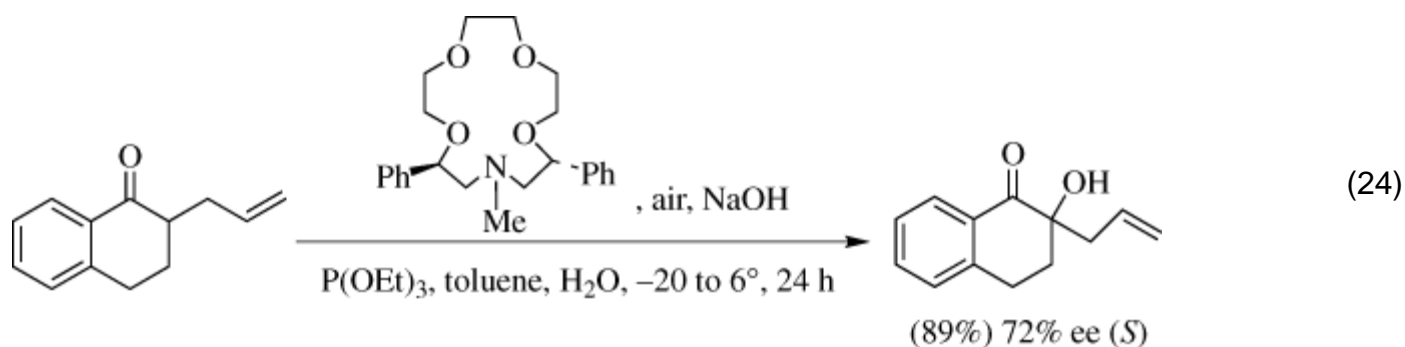
Enantiomerically enriched α -hydroxycarbonyl compounds can be obtained by a variety of methods. One employs chiral auxiliaries such as hydrazones for the asymmetric hydroxylation of aldehydes and ketones (Eq. 20). (43) Other auxiliaries include 2-oxazolidinones (177) and amines (258, 259) (Eq. 21). (258) In the latter example, the nature of the counter ion has a dramatic effect on the diastereoselectivity. The explanation advanced is based on intramolecular vs. intermolecular chelation for the lithium and sodium enolates, which shields the si and re faces, respectively. In a variation of this approach, the chiral group is attached to the α -carbon of a thiol ester; either of the two diastereomers can be obtained by chelation control or, in the presence of HMPA, by stereoelectronic control, respectively (Eq. 22). (260)



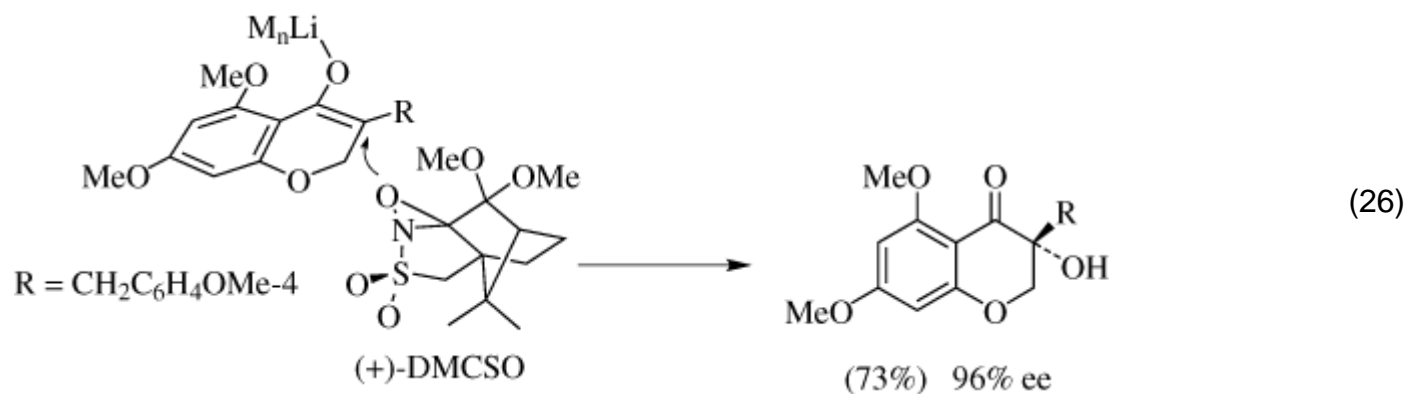
Another method employs chiral ligands attached to the enolate oxygen (Eq. 23); (261) oxidation with PSPO in this case proceeds with poorer selectivity (14% ee). Oxidation of β -hydroxy ketones under the conditions of the Katsuki-Sharpless reaction (262) also leads to enantiomerically enriched α -hydroxy carbonyl compounds



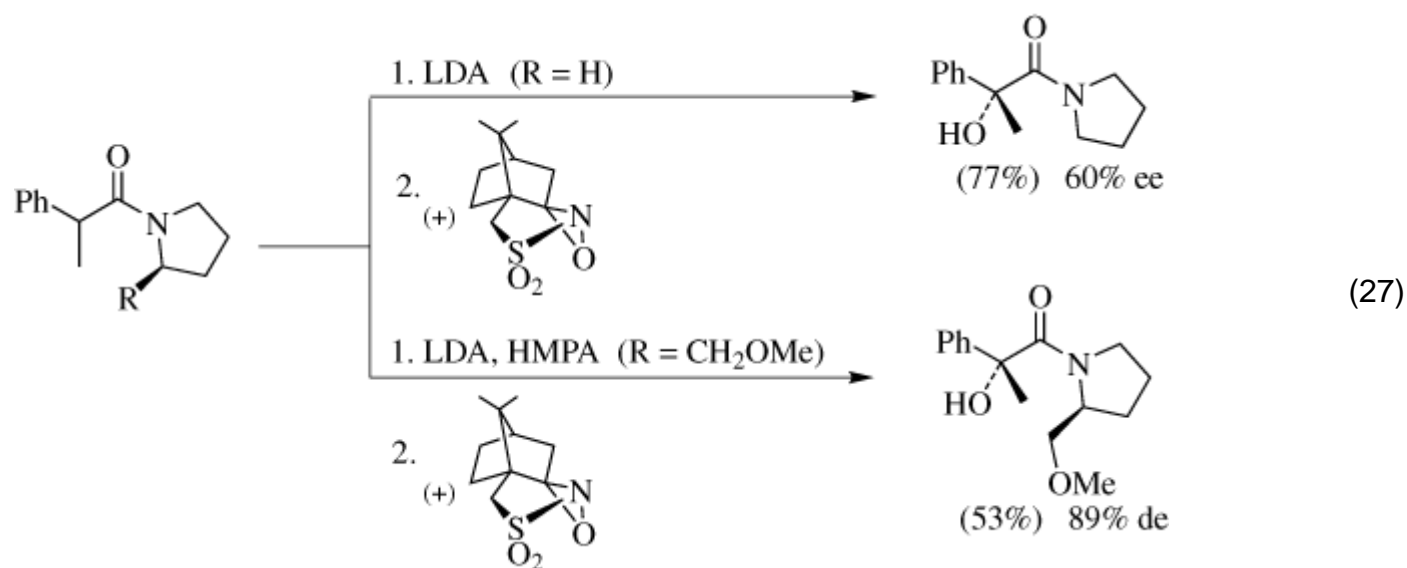
(See Eq. 41 in the Scope and Limitations section). (263) Other variations of this approach include air oxidation of cyclic ketones under phase-transfer conditions with chiral crown ethers (Eq. 24) (264) or alkaloid quaternary ammonium salts (265, 266) as transfer agents and oxidation of a β -dicarbonyl compound in the presence of a chiral base (Eq. 25). (267)



An important development in this area is the enantioselective hydroxylation of prochiral enolates with chiral camphorylsulfonyloxaziridines. (7) Particularly attractive, from a synthetic perspective, is that the absolute configuration of the oxaziridine three-membered ring controls the configuration of the product. Thus both enantiomers of a given α -hydroxy carbonyl product can be obtained simply by choice of the appropriate oxaziridine. In the example shown in Eq. 26, (268) the enolate is generated with lithium diisopropylamide in tetrahydrofuran. If it is assumed that the oxygen-lithium aggregate is the sterically most demanding area in the vicinity of the enolate double bond, then attack by the oxaziridine oxygen will occur from below the plane of the substrate to give the (*R*) isomer as shown. An added possibility is that the transition structure is stabilized by chelation of the metal with one of the methoxy groups. The (*S*)-isomer is formed in 72% yield and more than 96% ee by use of (–)-DMCSO.

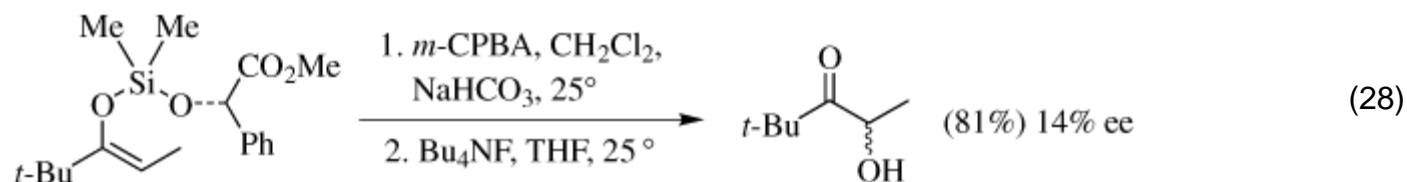


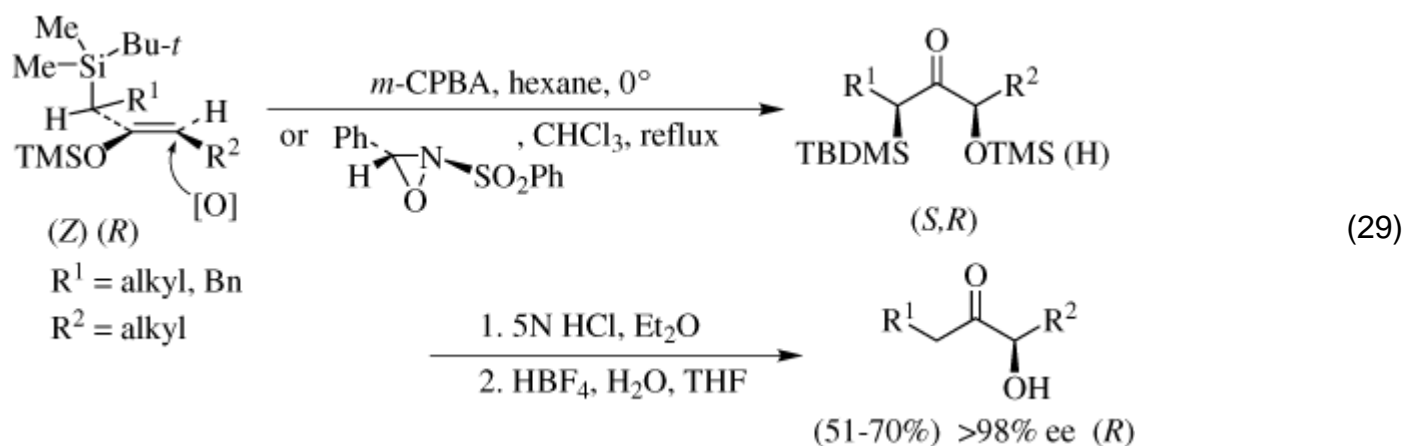
Hydroxylation of carbonyl compounds with tertiary carbon centers in the α -position usually proceeds with poor stereoselectivity. The situation can sometimes be improved by employing chiral enolates and enantiopure sulfonyloxaziridines (double asymmetric differentiation). An example is given in Eq. 27. (259, 269)



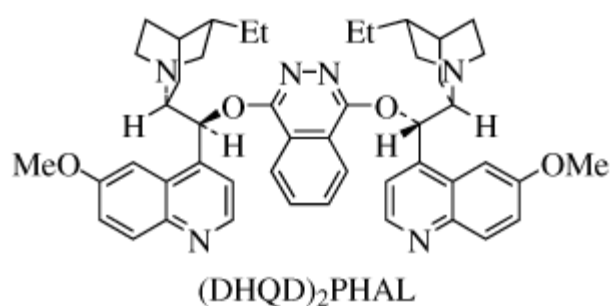
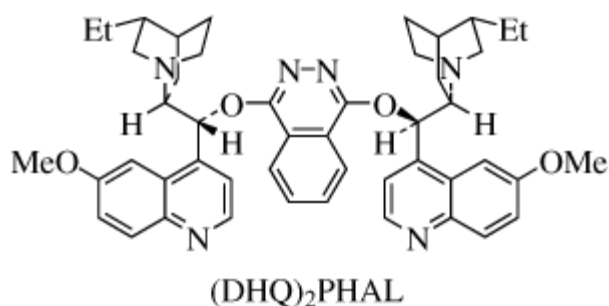
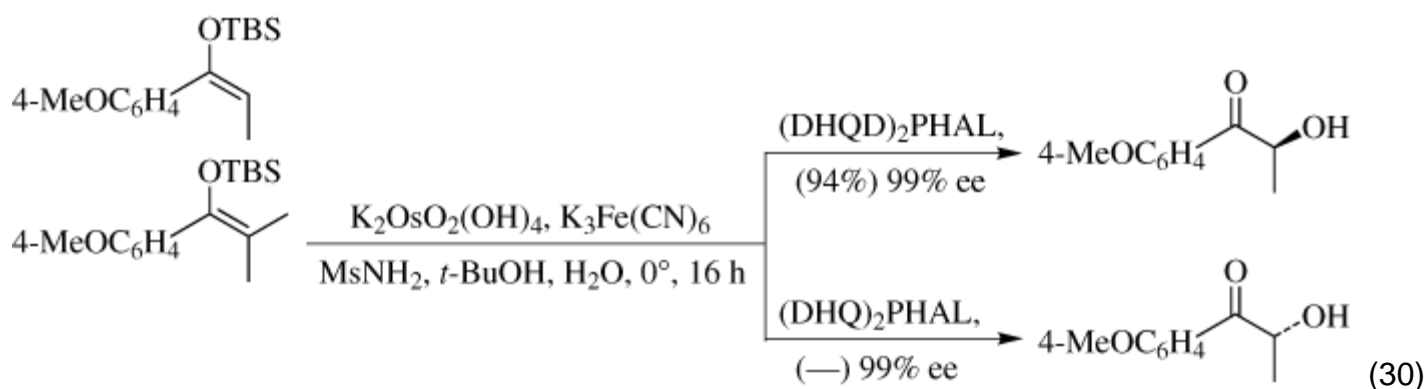
3.2.2. Silyl Enol Ethers

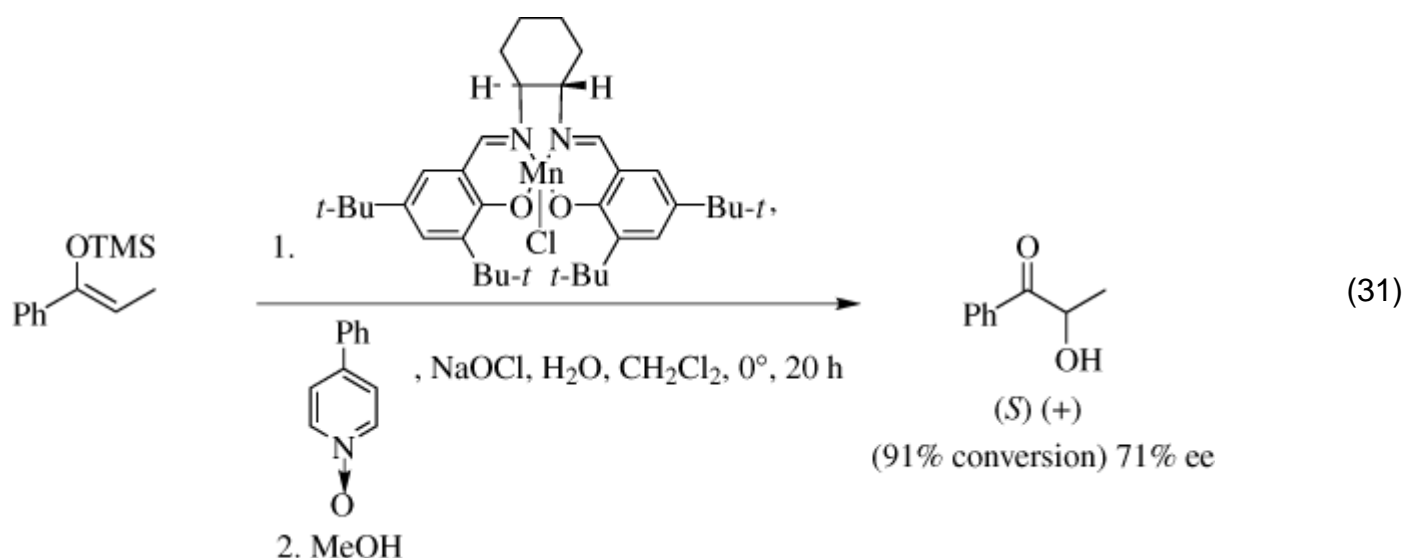
Oxidation of silyl enol ethers with a chiral substituent on silicon proceeds with poor enantioselectivity (Eq. 28). (270, 271) A better, albeit somewhat lengthy, strategy employs a substrate in which a chiral center is temporarily installed in the α -position using the SAMP/RAMP hydrazone method (272) (Eq. 29). (179)



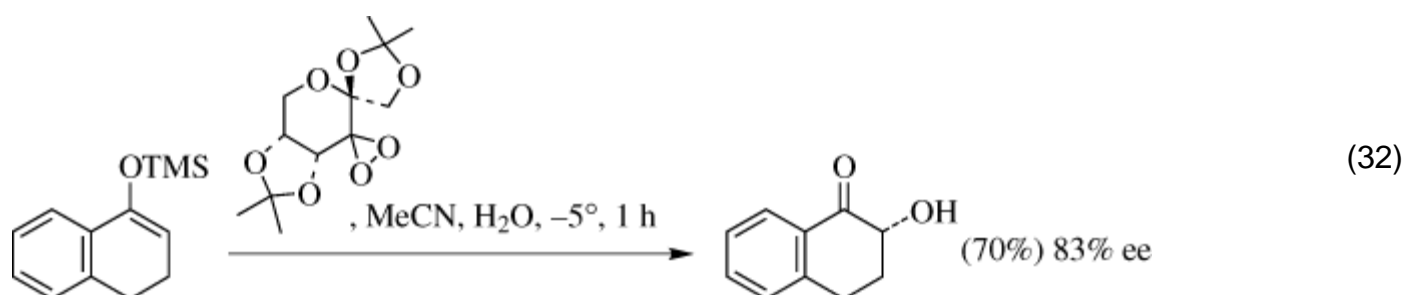


Osmium tetroxide catalyzed asymmetric dihydroxylation of ketone silyl enol ethers gives α -hydroxy ketones in good to excellent enantiomeric excess (Eq. 30). (158-160) The stereoselectivity of this reaction is efficiently controlled by chiral ligands. Good results are also obtained in the oxidation of silyl enol ethers catalyzed by (salen) manganese(III) complexes (145, 146, 273) (Eq. 31); (273) this method can also



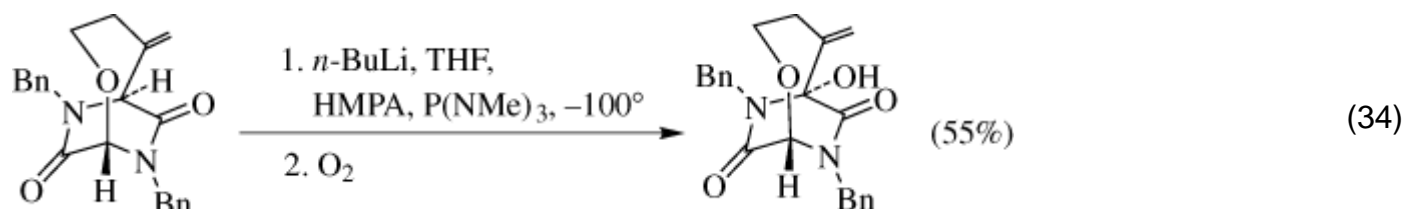
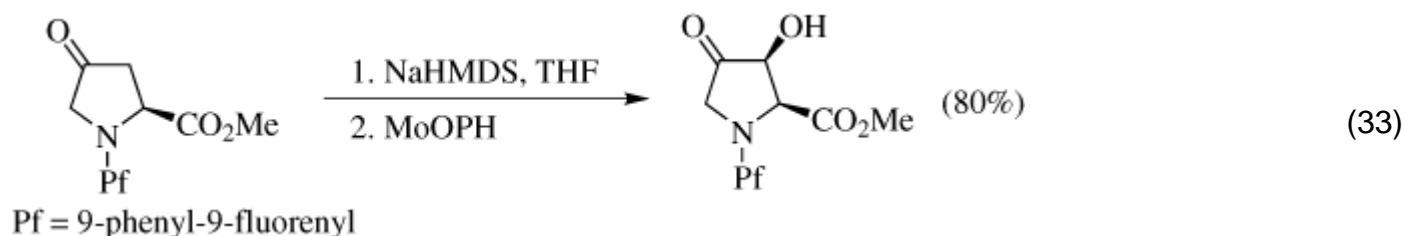


be applied to silyl ketene acetals but the selectivity is somewhat lower. Another promising method involves oxidation of silyl enol ethers with a sugar-derived dioxirane, generated in situ by oxidation of the sugar carbonyl derivative with potassium peroxydisulfate (117, 118) (Eq. 32). (117) When the reaction is carried out on the enol acetate, the intermediate epoxide can be manipulated to provide either of the two enantiomers (see Eq. 129 in the section on Comparison With Other Methods). (117)



3.3. Chemoselectivity

When two or more enolizable carbonyl groups are present in a molecule the acidity of the α -proton usually determines which enolate is formed. Thus α -hydroxylation of a ketone can be carried out in the presence of an ester group (Eq. 33). (274) In the example shown in Eq. 34, (39) the acidity of one of the two otherwise equivalent lactam α -protons is increased by an adjacent methyldene group.



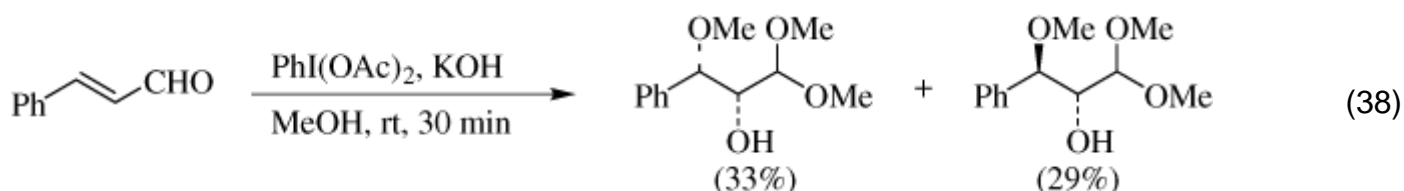
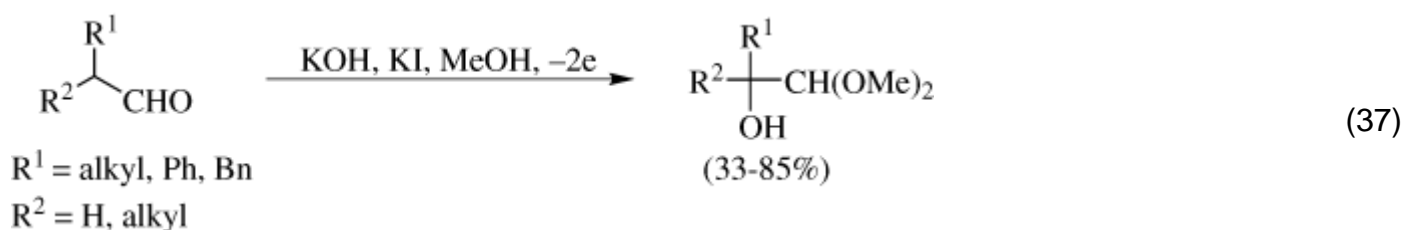
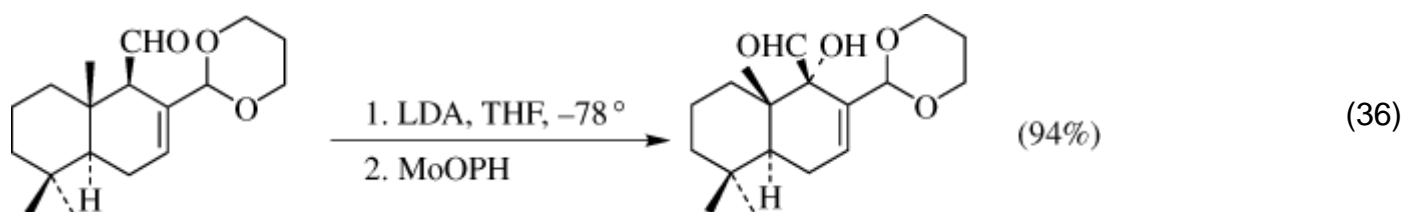
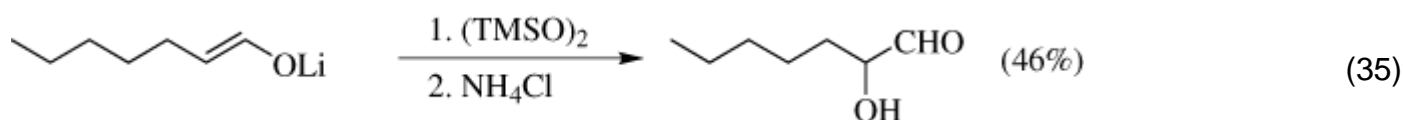
4. Scope and Limitations

Reports that compare the efficiency of the various hydroxylation agents for particular classes of enolates and silyl enol ethers are scarce. Studies involving new oxidants often use only a few substrates that tend to be chosen to maximize yields and/or stereoselectivity or to avoid regiochemical problems. The generality of some of the statements made in this section thus remains to be ascertained.

4.1. Hydroxylation of Enolates

4.1.1. Aldehyde Enolates (Table 1)

The α -hydroxylation of aldehyde enolates has received little study because of the difficulty encountered in generating the enolate without aldol self-condensation as well as the instability of the α -hydroxy products. Examples are shown in Eqs. 35(44) and 36 (275, 276); the yield is excellent in the second example because of the steric hindrance around the α -proton. Acetals of α -hydroxy aldehydes are obtained by electrochemical oxidation of aldehydes in basic solution (Eq. 37). (191) Enolates can also be generated by Michael addition of nucleophiles to α,β -unsaturated carbonyl compounds and α -hydroxylated in situ (Eq. 38). (277) α -Benzyloxy aldehydes are accessible by the method of Eq. 20. The hydroxylation of aldehyde silyl enol ethers is discussed in a later section.



4.1.2. Ketone Enolates

In contrast to aldehydes, reports on the direct α -hydroxylation of ketone enolates are abundant. Many oxidants have been explored for this transformation including oxygen, KO_2 , bis(trimethylsilyl) peroxide, $t\text{-BuO}_2\text{H}$, DMDO, hypervalent iodine reagents, MoOPH, MoOPD, and N -sulfonyloxaziridines. Hydrogen peroxide and $m\text{-CPBA}$ cannot be used in many cases since their acidic protons quench the enolates.

4.1.2.1. Acyclic Ketone Enolates (Table 2A)

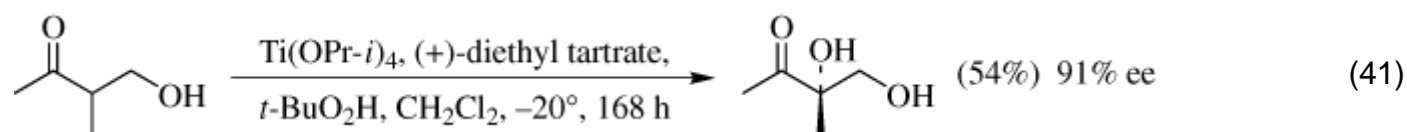
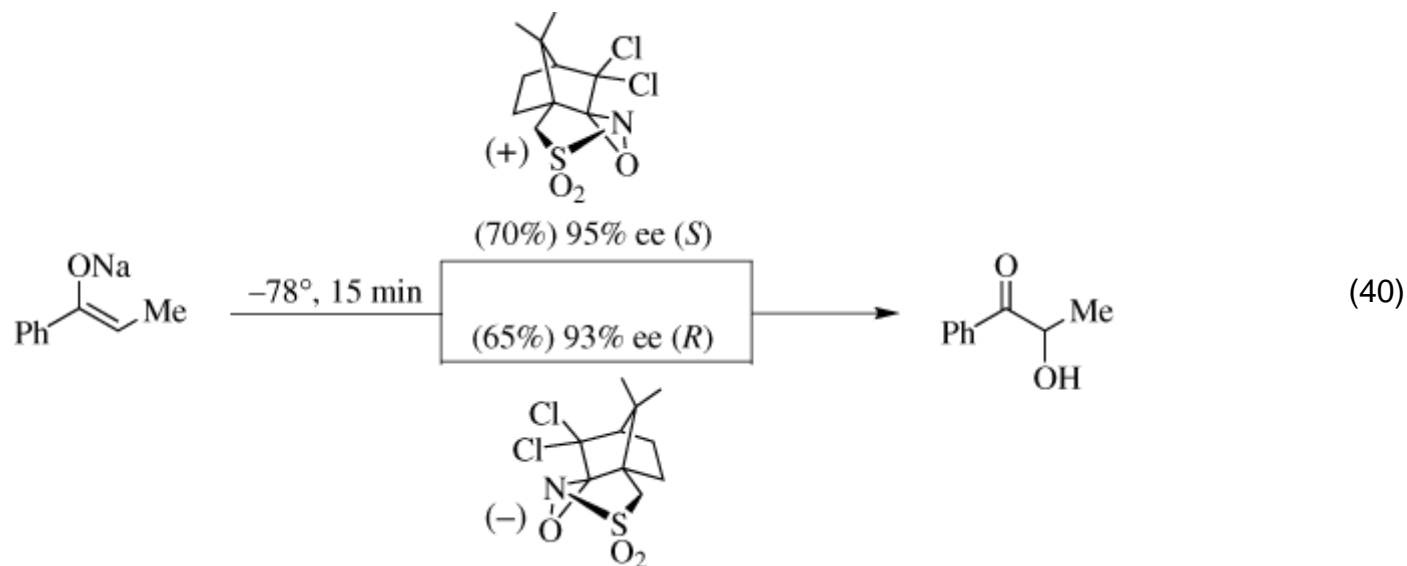
The hydroxylation of a selection of acyclic ketone enolates by a variety of oxidants is shown in Eq. 39. Asymmetric induction

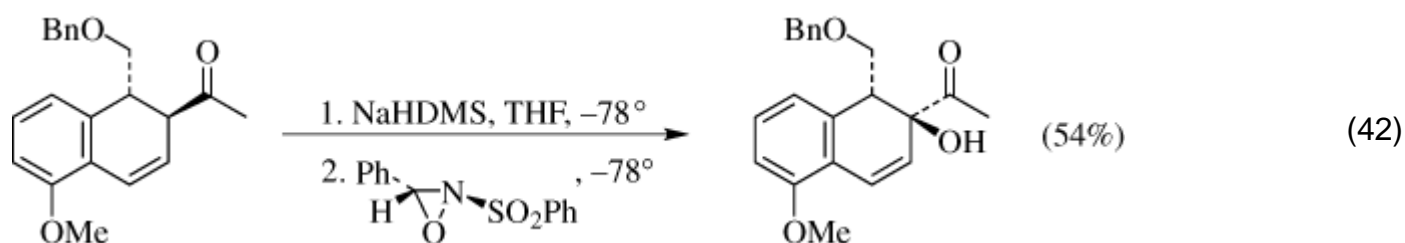


R ¹	R ²	Oxidant	Conditions	Yield	Ref.
Et	Me	<i>o</i> -HO ₂ CC ₆ H ₄ IO	KOH, MeOH, rt	(65%) ^a	227
<i>t</i> -Bu	Me	(+)-CSO	LDA, -78 to 0°	(55%) 32% ee	278 (39)
<i>n</i> -C ₆ H ₁₃	H	electrochemical	KOH, MeOH	(71%) ^a	191
<i>i</i> -PrCH ₂	<i>i</i> -Pr	<i>t</i> -BuO ₂ Li	TiCl(OPr- <i>i</i>) ₃ , 0°	(40%)	279
Me	Bn	(TMSO) ₂	<i>i</i> -Pr ₂ NMgBr, -78° to rt	(42%)	280
Ph	<i>i</i> -Pr	MoOPh	LDA, -22°	(65%)	40

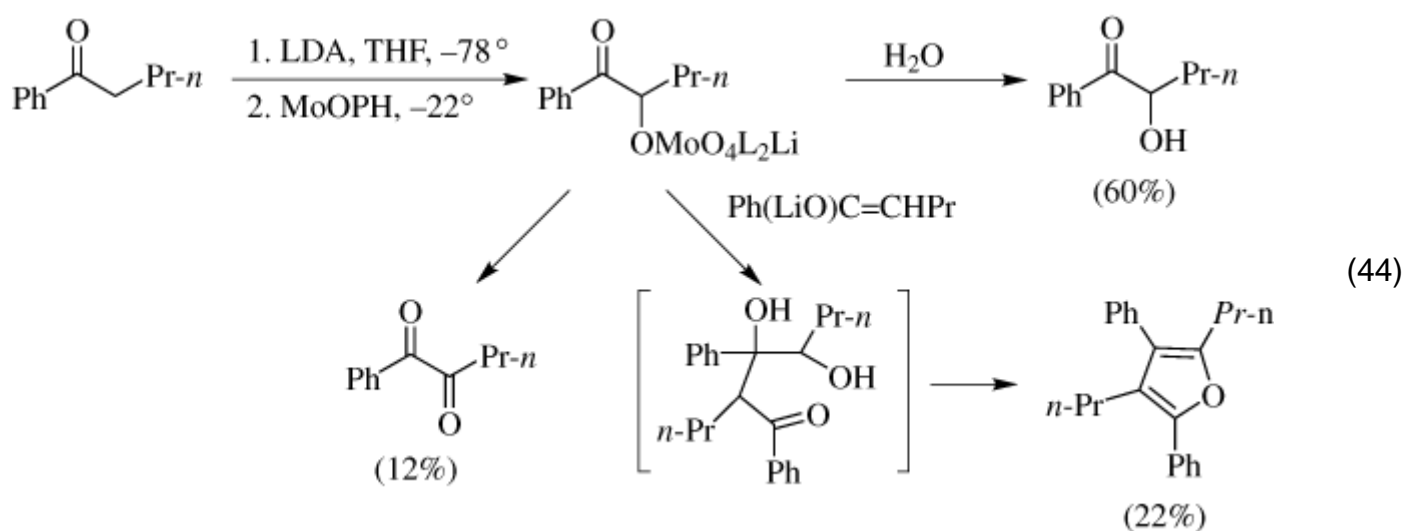
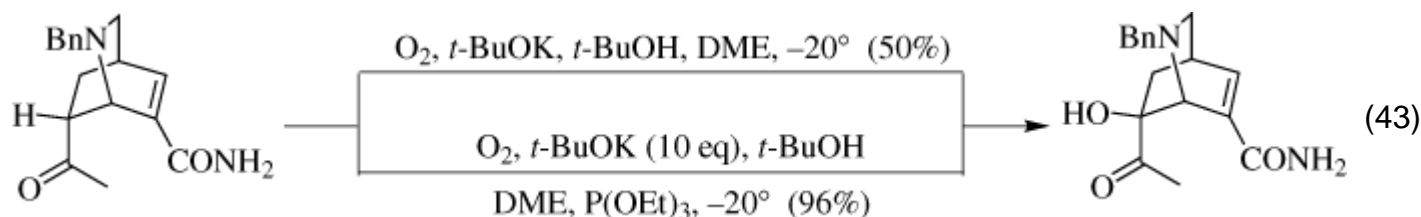
^aThe product is the dimethyl ketal.

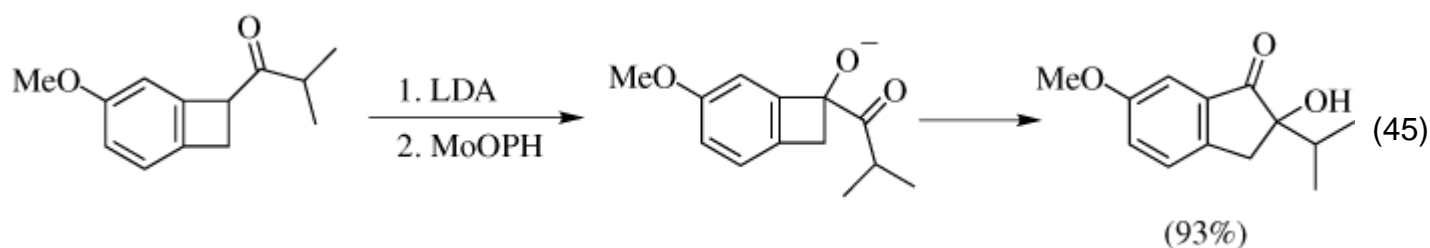
in the hydroxylation of *tert*-butyl ethyl ketone is modest. Much better results are obtained with DCCSO in the case of 1-phenyl-1-propanone enolate (Eq. 40). (278) Whether this efficiency will be observed with other acyclic ketone enolates remains to be seen. Dimethyldioxirane oxidation of a chiral enolate in the same 1-phenyl-1-propanone system gives the (*R*) enantiomer in 63% ee (Eq. 23); the (*S*) enantiomer is obtained by this method with only 5% ee. (261) α -Hydroxylation under the conditions of the Katsuki-Sharpless reaction (262) has been reported but it is limited to β -hydroxy ketone enolates (Eq. 41). (263) No aromatization is observed in the reaction of Eq. 42. (281)





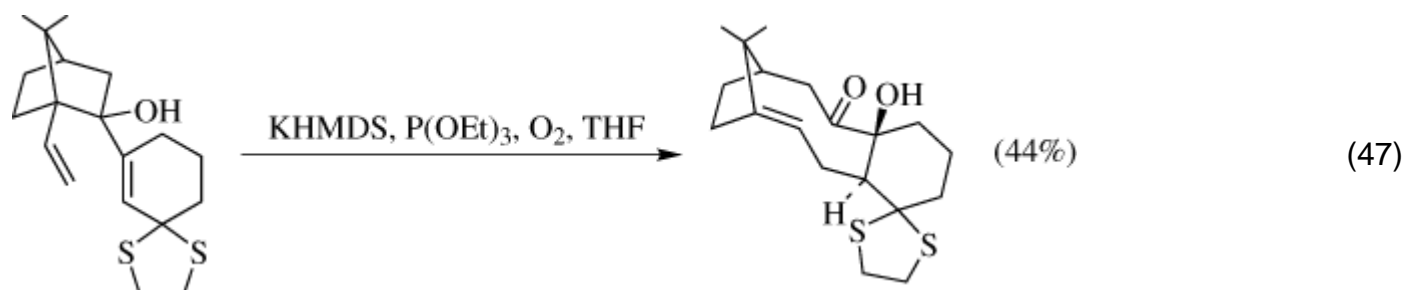
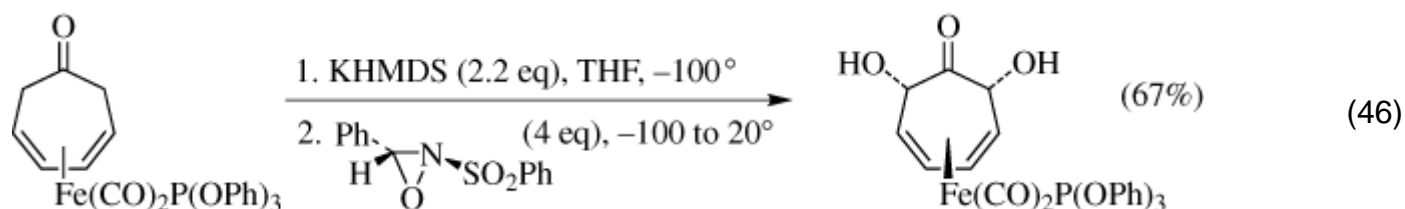
In a number of oxygenations α -hydroxylation products are obtained in the absence of a reductant. An example is shown in Eq. 43 (201) where direct formation of the α -ketol is attributed to the basic nitrogen since tertiary amines are known to reduce hydroperoxides to alcohols. (282) Nevertheless, higher yields are achieved by adding triethyl phosphite. In general, added reducing agents in α -hydroxylations with oxygen also suppress over-oxidation and carbon-carbon cleavage. The oxygenation of enolates under phase-transfer conditions (264-266) (Eq. 24) has only been applied to cyclic ketones but may operate with acyclic ones as well. Overoxidations or aldol condensations of the products with the substrates occasionally occur in α -hydroxylations with the MoOPH and MoOPD reagents (Eq. 44); they can usually be minimized by lowering the temperature and/or decreasing the concentration. (40) Another potential side reaction involving ring expansion of the intermediate alkoxide is illustrated in Eq. 45. (283) In α -hydroxylations with PSPO, lithium enolates sometimes give lower yields than sodium or potassium enolates because of imino aldol condensations of the enolate with (*N*-phenylsulfonyl)phenylimine, the reduction product of PSPO (Eq. 9). This side reaction is completely avoided by use of camphorylsulfonyloxaziridines. (284) Additional examples of the α -hydroxylation of acyclic ketones are found in Eqs. 12 and 20. In the example of Eq. 13, the lithium enolate is generated from a silyl enol ether.





4.1.2.2. Cyclic Ketone Enolates (Table 2B)

The α -hydroxylation of cyclic ketone enolates parallels that of acyclic ones. Examples are found in Eqs. 10, 11, 16, 17, 19, and 26. Apparently the only example of a sequential α,α' -dihydroxylation of a ketone enolate is shown in Eq. 46. (285) The Oxy-Cope rearrangement (286) is another method for generating cyclic ketone enolates that can be α -hydroxylated in situ (Table 14; Eq. 47). (198) Enolates of 3-alkyl-1,2-cyclopentanediones under the conditions of the Katsuki-Sharpley reaction (cf. Eq. 41) give complex mixtures containing 3-hydroxy-1,2-cyclopentanediones and their hemiketals as well as products of Baeyer-Villiger rearrangements (see Table 9A). (287) A better method for the α -hydroxylation of α -diketones is oxidation of the enol silyl ethers with *m*-CPBA (288) (cf. also Eq. 92).



4.1.3. Ester Enolates (Table 3)

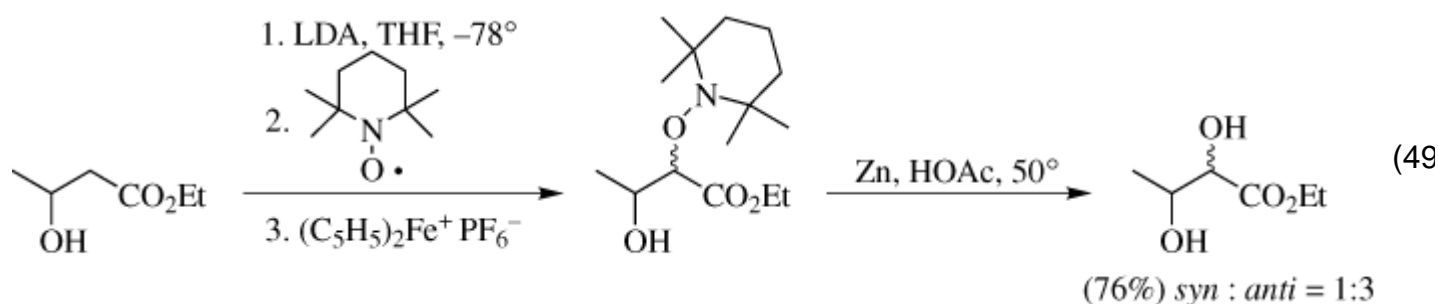
Because of the potential for transesterification, alkoxide bases are usually not employed for the generation of ester enolates unless the alcohols are matched. The MoOPH and MoOPD reagents and the *N*-sulfonyloxaziridines are the most widely used oxidants for this class of substrates. Hydroxylation of an ester enolate and a benzylic anion in the same molecule with PSPO has been reported. (289) Other oxidants that have been used with ester enolates include oxygen, DMDO, and *t*-BuO₂Li (Eq. 48). Another method involves oxidation of ester enolates with ferrocenium hexafluorophosphate, (190) iodobenzene diacetate, (290) or cupric chloride, (291) trapping of the intermediate radical with 2,2,6,6-tetramethyl-1-piperidinyloxy, and reduction (Eq. 49). (190) Hypervalent iodine reagents have been used especially for arylacetates (Eq. 50). The acids are obtained when the reaction is carried out with potassium hydroxide in benzene-water; with sodium methoxide in methanol, the α -methoxy ester is formed. (138) Despite the presence of an acidic proton *m*-CPBA has also been employed on occasion. However, substantial amounts of starting material are recovered. In the example illustrated (Eq. 51), (292) oxygenation is even less efficient; the stable hydroperoxide is isolated in 32% yield. The best yields are obtained when the enolate of ester 30 is generated by Birch reduction (293) and hydroxylated with CSO in situ; the enantiomeric

excess is only 5% when the ammonia is removed prior to oxidation. (292)

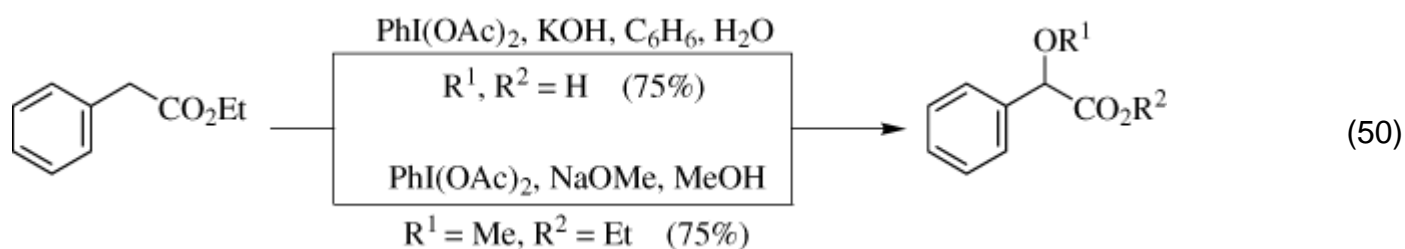


R ¹	R ²	Oxidant	Conditions	Yield	Ref.
Bn	Me	MoOPh	LDA, THF, -78°	(60%)	40
Bn	Me	(+)-CSO	LDA, THF, HMPA, -90°	(63%) 86% ee	269
Bn	<i>t</i> -Bu	O ₂	LDA, (<i>i</i> -PrO) ₃ TiCl, THF, -50°	(64%)	57
Bn	C ₆ H ₃ Me _{2-2,5}	DMDO	LDA, Cp ₂ TiCl ₂ , THF	(65%)	111
<i>n</i> -C ₆ H ₁₃	<i>t</i> -Bu	<i>t</i> -BuO ₂ Li	LDA, THF, -78 to 0°	(80%)	64

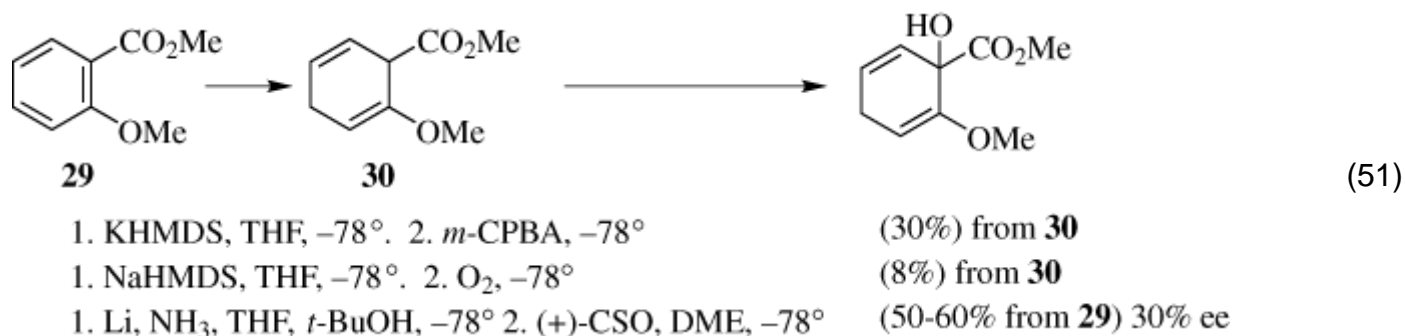
(48)



(49)

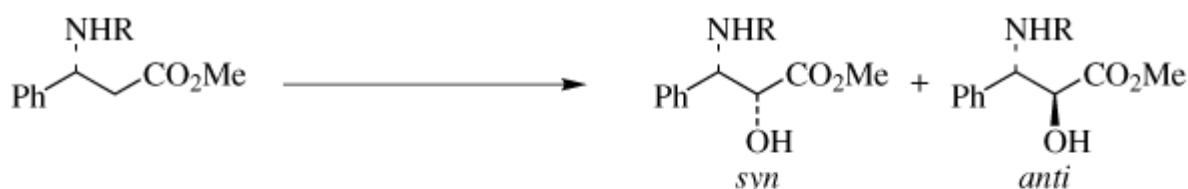


(50)

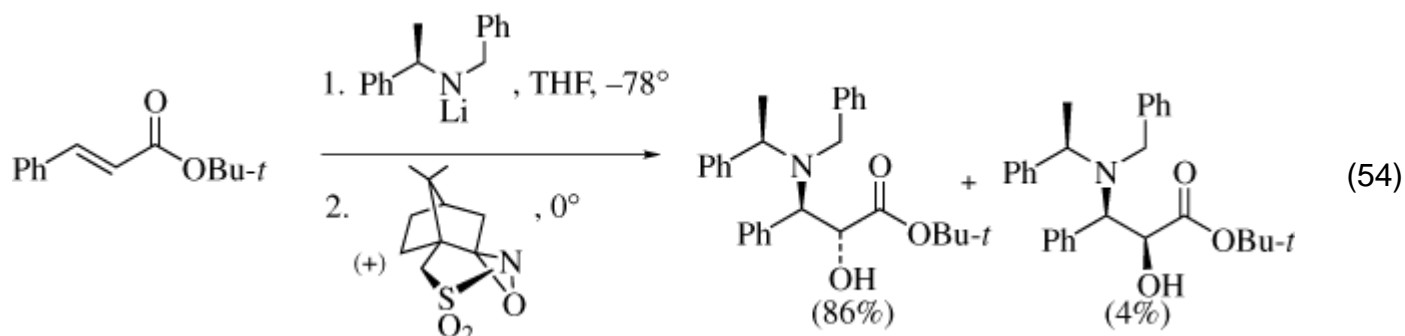
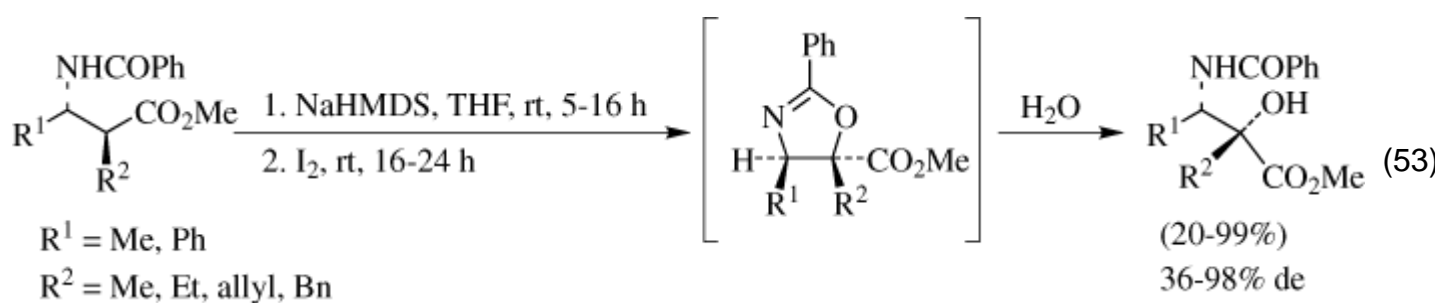


(51)

a-Hydroxy-*b*-amino esters have been prepared by a number of methods. In the examples of Eq. 52 chiral and non-chiral *N*-sulfonyloxaziridines give the same diastereoselection. The reversal in the *syn/anti* ratio in entries 2 and 3 has been explained in terms of intermediate eight- and six-membered chelates, respectively. (188) The oxidant in Eq. 53 is iodine and the reaction proceeds by way of an oxazoline. (295) The latter can be alkylated at the ester group when R² is hydrogen, thus further increasing the scope of this method. (296) Like other enolates, ester enolates can be generated by Michael additions and hydroxylated in situ. An example is given in Eq. 54. (297)



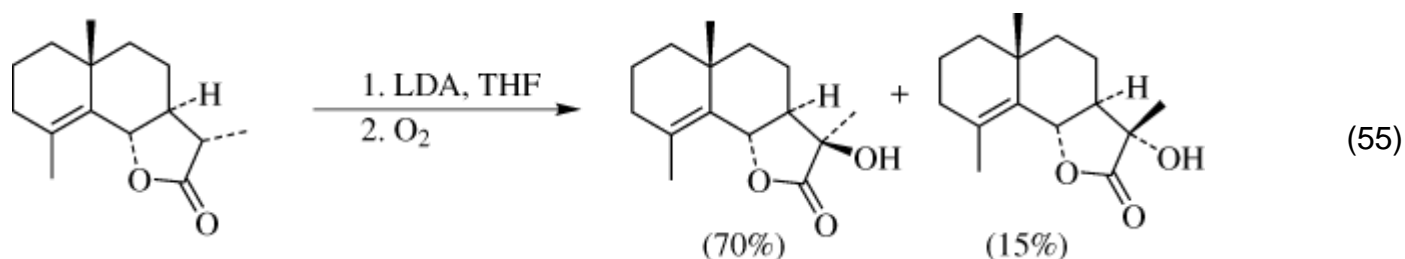
R	Oxidant	Conditions	Yield	<i>syn:anti</i>	Ref.
COPh	(+)-CSO	LDA, LiCl, THF, -100 to -78°	(58%)	86:14	294
COPh	PPSO	KHMDS, THF, -60°	(62%)	86:14	188
CO ₂ Bu- <i>t</i>	PPSO	LiHMDS, THF	(—)	10:90	188
COPh	MoOPh	KHMDS, THF, -60°	(83%)	86:14	188
CO ₂ Bu- <i>t</i>	MoOPh	KHMDS, THF, -60°	(65%)	86:14	188



α -Hydroxylation of a thiol ester with PPSO has been reported (Eq. 22). (260)

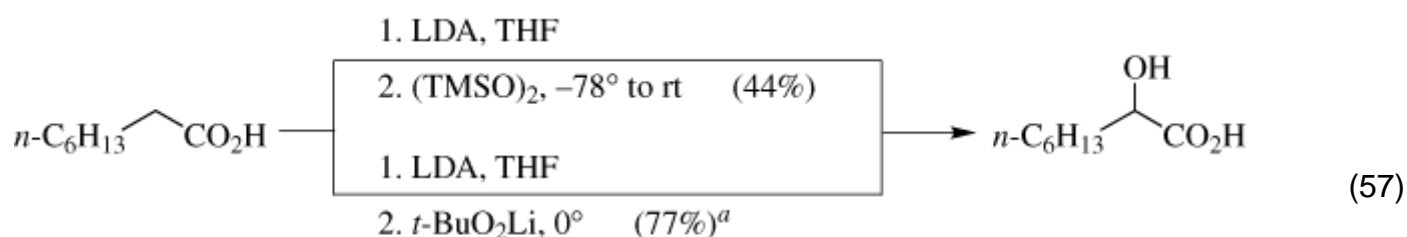
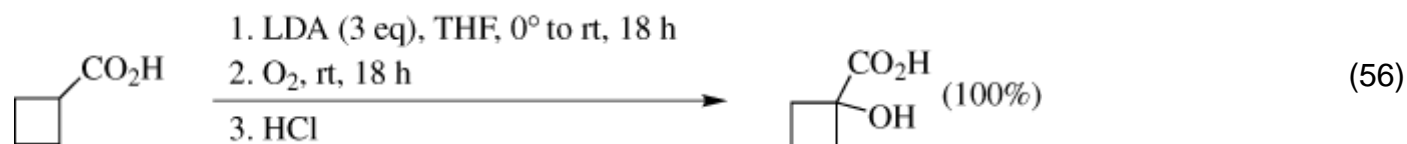
4.1.4. Lactone Enolates (Table 4)

Oxygen (Eq. 55), (298) the MoOPH (Eq. 18) and MoOPD reagents, and *N*-sulfonyloxaziridines (Eq. 18) are the most widely used oxidants in this class of compounds. Carbon-carbon bond cleavage is sometimes observed in oxygenations. (298) Examples of tandem Michael additions/hydroxylations of lactones are listed in Table 12.

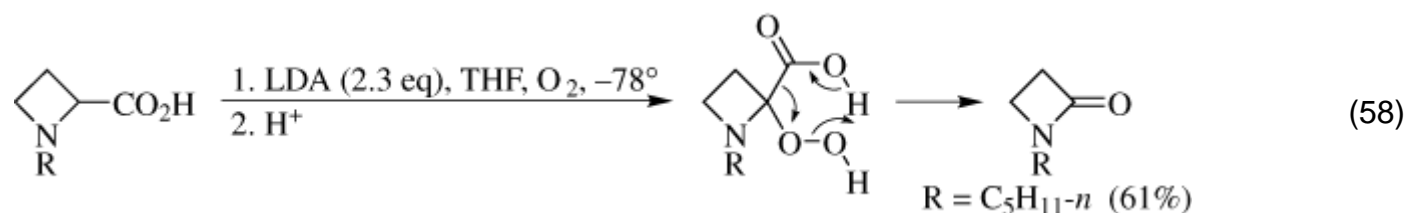


4.1.5. Carboxylic Acid Dianions (Table 5)

Air oxidation of carboxylic acid dianions, usually generated with an excess of LDA or *n*-butyllithium, is an excellent method for the preparation of α -hydroxy acids (299, 300) (Eq. 56). (301) Addition of reducing agents is not required. The hydroperoxides can be isolated when the reaction is carried out at low temperatures (56, 74, 76, 302, 303) and subjected to kinetic resolution by enantioselective reduction. (304) In the oxygenation of arylacetic acids extended reaction times can lead to formation of benzoic acids. (299) Other oxidants that have been used are (TMSO)₂ (109) and *t*-BuO₂Li (Eq. 57) (64), and PSPO. (305) Oxygenation of azetidine-2-carboxylic acid dianions gives 2-azetidinones (Eq. 58). (306)

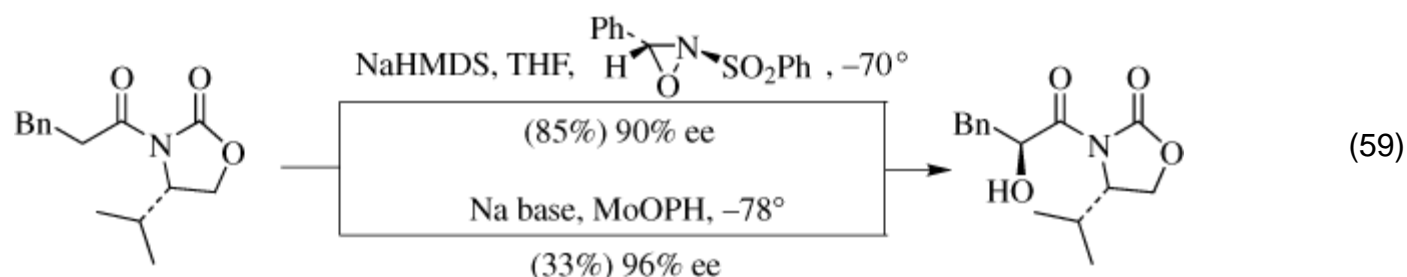


^a The yield is that of the methyl ester obtained on reaction of the crude acid with diazomethane.



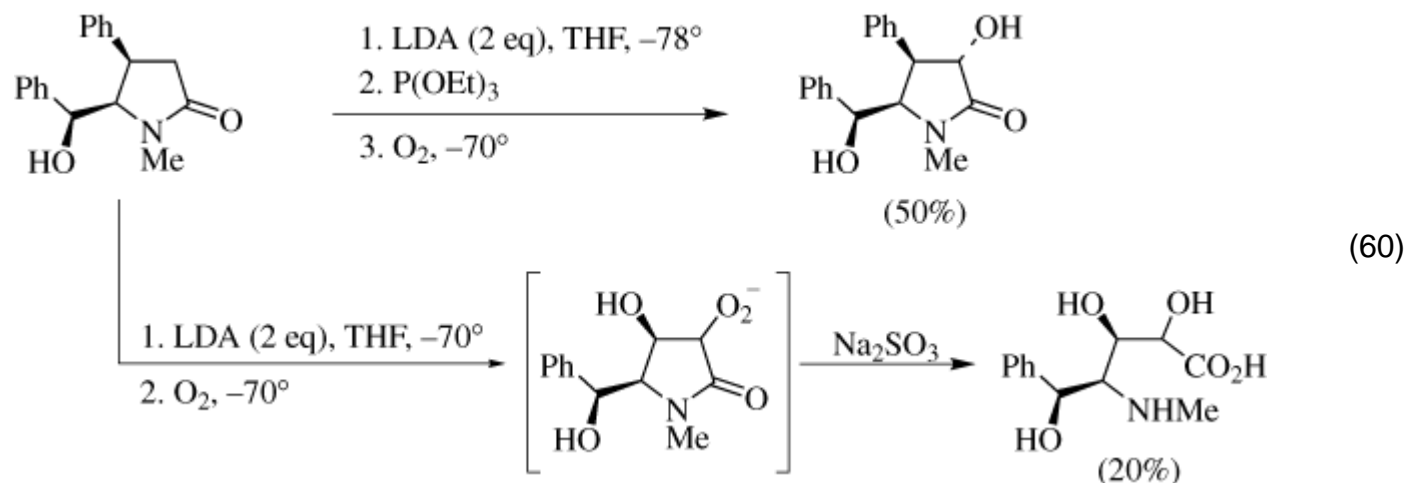
4.1.6. Amide Enolates and Related Compounds (Table 6)

Only *N,N*-disubstituted amide enolates have been subjected to the α -hydroxylation reaction. Oxygen, (TMSO)₂, and *N*-sulfonyloxaziridines are the most commonly used reagents. Lithium *tert*-butyl peroxide (64) has also been employed. Oxazolidinones are frequently used as chiral auxiliaries. In the example of Eq. 59, (177) the rare application of the MoOPH reagent to an amide gives somewhat better asymmetric induction than PSPO, but the yield is much lower. However, the poor yield observed in this instance may be an exception since the MoOPH reagent is an efficient hydroxylation reagent for lactams. Other examples involving enolates in this category are found in Eqs. 21 and 27. Hydroxylations of amide enolates obtained by Birch reduction of *N,N*-disubstituted arylcarboxamides are listed in Table 13.

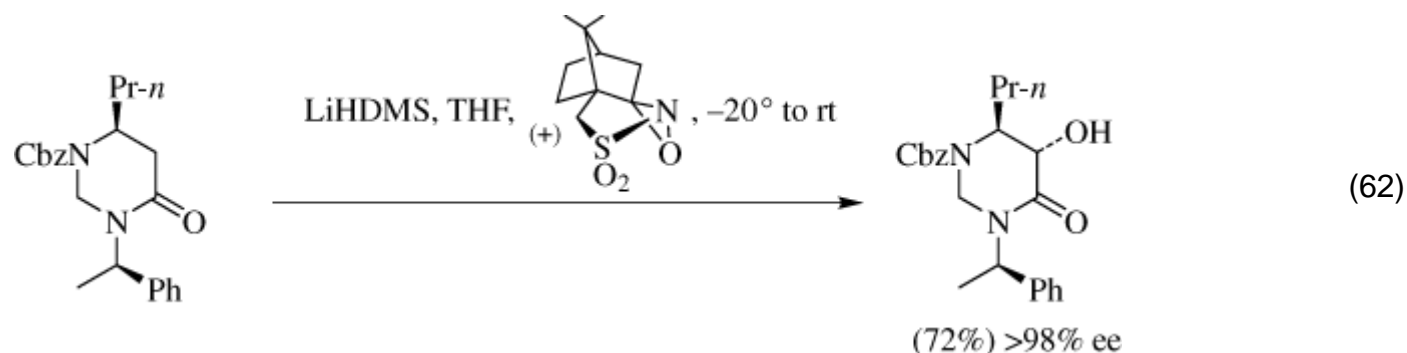
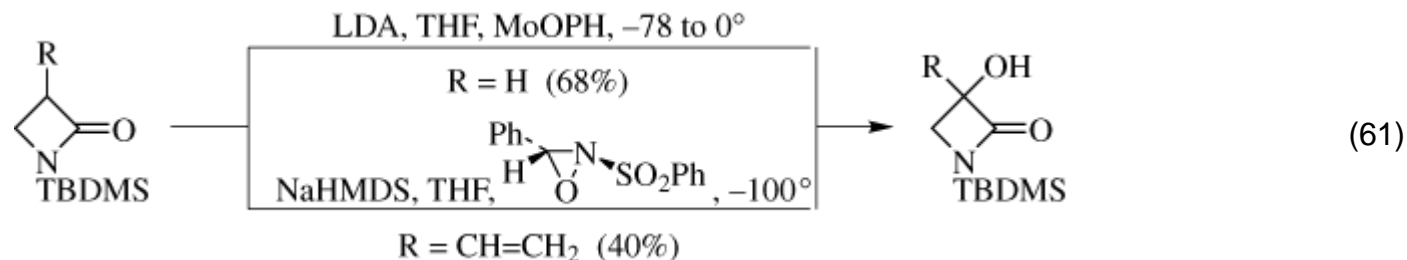


4.1.7. Lactam and Cyclic Imide Enolates (Table 7)

Oxygen (Eq. 34), MoOPH, and *N*-sulfonyloxaziridines are the most commonly used oxidants in this class of enolates. Low yields in oxygenations are sometimes encountered when the reduction of the intermediate hydroperoxide is carried out in a separate step rather than in situ (Eq. 60). (58) Ring opening of the lactam by the highly nucleophilic intermediate peroxide ion is believed to be responsible for the formation of the observed product. *b*-Lactams can be hydroxylated with MoOPH or *N*-sulfonyloxaziridines



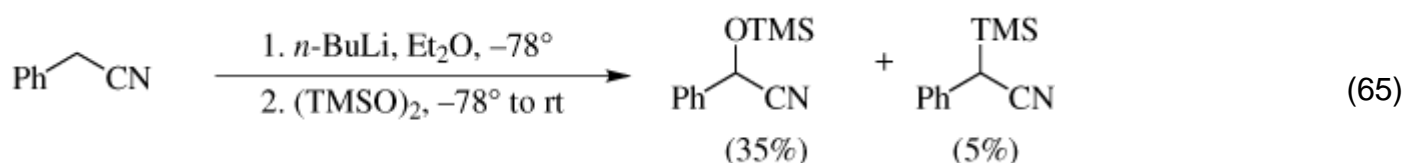
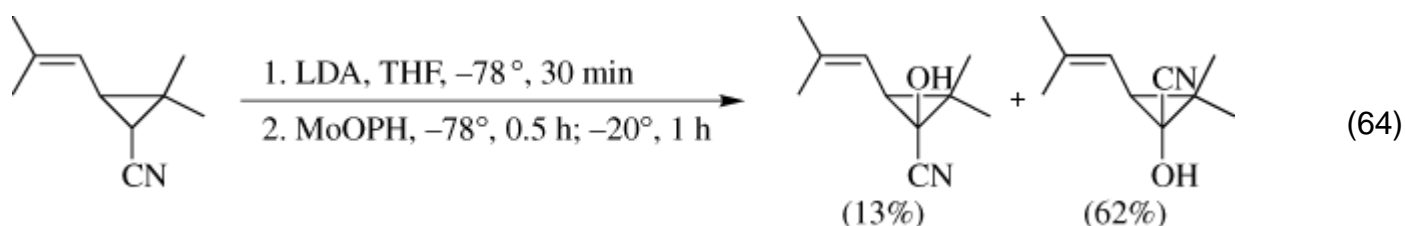
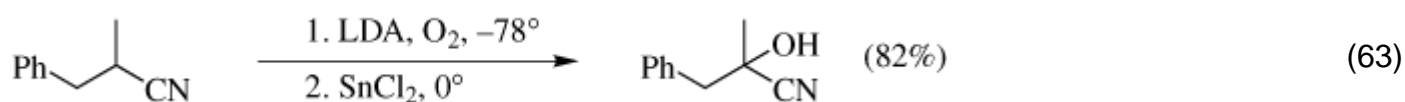
(Eq. 61). (307-309) High asymmetric induction is achieved in hydroxylations with chiral camphorylsulfonyloxaziridines (Eq. 62). (309a)



4.1.8. Nitrile Anions (Table 8)

Oxygen (Eq. 63) (310) and MoOPH (Eq. 64) (311, 312) have been used to convert nitrile anions into cyanohydrins. Bases used to generate the anions include LDA, lithium diethylamide, *n*-butyllithium, and potassium *tert*-butoxide. The intermediate hydroperoxides in the oxygenations can be isolated (310) or trapped as acetates. (30) The cyanohydrins are sometimes prone to hydrolysis to give ketones. (311, 313, 314) Oxidation of nitrile anions with (TMSO)₂ gives a-silylated products in

addition to α -siloxy nitriles (Eq. 65). (315)



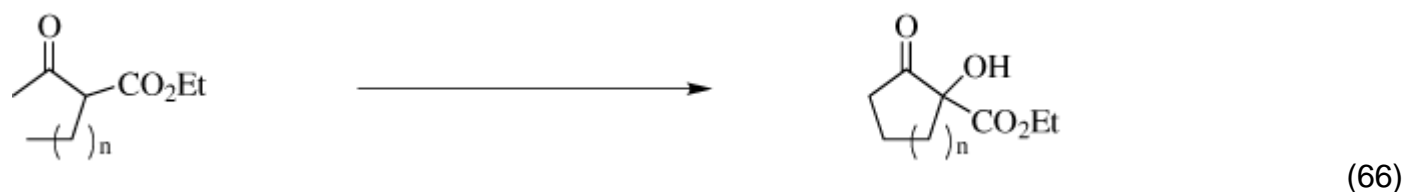
4.1.9. Enolates of β -dicarbonyl Compounds (Table 9)

Enolates of β -dicarbonyl compounds, on hydroxylation, give the α -hydroxy derivatives. The reaction has been applied to enols of β -diketones, (316) β -keto esters, (84, 110, 317, 318) malonic esters, (319) β -keto lactones, (110, 320) β -keto lactams, (321, 322) α -carbalkoxy lactams, (323, 324) and malonamide derivatives. (321) Because of the enhanced acidity of the α -proton, enolates of this class of compounds can be generated with weaker bases such as potassium fluoride, (84, 110, 317, 318) tetrabutylammonium fluoride, (84, 110, 318), cesium fluoride, (319) sodium hydroxide, (321, 322) potassium hydroxide, (325, 326) and sodium methoxide. (327)

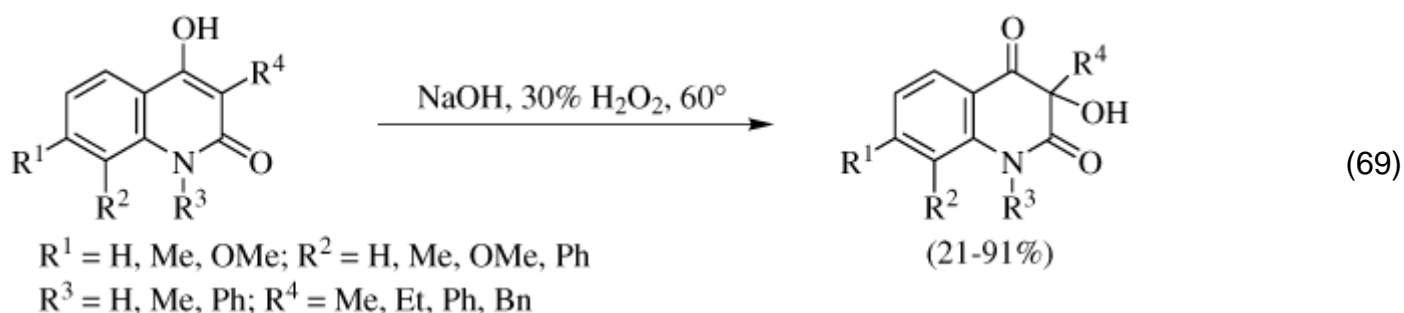
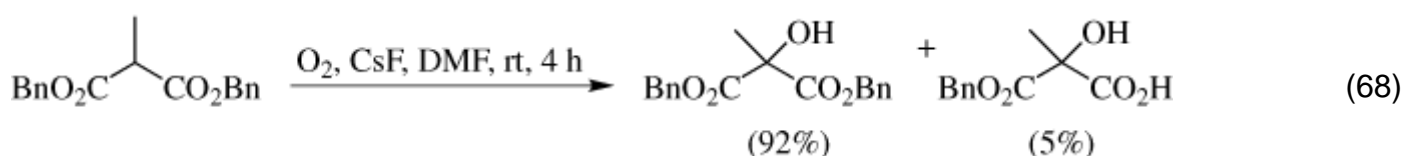
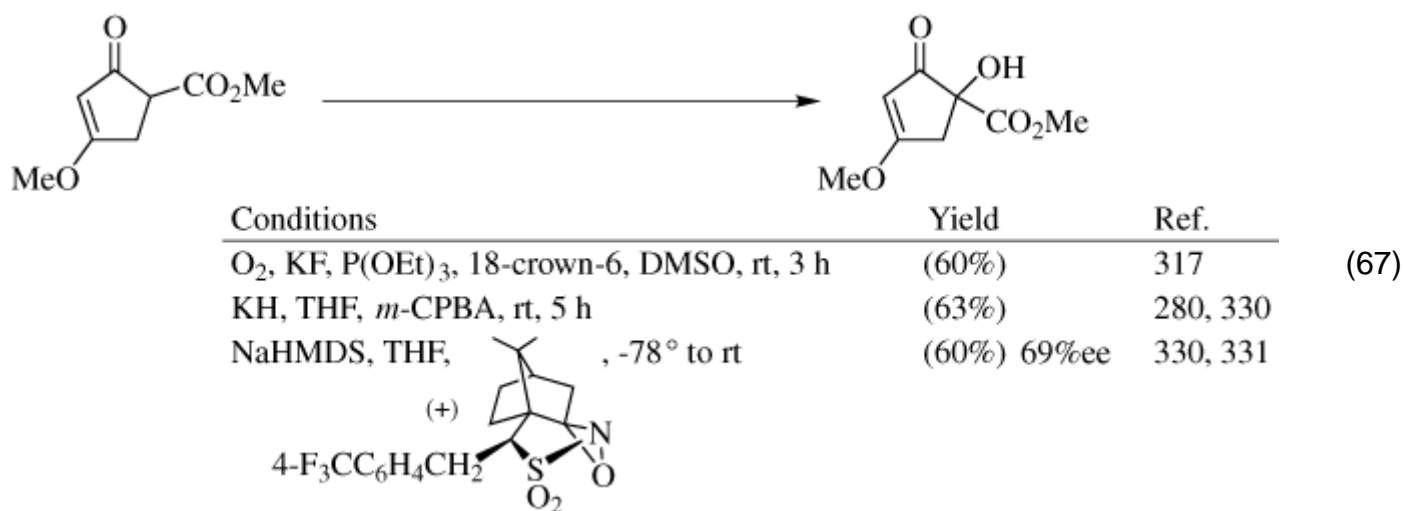
1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) has been used for sensitive chlorophyll derivatives. (328, 329)

β -Keto ester enolates have been α -hydroxylated with a variety of reagents (Eqs. 66 and 67).

Oxygenation of α -monosubstituted malonic ester enolates proceeds in high yield without an added reducing agent (Eq. 68). (319) β -Keto lactam enolates are efficiently hydroxylated by 30% hydrogen peroxide (Eq. 69). (322) For the hydroxylation of some β -keto esters 98% hydrogen peroxide with, (89) or without, (88) added oxygen, is required to achieve good yields. The MoOPH reagent usually fails to oxidize enolates of β -dicarbonyl compounds, probably because of formation of an unreactive chelate. (40, 151) Under forcing conditions, formation of Baeyer-Villiger products and ring-contracted α -diketones has been observed. (332) Hypervalent iodine reagents usually also cannot be used as oxidants because they form stable iodonium ylides with β -dicarbonyl compounds. An exception are compounds with a hydroxyl



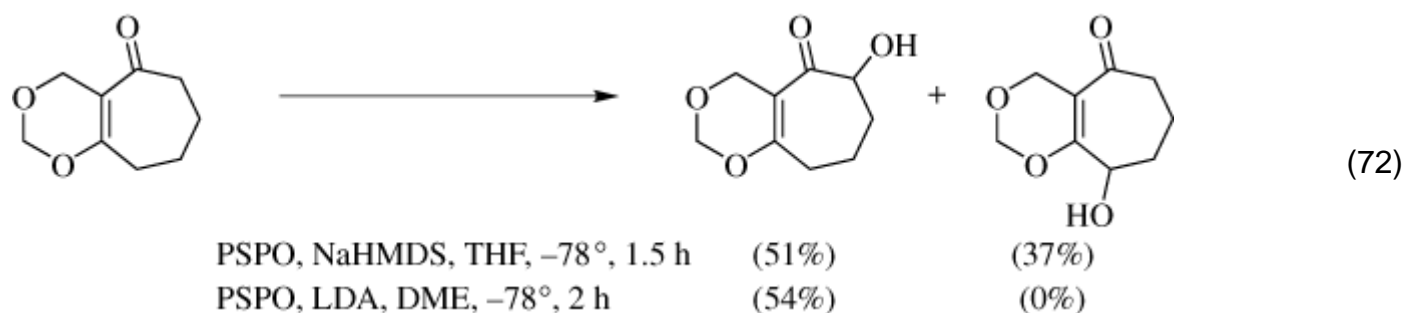
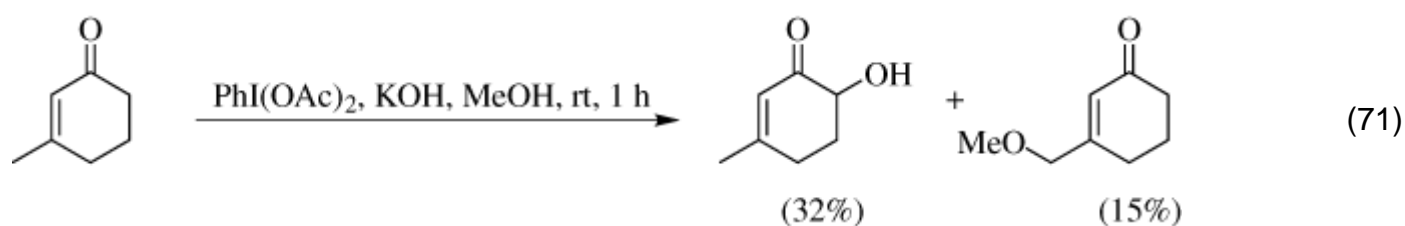
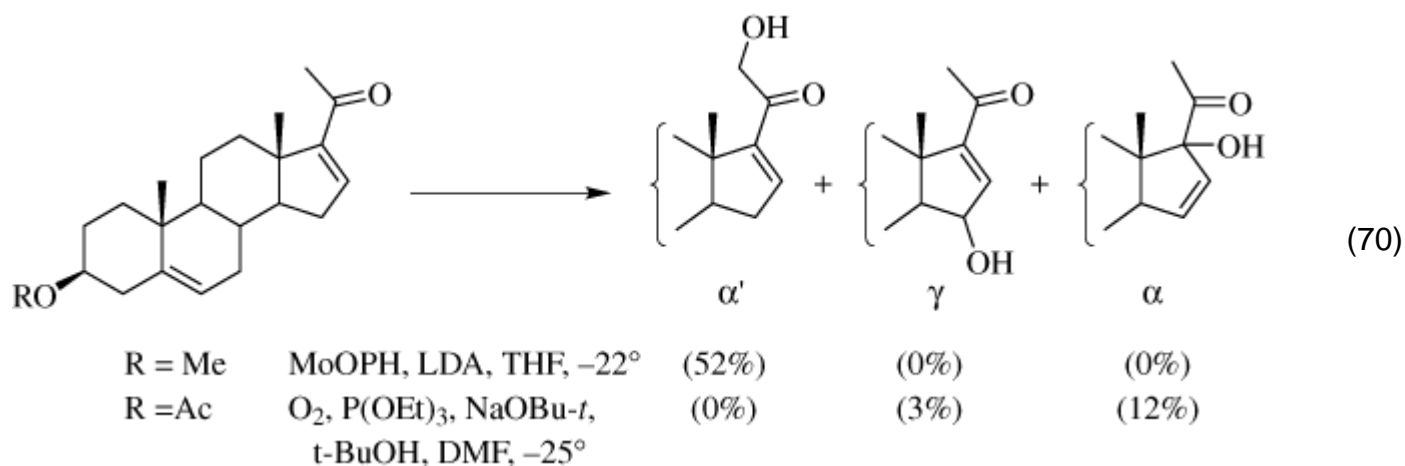
n	Oxidant	Conditions	Yield	Ref.
1	$^1\text{O}_2$	$^3\text{O}_2$, sens., hv, Bu_4NF , CHCl_3 , 2 h	(49%)	318, 84
2	DMDO	KF, Me_2CO , H_2O , 20°	(85%)	110



group in an appropriate position to permit intramolecular alkoxylation (see Eq. 109 in the section on Related Reactions). Asymmetric hydroxylation of a β -keto ester in the presence of a chiral base is shown in Eq. 25. γ -Hydroxylation of a β -keto lactone dianion is illustrated in Eq. 14.

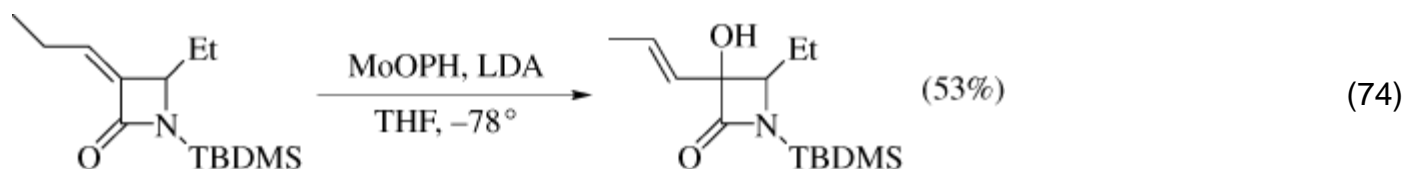
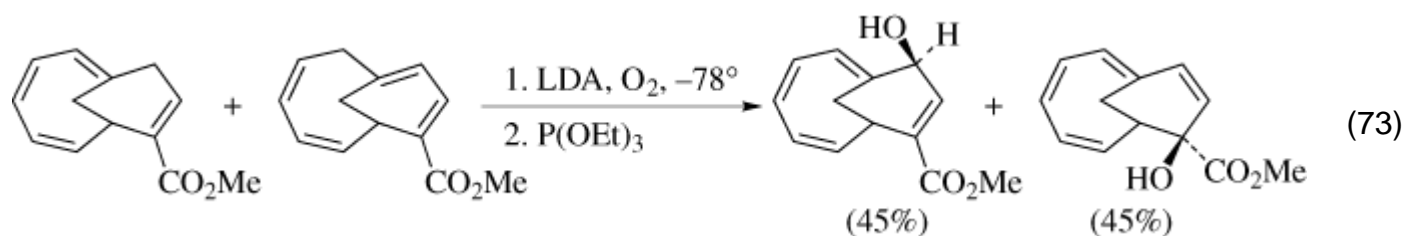
4.1.10. Enolates of α,β -unsaturated Carbonyl Compounds (Table 10)

In principle, hydroxylation of α,β -unsaturated ketone enolates can occur in the α' - and γ -positions as well in the α -position with concurrent allylic shift. This is illustrated in Eq. 70. (40, 333) Yields in the oxygenation of this type of steroid enolate are generally low. The specific α' -hydroxylation by MoOPH appears to be general for α,β -unsaturated ketones whereas it seems to occur in oxygenations only when the two other positions are blocked although there are exceptions. (334) With hypervalent iodine reagents (Eq. 71) (277) both α' - and γ -oxidations have been observed; when the β -carbon is monosubstituted, tandem Michael addition/hydroxylation takes place instead (cf. Eq. 38). With *N*-sulfonyloxaziridines α' - and γ - (Eq. 72) (176) as well as

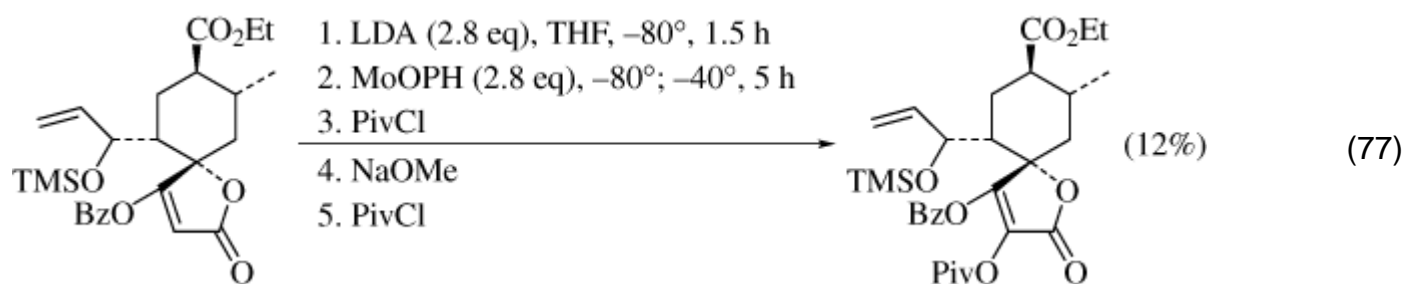
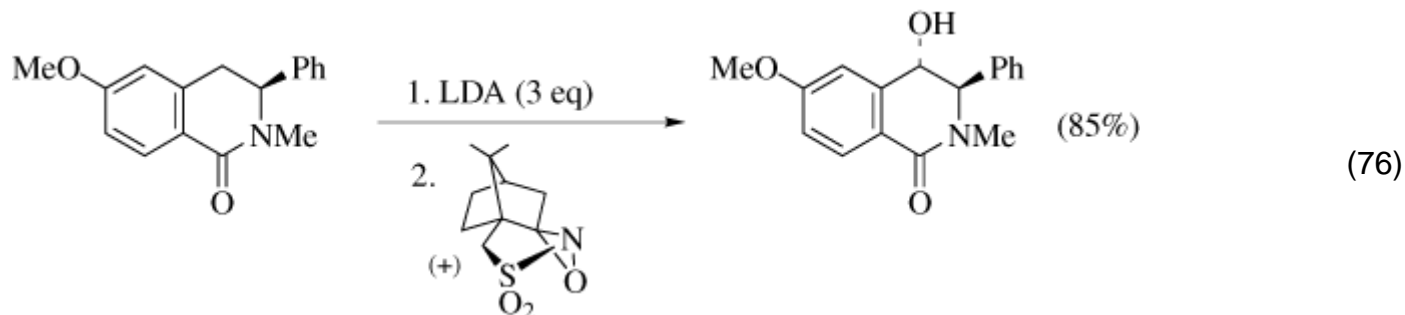
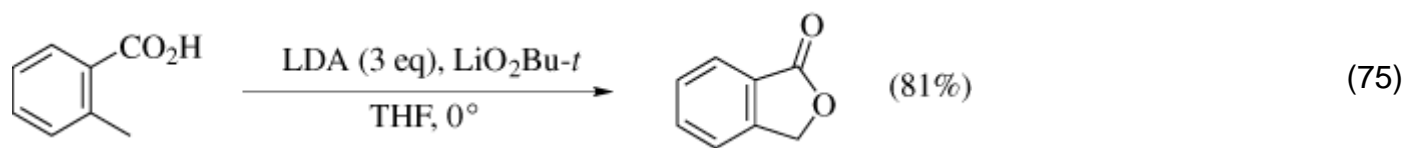


α -hydroxylation (246) have been reported. Hydrogen peroxide, (167) DMDO, (112) and silver oxide (167) have also been used. The hydroxylation of 2-siloxydienes is discussed in a later section.

α' -Hydroxylation is not possible in enolates of α,β -unsaturated esters and amides. Oxygen (Eq. 73) (335) and MoOPH usually give mixtures of α - and γ -hydroxylation products although cases where only α -hydroxylation occurs are known (Eq. 74). (336) *N*-Sulfonyloxaziridines have also been used. (176, 337, 338)

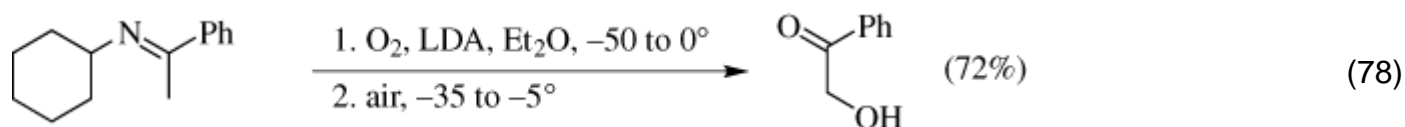


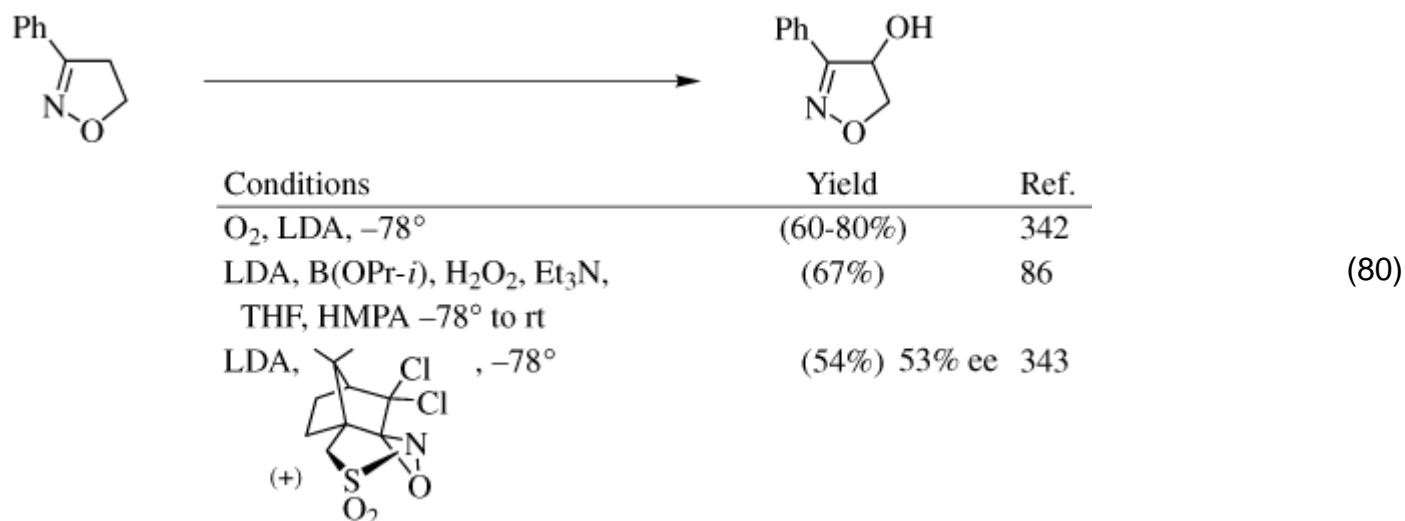
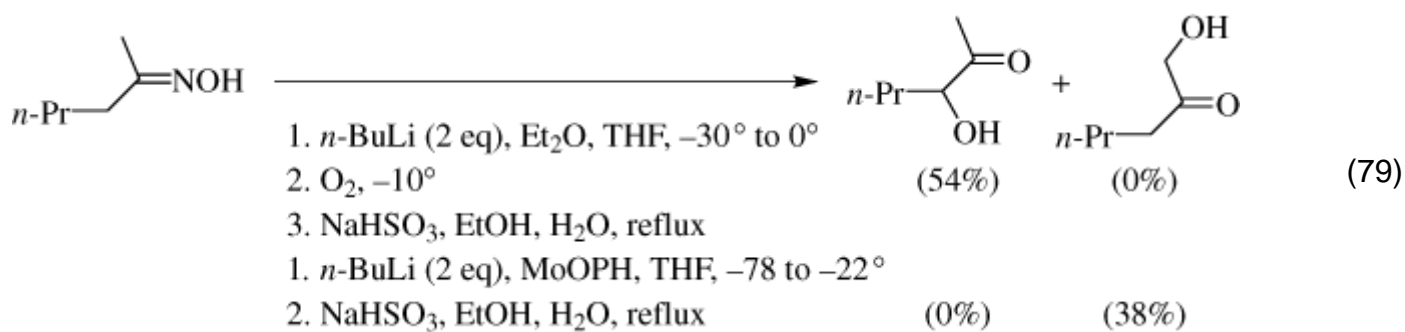
A special case involves aromatic carbonyl derivatives with an alkyl group in the ortho position that can be deprotonated and hydroxylated (Eqs. 75(64) and 76 (339)). The transformation shown in Eq. 77 involves hydroxylation of a vinyl anion. (340)



4.1.11. Aza-enolates (Table 11)

Imines (Eq. 78) (341), oximes (Eq. 79), (40, 341) and hydrazones (Eq. 20) are masked carbonyl compounds whose anions can be hydroxylated; hydrolysis of the products then gives the α -hydroxy carbonyl derivatives. This method does not seem to have an advantage over using the enolates directly when the racemic products are desired. Yields actually are often lower. However, when used as chiral auxiliaries these groups are useful in asymmetric synthesis. The anions of isooxazolines can also be hydroxylated (Eq. 80); the products are intermediates in the synthesis of amino polyols and amino sugars. The acyloxylation of enamine anions is discussed in the section on Related Reactions.



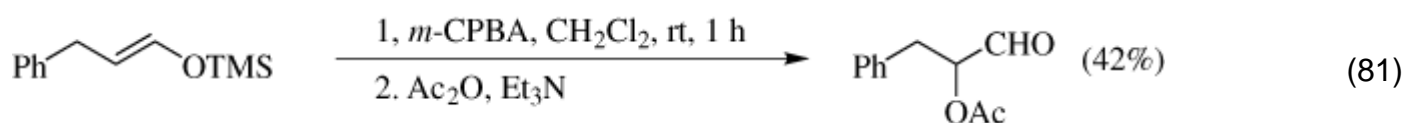


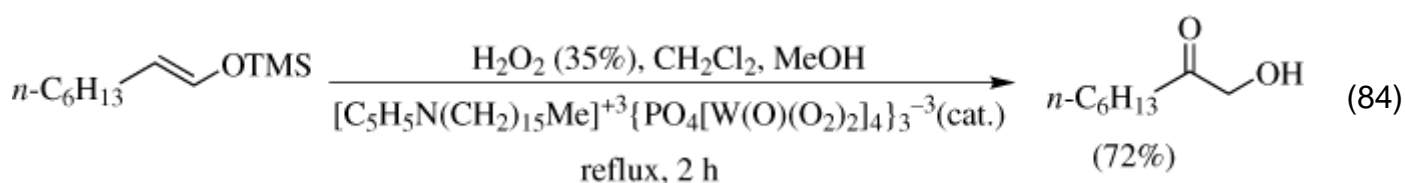
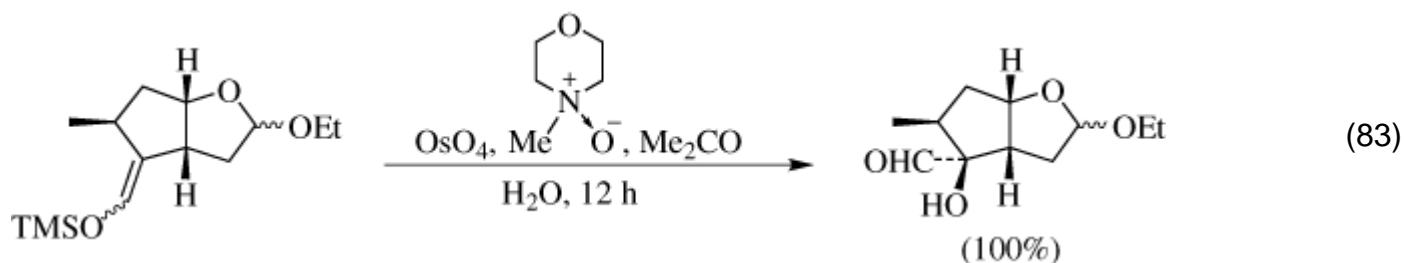
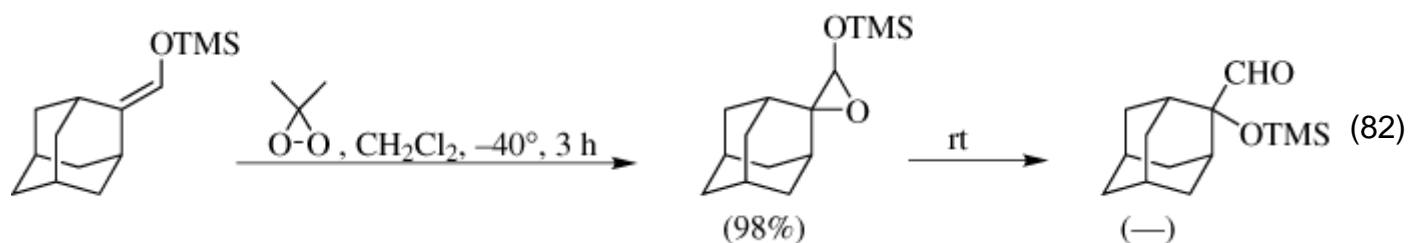
4.2. Hydroxylation of Silyl Enol Ethers

Silyl enol ethers as well as the related alkyl trialkylsilyl ketene acetals and bis (trialkylsilyl) ketene acetals are excellent synthetic equivalents of enolates, combining reasonable reactivity with high selectivity. (16, 48) Like enolates, these neutral compounds give in most cases α -hydroxy carbonyl products upon oxidation. A wide variety of oxidants have been employed. With the exceptions noted below, silyl enol ethers do not normally react with molecular oxygen and there appears to be only one report where the MoOPH reagent has been used. (344) α -Alkoxylation, α -acyloxylation, and α -sulfonyloxylation are discussed in the section on Related Reactions.

4.2.1. Aldehyde Silyl Enol Ethers (Table 15)

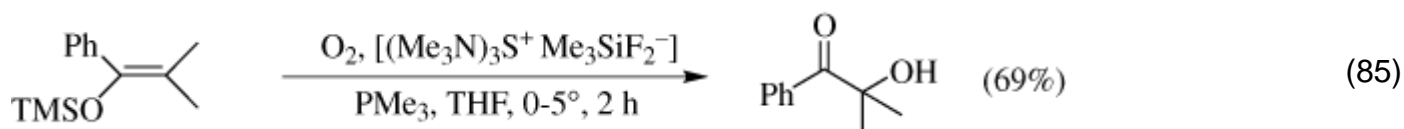
Hydroxylation of substrates in this class has been carried out with *m*-chloroperoxybenzoic acid (Eq. 81), (123) dimethyldioxirane (Eq. 82), (114, 116) and the OsO₄/*N*-methylmorpholine (Eq. 83) (153) and OsO₄/K₃Fe(CN)₆ (Eq. 30) (223) catalytic systems. (345) Less stable α -hydroxy aldehydes are acylated in situ (Eq. 81). Treatment of 1-silyloxy-1-octene with 35% hydrogen peroxide in the presence of catalytic amounts of cetylpyridinium peroxotungstophosphate gives the α -hydroxy ketone instead of the expected α -hydroxy aldehyde (Eq. 84). (91) The reaction has also been carried out with cycloalkanone silyl enol ethers but, since the two α positions are equivalent, it is not known whether the same unusual transposition takes place with these substrates as well.

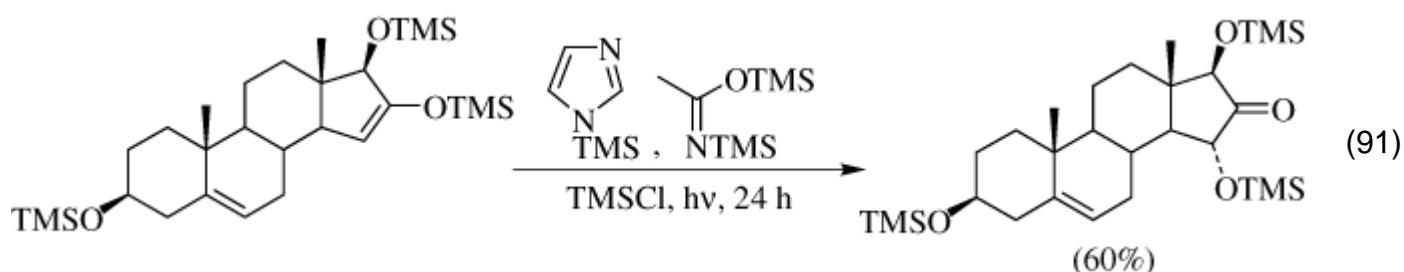
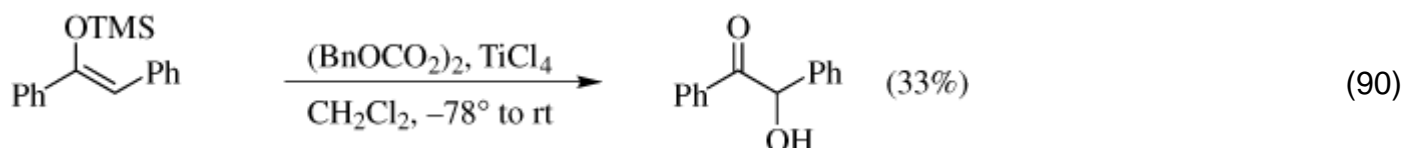
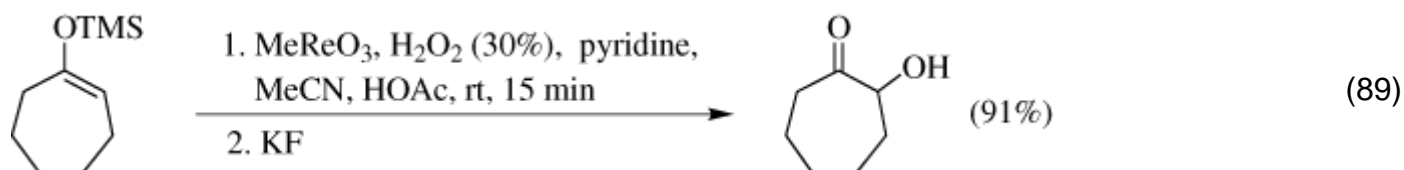
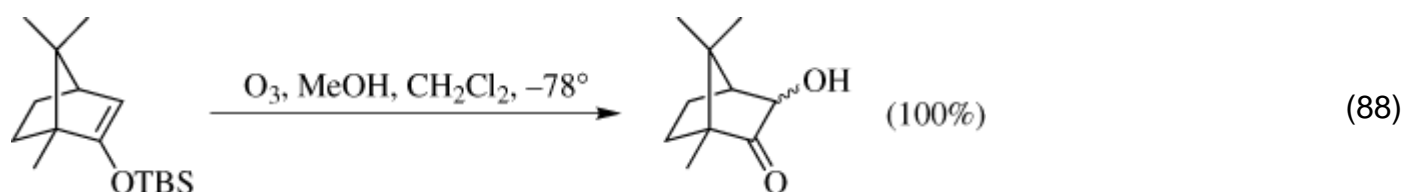
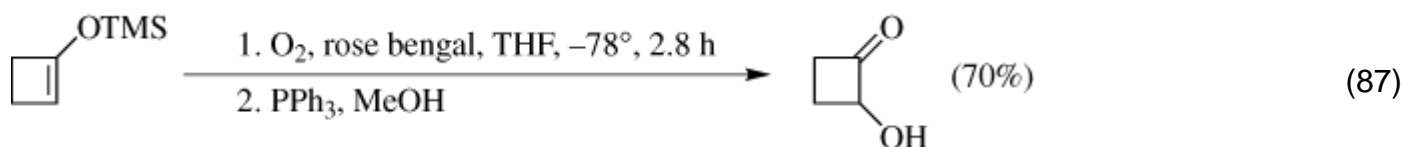
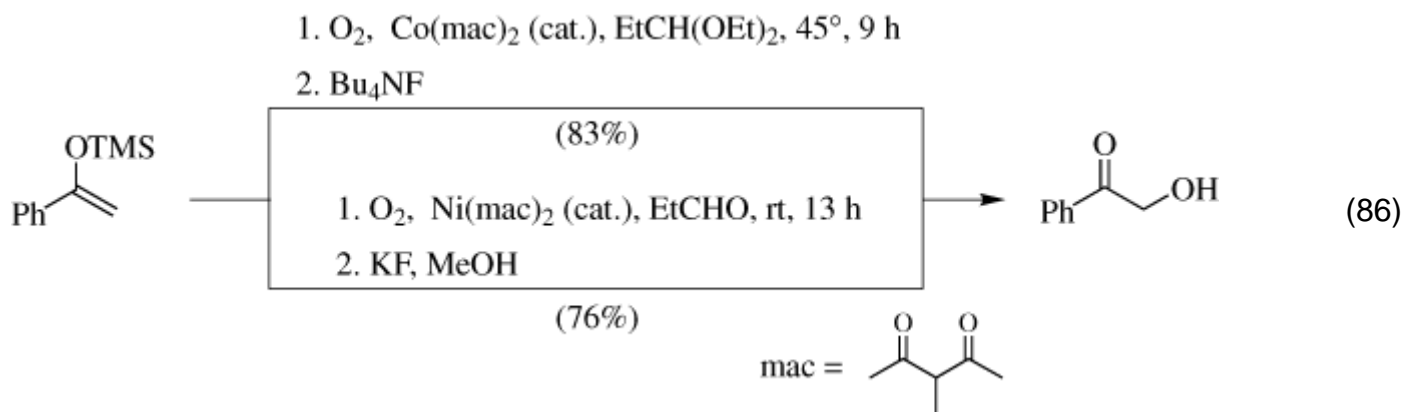




4.2.2. Ketone Silyl Enol Ethers (Acyclic Ketones, Table 16A; Cyclic Ketones, Table 16B)

A few ketone silyl enol ethers react with molecular oxygen in the presence of tris(dimethylaminosulfonium) (trimethylsilyl)difluoride (TAS-F) to give α -ketols (Eq. 85); others are cleaved back to the carbonyl compounds. (68) The application of the Co- or Ni(mac)₂/oxygen system to ketone silyl enol ethers is exemplified in Eq. 86; the added aldehyde or acetal serves to take up one of the two atoms of molecular oxygen. (66, 67) The reaction of ketone silyl enol ethers with singlet oxygen (Eq. 87) sometimes produces mixtures of α -hydroxy- and α -silyloxy products; elimination to give α,β -unsaturated ketones has also been observed. (78) In a few cases, ozone has been used to α -hydroxylate ketone silyl enol ethers (Eq. 88); (85, 123) however, cleavage of the double bond may occur instead. (346) A recently reported promising method employs 30% hydrogen peroxide with catalytic amounts of the commercially available methyltrioxorhenium (Eq. 89); (90) the reaction fails with monosilyl ethers of β -diketones. Reaction of acyl peroxides with silyl enol ethers usually gives α -acyloxy ketones (see section on Related Reactions) but when dibenzyl peroxydicarbonate is used in combination with Lewis acids such as tin or titanium chloride, α -ketols are formed directly in low to moderate yields (Eq. 90). (347) Irradiation of steroidal ketone silyl enol ethers with ultraviolet light produces the corresponding α -silyloxy ketones (Eq. 91); (104) in the presence of benzoyl peroxide, with or without irradiation, small amounts of the α -acetoxy products are also formed. A mechanism involving trimethylsilyloxy radicals has been invoked for these transformations. (104)

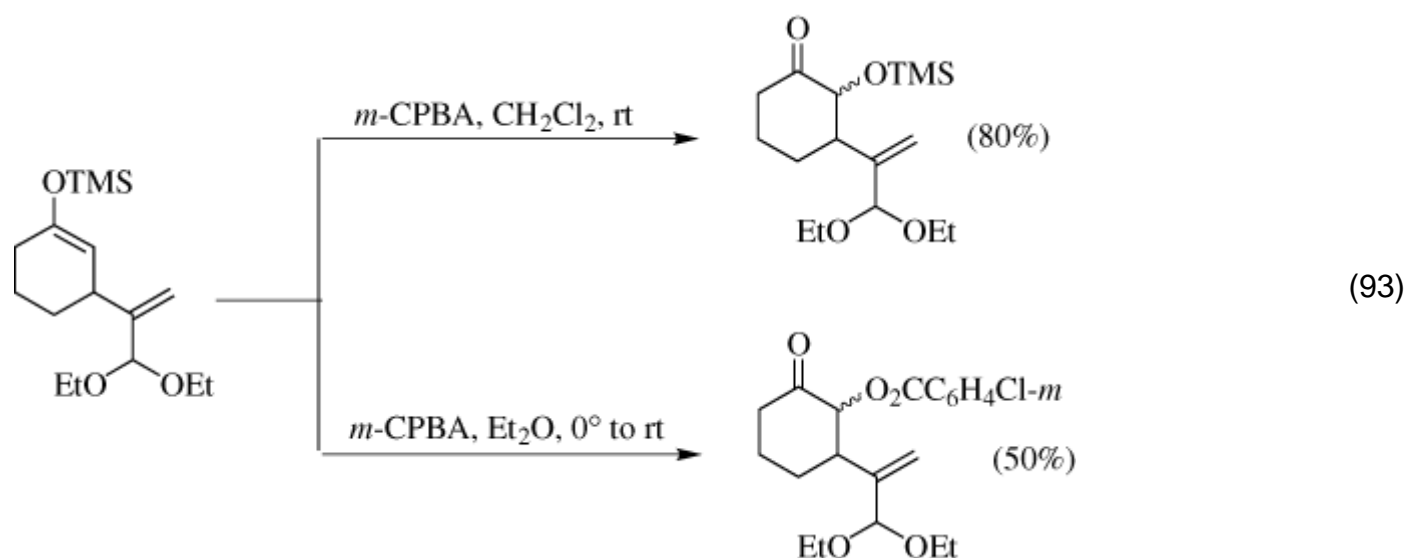
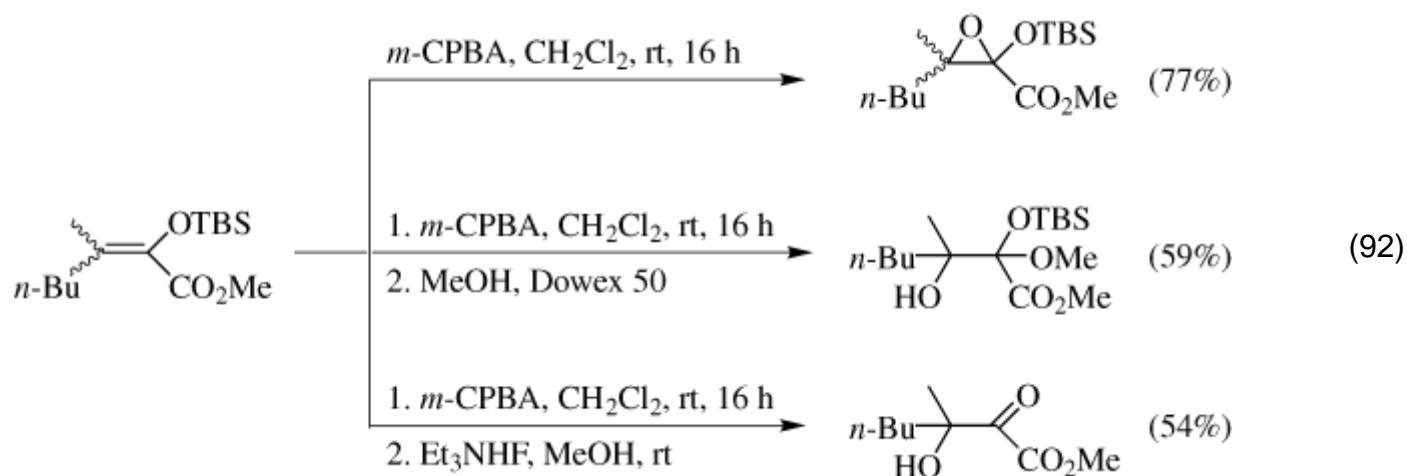




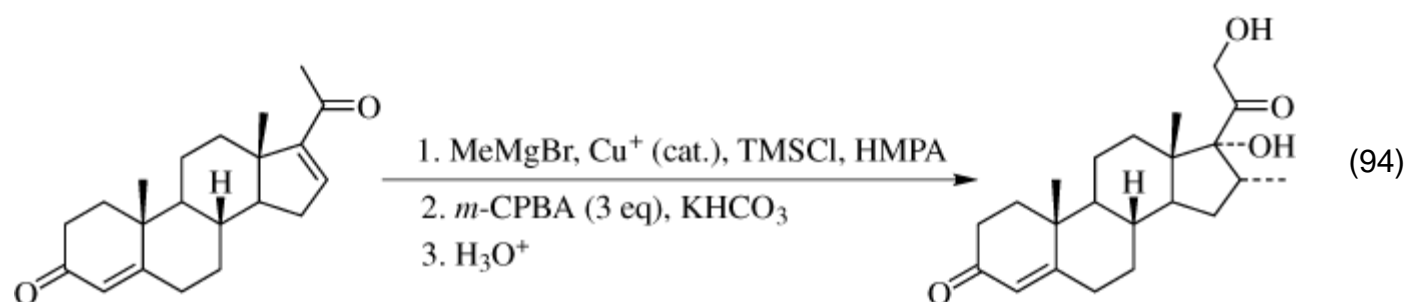
Treatment of ketone silyl enol ethers with the neutral dimethyldioxirane initially gives the epoxides which can be isolated (cf. Eq. 82). They readily rearrange to the α -silyloxy ketones thermally or with acid. The application of sugar-derived dioxiranes to the asymmetric synthesis of α -hydroxy ketones is illustrated in Eq. 32.

The most widely used oxidant for ketone silyl enol ethers is *m*-chloroperoxybenzoic acid. The

intermediate epoxides can be isolated when there is an electron-withdrawing group in the α -position or manipulated further as shown in Eq. 92. (128) As mentioned earlier (Eq. 4), α -silyloxyketones are formed when the reaction is carried out in hydrocarbon solvents or in methylene chloride; treatment with fluoride furnishes the α -ketols. In more polar solvents, such as ether, the α -(*m*-chlorobenzoyloxy) derivative is formed (Eq. 93). (129) An illustration of the

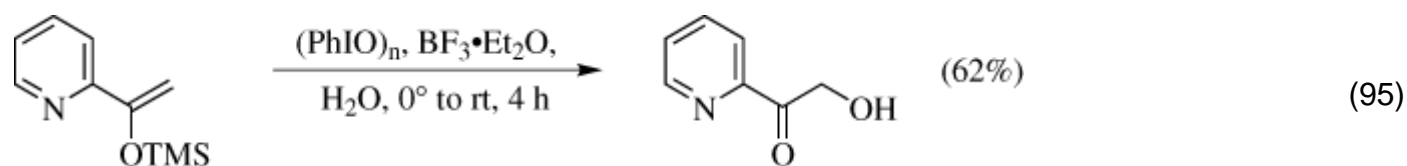


previously mentioned (Eq. 5) dihydroxylation observed with α,α -disubstituted ketone enol silyl ethers is provided in Eq. 94; the substrate in this case is generated by silylation of a cuprate 1,4-addition product. (131) The use of *m*-chloroperoxybenzoic acid in the asymmetric synthesis of α -ketols is shown in Eqs. 28 and 29.

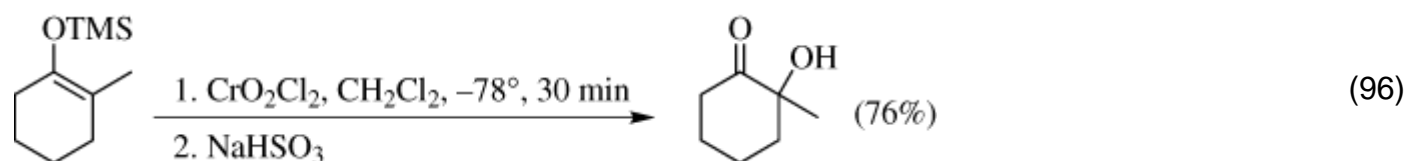


Treatment of ketone silyl enol ethers with iodosobenzene and boron trifluoride etherate in an aqueous system furnishes α -ketols (Eq. 95). (140, 141) In the presence of racemic or non-racemic

(salen) manganese(III) complexes, iodosobenzene reacts with ketone silyl enol ethers to give mixtures of α -hydroxy and α -silyloxy ketones. (145) However, the (salen) manganese(III) complex/sodium hypochlorite system illustrated in Eq. 31 gives only α -hydroxy ketones and the enantiomeric excesses achieved are higher.

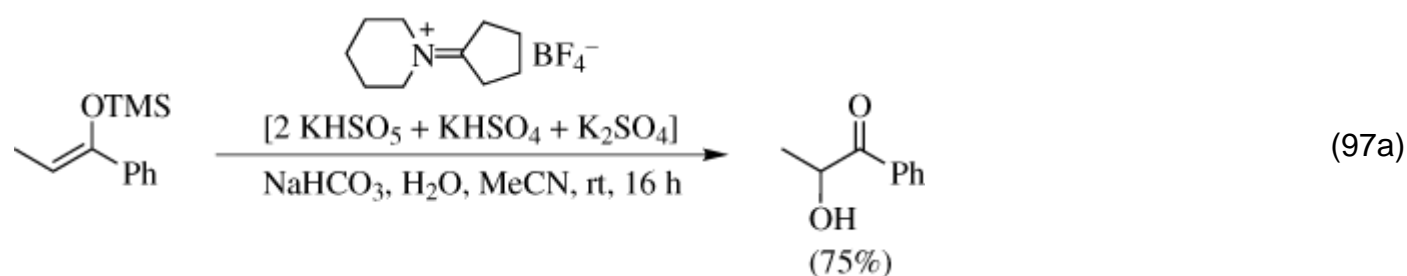
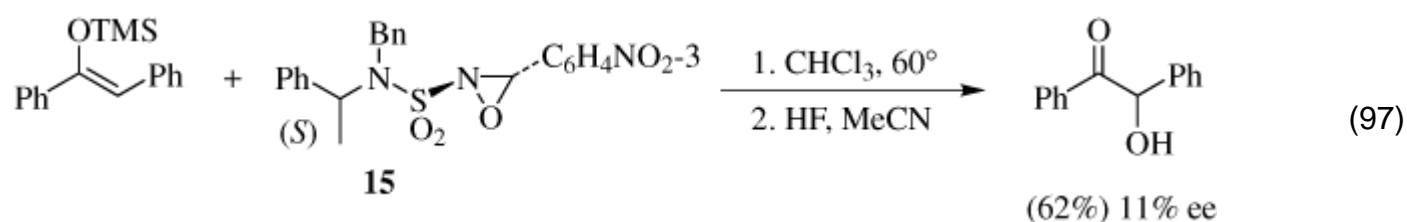


Chromyl chloride is an efficient hydroxylating agent for silyl enol ethers (Eq. 96). (166)



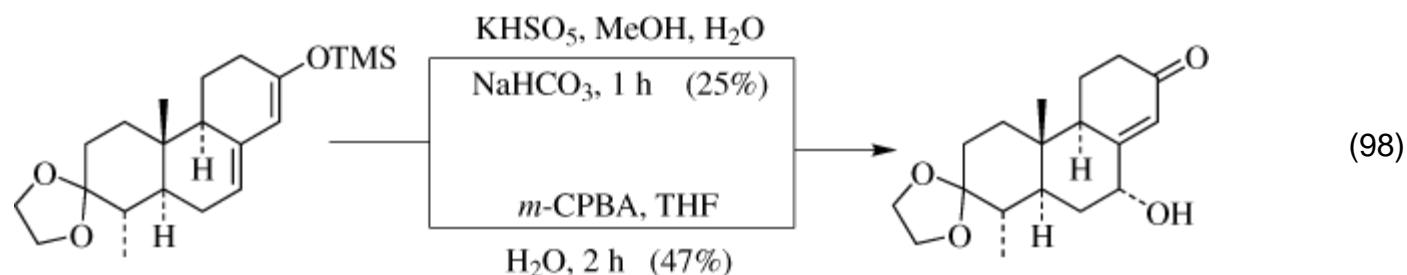
Application of the $K_2OsO_2(OH)_2/Fe_3(CN)_6$ and OsO_4/N -methylmorpholine N -oxide catalytic systems to the hydroxylation of silyl enol ethers is exemplified in Eqs. 30 and 83, respectively.

(Camphoryl)sulfonyloxaziridines are not sufficiently reactive to oxidize silyl enol ethers. The only members of this class that have been reported to be effective are *trans*-2-(phenylsulfonyl)-3-phenyloxaziridine (Eq. 29), 3-(*p*-nitrophenyl)-2-(phenylsulfonyl)oxaziridine, and the non-racemic sulfamyl derivative 15; fairly high reaction temperatures are required and asymmetric induction is low (Eq. 97). (180) On the other hand, α -hydroxylation of a ketone silyl enol ether at room temperature has been accomplished with oxaziridinium salts, generated in situ from ketiminium salts and potassium peroxymonosulfate (Eq. 97a). (180a) The strategy of using methyl lithium to convert silyl enol ethers into lithium enolates (26, 347) which can then be oxidized with (camphoryl)sulfonyloxaziridines is illustrated in Eq. 13. The silyl enol ethers of α -tetralone and acetophenone give the corresponding α -hydroxy ketones in high yields by treatment with the HOF/MeCN complex at room temperature. (187)

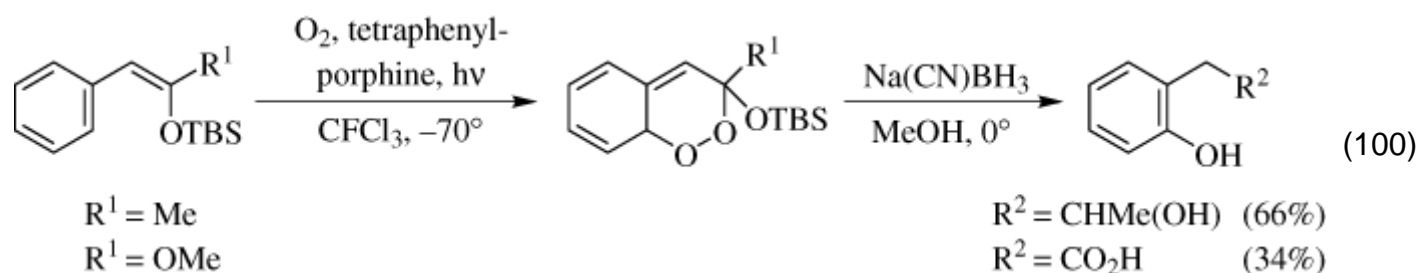
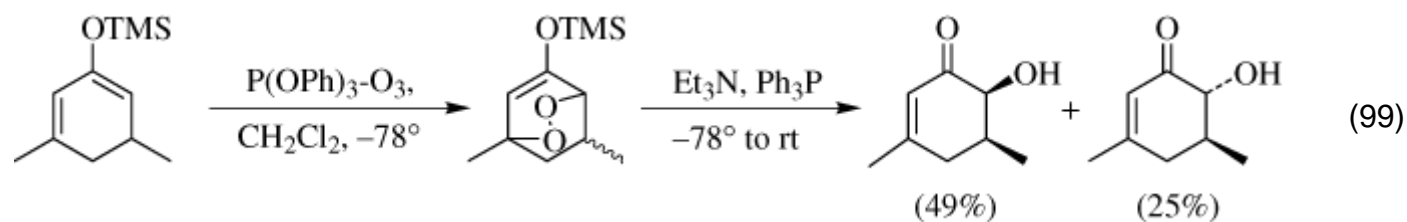


4.2.3. 1-silyloxy-1,3-dienes (Table 17A) and 2-silyloxy-1,3-dienes (Table 17B)

Only a few examples of the hydroxylation of 1-silyloxy-1,3-dienes were found in the literature. Hydroxylation occurs at the 2-position. An exception is shown in Eq. 98 where both *m*-chloroperoxybenzoic acid and potassium peroxymonosulfate produce the *g*-hydroxy enone; (95) this also appears to be the only instance where the latter oxidant has been used to hydroxylate enolates or silyl enol ethers.



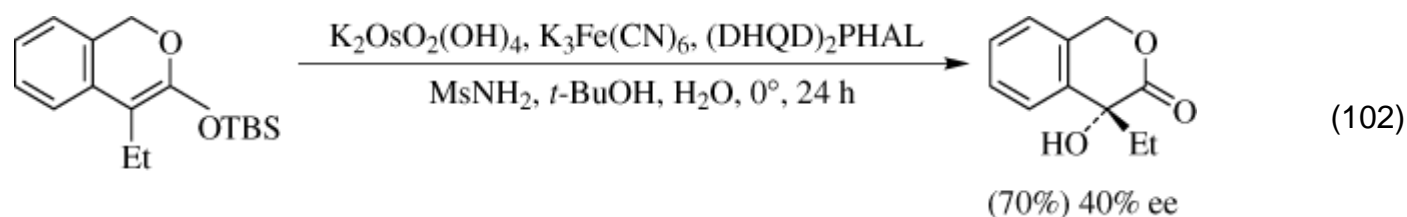
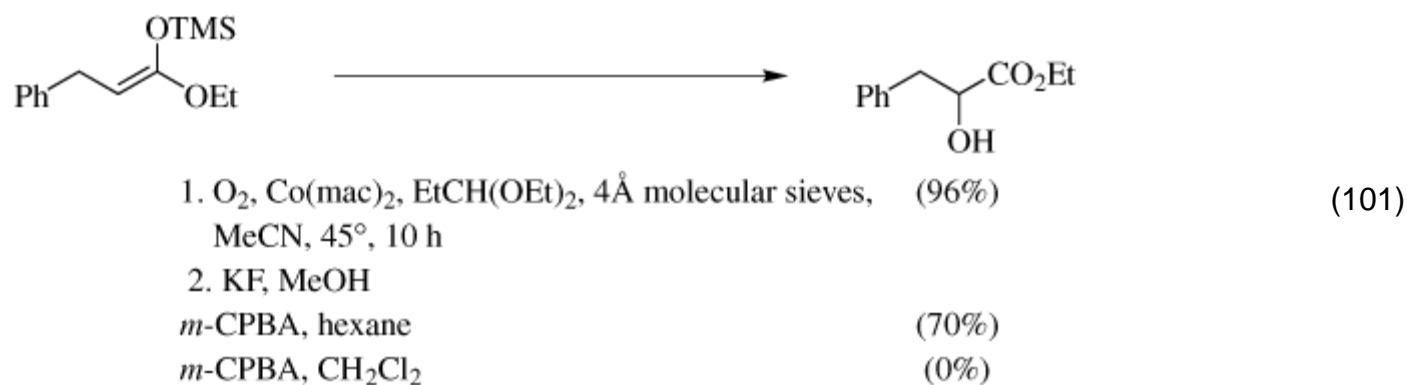
Hydroxylation of 2-silyloxy-1,3-dienes occurs in the 1-position. *m*-Chloroperoxybenzoic acid, peroxybenzoic acid, (134, 135) and the O₂/Co(mac)₂ (cf. Eq. 86) (65, 66) and OsO₄/NMO (Eq. 83) (348) systems appear to be the most efficient oxidants. Others include *trans*-2-(phenylsulfonyl)-3-phenyloxaziridine (238) and *tert*-butyl hydroperoxide with cuprous chloride. (93) The adduct of triphenylphosphite with ozone, which is a source of singlet oxygen, also furnishes 1-hydroxylated products after reduction of the intermediate Diels-Alder adducts (Eq. 99). (82) Initial [4 + 2] cycloaddition is also observed with *b*-silyloxystyrenes (Eq. 100). (83)



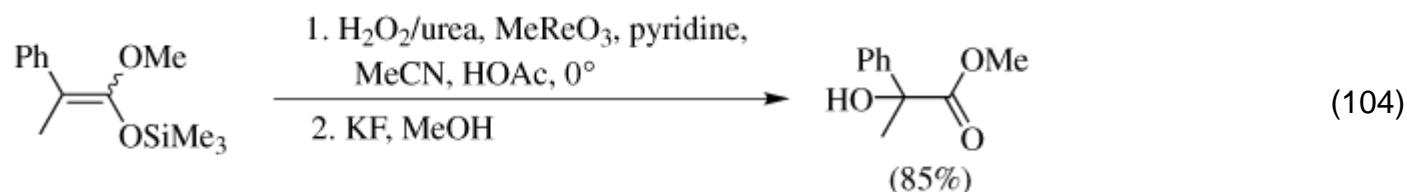
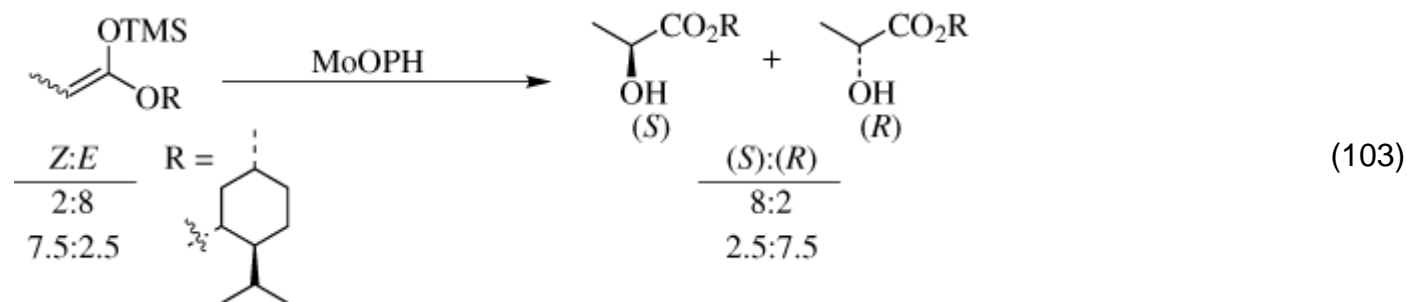
4.2.4. Alkyl Trialkylsilyl Ketene Acetals and Related Systems (Table 18)

Hydroxylation of alkyl trialkylsilyl ketene acetals followed by desilylation gives α -hydroxy esters or lactones. *m*-Chloroperoxybenzoic acid in hexane and the O₂/Ni- or Co/(mac)₂ systems appear to be the most efficient oxidants (Eq. 101). (66) The reaction failed when methylene chloride was used with the former reagent. (66) In another case, higher yields with the O₂/Ni(mac)₂ system were obtained when an excess of *N*-methyl-*N*-trimethylsilyltrifluoroacetamide was added to suppress decomposition of the sensitive trialkylsilyl ketene acetal. (67) Double bond cleavage to give ketones is sometimes observed in hydroxylations with *m*-chloroperoxybenzoic acid (40, 124) and, more frequently, with ozone. (349) Other oxidants that have been used are singlet oxygen, (75) DMDO, (350) iodosobenzene, (351, 352) 3-(*p*-nitrophenyl)-2-(phenylsulfonyl) oxaziridine, (180) the catalytic OsO₄/K₃Fe(CN)₆ system (Eq. 102), (353) and the MoOPH reagent (Eq. 103). The

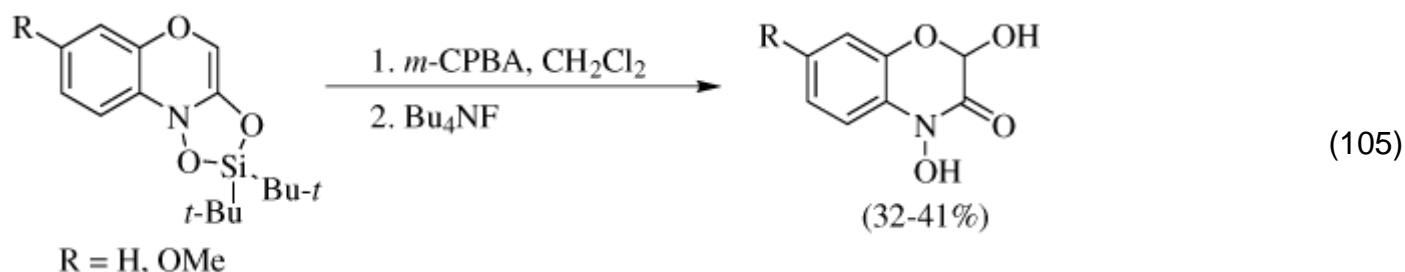
diastereoselectivity is excellent in the latter case but unfortunately yields and experimental details were not reported. (344) The



methyltrioxorhenium-catalyzed oxidation of silyl enol ethers with hydrogen peroxide (Eq. 89) has been extended to methyl trimethylsilyl ketene acetals except that the hydrogen peroxide/urea complex was used as an anhydrous source of the oxidant (Eq. 104). (92) The procedure works well with dialkyl-, monoaryl-, and diarylsubstituted alkyl trialkylsilyl ketene acetals; monoalkylsubstituted derivatives are hydrolyzed to a significant extent and give only modest yields. Since both the catalyst and the urea complex are available commercially and the reaction is simple to carry out this may prove to be a preferred method for the synthesis of α -hydroxy esters from alkyl trialkylsilyl ketene acetals.

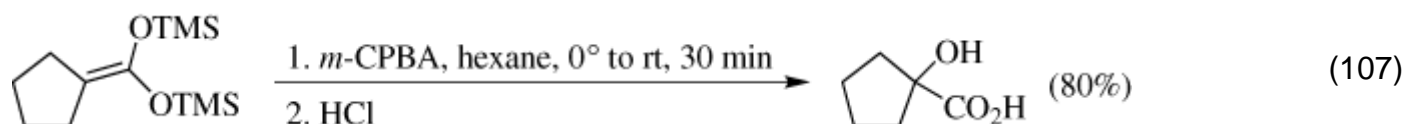
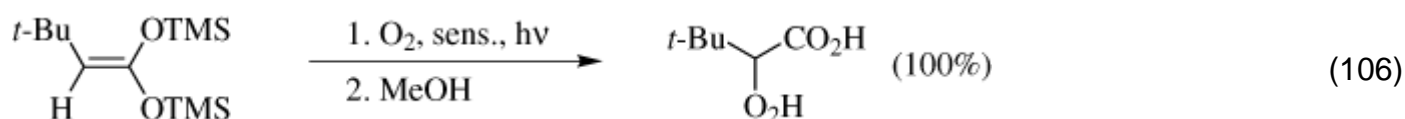


A few examples of the α -hydroxylation of silyl ketene acetals derived from lactams are also known (Eq. 105). (354)



4.2.5. Bis(trialkylsilyl) Ketene Acetals (Table 19)

These compounds are prepared by silylation of carboxylic acid dianions. Reaction with singlet oxygen followed by desilylation gives α -hydroperoxy acids in some cases. (73, 77) (Eq. 106). (77) However, the reaction is not general because of competition with the ene reaction (Eq. 3) when the β -substituents are non-tertiary and Diels-Alder reaction when the β -substituent is a phenyl group. (355) Hydroxylation with *m*-chloroperoxybenzoic acid as the oxidant appears to be general; the products are α -hydroxy acids (Eq. 107). (125)



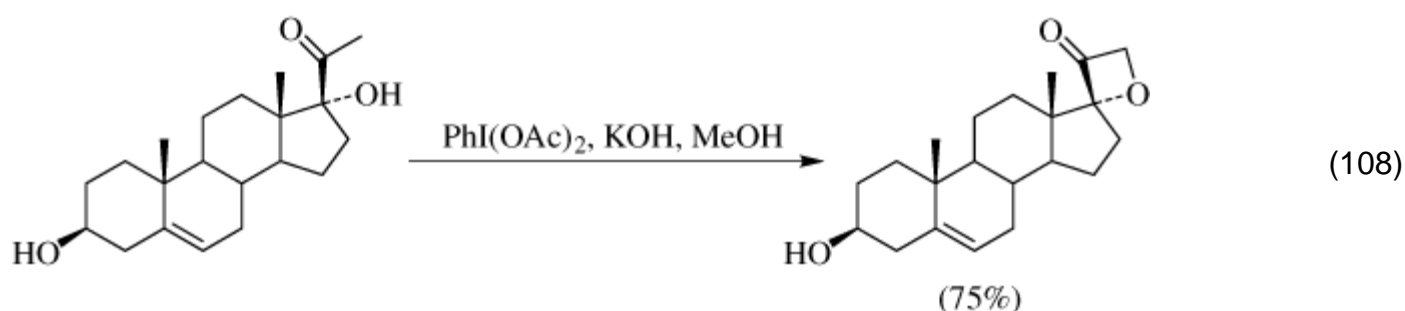
4.3. Related Reactions

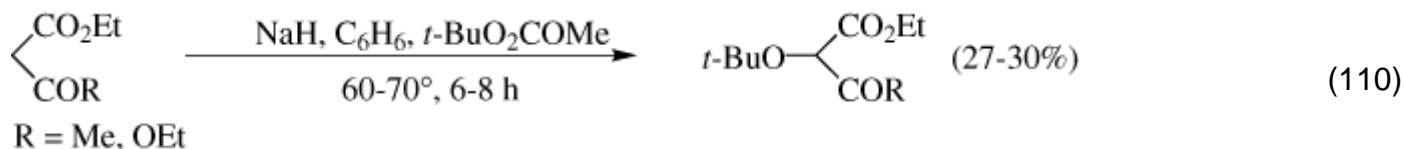
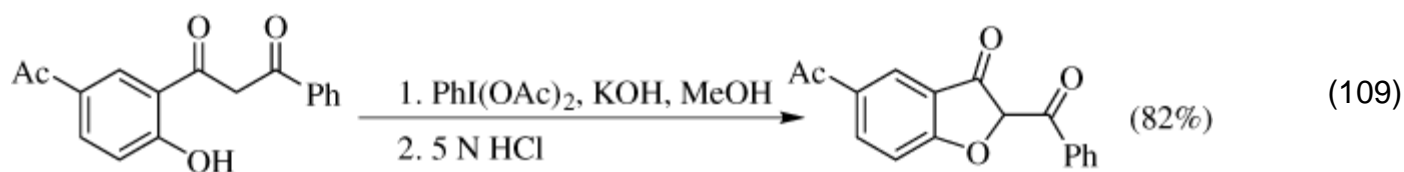
There are no separate tables for α -alkoxylation, α -acyloxylation, and α -sulfonyloxylation; they are included in Tables 1–19.

4.3.1. α -Alkoxylation

4.3.1.1. Enolates

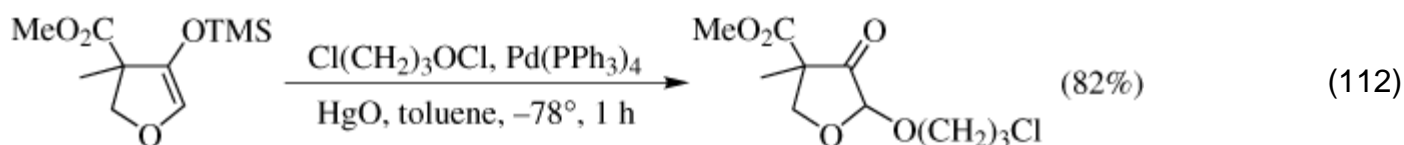
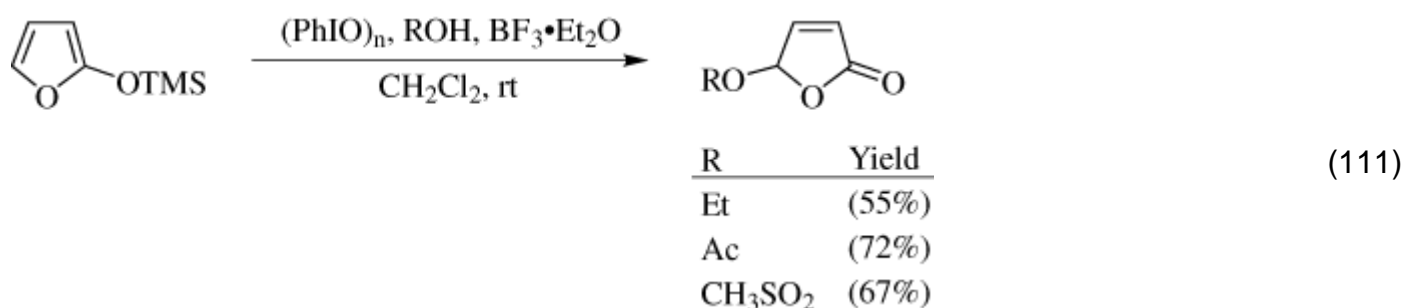
Reaction of hypervalent iodine reagents with enolates in alcoholic solutions normally gives α -hydroxy ketones but in some instances α -alkoxylation (219, 223) and α,α -dialkoxylation (356) have been observed. Similarly, γ -alkoxylation of α,β -unsaturated ketones occurs in some instances. (218, 357) As mentioned in connection with Eq. 50, α -alkoxy esters are obtained when the reaction of aryl acetates with hypervalent iodine reagents is carried out in alcoholic solvents. (138) Intramolecular alkoxylation can take place when a hydroxy group is present at a stereoelectronically favorable position (Eq. 108). (358) β -Dicarbonyl compounds usually form stable ylides with hypervalent iodine reagents but intramolecular aryloxylation have been observed (Eq. 109). (326) *tert*-Butyl peracetate reacts with enolates of β -dicarbonyl compounds to give the α -*tert*-butoxy derivatives (Eq. 110); (98, 99) the reaction does not appear to have been extended to other peracetates.





4.3.1.2. Silyl Enol Ethers

Iodosobenzene reacts with silyl enol ethers in alcoholic solvents in the presence of boron trifluoride etherate to give α -alkoxy ketones. (141, 142, 351) α -Alkoxylation (as well as α -acyloxylation and α -sulfonyloxylation) is observed with furyl silyl ethers (Eq. 111). (162) Methyl hypofluorite alkoxyates silyl enol ethers (186) but elemental fluorine is required to prepare the reagent. A more convenient method involves palladium-catalyzed addition of alkyl hypochlorites. In the example shown in Eq. 112, a single diastereomer of unknown configuration is formed; alkyl hypochlorites are prepared from the alcohols and sodium hypochlorite. (185) This approach has also been applied to 2-silyloxy-1,3-dienes. (185) The reaction of DDQ with silyl enol ethers derived from cyclic ketones gives α -(2,3-dichloro-5,6-dicyano-4-trimethylsilyloxy)phenoxy ketones (184) which do not appear to be of any value in synthesis.



4.3.1.3. Alkyl Trialkylsilyl Ketene Acetals

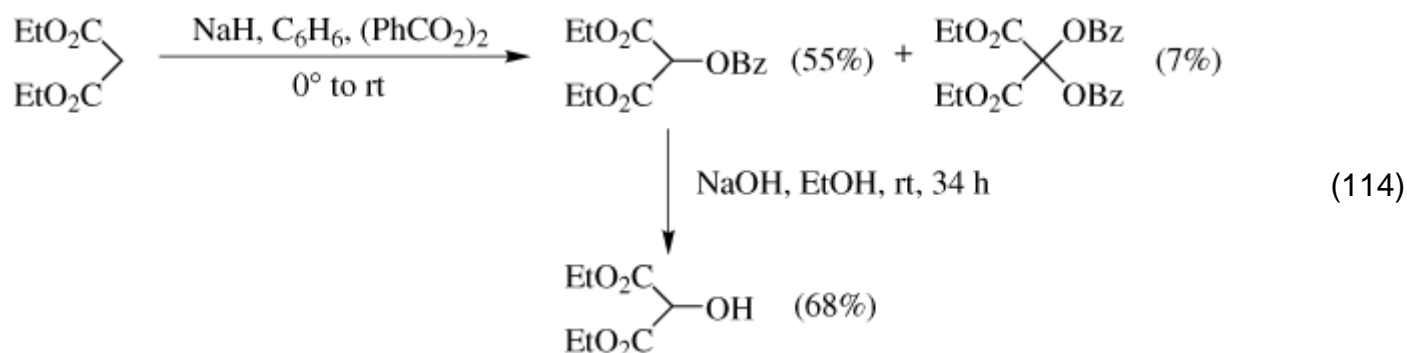
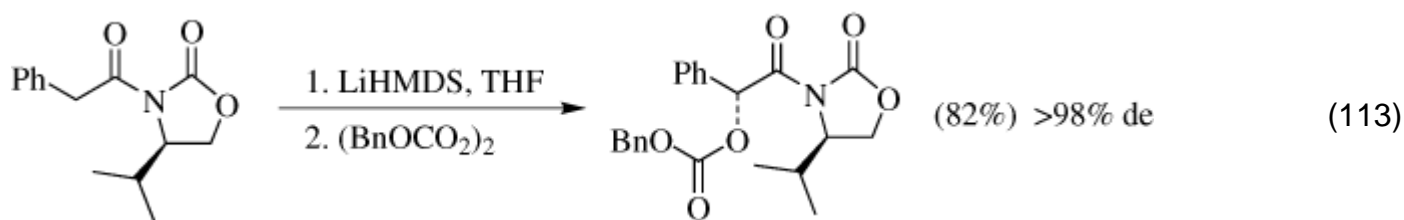
Reaction of alkyl trialkylsilyl ketene acetals with iodosobenzene in methanol gives α -methoxy esters in good yield. (352).

4.3.2. α -Acyloxylation (359-362)

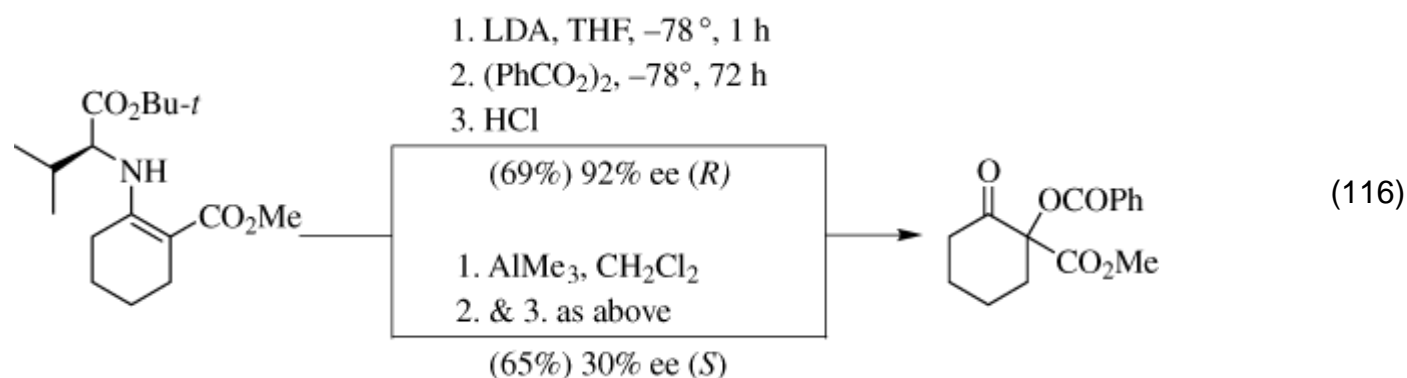
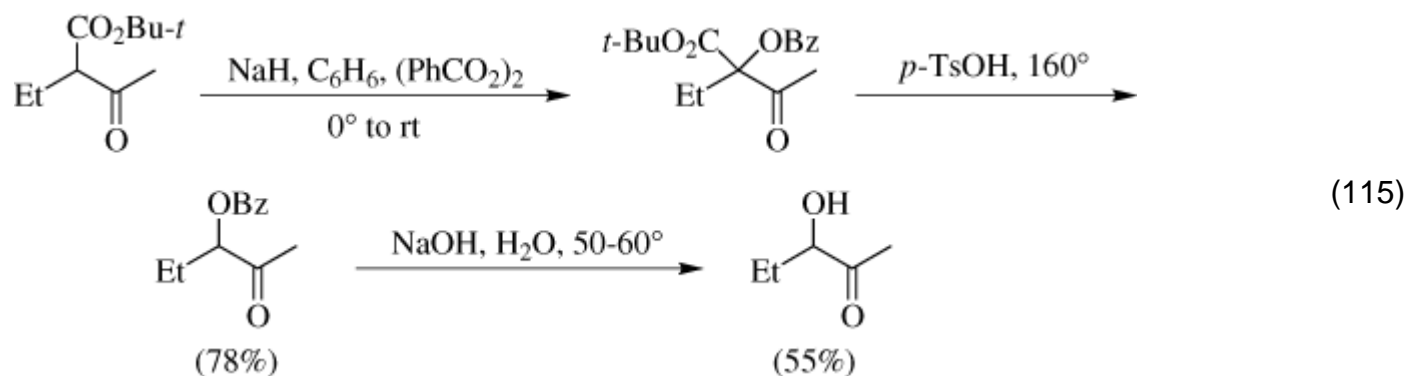
4.3.2.1. Enolates and Aza-enolates

Enolates of imides (Eq. 113) (347) and β -keto esters (347) react with dibenzyl peroxydicarbonate to give (benzyloxy)carbonyloxy derivatives that are readily hydrogenolyzed to give the corresponding α -hydroxy compounds. Ketone enolates give better yields when *n*-BuLi or KHMDS rather than LiHMDS is used as the base. (347) Benzoyl peroxide and some of its analogs have been used to

α -acyloxy ketone, (96) lactone, (38) β -diketone, (97) β -keto ester, (98) cyanoacetate, (363) and malonic ester (99-102) enolates. Diacyloxylation occurs to some extent (Eq. 114) (97) or exclusively (97, 327) when the α -position is unsubstituted. A method for avoiding this undesired side reaction takes advantage of

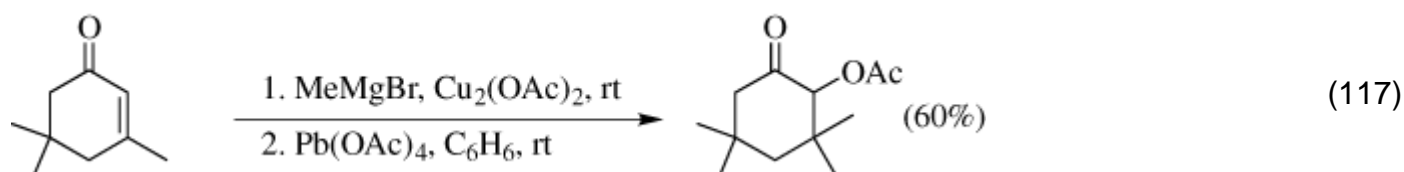


the ready decarboxylation of *tert*-butyl esters (Eq. 115). (100) α -acyloxy ketones (27) and β -keto esters (Eq. 116) (45, 103) are formed in the reaction of enamine anions with dibenzyl peroxydicarbonate and benzoyl peroxide, respectively. Ketones react with lead tetraacetate to give the α -acetoxy derivatives; (17) the reaction proceeds at much lower temperatures when the enolate is used (Eq. 117). (364)



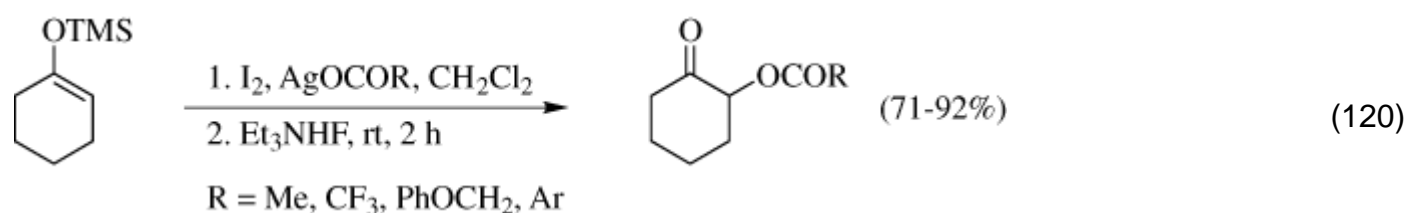
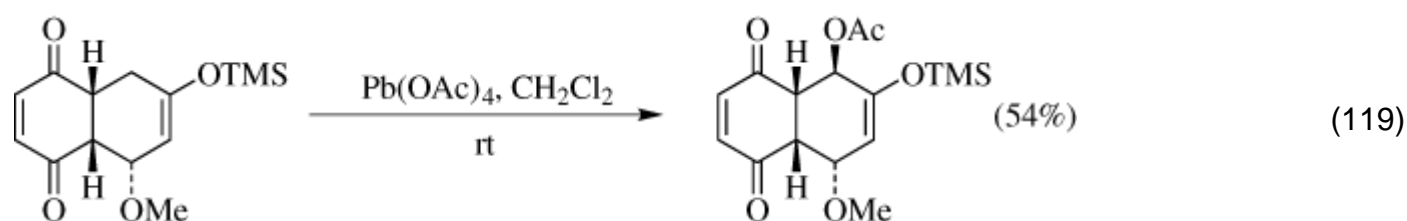
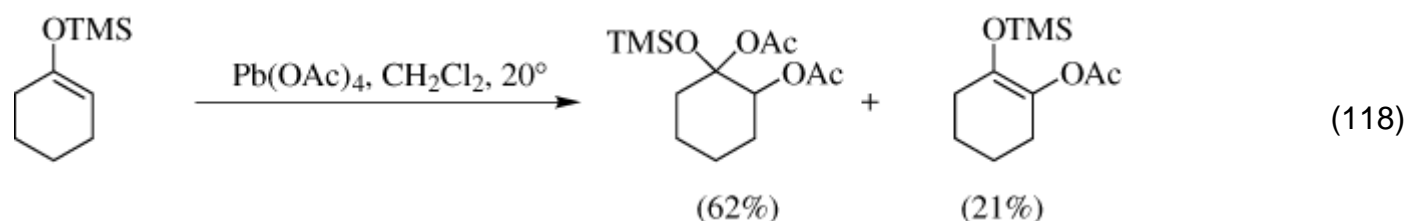
1. AlMe₃, CH₂Cl₂
2. & 3. as above

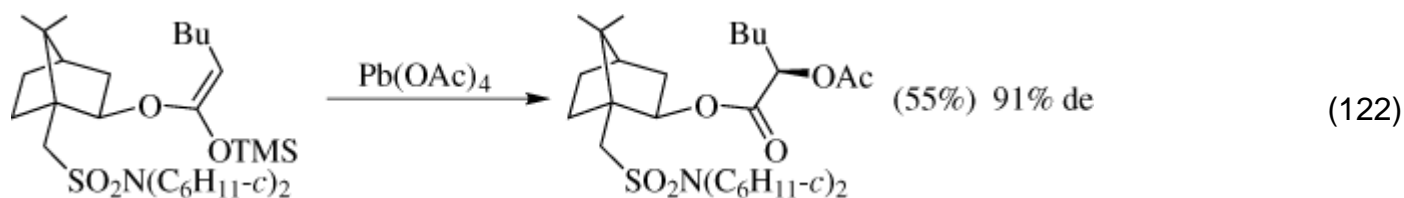
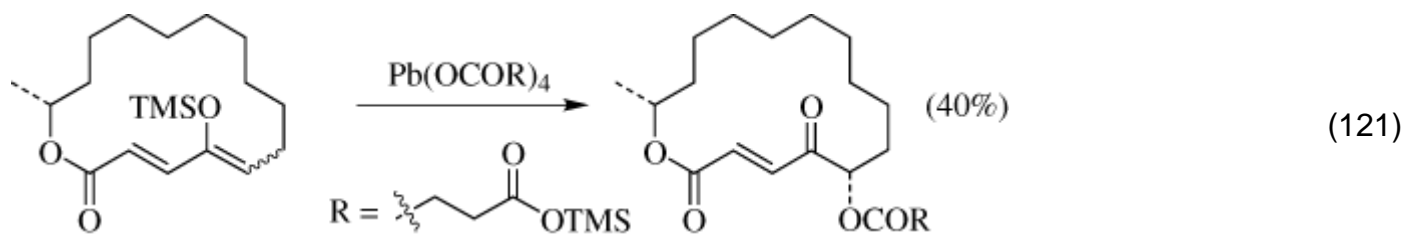
(65%) 30% ee (*S*)



4.3.2.2. Silyl Enol Ethers, Silyloxy-1,3-dienes, and Alkyl Trialkylsilyl Ketene Acetals

Silyl enol ethers (365, 366) and 2-silyloxy-1,3-dienes (365) react with phenyl iodonium diacetate in methylene chloride to give α - and 1-acetoxy ketones, respectively. Use of aryl peroxides in the acyloxylation of silyl enol ethers is rare and fairly long reaction times are required. (104) Lead tetraacetate reacts with aldehyde (367, 368) and ketone enol silyl ethers to give α -acetoxy aldehydes and ketones, respectively. The intermediate 1,2-diacetates can be isolated (Eq. 118). (366) Lead tetrabenzoate reacts in the same way. (161) α -Acetoxylation has been observed in a number of instances (Eq. 119). (369) A mechanism has been suggested but the reason for the dichotomy of reaction paths is not clear. α -Acyloxy ketones are also formed on treatment of silyl enol ethers with iodine and two equivalents of the silver salt of a carboxylic acid (Eq. 120). (189) With one equivalent α -iodo ketones are obtained instead. The transformation apparently has been carried out only with silyl enol ethers of cyclic ketones. Treatment of 1-silyloxy-1,3-dienes with lead tetrabenzoate gives α -benzoyloxy- β,γ -unsaturated ketones. (370) Reaction of 2-silyloxy-1,3-dienes with lead(IV) salts of carboxylic acids gives either 2,3-(diacyloxy) ketones (370) or the product of attack in the 1-position; (370) an example of the latter employing a rather complex lead salt to generate a desired side chain is shown in Eq. 121. (163) Alkyl trialkylsilyl ketene acetals react normally with lead(IV) salts of carboxylic acids to give α -acyloxy esters or lactones (371-373) (Eq. 122). (372)

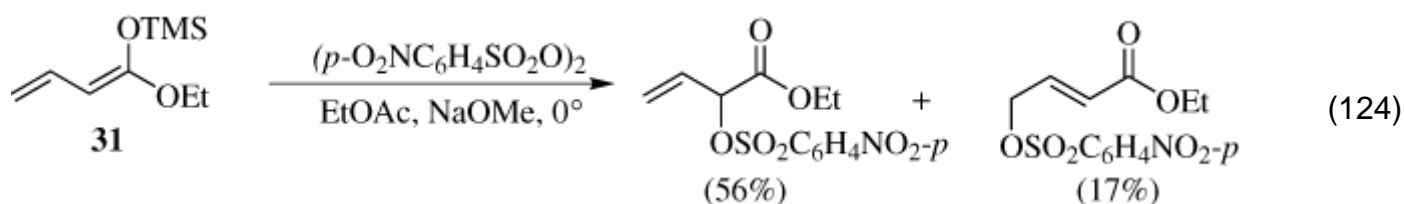
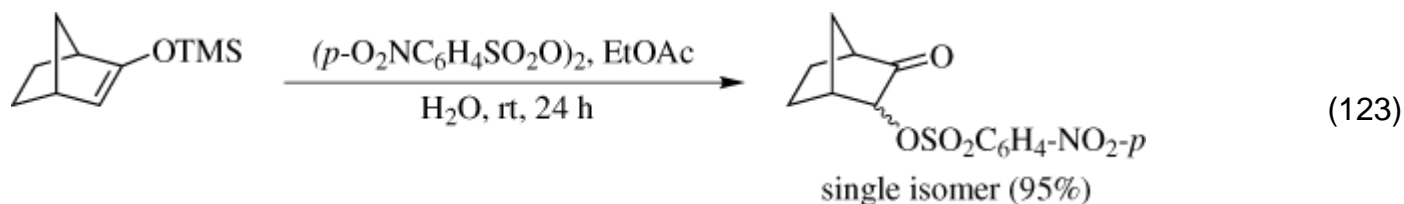




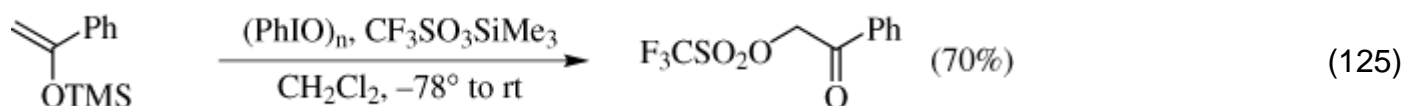
α -Acetoxy ketones are excellent substrates for kinetic resolution. (374-377)

4.3.3. α -Sulfonyloxylation

p-Nitrophenylsulfonyl peroxide is a versatile electrophilic oxidizing reagent which reacts with a variety of electron-rich double bonds including silyl enol ethers (105, 107) (Eq. 123) (105) and alkyl trialkylsilyl ketene acetals (107, 108) to give α -(*p*-nitrophenyl)sulfonyloxy ketones and esters, respectively. The diene **31** gives a mixture of α - and γ -sulfonyloxy products (Eq. 124). (108) Hypervalent iodine reagents have also been used to prepare α -sulfonyloxy ketones and esters. These include hydroxy(tosyloxy)iodobenzene, (378, 379) hydroxy (mesyloxy)iodobenzene, (379)



and a mixture of iodosobenzene and trimethylsilyl trifluoromethanesulfonate (Eq. 125). (378) Alkyl trialkylsilyl ketene acetals similarly give α -sulfonyloxy esters and lactones. (378)

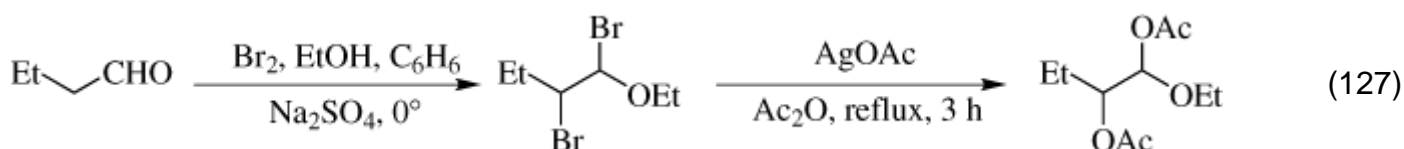
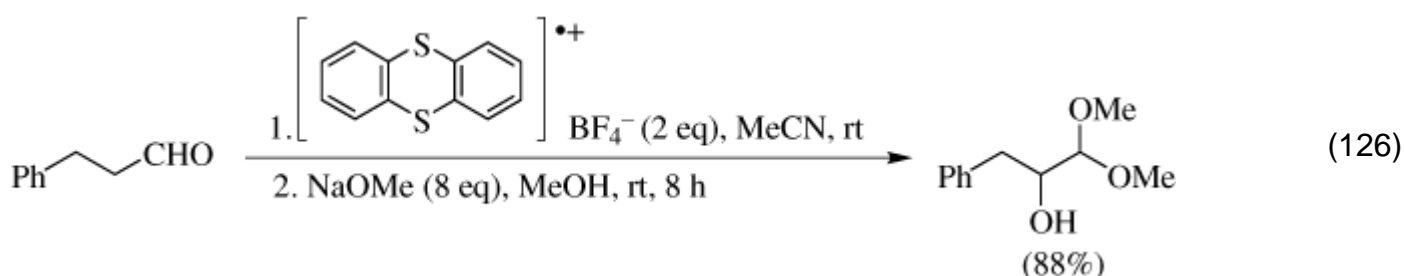


5. Comparison with Other Methods

5.1. Hydroxylation of Carbonyl Compounds and Their Derivatives

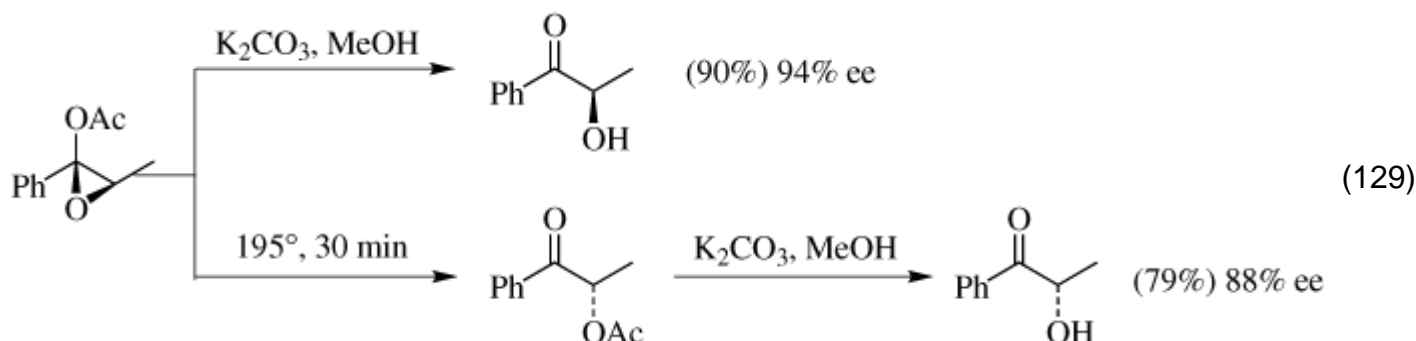
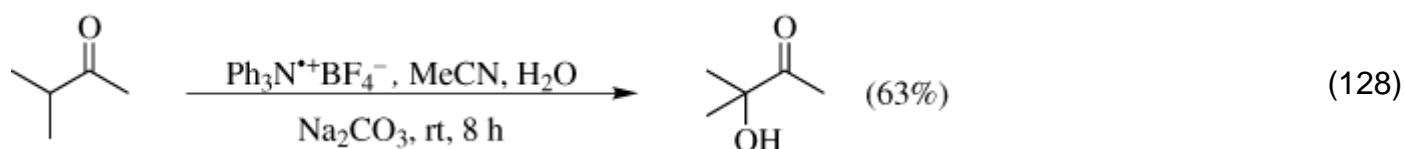
The methods for the α -hydroxylation of enolates discussed in this chapter were developed because the older ones lacked selectivity, gave moderate yields, required harsher conditions, and/or employed highly toxic reagents. Many of these methods involved the two steps of acyloxylation of carbonyl compounds with metal salts (316) followed by hydrolysis. Acetoxylation of aldehydes, (17) ketones, (17) and carboxylic acid derivatives (380) with lead tetraacetate usually requires high temperatures (refluxing acetic acid) and yields are moderate. β -Dicarbonyl compounds (381) react at lower temperatures. Acetoxylation with mercuric acetate offers no advantage and can lead to the formation of organomercurials as side products. (382) Other metal salts that have been used include manganese triacetate (375, 377, 383) and thallium triacetate, which is particularly suitable for the α -acyloxylation of carboxylic acids. (384, 385) Reaction of cyclohexanone with thallium triacetate gives α -hydroxycyclohexanone directly. (386) Treatment of enolizable ketones with thallium(III) toluenesulfonate (387) or thallium(III) *p*-nitrobenzenesulfonate (388) gives α -tosyloxy ketones and *p*-nitrobenzenesulfonyloxy ketones, respectively, in excellent yields. The acetoxylation of carbonyl compounds with peroxides has been reviewed. (360) α -Acetoxyketones are formed by rearrangement of *O*-acetyl oximes followed by hydrolysis. (389)

α -Hydroxyaldehyde dimethyl acetals are obtained in moderate to excellent overall yield by reaction of aldehydes with thianthrenium fluoroborate followed by basic hydrolysis (Eq. 126). (390) A simple method for the preparation of masked α -hydroxyaldehydes is shown in Eq. 127. (391) An α -hydroxy aldehyde was obtained by oxidation of the aldehyde enol ether with stoichiometric amounts of osmium tetroxide. (392) α -Hydroxy aldehyde acetals are formed by oxidation of aldehyde enol ethers in alcohols with *m*-CPBA (393, 394) or with hydrogen peroxide in the presence of a peroxotungstophosphate. (91)



α -Hydroxy ketones are obtained by oxidation of ketones with triarylaminium radical cations; hydroxylation occurs on the more substituted α carbon (Eq. 128). (395, 396) A range of ketones is α -hydroxylated in moderate to good yields but with poor regioselectivity by bis(trifluoroacetoxy)iodobenzene in refluxing trifluoroacetic acid. (397) Ketone enol ethers furnish α -hydroxy ketones or ketals on oxidation with *m*-CPBA, (251, 393, 394, 398, 399) methyltrifluoromethyldioxirane, (400) singlet oxygen (to give α -hydroperoxy ketones), (401) *tert*-amyl hydroperoxide in the presence of molybdenum or vanadium catalysts, (402) and iodosobenzene in the presence of (salen) manganese complexes. (403) Similarly, ketone enol esters have been acetoxylation with lead tetraacetate (404) and hydroxylated with peracids, (405) sodium hypochlorite in the presence of (salen) manganese complexes, (146, 403, 406) *tert*-amyl hydroperoxide in the presence of molybdenum or vanadium catalysts, (402) and with a sugar-derived dioxirane (cf. Eq. 32). (117) The intermediate epoxide generated in the latter reaction can be manipulated to provide

either of the two enantiomers (Eq. 129). (117) The rearrangement



of ketone enol ester epoxides has been studied. (407, 408) Ketone enol phosphates have been α -hydroxylated with dimethyldioxirane (409) and the OsO₄/*N*-methylmorpholine *N*-oxide system. (410) α -Silyloxyketones are obtained by hydroboration of ketone silyl enol ethers followed by oxidation. (411)

Carboxylic acids with an α -methine group are hydroxylated in moderate yields by potassium permanganate in strongly alkaline medium. (383)

α -Hydroxylation of β -dicarbonyl compounds has been accomplished with oxygen in the presence of manganese(II) acetate (412) or cobalt(II) chloride, (413) air in the presence of zinc acetate, (414) singlet oxygen, (415) peracetic acid, (416) and dimethyldioxirane in the presence of nickel catalysts, (417) and by reaction of enol ethers of β -dicarbonyl compounds with DMDO. (418)

Acetoxylation of α,β -unsaturated carbonyl compounds in the α' position with lead tetraacetate (419) and manganese(III) acetate (420, 421) has been reported.

The biocatalytic α -hydroxylation of carbonyl compounds has been reviewed. (422)

5.2. Other Methods

The following is an incomplete summary of other methods for the preparation of α -hydroxy carbonyl compounds that the authors came across during the preparation of this chapter. The papers cited frequently contain lists of references to other pertinent literature.

α -Hydroxy aldehydes or their derivatives have been prepared by the reaction of tosylmethyl isocyanide with ketones (423) and of aldehydes with carbon monoxide and dimethyl(ethyl)silane, (424) by reductive cross-coupling of aldehydes or ketones with 1,3-dioxolane, (425) by reaction of aldehydes or ketones with dithiane anion, (426) dichloromethyl lithium, (427) lithium methylthioformamide, (428) or *p*-tolyl *p*-tolylthiomethyl sulfoxide, (429) via α -hydroxydithioketals, (430, 431) by reaction of methylthiomethyl sulfoxide anion with esters, (432, 433) by reaction of α -diketone amins with Grignard reagents, (434) and by Pummerer rearrangement of protected β -hydroxy sulfoxides. (435)

α -Hydroxy ketones or their derivatives have been prepared by asymmetric reduction of α -diketones, (436-440) by oxidation of 1,2-diols with dioxiranes, (441-443) by oxidation of oxiranes with dimethyl sulfoxide, (444-447) by Wittig rearrangement of ketone α -allyloxyhydrazones, (448) by rearrangement of *O*-acetyloximes, (389) by Cu(acac)₂-catalyzed insertion of α -diazo ketones into carboxylic acids, (449, 450) by peroxotungstophosphate-catalyzed oxidation of allenes with

hydrogen peroxide, (451) by reaction of α -halo ketones with base, (410, 452, 453) and by reaction of aldehydes or ketones with substituted dithiane anions. (426) α -Acyloxy aldehydes and α -acyloxy cyclic ketones are obtained by reaction of the corresponding nitrones with acid chlorides followed by spontaneous [3.3]-sigmatropic rearrangement of the *N*-vinyl-*O*-acylhydroxylamines formed as intermediates. (454, 455)

α -Hydroxy esters have been obtained by asymmetric reduction of α -keto esters, (456-463) by carbonyl ene reaction of glyoxylates, (464) by reaction of the nitromethane anion with glyoxylates, (465) by rhodium(II)-catalyzed decomposition of phenyldiazoacetates in the presence of water or alcohols, (466) by air oxidation of certain α,β -unsaturated esters in the presence of activated carbon, (467) and by hydrogenation of enol esters of α -diketones. (468)

α -Hydroxy amides have been prepared by asymmetric reduction of α -keto amides, (460) by hydrolysis of cyanhydrin TMS ethers, (469) by base hydrolysis of cyanohydrins, (470) by rearrangement of *O*-acyl hydroxamic acid derivatives, (471) by reaction of *N,N*-dialkylcarbamoyllithium with aldehydes, (472) and by reaction of *N*-methyl-*C*-(trichlorotitanio)formidoyl chloride with aldehydes or ketones. (473)

$\alpha^{\check{}}$ -Hydroxy- α,β -unsaturated ketones are formed in the addition of metallated β,γ -unsaturated α -aminonitriles to aldehydes. (474)

6. Experimental Conditions

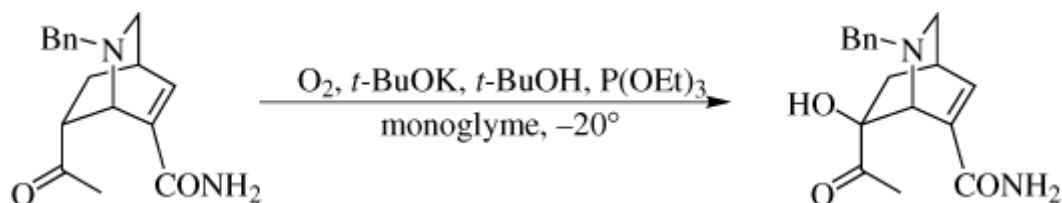
The following reagents are available commercially (only selected suppliers are mentioned for some of the compounds): Bis(trimethylsilyl) peroxide: Fluorochemicals for Research and Development (catalog name) and Gelest, Inc. Preparations are described in refs. [94](#) and [475-477](#). Iodosobenzene: TCI America, ICN. Iodosobenzene diacetate: Aldrich, Acros. *o*-Iodosylbenzoic acid: Aldrich, Lancaster Synthesis, TCI, ICN. Phenylseleninic anhydride: Aldrich, Fluka, Lancaster Synthesis. Camphorylsulfonyloxaziridine: Aldrich, Fluka, Acros, TCI, Oxford Asymmetry. The synthesis is described in ref. [478](#). 8,8-Dichlorocamphorylsulfonyloxaziridine: Fluka, Oxford Asymmetry. Its synthesis as well as that of the 8,8-dimethoxy analog are described in ref. [479](#). See ref. [480](#) for the preparation of (+/–)-*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine. Exposure of this reagent to room temperature must be minimized in order to avoid explosive decomposition; storage in plastic containers at – 10° is recommended. ([480a](#)) The preparation of the MoOPH reagent is described in refs. [481](#) and [482](#); the latter also provides information on its storage. Purification of *m*-CPBA (to remove *m*-chlorobenzoic acid) is described in ref. [483](#). The preparation of an acetone solution of dimethyldioxirane is described in refs. [484](#) and [485](#); for in situ generation of this reagent see refs. [485 to 486a](#). The in situ generation of the more electrophilic methyl(trifluoromethyl)dioxirane is described in ref. ([487](#)).

Osmium, lead, and thallium salts are highly toxic. HMPA is a suspected carcinogen. Many organic peroxides are shock sensitive. *As with all oxidations of organic compounds, the absence of peroxides or hydroperoxides in the crude product must be ascertained before purification, especially if it involves distillation.* The test for peroxides is carried out with iodide-starch test strips (Aldrich and other suppliers) moistened with acetic acid or as follows: ([488](#)) a few drops of the reaction mixture are added to a dilute solution of sodium iodide in glacial acetic acid. Absence of peroxides is indicated if no brown ring is formed.

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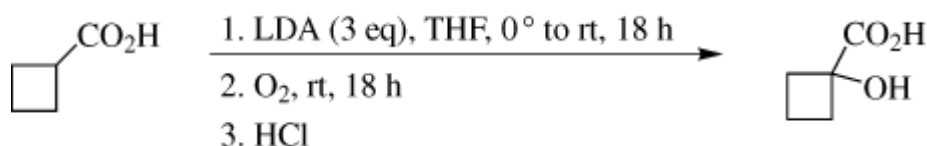
7. Experimental Procedures

The experimental procedures are arranged according to oxidants in the order given in the section on Reagents and Mechanisms.



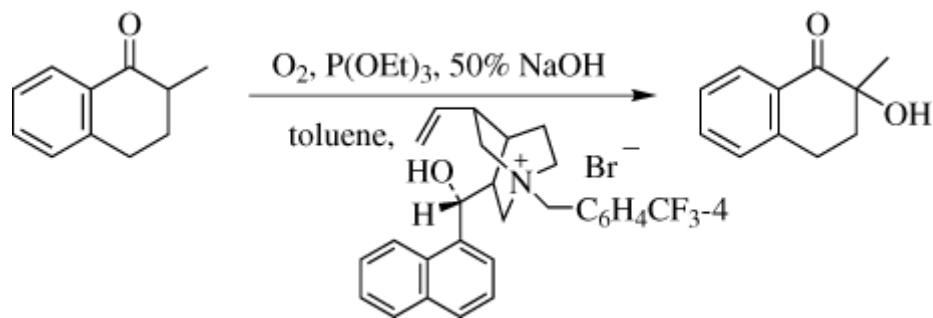
7.1.1. 2-Benzyl-7-acetyl-7-hydroxy-2-azabicyclo[2.2.2]oct-5-ene-6-carboxamide [Hydroxylation of a Ketone Enolate with Oxygen] (201, 202)

A solution of 50 g (0.446 mol) of $t\text{-BuOK}$ in $t\text{-BuOH}$ (300 mL) was mixed with 12 g (72.3 mmol) of triethyl phosphite in monoglyme (100 mL) and cooled to -20° (dry ice/ CCl_4 bath). A solution of 2-benzyl-7-acetyl-2-azabicyclo[2.2.2]oct-5-ene-6-carboxamide (12.9 g, 45.6 mmol) in CH_2Cl_2 (150 mL) was added and dry O_2 was bubbled through the stirred reaction mixture for 2.5 h at -20° . Acetic acid (30 mL) was added and the $t\text{-BuOH}$ and monoglyme were removed under high vacuum (bath below 50°). The pale yellow concentrate was dissolved in cold 6 N H_2SO_4 and the mixture was washed with benzene (2×50 mL). The acid layer was made alkaline with saturated Na_2CO_3 solution, extracted with CH_2Cl_2 , and the extracts were washed with saturated NaCl solution. Evaporation of the solvent and crystallization of the residue from benzene gave 13.2 g (96%) of the title compound, mp $155\text{--}157^\circ$. An analytical sample (CHCl_3 -benzene) had mp $160\text{--}161^\circ$; IR (Nujol) $3350, 1705, 1670, 1630, 1580\text{ cm}^{-1}$; ^1H NMR (DMSO-d_6) δ 1.60 (m, 2 H), 2.08 (s, 3 H), 2.30–2.80 (m, 3 H), 3.09 and 3.75 (AB q, $J = 15$ Hz, 2 H), 4.25 (s, 1 H), 5.25 (s, 1 H, exchanged with D_2O), 7.22 (br s, 8 H); Anal. Calcd for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_2$: C, 67.98; H, 6.71; N, 9.33. Found: C 67.87; H, 6.63; N, 8.93.



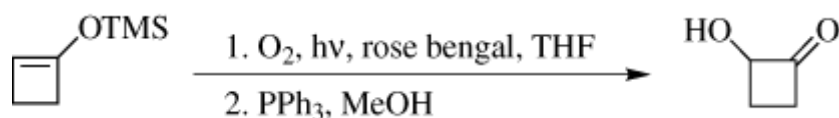
7.1.2. 1-Hydroxycyclobutanecarboxylic Acid [Hydroxylation of an Acid Dianion with Oxygen] (301)

To a solution of 23.38 mL (0.202 mol) of diisopropylamine in 400 mL of THF was added dropwise within 45 minutes at 0° 150 mL of a 1.6 M solution of $n\text{-BuLi}$ (0.24 mol) in hexane followed by a solution of 6.64 g (66.4 mmol) of cyclobutanecarboxylic acid in 100 mL of THF . The mixture was stirred at 0° for 30 minutes and at room temperature for 18 hours after which dry O_2 was bubbled through the mixture for 18 hours. Water (800 mL) was added, the aqueous layer was washed twice with Et_2O (200 mL) and acidified with concentrated HCl . Extraction with Et_2O (3×300 mL) and concentration of the dried (Na_2SO_4) extracts gave 7.7 g (100%) of the title compound as an oil. ^1H NMR (CDCl_3) δ 1.85–2.15 (m, 2 H); 2.25–2.45 (m, 2 H); 2.55–2.70 (m, 2 H), 5.60 (broad s, 2 H); MS, m/z 116, 88, 60, 42.



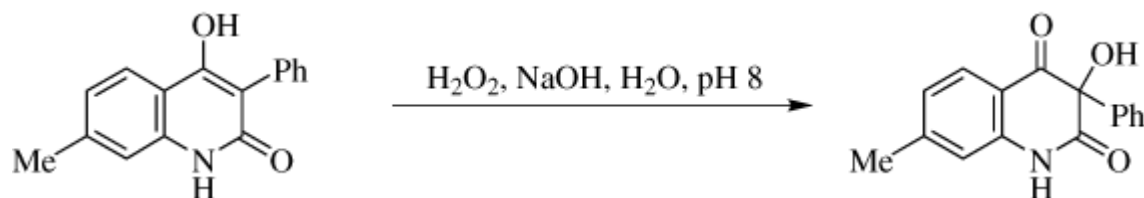
7.1.3. 2-Hydroxy-2-methyl-3,4-dihydro-1(2H)-naphthalenone [Asymmetric Hydroxylation of a Ketone Enolate with Oxygen under Phase-Transfer Conditions] (265)

A solution of 160 mg (1 mmol) of 2-methyl-3,4-dihydro-1(2H)-naphthalenone in 10 mL of toluene, triethyl phosphite (0.2 mL), and 27 mg (0.05 mmol) of cinchoninium *N*-(4-trifluoromethylbenzyl) bromide were added successively to a mixture of 2.5 g of NaOH and 2.5 mL of water while O₂ was bubbled through the mixture and oxygenation was continued for 24 hours. Water (10 mL) was added and the aqueous layer was extracted with benzene. The combined organic layers were washed with dilute HCl and brine and concentrated. Chromatography of the residue gave 167 mg (95%) of the title compound. The enantiomeric excess, determined by ¹H NMR spectroscopy using the chiral shift reagent Eu(hfc)₃, was 70%.



7.1.4. 2-Hydroxycyclobutanone [Hydroxylation of a Silyl Enol Ether with Singlet Oxygen] (78)

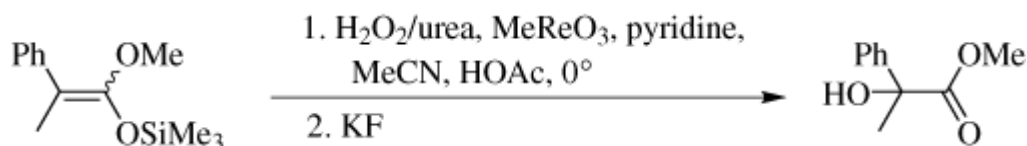
A solution of 2.84 g (20 mmol) of 1-trimethylsilyloxycyclobutene and 20 mg (0.02 mmol) of rose bengal in 140 mL of THF, contained in a Pyrex vessel and cooled with MeOH/dry ice, was irradiated through a 2% K₂CrO₇ filter solution with two Hanovia 450 W medium pressure mercury lamps for 2.8 hours while O₂ was bubbled through the reaction mixture at a rate of 20 g/L/hour. A solution of triphenylphosphine (5.76 g, 22 mmol) in 50 mL of Et₂O was added to the cold mixture which was then stirred at room temperature for 2 hours. The solvents were removed under vacuum at 30–40° and the residue was distilled to give 1.20 g (70%) of the title product, bp 96–98° (15 mm), IR (neat) 3300–3500, 1760–1785 cm⁻¹; ¹H NMR (CDCl₃) δ 1.2–2.95 (m, 4 H), 4.17 (t, *J* = 7 Hz, 1 H), 4.77 (s, 1 H); Anal. Calcd for C₄H₆O₂: C, 55.80; H, 7.02. Found: C, 55.25; H, 7.11.



7.1.5. 3-Hydroxy-7-methyl-3-phenyl-1,2,3,4-tetrahydroquinolin-2,4-dione [Hydroxylation of an Enol of a b-Dicarbonyl Compound with Hydrogen Peroxide] (322)

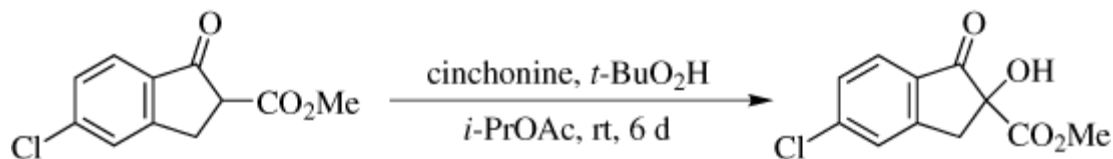
A mixture of 1.0 g of 7-methyl-3-phenyl-1,2,3,4-tetrahydroquinolin-2,4-dione and 30 mL of 0.5 N NaOH solution was heated to 60° and 1 N KH₂PO₄ solution was added with stirring to pH 8. Hydrogen peroxide (30%, 5 mL) was added and the mixture was stirred at room temperature for 4–10 hours. The precipitate was collected and crystallized from aqueous EtOH to give 0.84 g (79%)

of the title compound, m.p. 242°. IR 3320, 1705, 1640, 1620 cm^{-1} . Anal. Calcd for $\text{C}_{16}\text{H}_{13}\text{NO}_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.65; H, 4.98; N, 5.40.



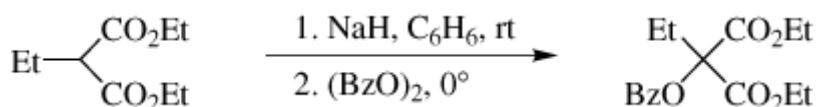
7.1.6. Methyl 2-Hydroxy-2-phenylpropanoate [Hydroxylation of an Alkyl Trialkylsilyl Ketene Acetal with Urea/Hydrogen Peroxide Catalyzed by Methyltrioxorhenium] (92, 489)

(1-Methoxy-2-phenylprop-1-en-1-yloxy)trimethylsilane (0.59 g, 2.5 mmol) was added dropwise over 5 minutes to a cooled (0°) mixture of urea/ H_2O_2 (0.35 g, 3.75 mmol), methyltrioxorhenium (0.031 g, 0.125 mmol), and pyridine (0.05 g, 0.625 mmol) in 99:1 MeCN/AcOH (5 mL). After being stirred for an additional 5 minutes at room temperature, the reaction mixture was treated with a minimal amount of saturated NaHCO_3 solution to neutralize the AcOH and destroy the catalyst. The mixture was then dissolved in CH_2Cl_2 and the organic layer was separated and dried. After filtration and solvent removal, the mixture of the 2-hydroxy and 2-siloxy esters was dissolved in a saturated solution of KF in MeOH, the mixture was stirred for one hour and water was added. Extraction with CH_2Cl_2 , removal of the solvent from the dried (Na_2SO_4) extracts, and flash chromatography of the crude residue gave 0.38 g (85%) of the title product as an oil. ^1H NMR (CDCl_3) δ 1.77 (s, 3 H), 3.71 (s, 3 H), 7.22–7.34 (m, 3 H), 7.52–7.55 (m, 2 H); ^{13}C NMR δ 26.6, 52.9, 75.6, 125.0, 127.6, 128.1, 142.6, 175.8.



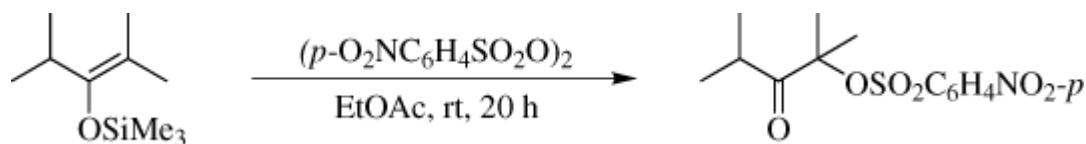
7.1.7. (+)-Methyl 5-Chloro-2-hydroxy-1-oxo-2,3-dihydro-2H-indene-2-carboxylate [Hydroxylation of a b-Keto Ester with tert-Butylhydroperoxide in the Presence of a Chiral Base] (267)

A mixture of 10 g of methyl 5-chloro-1-oxo-2,3-dihydro-2H-indene-2-carboxylate, 17 mL of a 3.0 M solution of *tert*-butylhydroperoxide in isooctane, 0.2 g of cinchonine, and 70 mL of isopropyl acetate was stirred at room temperature for six days. Ethyl acetate (100 mL), 30 mL of dilute sodium bisulfite solution, and 20 mL of 2 N HCl were added and the mixture was shaken. The organic layer was washed with water and brine and concentrated. Crystallization of the residue from hexane gave 4–5 g (37–46%) of the title compound, mp. 163–165°, $[\alpha]_{\text{D}} + 115.1^\circ$ ($\text{CHCl}_3, c = 1.0$); ^1H NMR (CDCl_3) δ 3.21 (d, $J = 18$ Hz, 1 H), 3.67 (d, $J = 18$ Hz, 1 H), 3.72 (s, 3 H), 4.07 (s, 1 H), 7.38, dd, $J = 8/1$ Hz, 1 H), 7.47 (d, $J = 1$ Hz, 1 H) and 7.70 (d, $J = 8$ Hz, 1 H).



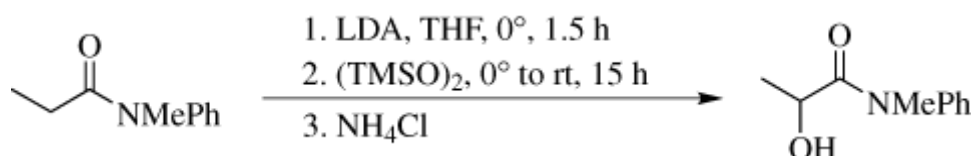
7.1.8. Diethyl 2-Benzoyloxy-2-ethylmalonate [Aroyloxylation of an Enolate of a b-Dicarbonyl Compound]

This preparation is described in *Organic Syntheses*. (488)



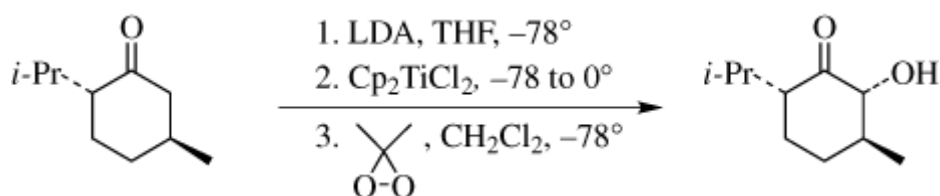
7.1.9. 2,4-Dimethyl-2[(*p*-nitrophenyl)sulfonyloxy]-3-pentanone [Sulfonyloxylation of a Silyl Enol Ether] (105)

To a solution of 0.28 g (1.5 mmol) of 2,4-dimethyl-3-(trimethylsilyloxy)-2-pentene in 30 mL of ethyl acetate was added 0.60 g (1.5 mmol) of [(*p*-nitrophenyl)sulfonyl]peroxide (490) and the pale yellow mixture was stirred at room temperature for 20 hours after which time iodometry showed that all the peroxide had been consumed. The mixture was washed with 2.5 M HCl (2 × 20 mL) and water (2 × 20 mL), and dried (MgSO₄). Concentration gave 0.36 g (77%) of the title product as a clear oil that showed only one component by TLC. Crystallization from EtOAc gave a colorless solid, mp 84.5–85.5°; IR 1725, 1610, 1540, 1360, 1190 cm⁻¹; ¹H NMR d 1.15 (d, *J* = 7 Hz, 6 H), 1.72 (s, 6 H), 3.2 (septet, *J* = 7 Hz, 1 H), 8.25 (AA'BB', 4 H); Anal. Calcd for C₁₃H₁₇NO₄S : C, 49.67; H, 5.43; N, 4.46; S, 10.20. Found: C, 49.57; H, 5.53; N, 4.26; S, 10.01.



7.1.10. *N*-Methyl-*N*-phenyl-2-hydroxypropanamide [Hydroxylation of an Amide Enolate with Bis(trimethylsilyl) Peroxide] (109)

To a solution of LDA (3 mmol) in THF (10 mL) was added at 0° a solution of *N*-methyl-*N*-phenylpropanamide (0.41 g, 2.5 mmol) in 2 mL of THF. After stirring for 1.5 h at 0°, bis(trimethylsilyl)peroxide (0.54 g, 3 mmol) in THF (2 mL) was added. The mixture was warmed to room temperature (15 h), NH₄Cl solution was added and the mixture was extracted with EtOAc (3 × 60 mL). The combined extracts were washed with water and brine, dried (Na₂SO₄), and concentrated. Preparative thin-layer chromatography (silica gel, 1:1 EtOAc/hexane) and crystallization from CHCl₃/hexane provided the title compound (0.23 g, 51%) as colorless crystals, mp 86–88°; IR (Nujol) 3250, 1630 cm⁻¹; ¹H NMR (CDCl₃) d 1.1 (d, *J* = 7 Hz, 3 H), 3.5 (br. s, 1 H), 4.25 (m, 1 H), 7.35 (m, 5 H).

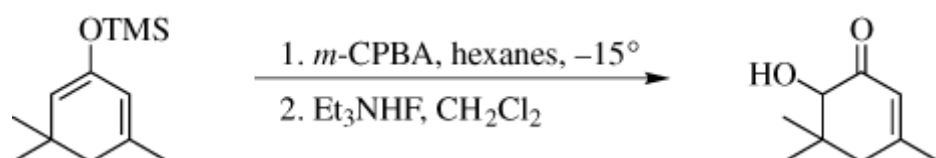


7.1.11. (2*S**,3*R**,6*S**)-2-Hydroxy-3-methyl-6-(1-methylethyl)cyclohexanone [Hydroxylation of a Titanium Enolate with Dimethyldioxirane] (111)

The preparation of an acetone solution of dimethyldioxirane in 1–2% yield is described in ref. (485); the solution was dried over 4L molecular sieves at –20° for two days before use.

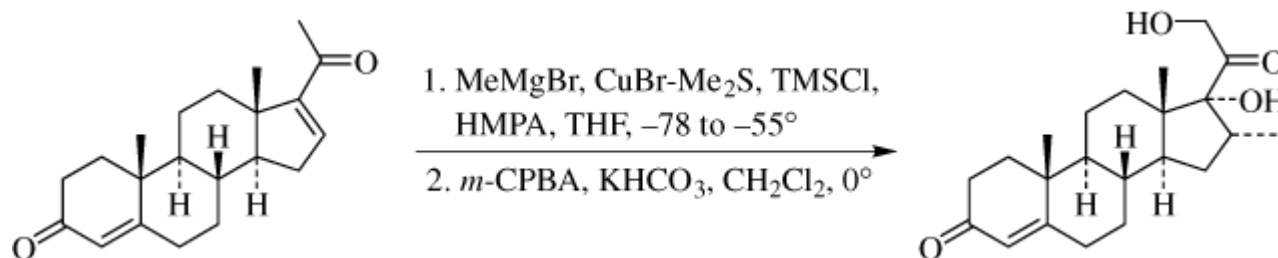
A solution of (3*R**,6*S**)-3-methyl-6-(1-methylethyl)cyclohexanone (154 mg, 1.00 mmol) in 2 mL of

THF was added dropwise under argon at -78° to 1.10 mmol of LDA in THF. After stirring for 30 minutes, the reaction mixture was slowly added at -78° to a solution of Cp_2TiCl_2 (275 mg, 1.10 mmol) in THF (about 0.06 M), the reaction mixture was kept at -50° for 12 hours and the solvent was removed by distillation (-30 to $-25^{\circ}/0.1$ mm). The residue was cooled to -78° and taken up in 10 mL of CH_2Cl_2 . To the reddish brown solution was rapidly added 14 mL of a 0.0870 M (1.22 mmol) dimethyldioxirane solution in acetone under vigorous stirring. After 1 minute, 1 mL of an aqueous, saturated NH_4F solution was added and the mixture was stirred for about 12 hours at room temperature, filtered through Celite, and concentrated ($20^{\circ}/20$ mm). The residue was taken up in 20 mL of *tert*-butyl methyl ether and the solution was dried (Na_2SO_4). The solvent was evaporated under vacuum ($20^{\circ}/20$ mm) and the residue was purified by column chromatography [silica gel, 20:1 petroleum ether (50 – 60°)/*tert*-butyl methyl ether] to yield 91 mg (54%) of the title product as a colorless liquid. The $2S^*/2R^*$ ratio was 76:24 as determined by ^1H NMR analysis of the α -hydroxy protons ($2S^*$)-H [δ 3.63 (dd)] and ($2R^*$)-H [δ 4.35 (dd)] directly on the crude reaction mixture. IR (NaCl) 3500–2400, 2935, 2900, 2850, 1690 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 0.88 (d, $J = 6.6$ Hz, 3 H), 0.93 (d, $J = 6.5$ Hz, 3 H), 1.16 (d, $J = 6.1$ Hz, 3 H), 1.25–1.62 (m, 3 H), 1.80–1.87 (m, 1 H), 2.02–2.21 (m, 3 H), 3.63 (dd, $J = 10.1/4.0$ Hz, 1 H), 3.68 (d, $J = 4.2$ Hz, 1 H); ^{13}C NMR (63 MHz, CDCl_3) δ 18.8 (q), 19.2 (q), 21.2 (q), 26.1 (d), 28.6 (t), 31.3 (t), 44.0 (d), 54.4 (d), 80.8 (d), 212.0 (s). Anal. Calcd for $\text{C}_{10}\text{H}_{18}\text{O}_2$: C, 70.55; H, 10.66. Found: C, 70.65; H, 10.99.



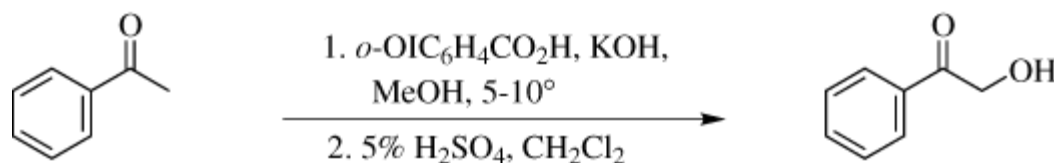
7.1.12. 6-Hydroxy-3,5,5-trimethyl-2-cyclohexene-1-one [Hydroxylation of a 2-Silyloxydiene with *m*-Chloroperoxybenzoic Acid]

This preparation and the synthesis of the substrate are described in *Organic Syntheses*. (254)



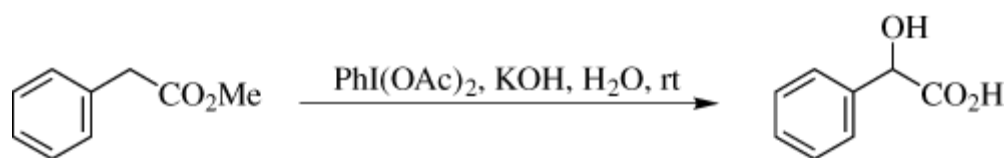
7.1.13. (+/-)-17,21-Dihydroxy-16 α -methylpregn-4-ene-3,20-dione [Dihydroxylation of a Silyl Enol Ether with *m*-Chloroperoxybenzoic Acid]

This preparation is described in *Organic Syntheses*. (491)



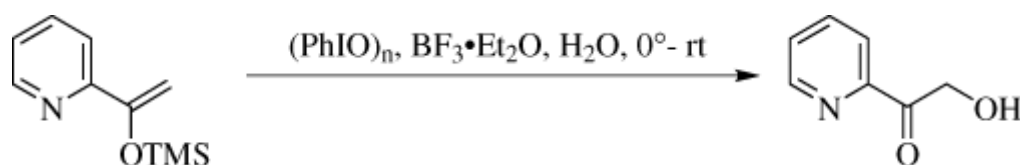
7.1.14. α -Hydroxyacetophenone [Hydroxylation of a Ketone Enolate with *o*-Iodosylbenzoic Acid]

This preparation is described in *Organic Syntheses*. (139)



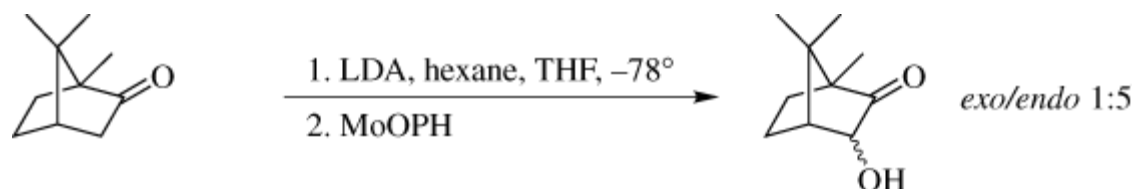
7.1.15. *alpha*-Hydroxyphenylacetic Acid [Hydroxylation of an Ester with Iodobenzene Diacetate] (136, 138)

A mixture of 1.50 g (10 mmol) of methyl phenylacetate, 1.68 g (30 mmol) of KOH, 3.22 g of iodobenzene diacetate, 10 mL of benzene, and 10 mL of water was stirred until the starting material had disappeared. Extraction with diisopropyl ether, removal of the solvent from the dried extracts, and crystallization of the residue from CHCl₃ gave 0.70 g (50%) of the title compound, mp 118–120° (mp. 131–132° in ref. 138); ¹H NMR [in (CD₃)₂CO] δ 5.20 (s, 1 H) and 7.00–7.60 (m, 7 H).



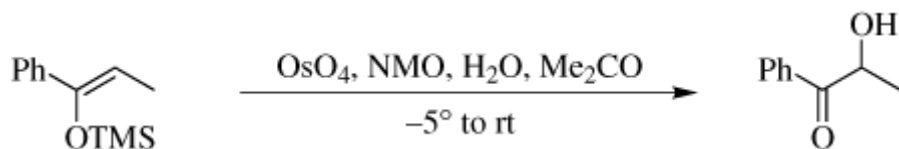
7.1.16. 2-(Hydroxyacetyl)pyridine [Hydroxylation of a Silyl Enol Ether with Iodosobenzene and Boron Trifluoride Etherate] (141)

Boron trifluoride etherate (2.84 g, 20 mmol) followed by 2-[(1-trimethylsilyloxy)ethenyl]pyridine (1.94 g, 10 mmol) were added to a stirred and ice-cooled (0–5°) suspension of iodosobenzene (2.42 g, 11 mmol) in water (50 mL). The mixture was stirred for 2 hours after which the temperature was raised to room temperature and stirring was continued for a further 2 hours. During this time all of the iodosobenzene went into solution indicating completion of the reaction. The solution was made basic with an excess of solid NaHCO₃ and extracted with CH₂Cl₂ (5 × 50 mL). The combined extracts were dried (MgSO₄) and concentrated under reduced pressure to yield the crude product which contained iodobenzene as a major impurity. Addition of a mixture of hexane and Et₂O (20 mL each) to the crude product, followed by filtration and cooling of the filtrate at 0° gave 0.85 g (62%) of the title product, mp. 70–71°; IR (Nujol) 1720, 3510 cm⁻¹; ¹H NMR (CDCl₃) δ 3.30 (br, 1 H), 5.13 (s, 2 H), 7.30–8.72 (m, 4 H); MS (70 eV), m/z 137 (M⁺, 40%), 107 (88), 106 (35), 79 (95), and 78(100); Anal. Calcd for C₇H₇NO₂: C, 61.31; H, 5.15; N, 10.22. Found: C, 61.1; H, 5.2; N, 10.15.



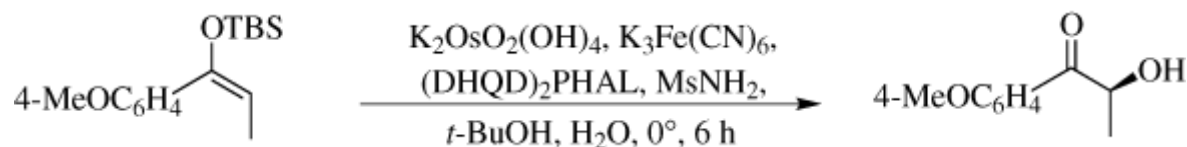
7.1.17. 3-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one [Hydroxylation of a Ketone Enolate with the MoOPH Reagent]

This synthesis as well as the preparation of the reagent are described in *Organic Syntheses*. (482)



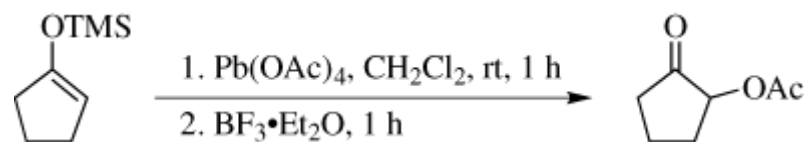
7.1.18. 2-Hydroxy-1-phenyl-1-propanone [Hydroxylation of a Silyl Enol Ether with the OsO₄/N-Methylmorpholine N-Oxide System] (154)

To a mixture of 284 mg (2.1 mmol) of *N*-methylmorpholine *N*-oxide hydrate, 4 mL of water, and 9 mL of acetone was added a solution of 10 mg (0.04 mmol) of osmium tetroxide in 0.91 mL of *t*-BuOH followed at -5° by a solution of 412 mg (2.0 mmol) of 1-phenyl-1-(trimethylsilyloxy)-1-propene in 3 mL of acetone. The resulting mixture was stirred at 0° for 3 hours, allowed to warm to 25° , and stirred an additional 6 hours. Sodium hydrosulfite (0.35 g) and Florisil (1.34 g) were added, the suspension was stirred and filtered, the filtrate was neutralized with 1 N H₂SO₄, and the acetone was removed under vacuum. The residual aqueous mixture was acidified to pH 2, saturated with NaCl, and extracted with EtOAc. Removal of the solvent from the dried (MgSO₄) extracts and chromatography of the product on silica gel (EtOAc/hexane 2:3) gave 293 mg (98%) of the title product.



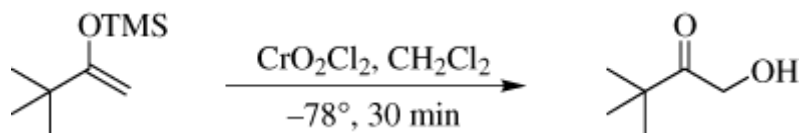
7.1.19. (R)-2-Hydroxy-1-(4-methoxyphenyl)-1-propanone [Asymmetric Hydroxylation of a Silyl Enol Ether with the K₂OsO₂(OH)₄/K₃Fe(CN)₆/(DHQD)₂PHAL System] (158)

To a well-stirred mixture of 1.4 g of AD-mix b [0.98 g of K₃Fe(CN)₆, 0.74 mg of K₂OsO₂(OH)₄, 7.8 mg of (DHQD)₂PHAL (Eq. 30), and 410 mg of K₂CO₃; like the AD-mix a available from Aldrich], 95 mg (1 mmol) of MeSO₂NH₂, 10 mL of water, and 10 mL of *t*-BuOH was added at 0° 278 mg (1 mmol) of (Z)-1-(4-methoxyphenyl)-1-(*tert*-butylidimethylsilyloxy)-1-propene and the mixture was stirred at 0° for 16 hours. Solid sodium sulfite (1 g) was added and stirring was continued for one hour. CH₂Cl₂ (30 mL) was added, and the aqueous layer was extracted with an additional 30 mL of CH₂Cl₂. Concentration of the dried (MgSO₄) organic phases and flash chromatography of the residue gave 172 mg (94%) of the title product as a colorless oil. $[\alpha]_D^{25} +32.8^\circ$ ($c = 1.36$, MeOH).



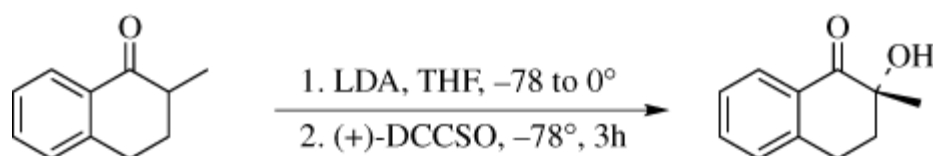
7.1.20. 2-Acetoxycyclopentanone [Acetoxylation of a Silyl Enol Ether with Lead Tetraacetate] (366)

A solution of 1-trimethylsilyloxycyclopentene (1.56 g, 10 mmol) in 10 mL of CH₂Cl₂ was added to a stirred solution of 4.43 g (10 mmol) of lead tetraacetate in 30 mL of CH₂Cl₂ and stirring was continued at 20° for one hour. The lead diacetate was removed by filtration, 0.5 mL of boron trifluoride etherate was added to the filtrate, and the mixture was left for one hour, washed with water (2 × 20 mL), and the aqueous layer was extracted with CH₂Cl₂ (3 × 5 mL). Removal of the solvent from the dried (Na₂SO₄) extracts and distillation of the residue gave 1.12 g (79%) of the title product, bp 95° (7 mm), $n_D^{19} 1.4572$.



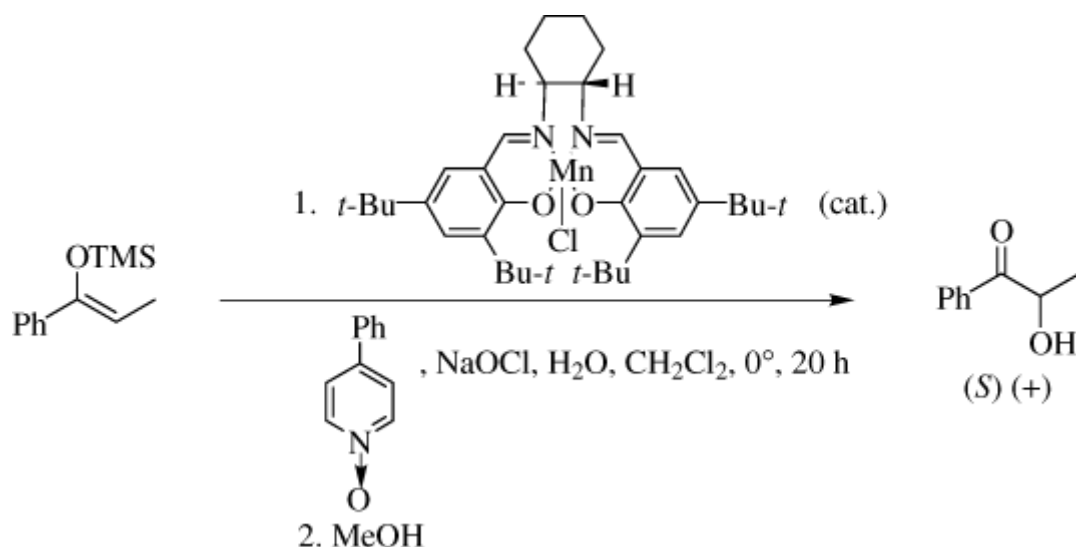
7.1.21. 3,3-Dimethyl-1-hydroxy-2-butanone [Hydroxylation of a Silyl Enol Ether with Chromyl Chloride] (166)

A solution of chromyl chloride (0.54 g, 3.53 mmol) in 5 mL of dry CH_2Cl_2 was added at -78° under N_2 to a stirred solution of 466 mg (2.71 mmol) of 3,3-dimethyl-2-trimethylsilyloxy-1-butene in 5 mL of CH_2Cl_2 . After 30 minutes at -78° the dark-red mixture was added to a cold aqueous sodium bisulfite solution and the mixture was stirred for 15 minutes and neutralized with NaHCO_3 . Extraction with CH_2Cl_2 , concentration of the dried (Na_2SO_4) extracts, and flash chromatography of the residue gave 258 mg (82%) of the title compound.



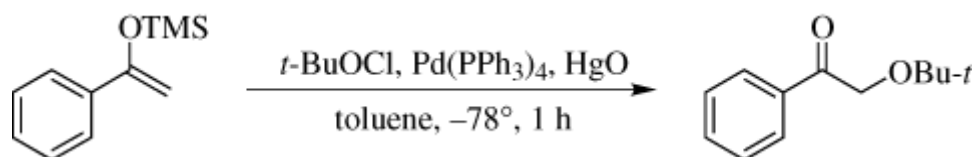
7.1.22. (+)-(R)-2-Hydroxy-2-methyl-1-tetralone {Enantioselective Hydroxylation of a Prochiral Enolate with (+)-[(8,8-Dichlorocamphoryl)sulfonyl]oxaziridine} (492)

In a 25-mL oven-dried two-necked round-bottomed flask fitted with an argon bubbler, rubber septum, and magnetic stirring bar was placed 3 mL of freshly distilled THF. The reaction flask was cooled to -78° and 0.6 mL (0.6 mmol, 1.2 equivalents) of a 1.0 M solution of LDA in THF was added. A solution of 80 mg (0.5 mmol) of 2-methyl-1-tetralone in 2 mL of THF was added dropwise and after 5 minutes the reaction mixture was warmed to 0° for 30 minutes and cooled to -78° . A solution of 180 mg (0.6 mmol, 1.2 equivalents) of (+)-[(8,8-dichlorocamphoryl)sulfonyl]-oxaziridine in 5 mL of THF was then added dropwise. The reaction was monitored by TLC and quenched when complete (3 hours) by addition of 3 mL of a saturated aqueous NH_4Cl solution. Ethyl ether (10 mL) was added and the mixture was warmed to room temperature. The aqueous layer was extracted with Et_2O (2×5 mL), the combined organic extracts were washed with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution (2×15 mL) and brine (2×10 mL), and dried (MgSO_4). Concentration and preparative TLC of the residue (pentane/ Et_2O , 3:1) or flash chromatography (*n*-pentane/ EtOAc 19:1) produced 53 mg (66%) of the title product in 95% ee, $[\alpha]_D^{20} +17.3^\circ$ ($c = 2.0$, MeOH).



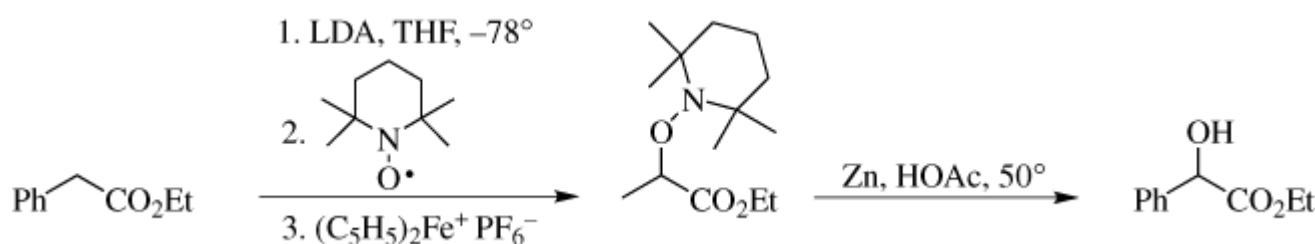
7.1.23. 1-Hydroxy-1-phenyl-2-propanone [Hydroxylation of a Silyl Enol Ether with Sodium Hypochlorite Catalyzed by a (Salen) Manganese(III) Complex] (273)

A solution of 1 mmol of (*Z*)-trimethyl[(1-phenyl-2-propenyl)oxy]silane, 0.07 mmol of chloro-(*R,R*)-{2,2'-[(1,2-cyclohexanediyl)bis(nitrilomethylidene)]bis[2-(1,1-dimethylethyl)phenolato]}-*N*, and 0.30 mmol of 4-phenylpyridine *N*-oxide in 5 mL of CH₂Cl₂ was cooled to 0°. Buffered bleach (7.50 mmol, pH 11.5) was added and the mixture was stirred at 0° for 24 hours and then allowed to warm to room temperature. The layers were separated and the aqueous phase was extracted with CH₂Cl₂ (3 × 5 mL). The solvent was removed at 40° from the dried (MgSO₄) solution, the residue was dissolved in MeOH (5 mL), and the resulting mixture was stirred for 2 hours to complete desilylation. The conversion into the title product was 91%, the ee was 79%, and the configuration was *S*(+) as determined by HPLC on a Chiralcel OD column. Purification was effected by chromatography on silica gel (petrol ether/ Et₂O 2:1). No further data were reported.



7.1.24. *tert*-Butoxyacetophenone [Alkoxylation of a Silyl Enol Ether with *tert*-Butyl Hypochlorite] (185)

A solution of 96 mg (0.5 mmol) of 1-phenyl-1-trimethylsilyloxyethene in 1 mL of toluene was added dropwise at -78° under argon in the dark to a stirred suspension of 23 mg (0.02 mmol) of Pd(PPh₃)₄ and 108 mg (0.5 mmol) of yellow mercuric oxide in 0.5 mL of toluene followed by a solution of 55 mg (0.5 mmol) of *tert*-butyl hypochlorite in 1 mL of toluene. Stirring was continued at -78° for one hour, 10 mL of Et₂O were added, and the insoluble material was removed by filtration. The solvents were removed from the filtrate and the residue was purified by preparative thin-layer chromatography and bulb-to-bulb distilled (100°/8 mm) to give 61 mg (64%) of the title product.



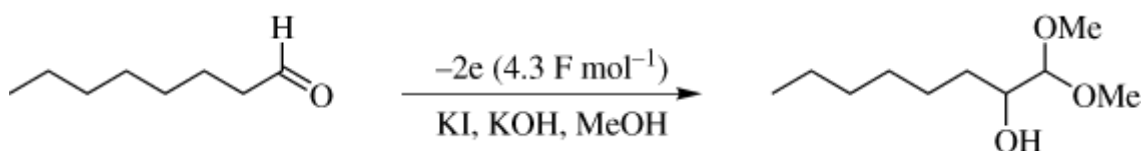
7.1.25. Ethyl *α*-Hydroxyphenylacetate [Reaction of an Ester Enolate with Ferrocenium Hexafluorophosphate and 2,2,6,6-Tetramethyl-1-piperidinyloxy Followed by Reduction] (190)

To a solution of 8.2 mL (62.5 mmol) of diisopropylamine in 450 mL of dry THF were added, at -40°, 36.1 mL (62.5 mmol) of 1.6 M *n*-BuLi in hexane. The mixture was stirred for 20 minutes, cooled to -78°, and treated with a solution of 8.2 g (50 mmol) of ethyl phenylacetate in 20 mL of THF. After stirring for 30 minutes at -78°, 10.9 g (70 mmol) of 2,2,6,6-tetramethyl-1-piperidinyloxy were added followed 5 minutes later by 23.2 g (70 mmol) of ferrocenium hexafluorophosphate in portions with vigorous stirring. After one hour 0.5 mL of water was added, the mixture was left to warm to room temperature, and 200 mL of Et₂O were added. The mixture was filtered through a pad of silica and the solvent was removed. Purification by flash chromatography (silica gel, hexane/EtOAc 50:1 to 20:1) gave 15.1 g (95%) of ethyl 2-(2,2,6,6-tetramethylpiperidinyl-1-oxy)phenylacetate as a colorless

oil in addition to 12.25 g of ferrocene and 5% of a mixture of *meso* and *d,l* diethyl

2,3-diphenylsuccinate. $^1\text{H NMR}$ (CDCl_3) δ 0.64 (s, 3 H), 1.00 (s, 3 H), 1.08 (s, 3 H), 1.11 (t, $J = 7.1$ Hz, 3 H), 1.16 (s, 3 H), 1.33 (m, 6 H), 4.03 (ABX₃, $J = 10.8, 7.1$ Hz, 2 H), 5.11 (s, 1 H), 7.22 (m, 3 H); 7.37 (m, 2 H); Anal. Calcd for $\text{C}_{19}\text{H}_{29}\text{NO}_3$: C, 71.44; H, 9.15; N, 4.38. Found: C, 71.36; H, 9.13; N, 4.17.

A mixture of 320 mg (1 mmol) of the above intermediate, 6 mL of acetic acid, 2 mL of THF, and 2 mL of water was treated with 2.61 g (40 mmol) of zinc dust and stirred in a 50° oil bath for 30–60 minutes. The cooled mixture was diluted with ether and filtered through a pad of silica. The solvents were removed and the residue was purified by chromatography to give 139 mg (85%) of ethyl *a*-hydroxyphenylacetate. Anal. Calcd for $\text{C}_{10}\text{H}_{12}\text{O}_3$: C, 66.65; H, 6.71. Found: C, 66.43; H, 6.81.



7.1.26. 2-Hydroxyoctanal Dimethyl Acetal [Electrochemical Hydroxylation of an Aldehyde Enolate] (191)

In a cell equipped with a platinum plate anode (2 cm \times 2 cm) and a carbon rod cathode (8 mm diameter) was placed a solution of 512 mg (4 mmol) of octanal, 332 mg (2 mmol) of KI, and 224 mg (4 mmol) of KOH in 30 mL of MeOH. With external cooling provided by an ice-water bath, a constant current of 0.3 A (terminal voltage ca. 5 V) was passed through the solution for 1.5 hours (4.3 F mol^{-1} of electricity). The solvent was removed under reduced pressure, the residue was taken up in CH_2Cl_2 (3 \times 50 mL) and the organic solution was dried (MgSO_4). Removal of the solvent and Kugelrohr distillation of the residue gave 570 mg (75%) of the title product, bp 88–90° (1–3 mm). IR (neat) 3450, 2925, 2850, 1470, 1070, 970 cm^{-1} ; $^1\text{H NMR}$ (CCl_4) δ 0.90 (t, $J = 6$ Hz, 3 H), 1.07–1.08 (m, 10 H), 2.08 (br s, 1 H), 3.30 (s, 3 H), 3.37 (s, 3 H), 3.30–3.60 (m, 1 H), and 4.00 (d, $J = 6$ Hz, 1 H); Anal. Calcd for $\text{C}_{10}\text{H}_{22}\text{O}_3$: C, 63.12; H, 11.65. Found: C, 62.9; H, 11.95. A scale-up of this reaction is achieved by using a carbon rod anode.

8. Tabular Survey

An effort was made to include all references published to the end of 2000, but in view of the complexity of the subject omissions are inevitable. The tables are arranged according to substrates and follow the organization of the section on Scope and Limitations except that alkoxylation, acyloxylation, and sulfonyloxylation, the coverage of which is not exhaustive, are listed in the tables dealing with the corresponding α -hydroxylation. Hydroxylations in which the ketone enolate is generated from a silyl enol ether (Eq. 13) are listed in Tables 16A and 16B rather than in Tables 2A and 2B. Hydroxylations of thioesters are listed with those of esters in Table 3. Within each table, entries are arranged in the order of increasing carbon count of the substrate. In order to group similar substrates together, protecting groups are not included in the carbon count. Thus the substituents on silicon in silyl enol ethers and alkyl trialkylsilyl ketene acetals are not counted nor are the alkyl groups in the latter. The groups on oxygen in aromatic ethers are not considered to be protecting groups, but those in aliphatic or vinylic ethers are excluded from the count, as are common nitrogen protecting groups such as Bn, Boc, or Cbz. Esters are usually counted in full unless they are obvious protecting groups such as acetates in steroids. In metal complexes ligands are also excluded but ferrocene is counted as C₁₀. A dash enclosed in parentheses [(—)] next to a product signifies that the product was isolated but no yield was given. When a reaction involving the same oxidant has been reported in more than one publication, the conditions producing the highest yield are shown and the reference to that paper is given first. Reactions involving minor structural changes in the oxidant structure (mostly in the case of sulfonyloxaziridines) are usually not included in the tables unless the yields or diastereomeric excesses produced are significantly higher.

Footnotes are listed at the end of each table.

The following abbreviations are used in the tables:

Ac	acetyl
acac	2,4-pentadionato
AD mix-a	see ref. (158); 1.4 g of this mix, which is available from Aldrich, is required for the asymmetric dihydroxylation of 1 mmol of substrate. It contains K ₃ Fe(CN) ₆ (980 mg), K ₂ CO ₃ (410 g), (DHQ) ₂ -PHAL (7.8 mg), and K ₂ O ₂ (OH) ₄ (0.74 mg).
AD mix-b	this is the same as AD mix-a except that (DHQ) ₂ -PHAL is replaced by (DHQD) ₂ -PHAL
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
BOM	benzyloxymethyl
Bu	butyl
Bz	benzoyl
Cbz	benzyloxycarbonyl
Cp	h ⁵ -cyclopentadienyl
Cs	10-camphorylsulfonyl
CSO	(camphorylsulfonyl)oxaziridine
DBCOS	[(8,8-dibromocamphoryl)sulfonyl]oxaziridine
DCCSO	[(8,8-dichlorocamphoryl)sulfonyl]oxaziridine
DCE	1,2-dichloroethane
(DHQ) ₂ -PHAL	see Eq. 30
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DFCSO	[(8,8-difluorocamphoryl)sulfonyl]oxaziridine

DMAP	4-dimethylaminopyridine
DMCSO	[(8,8-dimethoxycamphoryl)sulfonyl]oxaziridine
DMDO	dimethyldioxirane
DME	dimethoxyethane
DMEU	dimethylethyleneurea
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1 <i>H</i>)-pyrimidinone
DMTS	dimethylhexylsilyl
Et	ethyl
GC	gas chromatography
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoric triamide
LiCA	lithium cyclohexylisopropylamide
mac	3-methyl-2,4-pentadionato
Me	methyl
MEM	(2-methoxyethoxy)methyl
MOM	methoxymethyl
MoOPD	oxodiperoxymolybdenum(pyridine)-1,3-dimethyl-3,4,5,6-tetrahydro-2(1 <i>H</i>)-pyrimidinon
MoOPH	oxodiperoxymolybdenum(pyridine)hexamethylphosphoric triamide
MS	molecular sieves
NPSO	3-(<i>p</i> -nitrophenyl)-2-(phenylsulfonyl)oxaziridine
NTSO	3-(<i>p</i> -nitrophenyl)-2-(<i>p</i> -toluenesulfonyl)oxaziridine
NMO	<i>N</i> -methylmorpholine <i>N</i> -oxide
Ns	<i>p</i> -nitrophenylsulfonyl
Piv	pivaloyl (2,2-dimethylpropionyl)
Pf	9-phenyl-9-fluorenyl
Ph	phenyl
PMB	<i>p</i> -methoxybenzyl
PMP	<i>p</i> -methoxyphenyl
PMDET	<i>N,N,N',N',N'</i> -pentamethyldiethylenetriamine
PPSO	3-phenyl-2-(phenylsulfonyl)oxaziridine
Pr	propyl
PTSO	3-phenyl-2-(<i>p</i> -toluenesulfonyl)oxaziridine
Py	pyridine
SEM	2-(trimethylsilyl)ethoxymethyl
TAS-F	tris(dimethylamino)sulfonium (trimethylsilyl)difluoride
TBDMS	<i>tert</i> -butyldimethylsilyl
TBDPS	<i>tert</i> -butyldiphenylsilyl
TCCSO	[(4,4,8,8-tetrachlorocamphoryl)sulfonyl]oxaziridine
TEA	triethylamine
TEAF	triethylammonium fluoride
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy free radical
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
THP	tetrahydropyranyl
TIPS	triisopropylsilyl

TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TPS	triphenylsilyl
TPT	2,4,6-triphenylpyrylium tetrafluoroborate
Tr	trityl
Ts	<i>p</i> -toluenesulfonyl

Table 1. α -Hydroxylation of Aldehyde Enolates

[View PDF](#)

Table 2A. α -Hydroxylation of Acyclic Ketone Enolates

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Table 2B. α -Hydroxylation of Cyclic Ketone Enolates

[View PDF](#)

Table 3. α -Hydroxylation of Ester Enolates

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Table 4. α -Hydroxylation of Lactone Enolates

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Table 5. α -Hydroxylation of Carboxylic Acid Dianions

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Table 6. α -Hydroxylation of Amide Enolates

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Table 7. α -Hydroxylation of Lactam Enolates

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Table 8. α -Hydroxylation of Nitrile Anions

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Table 9A. α -Hydroxylation of Enolates of α -Diketones

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Table 9B. Hydroxylation of Enolates of β -Dicarbonyl Compounds

[View PDF](#)

Table 10. Hydroxylation of Enolates of α , β -Unsaturated Carbonyl Compounds

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Table 11. α -Hydroxylation of Aza-Enolates

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Table 12. Tandem Michael Addition/ α -Hydroxylation

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Table 13. Tandem Birch Reduction/ α -Hydroxylation

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Table 14. Tandem Oxy Cope Rearrangement/ α -Hydroxylation

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Table 15. α -Hydroxylation of Aldehyde Silyl Enol Ethers

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Table 16A. α -Hydroxylation of Acyclic Ketone Silyl Enol Ethers

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Table 16B. α -Hydroxylation of Cyclic Ketone Silyl Enol Ethers

[View PDF](#)

Table 17A. α -Hydroxylation of 1-Silyloxy-1,3-Dienes

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Table 17B. α -Hydroxylation of 2-Silyloxy-1,3-Dienes

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Table 18. α -Hydroxylation of Alkyl Trialkylsilyl Ketene Acetals and Related Systems

[View PDF](#)

Table 19. α -Hydroxylation of Bis(Trialkylsilyl) Ketene Acetals

[View PDF](#)

TABLE 1. α -HYDROXYLATION OF ALDEHYDE ENOLATES

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																																	
C ₅ -C ₉ 	-2e, KOH, KI, MeOH	 <table border="1"> <thead> <tr> <th>R¹</th> <th>R²</th> <th>Yield (%)</th> </tr> </thead> <tbody> <tr> <td><i>n</i>-Pr</td> <td>H</td> <td>(62)</td> </tr> <tr> <td><i>i</i>-Pr</td> <td>H</td> <td>(62)</td> </tr> <tr> <td>Et</td> <td>Et</td> <td>(67)</td> </tr> <tr> <td>(CH₂)₃CO₂Me</td> <td>H</td> <td>(33)</td> </tr> <tr> <td>—(CH₂)₅—</td> <td></td> <td>(76)</td> </tr> <tr> <td><i>n</i>-C₆H₁₃</td> <td>H</td> <td>(75)</td> </tr> <tr> <td><i>n</i>-Bu</td> <td>Et</td> <td>(78)</td> </tr> <tr> <td>Bn</td> <td>H</td> <td>(80)</td> </tr> <tr> <td>Ph</td> <td>Me</td> <td>(51)</td> </tr> <tr> <td><i>n</i>-C₈H₁₇</td> <td>H</td> <td>(85)</td> </tr> </tbody> </table>	R ¹	R ²	Yield (%)	<i>n</i> -Pr	H	(62)	<i>i</i> -Pr	H	(62)	Et	Et	(67)	(CH ₂) ₃ CO ₂ Me	H	(33)	—(CH ₂) ₅ —		(76)	<i>n</i> -C ₆ H ₁₃	H	(75)	<i>n</i> -Bu	Et	(78)	Bn	H	(80)	Ph	Me	(51)	<i>n</i> -C ₈ H ₁₇	H	(85)	191
R ¹	R ²	Yield (%)																																		
<i>n</i> -Pr	H	(62)																																		
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Ph	Me	(51)																																		
<i>n</i> -C ₈ H ₁₇	H	(85)																																		
C ₇ 	1. <i>i</i> -Pr ₂ NMgBr, Et ₂ O, 0°, 12 h 2. (TMSO) ₂ , -78° to rt, 2 h 3. NH ₄ Cl	 (46)	44																																	
C ₁₅ 	O ₂ or MoOPH	 (—)	493																																	
	1. LDA, THF, -20 to -78° 2. MoOPH, -78 to 0°	 (49) + (—)	494																																	
C ₁₅ 	1. LiHMDS, THF, HMPA, -78° 2. MoOPH, -78°	 (24)	495																																	
+	1. KH, THF, 5°, 2 h 2. MoOPH, -78 to -55°, 1 h	 I (60)	496																																	
C ₁₅₋₁₆ 	1. LDA 2. MoOPH	 <table border="1"> <thead> <tr> <th>R</th> <th>Yield (%)</th> </tr> </thead> <tbody> <tr> <td>Me</td> <td>(96)</td> </tr> <tr> <td>CO₂Me</td> <td>(77)</td> </tr> </tbody> </table>	R	Yield (%)	Me	(96)	CO ₂ Me	(77)	275, 276 275																											
R	Yield (%)																																			
Me	(96)																																			
CO ₂ Me	(77)																																			

TABLE 2A. α -HYDROXYLATION OF ACYCLIC KETONE ENOLATES

	Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.										
C ₂		1. Base 2. MoOPH	(—)	497										
C ₅		1. KOH, MeOH, 0 to 5°, 5 min 2. PhI(OAc) ₂ , 0 to 5°, 2 h; rt overnight 3. 6N HCl, rt, 14 h	(57)	226										
		<i>o</i> -HO ₂ CC ₆ H ₄ IO, KOH, MeOH, rt, 16 h	(65)	227										
		1. <i>o</i> -HO ₂ CC ₆ H ₄ IO, KOH, MeOH, rt, 16 h 2. 5% H ₂ SO ₄ , CHCl ₃	(45) + (8)	227										
66		<i>t</i> -BuO ₂ H, (+) diethyl tartrate, Ti(OPr- <i>i</i>) ₄ , -20°, 72-168 h	(29-54) 95-91% ee	263										
C ₆		1. KOH, MeOH, 30 min 2. PhI(OAc) ₂ , rt, overnight	(62)	224										
C ₇		1. KOH, MeOH, 30 min 2. PhI(OAc) ₂ , rt, overnight	(61)	224, 141										
		1. (PhIO) _n , OH ⁻ , MeOH 2. H ₃ O ⁺	(—)	498										
		1. KOH, MeOH, 30 min 2. PhI(OAc) ₂ , rt, overnight	(61)	224, 141										
		1. KOH, MeOH, 30 min 2. PhI(OAc) ₂ , rt, overnight	(58)	224										
C ₇₋₁₂		1. KOH, MeOH, 30 min 2. PhI(OAc) ₂ , rt, overnight	<table border="1"> <thead> <tr> <th>R</th> <th>Yield (%)</th> </tr> </thead> <tbody> <tr> <td>Me</td> <td>(69)</td> </tr> <tr> <td>2-thienyl</td> <td>(58)</td> </tr> <tr> <td>2-pyridyl</td> <td>(56)</td> </tr> <tr> <td>Ph</td> <td>(59)</td> </tr> </tbody> </table>	R	Yield (%)	Me	(69)	2-thienyl	(58)	2-pyridyl	(56)	Ph	(59)	226
R	Yield (%)													
Me	(69)													
2-thienyl	(58)													
2-pyridyl	(56)													
Ph	(59)													
		1. KOH, MeOH, 30 min 2. PhI(OAc) ₂ , rt, overnight 3. 6N HCl, rt, 12-14 h	<table border="1"> <thead> <tr> <th>R</th> <th>Yield (%)</th> </tr> </thead> <tbody> <tr> <td>Me</td> <td>(66)</td> </tr> <tr> <td>2-thienyl</td> <td>(45)</td> </tr> <tr> <td>2-pyridyl</td> <td>(44)</td> </tr> <tr> <td>Ph</td> <td>(46)</td> </tr> </tbody> </table>	R	Yield (%)	Me	(66)	2-thienyl	(45)	2-pyridyl	(44)	Ph	(46)	226
R	Yield (%)													
Me	(66)													
2-thienyl	(45)													
2-pyridyl	(44)													
Ph	(46)													
		1. LDA, THF, -78°, 30 min 2. (+)-CSO, -78 to 0°, 15 min	(55) <i>R</i> 32% ee	278										
C ₈		1. LDA, THF, -78°, 1 h 2. DMDO, inverse addition, -78°, 30 min	(77)	112										
		1. (PhIO) _n , NaOH, MeOH, 10° 2. H ₃ O ⁺	I (54)	139, 498										
		1. <i>o</i> -HO ₂ CC ₆ H ₄ IO, NaOH, MeOH, rt, 16 h 2. 5% H ₂ SO ₄ , CHCl ₃	I (65)	227, 499										

TABLE 2A. α -HYDROXYLATION OF ACYCLIC KETONE ENOLATES (Continued)

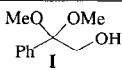
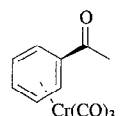
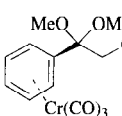
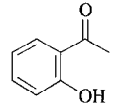
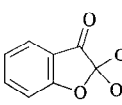
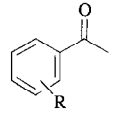
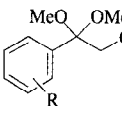
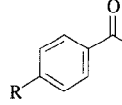
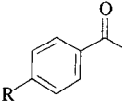
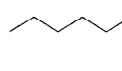
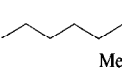
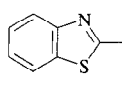
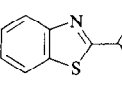
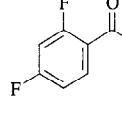
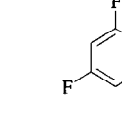
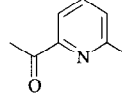
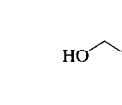
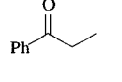
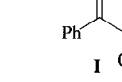
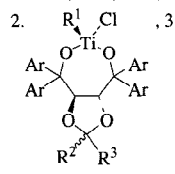
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																																																					
	PhI(OAc) ₂ , KOH, MeOH	 (—)	500																																																					
	<i>o</i> -HO ₂ CC ₆ H ₄ IO, NaOH, MeOH, rt, 16 h	I (81)	227, 499																																																					
	1. KOH, MeOH, 30 min 2. PhI(OAc) ₂ , rt, overnight	 (60)	228, 240																																																					
	PhI(OAc) ₂ , KOH, MeOH	 (20)	356, 501																																																					
	PhI(OAc) ₂ , KOH, MeOH	 $\frac{R}{3-NH_2}$ (35) $\frac{R}{4-NH_2}$ (29)	222																																																					
	1. (PhIO) _n , NaOH, MeOH, 10° 2. H ₃ O ⁺	 $\frac{R}{F}$ (70) $\frac{R}{Cl}$ (63) $\frac{R}{Br}$ (70) $\frac{R}{I}$ (71) $\frac{R}{NO_2}$ (48) $\frac{R}{Me}$ (45) $\frac{R}{MeO}$ (50)	498																																																					
	— 2c, KOH, KI, MeOH	 (71)	191																																																					
	1. KOH, MeOH, 30 min 2. PhI(OAc) ₂ , rt, overnight 3. 6N HCl, rt, 12-14 h	 (45)	226																																																					
	1. TeO ₂ , THF, -78° 2. NaHMDS 3. (-)-DCCSO 4. NH ₄ Cl, H ₂ O, to rt	 (82) <i>R</i> 93% ee	502, 503																																																					
	1. NaHMDS, THF, -65 to -60° 2. (-)-CSO, -90 to -85°	I (80) <i>R</i> 70% ee	503																																																					
	1. (PhIO) _n , NaOH, MeOH 2. H ₃ O ⁺	 (63)	498																																																					
	1. LDA, THF 2. Cp ₂ TiCl ₂ 3. DMDO	 (77)	111																																																					
	1. LDA, THF, -78°, 30 min 2.  , 3 h	I	261																																																					
	3. Oxidant 4. NH ₄ F, H ₂ O, 12 h	<table border="1"> <thead> <tr> <th>R¹</th> <th>R²</th> <th>R³</th> <th>Ar</th> <th>Oxidant</th> <th>% ee</th> </tr> </thead> <tbody> <tr> <td>Cp</td> <td>Me</td> <td>Me</td> <td>Ph</td> <td>DMDO (39)^a</td> <td><i>R</i> 43</td> </tr> <tr> <td>Cp</td> <td>Me</td> <td>Me</td> <td>Ph</td> <td>PSPO (35)^a</td> <td><i>R</i> 14</td> </tr> <tr> <td>C₅H₄TMSMe</td> <td>Me</td> <td>Me</td> <td>Ph</td> <td>DMDO (41)^a</td> <td><i>R</i> 38</td> </tr> <tr> <td>C₅H₄TMSMe</td> <td>Me</td> <td>Me</td> <td>Ph</td> <td>PSPO (25)^a</td> <td><i>S</i> 12</td> </tr> <tr> <td>O<i>Pr</i>-<i>i</i></td> <td>Me</td> <td>Me</td> <td>Ph</td> <td>DMDO (24)^a</td> <td><i>S</i> 5</td> </tr> <tr> <td>Cp</td> <td>H</td> <td>Bu-<i>t</i></td> <td>Ph</td> <td>DMDO (39)^a</td> <td><i>R</i> 13</td> </tr> <tr> <td>Cp</td> <td>H</td> <td>Bu-<i>t</i></td> <td>Ph</td> <td>PSPO (25)^a</td> <td><i>R</i> 3</td> </tr> <tr> <td>Cp</td> <td>Me</td> <td>Me</td> <td>1-C₁₀H₇</td> <td>DMDO (20)^a</td> <td><i>R</i> 63</td> </tr> </tbody> </table>	R ¹	R ²	R ³	Ar	Oxidant	% ee	Cp	Me	Me	Ph	DMDO (39) ^a	<i>R</i> 43	Cp	Me	Me	Ph	PSPO (35) ^a	<i>R</i> 14	C ₅ H ₄ TMSMe	Me	Me	Ph	DMDO (41) ^a	<i>R</i> 38	C ₅ H ₄ TMSMe	Me	Me	Ph	PSPO (25) ^a	<i>S</i> 12	O <i>Pr</i> - <i>i</i>	Me	Me	Ph	DMDO (24) ^a	<i>S</i> 5	Cp	H	Bu- <i>t</i>	Ph	DMDO (39) ^a	<i>R</i> 13	Cp	H	Bu- <i>t</i>	Ph	PSPO (25) ^a	<i>R</i> 3	Cp	Me	Me	1-C ₁₀ H ₇	DMDO (20) ^a	<i>R</i> 63
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	1. (PhIO) _n , OH ⁻ , MeOH 2. H ₃ O ⁺	I (—)	498																																																					
	1. <i>o</i> -HO ₂ CC ₆ H ₄ IO, KOH, MeOH, rt, 16 h 2. 5% H ₂ SO ₄ , CHCl ₃	I (59)	227																																																					

TABLE 2A. α -HYDROXYLATION OF ACYCLIC KETONE ENOLATES (Continued)

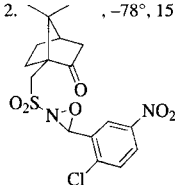
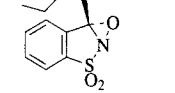
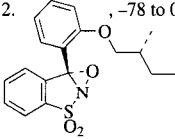
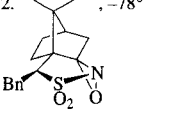
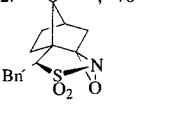
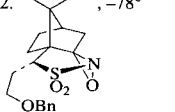
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. NaHMDS, THF, -78° , 15-20 min 2. (+)-CSO, -78° , 15 min	I (77) <i>S</i> 69% ee	504, 174, 278, 505
	1. LDA, THF, -78° , 15-20 min 2. (+)-CSO, -78° to 0° , 15 min	I (51) <i>S</i> 43% ee	504, 174, 505
	1. NaHMDS, THF, -78° , 15-20 min 2. (-)-CSO, -78° , 15 min	I (80) <i>R</i> 65% ee	504, 174, 506
	1. NaHMDS, THF, -78° , 30 min 2. (+)-DFCSO, -78° , 15 min	I (71) <i>S</i> 94% ee	278
	1. NaHMDS, THF, -78° , 30 min 2. (+)-DCCSO, -78° , 15 min	I (70) <i>S</i> 95% ee	278, 492
	1. NaHMDS, THF, -78° , 30 min 2. (-)-DCCSO, -78° , 15 min	I (65) <i>R</i> 93% ee	278, 506
	1. NaHMDS, THF, -78° , 30 min 2. (+)-DBCOS, -78° , 15 min	I (51) <i>S</i> 90% ee	278
	1. NaHMDS, THF, -78° , 30 min 2. (+)-TCCSO, -78° , 15 min	I (45) <i>S</i> 8% ee	278
	1. NaHMDS, THF 2. (+)-DMCSO, -78°	I (73) <i>S</i> 79% ee	507
	1. NaHMDS, THF, -78° , 15-20 min 2.  , -78° , 15 min	I (62) <i>R</i> 28% ee	504
	1. LDA, THF 2.  , -78 to 0° , 1.5 h	I (40) <i>R</i> 60% ee	508
	1. LDA, THF 2.  , -78 to 0° , 1.5 h	I (45) <i>R</i> 81% ee	508
	1. NaHMDS, THF 2.  , -78°	I (50) <i>R</i> 83% ee	509
	1. NaHMDS, THF 2.  , -78°	I (54) <i>R</i> 61% ee	509
	1. NaHMDS, THF 2.  , -78°	I (82) <i>S</i> 42% ee	509

TABLE 2A. α -HYDROXYLATION OF ACYCLIC KETONE ENOLATES (Continued)


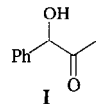
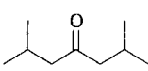
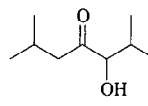
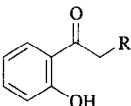
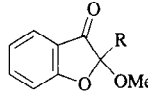
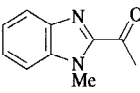
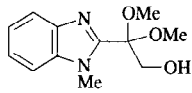


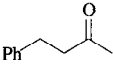

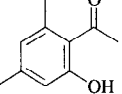
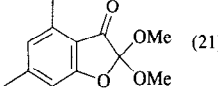
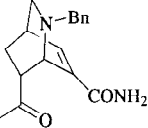

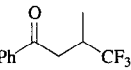
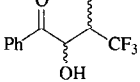
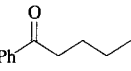
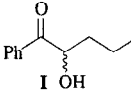
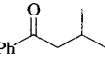
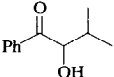
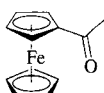
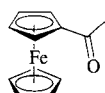
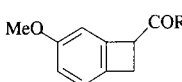
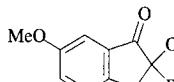

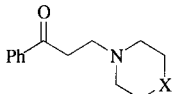
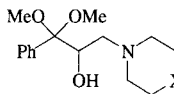
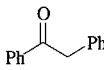
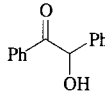
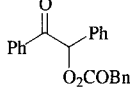
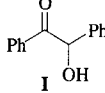
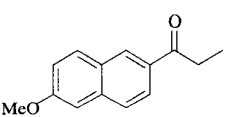
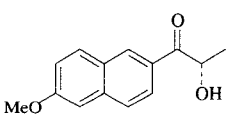
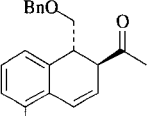
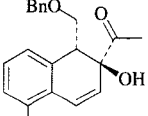
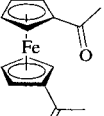
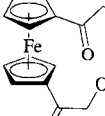
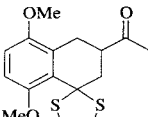
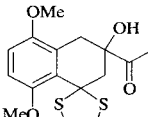
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. NaHMDS, THF, -10° , 60 min 2. DMDO, -78° , 2 min	 (74)	110
	1. NaHMDS, THF, HMPA, -78° , 30 min 2. (+)-CSO, -78° , 15 min	I (76) <i>R</i> 76% ee	174
	1. NaHMDS, THF, -78° , 30 min 2. (+)-CSO, -78° , 15 min	I (70) <i>S</i> 40% ee	174, 505
	1. LDA, Et ₂ O 2. TiCl ₂ (OPr- <i>i</i>) ₂ 3. LiO ₂ Bu- <i>t</i> , 0°, 1.75 h	 (40)	279
	1. NaHMDS, THF, -78° , 30 min 2. (+)-CSO, -78° , 15 min	 $\frac{\text{R}}{\text{Me (35)}}$ Bn (40)	356
	1. KOH, MeOH, 30 min 2. PhI(OAc) ₂ , rt, overnight	 (65)	224
	1. LDA, THF 2. MoOPH, -22°	 (65)	482
	1. <i>i</i> -Pr ₂ MgBr, Et ₂ O, 0°, 12 h 2. (TMSO) ₂ , -78° to rt, 2 h 3. NH ₄ Cl	 (42)	44
	PhI(OAc) ₂ , KOH, MeOH	 (21)	356
	O ₂ , KOBu- <i>t</i> , HOBU- <i>t</i> , P(OEt) ₃ , monoglyme, -20°	 (96)	202, 201
	1. LDA 2. MoOPH	 (58) >98% dc	510
	1. LDA, -78° , 15 min 2. MoOPH, reverse addition, -22°	 (70)	40, 482
	1. LDA, -78° , 15 min 2. MoOPH, -22°	I (60)	40, 482, 511
	1. NaHMDS, THF, -78° , 30 min 2. (+)-CSO, -78° , 15 min	I (73) <i>S</i> 53% ee	278
	1. NaHMDS, THF, -78° , 30 min 2. (+)-DCCSO, -78° , 15 min	I (76) <i>S</i> 95% ee	278
	1. KHMDS, THF 2. PSPO, -78°	I (75)	511
	1. LDA, -78° , 15 min 2. MoOPH, -22°	 (65)	40, 151

TABLE 2A. α -HYDROXYLATION OF ACYCLIC KETONE ENOLATES (Continued)

	Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₁₂		1. (PhIO) _n , OH ⁻ , MeOH 2. H ₃ O ⁺	 (—)	498
C ₁₂₋₁₉		LDA, MoOPH	 R Et (48) <i>i</i> -Pr (93) <i>t</i> -Bu (97) Ph (91) 4-MeOC ₆ H ₄ (CH ₂) ₂ (93)  (76)	283
C ₁₃₋₁₄		1. KOH, MeOH, 30 min 2. PhI(OAc) ₂ , rt, overnight	 X — (24) O (60) S (65) CH ₂ (55)	224 224, 222 224, 222 224, 222
C ₁₄		1. NaHMDS, THF, -10°, 60 min 2. DMDO, -78°, 2 min	 (92)	110, 111
		1. KHMDS, THF, -78°, 30 min 2. (BnOCO ₂) ₂ , -78°, 30 min	 (70)	347
		1. LDA, -78° 2. MoOPH, -30°	 (50) I	152, 40, 151, 511
		1. (PhIO) _n , OH ⁻ , MeOH 2. H ₃ O ⁺	I (—)	498
		1. KHMDS, THF 2. PSPO	I (75)	511
		1. NaHMDS, THF, -78°, 15-20 min 2. (+)-CSO, -78°, 15 min	I (84) <i>S</i> 95% ee	504, 174, 278, 512
		1. NaHMDS, THF, -78°, 15-20 min 2. (-)-CSO, -78°, 15 min	I (88) <i>R</i> 95% ee	504, 278, 505
		1. NaHMDS, THF, -78°, 15-20 min 2. (+)-DCCSO, -78°, 15 min	I (70) <i>S</i> 40% ee	278
		1. NaHMDS, THF, -78°, 30 min 2. (+)-DCCSO, -78°, 15 min	 (56) <i>S</i> >95% ee	278
		1. NaHMDS, THF, -78°, 30 min 2. PSPO, -78°, 40 min	 (54)	281
		1. (PhIO) _n , NaOH, MeOH 2. H ₃ O ⁺	 (—)	498
		1. KO <i>Bu-t</i> , HO <i>Bu-t</i> , DMF, P(OEt) ₃ , -50° 2. O ₂ , 15 min	 (65)	199

74

75

TABLE 2A. α -HYDROXYLATION OF ACYCLIC KETONE ENOLATES (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.												
	O ₂ , KOBu- <i>t</i> , DMF, THF, P(OMe) ₃ , -23°, 14 min	(70)	513												
	O ₂ , KOBu- <i>t</i> , DMF, THF, P(OMe) ₃ , -23°, 14 min	(70)	513												
	1. KOH, MeOH, 30 min 2. PhI(OAc) ₂ , rt, overnight	(44)	224												
	1. (PhIO) _n , OH ⁻ , MeOH 2. H ₃ O ⁺	(-)	498												
	1. NaHMDS, THF, -78°, 30 min 2. (+)-CSO, -78 to 0°, 30 min	(62) <i>S</i> 21% ee	174												
	1. LDA, THF, HMPA, -78°, 30 min 2. (+)-CSO, -78°, 30 min	I (57) <i>R</i> 20% ee	174												
	1. LDA, THF, -78° 2. MoOPH, -78°, 1 h	(47)	232, 514												
	(PhIO) _n , KOH, MeOH, rt, 48 h	(17)	514												
	1. Base (thermodynamic enolate) 2. PSPO or MoOPH	(0)	515												
	1. KOH, MeOH, C ₆ H ₆ , rt, 30 min 2. PhI(OAc) ₂ , rt, 25 h 3. HCl, H ₂ O	I + II	516												
			<table border="1"> <thead> <tr> <th>R</th> <th>I</th> <th>II</th> </tr> </thead> <tbody> <tr> <td>H</td> <td>(25)</td> <td>(0)</td> </tr> <tr> <td>Me</td> <td>(35)</td> <td>(0)</td> </tr> <tr> <td>Ph</td> <td>(37)</td> <td>(10)</td> </tr> </tbody> </table>	R	I	II	H	(25)	(0)	Me	(35)	(0)	Ph	(37)	(10)
R	I	II													
H	(25)	(0)													
Me	(35)	(0)													
Ph	(37)	(10)													
	1. KHMDS, THF 2. [O]	R [O] H (+)-CSO (47) TBDMS PSPO (17)	241												

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C₁₅C₁₇C₁₇₋₂₃C₁₈

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TABLE 2A. α -HYDROXYLATION OF ACYCLIC KETONE ENOLATES (Continued)

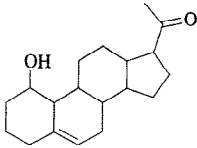
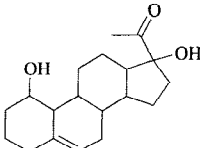
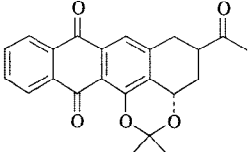
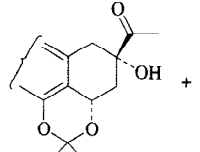
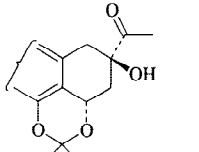
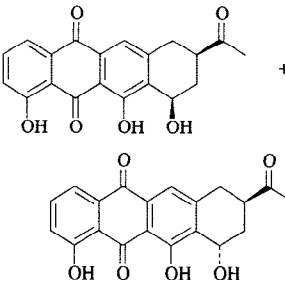
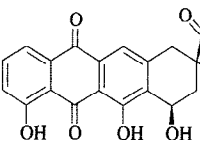
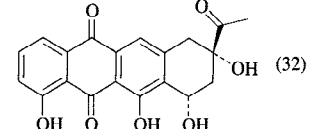
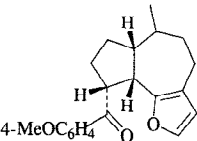
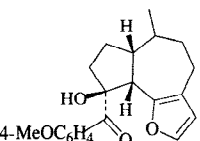
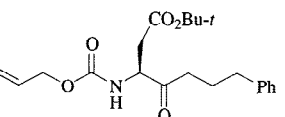
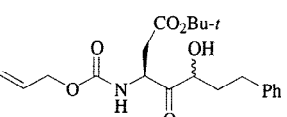
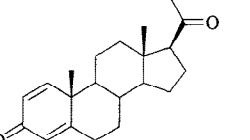
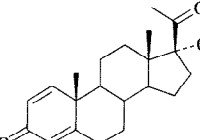
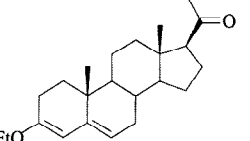
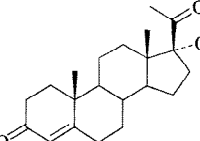
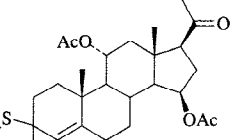
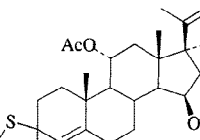
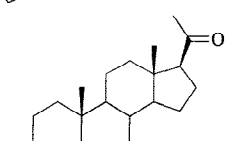
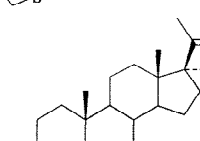

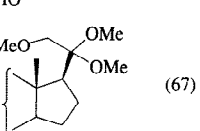
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₁₉ 	1. KHMDS, THF 2. PSPO	 (53)	511
C ₂₀ 	O ₂ , KOBu- <i>t</i> , HOBu- <i>t</i> , THF, P(OMe) ₃ , -23°	 (26) +  (51)	517
78 	O ₂ , KOBu- <i>t</i> , HOBu- <i>t</i> , THF, P(OMe) ₃ , -23°	 (11) +  (32)	196
C ₂₁ 	1. LDA 2. MoOPH	 (60)	518
	1. LiHMDS, THF, -20°, 2 h 2. PSPO, -78°, 8 h	 (59)	519
	1. O ₂ , NaOBu- <i>t</i> , HOBu- <i>t</i> , DMF, P(OEt) ₃ , -20°, 45 min 2. HOAc	 (18)	55
	1. O ₂ , KOBu- <i>t</i> , HOBu- <i>t</i> , 30 min 2. Zn, HOAc, rt, 2.5 h	 (23)	6
	1. NaH, DMF, HOBu- <i>t</i> , -25° 2. O ₂ , P(OEt) ₃ , -25°, 1 h	 (—)	200
	1. KO ₂ , O ₂ , C ₆ H ₆ , THF, 18-crown-6, 6-7°, 2.75 h 2. PPh ₃ , CH ₂ Cl ₂	 (64)	62
	(PhIO) _n , KOH, MeOH	 (67)	251

TABLE 2A. α -HYDROXYLATION OF ACYCLIC KETONE ENOLATES (Continued)

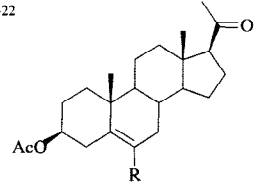
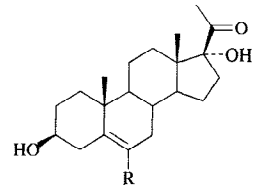
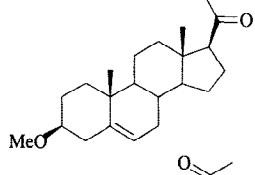
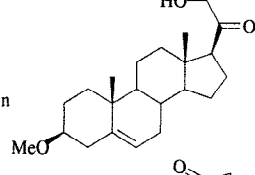
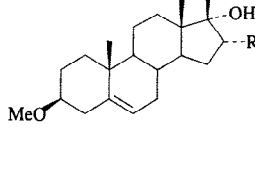
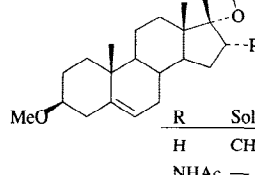
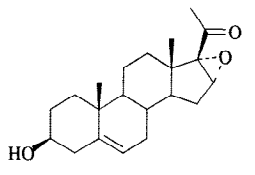
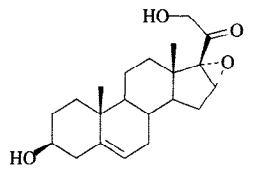
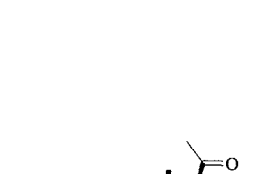
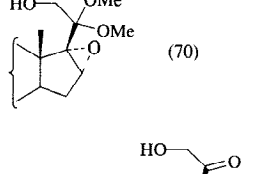
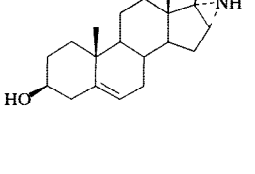
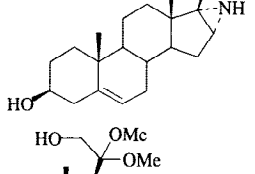
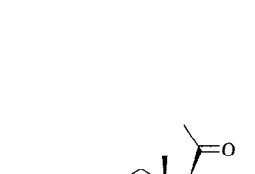
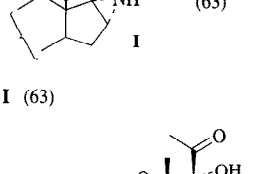
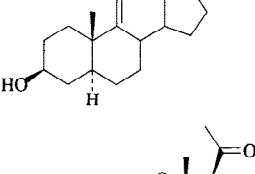
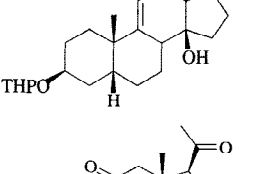
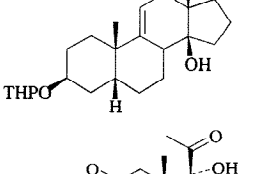
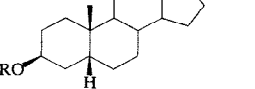
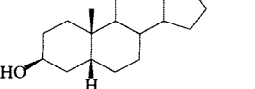


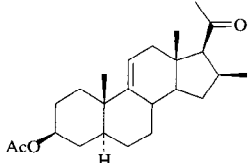
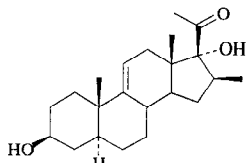
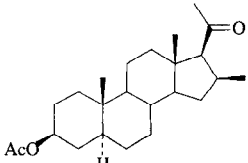
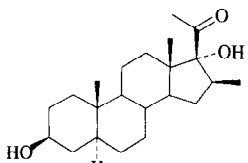
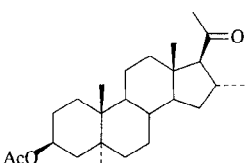
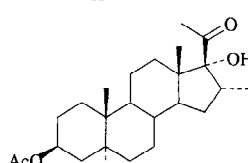
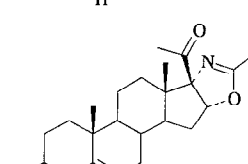
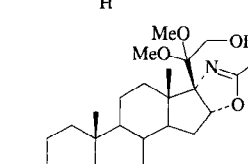
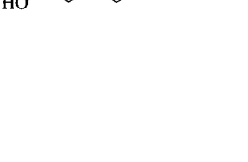
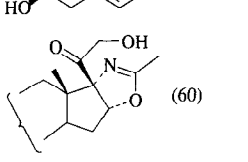
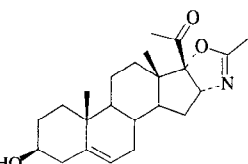
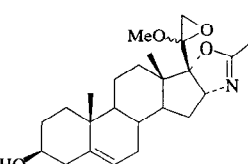

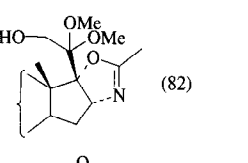
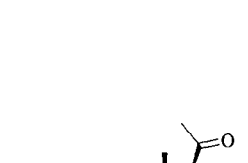
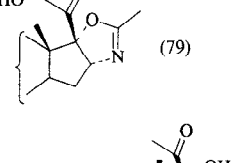
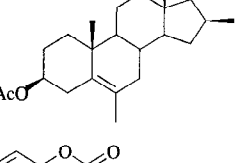
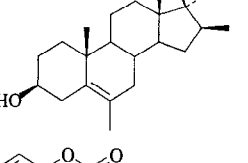
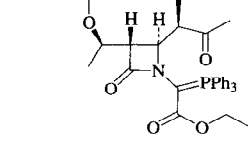
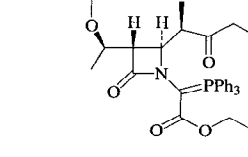
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.									
C ₂₁₋₂₂ 	KOBu- <i>t</i> , O ₂ , <i>t</i> -BuOH, DMF, P(OEt) ₃ , -25°, time	 <table border="1"> <thead> <tr> <th>R</th> <th>Time</th> </tr> </thead> <tbody> <tr> <td>H</td> <td>2.5 h (67)</td> </tr> <tr> <td>Me</td> <td>22 h (63)</td> </tr> </tbody> </table>	R	Time	H	2.5 h (67)	Me	22 h (63)	55			
R	Time											
H	2.5 h (67)											
Me	22 h (63)											
C ₂₁ 	1. LDA, THF, -22°, 10 min 2. MoOPH, reverse addition, -22°, 5 min	 (20-58)	40									
	PhI(OAc) ₂ , KOH, MeOH, 20°	 <table border="1"> <thead> <tr> <th>R</th> <th>Solv</th> <th>Time</th> </tr> </thead> <tbody> <tr> <td>H</td> <td>CH₂Cl₂</td> <td>5 h (70)</td> </tr> <tr> <td>NHAc</td> <td>—</td> <td>40 min (70-80)</td> </tr> </tbody> </table>	R	Solv	Time	H	CH ₂ Cl ₂	5 h (70)	NHAc	—	40 min (70-80)	358, 520 521, 520
R	Solv	Time										
H	CH ₂ Cl ₂	5 h (70)										
NHAc	—	40 min (70-80)										
	1. PhI(OAc) ₂ , NaOH, MeOH, 20°, 3 h 2. TsOH, acetone, 20°, 90 min	 (63)	221									
	PhI(OAc) ₂ , NaOH, MeOH, 20°, 2-3 h	 (70)	221									
	1. PhI(OAc) ₂ , NaOH, MeOH, 20°, 2 h 2. Tartaric acid, EtOH, reflux, 2.5 h 3. 5% HCl, MeOH, H ₂ O, reflux, 5 min	 (45)	221									
	(PhIO) _n , NaOH, MeOH, 20°, 2 h	 (63)	220									
	PhI(OAc) ₂ , NaOH, MeOH, 20°, 2-3 h	I (63)	221, 220									
	1. O ₂ , KOBu- <i>t</i> , HOBU- <i>t</i> , 18 min 2. Zn, HOAc	 (24)	6									
	1. LDA, THF, HMPA, -78°, 30 min 2. MoOPH, -78 to -10°	 (27)	522									
	1. O ₂ , KOBu- <i>t</i> , HOBU- <i>t</i> , 25 min 2. Zn, HOAc, 4.25 h	 <table border="1"> <thead> <tr> <th>R</th> </tr> </thead> <tbody> <tr> <td>H (22)</td> </tr> <tr> <td>Ac (38)</td> </tr> </tbody> </table>	R	H (22)	Ac (38)	6						
R												
H (22)												
Ac (38)												

TABLE 2A. α -HYDROXYLATION OF ACYCLIC KETONE ENOLATES (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. O ₂ , KOBu- <i>t</i> , HOBu- <i>t</i> , time 2. Zn, HOAc, 4 h	 R Time H 10 min (39) 6 Ac 20 min (38)	
	1. O ₂ , KOBu- <i>t</i> , HOBu- <i>t</i> , 45 min 2. Zn, HOAc	(26)	6
	1. O ₂ , KO ₂ , C ₆ H ₆ , THF, 18-crown-6, 6-7°, 2.75 h 2. PPh ₃ , CH ₂ Cl ₂	(72)	62
	1. O ₂ , NaOBu- <i>t</i> , HOBu- <i>t</i> , DMF, (POEt) ₃ , -25°, 45 min 2. NaOH, MeOH, H ₂ O 3. HOAc	(67)	55, 6
	1. O ₂ , KOBu- <i>t</i> , HOBu- <i>t</i> , 45 min 2. Zn, HOAc		6
	1. LDA, THF, HMPA 2. MoOPH		252
	1. O ₂ , KOBu- <i>t</i> , HOBu- <i>t</i> , THF, P(OMe) ₃ , -23°, 15 min 2. TsOH, CH ₂ Cl ₂ , H ₂ O, rt, 30 min		513
	1. O ₂ , KOBu- <i>t</i> , HOBu- <i>t</i> , THF, 0°, 15 min 2. Zn, HOAc	(9)	52
	1. O ₂ , NaOBu- <i>t</i> , HOBu- <i>t</i> , DMF, P(OEt) ₃ , -25°, 2.5 h 2. NaOH, MeOH, H ₂ O 3. HOAc	(63)	55
	1. KOH, MeOH, CH ₂ Cl ₂ , 20°, 30 min 2. PhI(OAc) ₂ , 4.5 h	(75)	358, 520

TABLE 2A. α -HYDROXYLATION OF ACYCLIC KETONE ENOLATES (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. O ₂ , NaOBu- <i>t</i> , HOBu- <i>t</i> , 10 min 2. Zn, HOAc, rt, 4.25 h	 (46)	6
	1. O ₂ , NaOBu- <i>t</i> , HOBu- <i>t</i> , DMF, P(OEt) ₃ , -25°, 45 min 2. NaOH, MeOH, H ₂ O 3. HOAc	 (62)	55, 6
	1. O ₂ , NaOBu- <i>t</i> , HOBu- <i>t</i> , DMF, P(OEt) ₃ , -25°, 45 min 2. NaOH, MeOH, H ₂ O 3. HOAc 4. Ac ₂ O, pyridine	 (1)	55
	PhI(OAc) ₂ , NaOH, MeOH, 20°, 3.5 h	 (60)	221
	1. PhI(OAc) ₂ , NaOH, MeOH, 20°, 3.5 h 2. HCl (conc.), MeOH, reflux, 3 h	 (60)	221
	PhI(OAc) ₂ , NaOH, MeOH, 20°, 7 h	 (80)	221, 523
	PhI(OAc) ₂ , NaOH, MeOH, 20°, 120 h	 (82)	221, 523
	1. PhI(OAc) ₂ , NaOH, MeOH, 20°, 7 h 2. HCl (conc.), dioxane, 20°, 1 h	 (79)	221, 523
	1. O ₂ , NaOBu- <i>t</i> , HOBu- <i>t</i> , DMF, P(OEt) ₃ , -25°, 22 h 2. NaOH, MeOH, H ₂ O 3. HOAc	 (65)	55
	1. LDA, THF, -78°, 30 sec 2. MoOPH, -78 to -30°, 1 h	 (58)	524

^a The number is the conversion.

TABLE 2B. α -HYDROXYLATION OF CYCLIC KETONE ENOLATES


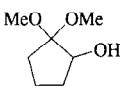
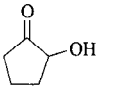

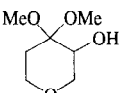

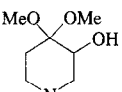
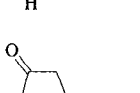
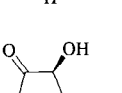

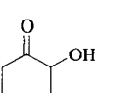
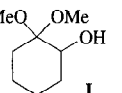
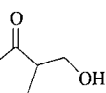
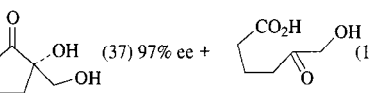

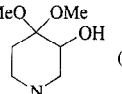

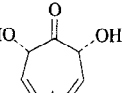
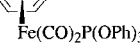
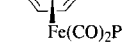

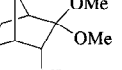
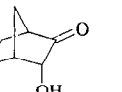
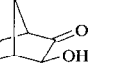
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₅ 	<i>o</i> -HO ₂ CC ₆ H ₄ IO, KOH, MeOH, rt, 16 h	 (78)	227
	1. <i>o</i> -HO ₂ CC ₆ H ₄ IO, KOH, MeOH, rt, 16 h 2. 5% H ₂ SO ₄ , CHCl ₃	 (63)	227
	-2e, KOH, KI, MeOH	 (74)	191
	PhI(OAc) ₂ , KOH, MeOH	 (42)	222, 219
C ₆ 	1. NaHMDS, THF 2. MoOPH, -78 to -23°	 (80)	274
		1. LDA, Et ₂ O 2. Ti(OPr- <i>i</i>) ₄ 3. <i>t</i> -BuO ₂ H, -78° to rt, 1.75 h	 (53 GC)
	1. LDA, LiBr, Et ₂ O, 0° to rt 2. (TMSO) ₂ , rt, 12 h 3. NH ₄ Cl	I I (54)	44
	PhI(OAc) ₂ , NaOH, MeOH	I (80)	525, 526
	1. <i>o</i> -HO ₂ CC ₆ H ₄ IO, KOH, MeOH, rt, 16 h 2. 5% H ₂ SO ₄ , CHCl ₃	I (60)	227
	<i>o</i> -HO ₂ CC ₆ H ₄ IO, KOH, MeOH, rt, 16 h	 (75)	227
	-2e, KOH, KI, MeOH	I (64)	191
	<i>t</i> -BuO ₂ H, (+) diethyl tartrate, Ti(OPr- <i>i</i>) ₄ , -20°, 46 h	 (37) 97% ee + (12)	263
	PhI(OAc) ₂ , KOH, MeOH	 (54)	222, 225
C ₇ 	1. KHMDS (2.2 eq), -100° 2. PSPO (4 eq)	 (67)	285
			
	<i>o</i> -HO ₂ CC ₆ H ₄ IO, KOH, MeOH, rt, 16 h	 (47)	227
	1. <i>o</i> -HO ₂ CC ₆ H ₄ IO, KOH, MeOH, rt, 16 h 2. 5% H ₂ SO ₄ , CHCl ₃	 (16)	227
	1. KHMDS, THF, -80° 2. PSPO	 (100)	527

TABLE 2B. α -HYDROXYLATION OF CYCLIC KETONE ENOLATES (Continued)









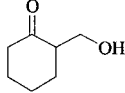


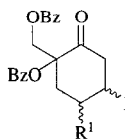
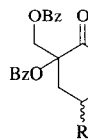
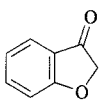
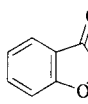
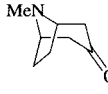


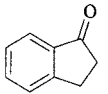

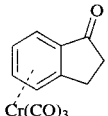
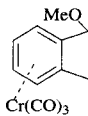
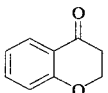

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. <i>i</i> -Pr ₂ NMgBr, Et ₂ O, 0°, 12 h 2. (TMSO) ₂ , -78° to rt, 2 h 3. NH ₄ Cl	 (61) I	44
	1. <i>o</i> -HO ₂ CC ₆ H ₄ IO, KOH, MeOH, rt, 16 h 2. 5% H ₂ SO ₄ , CHCl ₃	I (43) +  (7)	227
	<i>o</i> -HO ₂ CC ₆ H ₄ IO, KOH, MeOH, rt, 16 h	 (53) +  (9) I (53) II (9)	227
	-2 e, KOH, KI, MeOH	I (63) + II (14)	191
	1. <i>o</i> -HO ₂ CC ₆ H ₄ IO, KOH, MeOH, rt, 16 h 2. 5% H ₂ SO ₄ , CHCl ₃	 (44) I	227
	1. NaHMDS, THF, -78°, 30 min 2. (+)-CSO, -78°, 15-20 min	I (71) <i>R</i> 89% ee	278, 174, 505
	1. NaHMDS, THF, -78°, 30 min 2. (+)-DCCSO, -78°, 15-20 min	I (42) <i>R</i> 13% ee	278
	<i>o</i> -HO ₂ CC ₆ H ₄ IO, KOH, MeOH, rt, 16 h	 (68) I (63) + II (14)	227
	<i>t</i> -BuO ₂ H, (+) diethyl tartrate, Ti(OPr- <i>i</i>) ₄ , -20°, 46 h	 (58) 86% ee +  (8)	263
	1. LDA, THF, -70°, 30 min 2. MoOPH, -70 to -30°, 90 min	 (64) R ¹ R ² H H (64) Me H (—) H Me (—)	528
	PhI(OAc) ₂ , KOH, MeOH	 (50)	356
	1. LDA 2. O ₂	 (0) I	222, 529
	1. PhI(OAc) ₂ , KOH, MeOH 2. 3N HCl	I (21)	529
	PhI(OAc) ₂ , KOH, MeOH	 (33-35) I (21)	529
	1. LDA, THF, 2. Cp ₂ TiCl ₂ 3. DMDO	 (70)	111
	1. KOH, MeOH, 0°, 10 min 2. PhI(OAc) ₂ , 0°, 4-5 h, then rt, 16 h	 (80) I (21)	228, 530
	1. NaOH, MeOH, 0°, 5 min 2. PhI(OAc) ₂ , 0°, 1 h, then rt, 16 h 3. 3N HCl, EtOH, rt, 30 min	 (—)	531

TABLE 2B. α -HYDROXYLATION OF CYCLIC KETONE ENOLATES (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																																					
	1. NaOH, MeOH, 0°, 10 min 2. PhI(OAc) ₂ , 0°, 1 h; rt, 16 h	 (72)	531																																					
	1. NaOH, MeOH, 0°, 10 min 2. PhI(OAc) ₂ , 0°, 1 h; rt, 16 h	 (82)	532																																					
	1. LDA, THF, -78°, 1 h 2. MoOPH, -78°, 1 h	 (56)	533, 534																																					
	1. NaHMDS 2. PSPO	 (80)	535																																					
	1. NaHMDS 2. PSPO	 (75) + (8)	535																																					
	1. LDA, THF, -78° 2. MoOPH	 (0)	536																																					
	PhI(OAc) ₂ , KOH, MeOH, 0 to 5°, 2 h; 23-25°, 15 h	 (40)	223																																					
	PhI(OAc) ₂ , KOH, MeOH, 0 to 5°, 2 h 23-25°, 15 h	 (20)	223, 219																																					
C ₉₋₁₂ 	Air, , NaOH, P(OEt) ₃ , toluene, H ₂ O, -20 to 6°, 24 h	 (n) R	<table border="1"> <thead> <tr> <th>n</th> <th>R</th> <th>Yield (%)</th> <th>ee (%)</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>H</td> <td>(0)^a</td> <td>—</td> </tr> <tr> <td>1</td> <td>Me</td> <td>(93)</td> <td>R 52</td> </tr> <tr> <td>1</td> <td>Et</td> <td>(83)</td> <td>R 43</td> </tr> <tr> <td>2</td> <td>Me</td> <td>(89)</td> <td>R 66</td> </tr> <tr> <td>2</td> <td>Et</td> <td>(95)</td> <td>R 67</td> </tr> <tr> <td>2</td> <td>CH₂CH=CH₂</td> <td>(89)</td> <td>S 72</td> </tr> <tr> <td>2</td> <td>CH₂C≡CH</td> <td>(80)</td> <td>S 71</td> </tr> <tr> <td>2</td> <td>Ac</td> <td>(0)</td> <td>—</td> </tr> </tbody> </table>	n	R	Yield (%)	ee (%)	1	H	(0) ^a	—	1	Me	(93)	R 52	1	Et	(83)	R 43	2	Me	(89)	R 66	2	Et	(95)	R 67	2	CH ₂ CH=CH ₂	(89)	S 72	2	CH ₂ C≡CH	(80)	S 71	2	Ac	(0)	—	264
n	R	Yield (%)	ee (%)																																					
1	H	(0) ^a	—																																					
1	Me	(93)	R 52																																					
1	Et	(83)	R 43																																					
2	Me	(89)	R 66																																					
2	Et	(95)	R 67																																					
2	CH ₂ CH=CH ₂	(89)	S 72																																					
2	CH ₂ C≡CH	(80)	S 71																																					
2	Ac	(0)	—																																					
C ₁₀ 	1. LDA, THF, -78°, 1 h 2. DMDO, reverse addition, -78°, 10 min	 (82)	112																																					
	1. LDA, THF, -78°, 1 h 2. MoOPH, -22°	 I (48)	112, 40, 482																																					
	1. KOH, MeOH, 0° 2. PhI(OAc) ₂ , 0-5°, 1 h, then 23-25°, 20 h	 (70)	228, 537																																					
	1. NaHMDS, THF, -78° 2. (+)-CSO 3. Ac ₂ O	 (10) R 40% ee	538																																					
	1. NaHMDS, THF, -78° 2. (+)-DCCSO 3. Ac ₂ O	 I (60) R 81% ee	538																																					

TABLE 2B. α -HYDROXYLATION OF CYCLIC KETONE ENOLATES (Continued)

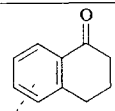
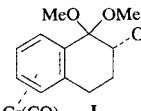
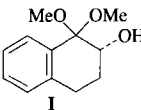
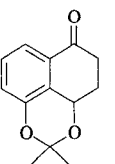
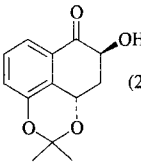
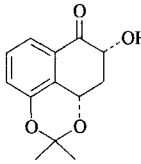
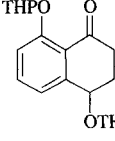
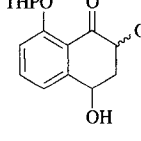
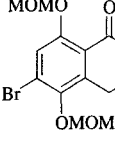
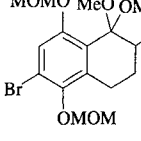
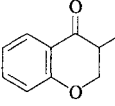
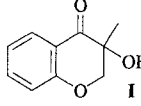
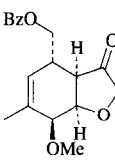
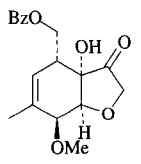
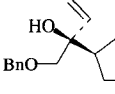
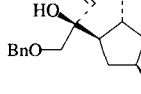
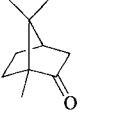
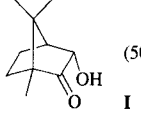
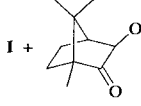
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
 Cr(CO) ₃ (+/-) (+)	1. KOH, MeOH, 0°, 10 min 2. PhI(OAc) ₂ , 0°, 4-5 h; rt, 16 h	 Cr(CO) ₃ I (80) (+/-)	228, 530
(+/-)	1. KOH, MeOH, 0°, 10 min 2. PhI(OAc) ₂ , 0°, 4-5 h; rt, 16 h	I (80) (-)	228, 530
(+)	1. PhI(OAc) ₂ , KOH, MeOH, 0° 2. Sunlight, air	 I	192
	1. KOH, MeOH, 0°, 10 min 2. PhI(OAc) ₂ , 0°, 4-5 h; rt, 16 h 3. Sunlight, Et ₂ O, 16 h	I (72) (-)	228
	1. LDA, THF 2. MoOPH, -25°, 30 min	 (21) +  (7)	539
 THPO OTHP	1. LDA 2. MoOPH	 (-)	539
 MOMO Br OMOM	PhI(OAc) ₂ , KOH, MeOH, 0°	 (-)	540
	1. NaHMDS, THF, -78°, 30 min 2. (+)-CSO, -78°, 30 min	 I (80) <i>R</i> 71% ee	492
	1. LDA, THF, 0°, 30 min 2. (+)-CSO, -78°, 1 h	I (56) <i>S</i> 30% ee	492
	1. NaHMDS, THF, -78°, 30 min 2. (+)-DCCSO, -78°, 30 min	I (77) <i>R</i> 96% ee	492
	1. LDA, THF, 0°, 30 min 2. (+)-DCCSO, -78°, 1 h	I (70) <i>S</i> 64% ee	492
 BzO OMe	1. LDA, -78 to -20°, 30 min 2. PSPO, -78°, 1 h	 (70)	541
 HO BnO	1. LDA, THF, -78°, 30 min 2. MoOPH, -30°, 10 min	 (40)	233
	1. LDA, THF 2. TiCl ₂ (OP <i>r</i> -i) ₂ 3. LiO ₂ Bu- <i>t</i> , 0°, 1.25 h	 (50) I	279
	1. LDA, THF, -78°, 30 min 2. DMDO, -78°, 15 min	I +  II I+II (70); I:II = 25:75	110, 112
	1. NaHMDS, THF, -10°, 60 min 2. DMDO, -78°, 2 min	I+II (57); I:II = 35:65	110, 111

TABLE 2B. α -HYDROXYLATION OF CYCLIC KETONE ENOLATES (Continued)

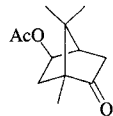
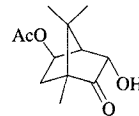
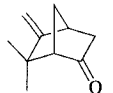
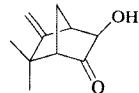
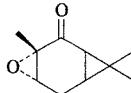
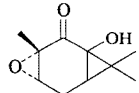
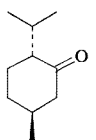
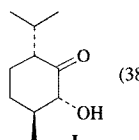
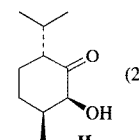
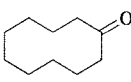
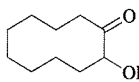
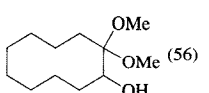
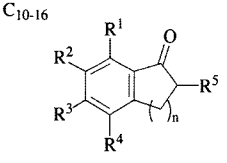
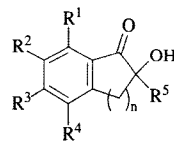
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																																																																								
	1. NaHMDS, THF, -10° , 60 min 2. (<i>i</i> -PrO) ₃ TiCl 3. DMDO	I+II (70); I:II = 1:3	111																																																																								
	1. LDA, THF 2. Cp ₂ TiCl ₂ 2. DMDO	I+II (67); I:II = 8:92	111																																																																								
	1. LDA, -78° 2. MoOPH, -30°	I+II (85); I:II = 5 : 1	152, 40, 112, 482																																																																								
	1. LDA, -78° , 15 min 2. MoOPH, -22°	I (70)	40, 511																																																																								
	1. KHMDS, THF 2. PSPO, -78°	I (85)	511																																																																								
94 	1. Base 2. MoOPH	 (—)	542																																																																								
	MoOPH	 (71)	543																																																																								
	1. LDA 2. O ₂ , (TMSO) ₂ , (PhCO ₂) ₂ , or PSPO	 (0)	544																																																																								
	1. NaHMDS, THF 2. DMDO	 (38) +  (25)	111																																																																								
	1. LDA, THF 2. Cp ₂ TiCl ₂ 3. DMDO	I+II (54); I:II = 96:4	111																																																																								
	1. LDA, -78° 2. MoOPH, -30°	II (74)	152																																																																								
	1. LDA, -78° 2. MoOPD, -30°	II (43)	152																																																																								
	1. <i>o</i> -HO ₂ CC ₆ H ₄ IO, KOH, MeOH, rt, 16 h 2. 5% H ₂ SO ₄ , CHCl ₃	 (40)	227																																																																								
	<i>o</i> -HO ₂ CC ₆ H ₄ IO, KOH, MeOH, rt, 16 h	 (56)	227																																																																								
95 	O ₂ , <i>N</i> -(4-trifluoromethyl)benzyl-cinchoninium bromide, 50% NaOH, (EtO) ₃ P, PhMe, time, rt		265																																																																								
		<table border="1"> <thead> <tr> <th>n</th> <th>R¹</th> <th>R²</th> <th>R³</th> <th>R⁴</th> <th>R⁵</th> <th>Time</th> <th>% ee</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>H</td> <td>H</td> <td>H</td> <td>H</td> <td>Me</td> <td>12 h (94)</td> <td><i>S</i> 73</td> </tr> <tr> <td>2</td> <td>H</td> <td>H</td> <td>H</td> <td>H</td> <td>Me</td> <td>24 h (95)</td> <td><i>S</i> 70</td> </tr> <tr> <td>2</td> <td>H</td> <td>H</td> <td>H</td> <td>H</td> <td>Et</td> <td>24 h (98)</td> <td><i>S</i> 72^b</td> </tr> <tr> <td>2</td> <td>Cl</td> <td>H</td> <td>H</td> <td>MeO</td> <td>Me</td> <td>5 h (95)</td> <td><i>S</i> 79</td> </tr> <tr> <td>2</td> <td>H</td> <td>H</td> <td>H</td> <td>MeO</td> <td>Me</td> <td>4.5 h (98)</td> <td>— 0</td> </tr> <tr> <td>2</td> <td>MeO</td> <td>H</td> <td>H</td> <td>MeO</td> <td>Me</td> <td>24 h (93)</td> <td><i>S</i> 27</td> </tr> <tr> <td>2</td> <td>H</td> <td>H</td> <td>H</td> <td>H</td> <td><i>i</i>-Pr</td> <td>48 h (87)</td> <td><i>R</i> 56</td> </tr> <tr> <td>1</td> <td>Cl</td> <td>Cl</td> <td>MeO</td> <td>H</td> <td>Ph</td> <td>5 h (94)</td> <td><i>R</i> 48</td> </tr> </tbody> </table>	n	R ¹	R ²	R ³	R ⁴	R ⁵	Time	% ee	1	H	H	H	H	Me	12 h (94)	<i>S</i> 73	2	H	H	H	H	Me	24 h (95)	<i>S</i> 70	2	H	H	H	H	Et	24 h (98)	<i>S</i> 72 ^b	2	Cl	H	H	MeO	Me	5 h (95)	<i>S</i> 79	2	H	H	H	MeO	Me	4.5 h (98)	— 0	2	MeO	H	H	MeO	Me	24 h (93)	<i>S</i> 27	2	H	H	H	H	<i>i</i> -Pr	48 h (87)	<i>R</i> 56	1	Cl	Cl	MeO	H	Ph	5 h (94)	<i>R</i> 48	
n	R ¹	R ²	R ³	R ⁴	R ⁵	Time	% ee																																																																				
1	H	H	H	H	Me	12 h (94)	<i>S</i> 73																																																																				
2	H	H	H	H	Me	24 h (95)	<i>S</i> 70																																																																				
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TABLE 2B. α -HYDROXYLATION OF CYCLIC KETONE ENOLATES (Continued)

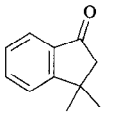
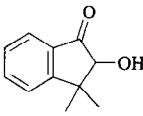
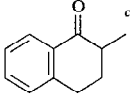
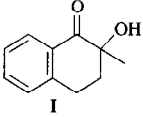
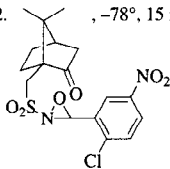
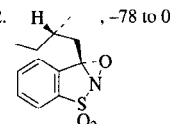
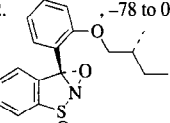
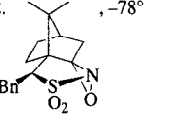
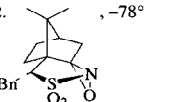
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.									
	1. NaHMDS, THF, -10° , 60 min 2. DMDO, -78° , 2 min	 (80)	110									
	1. LDA, THF, 0° , 30 min 2. (+)-CSO, -78 to 0° , 15 min	 (90) <i>R</i> 30% ee	174, 278, 492, 504									
	1. LDA, PhMe, -78 to 0° , 30 min 2. (+)-CSO, -78° , 15 min	I (41) <i>R</i> 64% ee	174, 278, 504									
	1. NaHMDS, THF, 0° , 30 min 2. (+)-CSO, -78° to 0°	I (90) <i>R</i> 16% ee	174, 278, 492, 504									
	1. NaHMDS, THF, HMPA, 0° , 30 min 2. (+)-CSO, -78° to 0°	I (70) <i>S</i> 22% ee	174, 278, 492, 504									
	1. KHMDS, THF, -78° , 30 min 2. (+)-CSO, -78° , 15 min	I (82) <i>R</i> 7% ee	504									
	1. NaHMDS, THF, 0° , 30 min 2. (+)-DFCSO, -78° to 0°	I (70) <i>R</i> 62% ee	278									
	1. NaHMDS, THF, 0° , 30 min 2. (+)-DCCSO, -78° , 15 min	I (66) <i>R</i> >95% ee	278, 492									
	1. NaHMDS, THF, 0° , 30 min 2. (+)-DBCOS, -78 to 0° , 15 min	I (58) <i>R</i> 80% ee	278									
	1. NaHMDS, THF, 0° , 30 min 2. (+)-TCCSO, -78 to 0° , 15 min	I (0)	278									
	1. NaHMDS, THF 2. (+)-DMCSO, -78° , 15-20 min	I (66) <i>R</i> 36% ee	507									
	1. NaHMDS, THF, -78° , 15-20 min 2.  , -78° , 15 min	I (74) <i>R</i> 24% ee	504									
	1. NaHMDS, THF 2.  , -78 to 0° , 1.5 h	I (21) <i>S</i> 10% ee	508									
	1. LDA, THF 2.  , -78 to 0° , 1.5 h	I (61) <i>S</i> 39% ee	508									
	1. NaHMDS, THF 2.  , -78°	I (61) <i>R</i> 67% ee	509									
	1. Base, THF 2.  , -78°	<table border="1"> <thead> <tr> <th>Base</th> <th></th> <th>% ee</th> </tr> </thead> <tbody> <tr> <td>LDA</td> <td>(45) <i>S</i></td> <td>26</td> </tr> <tr> <td>NaHMDS</td> <td>(64) <i>R</i></td> <td>31</td> </tr> </tbody> </table>	Base		% ee	LDA	(45) <i>S</i>	26	NaHMDS	(64) <i>R</i>	31	509
Base		% ee										
LDA	(45) <i>S</i>	26										
NaHMDS	(64) <i>R</i>	31										

TABLE 2B. α -HYDROXYLATION OF CYCLIC KETONE ENOLATES (Continued)

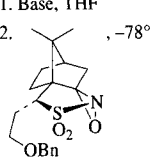
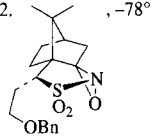
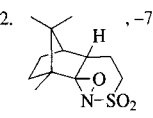
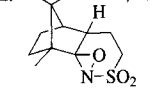
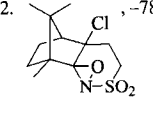
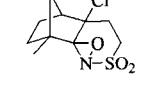
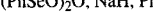
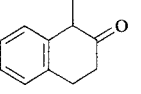
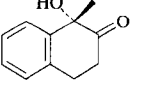
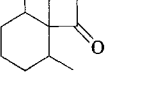
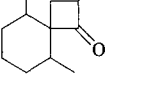
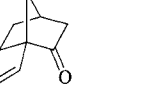
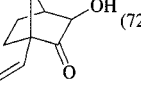
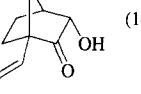
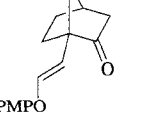
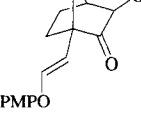
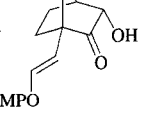
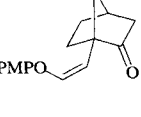
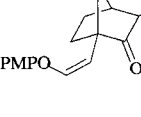
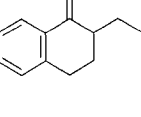
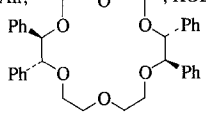
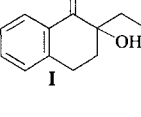

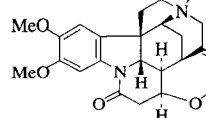
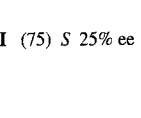

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																
	1. Base, THF 2.  , -78°	<table border="1"> <thead> <tr> <th>Base</th> <th>Yield (%)</th> <th>Configuration</th> <th>% ee</th> </tr> </thead> <tbody> <tr> <td>LDA</td> <td>(63)</td> <td>S</td> <td>21</td> </tr> <tr> <td>NaHMDS</td> <td>(76)</td> <td>R</td> <td>19</td> </tr> </tbody> </table>	Base	Yield (%)	Configuration	% ee	LDA	(63)	S	21	NaHMDS	(76)	R	19	509				
Base	Yield (%)	Configuration	% ee																
LDA	(63)	S	21																
NaHMDS	(76)	R	19																
	1. Base, THF, -78° to rt, 30 min 2.  , -78° to rt, 12 h	<table border="1"> <thead> <tr> <th>Base</th> <th>Yield (%)</th> <th>Configuration</th> <th>% ee</th> </tr> </thead> <tbody> <tr> <td>LDA</td> <td>(44)</td> <td>—</td> <td>0</td> </tr> <tr> <td>NaHMDS</td> <td>(57)</td> <td>R</td> <td>58</td> </tr> <tr> <td>KHMDS</td> <td>(48)</td> <td>—</td> <td>0</td> </tr> </tbody> </table>	Base	Yield (%)	Configuration	% ee	LDA	(44)	—	0	NaHMDS	(57)	R	58	KHMDS	(48)	—	0	545
Base	Yield (%)	Configuration	% ee																
LDA	(44)	—	0																
NaHMDS	(57)	R	58																
KHMDS	(48)	—	0																
	1. Base, THF, -78° to rt, 30 min 2.  , -78° to rt, 12 h	<table border="1"> <thead> <tr> <th>Base</th> <th>Yield (%)</th> <th>Configuration</th> <th>% ee</th> </tr> </thead> <tbody> <tr> <td>LDA</td> <td>(48)</td> <td>—</td> <td>0</td> </tr> <tr> <td>NaHMDS</td> <td>(67)</td> <td>R</td> <td>6</td> </tr> <tr> <td>KHMDS</td> <td>(53)</td> <td>—</td> <td>0</td> </tr> </tbody> </table>	Base	Yield (%)	Configuration	% ee	LDA	(48)	—	0	NaHMDS	(67)	R	6	KHMDS	(53)	—	0	545
Base	Yield (%)	Configuration	% ee																
LDA	(48)	—	0																
NaHMDS	(67)	R	6																
KHMDS	(53)	—	0																
	(PhSeO) ₂ O, NaH, PhMe, reflux, 3.5 h	I (80)	182																
	1. NaHMDS, THF, -78° , 30 min 2. (+)-CSO, -78° , 30 min	 (60) S 76% ee	492																
	1. LDA, -78° , 15 min 2. MoOPH, -22°	 (65)	40, 482																
	1. KHMDS, THF, -78° , 15 min; 0° , 1 h 2. PSPO, -78° , 1 h	 (72) +  (14)	240																
	1. KHMDS, THF, -78 to 0° 2. PSPO, -78° , 2 h	 (60) +  (9)	240																
	1. KHMDS, THF, -78 to 0° 2. PSPO, -78° , 1 h	 (52)	240																
	Air,  , KOBu- <i>t</i> , -78°	 I (—) 33% ee	546																
	Air, "A", NaOH, P(OEt) ₃ , PhMe, H ₂ O  Br ⁺ , CH ₂ C ₆ H ₄ CF ₃	 I (75) S 25% ee	266																
	(PhSeO) ₂ O, NaH, PhMe, reflux, 10 h	I (73)	182																

TABLE 2B. α -HYDROXYLATION OF CYCLIC KETONE ENOLATES (Continued)

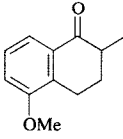
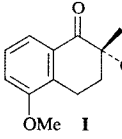
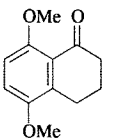
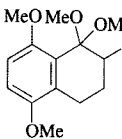
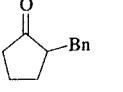
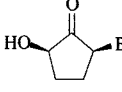
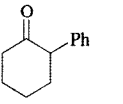
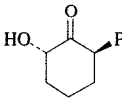
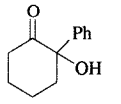
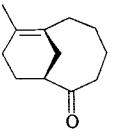
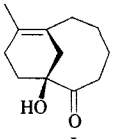
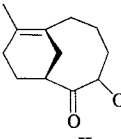
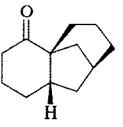
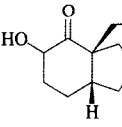
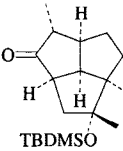
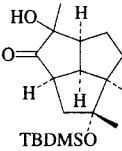
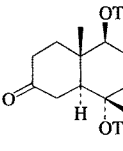
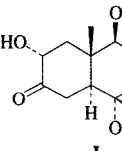
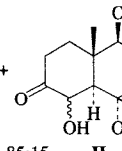
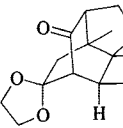
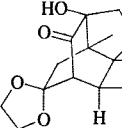
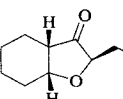
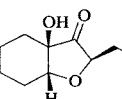
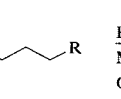
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. NaHMDS, THF, -78° , 30 min 2. (+)-DCCSO, -78° , 1 h	 (62) <i>R</i> >95% ee	492
	1. LDA, THF 2. (+)-DMCSO, 0°	I (66) <i>R</i> 19% ee	507
	1. NaHMDS, THF, -78° , 30 min 2. (+)-CSO, -78° , 1 h	I (68) <i>R</i> 14% ee	492
	PhI(OAc) ₂ , KOH, MeOH, 0° , 3 h	 (—)	137
	1. NaHMDS, THF 2. DMDO	 (37) 6% de	111
	1. LDA, THF 2. Cp ₂ TiCl ₂ 3. DMDO	I (50) 66% de	111
	1. KH, THF, 20° , 20 min 2. MoOPH, -44° , 10 min; 22° , 20 min	 (24) +  (30)	40
	1. LDA, -70° , 30 min 2. MoOPH, -70° , 1 h, then 0°	I (70)	151, 40, 482, 547
	1. NaHMDS, THF, DMPU, -78° 2. PSPO	 (77) +  (77)	250
		I II I:II = 30:1	
	MoOPH, THF, -78° , 1.5 h	 (—)	548
	O ₂ , KOBu- <i>t</i> , DMSO	 (0)	346
	1. KHMDS, THF, -78° , 1 h 2. PSPO, -78° , 1 h	 (73) +  (73)	244
		I II I:II = 85:15	
	1. LDA, THF, -78° 2. MoOPH, -78 to -50° , 1.5 h	 (87)	549
	1. NaHMDS 2. (+)-CSO	 (87) $\frac{R}{Me}$ (87)  (90) $\frac{R}{OMOM}$ (90)	550

TABLE 2B. α -HYDROXYLATION OF CYCLIC KETONE ENOLATES (Continued)

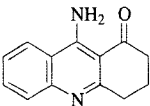
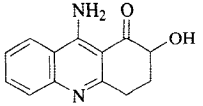
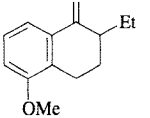
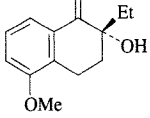
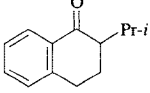
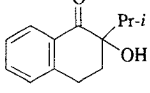
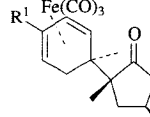
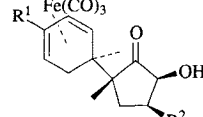
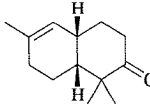
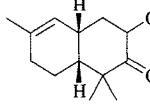
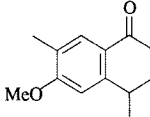
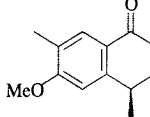
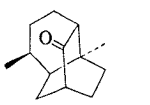
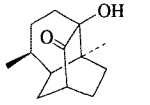
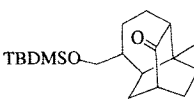
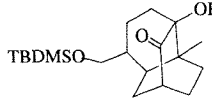
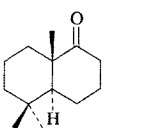
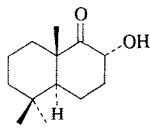
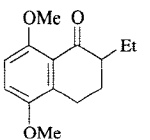
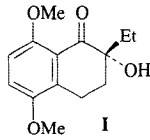
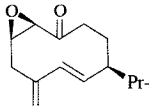
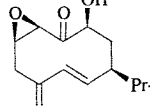
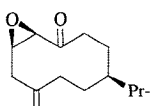
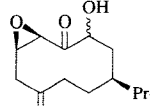
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.										
C ₁₃ 	1. KHMDS 2. PSPO	 (—)	182										
	1. LDA, THF, -78° 2. (+)-DMCSO, -78°, 4 h	 (76) 95% ee	551										
	(PhSeO) ₂ O, NaH, PhMe, reflux, 5.5 h	 (90)	182										
	1. LDA, THF, -78°, 15 min 2. MoOPH, -60°, 1 h		<table border="1" data-bbox="1217 697 1393 790"> <thead> <tr> <th>R¹</th> <th>R²</th> <th>Yield (%)</th> </tr> </thead> <tbody> <tr> <td>H</td> <td>H</td> <td>(60-75)</td> </tr> <tr> <td>OMe</td> <td>SiMe₂Ph</td> <td>(80)</td> </tr> </tbody> </table>	R ¹	R ²	Yield (%)	H	H	(60-75)	OMe	SiMe ₂ Ph	(80)	552 553
R ¹	R ²	Yield (%)											
H	H	(60-75)											
OMe	SiMe ₂ Ph	(80)											
	1. LDA 2. MoOPH	 (69)	554										
	1. KOH, MeOH, 0°, 10 min 2. PhI(OAc) ₂ , 0°, 1 h; rt, 16 h	 (67)	555										
	1. LDA, THF, -78°, 1 h 2. MoOPH, -50°, 1 h	 (74)	556										
	1. LDA, THF, -78°, 1 h 2. MoOPH, -50°, 1 h	 (73)	557, 558										
	1. LDA, THF, -78°, 30 min 2. PSPO, -78°, 45 min	 (72)	559, 255										
C ₁₄ 	1. NaHMDS, THF 2. (+)-CSO, -78°	 (72) <i>R</i> 83% ee	507										
	1. LDA, THF 2. (+)-DCCSO, -78°	I (55) <i>R</i> 73% ee	507										
	1. NaHMDS, THF 2. (+)-DMCSO, -78°	I (58) <i>R</i> 60% ee	507										
	1. LDA, THF 2. (+)-DCCSO, 0°	I (66) <i>R</i> 94% ee	507										
	1. LiHMDS, THF 2. MoOPH	 (86)	229										
	1. LiHMDS, THF, -70° 2. O ₂ , P(OEt) ₃	 (50)	61										

TABLE 2B. α -HYDROXYLATION OF CYCLIC KETONE ENOLATES (Continued)

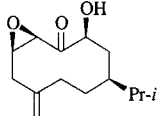
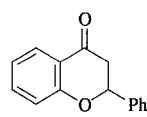
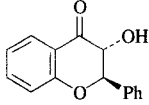
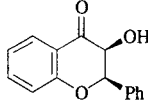
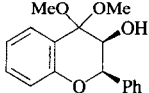
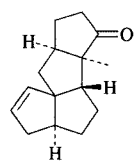
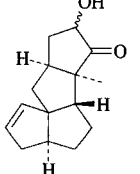
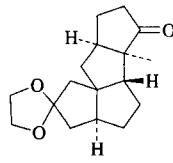
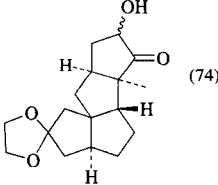
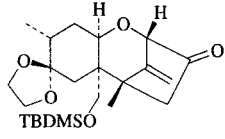
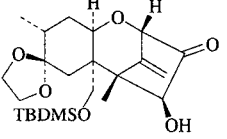
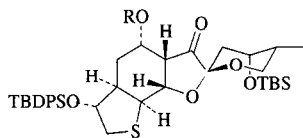
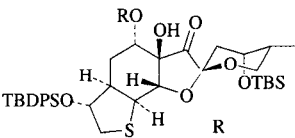


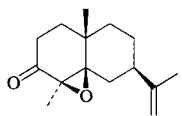
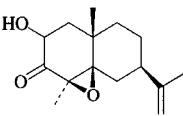
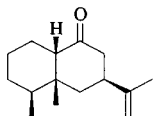
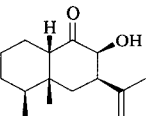
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. LiHMDS, THF, 30 min 2. MoOPH, -70° , 5 min	 (75-86)	235, 560, 561
C ₁₅ 	1. LiHMDS, THF 2. Cp ₂ TiCl ₂ 3. DMDO	 I  II I+II = (53); I:II = >98:<2	111
	PhI(OAc) ₂ , KOH, MeOH	 (68)	562
	1. LDA, THF, -78° , 30 min 2. MoOPH, -44° , 5 min	 (71)	563
	1. LDA, THF, -78° , 30 min 2. MoOPH, -44 to -30° , 15 min	 (74)	563
	1. KHMDS, THF, 0° , 1 h 2. NTSO, -78° to rt	 (—)	564
	1. KHMDS, THF, HMPA -78° , 45 min 2. (+)-CSO, -78° , 40 min; to 0° , 45 min	 R CH ₂ CH=CH ₂ (76) Bn (97)	246, 565
	1. LDA, THF, -70° , 0.5 h 2. MoOPH, -70 to -65° 1 h; rt	 (74)	566, 567
	1. LDA, THF, -78° , 1 h 2. MoOPH, -78° 1 h, rt, 30 min	 (0)	234
	1. LDA, THF, -78° , 10 min 2. MoOPH, -78° , 1 h; rt	 (27)	568

TABLE 2B. α -HYDROXYLATION OF CYCLIC KETONE ENOLATES (Continued)

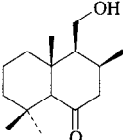
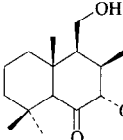
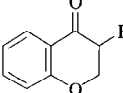
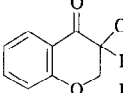
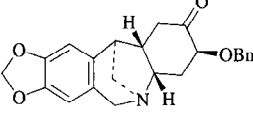
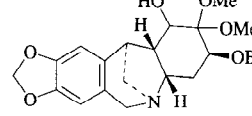
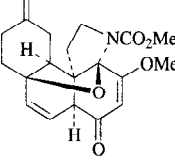
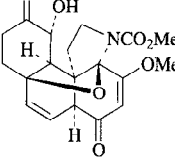
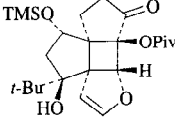
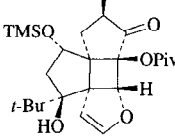
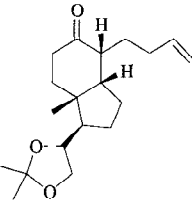
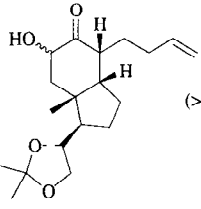
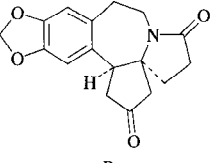
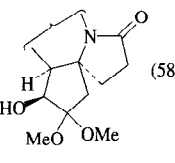
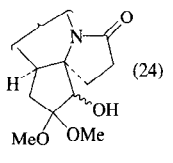
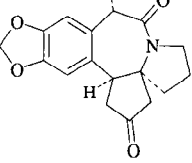
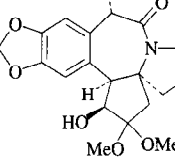
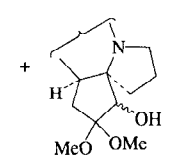
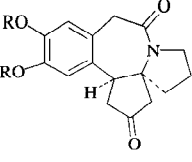
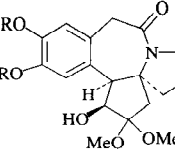
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. LDA, THF, -78° , 15 min; -15° , 15 min 2. MoOPH, -15° , 2 min	 (25)	231
C₁₆ 	1. NaHMDS, THF, -78° , 30 min 2. (+)-CSO, -78° , 1 h	 (70) <i>R</i> 15% ee	492
	1. NaHMDS, THF, -78° , 30 min 2. (+)-DCCSO, -78° , 0.5 h	I (71) <i>R</i> 91% ee	492
	1. NaHMDS, THF, -78° , 30 min 2. (-)-DCCSO, -78° , 0.5 h	I (67) <i>S</i> 92% ee	492
	PhI(OAc) ₂ , KOH, MeOH	 (0)	569
	1. KHMDS, THF, -78 to 0° , 15 min 2. PTSO, -78° , 1 h	 (70-88)	570
	1. LDA, THF, -78 to 0° , 15 min 2. MoOPH, 0° , 30 min	 (76)	213
	KHMDS, PSPO, -78° , 20 min	 (>71)	571
C₁₇ 	PhI(OAc) ₂ , KOH, MeOH, -8 to -5°	 (58) +  (24)	572
	PhI(OAc) ₂ , KOH, MeOH	 I +  II	573
		$\frac{R}{OMOM}$ I (54) II (18) $\frac{R}{SMe}$ (84) (6)	
C₁₇₋₁₈ 	(PhIO) _n , KOH, MeOH, 0°	 I $\frac{R}{-CH_2-}$ I (79) $\frac{R}{Me}$ (80)	574

TABLE 2B. α -HYDROXYLATION OF CYCLIC KETONE ENOLATES (Continued)

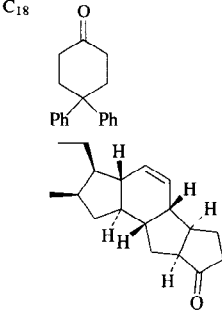
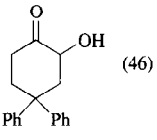
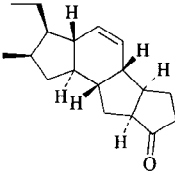
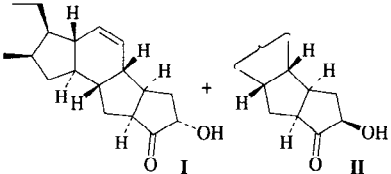
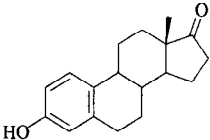
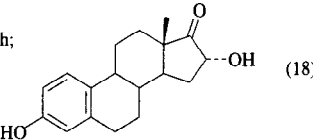
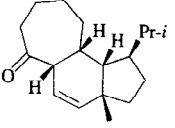
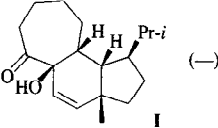
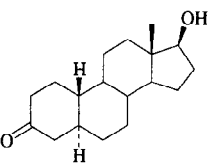
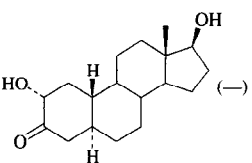
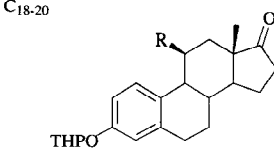
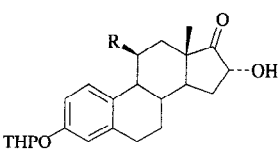
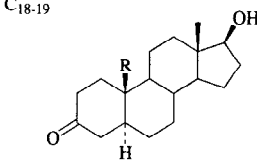
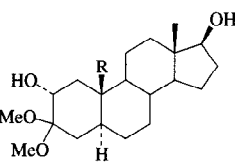
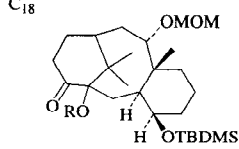
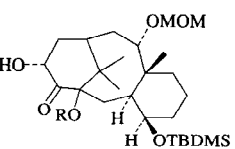
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	PhI(OAc) ₂ , KOH, MeOH, 0°, 3 h	I, R-R = CH ₂ (78)	575
	1. LDA, -78°, 15 min 2. MoOPH, -22°	 (46)	40, 482
	1. PhI(OAc) ₂ , KOH, MeOH, 25°, 8 h 2. Amberlist-15, THF, H ₂ O, 25°, 24 h	 I + II = (68); I:II = 4:1	576
	1. <i>o</i> -OIC ₆ H ₄ CO ₂ H, KOH, MeOH, 70°, 8 h; rt, 15 d 2. HCl (5%), MeOH, rt, 1 h	 (18)	218
	1. KHMDS 2. O ₂	 (—)	577
	1. KHMDS, THF, 15 min 2. (TMSO) ₂ , 45 min	I (46)	577
	1. KHMDS 2. PSPO	I (—)	577
	1. PhI(OAc) ₂ , KOH, MeOH, rt, overnight 2. Dowex 50W-X8, MeOH	 (—)	526
	1. LDA, THF, -78 to -23°, 30 min 2. MoOPH, -23°, 1 h	 R H (40) OMe (58) Et (36)	578
	PhI(OAc) ₂ , KOH, MeOH, rt, overnight	 R H (40) Me (0)	526
	1. KHMDS, THF, -78° 2. PSPO, -78°, 30 min	 R H (71) TMS (73)	579

TABLE 2B. α -HYDROXYLATION OF CYCLIC KETONE ENOLATES (Continued)

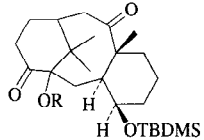
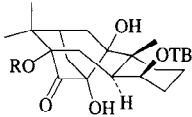
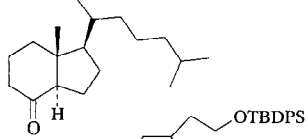
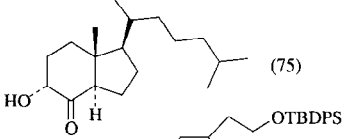
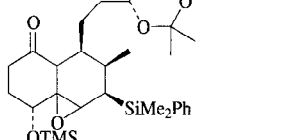
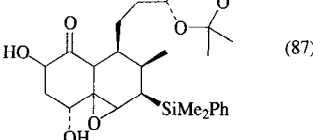
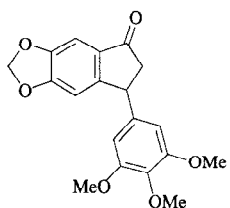
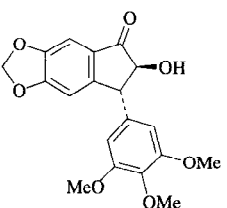
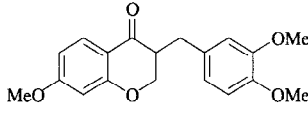
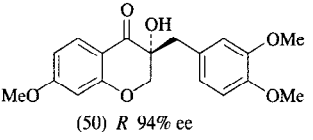
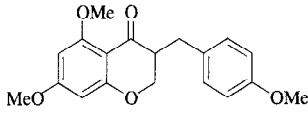
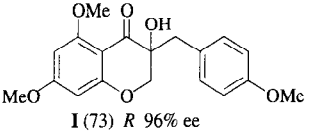

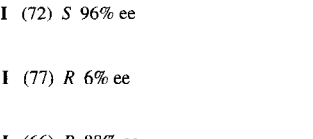
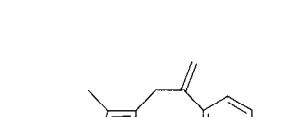
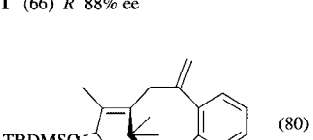
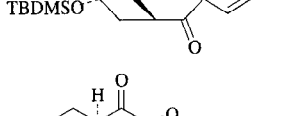
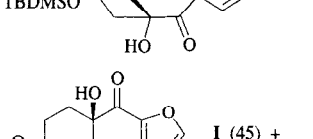
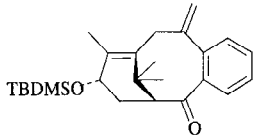
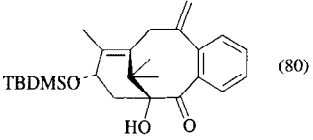
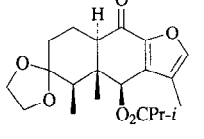
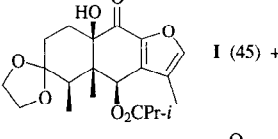
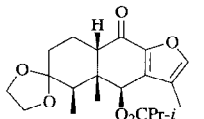
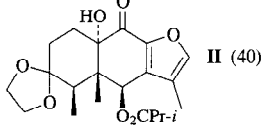
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
 R = TMS	1. KHMDS, THF, -78° 2. PSPO, -78° , 3 h; rt, overnight	 (36)	579
	1. LDA, THF, -78° , 30 min 2. MoOPH, -60° , 4 h	 (75)	580
	1. KHMDS, THF, -78° , 30 min 2. NPSO, -78° , 30 min 3. Bu ₄ NF, rt, 30 min	 (87)	210
C ₁₉ 	1. LDA 2. MoOPH	 (-)	581
	1. NaHMDS, THF, -78° , 30 min 2. (+)-DCCSO, -78° , 30 min	 (50) <i>R</i> 94% ee	582
	1. LDA, THF, -78° 2. (+)-DMCSO, -78 to 0°	 I (73) <i>R</i> 96% ee	268
	1. LDA, THF, -78° 2. (-)-DMCSO, -78 to 0°	 I (72) <i>S</i> 96% ee	268
	1. NaHMDS, THF, -78° 2. (+)-CSO, -78 to 0°	 I (77) <i>R</i> 6% ee	268
	1. NaHMDS, THF, -78° 2. (+)-DCCSO, -78 to 0°	 I (66) <i>R</i> 88% ee	268
	KOBu- <i>t</i> , O ₂ , DMSO, THF, 60°	 (80)	583
	(PhSeO) ₂ O, NaH, PhCl, reflux, 1.5 h	 I (45) +	181
	(PhSeO) ₂ O, NaH, PhCl, reflux, 1.5 h	 II (40)	181

TABLE 2B. α -HYDROXYLATION OF CYCLIC KETONE ENOLATES (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	o -OIC ₆ H ₄ CO ₂ H, KOH, MeOH, 70°, 8 h; rt 15 d	(26)	218
	1. o -OIC ₆ H ₄ CO ₂ H, KOH, MeOH, 70°, 8 h; rt 15 d 2. 5% HCl, MeOH, rt, 1 h	(20)	218
	1. LDA, THF, -78°, 1.5 h 2. MoOPH, -23°, 30 min	(75)	584
	o -OIC ₆ H ₄ CO ₂ H, KOH, MeOH, 70°, 8 h; rt 15 d	(19)	218
	1. o -OIC ₆ H ₄ CO ₂ H, KOH, MeOH, 70°, 8 h; rt 15 d 2. 5% HCl, MeOH, rt, 1 h	(13)	218
	PhI(OAc) ₂ , KOH, MeOH, THF	(10)	219
	1. LDA, -70°, 30 min 2. MoOPH, -70° to 0°	(75)	151, 40, 482
	PhI(OAc) ₂ , KOH, MeOH, THF	(10)	219
	o -OIC ₆ H ₄ CO ₂ H, KOH, MeOH, 70°, 8 h; rt, 15 d	(18)	218
	1. o -OIC ₆ H ₄ CO ₂ H, KOH, MeOH, 70°, 8 h; rt, 15 d 2. 5% HCl, MeOH, rt, 1 h	(13)	218
	KHMDS, O ₂ , THF, 18-crown-6, 0°, 10 min	(80)	585
	1. KHMDS, THF, -78°, 30 min 2. PSPO, -78°, 30 min	(50)	585

TABLE 2B. α -HYDROXYLATION OF CYCLIC KETONE ENOLATES (Continued)

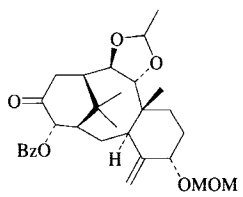
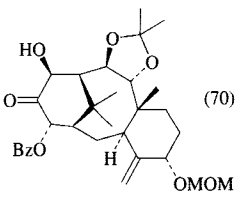
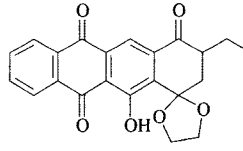
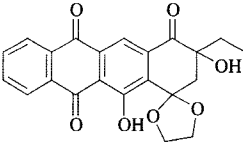
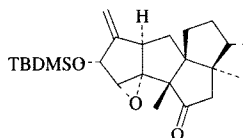
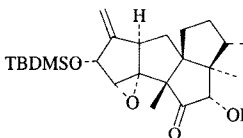
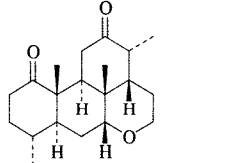
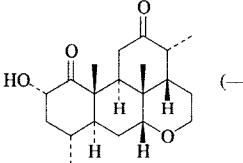
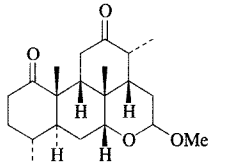
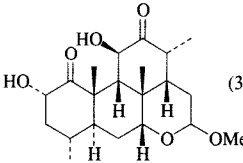
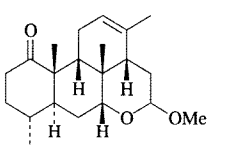
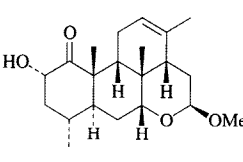
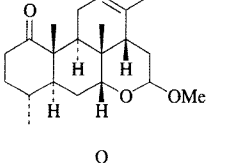
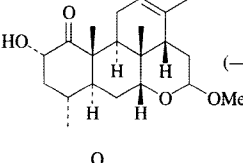
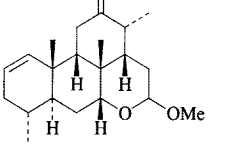
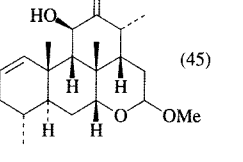
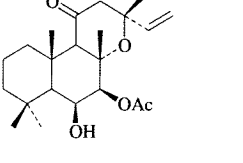
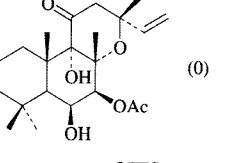
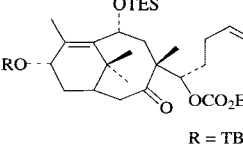
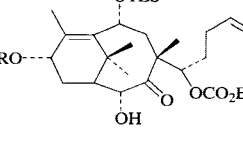
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. KHMDS, THF, -78° , 30 min 2. PSPO, -78° , 60 min	 (70)	585
	1. LDA, THF, HMPA, -78° , 30 min 2. MoOPH, -78° , 1 h; rt, 3 h	 (60)	586
	1. KHMDS, THF, -78° 2. PSPO, -78° , 45 min	 (68)	587
	1. LDA 2. MoOPH	 (-)	588
	1. LDA, THF, -78 to 0° 2. MoOPH, 0° , 15 min	 (35)	589, 590
	1. LDA, THF, -78° 2. MoOPH, 0°	 (57)	590
	1. Lithium base 2. MoOPH	 (-)	591
	1. LDA, THF, -78° , 20 min 2. MoOPH, -10° , 5 min	 (45)	592, 593
	KOBu- <i>t</i> , O ₂ , P(OEt) ₃	 (0)	594
 <p>R = TBDMS</p>	1. LDA, THF, -35° , 30 min 2. (+)-CSO, -78°	 (85)	32

TABLE 2B. α -HYDROXYLATION OF CYCLIC KETONE ENOLATES (Continued)

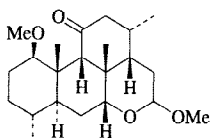
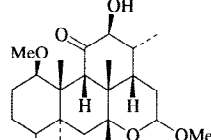
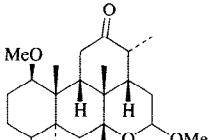
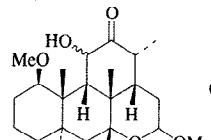
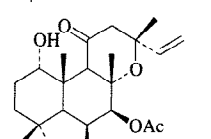
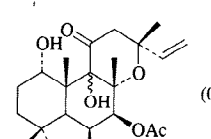
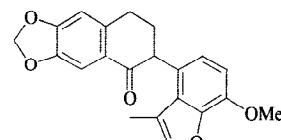
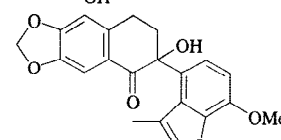
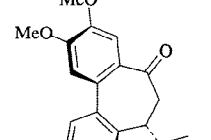
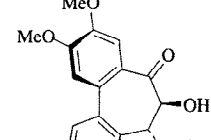
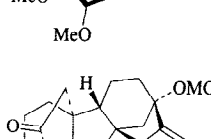
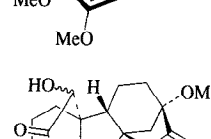
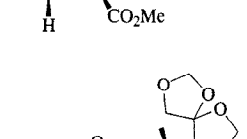
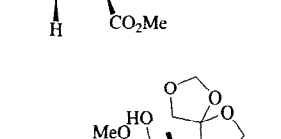
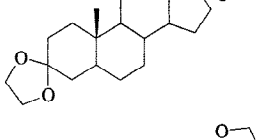
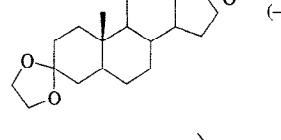
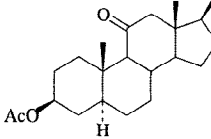
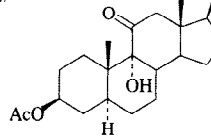
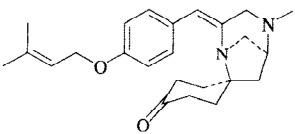
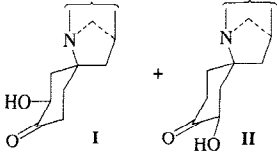
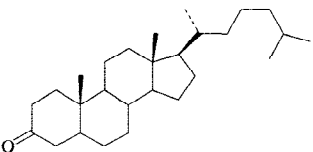
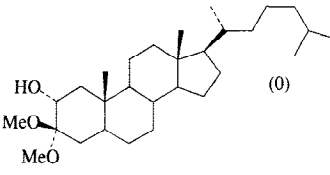
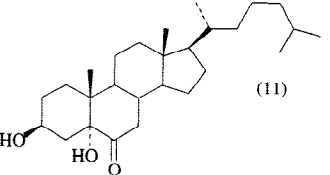
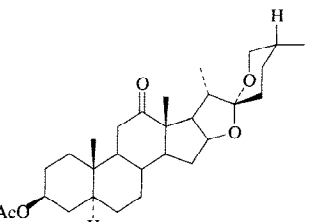
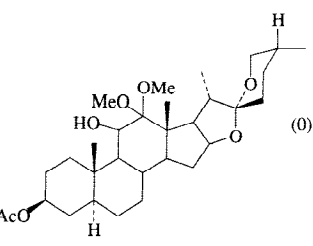
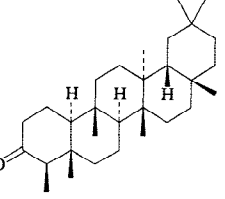
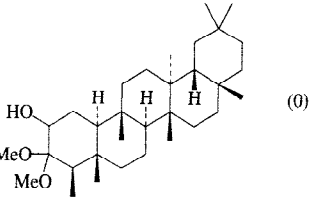
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. LDA, THF 2. MoOPH, -78 to 0°	 (58)	590
	1. LDA, THF 2. MoOPH	 (0)	590
	NaH, (PhSeO) ₂ O, PhMe, reflux	 (0)	595
	NaH, O ₂ , DMF, rt, 2.5 h	 (91)	596
	1. LiHMDS, THF, -78°, 1 h; -25°, 1 h 2. MoOPH	 (40)	597
	KH, MoOPH	 (—)	598
	PhI(OAc) ₂ , KOH, MeOH, THF	 (—)	219
	1. NaOBu- <i>t</i> , O ₂ , HOBu- <i>t</i> , DMF, P(OEt) ₃ , -25°, 50 min 2. NaOH, MeOH, H ₂ O 3. HOAc 4. Ac ₂ O, pyridine, 100°, 20 min	 (35)	55
	1. LDA, THF, -78°, 10 min 2. MoOPH, 0°, 10 min	 (80)	599

TABLE 2B. α -HYDROXYLATION OF CYCLIC KETONE ENOLATES (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₂₄ 	1. NaHMDS, THF, -78 to -40° 2. (+)-CSO, -78°, 20 min	 I+II = (50); I:II = 2:3	600
	1. NaHMDS, THF, -78 to -40° 2. (-)-CSO, -78°, 20 min	I+II (40); I:II = 2:1	600
C ₂₇ 	PhI(OAc) ₂ , KOH, MeOH, THF, or <i>o</i> -HO ₂ CC ₆ H ₄ IO, KOH, MeOH, THF, or (PhIO) _n , KOH, MeOH, THF	 (0)	219
	1. KOBu- <i>t</i> , O ₂ , HOBu- <i>t</i> , 36 min 2. Zn, HOAc, 4 h	 (11)	6
	KO ₂ , O ₂ , C ₆ H ₆ , 18-crown-6, 6-7°, 2.5-4 h	I (10-13)	62
	1. KO ₂ , O ₂ , C ₆ H ₆ , 18-crown-6, 6-7°, 3.5 h 2. PPh ₃ , CH ₂ Cl ₂	I (66)	62
C ₂₇ 	PhI(OAc) ₃ , KOH, MeOH, THF	 (0)	219
C ₃₀ 	PhI(OAc) ₃ , KOH, MeOH, THF	 (0)	219

^a A polymer was formed.

^b Other catalysts gave lower yields and enantiomeric excesses.

^c See also entries under C₁₀₋₁₆.

TABLE 3. α -HYDROXYLATION OF ESTER ENOLATES

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																																				
C4-11 	1. LiHMDS, THF, -78° 2. TEMPO 3. PhI(OAc)2, -78°, 6 h; rt, 30 min	 <table border="1"> <thead> <tr> <th>R</th> <th>I</th> <th>II</th> </tr> </thead> <tbody> <tr> <td>H</td> <td>(18)</td> <td>(—)</td> </tr> <tr> <td>Ph</td> <td>(97)</td> <td>(87)</td> </tr> <tr> <td>C6H4NO2-4</td> <td>(60)</td> <td>(—)</td> </tr> <tr> <td>C6H4Cl-4</td> <td>(60)</td> <td>(—)</td> </tr> <tr> <td>C6H4OMe-4</td> <td>(49)^a</td> <td>(—)</td> </tr> </tbody> </table>	R	I	II	H	(18)	(—)	Ph	(97)	(87)	C6H4NO2-4	(60)	(—)	C6H4Cl-4	(60)	(—)	C6H4OMe-4	(49) ^a	(—)	290																		
R	I	II																																					
H	(18)	(—)																																					
Ph	(97)	(87)																																					
C6H4NO2-4	(60)	(—)																																					
C6H4Cl-4	(60)	(—)																																					
C6H4OMe-4	(49) ^a	(—)																																					
C5 	1. KHMDS, THF, -78 to -50°, 2 h 2. MoOPH, -78 to -65°	 I+II = (30); I:II = 2:1	33																																				
	1. KHMDS, THF, -78 to -50°, 2 h 2. PSPO, -78 to -65°	I+II (86); I:II = 7:1	33																																				
	1. LiHMDS, THF, -78 to -50°, 2 h 2. PSPO, -78 to -65°	I+II (80); I:II = 1:4	33																																				
	1. LiCl (3 eq), THF 2. LDA (2.2 eq) 3. PSPO, -70°	 (25)	601																																				
C5-10 	1. LiHMDS 2. I2, THF 3. HCl, MeOH	 (76) 88% dc	296																																				
R = Ph	1. LiHMDS, THF, 0° 2. I2, -60°, 1 h 3. HCl, MeOH, reflux, 5 h	I (81)	602																																				
C5-7 	1. LDA 2. CuCl2, TEMPO, -78° to rt	 <table border="1"> <thead> <tr> <th>R¹</th> <th>R²</th> </tr> </thead> <tbody> <tr> <td>Me</td> <td>Me</td> </tr> <tr> <td><i>t</i>-Bu</td> <td>H</td> </tr> </tbody> </table>	R ¹	R ²	Me	Me	<i>t</i> -Bu	H	291																														
R ¹	R ²																																						
Me	Me																																						
<i>t</i> -Bu	H																																						
C6 	1. Base, addend, THF, -78°, 1.5 h 2. MoOPH, -78 to -65°	 <table border="1"> <thead> <tr> <th>Base</th> <th>Addend</th> <th>I+II</th> <th>I:II</th> </tr> </thead> <tbody> <tr> <td>LDA</td> <td>—</td> <td>(45)</td> <td>2:1</td> </tr> <tr> <td>LiHMDS</td> <td>—</td> <td>(65)</td> <td>1:8</td> </tr> <tr> <td>LiHMDS</td> <td>DMPU</td> <td>(92)</td> <td>8:1</td> </tr> <tr> <td>LiHMDS</td> <td>HMPA</td> <td>(74)</td> <td>11:1</td> </tr> <tr> <td>LiHMDS</td> <td>DME</td> <td>(74)</td> <td>1:2:5</td> </tr> <tr> <td>LiHMDS</td> <td>TMEDA</td> <td>(80)</td> <td>1:8</td> </tr> <tr> <td>LiHMDS</td> <td>PMDET</td> <td>(75)</td> <td>1:5</td> </tr> <tr> <td>LiHMDS</td> <td>14-Crown-4</td> <td>(0)</td> <td>—</td> </tr> </tbody> </table>	Base	Addend	I+II	I:II	LDA	—	(45)	2:1	LiHMDS	—	(65)	1:8	LiHMDS	DMPU	(92)	8:1	LiHMDS	HMPA	(74)	11:1	LiHMDS	DME	(74)	1:2:5	LiHMDS	TMEDA	(80)	1:8	LiHMDS	PMDET	(75)	1:5	LiHMDS	14-Crown-4	(0)	—	33, 603
Base	Addend	I+II	I:II																																				
LDA	—	(45)	2:1																																				
LiHMDS	—	(65)	1:8																																				
LiHMDS	DMPU	(92)	8:1																																				
LiHMDS	HMPA	(74)	11:1																																				
LiHMDS	DME	(74)	1:2:5																																				
LiHMDS	TMEDA	(80)	1:8																																				
LiHMDS	PMDET	(75)	1:5																																				
LiHMDS	14-Crown-4	(0)	—																																				

TABLE 3. α -HYDROXYLATION OF ESTER ENOLATES (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)				Refs.		
		Base	Addend	I:II	I:II			
		LTMP	—	(22)	1:2			
		<i>n</i> -BuLi, LiHMDS	—	(60)	1:20			
		<i>n</i> -BuLi, LiHMDS	HMPA	(95)	2:1			
		KHMDS	—	(90)	3:1			
		KHMDS	18-Crown-6	(0)	—			
C ₆₋₁₄	1. LiHMDS, THF, -78° 2. [O], -78°, 5-10 min					257		
		R ¹	R ²	R ³	Base	[O]	I+II	I:II
		Me	Cbz	Me	LiHMDS	MoOPH	(36)	1:2
		Me	Cbz	Me	NaHMDS	MoOPH	(30)	1:1
		Me	Cbz	Me	KHMDS	MoOPH	(50)	1:1
		Me	Cbz	Me	LDA	PSPO	(60)	1.5:1
		Me	Cbz	Me	LiHMDS	PSPO	(60)	2.5:1
		Me	Cbz	Me	NaHMDS	PSPO	(70)	7:1
		Me	Cbz	Me	KHMDS	PSPO	(70)	1.1:1
		<i>t</i> -Bu	Cbz	<i>t</i> -Bu	LiHMDS	MoOPH	(40)	1:4
		Me	Cbz	<i>t</i> -Bu	LiHMDS	PSPO	(40)	10:1
		<i>t</i> -Bu	Cbz	Me	LiHMDS	PSPO	(60)	10:1
		<i>t</i> -Bu	Cbz	<i>t</i> -Bu	LiHMDS	PSPO	(70)	10:1
		Me	Ts	Me	LiHMDS	PSPO	(60)	7:1
		<i>t</i> -Bu	Ts	<i>t</i> -Bu	LiHMDS	PSPO	(57)	45:1
C ₆₋₁₈	1. NaHMDS, THF, rt, time a 2. I ₂ , rt, time b 3. H ₂ O							
								295
		R ¹	R ²	Time a	Time b	% de		
		Me	Me	5 h	16 h (50)	36		
		Me	Et	16 h	24 h (20)	36		
		Me	allyl	7 h	16 h (30)	>98		
		Ph	Me	16 h	24 h (75)	20		
		Me	Bn	16 h	24 h (50)	50		
		Ph	Et	16 h	24 h (50)	>98		
		Ph	allyl	16 h	24 h (77)	52		
		Ph	Bn	16 h	24 h (99)	40		
C ₆₋₁₂	1. LDA, ferrocenium BF ₄ , -78° 2. TEMPO							190
		R ¹	R ²	R ³	R ⁴	I	II	
		Et	H	H	<i>n</i> -Bu ^b	(67)	(86)	
		Et	H	H	<i>i</i> -Pr ^b	(72)	(85)	
		Et	H	Ph	H	(94)	(85)	
		Me	H	Me	Et	(91)	(84)	
		Et	H	OH	Me	(90)	(84)	
		Me	Me	H	Me	(95)	(52)	
C ₇	1. KHMDS, THF, -78°, 40 min 2. PSPO, -78°, 2.5 h							604

TABLE 3. α -HYDROXYLATION OF ESTER ENOLATES (Continued)

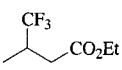
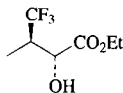
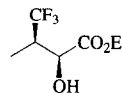
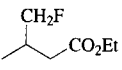
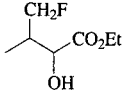
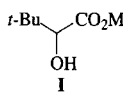
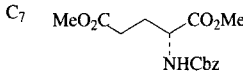
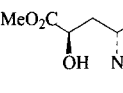
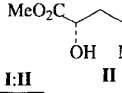
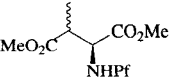
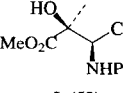
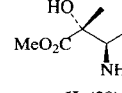
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. LDA 2. MoOPH, -20°, 3 h	 +  I I+II = (75); I:II = 97:3 II	510
	1. LiHMDS 2. MoOPH	I+II (-); I:II = 97:3	510
	1. KHMDS 2. PSPO	I+II (-); I:II = 95:5	510
	1. LDA 2. MoOPH	 (60)	510
<i>t</i> -BuCO ₂ Me	1. LDA, THF, -78° 2. (-)-CSO, -78°	 (29) <i>S</i> 58% ee	605
	1. LDA, THF, -78° 2. Remove solvent 3. (-)-CSO, -78°	I (16) 0% ee	605
	1. LDA, THF, -78° 2. (+)-CSO, -78°	I (35) <i>R</i> 68% ee	605
	1. LDA, THF, -78° 2. Remove solvent 3. (+)-CSO, -78°	I (17) 0% ee	605
	1. LDA, THF, -78° 2. (+)-CSO, 22°	I (37) <i>R</i> 57% ee	605
	1. LDA, THF, -78° 2. Remove solvent 3. (+)-CSO, -22°	I (15) 0% ee	605
	1. LDA, THF, -78° 2. (-)-DCCSO, -78°	I (48) <i>S</i> 73% ee	605
	1. LDA, THF, -78° 2. Remove solvent 3. (-)-DCCSO, -78°	I (14) 0% ee	605
	1. LDA, THF, -78° 2. (+)-DCCSO, -78°	I (66) <i>R</i> 75% ee	605
	1. LDA, THF, -78° 2. Remove solvent 3. (+)-DCCSO, -78°	I (20) 0% ee	605
	1. Base, THF, -78° 2. PSPO, -78°, 5-10 min	 +  I + II Base I:II LiHMDS (70) 9:1 NaHMDS (56) 2.6:1 KHMDS (70) 1:1	257
	1. KHMDS, THF, HMPA, -78 to -40°, 1 h 2. MoOPH, -78 to -65°	 +  I (52) II (28)	33
	1. LiHMDS, THF, HMPA, -78 to -40°, 2 h 2. PSPO, -78 to -65°	I+II (92); I:II = 1:1	33

TABLE 3. α -HYDROXYLATION OF ESTER ENOLATES (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. NaHMDS, THF, -78° 2. PSPO, -78°, 1 h	 (74)	606
	1. KHMDS, THF, -78° 2. PSPO, -78°, 3 h	 (90)	607, 608
	1. KHMDS 2. PSPO 3. TFA, CH ₂ Cl ₂	 (70)	609
	1. LDA, THF 2. MoOPH, -78°, 2 h	 I (40) + II (40)	610
	1. LDA, -78°, 15 min 2. MoOPH, -78°, 2.25 h	I (28) + II (56)	611
C_8 	1. LDA, -78°, 15 min 2. MoOPH, -78°, 2 h	 $n\text{-C}_5\text{H}_{11}$ (74)	40
C_{8-12} 	1. LDA 2. MoOPH	 I (65) + II (77) Et (65) 60:40 Ph (77) 85:15	510
C_9 	1. NaHMDS, THF, -10°, 60 min 2. DMDO, -78°, 2 min	 I (60)	110
	1. KHMDS, THF 2. PSPO (1 eq), -78°	I (50)	511
	1. KHMDS, THF 2. PSPO (1.5 eq), -78°	I (87)	511
	1. LDA, THF, -78°, 25-30 min 2. (+)-CSO, -78°, 15 min	I (84) <i>R</i> 54% ee	269
	1. LDA, THF, HMPA, -78°, 25-30 min 2. (+)-CSO, -78°, 15 min	I (88) <i>R</i> 12% ee	269
$C_{9,10}$ 	PhI(OAc) ₂ , KOH, C ₆ H ₆ , H ₂ O	 R ¹ R ² Me H (50) Me OH (30) Me Me (50) Me OMe (66) Et H (75) Et Br (60) Et Cl (60)	138
	PhI(OAc) ₂ , NaOR ³ , R ³ OH, 3 d	 R ¹ R ² R ³ Me H Me (70) Me H Et (45) Me OH Me (40) Me OH Et (30) Me Me Me (70) Me Me Et (60) Me OMe Me (80) Me OMe Et (50)	138

TABLE 3. α -HYDROXYLATION OF ESTER ENOLATES (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
		Et H Me (75) Et H Et (50) Et Br Me (75) Et Br Et (60) Et Cl Me (80) Et Cl Et (70)	
	1. NaHMDS 2. PSPO	(—)	612, 613
	1. NaHMDS, THF, -78° 2. O ₂ , 2 min	(8) I	292
	1. KHMDS, THF, -78°, 5 min 2. <i>m</i> -CPBA, 30 min	I (30)	292
	1. LDA 2. O ₂ 3. Na ₂ SO ₃	(76)	54
	PhI(OAc) ₂ , KOH, C ₆ H ₆ , H ₂ O	(40)	138
	PhI(OAc) ₂ , NaOR, ROH, 3 d	$\frac{R}{\text{Me}} (65)$ $\text{Et} (45)$	138
	1. KHMDS, THF, -78°, 1 h 2. MoOPH, -78 to -65°	I + II I+II = (95); I:II = 7:1	33
	1. LiHMDS, THF, HMPA, -78°, 1 h 2. MoOPH, -78 to -65°	I+II (70); I:II = 4:1	33
	1. KHMDS, THF, -78°, 1 h 2. PSPO, -78 to -65°	I+II (98); I:II = 1:2	33
	1. LDA, -78° 2. MoOPH, -78°	(75)	152, 40, 151, 511
	1. LDA, -78° 2. MoOPD, -78°	I (71)	152
	1. LiHMDS, THF 2. PSPO (2 eq), -78°	I (40)	511
	1. LiHMDS, THF, HMPA 2. PSPO (2 eq), -78°	I (17)	511
	1. KHMDS, THF 2. PSPO, -78°	I (83)	511
	1. KHMDS, THF, HMPA 2. PSPO, -78°	I (60)	511
	1. <i>s</i> -BuLi, THF 2. PSPO, -78°	I (45)	511
	1. LiHMDS, THF 2. PSPO, -78°	I (74)	511
	1. KHMDS, THF 2. PSPO, -78°	I (68)	511

TABLE 3. α -HYDROXYLATION OF ESTER ENOLATES (Continued)

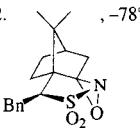
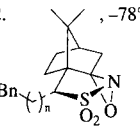
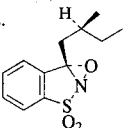
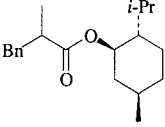
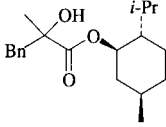
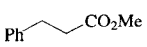
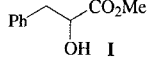
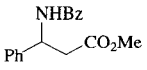
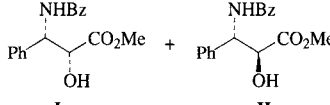
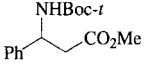
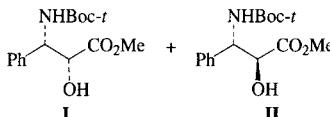
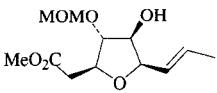
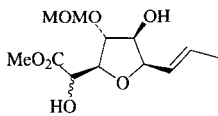
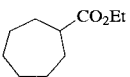
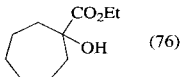
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.								
	1. LDA, THF, -78 to 0° 2. (+)-CSO, -78° , 30 min	I (61) <i>R</i> 24% ee	259								
	1. LDA, THF, -78 to 0° 2. (-)-CSO, -78° , 30 min	I (57) <i>S</i> 28% ee	259								
	1. LDA, THF 2.  , -78°	I (51) <i>R</i> 64% ee	511								
	1. LDA, THF 2.  , -78°	I <table border="1" style="display: inline-table; vertical-align: middle;"><thead><tr><th>n</th><th>% ee</th></tr></thead><tbody><tr><td>0 (65) <i>R</i></td><td>48</td></tr><tr><td>2 (72) <i>R</i></td><td>54</td></tr></tbody></table>	n	% ee	0 (65) <i>R</i>	48	2 (72) <i>R</i>	54	511		
n	% ee										
0 (65) <i>R</i>	48										
2 (72) <i>R</i>	54										
	1. LDA, THF 2.  , -78 to 0° , 1.5 h	I (60) <i>R</i> 15% ee	508								
	1. LDA (eq), THF, -78° 2. [O], -78°	 <table border="1" style="display: inline-table; vertical-align: middle;"><thead><tr><th>eq [O]</th><th>% ee</th></tr></thead><tbody><tr><td>1.5 (+)-CSO (71) <i>S</i></td><td>66</td></tr><tr><td>1.5 (-)-CSO (47) <i>R</i></td><td>50</td></tr><tr><td>0.5 (+)-CSO (33) <i>S</i></td><td>94</td></tr></tbody></table>	eq [O]	% ee	1.5 (+)-CSO (71) <i>S</i>	66	1.5 (-)-CSO (47) <i>R</i>	50	0.5 (+)-CSO (33) <i>S</i>	94	614
eq [O]	% ee										
1.5 (+)-CSO (71) <i>S</i>	66										
1.5 (-)-CSO (47) <i>R</i>	50										
0.5 (+)-CSO (33) <i>S</i>	94										
	1. LDA, THF, -78° , 15 min 2. MoOPH, -78° , 2 h	 (60)	40								
	1. LDA, THF, -78° , 25-30 min 2. (+)-CSO, -90°	I (73) <i>R</i> 58% ee	269								
	1. LDA, THF, HMPA, -78° , 25-30 min 2. (+)-CSO, -90°	I (33) <i>R</i> 85.5% ee	269								
	1. LDA, LiCl, THF, -42° 2. (+)-CSO, -100 to -78°	 I I+II = (58); I:II = 86:14	294								
	1. KHMDS, THF, -78 to -25° 2. MoOPH, -70 to -60° , 3 h	I+II (84); I:II = 86:14	188								
	1. LiHMDS, THF 2. PSPO, -60°	 I I+II = (-); I:II = 10:90	188								
	1. KHMDS, THF, -78 to -25° 2. MoOPH, -70 to -60° , 3 h	I+II (65); I:II = 86:14	188								
	1. KHMDS, THF, -78° 2. PSPO	 (63)	615								
	1. LDA 2. O_2 3. Na_2SO_3	 (76)	54								

TABLE 3. α -HYDROXYLATION OF ESTER ENOLATES (Continued)

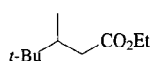
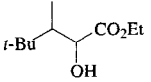
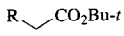
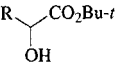
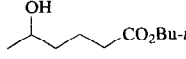
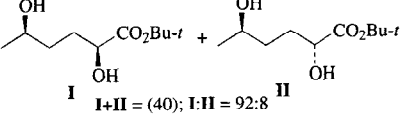
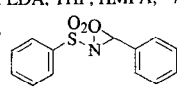
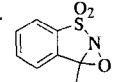
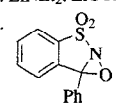
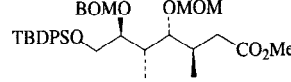
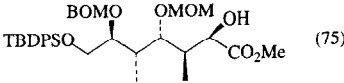
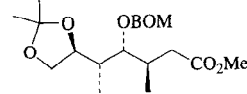
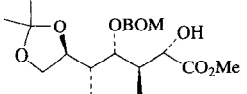
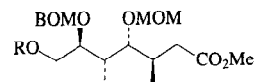
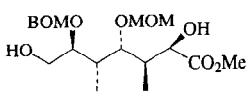
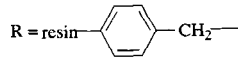
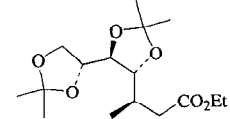
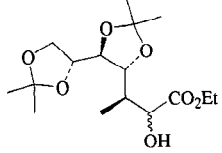
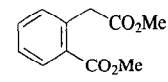
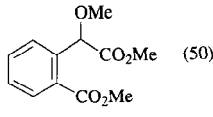
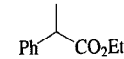
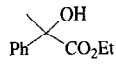
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. LDA 2. MoOPH	 (45) >90% de	510
C ₁₀₋₁₃ 	1. LDA, THF, -78° 2. (<i>i</i> -PrO) ₃ TiCl, -78 to -30°, 3 h 3. O ₂ , -50°, 30 min 4. NH ₄ F, H ₂ O, 1 h	 R Bu (67) R Bn (64)	57
C ₁₀ 	1. LiNEt ₂ , THF, HMPA, -100 to -78° 2. PSPO	 I I+II = (40); I:II = 92:8	243
	1. LDA, THF, HMPA, -78° 2. 	I+II (48); I:II = 89:11	243
	1. LiNEt ₂ , THF, HMPA, -78° 2. 	I+II (34); I:II = 88:12	243
	1. LiNEt ₂ , LiOTf (3 eq), THF, HMPA 2. 	I+II = (83); I:II = 92:8	243
	1. KHMDS, THF, -78° 2. PSPO, -78°, 3 h	 (75)	607
	1. KHMDS, THF, -78° 2. PSPO	 (70)	608
	1. KHMDS, THF 2. PSPO 3. TFA, CH ₂ Cl ₂	 (70)	609
R = resin-  -CH ₂ -			
	1. LiNEt ₂ , oxolane, -70°, 20 min 2. MoOPH, -70°, 1.5 h	 (52) 70% de	31
C ₁₁ 	1. NaOMe, MeOH 2. PhI(OAc) ₂ , MeOH, rt, 4 d	 (50)	164
	1. LDA 2. O ₂ 3. Na ₂ SO ₃	 (81)	54

TABLE 3. α -HYDROXYLATION OF ESTER ENOLATES (Continued)

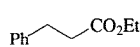
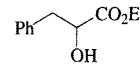
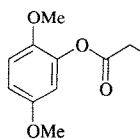
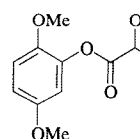
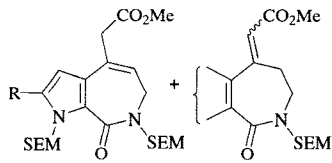
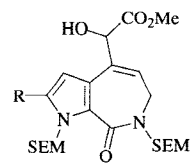
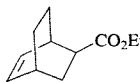
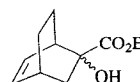
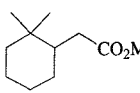
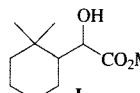
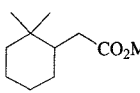
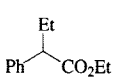
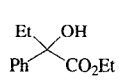
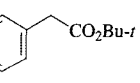
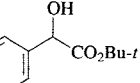
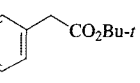
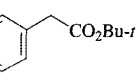
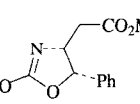
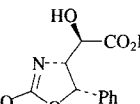
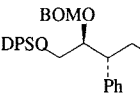
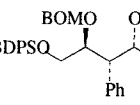
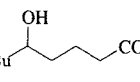
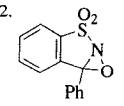
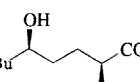
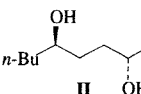
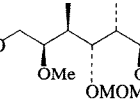
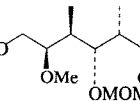
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. LDA, THF, -70° , 30 min 2. MoOPH, -70° ; 1h, 0°	 (60)	151
	1. LDA, THF 2. Cp ₂ TiCl ₂ 3. DMDO	 (65)	111
	1. KHMDS, THF, -78° , 2 h 2. PSPO	 $\frac{R}{H (72)}$ Br (78)	616
	1. LDA, THF, -70° , 30 min 2. MoOPH, -70° ; 1h, 0°	 (85)	151
	1. LDA, -78° 2. MoOPH, -78°	 (63)	152
	1. LDA, -78° 2. MoOPD, -78°	I (72)	152
	1. LDA 2. O ₂ 3. Na ₂ SO ₃	 (83)	54
	1. LDA, THF, -78° 2. (<i>i</i> -PrO) ₃ TiCl, -78 to -30° , 3 h 3. O ₂ , -50° , 30 min 4. NH ₄ F, H ₂ O, 1 h	 I (78)	57
	1. LDA, THF 2. Cp ₂ TiCl ₂ 3. DMDO	I (67)	111
	1. LDA, THF, -78° , 25-30 min 2. (+)-CSO, -90°	I (84) <i>R</i> 71% ee	269
	1. LiHMDS, THF, -78° , 1 h 2. PSPO, -78° , 1 h	 (62)	617
	1. KHMDS, THF, -78° 2. (+)-CSO, -90°	 (—) >90% ee	618
	1. LiNEt ₂ (3 eq), LiOTf (3 eq), THF, HMPA, -100° 2. 	 I +  II = (82); I:II = 92:8	243
	1. KHMDS, THF, -78° 2. PSPO	 (71)	607

TABLE 3. α -HYDROXYLATION OF ESTER ENOLATES (Continued)

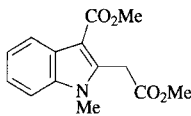
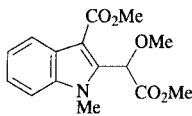
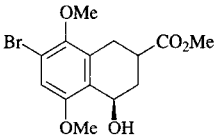
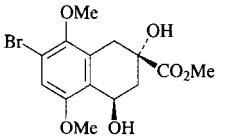
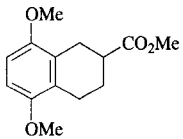
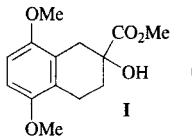
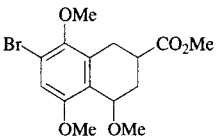
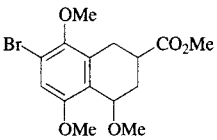
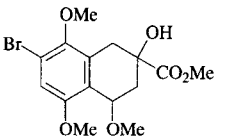
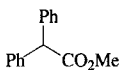
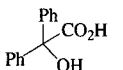
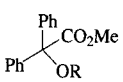
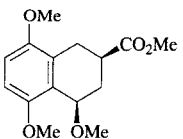
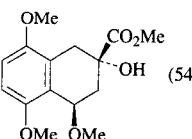
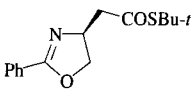
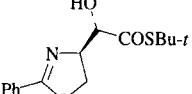
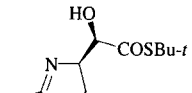
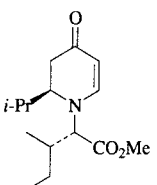
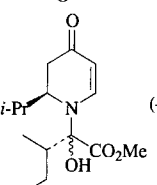
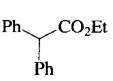
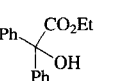
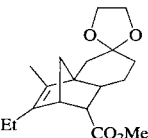
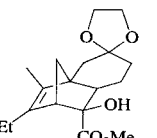
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₁₄ 	PhI(OAc) ₂ , KOH, MeOH, rt, 3 d	 (37)	619
	1. LiCA, THF, -70°, 1 h 2. MoOPH, -65°, 1.5 h; rt	 (57)	35
	1. LDA, THF, -78°, 30 min 2. MoOPH, -78°, 1.25 h; 0°, 30 min	 (67) I	620
	1. LDA 2. (+)-CSO or (+)-DMCSO	I (61-63) 3-4% ee	538
	1. LDA 2. MoOPH	 (74)	621
C ₁₅ 	PhI(OAc) ₂ , KOH, C ₆ H ₆ , H ₂ O	 (75)	138
	PhI(OAc) ₂ , NaOR, ROH, 3 d	 $\frac{R}{\text{Me (65) Et (65)}}$	138
	1. LiCA, THF, -78°, 1 h 2. MoOPH, -78° to rt, 3 h	 (54)	622
	1. NaHMDS, THF, -78° 2. PSPO	 (55)	260
	1. NaHMDS, THF, HMPA, -78° 2. PSPO	 (90)	260
	1. KHMDS, -78° 2. PSPO	 (—)	623
C ₁₆ 	1. LDA 2. O ₂ 3. Na ₂ SO ₃	 (85)	54
	1. LDA, THF, -78°, 1 h 2. O ₂ , -78°, 2 h	 (43)	624

TABLE 3. α -HYDROXYLATION OF ESTER ENOLATES (Continued)

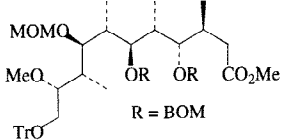
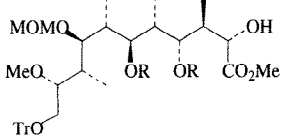
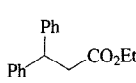
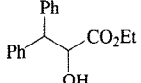
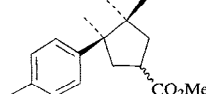
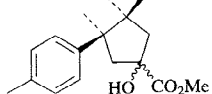
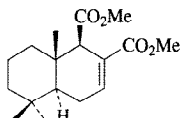
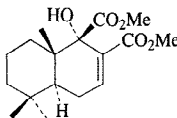
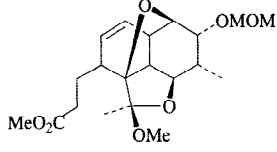
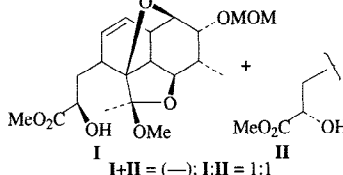
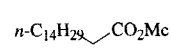
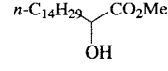
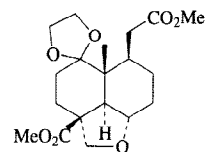
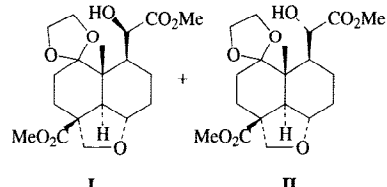

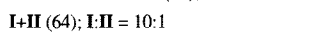
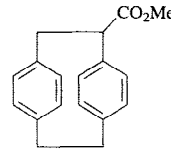
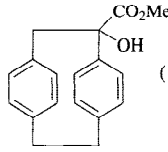
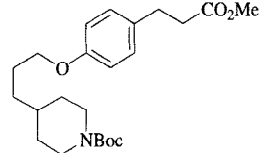
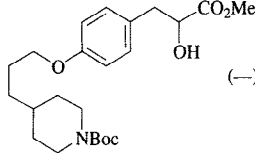
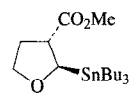
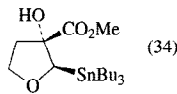
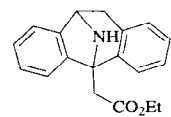
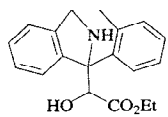
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. KHMDS, THF, -78° 2. PSPO, -78° , 3 h	 (71)	607
C17 	1. LDA 2. O ₂ 3. Na ₂ SO ₃	 (90)	54
	1. LDA, THF, -78° , 15 min 2. MoOPH, -20° , 2 h	 (75)	625
	1. LDA, THF, -78° 2. MoOPH, -78° to rt, 2-3 h	 (95)	626, 493
	1. LDA, THF 2. MoOPH, -78 to 0°	 I + II = (-); I:II = 1:1	236
	1. LDA, THF, -78° , 30 min 2. MoOPH, -78° , 1 h	 (50)	627
	1. LDA, -78° 2. MoOPH, -78°	 I + II = (52); I:II = 10:1	152
	1. LDA, -78° 2. MoOPD, -78°	 I + II = (64); I:II = 10:1	152
C18 	1. LDA, THF, -78° , 30 min 2. MoOPH, -70 to -10°	 (11)	628
	1. KHMDS, THF, -70° , 1 h 2. PSPO, -70° , 4 h	 (—)	628a
	1. LDA, THF, -70° 2. PSPO	 (34)	249
C19 	1. KHMDS, THF, -78° 2. PSPO, -70° , 15 min	 (85)	247

TABLE 3. α -HYDROXYLATION OF ESTER ENOLATES (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. LiNEt ₂ , THF, -78° 2. (+)-CSO	 (61) 1:1 mixture	629
	1. LDA, THF, HMPA 2. (+)-CSO	 (-) 10% ee	630
C ₂₀ 	1. LDA, THF, -78°, 1 h 2. O ₂ , P(OEt) ₃ , -78°, 80 min	 (64)	631
C ₂₀₋₂₅ 	1. LHMDS, THF, 0°, 30 min 2. (+)-CSO, -78°, 1.5 h; 0°, 15 min	 R % de Me (84) >98 Ph (68) 94	248
C ₂₀ 	1. LDA, THF, -78°, 2 h 2. O ₂ , P(OEt) ₃ , -78°, 35 min	 (30) (21) (18)	632
C ₂₁ 	1. LDA, THF, 0°, 30 min 2. MoOPH, 0° to rt, 2.5 h	 (44)	633
	1. LDA, THF, 0°, 30 min 2. MoOPH, 0° to rt, 2.5 h	 (5) (40)	633
	1. LDA, THF, -78°, 30 min 2. (-)-CSO, -70°, 50 min	 I II I+II = (64); I:II = 78:22	634
	1. LDA, THF, DMEU, -78° 2. (-)-CSO	 I+II (41); I:II = 58:42	634
	1. KHMDS (2 eq), KOBu-s (8 eq) 2. MoOPH, -52 to -46°, 2 h	 I II I+II = (74); I:II = 1:99	635

TABLE 3. α -HYDROXYLATION OF ESTER ENOLATES (Continued)

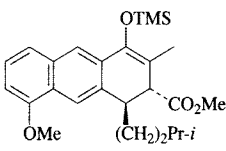
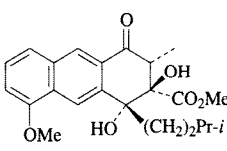
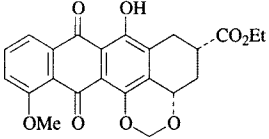
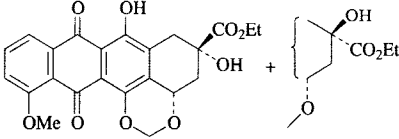
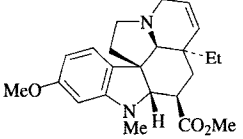
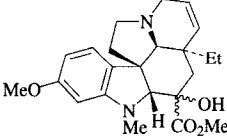
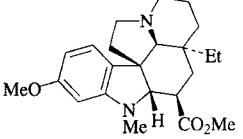
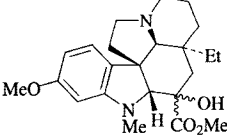
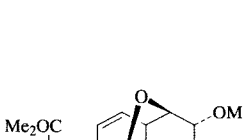
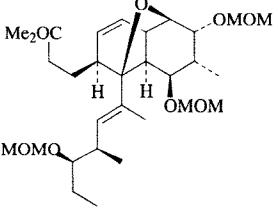
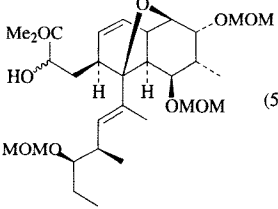
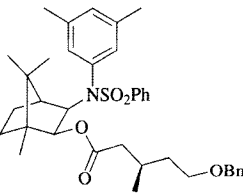
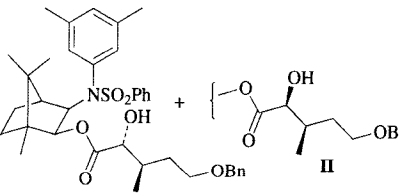
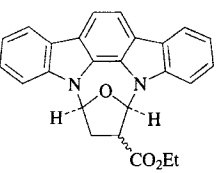
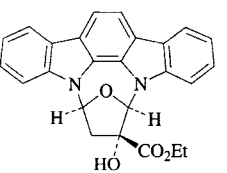
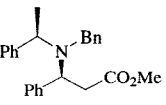
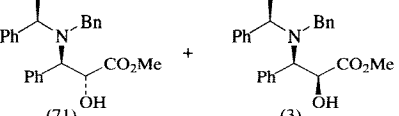
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₂₃ 	1. KHMDS (excess) 2. PSPO	 (66)	289
	1. LDA, THF, -78° 2. O ₂ , P(OEt) ₃ , -78°, 2 h	 I + II = (75); I:II = 1:1	636
	1. LDA, THF, 0°, 30 min; 25°, 1 h 2. MoOPH, 0°, 1 h	 (35)	237
	1. LDA, THF, 0°, 30 min; 25°, 2 h 2. O ₂ , 25°, 18 h	 (30)	237
	1. LDA, THF, 0°, 30 min; 25°, 2 h 2. MoOPH, 0°, 1 h	I (32)	237
	1. LDA, THF 2. MoOPH, -78°	 (50)	637
C ₂₄ 	1. KHMDS (2 eq), KOBu-s (8 eq) 2. MoOPH, -52 to -30°, 8 h	 I + II = (48); I:II = 1:99	635
C ₂₅ 	1. LDA, THF, -78° 2. CSO	 (77)	638
	1. LiHMDS, THF, 0°, 30 min 2. (-)-CSO, -78°, 1.5 h; 0°, 15 min	 (71) + (3)	248

TABLE 3. α -HYDROXYLATION OF ESTER ENOLATES (Continued)

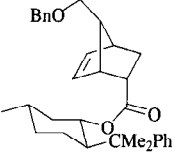
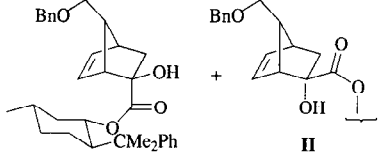
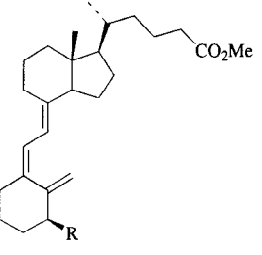
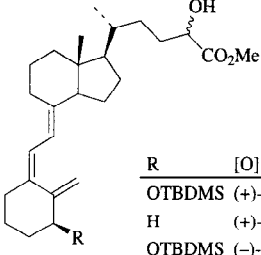
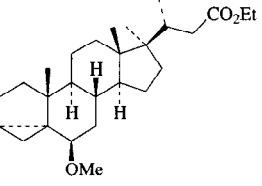
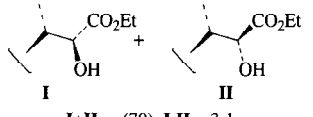
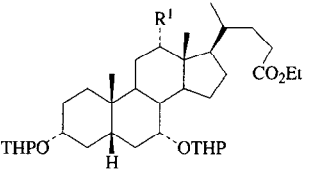
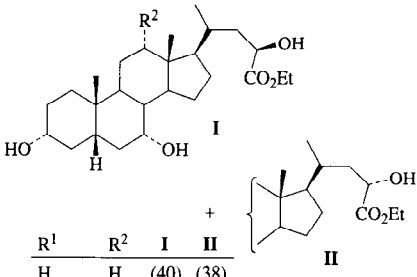
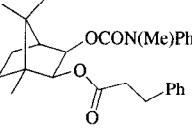
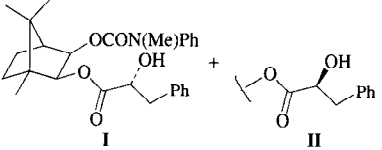
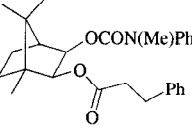
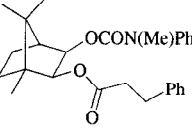
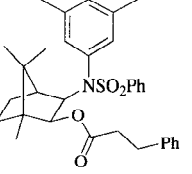
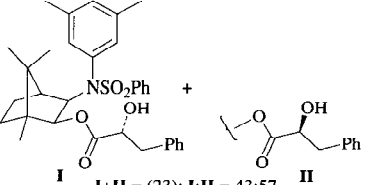
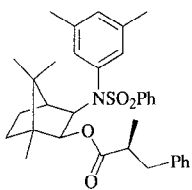
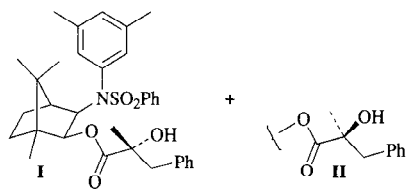
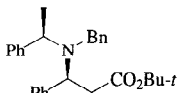
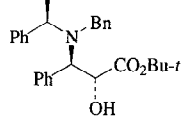
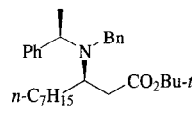
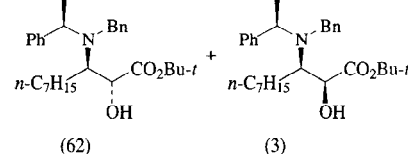
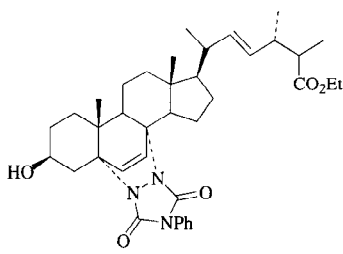
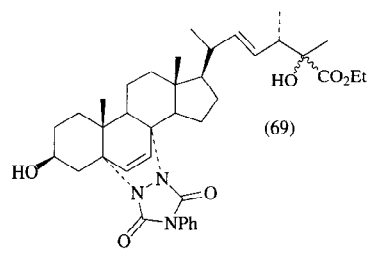
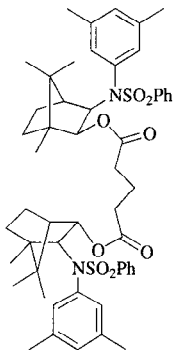
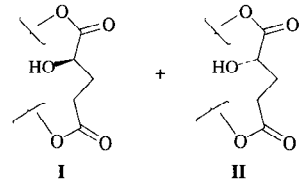
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.												
	1. LDA, -78°, 1 h 2. O ₂ , THF, -78°	 I I+II = (90); I:II = 2:1	639												
C26															
	1. LDA, THF 2. [O], -78°	 <table border="1" data-bbox="1119 780 1380 929"> <thead> <tr> <th>R</th> <th>[O]</th> </tr> </thead> <tbody> <tr> <td>OTBDMS (+)-DCCSO</td> <td>R (70)</td> </tr> <tr> <td>H (+)-DCCSO</td> <td>R (-)</td> </tr> <tr> <td>OTBDMS (-)-DCCSO</td> <td>S (-)</td> </tr> <tr> <td>H (-)-DCCSO</td> <td>S (-)</td> </tr> </tbody> </table>	R	[O]	OTBDMS (+)-DCCSO	R (70)	H (+)-DCCSO	R (-)	OTBDMS (-)-DCCSO	S (-)	H (-)-DCCSO	S (-)	640		
R	[O]														
OTBDMS (+)-DCCSO	R (70)														
H (+)-DCCSO	R (-)														
OTBDMS (-)-DCCSO	S (-)														
H (-)-DCCSO	S (-)														
	1. KHMDS, THF, -78°, 1 h 2. PSPO, -78°, 2 h	 I I+II = (70); I:II = 3:1	641												
	1. LDA, THF, -78°, 1 h 2. MoOPH, -78 to 0° 3. 5% HCl	 <table border="1" data-bbox="1006 1412 1215 1503"> <thead> <tr> <th>R¹</th> <th>R²</th> <th>I</th> <th>II</th> </tr> </thead> <tbody> <tr> <td>H</td> <td>H</td> <td>(40)</td> <td>(38)</td> </tr> <tr> <td>OTHP</td> <td>OH</td> <td>(-)</td> <td>(-)</td> </tr> </tbody> </table>	R ¹	R ²	I	II	H	H	(40)	(38)	OTHP	OH	(-)	(-)	642
R ¹	R ²	I	II												
H	H	(40)	(38)												
OTHP	OH	(-)	(-)												
C27															
	1. LiCA (2 eq), THF, -78° 2. MoOPH, -78 to -52°	 I I+II = (80); I:II = 20:80	36, 34												
	1. LiCA (2 eq), THF, HMPA, -78° 2. MoOPH, -78°	I+II (50); I:II = 14:86	36, 34												
	1. LiCA (2 eq), THF, HMPA, -78 to -52° 2. MoOPH, -52°	I+II (57); I:II = 43:57	36, 34												
	1. LDA 2. MoOPH, -78°, 5 h	 I I+II = (23); I:II = 43:57	34												

TABLE 3. α -HYDROXYLATION OF ESTER ENOLATES (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	LiCA (1 eq) 2. MoOPH, -78° , 3 h	I+II (29); I:II = 60:40	34
	LiCA (2 eq) 2. MoOPH, -78° , 8 h	I+II (65); I:II = 33:67	34, 36
	LiCA (2 eq), HMPA 2. MoOPH, -52° , 1 h	I+II (55); I:II = 82:18	34
	1. KHMDS (2 eq), KOBu- <i>s</i> (8 eq) 2. MoOPH, -52 to -46° , 40 min	I+II (73); I:II = 1:99	34, 635
C ₂₈ 	1. KHMDS (2 eq), KOBu- <i>s</i> (8 eq) 2. MoOPH, -52 to -30° , 60 h	 I+II = (10); I:II = 30:70	635
	1. LiHMDS, THF, 0° , 30 min 2. (+)-CSO, -78° , 1.5 h; 0° , 15 min	 (90) 97% de	248
C ₂₉ 	1. LDA, THF, -78° , 30 min 2. (+)-CSO, -78° , 1.5 h; 0° , 15 min	 (62) (3)	643
C ₃₈ 	1. LiCA, -78° , 1 h 2. O ₂ , P(OEt) ₃ , -78° , 30 min 3. NH ₄ Cl	 (69)	37
C ₄₁ 	1. KHMDS (2 eq), KOBu- <i>s</i> (8 eq) 2. MoOPH, -65 to -59° , 100 min	 I+II = (47); I:II = 5:95	635

^a The yield was 68% with ferrocenium tetrafluorophosphate.^b HMPA was added.

TABLE 4. α -HYDROXYLATION OF LACTONE ENOLATES

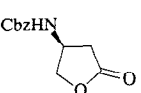
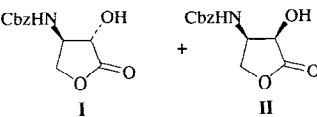
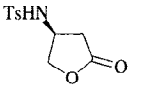
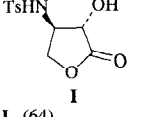
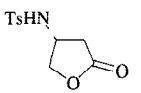
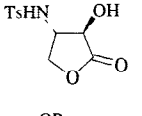

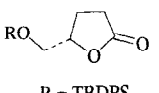
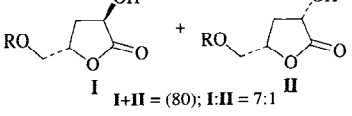
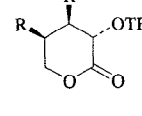
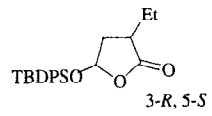
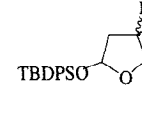
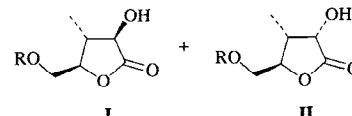
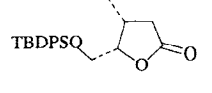
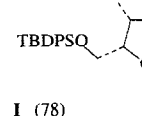
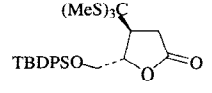
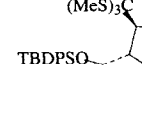
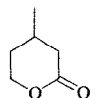
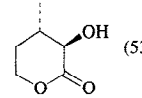
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.														
	1. KHMDS, THF 2. MoOPH, -78°, 6 h	 I + II = (40); I:II = 1:9	644														
	1. NaHMDS, THF 2. PSPO, -78°, 1 h	I + II (56); I:II = 14:1	644														
	1. KHMDS, THF 2. PSPO, -78°, 1 h	I + II (70); I:II = 6.5:1	644														
	1. NaHMDS, THF 2. PSPO, -78°, 2 h	 (64)	645														
	1. NaHMDS, THF, -78° 2. (+)-CSO, -78°, 2 h	I (64)	646														
	1. NaHMDS, THF, -78° 2. PSPO, -78°, 2 h	 (68)	646														
	1. NaHMDS, THF, -78° 2. [O], -78° to rt, 2 h 3. RCl	 <table border="1" style="display: inline-table; vertical-align: middle;"> <thead> <tr> <th>[O]</th> <th>R</th> <th>% ee</th> </tr> </thead> <tbody> <tr> <td>(+)-DCCSO</td> <td>PhMe₂Si (74)</td> <td>S 78</td> </tr> <tr> <td>(+)-DMCSO</td> <td>PhMe₂Si (69)</td> <td>S 84</td> </tr> <tr> <td>(+)-DMCSO</td> <td>Bz (70)</td> <td>S 84</td> </tr> <tr> <td>(-)-DMCSO</td> <td>Bz (70)</td> <td>R 84</td> </tr> </tbody> </table>	[O]	R	% ee	(+)-DCCSO	PhMe ₂ Si (74)	S 78	(+)-DMCSO	PhMe ₂ Si (69)	S 84	(+)-DMCSO	Bz (70)	S 84	(-)-DMCSO	Bz (70)	R 84
[O]	R	% ee															
(+)-DCCSO	PhMe ₂ Si (74)	S 78															
(+)-DMCSO	PhMe ₂ Si (69)	S 84															
(+)-DMCSO	Bz (70)	S 84															
(-)-DMCSO	Bz (70)	R 84															
 R = TBDPS	1. LiHMDS, THF, -78°, 30 min 2. MoOPH, 1 h	 I + II = (80); I:II = 7:1	647														
	1. NaHMDS, THF, -78° 2. PSPO 3. TBDMSCl, imidazole	 (65)	648														
 3-R, 5-S	1. KHMDS, THF, -78° 2. PSPO	 (-) 1:1	608														
	1. NaHMDS, THF, -78° 2. (-)-CSO	 I + II = (68); I:II = 30:1	649														
	1. LiHMDS, THF, -78°, 30 min 2. MoOPH, -78 to -55°, 40 min	 (83)	650, 651														
	1. KHMDS, -78° 2. MoOPH, -78 to -30°	I (78)	652														
	1. LiHMDS, THF, -78°, 30 min 2. MoOPH, -50°, 1 h	 (86)	651, 650														
	1. KHMDS, THF, HMPA, -60 to -65°, 1.5 h 2. MoOPH, -50°, 1 h	I (77)	651														
	1. LDA, THF, TMEDA, -78°, 30 min 2. (+)-CSO (0.5 eq), -78°, 4 h	 (53) >95% dc, 55% ee	653														

TABLE 4. α -HYDROXYLATION OF LACTONE ENOLATES (Continued)

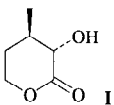
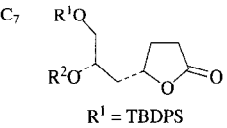
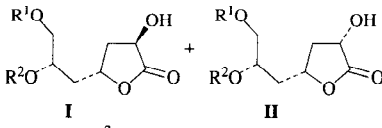
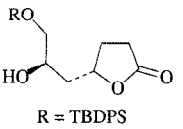
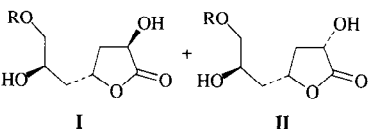
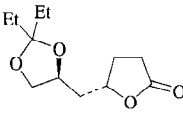
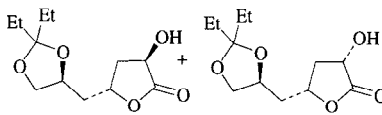
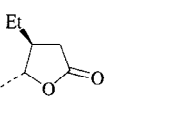
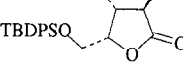
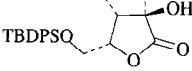
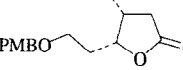
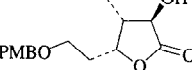
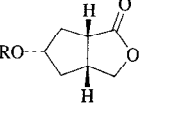
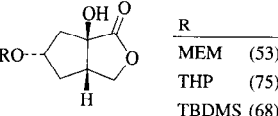
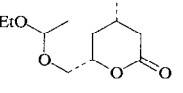
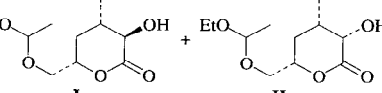
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. LDA, THF, TMEDA, -78° , 30 min 2. (-)-CSO (0.5 eq), -78° , 4 h	 (54) >95% de, 56% ee	653
	1. LDA, THF, TMEDA, -78° , 30 min 2. (-)-CSO (1 eq), -78° , 4 h	I (60) 90% de	653
	1. LDA, THF, TMEDA, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, -78° , 30 min 2. (-)-CSO (0.5 eq), -78° , 4 h	I (41) >95% de, 46% ee	653
	1. LDA, THF, TMEDA, LiCl, -78° , 30 min 2. (-)-CSO (0.5 eq), -78° , 4 h	I (46) >95% de, 56% ee	653
	1. LiCA, THF, TMEDA, -78° , 30 min 2. (-)-CSO (0.5 eq), -78° , 4 h	I (58) >95% de, 60% ee	653
	1. LDA, THF, TMEDA, -78° , 30 min 2. (-)-DCCSO (0.5 eq), -78° , 4 h	I (45) >95% de, 37% ee	653
	1. NaHMDS, THF, TMEDA, -78° , 30 min 2. (-)-DCCSO (0.5 eq), -78° , 4 h	I (21) >95% de, 50% ee	653
	1. LDA, THF, TMEDA, -78° , 30 min 2. (-)-DMCSO (0.5 eq), -78° , 4 h	I (32) >95% de, 31% ee	653
C7  R ¹ = TBDPS	1. LiHMDS, THF, -78° , 30 min 2. MoOPH, 1 h	 I + II R ² I+II I:II H (76) 4:1 TBDPS (78) 6:1	647
 R = TBDPS	1. LiHMDS 2. MoOPH	 I + II = (78); I:II = 2.5:1	647
	MoOPH	 I + II = (-); I:II = 4:1	647
	MoOPH	(0)	654
	1. KHMDS, THF, -78° , 1 h 2. MoOPH, -50° , 1 h	 (86)	651
	LiHMDS, THF, MoOPH	 (68)	655
	1. LDA, THF, -90° , 1.5 h 2. MoOPH, -55°	 R MEM (53) THP (75) TBDMS (68)	656
	1. LDA, THF 2. MoOPH	 I + II = (-); I:II = 8.5:1	657

TABLE 4. α -HYDROXYLATION OF LACTONE ENOLATES (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. LDA, THF, -78° 2. MoOPH, -78 to 0°	 (67)	658
	1. LDA, THF, -78° 2. MoOPH, -78° to rt	 (42)	659
	1. LDA, THF, -78° 2. MoOPH, -78° to rt	 I + II I+II = (81); I:II = 4:1	660, 152, 661
	1. LDA, THF, -78° , 15 min 2. MoOPH, -78° , 2 h	 (73)	40, 151
	O_2 , P(OEt) ₃	 I + II I+II = (-); I:II = 1:1	194
	1. Li base 2. MoOPH, -78°	I (63) + II (7)	194
	1. LDA 2. MoOPH	 (-)	662
	1. LDA 2. MoOPH, -20° , 0.5 h	 I + II I+II = (70); I:II = 2:1	663
	1. LiHMDS 2. MoOPH, -20° , 0.5 h	I+II (78-82); I:II = 4-8:1	663
	1. KHMDS 2. MoOPH, -20° , 0.5 h	I+II (70); I:II = 3:1	663
	1. LDA 2. PSPO, -78° , 1.5 h	I+II (35); I:II = 1:1	663
	1. LiHMDS 2. PSPO, -78° , 1.5 h	I+II (63); I:II = 1:1	663
	1. KHMDS 2. PSPO, -78° , 1.5 h	I+II (41); I:II = 1:1	663
	1. KHMDS, -78° , 30 min 2. MoOPH, -78 to -30°	 (31) + (53)	652
	1. LiHMDS, THF, -78° 2. MoOPH	 (80)	664

 C₈

TABLE 4. α -HYDROXYLATION OF LACTONE ENOLATES (Continued)

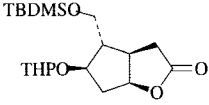
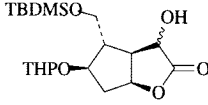
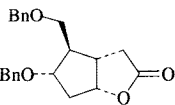
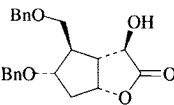
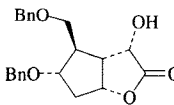
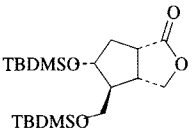
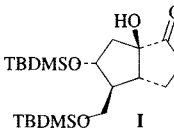
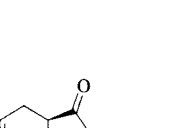
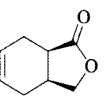
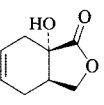
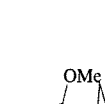
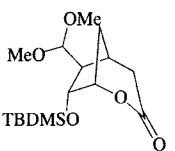
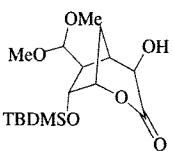
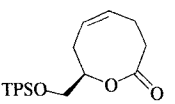
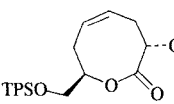
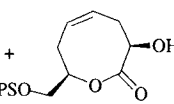
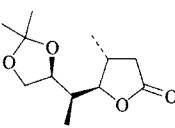
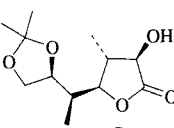
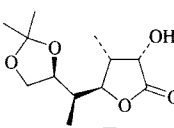
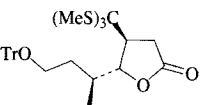
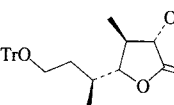
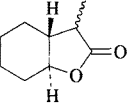
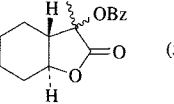
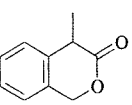
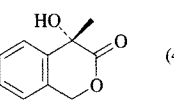



Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. LDA, THF, -78° 2. MoOPH, -78° to rt	 (80) 33% de	665
	1. LDA, THF, -78° , 1h 2. MoOPH, rt, 8 h	 +  I + II = (58); I:II = 5:1	666
	1. LDA, THF, -30° 2. O_2 , P(OMe) $_3$, -78 to 0°	 (—)	667
	1. LDA, THF, -30° , 30 min 2. MoOPH, -35° , 1 h	I (40)	656, 667
	1. LDA, THF, HMPA, -75° 2. O_2 , P(OMe) $_3$, -75° to rt, 1.5 h	 (73)	668
	1. LDA 2. MoOPH	I (10)	668
	1. KHMDS 2. PSPO	 (70)	669
	1. KHMDS, PhMe 2. (–)-CSO, -78°	 (26) +  (26)	256, 670, 671
	1. LiHMDS, THF, -78° , 30 min 2. MoOPH, -78 to -50° , 40 min	 +  I + II = (77); I:II = 4:1	650, 672
	1. LiHMDS, THF 2. MoOPH, -78° 3. Raney-Ni, MeOH	 (64)	664
	1. LiTr, DME 2. (PhCO $_2$) $_2$, DME, 5°	 (50)	38
	1. NaHMDS, THF, -78° , 30 min 2. (+)-CSO, -78° , 1 h	 (44) S 77% ee	492
	1. LDA, THF, 0° , 30 min 2. (+)-CSO, -78° , 1 h	I (45) S 23% ee	492
	1. NaHMDS, THF, -78° , 30 min 2. (+)-DCCSO, -78° , 1 h	I (60) S 45% ee	492
	1. LDA, THF, -0° , 30 min 2. (+)-DCCSO, -78° , 1 h	I (55) S 17% ee	492

TABLE 4. α -HYDROXYLATION OF LACTONE ENOLATES (Continued)

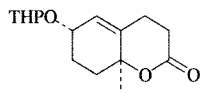
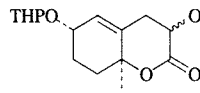
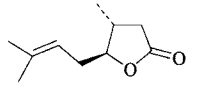
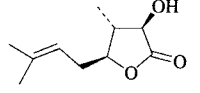
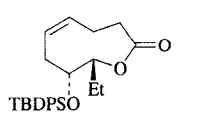
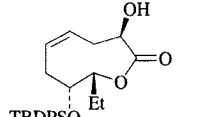
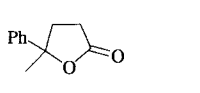
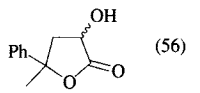
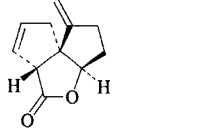
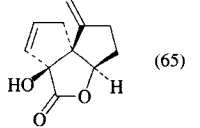
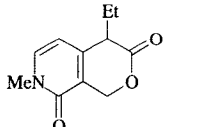
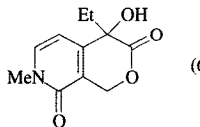
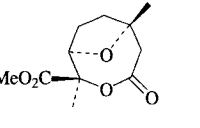
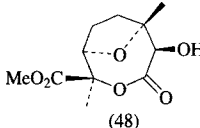
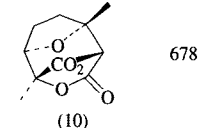
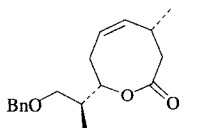
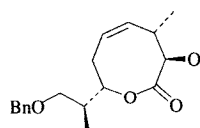
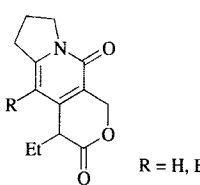
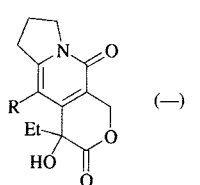
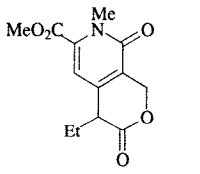
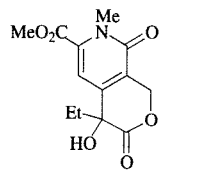
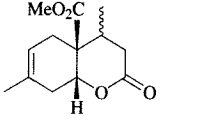
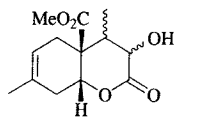
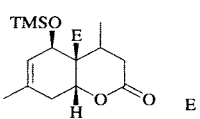
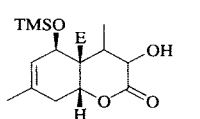
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. LDA, THF, -78° , 10 min 2. MoOPH, HMPA, -78° to rt	 (80)	673
	1. LiHMDS, THF, -78° 2. MoOPH	 (71)	674
	1. KHMDS, THF, PhMe, -78° 2. PSPO, -78°	 (79)	675
C₁₁ 	1. LDA, -70° , 30 min 2. MoOPH, -78° , 2 h	 (56)	151, 40
	1. KHMDS, THF 2. PSPO, -40° , 1 h	 (65)	676
	Base, O ₂ , P(OEt) ₃	 (68)	677
	1. KHMDS, THF, -78° , 20 min 2. PSPO, -78° , 30 min	 (48) +  (10)	678
	1. KHMDS, PhMe, -78° 2. PSPO	 (91)	679
C₁₃ 	Base, O ₂ , P(OEt) ₃	 (—)	677
	K ₂ CO ₃ , O ₂ , MeOH	 (—)	677
	1. LDA, THF, -78° , 10 min 2. MoOPH, -78° , 2 h; 0° , 15 min	 (75)	680
	1. LDA, THF, -78° , 30 min 2. MoOPH, -78° , 4 h; 0° , 30 min	 (73)	681

TABLE 4. α -HYDROXYLATION OF LACTONE ENOLATES (Continued)

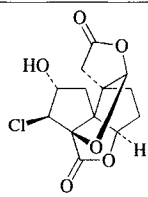
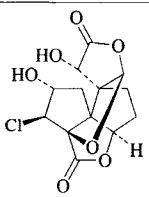
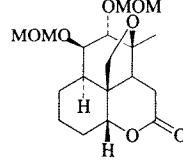
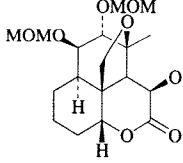
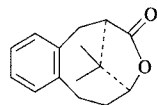
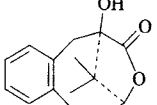
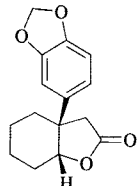
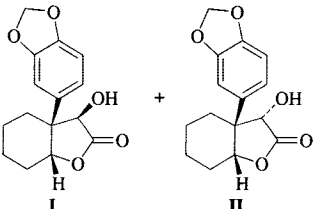
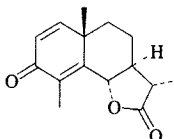
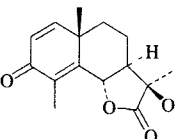
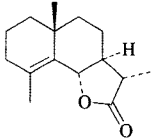
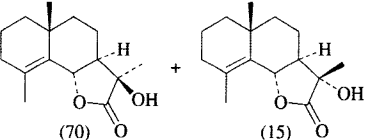
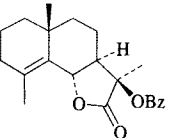
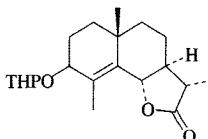
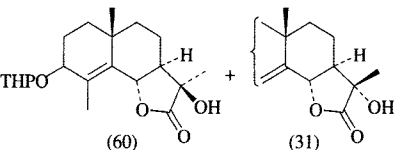
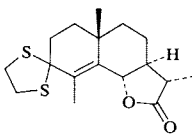
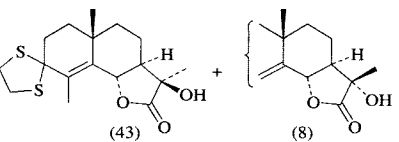
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. KHMDS, THF, -78° , 30 min 2. PSPO, THF, 30 min	 (64)	676
	1. LDA, THF, HMPA, -78° , 1 h; -20° , 2 h 2. MoOPH, -78° , 2 h	 (52)	682
	1. LDA, THF, HMPA (4 eq), -78° 2. O_2 , -78° , 12-16 h	 (83)	683
	1. LDA 2. MoOPH	 I + II	511
	1. LiHMDS 2. PSPO, -78°	I (62) I+II = (15) ⁶² ; I:II = 3:1	511
	1. KHMDS 2. PSPO, -78°	I (91)	511
	1. LDA 2. O_2	 (0)	298
	1. LDA, THF, -70° , 30 min 2. O_2 , 30 min	 (70) + (15)	298
	1. LiTr, DME, 5° , 2 h 2. $(PhCO_2)_2$, DME, 5° , 1 h	 (50)	38
	1. LDA, THF, -70° , 30 min 2. O_2 , 30 min	 (60) + (31)	298
	1. LDA, THF, -70° , 30 min 2. O_2 , 30 min	 (43) + (8)	298

TABLE 4. α -HYDROXYLATION OF LACTONE ENOLATES (Continued)

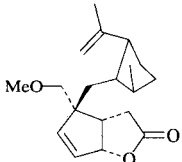
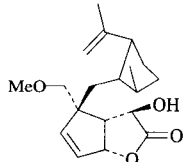
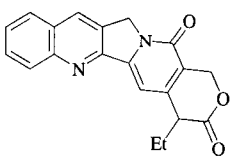
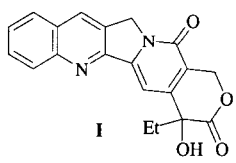
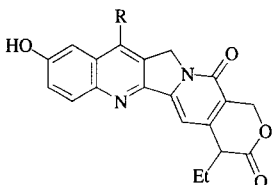
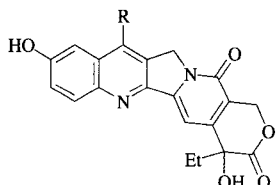
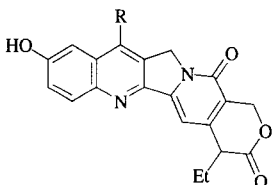
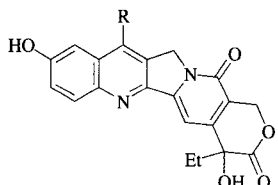
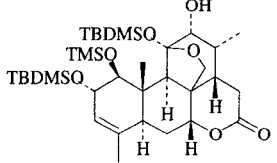
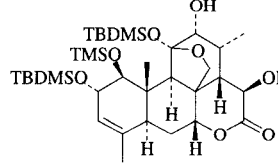
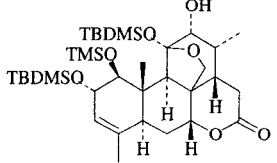
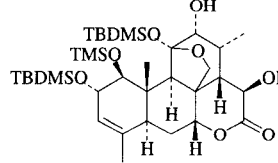
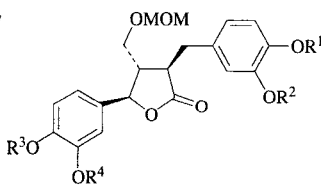
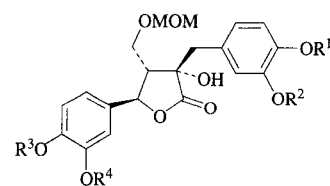
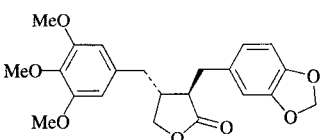
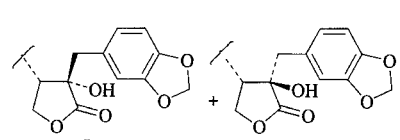
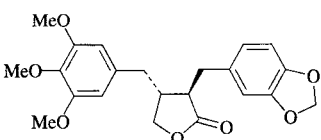
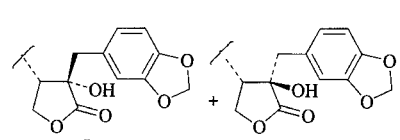
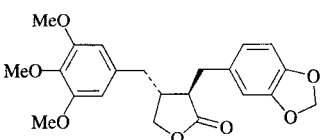
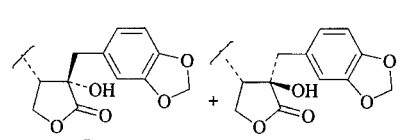
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																				
C ₁₈ 	1. LDA, THF, -70°, 1.5 h 2. MoOPH, -70 to -35°, 2.5 h	 (79)	584																				
C ₂₀ 	O ₂ , CuCl ₂ , DMF	 I (100)	688																				
C ₂₀₋₂₂ 	O ₂ , Me ₂ NH, CuCl ₂ , DMF, rt, 5 h	 I (99)	689, 690																				
C ₂₀ 	O ₂ , Me ₂ NH, CuCl ₂ , DMF, 8 h	 I (99) R H (83) Et (83)	690																				
C ₂₀ 	1. LDA, THF, -70°, 2 h 2. MoOPH, -44°, 4 h	 I (57)	644, 691																				
C ₂₀ 	1. KHMDS, THF, -78°, 1 h 2. PSPO, -78°, 2 h	 I (73)	691																				
C ₂₁₋₂₇ 	1. KHMDS, THF, -78° 2. MoOPH	 I (73)	692																				
		<table border="1"> <thead> <tr> <th>R¹</th> <th>R²</th> <th>R³</th> <th>R⁴</th> <th>% de</th> </tr> </thead> <tbody> <tr> <td>-CH₂-</td> <td>Me</td> <td>Me</td> <td>(76)</td> <td>98</td> </tr> <tr> <td>Me</td> <td>Me</td> <td>-CH₂-</td> <td>(70)</td> <td>96</td> </tr> <tr> <td>Bn</td> <td>Me</td> <td>-CH₂-</td> <td>(80)</td> <td>96</td> </tr> </tbody> </table>	R ¹	R ²	R ³	R ⁴	% de	-CH ₂ -	Me	Me	(76)	98	Me	Me	-CH ₂ -	(70)	96	Bn	Me	-CH ₂ -	(80)	96	
R ¹	R ²	R ³	R ⁴	% de																			
-CH ₂ -	Me	Me	(76)	98																			
Me	Me	-CH ₂ -	(70)	96																			
Bn	Me	-CH ₂ -	(80)	96																			
C ₂₂ 	1. KHMDS, THF, -78° 2. MoOPH	 I + II = (82); I:II = 63:37	693																				
C ₂₂ 	1. KHMDS, 18-crown-6, THF, -78° 2. MoOPH	 I + II (95); I:II = 83:17	693																				
C ₂₂ 	1. KHMDS, 18-crown-6, THF, -78° 2. MoOPH	 I + II = (93); I:II = 82:18	693																				

TABLE 4. α -HYDROXYLATION OF LACTONE ENOLATES (Continued)

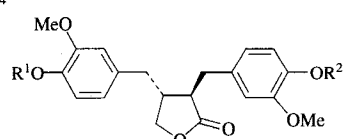
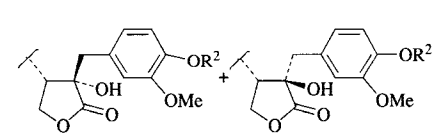
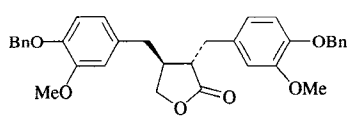
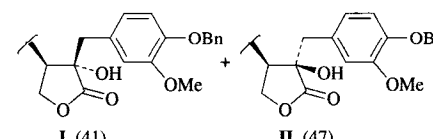
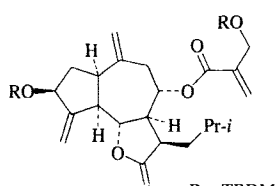
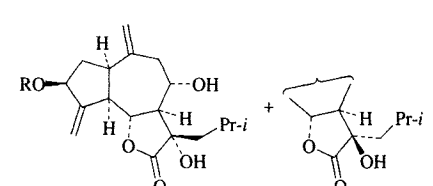
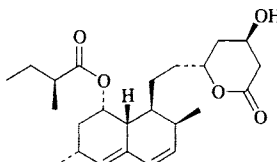
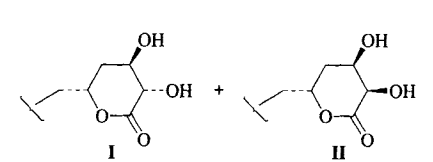
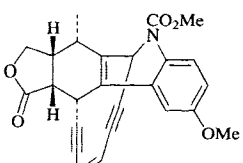
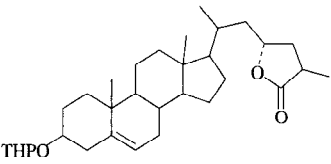
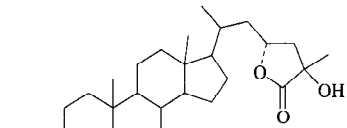
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																
C ₂₂₋₃₄ 	1. LiHMDS, 12-crown-4, C ₆ H ₆ 2. O ₂ , 3 h	 694 <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th>R¹</th> <th>R²</th> <th>I</th> <th>II</th> </tr> </thead> <tbody> <tr> <td>Me</td> <td>Me</td> <td>(36)</td> <td>(36)</td> </tr> <tr> <td>Bn</td> <td>Me</td> <td>(21)</td> <td>(24)</td> </tr> <tr> <td>Bn</td> <td>Bn</td> <td>(24)</td> <td>(24)</td> </tr> </tbody> </table>	R ¹	R ²	I	II	Me	Me	(36)	(36)	Bn	Me	(21)	(24)	Bn	Bn	(24)	(24)	
R ¹	R ²	I	II																
Me	Me	(36)	(36)																
Bn	Me	(21)	(24)																
Bn	Bn	(24)	(24)																
	1. KHMDS, THF, -78°, 1 h; 0°, 1.5 h 2. O ₂ , P(OEt) ₃ , -78 to 0°, 1 h 3. NH ₄ Cl	 I (41) II (47) 695, 696																	
	1. KHMDS, THF, -78°, 1 h; 0°, 1 h 2. MoOPH, -78°, 2 h 3. Na ₂ SO ₃	I+II (43); I:II = 1:2	695, 696																
	1. Lithium base 2. PSPO	I+II (40); I:II = 1:6	695, 696																
	1. KHMDS, THF, -78°, 1 h; 0°, 1.5 h 2. PSPO, -78°, 15 min 3. NH ₄ Cl	I+II (76); I:II = 1:5.8	695, 696																
C ₂₂ 	1. KHMDS, P(OEt) ₃ , THF, -73°, 1 h 2. O ₂ , -73°, 1 h; -20°	 (17) (4) 697																	
	1. KHMDS, P(OEt) ₃ , bipyridine, THF, -73°, 1 h 2. O ₂ , -73°, 1 h; -20°	(34)	697																
C ₂₄ 	1. LiHMDS 2. PSPO	 I II I+II = (35-45); I:II = 9:1 698																	
C ₂₅ 	1. KHMDS, THF, -95°, 15 min 2. MoOPH, -78°, 50 min	(72)	230																

TABLE 4. α -HYDROXYLATION OF LACTONE ENOLATES (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
<p>C₂₇</p> 	<p>1. LDA, THF 2. MoOPH, -78°</p>	 <p>(65)</p>	699

^a The number is the conversion.

TABLE 5. α -HYDROXYLATION OF CARBOXYLIC ACID DIANIONS

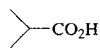
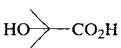
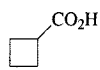

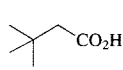
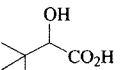
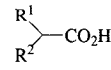
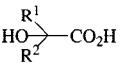
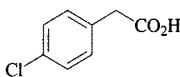
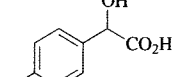
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																											
C ₄ 	1. LDA (2 eq), -78° 2. O ₂ , -90 to -100° 3. HCl	 (78)	74, 76																											
C ₅ 	1. LDA (3 eq), THF, 0°, 30 min 2. O ₂ , rt, 18 h 3. HCl	 (100)	301																											
C ₆ 	1. LDA (2 eq), -78° 2. O ₂ , -90 to -100° 3. HCl	 (72)	74, 76																											
C ₆₋₁₄ 	1. LDA (2 eq), 0 to 5°, 30 min; 40 to 45°, 1-1.5 h 2. Air, rt, 18 h 3. HCl	 <table border="1" data-bbox="1142 1212 1328 1464"> <thead> <tr> <th>R¹</th> <th>R²</th> <th>Yield (%)</th> </tr> </thead> <tbody> <tr> <td>Et</td> <td>Et</td> <td>(49)</td> </tr> <tr> <td><i>c</i>-C₅H₉</td> <td>H</td> <td>(51)</td> </tr> <tr> <td>C₆H₄Cl-4</td> <td>H</td> <td>(72)</td> </tr> <tr> <td>C₆H₄OMe-4</td> <td>H</td> <td>(48)</td> </tr> <tr> <td><i>n</i>-C₇H₁₅</td> <td>H</td> <td>(51)</td> </tr> <tr> <td>Ph</td> <td>Et</td> <td>(67)</td> </tr> <tr> <td>1-naphthyl</td> <td>H</td> <td>(32)</td> </tr> <tr> <td>Ph</td> <td>Ph</td> <td>(90)</td> </tr> </tbody> </table>	R ¹	R ²	Yield (%)	Et	Et	(49)	<i>c</i> -C ₅ H ₉	H	(51)	C ₆ H ₄ Cl-4	H	(72)	C ₆ H ₄ OMe-4	H	(48)	<i>n</i> -C ₇ H ₁₅	H	(51)	Ph	Et	(67)	1-naphthyl	H	(32)	Ph	Ph	(90)	299 299 299 299 299 299 299 299, 302
R ¹	R ²	Yield (%)																												
Et	Et	(49)																												
<i>c</i> -C ₅ H ₉	H	(51)																												
C ₆ H ₄ Cl-4	H	(72)																												
C ₆ H ₄ OMe-4	H	(48)																												
<i>n</i> -C ₇ H ₁₅	H	(51)																												
Ph	Et	(67)																												
1-naphthyl	H	(32)																												
Ph	Ph	(90)																												
C ₈ 	1. <i>n</i> -BuLi (2 eq), 0 to 5°, 30 min; 40 to 45°, 1-1.5 h 2. Air, rt, 18 h 3. HCl	 (72)	299																											

TABLE 5. α -HYDROXYLATION OF CARBOXYLIC ACID DIANIONS (Continued)

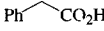
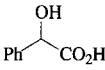
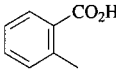
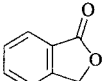
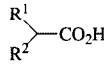
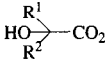
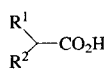
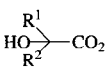
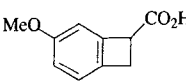
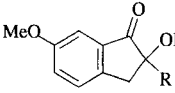
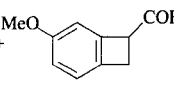



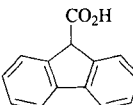
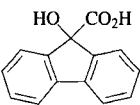
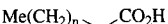
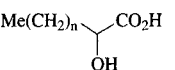
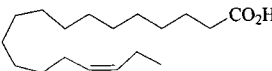
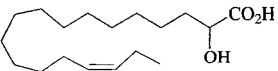
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																					
	1. <i>n</i> -BuLi (2 eq) 2. O ₂ , 20° 3. HCl	 (86)	302, 299																					
	1. LDA (3 eq), 0 to 25° 2. LiO ₂ Bu- <i>t</i> , 0°	 (81)	64																					
C ₈₋₁₄ 	1. LDA (2-2.5 eq), 0 to 25° 2. LiO ₂ Bu- <i>t</i> , 0° 3. CH ₂ N ₂	 <table border="1" data-bbox="1137 700 1328 895"> <thead> <tr> <th>R¹</th> <th>R²</th> <th></th> </tr> </thead> <tbody> <tr> <td>Ph</td> <td>H</td> <td>(91)</td> </tr> <tr> <td><i>n</i>-C₆H₁₃</td> <td>H</td> <td>(77)</td> </tr> <tr> <td><i>n</i>-Bu</td> <td>Et</td> <td>(82)</td> </tr> <tr> <td>-(CH₂)₅-</td> <td></td> <td>(79)</td> </tr> <tr> <td>Ph</td> <td>Et</td> <td>(80)</td> </tr> <tr> <td>Ph</td> <td>Ph</td> <td>(88)</td> </tr> </tbody> </table>	R ¹	R ²		Ph	H	(91)	<i>n</i> -C ₆ H ₁₃	H	(77)	<i>n</i> -Bu	Et	(82)	-(CH ₂) ₅ -		(79)	Ph	Et	(80)	Ph	Ph	(88)	64
R ¹	R ²																							
Ph	H	(91)																						
<i>n</i> -C ₆ H ₁₃	H	(77)																						
<i>n</i> -Bu	Et	(82)																						
-(CH ₂) ₅ -		(79)																						
Ph	Et	(80)																						
Ph	Ph	(88)																						
	1. LDA, THF, 0°, 1.5 h 2. (TMSO) ₂ , -78° to rt, 10-15 h 3. H ₂ SO ₄ (conc.), MeOH	 <table border="1" data-bbox="1137 918 1328 1090"> <thead> <tr> <th>R¹</th> <th>R²</th> <th></th> </tr> </thead> <tbody> <tr> <td>Ph</td> <td>H</td> <td>(—)</td> </tr> <tr> <td><i>n</i>-C₆H₁₃</td> <td>H</td> <td>(44)</td> </tr> <tr> <td>C₆H₄Me-4</td> <td>H</td> <td>(48)</td> </tr> <tr> <td>Bn</td> <td>H</td> <td>(48)</td> </tr> <tr> <td>Ph</td> <td>Ph</td> <td>(31)</td> </tr> </tbody> </table>	R ¹	R ²		Ph	H	(—)	<i>n</i> -C ₆ H ₁₃	H	(44)	C ₆ H ₄ Me-4	H	(48)	Bn	H	(48)	Ph	Ph	(31)	109			
R ¹	R ²																							
Ph	H	(—)																						
<i>n</i> -C ₆ H ₁₃	H	(44)																						
C ₆ H ₄ Me-4	H	(48)																						
Bn	H	(48)																						
Ph	Ph	(31)																						
C ₁₀ 	1. LDA (2.2 eq) 2. RCO ₂ Me, 0° 3. MoOPH, 0° to rt	 I +  II <table border="1" data-bbox="1032 1274 1293 1480"> <thead> <tr> <th>R</th> <th>I</th> <th>II</th> </tr> </thead> <tbody> <tr> <td>Et</td> <td>(26)</td> <td>(13)</td> </tr> <tr> <td><i>i</i>-Pr</td> <td>(53)</td> <td>(12)</td> </tr> <tr> <td><i>t</i>-Bu</td> <td>(58)</td> <td>(8)</td> </tr> <tr> <td>Ph</td> <td>(75)</td> <td>(0)</td> </tr> <tr> <td>4-MeOC₆H₄(CH₂)₂</td> <td>(11)</td> <td>(12)</td> </tr> <tr> <td></td> <td>(68)</td> <td>(15)</td> </tr> </tbody> </table>	R	I	II	Et	(26)	(13)	<i>i</i> -Pr	(53)	(12)	<i>t</i> -Bu	(58)	(8)	Ph	(75)	(0)	4-MeOC ₆ H ₄ (CH ₂) ₂	(11)	(12)		(68)	(15)	283
R	I	II																						
Et	(26)	(13)																						
<i>i</i> -Pr	(53)	(12)																						
<i>t</i> -Bu	(58)	(8)																						
Ph	(75)	(0)																						
4-MeOC ₆ H ₄ (CH ₂) ₂	(11)	(12)																						
	(68)	(15)																						
C ₁₄ 	1. <i>n</i> -BuLi (2 eq) 2. O ₂ , 20° 3. HCl	 (70)	302																					
C ₁₅₋₂₆ 	1. LDA (2.25 eq), THF, HMPA, -78 to 50°, 30 min; 40-45°, 1-1.5 h 2. NaI 3. O ₂ , rt, 30 min 4. MeOH, HCl, 60°, 1 h	 <table border="1" data-bbox="1154 1676 1258 1871"> <thead> <tr> <th>n</th> <th></th> </tr> </thead> <tbody> <tr> <td>13</td> <td>(35)</td> </tr> <tr> <td>15</td> <td>(47)</td> </tr> <tr> <td>17</td> <td>(44)</td> </tr> <tr> <td>19</td> <td>(40)</td> </tr> <tr> <td>21</td> <td>(44)</td> </tr> <tr> <td>23</td> <td>(43)</td> </tr> </tbody> </table>	n		13	(35)	15	(47)	17	(44)	19	(40)	21	(44)	23	(43)	300							
n																								
13	(35)																							
15	(47)																							
17	(44)																							
19	(40)																							
21	(44)																							
23	(43)																							
C ₁₈ 	1. LDA 2. PSPO	 (55)	305																					

TABLE 6. α -HYDROXYLATION OF AMIDE ENOLATES

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₅₋₆ 	1. LDA, 0°, 15 min 2. O ₂ 3. Na ₂ SO ₃	 R Me (72) Et (85)	54 54, 28
C ₆ 	1. LiNMe ₂ , THF, 0° 2. O ₂	 I (80)	28
C ₇ 	1. LiNMe ₂ , THF, HMPA 2. Air	I (85)	28
C ₇ 	1. LDA, 0°, 15 min 2. O ₂ 3. Na ₂ SO ₃	 (84)	54
C ₁₀ 	1. LiNEt ₂ , THF 2. Air	 (86)	28
C ₁₀ 	1. LDA, THF 2. (TMSO) ₂	 (51)	109
C ₁₀₋₁₅ 	1. LiHMDS, THF, -78°, 30 min 2. (BnOCO ₂) ₂ , -78°, 30 min	 I R Et (87) >98:<2 Ph (82) >99:<1 Bn (81) 94:6 II	347
C ₁₀ 	1. LiNMe ₂ , THF 2. Air	 (80)	28
C ₁₁ 	1. NaHMDS, THF, -78° 2. PSPO, -78°	 I II I+II = (86); I:II = 99:1	177
C ₁₂ 	1. LDA, THF 2. (TMSO) ₂	 (56)	109
	1. LDA, THF, -78°, 25-30 min 2. (+)-CSO, -78°, 15 min	 (70) S 30% ee	269
	1. LDA, THF, HMPA, -78°, 25-30 min 2. (+)-CSO, -78°, 15 min	I (74) R 50% ee	269
	1. LDA, THF, HMPA, -78°, 25-30 min 2. (+)-CSO, -78°, 15 min	I (71) S 41% ee	269
	1. LDA, THF, 0 to 20° 2. <i>t</i> -BuO ₂ Li, 0 to 25°	 R Ph (68) <i>n</i> -C ₆ H ₁₃ (70)	64

TABLE 6. α -HYDROXYLATION OF AMIDE ENOLATES (Continued)

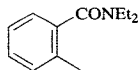
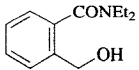
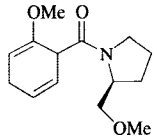
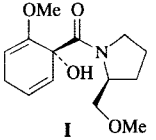
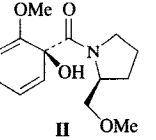

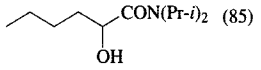
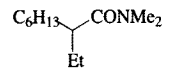
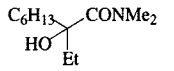

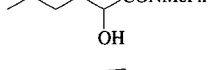
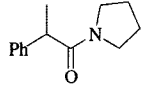
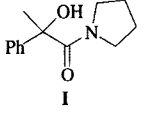
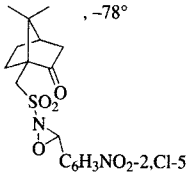
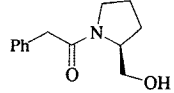
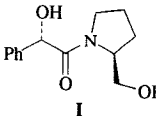
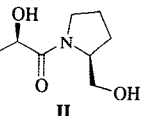
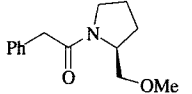
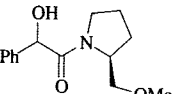
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. <i>s</i> -Bu-Li, TMEDA, 0 to 20° 2. <i>t</i> -BuO ₂ Li, 0 to 25°	 (80)	64
	1. KH, THF, rt, 1 h 2. (+)-CSO, -78°, 30 min	 +  I+II = (47); I:II = 27:1	292
	1. LDA, THF, 0° 2. (<i>i</i> -PrO) ₃ TiCl, -78 to -30°, 3 h 3. O ₂ , -30°, 30 min 4. NH ₄ F, H ₂ O, 1 h	 (85)	57
	1. LiNMe ₂ , THF 2. Air	 (81)	28
	1. LDA, THF 2. (TMSO) ₂	 (58)	109
	1. LDA, THF, 0°, 30 min 2. (+)-CSO, -78°	 (77) <i>R</i> 60% ee	269
	1. LDA, THF, -78 to 0°, 30 min 2. (+)-CSO, -78°, 30 min	I (40) <i>S</i> 35% ee	259
	1. LDA, THF, HMPA, -78 to 0°, 30 min 2. (+)-CSO, -78°, 30 min	I (35) <i>R</i> 20% ee	259
	1. LDA, THF, 0°, 30 min 2.  , -78°	I (60) <i>R</i> 40% ee	269
	1. LDA, THF, 0° 2. (<i>i</i> -PrO) ₃ TiCl, -78 to -30°, 3 h 3. O ₂ , -30°, 30 min 4. NH ₄ F, H ₂ O, 1 h	 +  I+II = (69); I:II = 67:33	258
	1. NaHMDS, THF, 25°, 30 min 2. PSPO, -78° to rt	I+II (87); I:II = 3.5:96.5	258
	1. LDA, THF, 25°, 30 min 2. PSPO, -78° to rt	I+II (85); I:II = >97.5:<2.5	258
	1. LDA, Et ₂ O, 25°, 30 min 2. PSPO, -78° to rt	 (70) <i>R</i> 46% de	258
	1. LDA, Et ₂ O/HMPA (30:1), 25°, 30 min 2. PSPO, -78° to rt	I (55) <i>R</i> 33% de	258
	1. LDA, THF/HMPA (30:1), 25°, 30 min 2. PSPO, -78° to rt	I (60) <i>R</i> 32% de	258
	1. NaHMDS, THF, 25°, 30 min 2. PSPO, -78° to rt	I (80) <i>R</i> 17% de	258

TABLE 6. α -HYDROXYLATION OF AMIDE ENOLATES (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.															
C ₁₄ 	1. NaHMDS, THF, -78° 2. PSPO, -78°	 I+II = (86); I:II = 94:6	177															
	1. LDA, THF, -78 to 0°, 30 min 2. PSPO, -78°, 30 min	 (35) <i>R</i> 67% de	259															
	1. LDA, THF, -78 to 0°, 30 min 2. (+)-CSO, -78°, 30 min	 I (24) (<i>S</i> -) 50% de	259															
	1. LDA, THF, -78 to 0°, 30 min 2. PSPO, -78°, 30 min	 (54) <i>S</i> 55% de	259															
	1. LDA, THF, HMPA, -78 to 0°, 30 min 2. (-)-CSO, -78°, 30 min	 I (55) <i>S</i> 91% de	259															
	1. LDA, THF, HMPA -78 to 0°, 30 min 2. (+)-CSO, -78°, 30 min	 I (53) <i>S</i> 89% de	259															
	1. LDA, THF, 0° 2. (<i>i</i> -PrO) ₃ TiCl, -78 to -30°, 3 h 3. O ₂ , -30°, 30 min 4. NH ₄ F, H ₂ O, 1 h	 (79)	57															
C ₁₅ 	1. NaHMDS, THF, -78° 2. PSPO, -78°	 I+II = (91); I:II = 95:5	177															
	1. Sodium base 2. MoOPH, -78°, 1 h	 I+II = (37); I:II = 98:2	177															
	1. NaHMDS, THF, -78° 2. PSPO, -78°	 I+II = (85); I:II = 95:5	177															
	1. LDA, THF, 0° 2. (<i>i</i> -PrO) ₃ TiCl, -78 to -30°, 3 h 3. O ₂ , -30°, 30 min 4. NH ₄ F, H ₂ O, 1 h	 (74)	57															
C ₁₆ 	1. LDA, 0°, 15 min 2. O ₂ 3. Na ₂ SO ₃	 (81)	54															
C ₁₆₋₁₉ 	1. NaHMDS, THF, -78° 2. PSPO, -78°	 I+II = (85); I:II = 95:5	177															
		<table border="1"> <thead> <tr> <th>R</th> <th>I+II</th> <th>I:II</th> </tr> </thead> <tbody> <tr> <td>CMe₃</td> <td>(94)</td> <td>99:1</td> </tr> <tr> <td>(CH₂)₂CO₂Me</td> <td>(68)</td> <td>96:4</td> </tr> <tr> <td>Ph</td> <td>(77)</td> <td>90:10</td> </tr> <tr> <td>Bn</td> <td>(86)</td> <td>96:4</td> </tr> </tbody> </table>	R	I+II	I:II	CMe ₃	(94)	99:1	(CH ₂) ₂ CO ₂ Me	(68)	96:4	Ph	(77)	90:10	Bn	(86)	96:4	
R	I+II	I:II																
CMe ₃	(94)	99:1																
(CH ₂) ₂ CO ₂ Me	(68)	96:4																
Ph	(77)	90:10																
Bn	(86)	96:4																
C ₁₈ 	1. LiHMDS, -78° 2. TEMPO, PhI(OAc) ₂	 (93)	290															

TABLE 6. α -HYDROXYLATION OF AMIDE ENOLATES (Continued)

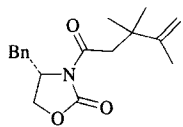
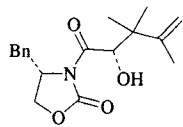
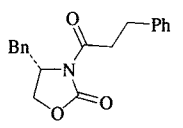
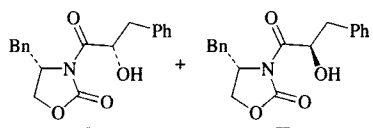
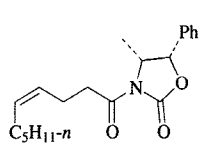
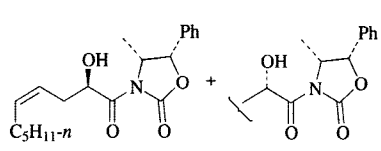
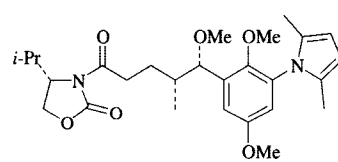
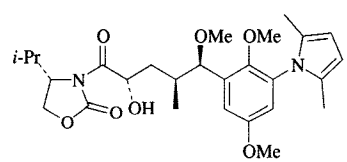
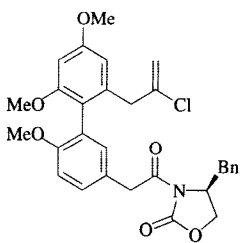
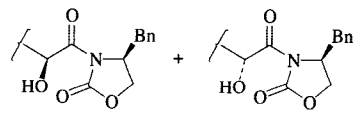
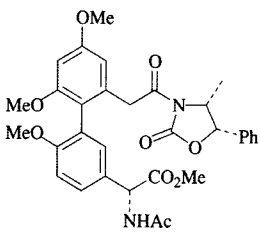
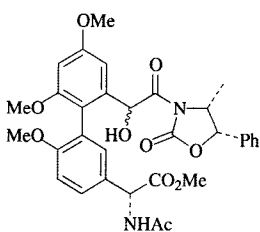
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
<p>C₁₈</p> 	1. NaHMDS, THF 2. PSPO, -78°	 (88) >99% dc	700, 701
<p>C₁₉</p> 	1. NaHMDS, THF 2. PSPO, -78°	 I + II = (83); I:II = 95:5	177
<p>C₂₀</p> 	1. NaHMDS, THF, -78° 2. PSPO, -78°	 I + II = (83); I:II = >98:<2	702
<p>C₂₆</p> 	1. NaHMDS, THF, -78°, 25 min 2. PSPO, -78°, 20 min	 (83)	703
<p>C₃₀</p> 	1. NaHMDS, THF 2. PSPO, -78°	 I + II = (95); I:II = 88:12	239, 704
<p>C₃₂</p> 	1. NaHMDS, THF 2. PSPO, -78°	 (85-92)	239, 704

TABLE 7. α -HYDROXYLATION OF LACTAM ENOLATES

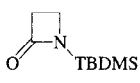
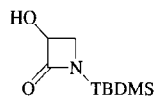
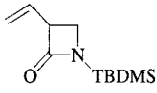
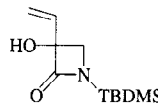
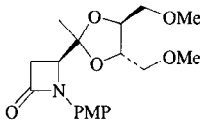

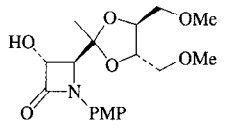
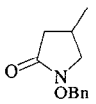
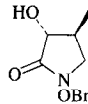
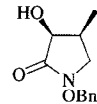
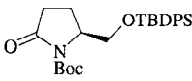

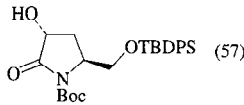
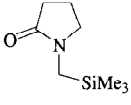
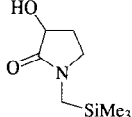


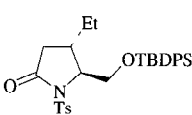
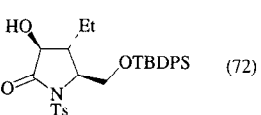
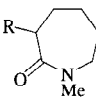
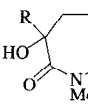
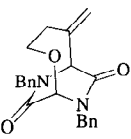
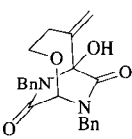
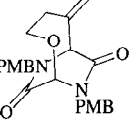
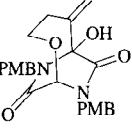


Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₃ 	1. LDA, THF, -78°, 30 min 2. MoOPH, -78 to 25°, 30 min	 (64-68)	307, 308
C ₅ 	1. NaHMDS, THF, -78° 2. PSPO, -78°, 15 min	 (46)	309
	1. LDA 2. 	 (57)	705, 706
	NaHMDS, THF, PSPO, -100°, 30 min	 I +  II I+II = (51); I:II = 3:2	707, 708
	1. KHMDS, -90° 2. PSPO	I+II (—)	709
	1. LDA, THF, -78 to -44° 2. MoOPH	 (57)	710
	1. LDA 2. MoOPH, -78°, 1.5 h; 20°	 (60)	59, 711
C ₆ 	1. LDA, 0°, 5 min 2. O ₂ 3. Na ₂ SO ₃	 (80)	54
C ₇ 	1. NaHMDS, THF, -78°, 15 min 2. PSPO	 (72)	712
C ₇₋₁₄ 	1. LiNMe ₂ , THF 2. Air	 R H (82) Bn (70)	28
C ₈ 	1. <i>n</i> -BuLi, HMPA, -100°, 1 min 2. O ₂ , -100°, 15 min; rt	 (36)	39
	1. <i>n</i> -BuLi, HMPA, -100°, 7 min 2. O ₂ , -78°, 10 min; 0°, 3 min	 (49)	39
C ₉ 	1. LiNMe ₂ , THF 2. Air	 R <i>n</i> -Bu (76) Bn (82-90)	28

TABLE 7. α -HYDROXYLATION OF LACTAM ENOLATES (Continued)

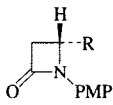
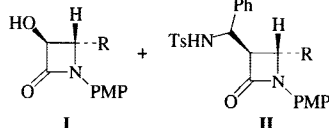
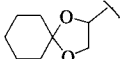
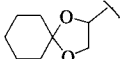
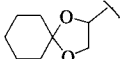
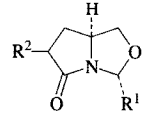
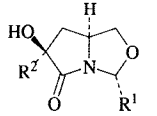
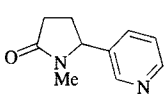
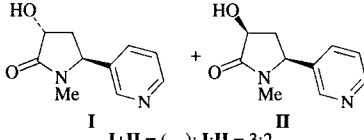
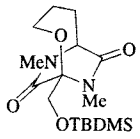
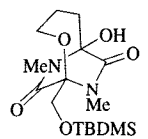
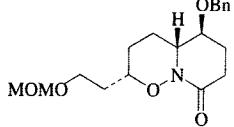
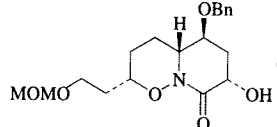
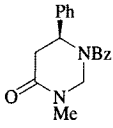
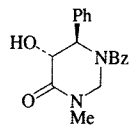
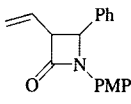
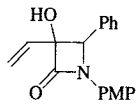
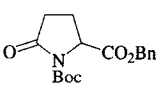
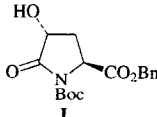
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																				
C ₉₋₁₂ 	1. LDA, THF, -78° 2. PSPO, -78° to rt, 15 h	 <table border="1"> <thead> <tr> <th>R</th> <th>I</th> <th>II</th> </tr> </thead> <tbody> <tr> <td>Ph</td> <td>(57)</td> <td>(15-25)</td> </tr> <tr> <td><i>c</i>-C₆H₁₁</td> <td>(54)</td> <td>(15-25)</td> </tr> <tr> <td>PhCH=CHCH₂ (<i>trans</i>)</td> <td>(57)</td> <td>(15-25)</td> </tr> <tr> <td></td> <td>(53)</td> <td>(15-25)</td> </tr> </tbody> </table>	R	I	II	Ph	(57)	(15-25)	<i>c</i> -C ₆ H ₁₁	(54)	(15-25)	PhCH=CHCH ₂ (<i>trans</i>)	(57)	(15-25)		(53)	(15-25)	713					
R	I	II																					
Ph	(57)	(15-25)																					
<i>c</i> -C ₆ H ₁₁	(54)	(15-25)																					
PhCH=CHCH ₂ (<i>trans</i>)	(57)	(15-25)																					
	(53)	(15-25)																					
C ₉₋₁₉ 	1. LDA, THF, -78° 2. [O], -78°	 <table border="1"> <thead> <tr> <th>R¹</th> <th>R²</th> <th>[O]</th> <th>% de</th> </tr> </thead> <tbody> <tr> <td><i>i</i>-Pr</td> <td>H</td> <td>MoOPH (45)</td> <td>84</td> </tr> <tr> <td>Ph</td> <td>H</td> <td>MOPD (78)</td> <td>80</td> </tr> <tr> <td>Ph</td> <td>CH₂CH=CH₂</td> <td>MOPD (61)</td> <td>100</td> </tr> <tr> <td>Ph</td> <td>CH₂C₆H_{11-c}</td> <td>MOPD (43)</td> <td>84</td> </tr> </tbody> </table>	R ¹	R ²	[O]	% de	<i>i</i> -Pr	H	MoOPH (45)	84	Ph	H	MOPD (78)	80	Ph	CH ₂ CH=CH ₂	MOPD (61)	100	Ph	CH ₂ C ₆ H _{11-c}	MOPD (43)	84	714
R ¹	R ²	[O]	% de																				
<i>i</i> -Pr	H	MoOPH (45)	84																				
Ph	H	MOPD (78)	80																				
Ph	CH ₂ CH=CH ₂	MOPD (61)	100																				
Ph	CH ₂ C ₆ H _{11-c}	MOPD (43)	84																				
C ₁₀ 	1. LDA 2. O ₂	 I+II = (-); I:II = 3:2 I+II = (-); I:II = 4:1	715																				
	1. <i>n</i> -BuLi, THF, -78° 2. MoOPH	 (62)	716																				
	1. LiHMDS 2. (+)-DCCSO, THF, -78°	 (82) 89% de	717																				
C ₁₁ 	1. LDA, THF, -40°, 30 min 2. (+)-CSO, -78°, 1 h; 25°, 5 min	 (71)	177, 718																				
	1. LDA, THF, -78°, 10 min 2. MoOPH, -78°	 (67)	336																				
C ₁₂ 	1. LiHMDS, -78° 2. PTSO	 (61)	719																				
	PSPO	I (30)	720																				

TABLE 7. α -HYDROXYLATION OF LACTAM ENOLATES (Continued)

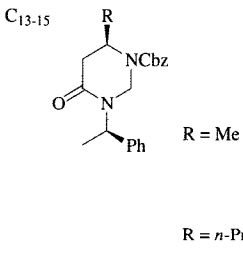
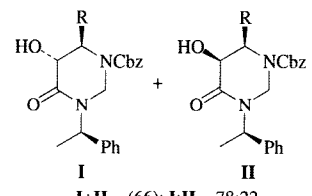
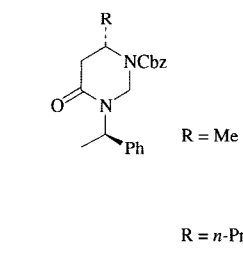
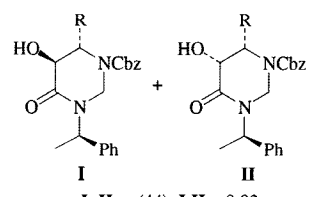
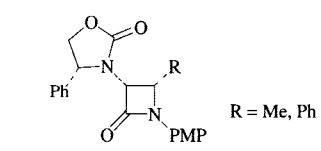
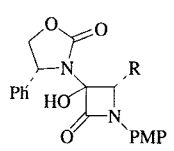
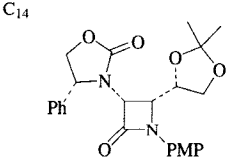
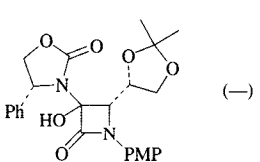
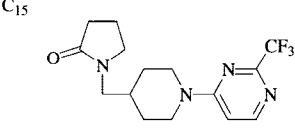
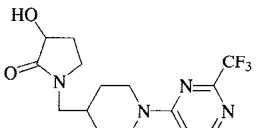
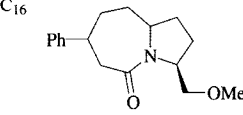
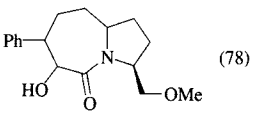
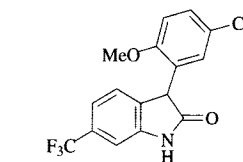
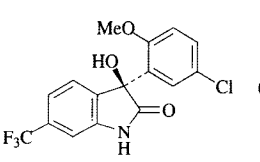

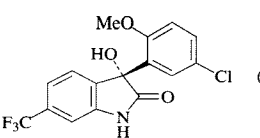
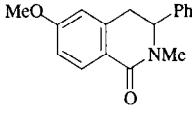
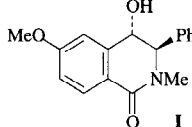
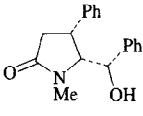
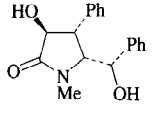
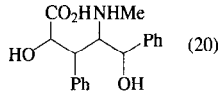
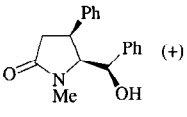
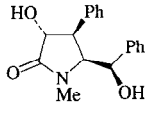
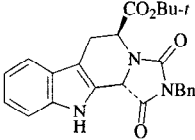
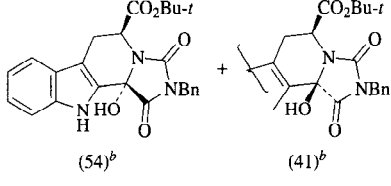
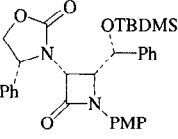
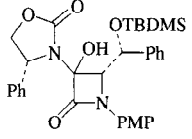
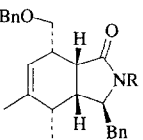
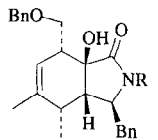
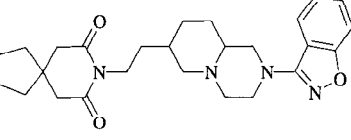
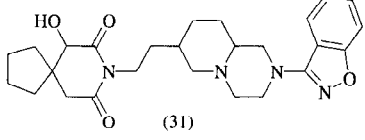
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
<p>C₁₃₋₁₅</p>  <p>R = Me</p> <p>R = <i>n</i>-Pr</p>	<p>1. LiHMDS, THF, 0°, 1 h</p> <p>2. (-)-CSO, -78° to rt, 16 h</p> <p>1. LiHMDS, THF, 0°, 1 h</p> <p>2. (+)-CSO, -20° to rt, 16 h</p>	 <p>I + II = (66); I:II = 78:22</p> <p>I + II = (72); I:II = >99:<1</p>	309a
 <p>R = Me</p> <p>R = <i>n</i>-Pr</p>	<p>1. NaHMDS, THF, 0° to rt, 2 h</p> <p>2. (+/-)-CSO, -78° to rt, 16 h</p> <p>1. LiHMDS, THF, 0°, 1 h</p> <p>2. (-)-CSO, -20° to rt, 16 h</p>	 <p>I + II = (44); I:II = 8:92</p> <p>I + II = (35); I:II = 99:1</p>	309a
<p>C₁₃₋₁₈</p>  <p>R = Me, Ph</p>	<p>1. LiHMDS, THF, -78°, 1.5 h</p> <p>2. MoOPH, -78°, 6 h</p>	 <p>(—)</p>	721
<p>C₁₄</p> 	<p>1. LiHMDS, THF, -78°, 1.5 h</p> <p>2. MoOPH, -78°, 6 h</p>	 <p>(—)</p>	721
<p>C₁₅</p> 	<p>1. LiHMDS, THF, -78°, 1.5 h</p> <p>2. PSPO, -78° to rt, 18 h</p>	 <p>(18)</p>	722
<p>C₁₆</p> 	<p>1. LDA, THF, -50 to -48°</p> <p>2. (+)-CSO</p>	 <p>(78)</p>	723
	<p>1. KHMDS, THF, Ar</p> <p>2. (+)-CSO, -78 to 0°</p>	 <p>(84) >95% ee^d</p>	724
	<p>1. KHMDS, THF, Ar</p> <p>2. (-)-CSO, -78 to 0°</p>	 <p>(78) >95% ee^d</p>	724

TABLE 7. α -HYDROXYLATION OF LACTAM ENOLATES (Continued)

	Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₁₇		1. LDA, -78° 2. (-)-CSO	 (85)	339
		1. LDA, -78° 2. PSPO	I (56)	339
C ₁₈		1. LDA, HMPA, -70 to -60°, 1 h 2. P(OEt) ₃ 3. O ₂ , -70°	 (41)	58
		1. LDA, -70° 2. O ₂ 3. Na ₂ SO ₃	 (20)	58
	 (+)	1. LDA, HMPA, -70 to -60°, 1 h 2. P(OEt) ₃ 3. O ₂ , -70°	 (46) (+)	58
		MoOPH or PSPO	I (0)	58
		O ₂ , NaOH, MeOH, rt, 10 min	 (54) ^b + (41) ^b	725
C ₁₉		1. LiHMDS, THF, -78°, 1.5 h 2. MoOPH, -78°, 6 h	 (-)	721
C ₂₀₋₂₅		1. LiHMDS, THF, 0°, 1 h 2. O ₂ , P(OMe) ₃ , 0°, 1 h	 R Et (60) Bn (50)	726, 727 727
C ₂₆		1. NaHMDS, THF, -78°, 15 min 2. (+)-CSO, -60 to -78°, 2.5 h	 (31)	728

^a The configuration shown is tentative.^b The yields were determined by HPLC.

TABLE 8. α -HYDROXYLATION OF NITRILE ANIONS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₂₋₈ 	1. BuLi, Et ₂ O, -78°; reflux 3 h 2. (TMSO) ₂ , -78° to rt, overnight	+ I II R I II TMS (48) (5) Ph (35) (5)	315
C ₆ 	1. <i>n</i> -BuLi, Et ₂ O, -70°, 5 min 2. O ₂ , -30°, 30 min 3. SnCl ₂ , HCl, 0°, 30 min	(—)	313
C ₇₋₁₆ 	1. LDA, -78° 2. O ₂ , -78°, 30 min 3. SnCl ₂ , HCl	 R ¹ R ² —(CH ₂) ₅ — (—) Me <i>n</i> -C ₅ H ₁₁ (—) Me <i>c</i> -C ₆ H ₁₁ (—) Me Bn (82) Bn Bn (—) Bn <i>n</i> -Bu (—) Bn <i>c</i> -C ₅ H ₉ (—) Ph Me (—) Ph Et (—) Ph <i>i</i> -Pr (—) Ph <i>c</i> -C ₆ H ₁₁ (—) Ph Ph (—) C ₆ H ₄ F-4 Me (—) C ₆ H ₄ Cl-4 Me (—) 1-naphthyl Me (—) C ₆ H ₄ Ph-4 Me (—)	310
C ₈ 	1. LDA, THF, -78°, 15 min 2. MoOPH, -78°, 10 min; -23°, 40 min	(35-40)	311
	1. LDA 2. MoOPH	(45) + (30)	622
	1. LDA 2. MoOPH	(25) + (45)	622
C ₁₀ 	1. LDA, THF, -78°, 30 min 2. MoOPH, -78°, 30 min; -20°, 1 h	(13) + (62)	312
	1. LDA, THF, -78°, 15 min 2. MoOPH, -78°, 10 min; -23°, 40 min	(57)	311
C ₁₁ 	1. LiNEt ₂ , -78° 2. O ₂ , -78°, 30 min 3. SnCl ₂ , HCl	(70) + (9)	30
C ₁₃ 	1. LiNEt ₂ , -78° 2. O ₂ , -78°, 30 min 3. SnCl ₂ , HCl	(53)	30
	1. LiNEt ₂ , -78° 2. O ₂ , -78°, 30 min 3. SnCl ₂ , HCl	(60) + (17)	30

TABLE 8. α -HYDROXYLATION OF NITRILE ANIONS (Continued)



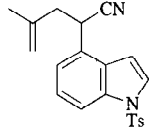
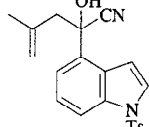
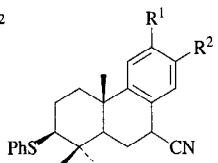
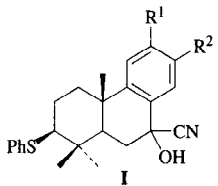
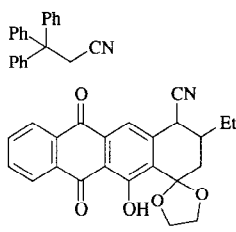

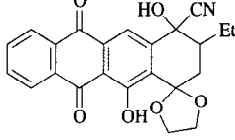
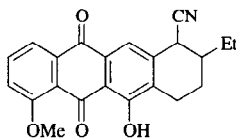
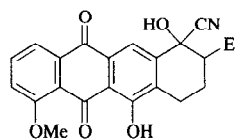
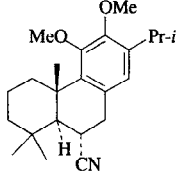
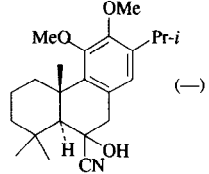
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₁₄ 	1. LDA, THF, -78°, 15 min 2. MoOPH, -78°, 10 min; -23°, 40 min	 (35)	311
	KOBu-t, O ₂ , -78°, or MoOPH	 (—)	195
C ₁₈ <i>n</i> -C ₁₆ H ₃₃ CH ₂ CN	1. LDA, THF, -78°, 15 min 2. MoOPH, -78°, 10 min; -23°, 40 min	<i>n</i> -C ₁₆ H ₃₃ CH(OH)CN (55-60)	311
C ₁₈₋₂₂ 	1. LDA, THF, -78°, 5 min 2. O ₂ , 1 h 3. SnCl ₂ , HCl, 0°, 30 min	 $\begin{array}{ccc} R^1 & R^2 & I \\ H & H & (-) \\ OMe & i-Pr & (-) \end{array}$	197
	1. LDA, THF, -78°, 5 min 2. MoOPH	I, R ¹ = OMe, R ² = <i>i</i> -Pr (—)	197
C ₂₁ 	1. LDA, THF, -78°, 15 min 2. MoOPH, -78°, 10 min; -23°, 40 min	 (55)	311
	1. LDA, THF, -78°, 30 min 2. O ₂ , -78°, 2 h; rt, 1 h 3. SnCl ₂ ,	 (—)	586
C ₂₂ 	1. LDA, THF, HMPA, -78° 2. O ₂ , -78°, 1 h	 (—)	586
C ₂₃ 	1. LDA, THF 2. O ₂ 3. SnCl ₂ , HCl	 (—)	729

TABLE 9A. α -HYDROXYLATION OF ENOLATES OF α -DIKETONES

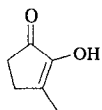
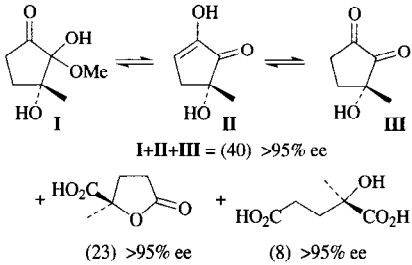
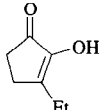
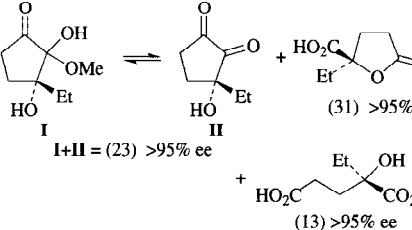
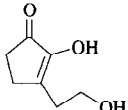
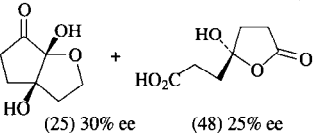
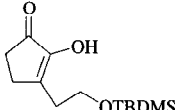
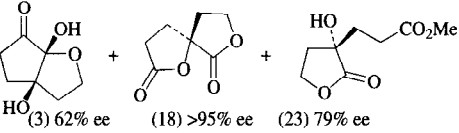
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. Ti(OPr- <i>i</i>) ₄ , (+) diethyl tartrate, <i>t</i> -BuO ₂ H, -20°, 42 h 2. Citric acid, MeOH, CH ₂ Cl ₂	 <p> $I+II+III = (40) >95\% ee$ $(23) >95\% ee$ $(8) >95\% ee$ </p>	287
	1. Ti(OPr- <i>i</i>) ₄ , (+) diethyl tartrate, <i>t</i> -BuO ₂ H, -20°, 42 h 2. Citric acid, MeOH, CH ₂ Cl ₂	 <p> $I+II = (23) >95\% ee$ $(31) >95\% ee$ $(13) >95\% ee$ </p>	287
	1. Ti(OPr- <i>i</i>) ₄ , (+) diethyl tartrate, <i>t</i> -BuO ₂ H, -20°, 42 h 2. Citric acid, MeOH, CH ₂ Cl ₂	 <p> $(25) 30\% ee$ $(48) 25\% ee$ </p>	287
	1. Ti(OPr- <i>i</i>) ₄ , (+) diethyl tartrate, <i>t</i> -BuO ₂ H, -20°, 42 h 2. Citric acid, MeOH, CH ₂ Cl ₂	 <p> $(3) 62\% ee$ $(18) >95\% ee$ $(23) 79\% ee$ </p>	287

TABLE 9B. HYDROXYLATION OF ENOLATES OF β -DICARBONYL COMPOUNDS

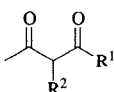
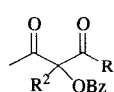
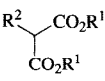
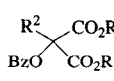
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																																																			
C_{5-17} 	1. NaH, C ₆ H ₆ 2. (PhCO ₂) ₂ , 0° to rt, overnight	 <table border="1" style="display: inline-table; vertical-align: middle;"> <thead> <tr> <th>R¹</th> <th>R²</th> <th>Yield (%)</th> </tr> </thead> <tbody> <tr><td>Me</td><td>H</td><td>(41)</td></tr> <tr><td>Me</td><td>Et</td><td>(82)</td></tr> <tr><td>Me</td><td>allyl</td><td>(90)</td></tr> <tr><td>Me</td><td><i>i</i>-Pr</td><td>(27)</td></tr> <tr><td>Me</td><td><i>n</i>-Bu</td><td>(89)</td></tr> <tr><td>Me</td><td><i>i</i>-C₅H₁₁</td><td>(86)</td></tr> <tr><td>Me</td><td>BzO</td><td>(35)</td></tr> <tr><td>Me</td><td>Bn</td><td>(76)</td></tr> <tr><td>Ph</td><td>H</td><td>(55)^a</td></tr> <tr><td>Ph</td><td>Me</td><td>(78)</td></tr> <tr><td>Ph</td><td>allyl</td><td>(72)</td></tr> <tr><td>Ph</td><td><i>n</i>-Bu</td><td>(61)</td></tr> <tr><td>Ph</td><td><i>sec</i>-Bu</td><td>(15)</td></tr> <tr><td>Ph</td><td><i>i</i>-C₅H₁₁</td><td>(55)</td></tr> <tr><td>Ph</td><td>BzO</td><td>(35)</td></tr> <tr><td>Ph</td><td>Bn</td><td>(76)</td></tr> </tbody> </table>	R ¹	R ²	Yield (%)	Me	H	(41)	Me	Et	(82)	Me	allyl	(90)	Me	<i>i</i> -Pr	(27)	Me	<i>n</i> -Bu	(89)	Me	<i>i</i> -C ₅ H ₁₁	(86)	Me	BzO	(35)	Me	Bn	(76)	Ph	H	(55) ^a	Ph	Me	(78)	Ph	allyl	(72)	Ph	<i>n</i> -Bu	(61)	Ph	<i>sec</i> -Bu	(15)	Ph	<i>i</i> -C ₅ H ₁₁	(55)	Ph	BzO	(35)	Ph	Bn	(76)	97
R ¹	R ²	Yield (%)																																																				
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	1. NaH, C ₆ H ₆ 2. (PhCO ₂) ₂ , 0° to rt, overnight	 <table border="1" style="display: inline-table; vertical-align: middle;"> <thead> <tr> <th>R¹</th> <th>R²</th> <th>Yield (%)</th> </tr> </thead> <tbody> <tr><td>Me</td><td>H</td><td>(68)</td></tr> <tr><td>Et</td><td>H</td><td>(55)^b</td></tr> <tr><td>Et</td><td>Me</td><td>(90)</td></tr> <tr><td>Et</td><td>Et</td><td>(75)</td></tr> <tr><td>Et</td><td>CO₂Et</td><td>(92)</td></tr> <tr><td>Et</td><td>allyl</td><td>(56)</td></tr> <tr><td>Et</td><td><i>n</i>-Bu</td><td>(86)</td></tr> <tr><td>Et</td><td><i>i</i>-Bu</td><td>(56)</td></tr> <tr><td>Et</td><td>Ph</td><td>(82)</td></tr> <tr><td>Et</td><td>Bn</td><td>(64)</td></tr> <tr><td>Et</td><td>1-C₁₀H₇</td><td>(97)</td></tr> </tbody> </table>	R ¹	R ²	Yield (%)	Me	H	(68)	Et	H	(55) ^b	Et	Me	(90)	Et	Et	(75)	Et	CO ₂ Et	(92)	Et	allyl	(56)	Et	<i>n</i> -Bu	(86)	Et	<i>i</i> -Bu	(56)	Et	Ph	(82)	Et	Bn	(64)	Et	1-C ₁₀ H ₇	(97)	99															
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Et	1-C ₁₀ H ₇	(97)																																																				

TABLE 9B. HYDROXYLATION OF ENOLATES OF β -DICARBONYL COMPOUNDS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																		
C ₆₋₇ 	NaH, C ₆ H ₆ , <i>t</i> -BuO ₂ Ac, 60-70°, 6-8 h	 R Me (30) EtO (27)	98 99																		
C ₆₋₁₈ 	NaH, C ₆ H ₆ , (PhCO ₂) ₂ , 0°, 12-16 h	 R ¹ R ² H Me (41) <i>i</i> -Pr Me (74) <i>n</i> -Bu Me (54) <i>i</i> -Bu Me (77) <i>sec</i> -Bu Me (85) H Ph (72) Bn Me (94) <i>i</i> -Pr Ph (43) allyl Ph (82) <i>n</i> -Bu Ph (67) <i>i</i> -Bu Ph (39) <i>sec</i> -Bu Ph (78) Bn Ph (82)	98																		
C ₇ 	DMDO, KF, CH ₂ Cl ₂ , H ₂ O, pH 7.3-7.5, 20°, 1 h	 (85)	110																		
	O ₂ , KF, DMSO, 60° to reflux, 30 min	 (6)	317																		
	O ₂ , KF, DMSO, 18-crown-6, P(OEt) ₃ , rt, 3 h	I (60)	317																		
	1. KH, THF, rt, 1 h 2. <i>m</i> -CPBA, 5 h	I (63)	330, 280																		
	1. NaHMDS, THF, 0°, 30 min 2. (+)-CSO, -78° to rt, 2 h	I (35-78) <i>R</i> 39-40% ee	330																		
	1. KHMDS, THF, 0°, 30 min 2. (+)-CSO, -78° to rt, 2 h	I (48) <i>R</i> 36% ee	330																		
	1. LDA, THF, 0°, 30 min 2. (+)-CSO, -78° to rt, 2 h	I (56) <i>R</i> 12% ee	330																		
	1. KHMDS, THF, 0°, 30 min 2. (-)-CSO, -78° to rt, 2 h	I (50) <i>S</i> 35% ee	330																		
	1. Base, THF, 0°, 30 min 2. , -78° to rt, 2 h	<table border="1"> <thead> <tr> <th rowspan="2">I</th> <th rowspan="2"><i>R</i></th> <th colspan="2">Base % ee</th> </tr> <tr> <th>Base</th> <th>% ee</th> </tr> </thead> <tbody> <tr> <td></td> <td></td> <td>LDA (60)</td> <td>12</td> </tr> <tr> <td></td> <td></td> <td>NaHMDS (64)</td> <td>57</td> </tr> <tr> <td></td> <td></td> <td>KHMDS (45)</td> <td>39</td> </tr> </tbody> </table>	I	<i>R</i>	Base % ee		Base	% ee			LDA (60)	12			NaHMDS (64)	57			KHMDS (45)	39	330
I	<i>R</i>	Base % ee																			
		Base	% ee																		
		LDA (60)	12																		
		NaHMDS (64)	57																		
		KHMDS (45)	39																		
	1. NaHMDS, THF, 0°, 30 min 2. , -78° to rt, 2 h	<table border="1"> <thead> <tr> <th rowspan="2">I</th> <th rowspan="2"><i>R</i></th> <th colspan="2">R % ee</th> </tr> <tr> <th>R</th> <th>% ee</th> </tr> </thead> <tbody> <tr> <td></td> <td></td> <td>CF₃ (60)</td> <td>68.5</td> </tr> <tr> <td></td> <td></td> <td>MeO (54)</td> <td>52</td> </tr> </tbody> </table>	I	<i>R</i>	R % ee		R	% ee			CF ₃ (60)	68.5			MeO (54)	52	330, 331 330				
I	<i>R</i>	R % ee																			
		R	% ee																		
		CF ₃ (60)	68.5																		
		MeO (54)	52																		
	1. KH, THF, rt, 1 h; -78°, 1 h 2. , -78°, 1 min	I (44) <i>S</i> 36.5% ee	330																		

TABLE 9B. HYDROXYLATION OF ENOLATES OF β -DICARBONYL COMPOUNDS (Continued)

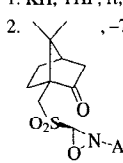
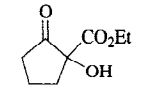
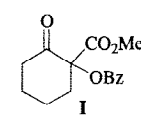
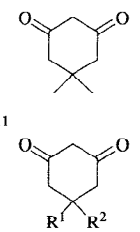
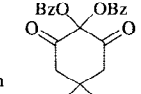
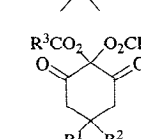
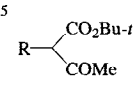
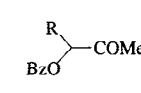
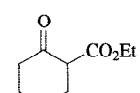
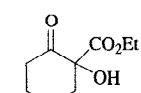
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																																											
	1. KH, THF, rt, 1 h; -78°, 1 h 2. , -78°, 1 min	I (42) <i>R</i> 33% ee	330																																											
	1. KH, THF, rt, 1 h; -78°, 1 h 2. , -78°, 1 min	I (33) <i>S</i> 12% ee	330																																											
	1. KH, THF, rt, 1 h; -78°, 1 h 2. , -78°, 1 min	I (43) <i>R</i> 8% ee	330																																											
	O ₂ , hv, dye sensitizer, CHCl ₃ , Bu ₄ NF, 2 h	 (49)	318, 84																																											
	1. LDA, PhMe, -78°, 1 h 2. (PhCO ₂) ₂ , -78 to 0°, 2 h	 (91)	103																																											
1. LDA, THF, -78° 2. (-)-CSO, -78 to 0° 3. BzCl, -78° to rt	I (49) <i>R</i> 86% ee	730																																												
1. LDA, THF, -78° 2. (+)-CSO, -78 to 0° 3. BzCl, -78° to rt	I (50) <i>S</i> 84% ee	730																																												
	1. NaOMe, MeOH, 0° 2. (PhCO ₂) ₂ , C ₆ H ₆ , BnEt ₃ NCl, rt, 12 h	 (28)	327																																											
	1. NaH, MeCN, 10°, 30 min 2. (R ³ CO ₂) ₂ , rt, 12 h	 <table border="1" style="margin-left: 20px;"> <thead> <tr> <th>R¹</th> <th>R²</th> <th>R³</th> <th></th> </tr> </thead> <tbody> <tr> <td>Me</td> <td>Me</td> <td>Ph</td> <td>(24)</td> </tr> <tr> <td>Me</td> <td>Me</td> <td>C₆H₄Cl-4</td> <td>(29)</td> </tr> <tr> <td>Me</td> <td>Me</td> <td>C₆H₄OMe-4</td> <td>(41)</td> </tr> <tr> <td>Me</td> <td>Me</td> <td>C₆H₄NO₂-4</td> <td>(—)</td> </tr> <tr> <td>Me</td> <td>Me</td> <td>BnO</td> <td>(35)</td> </tr> <tr> <td>—(CH₂)₅—</td> <td>Ph</td> <td></td> <td>(25)</td> </tr> <tr> <td>—(CH₂)₅—</td> <td>C₆H₄Cl-4</td> <td></td> <td>(—)</td> </tr> <tr> <td>—(CH₂)₅—</td> <td>C₆H₄OMe-4</td> <td></td> <td>(39)</td> </tr> <tr> <td>—(CH₂)₅—</td> <td>C₆H₄NO₂-4</td> <td></td> <td>(—)</td> </tr> <tr> <td>—(CH₂)₅—</td> <td>BnO</td> <td></td> <td>(30)</td> </tr> </tbody> </table>	R ¹	R ²	R ³		Me	Me	Ph	(24)	Me	Me	C ₆ H ₄ Cl-4	(29)	Me	Me	C ₆ H ₄ OMe-4	(41)	Me	Me	C ₆ H ₄ NO ₂ -4	(—)	Me	Me	BnO	(35)	—(CH ₂) ₅ —	Ph		(25)	—(CH ₂) ₅ —	C ₆ H ₄ Cl-4		(—)	—(CH ₂) ₅ —	C ₆ H ₄ OMe-4		(39)	—(CH ₂) ₅ —	C ₆ H ₄ NO ₂ -4		(—)	—(CH ₂) ₅ —	BnO		(30)
R ¹	R ²	R ³																																												
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	1. NaH, C ₆ H ₆ , (PhCO ₂) ₂ 2. <i>p</i> -TsOH, heat	 <table border="1" style="margin-left: 20px;"> <thead> <tr> <th>R</th> <th></th> <th></th> </tr> </thead> <tbody> <tr> <td>H</td> <td>(38)</td> <td>100</td> </tr> <tr> <td>Me</td> <td>(55)</td> <td>100</td> </tr> <tr> <td>Et</td> <td>(78)</td> <td>100</td> </tr> <tr> <td>(CH₂)₂CN</td> <td>(62)</td> <td>101</td> </tr> <tr> <td>allyl</td> <td>(78)</td> <td>100</td> </tr> <tr> <td><i>n</i>-Pr</td> <td>(66)</td> <td>100</td> </tr> <tr> <td><i>n</i>-Bu</td> <td>(73)</td> <td>100</td> </tr> <tr> <td><i>i</i>-Bu</td> <td>(73)</td> <td>100</td> </tr> <tr> <td><i>n</i>-C₅H₁₁</td> <td>(83)</td> <td>100</td> </tr> <tr> <td><i>i</i>-C₅H₁₁</td> <td>(73)</td> <td>100</td> </tr> <tr> <td><i>n</i>-C₆H₁₃</td> <td>(84)</td> <td>100</td> </tr> <tr> <td>Bn</td> <td>(86)</td> <td>100</td> </tr> </tbody> </table>	R			H	(38)	100	Me	(55)	100	Et	(78)	100	(CH ₂) ₂ CN	(62)	101	allyl	(78)	100	<i>n</i> -Pr	(66)	100	<i>n</i> -Bu	(73)	100	<i>i</i> -Bu	(73)	100	<i>n</i> -C ₅ H ₁₁	(83)	100	<i>i</i> -C ₅ H ₁₁	(73)	100	<i>n</i> -C ₆ H ₁₃	(84)	100	Bn	(86)	100					
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TABLE 9B. HYDROXYLATION OF ENOLATES OF β -DICARBONYL COMPOUNDS (Continued)

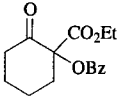
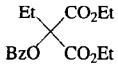
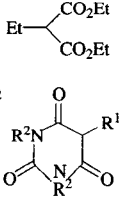
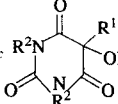
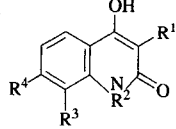
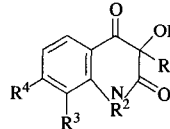
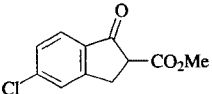
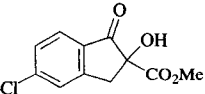
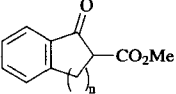
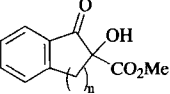
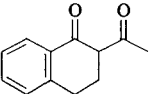
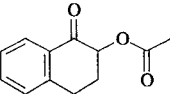
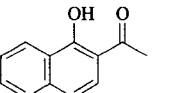
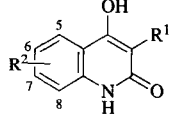
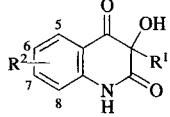
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																																																																												
	NaH, C ₆ H ₆ , (PhCO ₂) ₂ , 0°, 2 h	 (82)	98																																																																												
	1. NaH, C ₆ H ₆ , rt, 2 h 2. (PhCO ₂) ₂ , ice bath	(75)	99																																																																												
C ₁₀₋₂₂ 	H ₂ O ₂ (30%), NaOH, pH 8, 60°; rt 4-10 h ^c		<table border="1"> <thead> <tr> <th>R¹</th> <th>R²</th> <th></th> </tr> </thead> <tbody> <tr> <td>Ph</td> <td>H</td> <td>(67)</td> </tr> <tr> <td>Bn</td> <td>H</td> <td>(61)</td> </tr> <tr> <td>Ph</td> <td>Me</td> <td>(67)</td> </tr> <tr> <td>Ph</td> <td>Ph</td> <td>(28)</td> </tr> </tbody> </table>	R ¹	R ²		Ph	H	(67)	Bn	H	(61)	Ph	Me	(67)	Ph	Ph	(28)	321																																																												
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C ₁₁ 	<i>t</i> -BuO ₂ H, cinchonine (0.013 eq), <i>i</i> -PrOAc, rt, 6 d		(68) (+) 44% ee ^d	267																																																																											
C ₁₁₋₁₃ 	1. LDA, THF, -78° 2. (+)-CSO, -78° to rt 3. NH ₄ Cl, H ₂ O, -78° to rt		<table border="1"> <thead> <tr> <th>n</th> <th></th> <th>% ee</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>(59)</td> <td>0</td> </tr> <tr> <td>2</td> <td>(75)</td> <td>R 84</td> </tr> <tr> <td>3</td> <td>(62)</td> <td>18</td> </tr> </tbody> </table>	n		% ee	1	(59)	0	2	(75)	R 84	3	(62)	18	730																																																															
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C ₁₂ 	1. KHMDS 2. (+)-CSO		(58)	538																																																																											
	1. LDA, THF, Et ₂ O, -78° 2. (+)-CSO, -78° to rt 3. NH ₄ Cl, H ₂ O		(66)	730																																																																											
C ₁₂₋₂₁ 	NaOH, H ₂ O ₂ (30%), pH 8, 60°; rt, 4-10 h		<table border="1"> <thead> <tr> <th>R¹</th> <th>R²</th> <th></th> </tr> </thead> <tbody> <tr> <td>Et</td> <td>6-MeO</td> <td>(64)</td> </tr> <tr> <td>Ph</td> <td>6-Me</td> <td>(63)</td> </tr> <tr> <td>Ph</td> <td>8-Me</td> <td>(72)</td> </tr> <tr> <td>Ph</td> <td>6-MeO</td> <td>(78)</td> </tr> <tr> <td>Ph</td> <td>7-MeO</td> <td>(91)</td> </tr> <tr> <td>Ph</td> <td>8-MeO</td> <td>(59)</td> </tr> <tr> <td>Bn</td> <td>7-MeO</td> <td>(48)</td> </tr> <tr> <td>Ph</td> <td>8-Ph</td> <td>(58)</td> </tr> </tbody> </table>	R ¹	R ²		Et	6-MeO	(64)	Ph	6-Me	(63)	Ph	8-Me	(72)	Ph	6-MeO	(78)	Ph	7-MeO	(91)	Ph	8-MeO	(59)	Bn	7-MeO	(48)	Ph	8-Ph	(58)	321																																																
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TABLE 9B. HYDROXYLATION OF ENOLATES OF β -DICARBONYL COMPOUNDS (Continued)

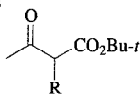
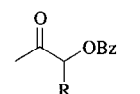
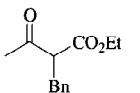
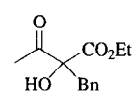
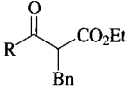
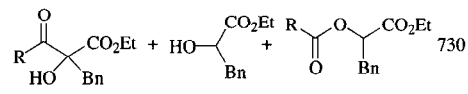
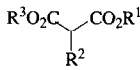
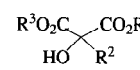
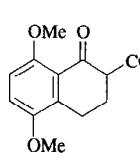
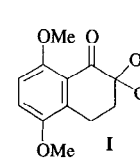
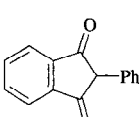
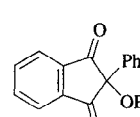
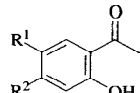
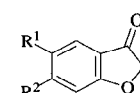
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																								
C_{12-18} 	1. NaH, C ₆ H ₆ , (PhCO ₂) ₂ 2. TsOH, 160°	 <table border="1"> <thead> <tr> <th>R</th> <th>Yield (%)</th> </tr> </thead> <tbody> <tr> <td>CH₂CO₂Et</td> <td>(86)</td> </tr> <tr> <td>CHMeCO₂Et</td> <td>(63)</td> </tr> <tr> <td>CHEtCO₂Et</td> <td>(44)</td> </tr> <tr> <td>CMe₂CO₂Et</td> <td>(56)</td> </tr> <tr> <td>CH(C₆H_{13-n})CO₂Et</td> <td>(73)</td> </tr> </tbody> </table>	R	Yield (%)	CH ₂ CO ₂ Et	(86)	CHMeCO ₂ Et	(63)	CHEtCO ₂ Et	(44)	CMe ₂ CO ₂ Et	(56)	CH(C ₆ H _{13-n})CO ₂ Et	(73)	102												
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C_{13} 	Bu ₄ NF, DMDO, CH ₂ Cl ₂ , H ₂ O, pH 7.3-7.5, 20°, 1 h	 (76)	110																								
C_{13-18} 	1. LDA, THF, -78° 2. (+)-CSO, -78° to rt 3. NH ₄ Cl, H ₂ O	 730																									
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R	I	% ee	II	III																							
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	Base, DMF, air, rt, time	 <table border="1"> <thead> <tr> <th>R¹</th> <th>R²</th> <th>R³</th> <th>Base</th> <th>Time</th> <th>Yield (%)</th> </tr> </thead> <tbody> <tr> <td>Me</td> <td>Bn</td> <td>Et</td> <td>Cs₂CO₃</td> <td>65 h</td> <td>(73)</td> </tr> <tr> <td>Et</td> <td>Bn</td> <td>Et</td> <td>CsF</td> <td>31 h</td> <td>(99)</td> </tr> <tr> <td>Bn</td> <td>Me</td> <td>Bn</td> <td>CsF</td> <td>4 h</td> <td>(92)^e</td> </tr> </tbody> </table>	R ¹	R ²	R ³	Base	Time	Yield (%)	Me	Bn	Et	Cs ₂ CO ₃	65 h	(73)	Et	Bn	Et	CsF	31 h	(99)	Bn	Me	Bn	CsF	4 h	(92) ^e	319
R ¹	R ²	R ³	Base	Time	Yield (%)																						
Me	Bn	Et	Cs ₂ CO ₃	65 h	(73)																						
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Bn	Me	Bn	CsF	4 h	(92) ^e																						
C_{14} 	1. LDA, THF, 0° 2. (+)-CSO, rt	 (35) <i>S</i> 72% ee	731, 538																								
	1. NaHMDS, THF, 0° 2. (+)-CSO, 0°	I (68) <i>S</i> 34% ee	731, 538																								
	1. KHMDS, THF, 0° 2. (+)-CSO, -78°	I (67) <i>S</i> 41% ee	731, 538																								
	1. NaHMDS, THF, 0° 2. (+)-DCCSO, 0°	I (63) <i>S</i> 47% ee	731, 538																								
	1. KHMDS, THF, 0° 2. (+)-DCCSO, -78°	I (72) <i>S</i> 6% ee	731, 538																								
	1. NaHMDS, THF, 0° 2. (+)-DMCSO, 0°	I (73) <i>S</i> 56% ee	731, 538																								
	1. KHMDS, THF, 0° 2. (+)-DMCSO, -78°	I (70) <i>S</i> 95% ee	731, 538																								
	1. KHMDS, THF, 0° 2. (-)-DMCSO, -78°	I (68) <i>R</i> 95% ee	731, 538																								
C_{15} 	1. (EtO ₂ C) ₂ CNaBu- <i>n</i> , C ₆ H ₆ 2. (PhCO ₂) ₂ , 0° to rt, 15 h	 ("small amount")	97																								
C_{15-16} 	1. KOH, MeOH, 0 to 5° 2. PhIO(Ac) ₂ , 0 to 5°, 1 h 3. 5N HCl	 <table border="1"> <thead> <tr> <th>R¹</th> <th>R²</th> <th>Yield (%)</th> </tr> </thead> <tbody> <tr> <td>H</td> <td>H</td> <td>(70-78)</td> </tr> <tr> <td>H</td> <td>Cl</td> <td>(—)</td> </tr> <tr> <td>Me</td> <td>Cl</td> <td>(—)</td> </tr> <tr> <td>H</td> <td>OMe</td> <td>(—)</td> </tr> </tbody> </table>	R ¹	R ²	Yield (%)	H	H	(70-78)	H	Cl	(—)	Me	Cl	(—)	H	OMe	(—)	325									
R ¹	R ²	Yield (%)																									
H	H	(70-78)																									
H	Cl	(—)																									
Me	Cl	(—)																									
H	OMe	(—)																									

TABLE 9B. HYDROXYLATION OF ENOLATES OF β -DICARBONYL COMPOUNDS (Continued)

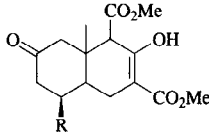
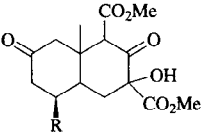
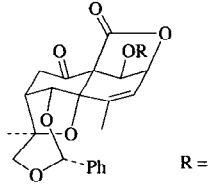
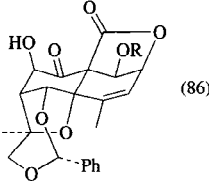
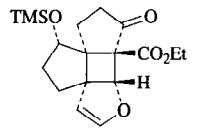
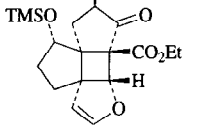
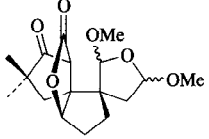
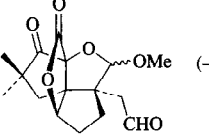
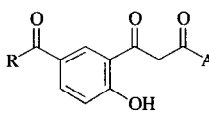
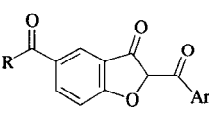
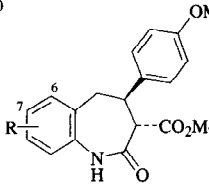
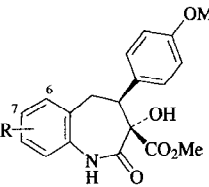
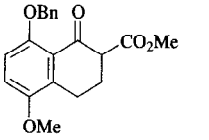
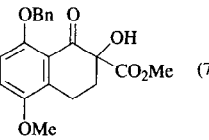
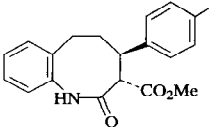
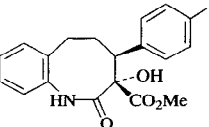
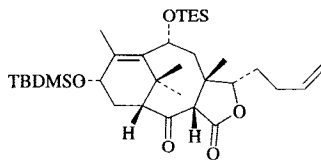
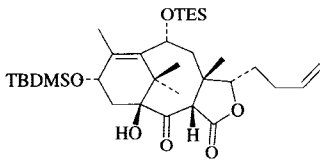
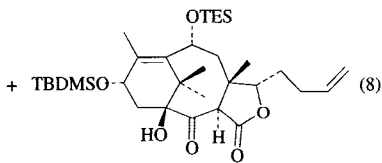
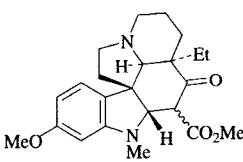
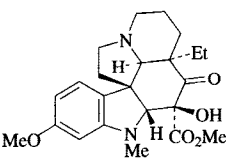
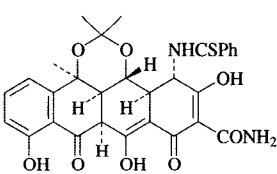
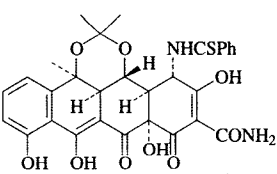
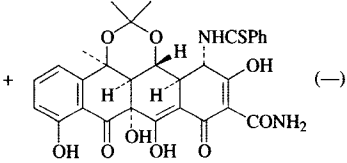
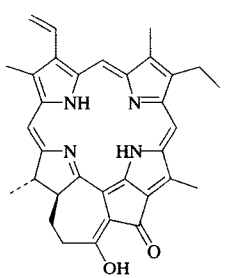
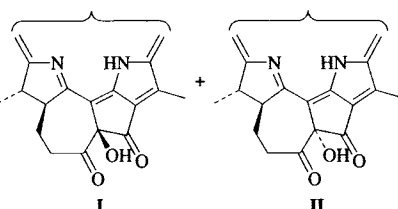
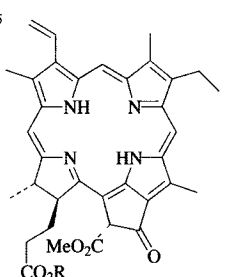
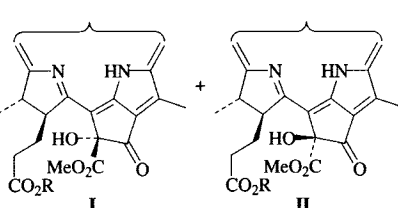
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																		
 C_{15}	KF, O ₂ , DMSO, 60°, 16 h	 R H (30) Me (57)	317																		
 R = TBDMS	1. KHMDS, THF 2. PSPO	 (86)	732, 733																		
	1. LDA 2. MoOPH	 (75)	213																		
 C_{17-19}	1. LiNEt ₂ , THF, 25° 2. PSPO, 0° 3. TsOH, CH ₂ Cl ₂	 (—)	320																		
	1. KOH, MeOH, 0 to 5° 2. PhI(OAc) ₂ , 0 to 5°, 1 h; rt, 2 h 3. 5N HCl		326																		
		<table border="1"> <thead> <tr> <th>R</th> <th>Ar</th> <th></th> </tr> </thead> <tbody> <tr> <td>Me</td> <td>Ph</td> <td>(82)</td> </tr> <tr> <td>Me</td> <td>C₆H₄Me-4</td> <td>(80)</td> </tr> <tr> <td>Me</td> <td>C₆H₄OMe-4</td> <td>(86)</td> </tr> <tr> <td>Et</td> <td>C₆H₄Me-4</td> <td>(79)</td> </tr> <tr> <td>Et</td> <td>C₆H₄OMe-4</td> <td>(82)</td> </tr> </tbody> </table>	R	Ar		Me	Ph	(82)	Me	C ₆ H ₄ Me-4	(80)	Me	C ₆ H ₄ OMe-4	(86)	Et	C ₆ H ₄ Me-4	(79)	Et	C ₆ H ₄ OMe-4	(82)	
R	Ar																				
Me	Ph	(82)																			
Me	C ₆ H ₄ Me-4	(80)																			
Me	C ₆ H ₄ OMe-4	(86)																			
Et	C ₆ H ₄ Me-4	(79)																			
Et	C ₆ H ₄ OMe-4	(82)																			
 C_{19-20}	1. LDA 2. O ₂ , P(OEt) ₃ , -78 to 0°, 30 min	 <table border="1"> <thead> <tr> <th>R</th> <th></th> </tr> </thead> <tbody> <tr> <td>H</td> <td>(—)</td> </tr> <tr> <td>6-Cl</td> <td>(—)</td> </tr> <tr> <td>7-Cl</td> <td>(94)</td> </tr> <tr> <td>6-OMe</td> <td>(—)</td> </tr> <tr> <td>7-OMe</td> <td>(—)</td> </tr> <tr> <td>6-CF₃</td> <td>(100)</td> </tr> <tr> <td>7-CF₃</td> <td>(—)</td> </tr> </tbody> </table>	R		H	(—)	6-Cl	(—)	7-Cl	(94)	6-OMe	(—)	7-OMe	(—)	6-CF ₃	(100)	7-CF ₃	(—)	324		
R																					
H	(—)																				
6-Cl	(—)																				
7-Cl	(94)																				
6-OMe	(—)																				
7-OMe	(—)																				
6-CF ₃	(100)																				
7-CF ₃	(—)																				
 C_{20}	1. KHMDS 2. (+)-CSO	 (72) S 65% ee	538																		
	1. KHMDS 2. (+)-DMCSO	I (78) S 65% ee	538																		
	1. KOcMe ₂ Et, THF, PhMe, DMF, -78°, 30 min 2. O ₂ , P(OEt) ₃ , 0°, 1.5 h 3. 1N HCl	 (78)	323																		

TABLE 9B. HYDROXYLATION OF ENOLATES OF β -DICARBONYL COMPOUNDS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																
C ₂₁ 	1. LTMP (4 eq), -10° 2. (+/-)-CSO, -40°	 (88) +  (8)	32																
C ₂₃ 	1. KOBu- <i>t</i> , HOBu- <i>t</i> , rt, 15 min 2. H ₂ O ₂ (98%), -35° 3. O ₂ , -35°, 21 h	 (59)	89																
C ₂₇ 	1. Base, O ₂ 2. MeOH, HCl, rt	 (22) +  (-)	316																
C ₃₃ 	1. DBU, THF, -25° 2. [O], -25°, 12 h	 I + II <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th></th> <th>[O]</th> <th>I+II</th> <th>I:II</th> </tr> </thead> <tbody> <tr> <td>(-)-CSO (94)</td> <td></td> <td></td> <td>5:95</td> </tr> <tr> <td>(+)-CSO (88)</td> <td></td> <td></td> <td>68:32</td> </tr> </tbody> </table>		[O]	I+II	I:II	(-)-CSO (94)			5:95	(+)-CSO (88)			68:32	328, 329				
	[O]	I+II	I:II																
(-)-CSO (94)			5:95																
(+)-CSO (88)			68:32																
C ₃₆₋₅₅ 	1. DBU, THF, -25° 2. [O], -25°, 12 h	 I + II <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th>R</th> <th>[O]</th> <th>I+II</th> <th>I:II</th> </tr> </thead> <tbody> <tr> <td>Me</td> <td>(-)-CSO (92)</td> <td></td> <td>95:5</td> </tr> <tr> <td>Me</td> <td>(+)-CSO (49)</td> <td></td> <td>57:43</td> </tr> <tr> <td>phytyl</td> <td>(-)-CSO (91)</td> <td></td> <td>100:1</td> </tr> </tbody> </table>	R	[O]	I+II	I:II	Me	(-)-CSO (92)		95:5	Me	(+)-CSO (49)		57:43	phytyl	(-)-CSO (91)		100:1	328, 329
R	[O]	I+II	I:II																
Me	(-)-CSO (92)		95:5																
Me	(+)-CSO (49)		57:43																
phytyl	(-)-CSO (91)		100:1																

^a The dibenzoyloxy derivative was formed in 11% yield.

^b The dibenzoyloxy derivative was formed in 7% yield.

^c Comparable yields were obtained with *m*-CPBA in refluxing ethanol.

^d The pure (+)-isomer was obtained in 37-46% yield by crystallization from 2-propanol.

^e Hydrolysis to the half ester occurred to the extent of 5%.

TABLE 10. HYDROXYLATION OF ENOLATES OF α,β -UNSATURATED CARBONYL COMPOUNDS

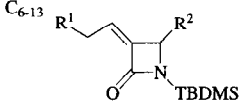
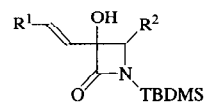
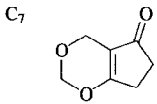
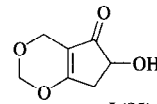
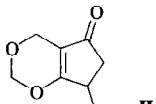
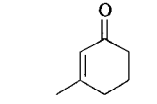
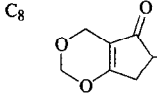
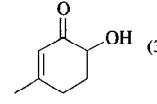
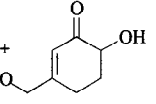
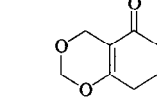
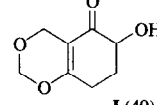
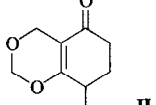

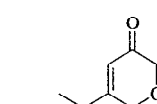
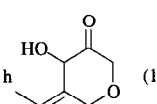
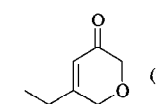
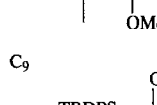
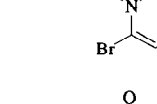
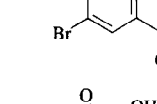
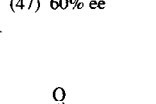
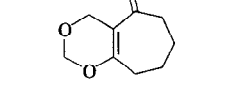
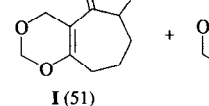

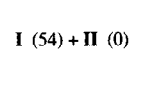

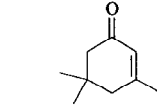

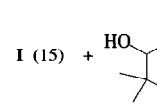
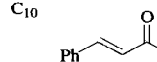



Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.															
C ₆₋₁₃ 	1. LDA, THF, -78°, 10 min 2. MoOPH, -78°	 <table border="1" style="display: inline-table; vertical-align: middle;"> <thead> <tr> <th>R¹</th> <th>R²</th> <th>Yield (%)</th> </tr> </thead> <tbody> <tr> <td>Me</td> <td>H</td> <td>(41)</td> </tr> <tr> <td>Me</td> <td>Et</td> <td>(53)</td> </tr> <tr> <td>Ph</td> <td>H</td> <td>(31)</td> </tr> <tr> <td>Ph</td> <td>Et</td> <td>(33)</td> </tr> </tbody> </table>	R ¹	R ²	Yield (%)	Me	H	(41)	Me	Et	(53)	Ph	H	(31)	Ph	Et	(33)	336
R ¹	R ²	Yield (%)																
Me	H	(41)																
Me	Et	(53)																
Ph	H	(31)																
Ph	Et	(33)																
C ₇ 	1. NaHMDS, THF, -78°, 1 h 2. PSPO, -78°, 1.5 h	 I (35) +  II (36)	176															
	1. LDA, THF, -78°, 1 h 2. (+)-CSO, -78°, 1.5 h	I (45) + II (4)	176															
	PhI(OAc) ₂ , KOH, MeOH, rt, 1 h	 (32) +  (15)	277															
C ₈ 	1. NaHMDS, THF, -78°, 1 h 2. PSPO, -78°, 1.5 h	 I (4) +  II (76)	176															
	1. LDA, THF, -85°, 1 h 2. (+)-CSO, -80°, 1 h; -45°, 1.5 h	I (68) + II (4)	176															
	1. NaHMDS, THF, -78°, 1 h 2. PSPO, -78°, 1.5 h	 I (49) +  II (37)	176															
	1. LDA, DME, -78°, 1 h 2. PSPO, -78°, 2 h	I (58)	176															
	NaHCO ₃ , air, DMF, BnNEt ₃ Cl, 80°, 37 h	 (12) +  (9)	734															
C ₉ 	1. LDA, THF, HMPA, heptane, PhEt, -5 to -78° 2. (+)-CSO 3. NH ₄ Cl, H ₂ O	 (47) 60% ee	735															
	1. NaHMDS, THF, -78°, 1 h 2. PSPO, -78°, 1.5 h	 I (51) +  II (37)	176															
	1. LDA, DME, -78°, 1 h 2. PSPO, -78°, 2 h	I (54) + II (0)	176															
	1. LDA, Et ₂ O 2. Ti(OPr- <i>i</i>) ₂ Cl ₂ 3. LiO ₂ Bu- <i>t</i> , 4Å MS	 I (42)	279															
	PhI(OAc) ₂ , KOH, MeOH, rt, 30 min	I (15) +  (8)	277															
C ₁₀ 	2-HO ₂ CC ₆ H ₄ IO, KOH, MeOH, rt, 16 h	 (—)	227															

TABLE 10. HYDROXYLATION OF ENOLATES OF α,β -UNSATURATED CARBONYL COMPOUNDS (Continued)

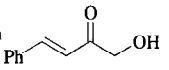
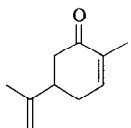
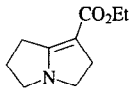
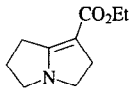
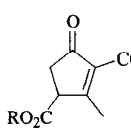
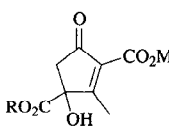
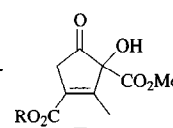
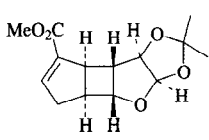
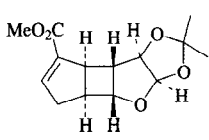
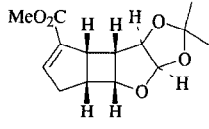
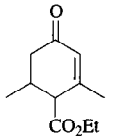
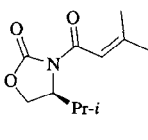
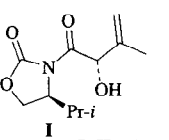
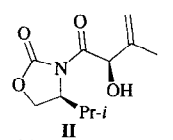
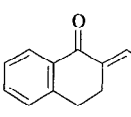
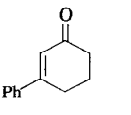
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. 2-HO ₂ CC ₆ H ₄ IO, KOH, MeOH, rt, 16 h 2. H ₂ SO ₄ (5%), CHCl ₃	(77)	227
	1. LDA, Et ₂ O 2. Ti(<i>i</i> -PrO) ₂ Cl ₂ 3. BaO, <i>t</i> -BuO ₂ H, 0°, 1.5 h	(20) <i>cis</i> isomer predominates	279
	1. LDA, THF, -78°, 100 min 2. O ₂ , P(OEt) ₃	(33)	60
	1. LDA, THF, -78°, 100 min 2. MoOPH, -78°, 20 min	I (52)	60
	Air, silica gel chromatography	 +  R I II Me (48) (21) Bn (43) (16)	736
	1. LDA, THF 2. PSPO, HMPA, -78°	(20)	337
	1. KHMDS, THF, HMPA, -78°, 2 h 2. (+)-CSO	I (90-94)	338, 337
	1. KHMDS, THF, HMPA, -78° 2. (+)-CSO	(79)	337
	KF, DMSO, O ₂ , 60°, 16 h	(62)	317
	1. Base 2. PSPO	 +  I+II = (75); I:II = 96:4	177
	NaOH (50%), O ₂ , toluene, P(OEt) ₃ , "A", rt	(73) 55% ee	265
	PhIO(Ac) ₂ , KOH, MeOH, rt, 30 min	(58) + (15)	277

TABLE 10. HYDROXYLATION OF ENOLATES OF α,β -UNSATURATED CARBONYL COMPOUNDS (Continued)

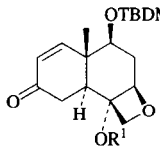
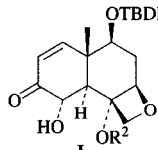

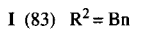
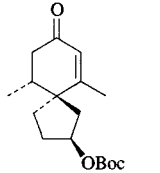
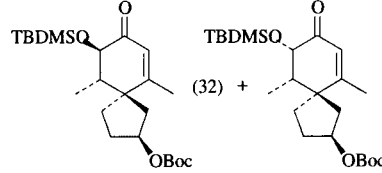
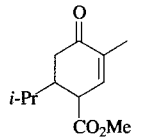
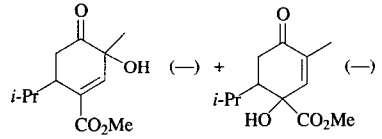
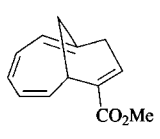
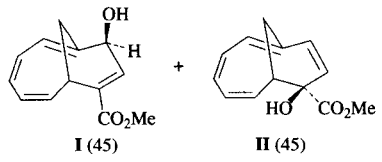
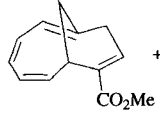
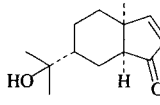
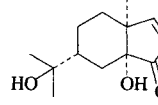
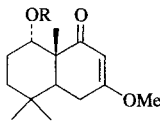
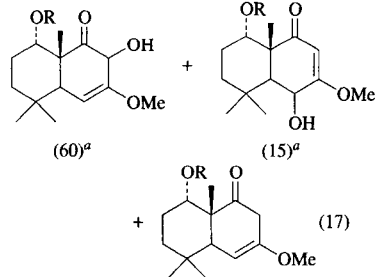

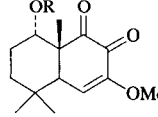
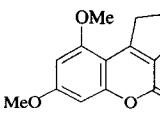
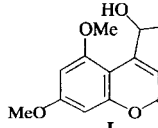

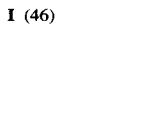
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
 $R^1 = \text{TMS}$	1. KHMDS, THF, -78° 2. PSPO 3. H_2O , -78° to rt	 $R^2 = \text{H}$ (77)	245
 $R^1 = \text{Bn}$	1. KHMDS, THF, -78° , 45 min 2. PSPO, -78° , 30 min	 I (83) $R^2 = \text{Bn}$	244
	1. LDA, THF, -78° , 30 min 2. MoOPH, -22° , 2 h 3. TBDMSCl, imidazole, rt, 6 h	 (32) + (17)	737
	KF, O_2 , DMSO	 (–) + (–)	321
C_{13} 	1. LDA, O_2 , -78° 2. $\text{P}(\text{OEt})_3$	 I (45) + II (45)	335
	1. LDA, O_2 , -78° 2. $\text{P}(\text{OEt})_3$	I (45) + II (45)	335
	1. NaH, THF, <i>t</i> -BuOH, DMF, $\text{P}(\text{OEt})_3$, -25° 2. O_2 , -25° , 3 h	 (64)	738
 $R = \text{TBDMMS}$	LDA, DMDO, THF, Me_2CO , inverse addition, -78° , 30 min	 (60) ^a + (15) ^a + (17)	112
	1. LDA, THF, -78° 2. MoOPH, THF, 22° , 15 h	 (8)	112
C_{14} 	TIOEt, H_2O_2 , CH_2Cl_2 , MeOH, 0° , 72 h	 (71)	167
	Ag_2O , NaOH (0.4N), MeOH, CH_2Cl_2 , 0° , 2.5 h	 I (46)	167

TABLE 10. HYDROXYLATION OF ENOLATES OF α,β -UNSATURATED CARBONYL COMPOUNDS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.										
	1. NaHMDS, THF, -18° , 30 min 2. PSPO, -78° , 1 h	(18)	739										
	1. NaHMDS, THF, -18° , 30 min 2. PSPO, -78° , 1 h	(42)	739										
	1. KOBu-t, THF, -78° , 30 min 2. PSPO, -78° , 30 min	(18)	740										
	1. LDA, THF, -18° , 30 min 2. PSPO, -78° , 1 h	(87)	741										
C_{14-16} 	1. KHMDS, THF, -78° , 15 min 2. PSPO, -78° , 30 min	 <table border="1"> <thead> <tr> <th>R</th> <th>Yield (%)</th> </tr> </thead> <tbody> <tr> <td>H</td> <td>(—)</td> </tr> <tr> <td>CN</td> <td>(—)</td> </tr> <tr> <td>CO₂Me</td> <td>(—)</td> </tr> <tr> <td>CH₂OTBDMS</td> <td>(92)</td> </tr> </tbody> </table>	R	Yield (%)	H	(—)	CN	(—)	CO ₂ Me	(—)	CH ₂ OTBDMS	(92)	242
R	Yield (%)												
H	(—)												
CN	(—)												
CO ₂ Me	(—)												
CH ₂ OTBDMS	(92)												
C_{15} 	1. NaHMDS 2. O ₂ , P(OEt) ₃ , -70°	(75) 13% de	690										
	1. LDA, DME, -78° 2. MoOPH, -50 to -15° , 15 min	(21) + (17)	742										
	1. LDA, THF, -70° 2. MoOPH	I + II I+II = (30); I:II = 3:1	743										
	1. LDA, THF, -78° , 1 h 2. MoOPH, -78° , 1.4 h; rt, 30 min	I + II I+II = (62); I:II = 2:1	234, 744, 745										
	1. LDA, THF, -78° , 1 h 2. MoOPH, -78° , 1 h; rt, 30 min	(57)	746										
	1. KHMDS, THF, HMPA, -10° , 1 h 2. (+)-CSO, -78° , 25 min	(81)	246										

TABLE 10. HYDROXYLATION OF ENOLATES OF α,β -UNSATURATED CARBONYL COMPOUNDS (Continued)

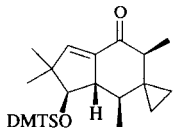
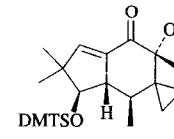
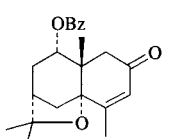
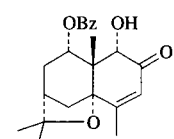
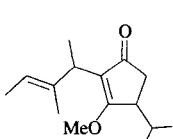
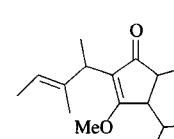
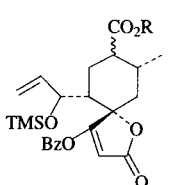
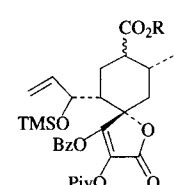
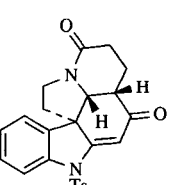
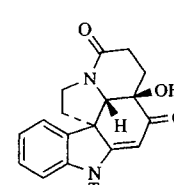
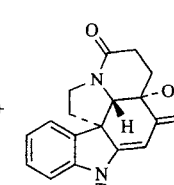
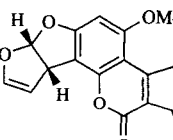
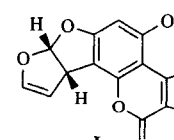
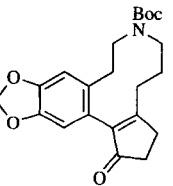
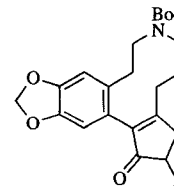
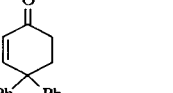
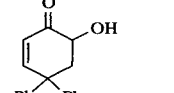
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.						
	LDA, MoOPH, THF, -20 to 20°, 3 h	 (57)	747, 748						
	1. LDA, THF, 0°, 45 min 2. (PhCO ₂) ₂ , THF, -10°, 2 h 3. KI, H ₂ O, HOAc	 (50)	749						
 R = (HOCH ₂) ₃ CNHCH ₂ SO ₂ —	1. LDA (2 eq), THF 2. PSFO	 (75)	750						
C ₁₅₋₁₆ 	1. LDA (2.8 eq), THF, -80°, 1.5 h 2. MoOPH (2.8 eq), -80°, -40°, 5 h 3. PivCl 4. NaOMe 5. PivCl	 <table border="1" style="display: inline-table; vertical-align: middle;"> <thead> <tr> <th>R</th> <th>Yield (%)</th> </tr> </thead> <tbody> <tr> <td>Me <i>cis</i></td> <td>(11)</td> </tr> <tr> <td>Et <i>trans</i></td> <td>(12)</td> </tr> </tbody> </table>	R	Yield (%)	Me <i>cis</i>	(11)	Et <i>trans</i>	(12)	340
R	Yield (%)								
Me <i>cis</i>	(11)								
Et <i>trans</i>	(12)								
C ₁₇ 	NaH, HOBu- <i>t</i> , DMF, O ₂ , P(OEt) ₃ , -25°, 2.5 h	 (51) +  (5)	751						
	O ₂ , <i>t</i> -BuOK, <i>t</i> -BuOH	 (I)	167						
	H ₂ O ₂ , <i>t</i> -BuOK, <i>t</i> -BuOH	I (—)	167						
	TIOEt, H ₂ O ₂ , CH ₂ Cl ₂ , 0°, 47 h	I (26)	167						
	<i>t</i> -BuO ₂ H, <i>t</i> -BuOK, <i>t</i> -BuOH	I (—)	167						
	LDA, MoOPH	I (—)	167						
	Ag ₂ O, NaOH (0.5N), MeOH, CH ₂ Cl ₂ , 0°, 160 min	I (30)	143						
	1. LDA, THF, -78° 2. (-)-CSO	 (78)	752						
C ₁₈ 	1. LDA, THF, -23°, 5 min 2. MoOPH (reverse addition), -22°, 5 min	 (53)	40						

TABLE 10. HYDROXYLATION OF ENOLATES OF α,β -UNSATURATED CARBONYL COMPOUNDS (Continued)

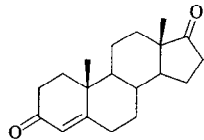
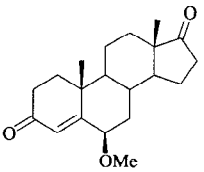
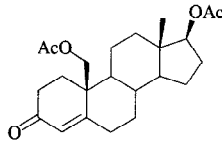
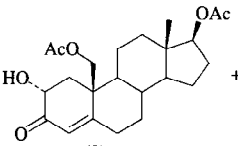
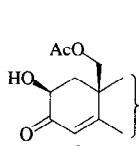
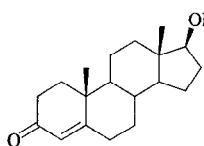
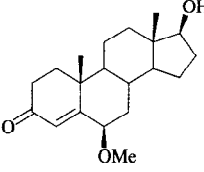
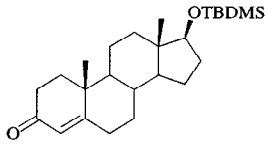
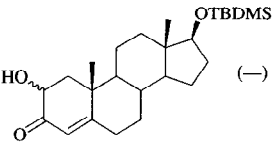
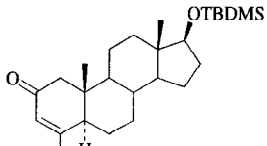
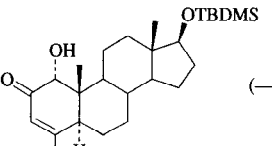
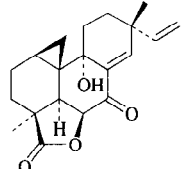
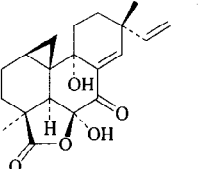
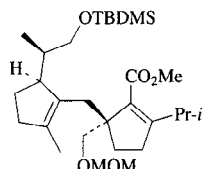
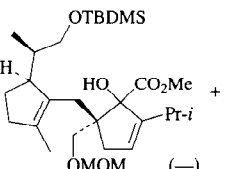
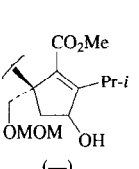
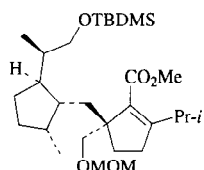
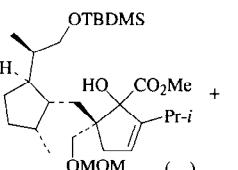
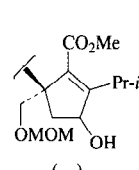
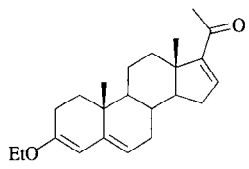
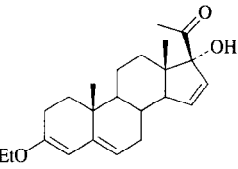
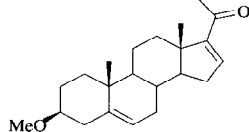
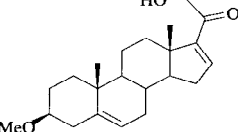
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
<p>C₁₉</p> 	<p>2-HO₂CC₆H₄IO, KOH, MeOH, 70°, 1 h</p>	 (33)	218, 357
	<p>1. LDA, THF, -78°, 30 min 2. MoOPH, -40 to -30°</p>	 (2) +  (2)	753
	<p>2-HO₂CC₆H₄IO, KOH, MeOH, 70°, 1 h</p>	 (47)	218
	<p>1. LDA, THF, -78°, 30 min 2. MoOPH, -78° to rt</p>	 (—)	754
<p>C₂₀</p> 	<p>1. Base 2. Oxygenation</p>	 (—)	334
	<p>1. KOBu-<i>t</i>, O₂, HOBu-<i>t</i>, THF 2. P(OEt)₃</p>	 (—)	192
<p>C₂₁</p> 	<p>1. LiHMDS 2. MoOPH</p>	 (—) +  (—)	755
	<p>1. LiHMDS 2. MoOPH</p>	 (—) +  (—)	755
	<p>NaOBu-<i>t</i>, O₂, HOBu-<i>t</i>, DMF, P(OEt)₃, -25°, 2.5 h</p>	 (8)	333
	<p>1. LDA, THF 2. MoOPH, -22°</p>	 (52)	40

TABLE 10. HYDROXYLATION OF ENOLATES OF α,β -UNSATURATED CARBONYL COMPOUNDS (Continued)

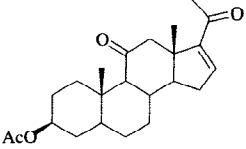
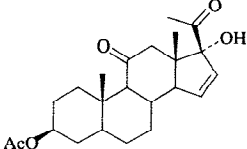
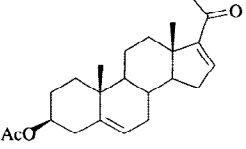
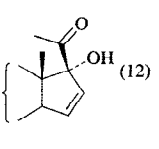
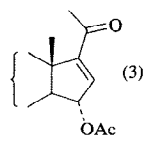
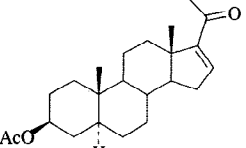
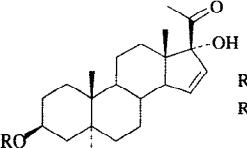
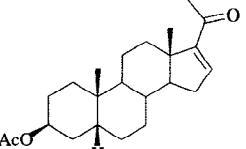
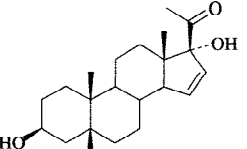
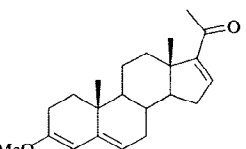
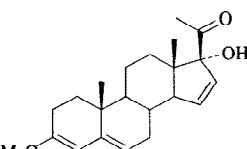
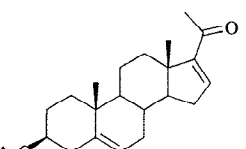
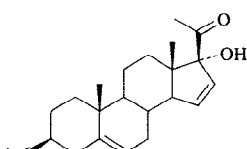
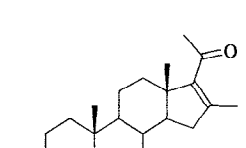
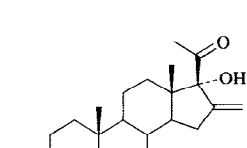
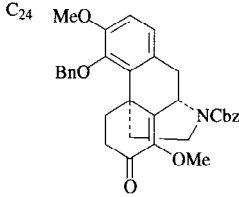
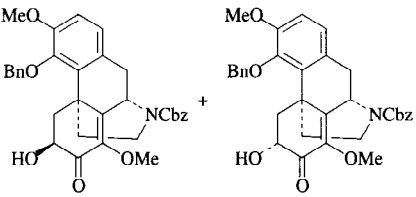
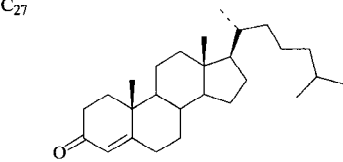
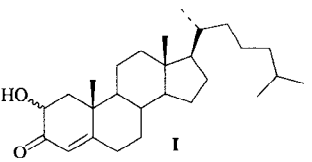
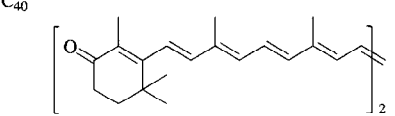
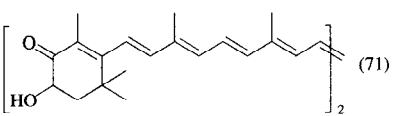
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	NaOBu- <i>t</i> , O ₂ , HOBu- <i>t</i> , DMF, THF, P(OEt) ₃ , -25°, 80 min	 (8)	333
	1. NaOBu- <i>t</i> , O ₂ (50-75 psi), HOBu- <i>t</i> , DMF, P(OEt) ₃ , -25°, 2.5 h 2. Ac ₂ O, pyridine, 100°	 (12) +  (3)	333
	NaOBu- <i>t</i> , O ₂ , HOBu- <i>t</i> , DMF, P(OEt) ₃ , -25°, 2.5 h	 R = Ac (18) + R = H (10)	333
	NaOBu- <i>t</i> , O ₂ , HOBu- <i>t</i> , DMF, P(OEt) ₃ , -25°, 2.5 h	 (20)	333
	NaOBu- <i>t</i> , O ₂ , HOBu- <i>t</i> , DMF, P(OEt) ₃ , -25°, 2.5 h	 (1)	333
	NaOBu- <i>t</i> , O ₂ , HOBu- <i>t</i> , DMF, P(OEt) ₃ , -25°, 2.5 h	 (8)	333
	NaOBu- <i>t</i> , O ₂ , HOBu- <i>t</i> , DMF, P(OEt) ₃ , -25°, 2.5 h	 (11)	333

TABLE 10. HYDROXYLATION OF ENOLATES OF α,β -UNSATURATED CARBONYL COMPOUNDS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₂₄ 	1. LiHMDS, THF 2. PSPO, -78°, 1 h	 I I+II = (82); I:II = 1:5 II	756
	1. LiHMDS, THF, HMPA 2. PSPO, -78°, 1 h	I+II (81); I:II = 1:5	756
	1. NaHMDS, THF 2. PSPO, -78°, 1 h	I+II (73); I:II = 1:2	756, 757
	1. KHMDS, THF 2. PSPO, -78°, 1 h	I+II (87); I:II = 1:3	756, 757
	1. LiHMDS, THF 2. (+) or (-)-CSO, -78°, 1 h	I+II (0)	756
	1. LDA, THF 2. (-)-CSO, -78°, 1 h	I+II (0)	756
	1. NaHMDS, THF 2. (-)-CSO, -78°, 1 h	I+II (65); I:II = 1:3.7	756
	1. KHMDS, THF 2. (-)-CSO, -78°, 1 h	I+II (67); I:II = 3:1	756, 757
	1. KHMDS, THF, HMPA 2. (-)-CSO, -78°, 1 h	I+II (49); I:II = 1:1	756
	1. NaHMDS, THF 2. (+)-CSO, -78°, 1 h	I+II (31); I:II = 2.5:1	756
	1. KHMDS, THF 2. (+)-CSO, -78°, 1 h	I+II (52); I:II = 2:3	756
	C ₂₇ 	1. LDA, THF, -78°, 1 h 2. DMDO, reverse addition, -78°, 10 min	 I (60)
1. LDA, THF, -78°, 1 h 2. MoOPH		I (40)	112
1. LDA, THF, -78°, 1 h 2. MoOPH (reverse addition), -22°		I (40)	40
C ₄₀ 	1. NaHMDS, THF, -20°, 0.5 h 2. PSPO, -78°, 0.5 h	 I (71)	238
	1. KHMDS, THF, -10°, 0.5 h 2. PSPO, -78°, 0.5 h	I (8)	238
	1. LiHMDS, THF, -20°, 0.5 h 2. PSPO, -78°, 0.5 h	I (—)	238
	1. NaHMDS, THF, -20°, 0.5 h 2. (+)-CSO, -78°, 1 h	I (46) 3 <i>S</i> ,3' <i>S</i> :3 <i>S</i> ,3' <i>R</i> :3 <i>R</i> ,3' <i>R</i> = 15:49:36	238

^a The product was obtained as a single diastereomer.

TABLE 11. α -HYDROXYLATION OF AZA-ENOLATES

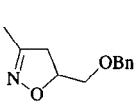
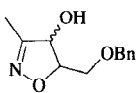
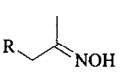

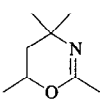
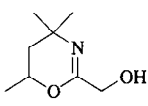
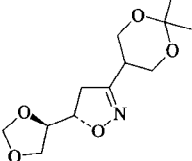
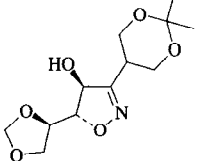








Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₅ 	MoOPH or PSPO	 (—)	758
C ₆₋₁₀ 	1. <i>n</i> -BuLi (2 eq), Et ₂ O, THF -30 to 0° 2. O ₂ , -10°	 R Pr (49) Bu (54) C ₇ H ₁₅ (58)	341
C ₈ 	1. <i>n</i> -BuLi, THF -60°, 1 h 2. O ₂ , -60°	 (57)	759
	1. LDA, THF, HMPA, -78° 2. B(OMe) ₃ , -90 to -78°, 2 h 3. H ₂ O ₂ (85%)	 (60)	760
C ₉ 	1. LDA, THF, -78° 2. O ₂ , -78°	 (60-80) I	342
	1. LDA, THF, HMPA, -78° 2. B(OP <i>r</i> - <i>i</i>) ₃ , -78° 3. H ₂ O ₂ , Et ₃ N, -78° to rt	I (67)	86
	1. LDA, THF, TMEDA, -78° 2. (+)-CSO, -78°, 1.5 h	I (50) 7% ee	343
	1. LDA, THF, B(OMe) ₃ , HMPA, -78° 2. (+)-CSO, -78°, 1.5 h	I (59) 0% ee	343
	1. LDA, THF, -78°, 1 h 2. (+)-DCCSO, -78°, 1.5 h	I (51) <i>R</i> 50% ee	343
	1. LDA, THF, HMPA, -78°, 1 h 2. (+)-DCCSO, -78°, 1.5 h	I (41) <i>R</i> 56% ee	343
	1. LDA, THF, TMEDA, -78°, 1 h 2. (+)-DCCSO, -78°, 1.5 h	I (52) <i>R</i> 58% ee	343
	1. LDA, THF, B(OMe) ₃ , HMPA, -78°, 1 h 2. (+)-DCCSO, -78°, 1.5 h	I (43) 22% ee	343
	1. LDA, THF, LiCl, TMEDA, -78°, 1 h 2. (+)-DCCSO, -78°, 1.5 h	I (54) 53% ee	343
	1. LDA, THF, TMEDA, -78°, 1 h 2. (+)-CSO, -78°, 1.5 h	 (0)	343
	1. LDA, THF, TMEDA, -78°, 1 h 2. (+)-CSO, -78°, 1.5 h	 (49) <i>R</i> 50% ee I	343
	1. LDA, THF, TMEDA, -78°, 1 h 2. (+)-DCCSO, -78°, 1.5 h	I (49) 31% ee	343
	1. LDA, THF, TMEDA, -78°, 1 h 2. (+)-DMCSO, -78°, 1.5 h	I (30) <i>R</i> 71% ee	343
	1. LDA, THF, TMEDA, -78°, 1 h 2. (+)-CSO, -78°, 1.5 h	 (0)	343

TABLE 11. α -HYDROXYLATION OF AZA-ENOLATES (Continued)

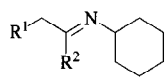
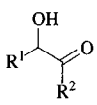
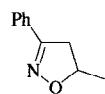
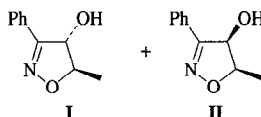
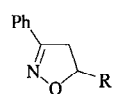
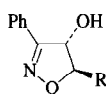
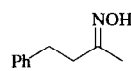
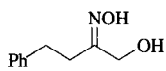
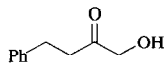
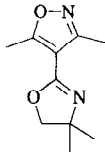
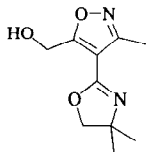

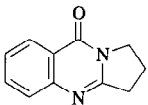
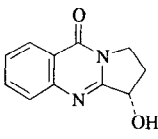
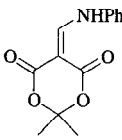
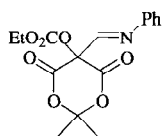
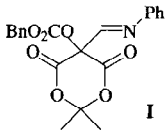

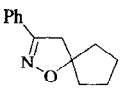
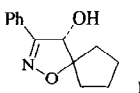

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																											
C ₉₋₁₇ 	1. LDA, Et ₂ O 2. O ₂	 <table border="1" style="display: inline-table; vertical-align: middle;"> <thead> <tr> <th>R¹</th> <th>R²</th> <th>Yield (%)</th> </tr> </thead> <tbody> <tr> <td>Me</td> <td>H</td> <td>(50)</td> </tr> <tr> <td><i>n</i>-Pr</td> <td>H</td> <td>(66)</td> </tr> <tr> <td><i>i</i>-Bu</td> <td>H</td> <td>(61)</td> </tr> <tr> <td>C₅H₁₁</td> <td>H</td> <td>(67)</td> </tr> <tr> <td>Me₂CH(CH₂)₂</td> <td>H</td> <td>(65)</td> </tr> <tr> <td>Ph</td> <td>H</td> <td>(72)</td> </tr> <tr> <td>C₅H₁₁</td> <td>C₄H₉</td> <td>(65)</td> </tr> <tr> <td>—(CH₂)₃—</td> <td></td> <td>(42)</td> </tr> </tbody> </table>	R ¹	R ²	Yield (%)	Me	H	(50)	<i>n</i> -Pr	H	(66)	<i>i</i> -Bu	H	(61)	C ₅ H ₁₁	H	(67)	Me ₂ CH(CH ₂) ₂	H	(65)	Ph	H	(72)	C ₅ H ₁₁	C ₄ H ₉	(65)	—(CH ₂) ₃ —		(42)	341
R ¹	R ²	Yield (%)																												
Me	H	(50)																												
<i>n</i> -Pr	H	(66)																												
<i>i</i> -Bu	H	(61)																												
C ₅ H ₁₁	H	(67)																												
Me ₂ CH(CH ₂) ₂	H	(65)																												
Ph	H	(72)																												
C ₅ H ₁₁	C ₄ H ₉	(65)																												
—(CH ₂) ₃ —		(42)																												
C ₁₀ 	1. LDA, THF, HMPA, -78° 2. B(OP <i>i</i> -t) ₃ , -78° 3. H ₂ O ₂ , Et ₃ N, -78° to rt	 <p>I + II = (78); I:II = >90:<10</p>	86																											
C ₁₀₋₁₄  <p>R = Me, Et, <i>n</i>-C₅H₁₁</p>	1. LDA, THF, -78° 2. O ₂ , -78°	 <p>(60-80)</p>	342																											
C ₁₀ 	1. <i>n</i> -BuLi (2 eq), THF, -22° 2. MoOPH, -78°, 1 h; -22°, 20 min	 <p>(36)</p>	40																											
	1. <i>n</i> -BuLi (2 eq), THF, -22° 2. MoOPH, -78°, 1 h; -22°, 20 min 3. NaHSO ₃ , EtOH	 <p>(38)</p>	40																											
	1. <i>n</i> -BuLi 2. MoOPH, -78°, 2 h	 <p>I (32-53)</p>	41, 761																											
	1. <i>n</i> -BuLi 2. PSPO, -78°, 2 h	 <p>I (32-53)</p>	41, 761																											
C ₁₁ 	1. NaHMDS, THF, -78°, 1 h 2. (+)-CSO, -78°, 30 min	 <p>(39) 71% ee</p>	762																											
C ₁₃ 	1. NaH, MeCN, 40°, 2 h 2. (EtO ₂ CO) ₂ , 0° to rt	 <p>(54)</p>	27																											
	1. NaH, MeCN, 40°, 2 h 2. (BnO ₂ CO) ₂ , 0° to rt	 <p>(70)</p>	27																											
	1. LiH, MeCN, 40°, 2 h 2. (BnO ₂ CO) ₂ , 0° to rt	 <p>I (75)</p>	27																											
	1. LDA, THF, HMPA, -78°, 1 h 2. (+)-CSO, -78°, 1.5 h	 <p>(65) <i>R</i> 26% ee</p>	343																											
	1. LDA, THF, TMEDA, -78°, 1 h 2. (+)-CSO, -78°, 1.5 h	 <p>I (0)</p>	343																											

TABLE 11. α -HYDROXYLATION OF AZA-ENOLATES (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. LDA, THF, TMEDA, -78°, 1 h 2. (+)-CSO, -78°, 1.5 h	 I + II = (85); I:II = >95:5	343
	1. LDA, THF, 0°, 5 h 2. PSPO, -85 to -50°, 1.5 h 3. NaH, BnCl, DMF 4. O ₃ , CH ₂ Cl ₂	 (63) <i>R</i> 56% ee	43
	1. KOBu- <i>t</i> , THF, -35° 2. O ₂ , -35 to -25°, 1 h 3. NaBH ₄ , EtOH, 0 to 5°, 2 h	 (89)	763
	1. <i>n</i> -BuLi 2. O ₂ 3. Na ₂ SO ₃	 (100)	54
	1. LDA, THF, -78°, 1 h 2. (PhCO ₂) ₂ , -78°, 72 h 3. 2N HCl	 (50) <i>R</i> 70% ee	45
	1. AlMe ₃ , CH ₂ Cl ₂ 2. (PhCO ₂) ₂ , -78°, 72 h 3. 2N HCl	 I (40) 0% ee	45
	1. LDA, THF, 0°, 5 h 2. PSPO, -85 to -50°, 1.5 h 3. O ₃ , CH ₂ Cl ₂ 4. Ac ₂ O, DMAP, CH ₂ Cl ₂	 (51) <i>R</i> 93% ee	43
	1. LDA, THF, -78°, 1 h 2. (PhCO ₂) ₂ , -78°, 72 h 3. 2N HCl	 (53) 0% ee	45
	1. LDA, THF, -78°, 1 h 2. (PhCO ₂) ₂ , -78°, 72 h 3. 2N HCl	 (63) <i>R</i> 85% ee	45
	1. AlMe ₃ , CH ₂ Cl ₂ 2. (PhCO ₂) ₂ , -78°, 72 h 3. 2N HCl	 I (66) <i>S</i> 12% ee	45
	1. LDA, THF, -78°, 1 h 2. (PhCO ₂) ₂ , -78°, 72 h 3. 2N HCl	 (50) 85% ee	45
	1. AlMe ₃ , CH ₂ Cl ₂ 2. (PhCO ₂) ₂ , -78°, 72 h 3. 2N HCl	 I (51) <i>S</i> 25% ee	45
	1. LDA, THF, 0°, 5 h 2. PSPO, -85 to -50°, 1.5 h 3. NaH, BnCl, DMF 4. Separation of major isomer 5. O ₃ , CH ₂ Cl ₂	 (44) <i>S</i> >98% ee	43

TABLE 11. α -HYDROXYLATION OF AZA-ENOLATES (Continued)

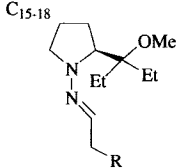
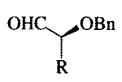
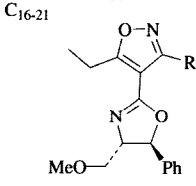
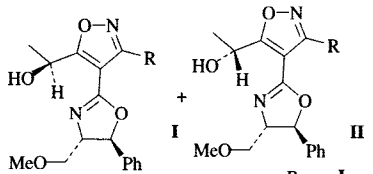
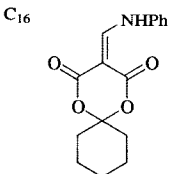
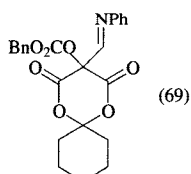
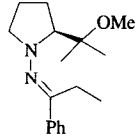

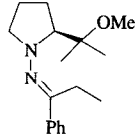

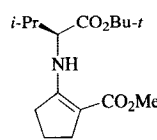
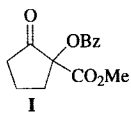
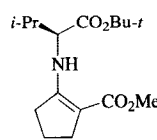
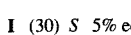
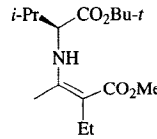
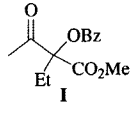
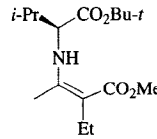
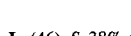
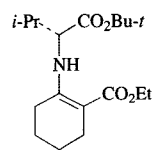
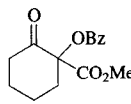
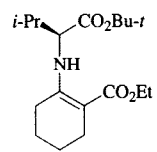
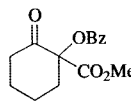
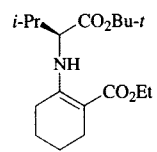
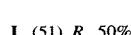
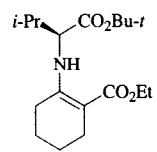
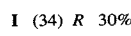
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.									
 C ₁₅₋₁₈	1. LDA, THF, 0°, 5 h 2. PSPO, -85 to -50°, 1.5 h 3. NaH, BnCl, DMF 4. Separation of major isomer 5. O ₃ , CH ₂ Cl ₂	 S >96% ee <table border="1" style="margin-left: 20px;"> <thead> <tr> <th>R</th> <th>Yield (%)</th> </tr> </thead> <tbody> <tr> <td>n-Bu</td> <td>(53)</td> </tr> <tr> <td>n-C₆H₁₃</td> <td>(55)</td> </tr> <tr> <td>Bn</td> <td>(66)</td> </tr> </tbody> </table>	R	Yield (%)	n-Bu	(53)	n-C ₆ H ₁₃	(55)	Bn	(66)	43	
R	Yield (%)											
n-Bu	(53)											
n-C ₆ H ₁₃	(55)											
Bn	(66)											
 C ₁₆₋₂₁	1. <i>n</i> -BuLi, THF 2. PSPO	 <table border="1" style="margin-left: 20px;"> <thead> <tr> <th>R</th> <th>I (%)</th> <th>II (%)</th> </tr> </thead> <tbody> <tr> <td>Me</td> <td>(24)</td> <td>(38)</td> </tr> <tr> <td>Ph</td> <td>(33)</td> <td>(49)</td> </tr> </tbody> </table>	R	I (%)	II (%)	Me	(24)	(38)	Ph	(33)	(49)	42
R	I (%)	II (%)										
Me	(24)	(38)										
Ph	(33)	(49)										
 C ₁₆	1. LiH, MeCN 2. (BnOCO ₂) ₂	 (69)	27									
	1. <i>n</i> -BuLi, THF, 0°, 5 h 2. PSPO, -85 to -50°, 1.5 h 3. O ₃ , CH ₂ Cl ₂ 4. Ac ₂ O, DMAP, CH ₂ Cl ₂	 (62) R 85% ee	43									
	1. LDA, THF, 0°, 5 h 2. PSPO, -85 to -50°, 1.5 h 3. O ₃ , CH ₂ Cl ₂ 4. Ac ₂ O, DMAP, CH ₂ Cl ₂	 I (73) R 88% ee	43									
	1. LDA, THF, -78°, 1 h 2. (PhCO ₂) ₂ , -78°, 72 h 3. 2N HCl	 (57) R 78% ee	45									
	1. AlMe ₃ , CH ₂ Cl ₂ 2. (PhCO ₂) ₂ , -78°, 72 h 3. 2N HCl	 I (30) S 5% ee	45									
	1. LDA, THF, -78°, 1 h 2. (PhCO ₂) ₂ , -78°, 72 h 3. 2N HCl	 (70) R 78% ee	45									
	1. AlMe ₃ , CH ₂ Cl ₂ 2. (PhCO ₂) ₂ , -78°, 72 h 3. 2N HCl	 I (46) S 38% ee	45									
 C ₁₈	1. LDA, PhMe, THF, -78°, 1 h 2. (PhCO ₂) ₂ , -78°, 72 h 3. 2N HCl	 (60) S 90% ee	45									
	1. LDA, PhMe, THF, -78°, 1 h 2. (PhCO ₂) ₂ , -78°, 72 h 3. 2N HCl	 (60) R 71% ee	45									
	1. LDA, PhMe, -78°, 1 h 2. (PhCO ₂) ₂ , -78°, 72 h 3. 2N HCl	 I (51) R 50% ee	45									
	1. LDA, PhMe, HMPA, -78°, 1 h 2. (PhCO ₂) ₂ , -78°, 72 h 3. 2N HCl	 I (34) R 30% ee	45									

TABLE 11. α -HYDROXYLATION OF AZA-ENOLATES (Continued)

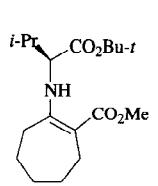
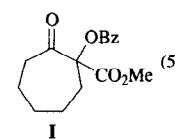
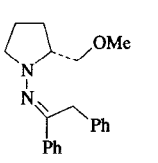
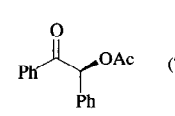
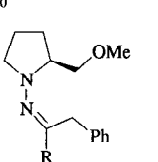
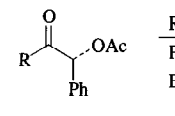
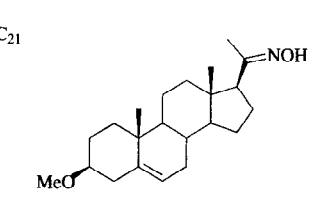
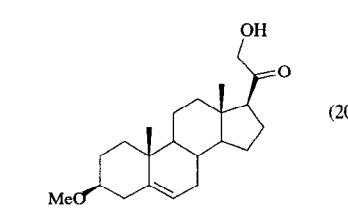
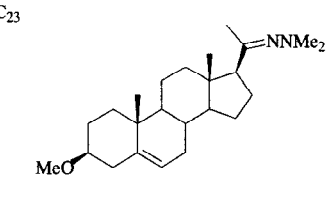
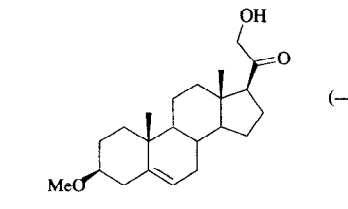
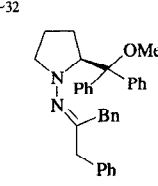
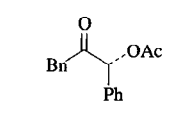
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.						
	1. LDA, THF, -78° , 1 h 2. $(\text{PhCO}_2)_2$, -78° , 72 h 3. 2N HCl	I (69) <i>R</i> 92% ee	45						
	1. AlMe_3 , CH_2Cl_2 2. $(\text{PhCO}_2)_2$, -78° , 72 h 3. 2N HCl	I (65) <i>S</i> 30% ee	45						
C ₁₈ 	1. LDA, PhMe, THF, -78° , 1 h 2. $(\text{PhCO}_2)_2$, -78° , 72 h 3. 2N HCl	 I (58) <i>R</i> 80% ee	45						
	1. AlMe_3 , CH_2Cl_2 2. $(\text{PhCO}_2)_2$, -78° , 72 h 3. 2N HCl	I (52) <i>S</i> 50% ee	45						
C ₁₉ 	1. <i>t</i> -BuLi, THF, 0° , 5 h 2. PSPO, -85 to -50° , 1.5 h 3. O_3 , CH_2Cl_2 4. Ac_2O , DMAP, CH_2Cl_2	 (74) <i>S</i> >96% ee	43						
C ₁₉₋₂₀ 	1. <i>t</i> -BuLi, THF, 0° , 5 h 2. PSPO, -85 to -50° , 1.5 h 3. O_3 , CH_2Cl_2 4. Ac_2O , DMAP, CH_2Cl_2	 <table border="1" style="display: inline-table; vertical-align: middle;"> <thead> <tr> <th>R</th> <th>% ee</th> </tr> </thead> <tbody> <tr> <td>Ph (54)</td> <td>>96</td> </tr> <tr> <td>Bn (48)</td> <td>36</td> </tr> </tbody> </table>	R	% ee	Ph (54)	>96	Bn (48)	36	43
R	% ee								
Ph (54)	>96								
Bn (48)	36								
C ₂₁ 	1. <i>n</i> -BuLi (2 eq), THF, -78 to 0° , 30 min 2. MoOPH 3. NaHSO_3	 (20)	40						
C ₂₃ 	1. LDA 2. MoOPH	 (—)	40						
C ₃₂ 	1. LDA, THF, 0° , 5 h 2. PSPO, -85 to -50° , 1.5 h 3. O_3 , CH_2Cl_2 4. Ac_2O , DMAP, CH_2Cl_2	 (62) <i>R</i> 89% ee	43						

TABLE 12. TANDEM MICHAEL ADDITION/ α -HYDROXYLATION

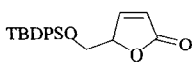
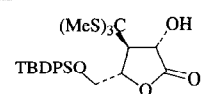

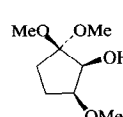
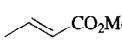
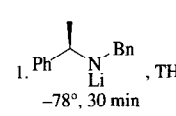
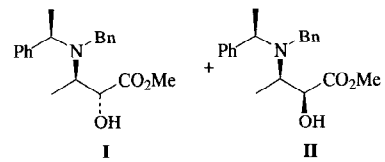
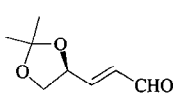
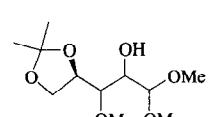

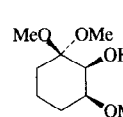
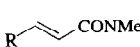
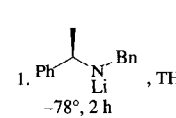
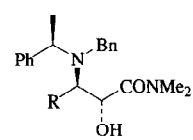
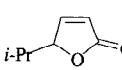
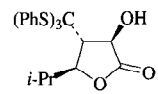
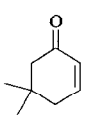
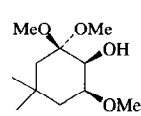
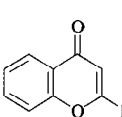
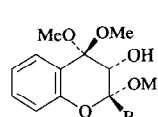
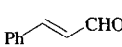
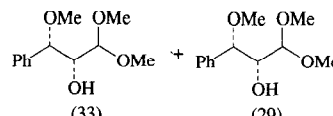

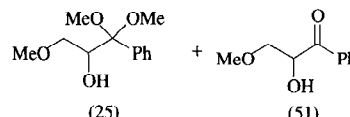
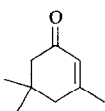
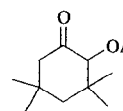
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₅ 	1. (MeS) ₃ CLi, THF, -78°, 30 min 2. MoOPH, -78 to 30°	 (78)	650
	PhI(OAc) ₂ , KOH, MeOH, 0°, 40 min	 (55)	277
	1.  , THF, -78°, 30 min 2. (+)-CSO, -78°, 1 h; 0°, 15 min	 I + II = (55); I:II = >88:<12	248
	PhI(OAc) ₂ , KOH, MeOH, 0°, 40 min	 (67), 4 diastereomers, ratio 15:5:5:3	277
C ₆ 	PhI(OAc) ₂ , KOH, MeOH, 0°, 40 min	 (52)	492
C ₆₋₁₁ 	1.  , THF, -78°, 2 h 2. (+)-CSO, -78°, 1 h; 0°, 15 min	 R % dc Me (85) >95 Ph (42) >95	248
C ₇ 	1. (PhS) ₃ CLi, THF, -78° 2. MoOPH, 0°	 (—)	764, 765, 766
C ₈ 	PhI(OAc) ₂ , KOH, MeOH, 0°, 20 min	 ((23)	277
C ₉₋₁₅ 	1. KOH, MeOH, 5-10°, 10 min 2. PhI(OAc) ₂ , overnight	 R H (53) Ph (67)	767, 562
C ₉ 	PhI(OAc) ₂ , KOH, MeOH, 0°, 30 min	 (33) (29)	277
	PhI(OAc) ₂ , KOH, MeOH, 0°, 20 min	 (25) (51)	277
	1. MeMgBr, rt 2. Pb(OAc) ₄ , PhH, rt	 (60)	364

TABLE 12. TANDEM MICHAEL ADDITION/ α -HYDROXYLATION (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. THF, -78°, 2 h 2. (+)-CSO, -78°, 1 h; 0°, 15 min	 (54) 83% de	248
C ₁₀ 	1. THF, -78°, 2 h 2. (+)-CSO, -78°, 1 h; 0°, 15 min	 (43) >90% de	248
	1. Me ₂ CuLi, LiBr, Et ₂ O, 0°, 24 h 2. (PhCO ₂) ₂ , Et ₂ O, 0°, 2.5 h	 I + II = (23); I:II = 45:55	96
C ₁₃ 	1. THF, -78°, 2 h 2. (+)-CSO, -78°, 1 h; 0°, 15 min	 (86) (4)	297, 248, 643, 768, 769, 770
	1. THF, -78°, 2 h 2. (+)-CSO, -78°, 1 h; 0°, 15 min	 (89) >98% de	248, 770
C ₁₄ 	1. Me ₂ AlCl, <i>n</i> -hexane, PhMe, hv, -40° 2. O ₂ , 96 h	 I + II = (92); I:II = 33:67	771
	1. (<i>n</i> -Pr) ₃ SiH, RhCl(PPh ₃) ₃ (cat.) 2. <i>m</i> -CPBA, KHCO ₃	 (51)	131
	1. THF, -78°, 2 h 2. (+)-CSO, -78°, 1 h; 0°, 15 min	 I + II = (41); I:II = 40:60	768, 769
	1. THF, -78°, 3 h 2. AcOH, -78 to 0°, 40 min 3. LDA, -78°, 45 min 4. (+)-CSO, -78°, 1 h; 0°, 15 min	 I + II (49); I:II = >98:<2	768, 769
	1. THF, -78°, 3 h 2. (+)-CSO, -78°, 1 h; 0°, 15 min	 I + II = (63); I:II = 22:1	768, 769

TABLE 12. TANDEM MICHAEL ADDITION/ α -HYDROXYLATION (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. , THF, -78°, 3 h 2. (+)-CSO, -78°, 1 h; 0°, 15 min	 (63) + (4)	643, 772
	1. , THF, -78°, 3 h 2. (+)-CSO, -78°, 1 h; 0°, 15 min	 I + II = (85); I:II = 22:1	643
C ₁₅ 	PhI(OAc) ₂ , KOH, MeOH	 I	562
	(PhIO) _n , KOH, MeOH	I (—)	773
	1. Me ₂ AlCl, <i>n</i> -hexane, PhMe, hv, -55° 2. O ₂ , 96 h	 (24) + (4) (13) + (7)	771
	1. CeCl ₃ ·7H ₂ O, NaBH ₄ , MeOH, 0°, 5 min 2. O ₂	 (10)	774
C ₁₆ 	1. Me ₂ AlCl, <i>n</i> -hexane, PhMe, hv, -55° 2. O ₂ , 96 h	 (40) + (7) (21) + (14)	771
C ₁₉ 	1. KOH, MeOH, 5-10°, 10 min 2. PhI(OAc) ₂ , overnight	 (—)	767
	1. Me ₂ AlCl, <i>n</i> -hexane, PhMe, hv, -40° 2. O ₂ , 80 h	 (39) + (6) (3) + (2)	771

TABLE 12. TANDEM MICHAEL ADDITION/ α -HYDROXYLATION (Continued)

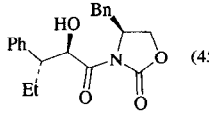
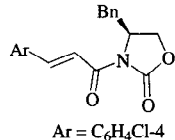
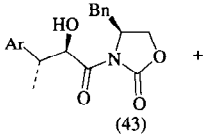
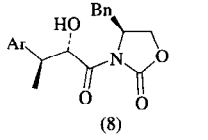
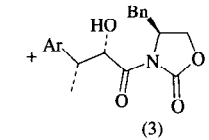
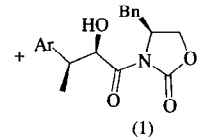
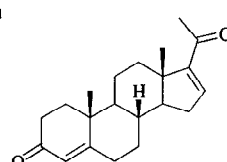
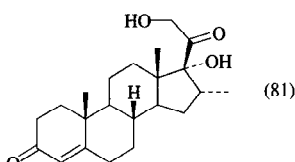
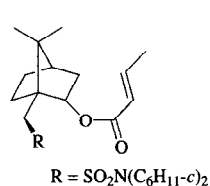
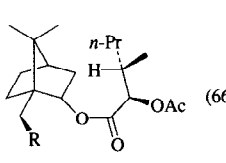
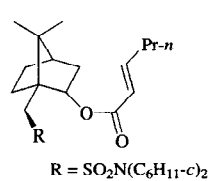
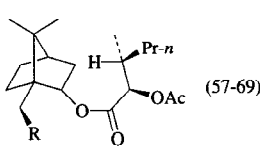
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. Et ₂ AlCl, <i>n</i> -hexane, PhMe, -78°, 9 h 2. PSPO, -78 to 5°, 15 h	 (45)	771
 Ar = C ₆ H ₄ Cl-4	1. Me ₂ AlCl, <i>n</i> -hexane, PhMe, hv, -45° 2. O ₂ , 72 h	 (43) +  (8)	771
		+  (3) +  (1)	
C ₂₁ 	1. MeMgBr, Cu ⁺ (cat.), TMSCl, HMPA 2. <i>m</i> -CPBA (2.9 eq), KHCO ₃ 3. H ₃ O ⁺	 (81)	131
C ₂₆  R = SO ₂ N(C ₆ H ₁₁ - <i>c</i>) ₂	1. (<i>n</i> -Pr) ₂ Cu 2. LDA, TMSCl 3. Pb(OAc) ₄	 (66)	372
C ₂₈  R = SO ₂ N(C ₆ H ₁₁ - <i>c</i>) ₂	1. Me ₂ Cu 2. LDA, TMSCl 3. Pb(OAc) ₄	 (57-69)	372

TABLE 13. TANDEM BIRCH REDUCTION/ α -HYDROXYLATION

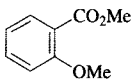
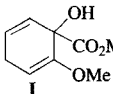
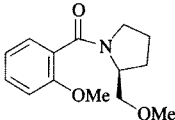
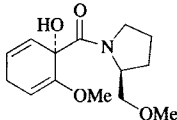
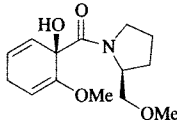
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₉ 	1. Li, NH ₃ , THF, <i>t</i> -BuOH, -78°, 15 min 2. (+)-CSO, DME, 5 min	 (58) 30% ee	292
	1. Li, NH ₃ , THF, <i>t</i> -BuOH, -78°, 15 min 2. Removal of NH ₃ 3. (+)-CSO	I (50-60) 5% ee	292
C ₁₃ 	1. K, NH ₃ , THF, <i>t</i> -BuOH, -78°, 30 min 2. (+)-CSO, DME, 5 min	 +  I+II = (16); I:II = 13:1	292
	1. K, NH ₃ , THF, <i>t</i> -BuOH, -78°, 30 min 2. PSPO, DME, 5 min	I+II (—); I:II = 58.5:41.5	292
	1. K, NH ₃ , THF, <i>t</i> -BuOH, -78°, 30 min 2. (–)-CSO, DME, 5 min	I+II (11); I:II = 1:2	292
	1. K, NH ₃ , THF, <i>t</i> -BuOH, -78°, 30 min 2. Removal of NH ₃ 3. (+)-CSO, DME, 5 min	I+II (57); I:II = 12:1	292
	1. K, NH ₃ , THF, <i>t</i> -BuOH, -78°, 30 min 2. Removal of NH ₃ 3. (–)-CSO, DME, 5 min	I+II (25); I:II = 1.6:1	292

TABLE 14. TANDEM OXY COPE REARRANGEMENT/ α -HYDROXYLATION

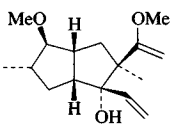
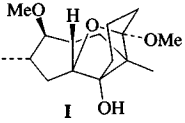
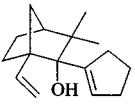
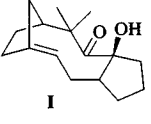
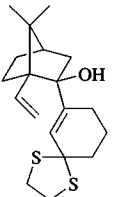
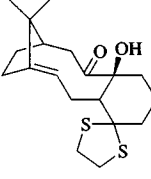
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₁₄ 	1. KHMDS, THF, 18-crown-6, rt, 30 min 2. O ₂ , P(OEt) ₃ , 10 min	 (38)	198
	1. KHMDS, THF, 18-crown-6, rt, 30 min 2. O ₂ , 10 min	I (85)	198
C ₁₆ 	1. KHMDS, THF, 18-crown-6, rt, 30 min 2. O ₂ , 10 min	 (87)	198
	1. KH, THF, 18-crown-6 rt, 30 min 2. O ₂ , P(OEt) ₃ , 10 min	I (59)	198
	1. KOBu- <i>t</i> , THF, 18-crown-6, rt, 10 min 2. O ₂ , P(OEt) ₃ , 10 min	I (78)	198
C ₁₇ 	1. KHMDS, THF, rt, 10 min 2. O ₂ , P(OEt) ₃ , 2 min	 (44)	198

TABLE 14. TANDEM OXY COPE REARRANGEMENT/ α -HYDROXYLATION (Continued)

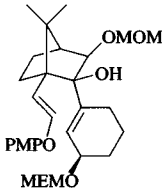
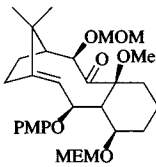
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. KHMDS, THF, -78° to rt 2. O ₂ 3. MeI	 (69)	240

TABLE 15. α -HYDROXYLATION OF ALDEHYDE SILYL ENOL ETHERS

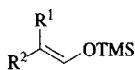
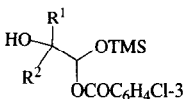
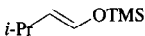
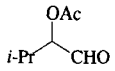
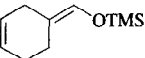
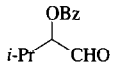
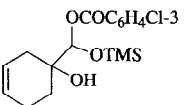
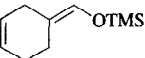
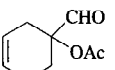
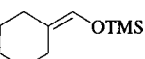
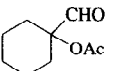
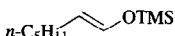
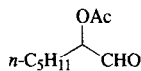
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.															
C ₄₋₁₀ 	<i>m</i> -CPBA, CH ₂ Cl ₂ , rt, 1 h	 <table border="1" style="display: inline-table; vertical-align: middle;"> <thead> <tr> <th>R¹</th> <th>R²</th> <th></th> </tr> </thead> <tbody> <tr> <td>Me</td> <td>Me</td> <td>(74)</td> </tr> <tr> <td>Me</td> <td>Ph</td> <td>(85)</td> </tr> <tr> <td>H</td> <td>Bn</td> <td>(72)</td> </tr> <tr> <td>H</td> <td>C₈H₁₇</td> <td>(84)</td> </tr> </tbody> </table>	R ¹	R ²		Me	Me	(74)	Me	Ph	(85)	H	Bn	(72)	H	C ₈ H ₁₇	(84)	123
R ¹	R ²																	
Me	Me	(74)																
Me	Ph	(85)																
H	Bn	(72)																
H	C ₈ H ₁₇	(84)																
C ₅ 	Pb(OAc) ₄ , HOAc, KOAc	 (72)	367															
C ₇ 	1. Pb(OBz) ₄ , CH ₂ Cl ₂ , 0° to rt 2. TEAF, rt, 8 h	 (97)	161															
	<i>m</i> -CPBA, CH ₂ Cl ₂ , rt, 1 h	 (79)	123															
	1. <i>m</i> -CPBA, CH ₂ Cl ₂ , rt, 1 h 2. Ac ₂ O, Et ₃ N	 (39)	123															
	Pb(OAc) ₄ , HOAc, KOAc	I I (73)	367, 368															
	Pb(OAc) ₄ , HOAc, KOAc	 (45)	367															
	Pb(OAc) ₄ , HOAc, KOAc, rt, 1 h	 (78)	367															

TABLE 15. α -HYDROXYLATION OF ALDEHYDE SILYL ENOL ETHERS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.									
	Pb(OBz) ₄ , CH ₂ Cl ₂ , 0° to rt, 0.5	(90)	161									
	1. <i>m</i> -CPBA, CH ₂ Cl ₂ , 1 h 2. TsOH, MeOH, reflux, 2 h	(53)	368, 230									
	H ₂ O ₂ (35%), octylpyridinium peroxotungstophosphate (cat.), CH ₂ Cl ₂ , MeOH, 40°, 2 h	(72) + (12) + (9)	91									
	1. <i>m</i> -CPBA, CH ₂ Cl ₂ , 1 h 2. Ac ₂ O, Et ₃ N	(42) I	123									
	1. Pb(OAc) ₄ , CH ₂ Cl ₂ , -20° to rt, 30 min 2. Et ₃ NHF, 30 min	I (59) + (22)	367									
	1. Pb(OBz) ₄ , CH ₂ Cl ₂ , 0° to rt, 0.5 h 2. TEAF, rt, 8 h	(87)	161									
	OsO ₄ , NMO, Me ₂ CO, H ₂ O, 12 h	(100)	153									
	1. OsO ₄ , Et, HOBu- <i>t</i> , H ₂ O, K ₃ Fe(CN) ₆ , K ₂ CO ₃ , 0°, time 2. MeNH(CH ₂) ₂ NHMe 3. SiO ₂	<table border="1" style="display: inline-table; vertical-align: middle;"><thead><tr><th>R</th><th>Time</th><th>% ee</th></tr></thead><tbody><tr><td><i>i</i>-Pr</td><td>4 h (88)</td><td>R 94</td></tr><tr><td>Bu</td><td>3 h (78)</td><td>R 78</td></tr></tbody></table>	R	Time	% ee	<i>i</i> -Pr	4 h (88)	R 94	Bu	3 h (78)	R 78	345
R	Time	% ee										
<i>i</i> -Pr	4 h (88)	R 94										
Bu	3 h (78)	R 78										
	1. OsO ₄ , Et, HOBu- <i>t</i> , H ₂ O, K ₃ Fe(CN) ₆ , K ₂ CO ₃ , 0°, 6 h 2. MeNH(CH ₂) ₂ NHMe 3. SiO ₂	(96) S 90% ee	345									

 C₉

 C₁₀

TABLE 15. α -HYDROXYLATION OF ALDEHYDE SILYL ENOL ETHERS (Continued)

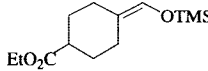
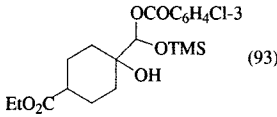
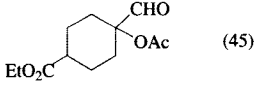
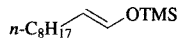
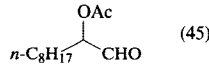
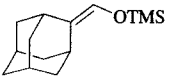
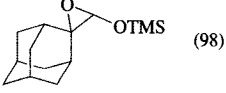
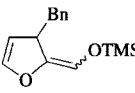
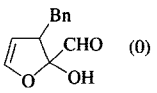
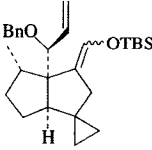
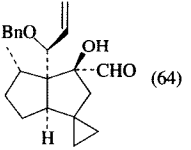
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	<i>m</i> -CPBA, CH ₂ Cl ₂ , rt, 1 h	 (93)	123
	1. <i>m</i> -CPBA, CH ₂ Cl ₂ , rt, 1 h 2. Ac ₂ O, Et ₃ N	 (45)	123
	1. <i>m</i> -CPBA, CH ₂ Cl ₂ , rt, 1 h 2. Ac ₂ O, Et ₃ N	 (45)	123
	DMDO, CH ₂ Cl ₂ , -40°, 3 h	 (98)	116, 114
	<i>m</i> -CPBA, THF, 0°, 1 h	 (0)	775
	1. <i>m</i> -CPBA 2. Bu ₄ NF	 (64)	776

TABLE 16A. α -HYDROXYLATION OF ACYCLIC KETONE SILYL ENOL ETHERS

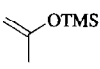
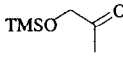
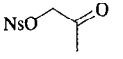
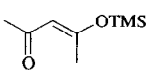
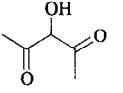
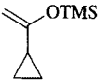
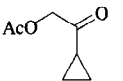
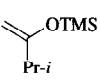
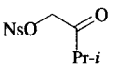
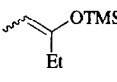
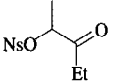
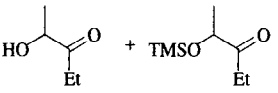
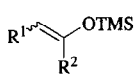
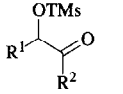
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.												
C ₃ 	<i>m</i> -CPBA, CH ₂ Cl ₂ , 0°	 (60)	179												
	(NsO) ₂ , EtOAc, H ₂ O, rt, 5 h	 (30)	105												
C ₅ 	H ₂ O ₂ (30%), MeReO ₃ , pyridine, MeCN, EtOAc, 15 min	 (0)	90												
	1. PhI(OAc) ₂ , CH ₂ Cl ₂ , rt, 2-8 h 2. H ₂ O	 (67)	365												
	(NsO) ₂	 (35)	777												
	(NsO) ₂ , EtOAc, H ₂ O, rt, 10 h	 (69)	105												
	H ₂ O ₂ (30%), MeReO ₃ , pyridine, MeCN, EtOAc, 15 min	 (99) ^a	90												
C ₅₋₈ 	<i>m</i> -CPBA, CH ₂ Cl ₂ , rt, 1 h	 <table border="1" data-bbox="1119 1492 1258 1607"> <thead> <tr> <th>R¹</th> <th>R²</th> <th>Yield (%)</th> </tr> </thead> <tbody> <tr> <td>Me</td> <td>Et</td> <td>(75)</td> </tr> <tr> <td>Me</td> <td>Bu-<i>t</i></td> <td>(73)</td> </tr> <tr> <td>H</td> <td>Ph</td> <td>(90)</td> </tr> </tbody> </table>	R ¹	R ²	Yield (%)	Me	Et	(75)	Me	Bu- <i>t</i>	(73)	H	Ph	(90)	123
R ¹	R ²	Yield (%)													
Me	Et	(75)													
Me	Bu- <i>t</i>	(73)													
H	Ph	(90)													

TABLE 16A. α -HYDROXYLATION OF ACYCLIC KETONE SILYL ENOL ETHERS (Continued)

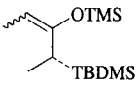

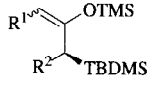
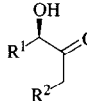
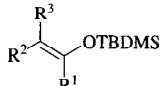
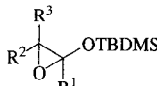
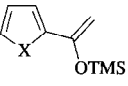
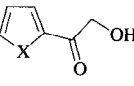
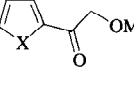
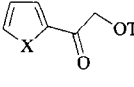
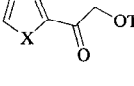
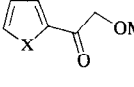

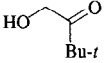
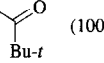
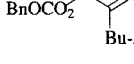
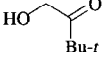
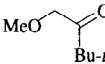
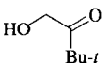
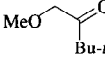
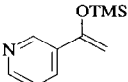
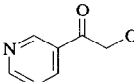
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																																
C ₅ 	1. <i>m</i> -CPBA, hexane, 0°; or PSPO, CHCl ₃ , reflux 2. HCl (5N), H ₂ O, ether 3. HBF ₄ , H ₂ O, THF	 (61) >98% ee	179																																
C ₅₋₁₂ 	1. <i>m</i> -CPBA, hexane, 0°; or PSPO, CHCl ₃ , reflux 2. HCl (5N), H ₂ O, ether 3. HBF ₄ , H ₂ O, THF	 >98% ee	<table border="1"> <thead> <tr> <th>R¹</th> <th>R²</th> <th></th> </tr> </thead> <tbody> <tr> <td>Me</td> <td>Me</td> <td>(58)</td> </tr> <tr> <td>Me</td> <td>Et</td> <td>(55)</td> </tr> <tr> <td>Et</td> <td>Me</td> <td>(58)</td> </tr> <tr> <td>Me</td> <td>Pr</td> <td>(70)</td> </tr> <tr> <td>Et</td> <td>Et</td> <td>(70)</td> </tr> <tr> <td>Me</td> <td>Bn</td> <td>(51)</td> </tr> <tr> <td>Et</td> <td>Bn</td> <td>(58)</td> </tr> </tbody> </table>	R ¹	R ²		Me	Me	(58)	Me	Et	(55)	Et	Me	(58)	Me	Pr	(70)	Et	Et	(70)	Me	Bn	(51)	Et	Bn	(58)	179							
R ¹	R ²																																		
Me	Me	(58)																																	
Me	Et	(55)																																	
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Me	Bn	(51)																																	
Et	Bn	(58)																																	
C ₅₋₁₀ 	DMDO, Me ₂ CO, -78°, 2-5 min; rt	 (—)	<table border="1"> <thead> <tr> <th>R¹</th> <th>R²</th> <th>R³</th> <th></th> </tr> </thead> <tbody> <tr> <td>Et</td> <td>H</td> <td>Me</td> <td>115</td> </tr> <tr> <td>Bu-<i>t</i></td> <td>H</td> <td>H</td> <td></td> </tr> <tr> <td>—(CH₂)₄—</td> <td></td> <td>H</td> <td></td> </tr> <tr> <td>—(CH₂)₄—</td> <td></td> <td>Me</td> <td></td> </tr> <tr> <td>H</td> <td>—(CH₂)₅—</td> <td></td> <td></td> </tr> <tr> <td>Ph</td> <td>H</td> <td>H</td> <td></td> </tr> <tr> <td>Ph</td> <td>Me</td> <td>Me</td> <td></td> </tr> </tbody> </table>	R ¹	R ²	R ³		Et	H	Me	115	Bu- <i>t</i>	H	H		—(CH ₂) ₄ —		H		—(CH ₂) ₄ —		Me		H	—(CH ₂) ₅ —			Ph	H	H		Ph	Me	Me	
R ¹	R ²	R ³																																	
Et	H	Me	115																																
Bu- <i>t</i>	H	H																																	
—(CH ₂) ₄ —		H																																	
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H	—(CH ₂) ₅ —																																		
Ph	H	H																																	
Ph	Me	Me																																	
C ₆ 	(PhIO) _n , BF ₃ •Et ₂ O, H ₂ O, 0°, 2h; rt, 2 h		<table border="1"> <thead> <tr> <th>X</th> <th></th> </tr> </thead> <tbody> <tr> <td>O</td> <td>(78)</td> </tr> <tr> <td>S</td> <td>(50)</td> </tr> </tbody> </table>	X		O	(78)	S	(50)	141																									
X																																			
O	(78)																																		
S	(50)																																		
	(PhIO) _n , BF ₃ •Et ₂ O, MeOH		<table border="1"> <thead> <tr> <th>X</th> <th></th> </tr> </thead> <tbody> <tr> <td>O</td> <td>(60)</td> </tr> <tr> <td>S</td> <td>(54)</td> </tr> </tbody> </table>	X		O	(60)	S	(54)	142																									
X																																			
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S	(54)																																		
	(PhIO) _n , TMSOTf, CH ₂ Cl ₂ , -78° to rt		<table border="1"> <thead> <tr> <th>X</th> <th></th> </tr> </thead> <tbody> <tr> <td>O</td> <td>(70)</td> </tr> <tr> <td>S</td> <td>(69)</td> </tr> </tbody> </table>	X		O	(70)	S	(69)	379																									
X																																			
O	(70)																																		
S	(69)																																		
	PhI(OH)Ts, CH ₂ Cl ₂ , rt, 2 h		<table border="1"> <thead> <tr> <th>X</th> <th></th> </tr> </thead> <tbody> <tr> <td>O</td> <td>(88)</td> </tr> <tr> <td>S</td> <td>(90)</td> </tr> </tbody> </table>	X		O	(88)	S	(90)	378																									
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	PhI(OH)Ms, CH ₂ Cl ₂ , rt, 2 h		<table border="1"> <thead> <tr> <th>X</th> <th></th> </tr> </thead> <tbody> <tr> <td>O</td> <td>(90)</td> </tr> <tr> <td>S</td> <td>(89)</td> </tr> </tbody> </table>	X		O	(90)	S	(89)	378																									
X																																			
O	(90)																																		
S	(89)																																		
	H ₂ O ₂ (30%), MeReO ₃ , pyridine, MeCN, EtOAc, 15 min	 +  (100) ^a	90																																
	1. <i>n</i> -BuLi, THF, 0°, 1.5 h 2. (BnOCO ₂) ₂ , -78°, 15 min; -40°, 1 h	 (62)	347																																
	(PhIO) _n , BF ₃ •Et ₂ O, H ₂ O, 0°, 2 h; rt, 2 h	 (83)	141																																
	(PhIO) _n , BF ₃ •Et ₂ O, MeOH	 (85)	142																																
	1. CrO ₂ Cl ₂ , CH ₂ Cl ₂ , -78°, 0.5 h 2. NaHSO ₃ , 15 min	 (82)	166																																
	MeOF, MeCN	 (90)	186																																
C ₇ 	(PhIO) _n , BF ₃ •Et ₂ O, H ₂ O, 0°, 2 h; rt, 2 h	 (54)	141, 140																																

TABLE 16A. α -HYDROXYLATION OF ACYCLIC KETONE SILYL ENOL ETHERS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	(PhIO) _n , BF ₃ •Et ₂ O, H ₂ O, 0°, 2h; rt, 2 h	 (62)	141, 140
	(PhIO) _n , BF ₃ •Et ₂ O, MeOH	 (70)	142, 778
	(PhIO) _n , BF ₃ •Et ₂ O, EtOH, -70°, 1 h; rt, 30 min	 (56)	778
	PhI(OH)Ts, CH ₂ Cl ₂ , rt, 2 h	 (78)	378
	1. <i>m</i> -CPBA 2. H ₃ O ⁺	 (90)	779
	<i>m</i> -CPBA, CH ₂ Cl ₂ , rt, overnight	 R ¹ R ² H <i>n</i> -Pr (75) H <i>n</i> -C ₅ H ₁₁ (95) Me <i>n</i> -Pr (80) Me <i>n</i> -Bu (77) H Ph (84)	128
	1. <i>m</i> -CPBA, CH ₂ Cl ₂ , rt, overnight 2. MeOH, Dowex 50-H ⁺ (cat.)	 R ¹ R ² H <i>n</i> -Pr (54) H <i>n</i> -C ₅ H ₁₁ (90) Me <i>n</i> -Bu (77) H Ph (80)	128
	1. <i>m</i> -CPBA, CH ₂ Cl ₂ , rt, overnight 2. HF, H ₂ O, MeCN, 80°, 0.5 h; or HF, Et ₃ N, MeOH, rt, 5 h	 R ¹ R ² Me <i>n</i> -Pr (64) Me <i>n</i> -Bu (54)	128
	1. <i>m</i> -CPBA, DCE, 90°, 1 h 2. Na ₂ CO ₃ (10%)	 R Me (0) Ph (7)	217
	H ₂ O ₂ (30%), MeReO ₃ , pyridine, MeCN, EtOAc, 15 min	 Pr- <i>i</i> + (95) ^a	90
	Ns ₂ O, EtOAc, H ₂ O, rt, 20 h	 (71)	105
	<i>m</i> -CPBA, hexane, 0°, 1 h	 (90) 90% de	179
	(PhIO) _n , BF ₃ •Et ₂ O, CH ₂ Cl ₂ , H ₂ O, -40°, 1 h; rt, 1 h	 R = H (63)	140
	(PhIO) _n , TMSOTf, CH ₂ Cl ₂ , H ₂ O, -78° to rt	 I R = Tf (53)	379

TABLE 16A. α -HYDROXYLATION OF ACYCLIC KETONE SILYL ENOL ETHERS (Continued)

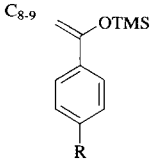
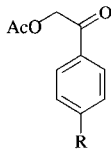
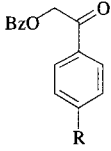
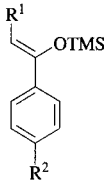
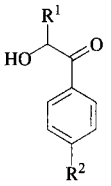
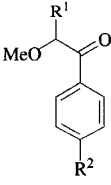
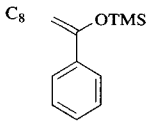
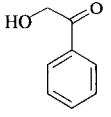
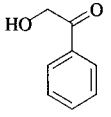
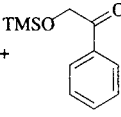
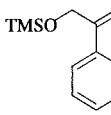
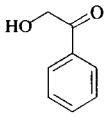
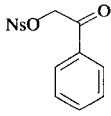
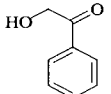
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																		
 C ₈₋₉	Pb(OAc) ₄ , C ₆ H ₆	 <table border="1"> <tr><td>R</td><td></td></tr> <tr><td>F</td><td>(94)</td></tr> <tr><td>Cl</td><td>(95)</td></tr> <tr><td>H</td><td>(95)</td></tr> <tr><td>OMe</td><td>(91)</td></tr> </table>	R		F	(94)	Cl	(95)	H	(95)	OMe	(91)	780								
R																					
F	(94)																				
Cl	(95)																				
H	(95)																				
OMe	(91)																				
	1. Pb(OBz) ₄ , CH ₂ Cl ₂ , 0° to rt, 0.5 h 2. TEAF, rt, 8 h	 <table border="1"> <tr><td>R</td><td></td></tr> <tr><td>F</td><td>(97)</td></tr> <tr><td>Cl</td><td>(96)</td></tr> <tr><td>H</td><td>(99)</td></tr> <tr><td>OMe</td><td>(90)</td></tr> </table>	R		F	(97)	Cl	(96)	H	(99)	OMe	(90)	161								
R																					
F	(97)																				
Cl	(96)																				
H	(99)																				
OMe	(90)																				
	(PhIO) _n , BF ₃ ·Et ₂ O, H ₂ O, 0°, 2 h; rt, 2 h	 <table border="1"> <tr><td>R¹</td><td>R²</td><td></td></tr> <tr><td>H</td><td>Cl</td><td>(68)</td></tr> <tr><td>H</td><td>NO₂</td><td>(70)</td></tr> <tr><td>H</td><td>H</td><td>(65)</td></tr> <tr><td>H</td><td>OMe</td><td>(72)</td></tr> <tr><td>Me</td><td>H</td><td>(74)</td></tr> </table>	R ¹	R ²		H	Cl	(68)	H	NO ₂	(70)	H	H	(65)	H	OMe	(72)	Me	H	(74)	141
R ¹	R ²																				
H	Cl	(68)																			
H	NO ₂	(70)																			
H	H	(65)																			
H	OMe	(72)																			
Me	H	(74)																			
	(PhIO) _n , BF ₃ ·Et ₂ O, MeOH	 <table border="1"> <tr><td>R¹</td><td>R²</td><td></td></tr> <tr><td>H</td><td>Cl</td><td>(76)</td></tr> <tr><td>H</td><td>NO₂</td><td>(68)</td></tr> <tr><td>H</td><td>H</td><td>(79)</td></tr> <tr><td>H</td><td>OMe</td><td>(71)</td></tr> <tr><td>Me</td><td>H</td><td>(75)</td></tr> </table>	R ¹	R ²		H	Cl	(76)	H	NO ₂	(68)	H	H	(79)	H	OMe	(71)	Me	H	(75)	142
R ¹	R ²																				
H	Cl	(76)																			
H	NO ₂	(68)																			
H	H	(79)																			
H	OMe	(71)																			
Me	H	(75)																			
 C ₈	1. O ₂ , Ni(mac) ₂ , Me ₂ CHCHO, CH ₂ Cl ₂ , rt, 6 h 2. KF, MeOH	 (76)	67																		
	1. O ₂ , Co(mac) ₂ , Me ₂ CHCH(OEt) ₂ , 4Å MS, 45°, 9 h 2. Bu ₄ NF, THF, rt, 3 h	I (83)	66, 65																		
	H ₂ O ₂ (30%), MeReO ₃ , pyridine, MeCN, EtOAc, 15 min	 +  (60) ^a	90																		
	<i>m</i> -CPBA, CH ₂ Cl ₂ , 0°	 (70)	122																		
	1. <i>m</i> -CPBA, hexane 2. 1.5N HCl, 2 h	 (74)	120																		
	(NsO) ₂ , EtOAc, H ₂ O, rt, 33 h	 (76)	105																		
	(PhIO) _n , BF ₃ ·Et ₂ O, CH ₂ Cl ₂ , H ₂ O, -40°, 1 h; rt, 1 h	 (57)	140																		

TABLE 16A. α -HYDROXYLATION OF ACYCLIC KETONE SILYL ENOL ETHERS (Continued)

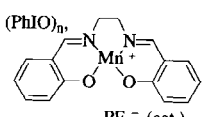
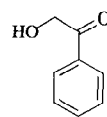
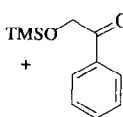
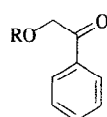
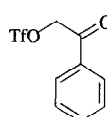
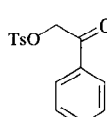
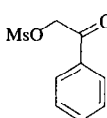
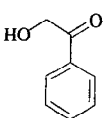
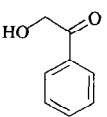
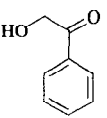
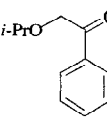
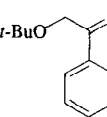
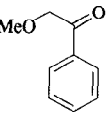
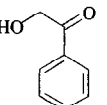
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
 $(\text{PhIO})_n$, PF_6^- (cat.), MeCN, 25°, 10 min	 (52) +  (42)	145	
$(\text{PhIO})_n$, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, ROH	 R Et (80) <i>i</i> -Pr (45)	142	
$(\text{PhIO})_n$, TMSOTf, CH_2Cl_2 , -78° to rt	 (70)	379	
PhI(OH)OTs, CH_2Cl_2 , rt, 2 h	 (92)	378	
PhI(OH)OMs, CH_2Cl_2 , rt, 2 h	 (89)	378	
1. OsO_4 (cat.), NMO, H_2O , Me_2CO , -10 to 25° 2. 1N H_2SO_4	 (70)	154	
1. CrO_2Cl_2 , CH_2Cl_2 , -78°, 30 min 2. NaHSO_3 , 15 min	 (62)	166	
1. NPSO, CHCl_3 , 60°, 3 h 2. HCl (5%), THF	 (65)	180	
<i>i</i> -PrOCl, $\text{Pd}(\text{PPh}_3)_4$, HgO, PhMe, -78°, 1 h	 (56)	185	
<i>t</i> -BuOCl, $\text{Pd}(\text{PPh}_3)_4$, HgO, PhMe, -78°, 1 h	 (64)	185	
<i>t</i> -BuOCl, $\text{RhCl}(\text{PPh}_3)_3$, PhMe	I (20)	185	
<i>t</i> -BuOCl, $\text{Ni}(\text{PPh}_3)_4$, PhMe	I (0)	185	
MeOF, MeCN	 (85)	186	
F_2 , N_2 , MeCN, H_2O , rt, 5-10 min	 (>90)	187	

TABLE 16A. α -HYDROXYLATION OF ACYCLIC KETONE SILYL ENOL ETHERS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	O ₂ , Ni(mac) ₂ , Me ₂ CHCHO, (CH ₂ Cl) ₂ , rt, 4 h	(93)	67
	<i>m</i> -CPBA, CH ₂ Cl ₂ , 0°	(61)	122
	(PhIO) _n , BF ₃ ·Et ₂ O, H ₂ O, -40°, 1 h; rt, 1 h	(25) + (31)	501
	<i>t</i> -BuOCl, Pd(PPh ₃) ₄ , HgO, PhMe, -78°, 1 h	(85)	185
	1. OsO ₄ (cat.), NMO, Me ₂ CO, H ₂ O, -10 to 25° 2. 1N H ₂ SO ₄	(68)	154
	<i>m</i> -CPBA (2.5 eq), KHCO ₃ , CH ₂ Cl ₂ , 0°, 90 min	(72)	131
	1. OsO ₄ (cat.), NMO, Me ₂ CO, H ₂ O, -10 to 25° 2. 1N H ₂ SO ₄	(59)	154
	<i>m</i> -CPBA, CH ₂ Cl ₂ , rt, overnight	(71) R ¹ Bn (0) R ² Bn (0)	128
	1. OsO ₄ (cat.), NMO, Me ₂ CO, H ₂ O, -10 to 25° 2. 1N H ₂ SO ₄	(57)	154
	1. MeLi, 0°, 15 min 2. (+)-CSO, -78 to 0°	(57) <i>S</i> 12% ee	26
	1. OsO ₄ (cat.), NMO, Me ₂ CO, H ₂ O, -10 to 25° 2. 1N H ₂ SO ₄	(69)	154
	1. OsO ₄ (cat.), NMO, Me ₂ CO, H ₂ O, -10 to 25° 2. 1N H ₂ SO ₄	(54)	154
	(PhIO) _n , BF ₃ ·Et ₂ O, MeOH	(71)	142
	1. CrO ₂ Cl ₂ , CH ₂ Cl ₂ , -78°, 30 min 2. NaHSO ₃ , 15 min	(67)	166

TABLE 16A. α -HYDROXYLATION OF ACYCLIC KETONE SILYL ENOL ETHERS (Continued)

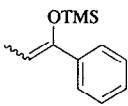
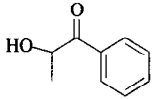
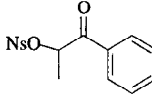
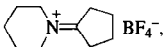
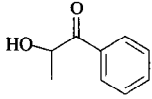
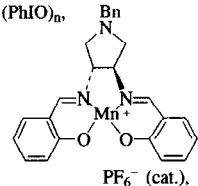
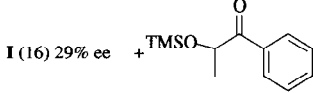
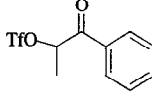
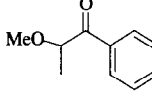
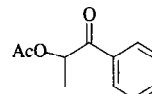
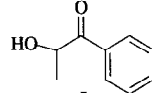
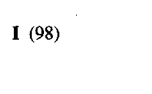
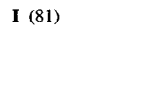
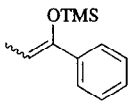
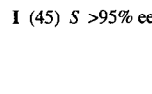
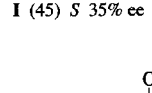
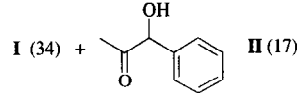
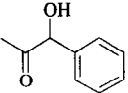
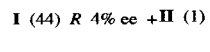
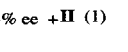
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
 Z	1. O ₂ , Ni(mac) ₂ , Me ₂ CHCHO, (CH ₂ Cl) ₂ , rt, 6 h 2. KF, MeOH	 (75)	67
	(NsO) ₂ , EtOAc, H ₂ O, rt, 24 h	 (>95)	105
	 [2 KHSO ₅ + KHSO ₄ + K ₂ SO ₄], NaHCO ₃ , H ₂ O, MeCN, rt, 16 h	 (75)	180a
	 (PhIO) _n , MeCN, 25°, 15 min	 (67)	145
	(PhIO) _n , TMSOTf, CH ₂ Cl ₂ , -78, to rt	 (77)	379
	(PhIO) _n , BF ₃ •Et ₂ O, MeOH	 (—)	781
	1. PhI(OAc) ₂ , CH ₂ Cl ₂ , rt, 2-8 h 2. H ₂ O	 (90)	365
	1. OsO ₄ (cat.), NMO, dihydroquinidine <i>p</i> -chlorobenzoate, H ₂ O, Me ₂ CO, PhMe, Me ₄ NOH, 0°, 23 h 2. Na ₂ S ₂ O ₅ , rt, 5 min	 (—) 78-85% ee	160, 782
	1. OsO ₄ (cat.), NMO, H ₂ O, Me ₂ CO, -10 to 25° 2. 1 N H ₂ SO ₄	 (98)	154
	1. NPSO, CHCl ₃ , 60°, 1 h 2. HCl (5%), THF	 (81)	180
 Z:E = > 97:<3	1. MeLi, THF, 0°, 1 h 2. (+)-DCCSO, -78°, 30 min	 (45) <i>S</i> >95% ee	278
	1. MeLi (0.95 eq), THF, 0°, 1 h 2. (+)-CSO, -78°, 30 min; 0°, 10 min	 (45) <i>S</i> 35% ee	505, 174
	1. MeLi (1.25 eq), THF, HMPA, 0°, 1 h 2. (+)-CSO, -78°, 30 min; 0°, 10 min	 (34) +  (17)	505, 174
	1. MeLi (1.0 eq), THF, 0° 2. (+)-CSO, -78°, 30 min; 0°, 10 min	 (44) <i>R</i> 4% ee +  (1)	505, 174

TABLE 16A. α -HYDROXYLATION OF ACYCLIC KETONE SILYL ENOL ETHERS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																																				
	 , [2 KHSO ₅ •KHSO ₄ •K ₂ SO ₄], MeCN, H ₂ O, 0°, 2 h	 (80) 90% ee	117																																				
	O ₂ , Ni(mac) ₂ , Me ₂ CHCHO, (CH ₂ Cl) ₂ , rt, 6 h	 (91)	67																																				
 Z:E = 11:98	<i>m</i> -CPBA, CH ₂ Cl ₂ , 0°	 (3)	122																																				
	(PhIO) _n , BF ₃ •Et ₂ O, MeOH	 (—)	781																																				
	1. OsO ₄ (cat.), NMO, H ₂ O, Me ₂ CO, -10 to 25° 2. IN H ₂ SO ₄	 (91)	154																																				
	1. MeLi (0.95 eq), THF, HMPA, 0°, 1 h 2. (+)-CSO, -78°	 I (68) <i>R</i> 68% ee	505, 174																																				
	(PhIO) _n , BF ₃ •Et ₂ O, CH ₂ Cl ₂ , H ₂ O, -40°, 1 h; rt, 1 h	 (65)	140																																				
	1. NaOCl, 4-phenylpyridine <i>N</i> -oxide, CH ₂ Cl ₂ , H ₂ O, 5°, 20 h 2. HCl, MeOH	 <table border="1"> <thead> <tr> <th>R¹</th> <th>R²</th> <th>R³</th> <th>% ee</th> </tr> </thead> <tbody> <tr> <td>Me</td> <td>Ph</td> <td>Me</td> <td>(99)^b <i>R</i> 50</td> </tr> <tr> <td>Me</td> <td>Ph</td> <td>Bu-<i>t</i></td> <td>(>95)^b <i>R</i> 81</td> </tr> </tbody> </table>	R ¹	R ²	R ³	% ee	Me	Ph	Me	(99) ^b <i>R</i> 50	Me	Ph	Bu- <i>t</i>	(>95) ^b <i>R</i> 81	783																								
R ¹	R ²	R ³	% ee																																				
Me	Ph	Me	(99) ^b <i>R</i> 50																																				
Me	Ph	Bu- <i>t</i>	(>95) ^b <i>R</i> 81																																				
<i>C</i> ₉₋₁₄ 	1. NaOCl, 4-phenylpyridine <i>N</i> -oxide, CH ₂ Cl ₂ , H ₂ O, 0°, 24 h 2. HCl, MeOH, 2 h	 <table border="1"> <thead> <tr> <th>R¹</th> <th>R²</th> <th>R³</th> <th>% ee</th> </tr> </thead> <tbody> <tr> <td>Me</td> <td>Ph</td> <td>Me</td> <td>(95)^b <i>R</i> 42</td> </tr> <tr> <td>Me</td> <td>Ph</td> <td>Bu-<i>t</i></td> <td>(95)^b <i>R</i> 81</td> </tr> <tr> <td>Ph</td> <td>Me</td> <td>Me</td> <td>(91)^b <i>S</i> 79</td> </tr> <tr> <td>Ph</td> <td>Me</td> <td>Bu-<i>t</i></td> <td>(59)^b <i>S</i> 86</td> </tr> <tr> <td>Et</td> <td>Ph</td> <td>Me</td> <td>(84)^b <i>R</i> 60</td> </tr> <tr> <td>Ph</td> <td>Et</td> <td>Me</td> <td>(82)^b <i>S</i> 87</td> </tr> <tr> <td>Ph</td> <td>Bu-<i>t</i></td> <td>Me</td> <td>(96)^b <i>S</i> 35</td> </tr> <tr> <td>Ph</td> <td>Ph</td> <td>Me</td> <td>(84)^b <i>R</i> 60</td> </tr> </tbody> </table>	R ¹	R ²	R ³	% ee	Me	Ph	Me	(95) ^b <i>R</i> 42	Me	Ph	Bu- <i>t</i>	(95) ^b <i>R</i> 81	Ph	Me	Me	(91) ^b <i>S</i> 79	Ph	Me	Bu- <i>t</i>	(59) ^b <i>S</i> 86	Et	Ph	Me	(84) ^b <i>R</i> 60	Ph	Et	Me	(82) ^b <i>S</i> 87	Ph	Bu- <i>t</i>	Me	(96) ^b <i>S</i> 35	Ph	Ph	Me	(84) ^b <i>R</i> 60	273
R ¹	R ²	R ³	% ee																																				
Me	Ph	Me	(95) ^b <i>R</i> 42																																				
Me	Ph	Bu- <i>t</i>	(95) ^b <i>R</i> 81																																				
Ph	Me	Me	(91) ^b <i>S</i> 79																																				
Ph	Me	Bu- <i>t</i>	(59) ^b <i>S</i> 86																																				
Et	Ph	Me	(84) ^b <i>R</i> 60																																				
Ph	Et	Me	(82) ^b <i>S</i> 87																																				
Ph	Bu- <i>t</i>	Me	(96) ^b <i>S</i> 35																																				
Ph	Ph	Me	(84) ^b <i>R</i> 60																																				

TABLE 16A. α -HYDROXYLATION OF ACYCLIC KETONE SILYL ENOL ETHERS (Continued)

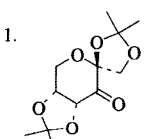
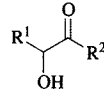
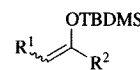
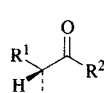
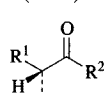
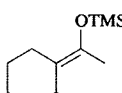
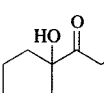
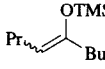
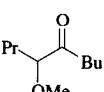
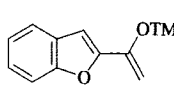
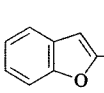
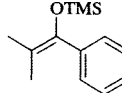
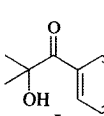
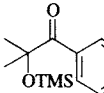
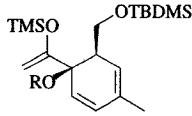
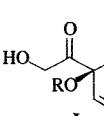
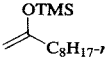
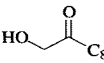
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1.  (3 eq), [2 KHSO ₅ •KHSO ₄ •K ₂ SO ₄] (5 eq), MeCN, H ₂ O, EDTA, NaHCO ₃ , pH 8-10.5, 0°, time 2. HCl, MeOH	 R ¹ R ² R ³ Time % ee	118
		Me Ph Me 1.5 h (46) ^b R 54 Me Ph Bu- <i>t</i> 3.0 h (92) ^b R 82 Ph Me Me 1.5 h (35) ^b R 18 Et Ph Me 1.5 h (33) ^b R 67 Ph Bu- <i>t</i> Me 3.0 h (30) ^b S 52 Ph Ph Me 1.5 h (36) ^b R 61	
	AD-mix- α , MeSO ₂ NH ₂ , <i>t</i> -BuOH, H ₂ O, 0°, 16 h	 R ¹ R ² E:Z R ¹ R ² % ee	158
		25:75 <i>n</i> -Bu <i>n</i> -C ₅ H ₁₁ 86 <1:>99 Me C ₆ H ₄ OMe-4 97 <1:>99 <i>n</i> -C ₆ H ₁₃ Ph 99	
	AD-mix- β , MeSO ₂ NH ₂ , <i>t</i> -BuOH, H ₂ O, 0°, 16 h	 R ¹ R ² E:Z R ¹ R ² % ee	158
		12:88 <i>i</i> -Pr CH ₂ Pr- <i>i</i> 79 <1:>99 Me Ph 97 <1:>99 Me C ₆ H ₄ OMe-4 99 25:75 <i>n</i> -Bu <i>n</i> -C ₅ H ₁₁ 89 <1:>99 <i>n</i> -C ₆ H ₁₃ Ph 99 3:>97 Ph Ph 97	
C ₉ 	1. <i>m</i> -CPBA (2.5 eq), KHCO ₃ , (CH ₂ Cl) ₂ , 0°, 1.5 h 2. H ₃ O ⁺	 (79)	131
	MeOF, MeCN	 (—)	186
C ₁₀ 	(PhIO) _n , BF ₃ •Et ₂ O, H ₂ O, 0°, 2 h; rt, 2 h	 (59)	141
	1. O ₂ , tetraphenylporphine, CCl ₄ , 0.5 h 2. H ₂ , Pd/C, MeOH	 (53) I	80, 784
	O ₂ , Ph ₃ P, TAS-F, THF, 0 to 5°, 2 h	I (69)	68
	<i>m</i> -CPBA, hexane	 (74)	120
	1. <i>m</i> -CPBA, hexane 2. LiF, H ₂ O, Et ₂ O, HMPA, 60 h	I (60)	120
	1. NPSO, CHCl ₃ , 25°, 4.5 h 2. Bu ₄ NF, THF	I (79)	180
	1. <i>m</i> -CPBA 2. H ₂ O, MgSO ₄	 R = TMS (60) I	204
	1. <i>m</i> -CPBA 2. K ₂ CO ₃ , MeOH	I R = TBDMS (75)	204
	1. O ₂ , Co(mac) ₂ , EtCH(OEt) ₂ , 4 Å MS, 45°, 10 h 2. Bu ₄ NF, THF, rt, 3 h	 (77)	66, 65

TABLE 16A. α -HYDROXYLATION OF ACYCLIC KETONE SILYL ENOL ETHERS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.										
	<i>m</i> -CPBA (1.0 eq), KHCO ₃ , CH ₂ Cl ₂ , 0°, 1.5 h	+	131										
	<i>m</i> -CPBA (1.0 eq), KHCO ₃ , CH ₂ Cl ₂ , 0°, 1.5 h	+	131										
C ₁₁ 	1. OsO ₄ (cat.), NMO, Me ₂ CO, H ₂ O, -10 to 25° 2. 1N H ₂ SO ₄		154										
	<i>m</i> -CPBA, CH ₂ Cl ₂ , NaHCO ₃ , 0°		126										
	1. <i>m</i> -CPBA, CH ₂ Cl ₂ , NaHCO ₃ , 0° 2. Py•TsOH, CH ₂ Cl ₂ , rt, 1.5 h		126										
	1. O ₂ , Ni(mac) ₂ , Me ₂ CHCHO, (CH ₂ Cl) ₂ , rt, 6 h 2. KF, MeOH		67										
C ₁₂ 	1. <i>m</i> -CPBA, DCE, 0° to rt, 1 h 2. Na ₂ CO ₃ (10%)		217										
	<i>m</i> -CPBA (2.0 eq), KHCO ₃ , CH ₂ Cl ₂ , 0°, 1.5 h	+	131										
C ₁₃ 	1. <i>m</i> -CPBA (3.3 eq), KHCO ₃ , CH ₂ Cl ₂ , 0°, 1.5 h 2. H ₃ O ⁺		131										
C ₁₄ 	1. TiCl ₄ , CH ₂ Cl ₂ , -78°, 15 min 2. (BnOCO) ₂ , -78 to 20°, 30 min		347										
	1. NPSO, CHCl ₃ , 60°, 7.5 h 2. HF, MeCN	I (98)	180										
	1. <i>n</i> -BuLi, THF, 0°, 1.5 h 2. (BnOCO) ₂ , -78°, 15 min; -40°, 1 h		347										
C ₁₅ 	OsO ₄ (cat.), ligand, K ₃ Fe(CN) ₆ , K ₂ CO ₃ , MeSO ₂ NH ₂ , <i>t</i> -BuOH, H ₂ O, 0°		<table border="1"> <thead> <tr> <th>Ligand</th> <th>% ee</th> </tr> </thead> <tbody> <tr> <td>(DHQD)₂-PHAL</td> <td><i>R</i> 75</td> </tr> <tr> <td>(DHQ)₂-PHAL</td> <td><i>S</i> 81</td> </tr> <tr> <td>(DHQD)₂-PYR</td> <td><i>R</i> 79</td> </tr> <tr> <td>(DHQ)₂-PYR</td> <td><i>S</i> 79</td> </tr> </tbody> </table>	Ligand	% ee	(DHQD) ₂ -PHAL	<i>R</i> 75	(DHQ) ₂ -PHAL	<i>S</i> 81	(DHQD) ₂ -PYR	<i>R</i> 79	(DHQ) ₂ -PYR	<i>S</i> 79
Ligand	% ee												
(DHQD) ₂ -PHAL	<i>R</i> 75												
(DHQ) ₂ -PHAL	<i>S</i> 81												
(DHQD) ₂ -PYR	<i>R</i> 79												
(DHQ) ₂ -PYR	<i>S</i> 79												

TABLE 16A. α -HYDROXYLATION OF ACYCLIC KETONE SILYL ENOL ETHERS (Continued)

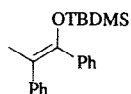
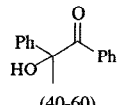
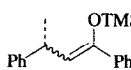
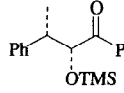
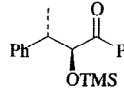
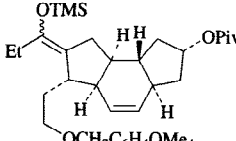
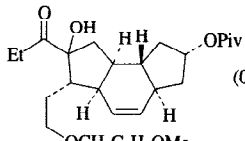
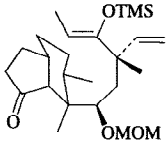
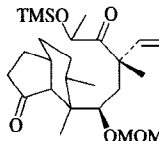
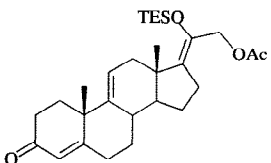
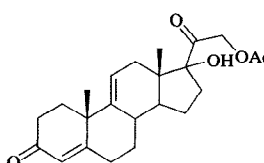
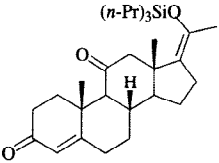
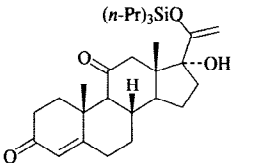

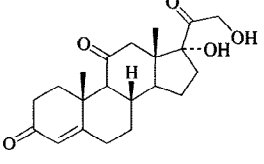
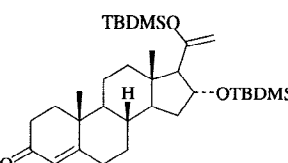
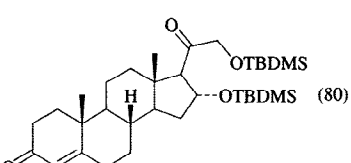
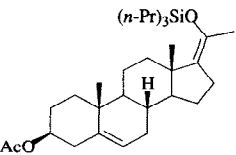
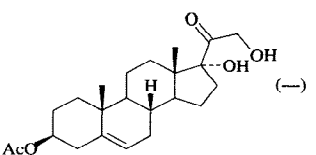
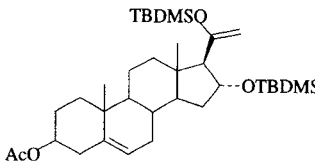
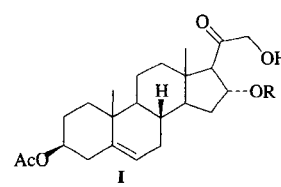
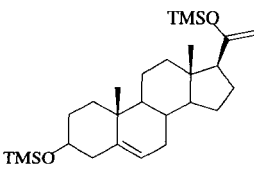
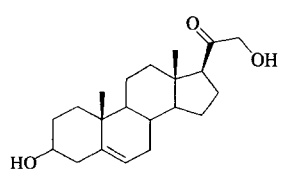
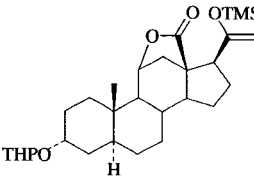
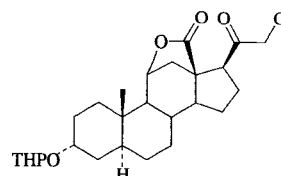
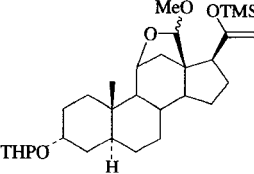
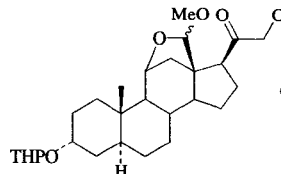
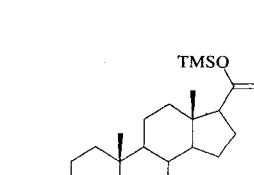
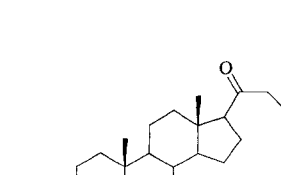
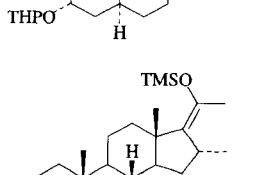
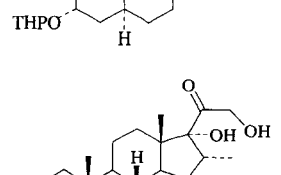
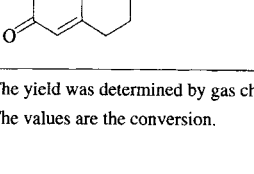
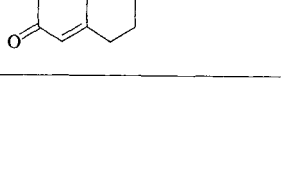
Substrate	Conditions	Product(s) and Yield(s) (%)		Refs.
		Ligand	% ee	
 C16	OsO ₄ (cat.), ligand, K ₃ Fe(CN) ₆ , K ₂ CO ₃ , MeSO ₂ NH ₂ , <i>t</i> -BuOH, H ₂ O, 0°	 (40-60)	(DHQD) ₂ -PHAL <i>R</i> 53 (DHQ) ₂ -PHAL <i>S</i> 63 (DHQD) ₂ -PYR <i>R</i> 60 (DHQ) ₂ -PYR <i>S</i> 33	159
 C17	<i>m</i> -CPBA, CH ₂ Cl ₂	 (57) +  (17)		785
 C17	<i>m</i> -CPBA, MoOPH, or PSPO	 (0)		515
 C20	<i>m</i> -CPBA, CH ₂ Cl ₂ , reflux, 4 h	 (69)		786
 C21	AcO ₂ H	 (—)		133
 C21	1. <i>m</i> -CPBA (1 eq), KHCO ₃ , CH ₂ Cl ₂ , 0°, 1.5 h	 (91)		131, 207
 C21	1. <i>m</i> -CPBA (3 eq), CH ₂ Cl ₂ , KHCO ₃ , 0°, 1.5 h 2. 1N HCl, THF	 (83)		208, 207
 C21	<i>m</i> -CPBA, C ₆ H ₁₂ , -15° to rt, 3 h	 (80)		787
 C21	1. <i>m</i> -CPBA (3 eq), KHCO ₃ , 2. H ₃ O ⁺	 (—)		207

TABLE 16A. α -HYDROXYLATION OF ACYCLIC KETONE SILYL ENOL ETHERS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. <i>m</i> -CPBA, C ₆ H ₁₂ , -15° to rt, 3 h 2. Bu ₄ NF, CH ₂ Cl ₂ , THF, rt, 24 h	 R = H (79)	787
	1. <i>m</i> -CPBA, C ₆ H ₁₂ , -15° to rt, 3 h 2. Bu ₄ NF, Ac ₂ O, Et ₃ N, THF, rt, 24 h	 I R = Ac (82)	787
	1. OsO ₄ (cat.), NMO, Me ₂ CO, H ₂ O, -10 to 25° 2. 1N H ₂ SO ₄	 (59)	154
	<i>m</i> -CPBA, DME, rt, 7 d	 (23)	788
	<i>m</i> -CPBA, DME, rt to 65°, 24 h	 (48)	788
	<i>m</i> -CPBA, DME, rt, 6 d	 (73)	788
C ₂₂ 	1. <i>m</i> -CPBA (2.9 eq), KHCO ₃ 2. H ₃ O ⁺	 (86)	207, 131

^a The yield was determined by gas chromatography.

^b The values are the conversion.

TABLE 16B. α -HYDROXYLATION OF CYCLIC KETONE SILYL ENOL ETHERS



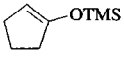



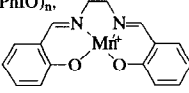


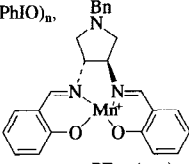


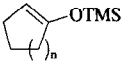


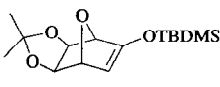
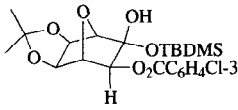
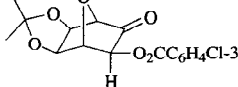
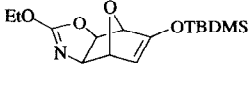
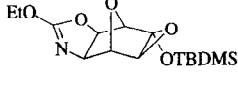
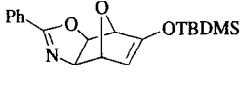
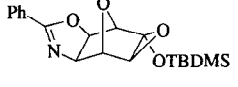
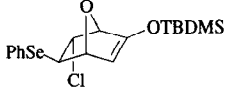
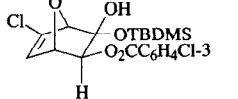
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																
C ₄ 	1. O ₂ , hv, rose bengal, THF, -78°, 2.8 h 2. PPh ₃ , MeOH	 (70)	78																
C ₅ 	1. O ₂ , hv, rose bengal, THF, -78°, 3 h 2. PPh ₃ , MeOH	 (37) +  (22)	78																
	<i>m</i> -CPBA	 O ₂ CC ₆ H ₄ Cl-3 (—)	132																
	(PhIO) _n ,  PF ₆ ⁻ (cat.), MeCN, 25°, 3 h	 I +  II I+II = (85); I:II = 1:1.4	145																
	(PhIO) _n ,  PF ₆ ⁻ (cat.), MeCN, 25°, 4 h	I+II (70) 30% ee; I:II = 1:2.6	145																
	1. Pb(OAc) ₄ , CH ₂ Cl ₂ , 20°, 1 h 2. BF ₃ •Et ₂ O, 20°, 1 h	 (79) I	366																
	1. AgOAc, I ₂ , CH ₂ Cl ₂ , 2 h 2. Et ₃ NHF, rt, 2 h	I (68)	189																
	1. Pb(OBz) ₄ , CH ₂ Cl ₂ , 0° to rt, 0.5 h 2. BF ₃ •Et ₂ O, 20°, 8 h	 (77) I	161																
	1. AgOBz, I ₂ , CH ₂ Cl ₂ , 2 h 2. Et ₃ NHF, rt, 2 h	I (72)	189																
C ₅₋₈ 	1. H ₂ O ₂ (30%), MeReO ₃ , pyridine, MeCN, HOAc, 15 min 2. KF	 I +  II	<table border="1"> <thead> <tr> <th>n</th> <th>I</th> <th>I+II</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>—</td> <td>(96)^a</td> </tr> <tr> <td>2</td> <td>(90)</td> <td>—</td> </tr> <tr> <td>3</td> <td>(91)</td> <td>—</td> </tr> <tr> <td>4</td> <td>—</td> <td>(99)^a</td> </tr> </tbody> </table>	n	I	I+II	1	—	(96) ^a	2	(90)	—	3	(91)	—	4	—	(99) ^a	90
n	I	I+II																	
1	—	(96) ^a																	
2	(90)	—																	
3	(91)	—																	
4	—	(99) ^a																	
C ₆ 	<i>m</i> -CPBA, THF, 20°, 45 min	 (69)	789, 790, 791																
	1. <i>m</i> -CPBA, THF, 20°, 45 min 2. 200°, 12 min	 (51)	789																
	DMDO, Me ₂ CO, CH ₂ Cl ₂ , -20 to 20°, 6 h	 (100)	792																
	DMDO, Me ₂ CO, CH ₂ Cl ₂ , 0°, 3 h	 (100)	792																
	<i>m</i> -CPBA, NaOAc, CH ₂ Cl ₂ , 0 to 20°, 30 min	 (69)	793																

TABLE 16B. α -HYDROXYLATION OF CYCLIC KETONE SILYL ENOL ETHERS (Continued)

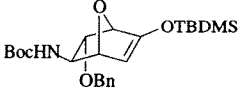
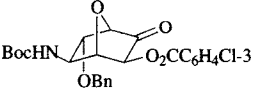
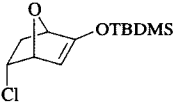
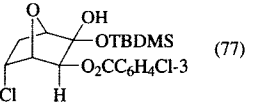
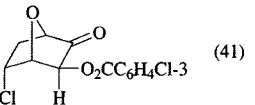
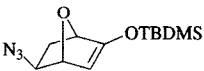
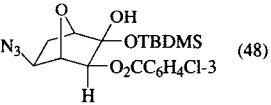
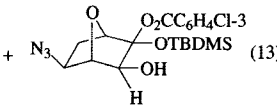
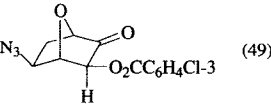
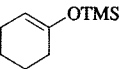



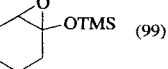


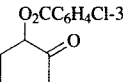


Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	<i>m</i> -CPBA, CH ₂ Cl ₂	 (63)	790, 794
	<i>m</i> -CPBA, THF, 25°, 1 h	 (77)	130
	1. <i>m</i> -CPBA, THF, 25°, 1 h 2. 180°, 10 min	 (41)	130
	<i>m</i> -CPBA, CH ₂ Cl ₂ , 0°, 0.5 h	 (48) +  (13)	130
	1. <i>m</i> -CPBA, CH ₂ Cl ₂ , 0°, 0.5 h 2. 120°, 20 min	 (49)	130
	1. O ₂ , hv, rose bengal, THF, -78°, 5.5 h 2. PPh ₃ , MeOH	 (11) +  (1)	78
	(NsO) ₂ , EtOAc, H ₂ O, rt, 5 h	 (77)	105
	DMDO, CH ₂ Cl ₂ , rt, 2 h	 (99)	116, 114
	<i>m</i> -CPBA, hexane	 (81)	119
	<i>m</i> -CPBA, CH ₂ Cl ₂ , 0°	I (68)	122
	1. <i>m</i> -CPBA, Et ₂ O, 5 sec 2. HOAc	 I (20) +  II (22)	119
	1. <i>m</i> -CPBA, Et ₂ O, 10 min 2. HOAc	II (81)	119, 129
	1. <i>m</i> -CPBA, hexane 2. NaOH (10%), 3 h	 I (64)	120
(PhIO) _n , BF ₃ •Et ₂ O, H ₂ O, 0°, 2 h; rt, 2 h	I (80)	141	
(PhIO) _n , BF ₃ •Et ₂ O, MeOH	 (78)	142	

TABLE 16B. α -HYDROXYLATION OF CYCLIC KETONE SILYL ENOL ETHERS (Continued)

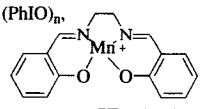
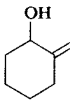
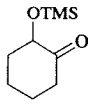
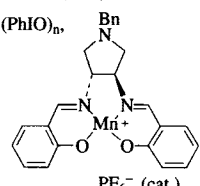





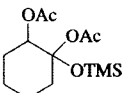
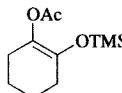





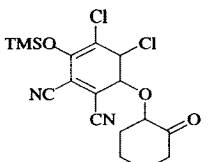
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																
 $(\text{PhIO})_n$ PF_6^- (cat.) MeCN, 25°, 3 h	 + 	I (51) II (36)	145																
 $(\text{PhIO})_n$ PF_6^- (cat.) MeCN, 25°, 1 h		I (46) 51% ee + II (32)	145																
1. $\text{PhI}(\text{OAc})_2$, CH_2Cl_2 , rt, 2-8 h 2. H_2O		(81)	365																
$(\text{PhIO})_n$, TMSOTf , CH_2Cl_2 , -78° to rt		(64)	379																
$\text{PhI}(\text{OTf})_2$, CH_2Cl_2 , rt, 2 h		I (60)	365																
$\text{PhI}(\text{OH})\text{OTs}$, CH_2Cl_2 , rt, 2 h		(85)	378																
1. OsO_4 (cat.), NMO, Me_2CO , H_2O , -10 to 25° 2. 1N H_2SO_4		(89)	154																
$\text{Pb}(\text{OAc})_4$, CH_2Cl_2 , 20°		(62) +  (21)	366																
1. $\text{Pb}(\text{OAc})_4$, CH_2Cl_2 , 20° 2. LiF , DMF, 140°, 6 h or $\text{BF}_3 \cdot \text{Et}_2\text{O}$, 20°, 1 h		(76)	366																
1. $\text{Pb}(\text{OBz})_4$, CH_2Cl_2 , 0° to rt, 30 min 2. TEAF, rt, 8 h		(91)	161																
1. CrO_2Cl_2 , CH_2Cl_2 , -78°, 30 min 2. NaHSO_3 , 15 min		(65)	166																
1. NPSO, CHCl_3 , 60°, 3 h 2. HCl (5%), THF		I (65)	180																
1. I_2 , AgOCOR , CH_2Cl_2 , 2 h 2. Et_3NHF , rt, 2 h		<table border="1" style="display: inline-table; vertical-align: middle;"> <thead> <tr> <th>R</th> <th></th> </tr> </thead> <tbody> <tr> <td>CF_3</td> <td>(90)</td> </tr> <tr> <td>Me</td> <td>(90)</td> </tr> <tr> <td>$\text{C}_6\text{H}_3(\text{NO}_2)_2$-3,5</td> <td>(92)</td> </tr> <tr> <td>$\text{C}_6\text{H}_4\text{Cl}$-3</td> <td>(84)</td> </tr> <tr> <td>$\text{C}_6\text{H}_4\text{NO}_2$-4</td> <td>(85)</td> </tr> <tr> <td>Ph</td> <td>(71)</td> </tr> <tr> <td>CH_2OPh</td> <td>(83)</td> </tr> </tbody> </table>	R		CF_3	(90)	Me	(90)	$\text{C}_6\text{H}_3(\text{NO}_2)_2$ -3,5	(92)	$\text{C}_6\text{H}_4\text{Cl}$ -3	(84)	$\text{C}_6\text{H}_4\text{NO}_2$ -4	(85)	Ph	(71)	CH_2OPh	(83)	189
R																			
CF_3	(90)																		
Me	(90)																		
$\text{C}_6\text{H}_3(\text{NO}_2)_2$ -3,5	(92)																		
$\text{C}_6\text{H}_4\text{Cl}$ -3	(84)																		
$\text{C}_6\text{H}_4\text{NO}_2$ -4	(85)																		
Ph	(71)																		
CH_2OPh	(83)																		
DDQ, THF, 22°, 30 min		(20)	184																

TABLE 16B. α -HYDROXYLATION OF CYCLIC KETONE SILYL ENOL ETHERS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	CF ₃ COCH ₃ , [2 KHSO ₅ + KHSO ₄ + K ₂ SO ₄], NaEDTA, MeCN, H ₂ O, 0-1°, 20 min	 (97)	487, 131
	<i>m</i> -CPBA, NaHCO ₃ , CH ₂ Cl ₂ , rt	 (35)	271
	<i>m</i> -CPBA, NaHCO ₃ , CH ₂ Cl ₂ , 0°	 (50)	271
	ROCl, Pd(PPh ₃) ₄ , HgO, PhMe, -78°, 1 h	 R Et (88) <i>i</i> -Pr (77) (CH ₂) ₃ Cl (82) <i>t</i> -Bu (73) C ₆ H ₁₁ - <i>c</i> (89)	185
	DMDO, Me ₂ CO, rt, 2 h	 (69)	795
	(PhIO) _n , BF ₃ •Et ₂ O, H ₂ O, rt, 2-3 h	 (67)	795
	O ₂ , hv, tetraphenylporphine, CCl ₄ , 30 min	 (95)	79
	O ₂ , hv, rose bengal, CD ₃ OD, -20°	 I + II (-) I:II = 85:15	72
	<i>m</i> -CPBA, NaHCO ₃ , H ₂ O, CH ₂ Cl ₂ , 0°, 2 h	 (55) + (19)	72, 527
	1. <i>m</i> -CPBA, NaHCO ₃ , pentane, -25°, 6 h 2. K ₂ CO ₃ , H ₂ O	 (100)	527
	(NsO) ₂ , EtOAc, H ₂ O, rt, 24 h	 (>95)	105
	O ₂ , hv, rose bengal, THF, -78°, 2.8 h	 I (66) + II (12)	78
	<i>m</i> -CPBA, hexane	I (85)	120
	1. <i>m</i> -CPBA, hexane 2. NaOH (10%), 3 h	II (77)	120
	1. CrO ₂ Cl ₂ , CH ₂ Cl ₂ , -78°, 30 min 2. NaHSO ₃ , 15 min	II (66)	166
	(PhIO) _n , TMSOTf, CH ₂ Cl ₂ , -78° to rt	 (74)	379

TABLE 16B. α -HYDROXYLATION OF CYCLIC KETONE SILYL ENOL ETHERS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. I ₂ , AgOAc, CH ₂ Cl ₂ , 2 h 2. Et ₃ NHF, rt, 2 h	(36) + (51)	189
	1. I ₂ , AgOBz, CH ₂ Cl ₂ , 2 h 2. Et ₃ NHF, rt, 2 h	(48) + (44)	189
	<i>m</i> -CPBA, CH ₂ Cl ₂ , 20°		796
	1. <i>m</i> -CPBA, CH ₂ Cl ₂ , 20° 2. NaHCO ₃ , H ₂ O		796
	1. O ₂ , hv, rose bengal, THF, -78°, 3 h 2. PPh ₃ , MeOH	(21) + (27)	78
	(NsO) ₂	(—)	777
	<i>m</i> -CPBA (2 eq), KHCO ₃ , CH ₂ Cl ₂ , 0°, 1.5 h	(—)	131
	1. CrO ₂ Cl ₂ , CH ₂ Cl ₂ , -78°, 30 min 2. NaHSO ₃ , 15 min	(76)	166
	1. Pb(OAc) ₄ , CH ₂ Cl ₂ , 20°, 1 h 2. BF ₃ ·Et ₂ O, 20°, 1 h	(65)	366
	1. Pb(OBz) ₄ , CH ₂ Cl ₂ , 0° to rt, 0.5 h 2. TEAF, rt, 8 h	(80)	161
	1. I ₂ , AgOBz, CH ₂ Cl ₂ , 2 h 2. TEAF, rt, 2 h	I (12)	189
	DDQ, THF, 22°, 30 min		184
	1. O ₂ , hv, rose bengal, THF, -78°, 2.5 h 2. PPh ₃ , MeOH	(0)	78
	(NsO) ₂	(—)	777
	<i>m</i> -CPBA, CH ₂ Cl ₂ , 0°	(76)	797, 129

TABLE 16B. α -HYDROXYLATION OF CYCLIC KETONE SILYL ENOL ETHERS (Continued)

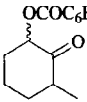
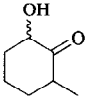
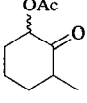
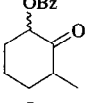

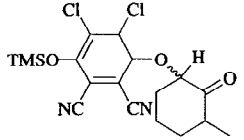
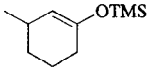


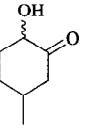


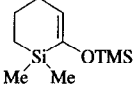

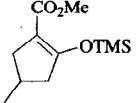
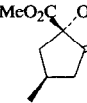
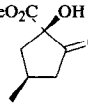
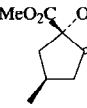
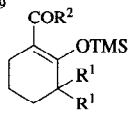
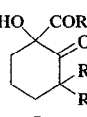
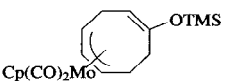
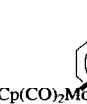
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	<i>m</i> -CPBA, Et ₂ O, 0°, 10 min	 OCOC ₆ H ₄ Cl-3 (50)	129
	1. <i>m</i> -CPBA, THF, 0° 2. Bu ₄ NF	 (—)	798
	1. Pb(OAc) ₄ , CH ₂ Cl ₂ , 20°, 1 h 2. BF ₃ ·Et ₂ O, 20°, 1 h	 (71)	366
	1. Pb(OBz) ₄ , CH ₂ Cl ₂ , 0° to rt, 0.5 h 2. TEAF, rt, 8 h	 (92)	161
	1. I ₂ , AgOBz, CH ₂ Cl ₂ , 2 h 2. TEAF, rt, 2 h	 I I (87)	189
	DDQ, THF, 22°, 30 min	 (20)	184
	1. Pb(OBz) ₄ , CH ₂ Cl ₂ , 0° to rt, 0.5 h 2. TEAF, rt, 8 h	 (83)	161
 C ₇₋₈	1. O ₂ , hv, rose bengal, THF, -78°, 2.8 h 2. PPh ₃ , MeOH, HCl (cat.)	 (18)	78
 C ₇	1. O ₂ , hv, rose bengal, THF, -78°, 2.8 h 2. PPh ₃ , MeOH	 R Me (70) Et (83)	78
	<i>m</i> -CPBA, CH ₂ Cl ₂ , 0°	 (75)	122
 C ₈	OsO ₄ , NMO, Me ₂ CO, H ₂ O, -15 to 0°	 (53)	155
	<i>m</i> -CPBA, CH ₂ Cl ₂ , 0° to rt	 (5)	155
		 (40)	155
 C _{8,9}	<i>m</i> -CPBA, (CH ₂ Cl) ₂ , 0° to rt	 I II R ¹ R ² I II H Me (33)(17) H OMe (76) (0) Me OMe (70) (0)	217
 C ₈	1. <i>m</i> -CPBA, (CH ₂ Cl) ₂ , 0°, 1 h 2. Bu ₄ NF, THF, 30 min	 (70)	206

TABLE 16B. α -HYDROXYLATION OF CYCLIC KETONE SILYL ENOL ETHERS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	OsO ₄ , NMO; <i>m</i> -CPBA; or PhI(OAc) ₂ , BF ₃ •Et ₂ O	(0)	529
	1. <i>m</i> -CPBA, (CH ₂ Cl) ₂ , 0° to rt, 1 h 2. Na ₂ CO ₃ (10%)	(80)	217
	1. <i>m</i> -CPBA, (CH ₂ Cl) ₂ , 0° to rt, 1 h 2. Na ₂ CO ₃ (10%)	(33) + (17)	217
	1. <i>m</i> -CPBA, (CH ₂ Cl) ₂ , 0° to rt, 1 h 2. Na ₂ CO ₃ (10%)	(76)	57
	1. <i>m</i> -CPBA, hexane, -15°, 15 min; 22°, 1 h 2. Bu ₄ NF, rt, 3-5 h 3. TBDMSCl, imidazole, DMF, rt, 12-24 h	(44) + (29)	121
	<i>m</i> -CPBA, NaHCO ₃ , pentane, -25°, 6 h	(–) + O ₂ CC ₆ H ₄ Cl-3	527
	1. <i>m</i> -CPBA, NaHCO ₃ , pentane, -25°, 6 h 2. K ₂ CO ₃ , H ₂ O	(71)	527
	<i>m</i> -CPBA, NaHCO ₃ , pentane, -25°, 6 h	(–) + O ₂ CC ₆ H ₄ Cl-3	527
	1. <i>m</i> -CPBA, NaHCO ₃ , pentane, -25°, 6 h 2. K ₂ CO ₃ , H ₂ O	(80)	527
	OsO ₄ , NMO, THF, H ₂ O, rt, 12 h	(>82)	156
	OsO ₄ , NMO, THF, H ₂ O, rt, 12 h	(100)	156
	<i>m</i> -CPBA, petroleum ether, -10°, 1 h	(65-76)	799, 800
	<i>m</i> -CPBA, Et ₂ O, 0°, 10 min	O ₂ CC ₆ H ₄ Cl-3 (73)	129

TABLE 16B. α -HYDROXYLATION OF CYCLIC KETONE SILYL ENOL ETHERS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	<i>m</i> -CPBA, CH ₂ Cl ₂	 (—)	129
	1. AgOBz, I ₂ , CH ₂ Cl ₂ , 2 h 2. Et ₃ NHF, rt, 2 h	 (92)	189
	1. <i>m</i> -CPBA, hexane, -15°, 15 min; 22°, 1 h 2. Bu ₄ NF, rt, 3-5 h 3. TBDMSCl, imidazole, DMF rt, 12-24 h	 (80)	121
		 (82) + (11)	121
	1. OsO ₄ , hv, rose bengal THF, -78°, 2.5 h 2. Ph ₃ P, MeOH	 (62) + (27)	78
	(PhIO) _n , PF ₆ ⁻ (cat.), MeCN, 25°, 3 h	I (45) + II (41)	145
	(PhIO) _n , PF ₆ ⁻ (cat.), MeCN, 25°, 1 h	I (38) + II (30) 15% ee	145
	1. AgOAc, I ₂ , CH ₂ Cl ₂ , 2 h 2. Et ₃ NHF, rt, 2 h	 (11)	189
	1. AgOBz, I ₂ , CH ₂ Cl ₂ , 2 h 2. Et ₃ NHF, rt, 2 h	 (—)	189
C ₉ 	<i>m</i> -CPBA	 (—)	536
C ₉₋₁₅ R = Me, Bn	<i>m</i> -CPBA, THF, 0° to rt	 (—)	801
C ₉ 	1. OsO ₄ (cat.), NMO, <i>t</i> -BuOH, -10 to 25° 2. 1N H ₂ SO ₄	 (58)	154

TABLE 16B. α -HYDROXYLATION OF CYCLIC KETONE SILYL ENOL ETHERS (Continued)

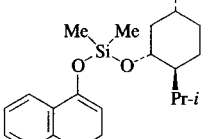
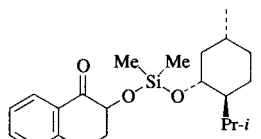
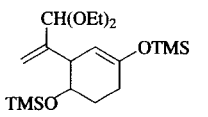
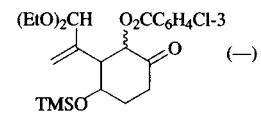
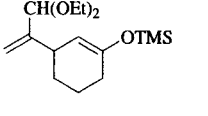
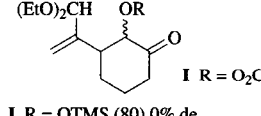
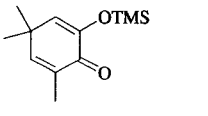
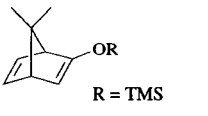
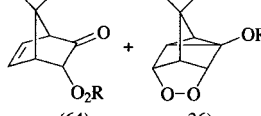
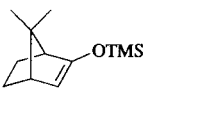
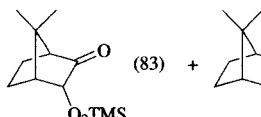

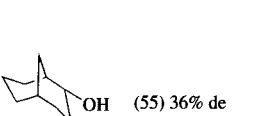
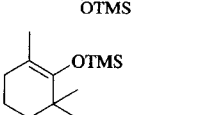
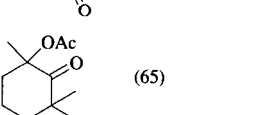
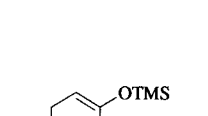
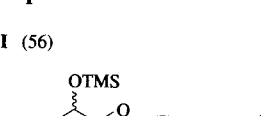
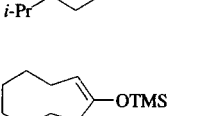
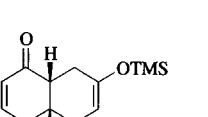
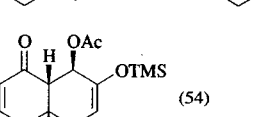
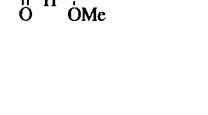
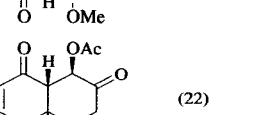

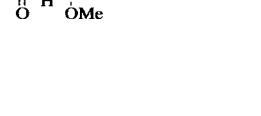


Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	<i>m</i> -CPBA, NaHCO ₃ , CH ₂ Cl ₂ , -50°	 (100)	271
	<i>m</i> -CPBA, CH ₂ Cl ₂ or Et ₂ O	 (—)	129
	<i>m</i> -CPBA, Et ₂ O, 0° to rt, 1.5 h	 (50) 33% de	129
	<i>m</i> -CPBA, CH ₂ Cl ₂	I R = OTMS (80) 0% de	129
	1. <i>m</i> -CPBA, hexane, 20°, 4 h 2. HCl (cat.), MeOH, 20°, 4 h	 (45; from the diketone)	288
	O ₂ , hv, tetraphenylporphine, CDCl ₃ , -20°	 (64) + (36) + (trace)	69
	O ₂ , hv, tetraphenylporphine, CCl ₄ , 10°, 40 min	 (83) + (5)	72
	<i>m</i> -CPBA, CH ₂ Cl ₂ , NaHCO ₃	 (55) 36% de	802
	1. <i>m</i> -CPBA, hexane, -15°, 10 min; rt, 1 h 2. Et ₃ NHF, rt, 10 h 3. Ac ₂ O, DMAP, Et ₃ N, rt, 24 h	 (65)	803
	Pb(OAc) ₄ , CH ₂ Cl ₂ , reflux, 36 h	I (56)	803
	1. O ₂ , hv, rose bengal, THF -78°, 3 h 2. Ph ₃ P, MeOH	 (7) + (12)	78
	1. O ₂ , hv, rose bengal, THF -78°, 2.5 h 2. Ph ₃ P, MeOH	 (12) + (41)	78
	Pb(OAc) ₄ , CH ₂ Cl ₂	 (54)	369
	1. Pb(OAc) ₄ , CH ₂ Cl ₂ 2. 0.1N HCl, THF	 (22)	369

TABLE 16B. α -HYDROXYLATION OF CYCLIC KETONE SILYL ENOL ETHERS (Continued)

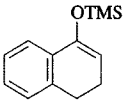
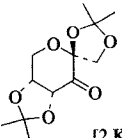
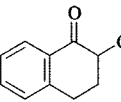
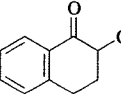
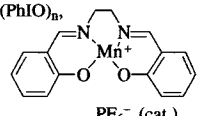
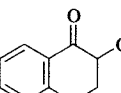
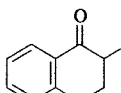
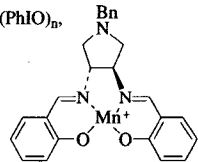
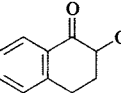
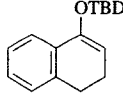
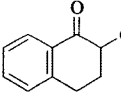
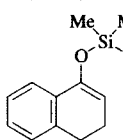
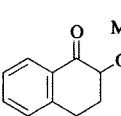

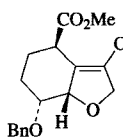
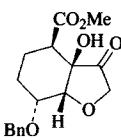
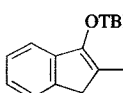
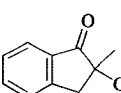
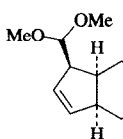
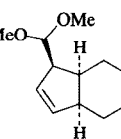
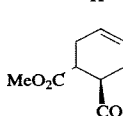
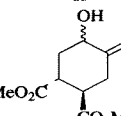
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.										
	 [2 KHSO ₅ ·KHSO ₄ ·K ₂ SO ₄], MeCN, H ₂ O, -5°, 1 h	 (70) 83% ee	117										
	(NsO) ₂ , EtOAc, H ₂ O, rt, 20 h	 (>95)	105										
	(PhIO) _n ,  PF ₆ ⁻ (cat.), MeCN, 25°, 30 min	 I (47) +  II (38)	145										
	(PhIO) _n ,  PF ₆ ⁻ (cat.), MeCN, 25°, 15 min	I (40) + II (32) 62% ee	145										
	F ₂ , N ₂ , MeCN, H ₂ O, rt 5 min	II (>90)	187										
	MeOF, MeCN	 (85)	186										
	O ₂ , Ni(mac) ₂ , Me ₂ CHCHO, Me ₂ CO, rt, 8 h	 (82)	67										
	<i>m</i> -CPBA, NaHCO ₃ , CH ₂ Cl ₂ , 0°	 (100)	271										
		 (96)	271										
	1. <i>m</i> -CPBA, NaHCO ₃ , CH ₂ Cl ₂ , -20° to rt 2. Bu ₄ NF, THF, 0°, 30 min	 (75)	804										
	OsO ₄ (cat.), ligand, K ₂ CO ₃ , K ₃ Fe(CN) ₆ , MeSO ₂ NH ₂ , <i>t</i> -BuOH, 0°	 (64-85)	159										
		<table border="1"> <thead> <tr> <th>Ligand</th> <th>% ee</th> </tr> </thead> <tbody> <tr> <td>(DHQD)₂-PHAL S</td> <td>85</td> </tr> <tr> <td>(DHQ)₂-PHAL R</td> <td>81</td> </tr> <tr> <td>(DHQD)₂-PYR S</td> <td>59</td> </tr> <tr> <td>(DHQ)₂-PYR R</td> <td>80</td> </tr> </tbody> </table>	Ligand	% ee	(DHQD) ₂ -PHAL S	85	(DHQ) ₂ -PHAL R	81	(DHQD) ₂ -PYR S	59	(DHQ) ₂ -PYR R	80	
Ligand	% ee												
(DHQD) ₂ -PHAL S	85												
(DHQ) ₂ -PHAL R	81												
(DHQD) ₂ -PYR S	59												
(DHQ) ₂ -PYR R	80												
	1. <i>m</i> -CPBA, hexane, 25° 2. Bu ₄ NF, CH ₂ Cl ₂ , 25°	 (85)	805										
	1. <i>m</i> -CPBA, pentane, 0°, 1 h 2. Ion exchange chromatography (Dowex Ag-1-X8, basic)	 (61)	806										

TABLE 16B. α -HYDROXYLATION OF CYCLIC KETONE SILYL ENOL ETHERS (Continued)

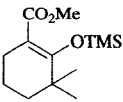
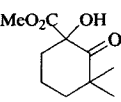
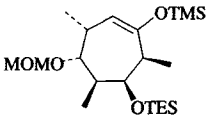
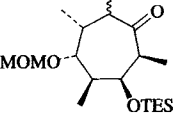
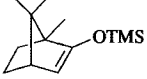
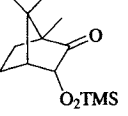
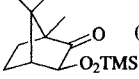
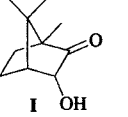
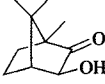
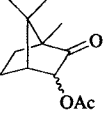
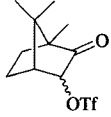
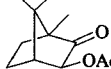
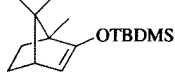
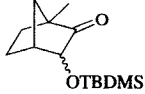
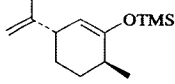
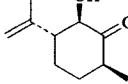
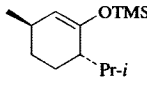
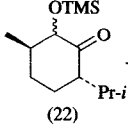
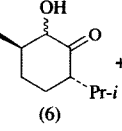
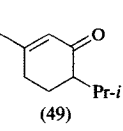
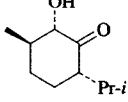
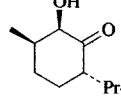
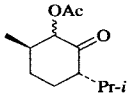
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. <i>m</i> -CPBA, DCE, 0° to rt, 1 h 2. Na ₂ CO ₃ (10%)	 (70)	217
	1. <i>m</i> -CPBA 2. Bu ₄ NF	 (95)	285
	O ₂ , hv, tetraphenylporphine, CCl ₄ , -5°, 3 h	 (80) +  (5)	72
	O ₂ , TAS-F, PPh ₃ , THF, 0 to 5°, 5 h	 I  II I+II = (-); I:II = 1:1	68
	1. DMDO, CH ₂ Cl ₂ , -78° 30 min 2. NH ₄ F, MeOH, to rt, 3 h	I+II (91); I:II = 3:97	111, 110
	1. <i>m</i> -CPBA, hexane, 0° to rt, 24 h 2. 2N NaOH	I+II (7); I:II = 1:1	807
	PhI(OAc) ₂ , CH ₂ Cl ₂ , rt	 (0)	365
	PhI(OTf) ₂ , CH ₂ Cl ₂ , rt	 (0)	365
	1. Pb(OAc) ₄ , CH ₂ Cl ₂ , 20°, 1 h 2. BF ₃ •Et ₂ O, 20°, 2 h	 (58)	366
	O ₃ , MeOH, CH ₂ Cl ₂ , -78°	 (100)	85, 123
	<i>m</i> -CPBA, hexane	 (-)	808
	1. O ₂ , hv, rose bengal, THF, -78°, 7.5 h 2. Ph ₃ P, MeOH	 (22) +  (6) +  (49)	78
	1. DMDO, CH ₂ Cl ₂ , -78°, 30 min 2. NH ₄ F, MeOH, to rt, 3 h	 (78) +  (19)	111
	1. Pb(OAc) ₄ , CH ₂ Cl ₂ , 20°, 1 h 2. BF ₃ •Et ₂ O, 20°, 2 h	 (56)	366

TABLE 16B. α -HYDROXYLATION OF CYCLIC KETONE SILYL ENOL ETHERS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.										
	1. O ₂ , hv, rose bengal, THF, -78°, 7.8 h 2. Ph ₃ P, MeOH, HCl (cat.)	 (12) + (45)	78										
	O ₂ , PPh ₃ , TAS-F	 (0)	68										
	1. <i>m</i> -CPBA, CH ₂ Cl ₂ , -20°, 1.5 h 2. Bu ₄ NF, THF, rt, 1 h	 (36) + (4)	799										
	(PhIO) _n , BF ₃ ·Et ₂ O, MeOH, -78°, 3 h; rt, 3 h	 (44) + (11)	809										
	MeOF, MeCN	 (30)	186										
	1. <i>m</i> -CPBA, hexane, -15°, 15 min; 22°, 1 h 2. Bu ₄ NF, rt, 3-5 h 3. TBDMSCl, imidazole, DMF, rt, 12-24 h	 (84) + (9)	121										
	1. O ₂ , hv, rose bengal, THF, -78°, 4.5 h 2. Ph ₃ P, MeOH, HCl (cat.)	 (49)	78										
	<i>m</i> -CPBA, CH ₂ Cl ₂ , 0°, 0.5 h	 (10)	810										
	<i>m</i> -CPBA, CH ₂ Cl ₂ , 0°, 0.5 h	 (28)	810										
	OsO ₄ (cat.), ligand, K ₂ CO ₃ , K ₃ Fe(CN) ₆ , MeSO ₂ NH ₂ , <i>t</i> -BuOH, 0°	 (89-92)	<table border="1"> <thead> <tr> <th>Ligand</th> <th>% ee</th> </tr> </thead> <tbody> <tr> <td>(DHQD)₂-PHAL <i>S</i></td> <td>67</td> </tr> <tr> <td>(DHQD)₂-PHAL <i>R</i></td> <td>65</td> </tr> <tr> <td>(DHQD)₂-PYR <i>R</i></td> <td>6</td> </tr> <tr> <td>(DHQD)₂-PYR <i>R</i></td> <td>37</td> </tr> </tbody> </table>	Ligand	% ee	(DHQD) ₂ -PHAL <i>S</i>	67	(DHQD) ₂ -PHAL <i>R</i>	65	(DHQD) ₂ -PYR <i>R</i>	6	(DHQD) ₂ -PYR <i>R</i>	37
Ligand	% ee												
(DHQD) ₂ -PHAL <i>S</i>	67												
(DHQD) ₂ -PHAL <i>R</i>	65												
(DHQD) ₂ -PYR <i>R</i>	6												
(DHQD) ₂ -PYR <i>R</i>	37												
	1. OsO ₄ (cat.), NMO, Me ₂ CO, H ₂ O, -10 to 25° 2. 1N H ₂ SO ₄	 (60)	154										
	1. OsO ₄ (cat.), NMO, <i>t</i> -BuOH, -10 to 25° 2. 1N H ₂ SO ₄	 (54)	154										

TABLE 16B. α -HYDROXYLATION OF CYCLIC KETONE SILYL ENOL ETHERS (Continued)

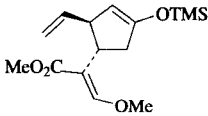
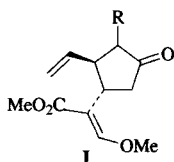
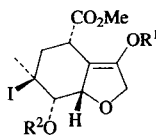
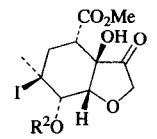
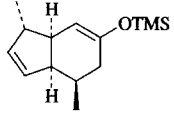
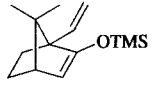
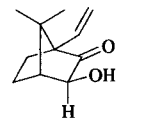
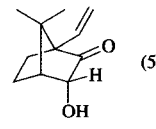
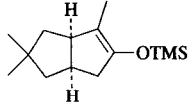
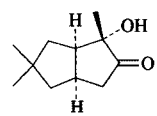
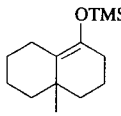
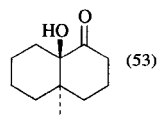
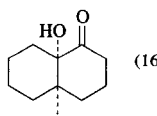
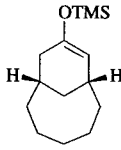
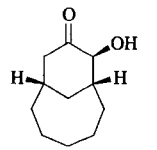
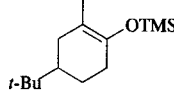
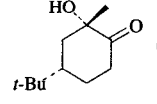
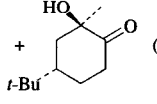
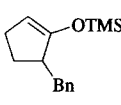
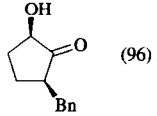
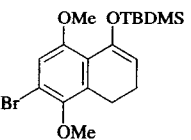
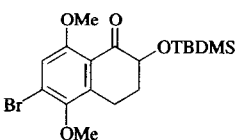
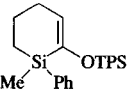
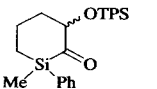
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.									
	<i>m</i> -CPBA, hexane	 R = O ₂ CC ₆ H ₄ Cl-3 (—)	132									
	HO ₂ Ac, CH ₂ Cl ₂ , 0° to rt	I R = OAc (55)	132									
	<i>m</i> -CPBA, CH ₂ Cl ₂ , 0°, 30 min	 <table border="1" style="display: inline-table; vertical-align: middle;"> <thead> <tr> <th>R¹</th> <th>R²</th> <th>Product</th> </tr> </thead> <tbody> <tr> <td>TES</td> <td>Ac</td> <td>(53)</td> </tr> <tr> <td>TBDMS</td> <td>THP</td> <td>(64)</td> </tr> </tbody> </table>	R ¹	R ²	Product	TES	Ac	(53)	TBDMS	THP	(64)	810
R ¹	R ²	Product										
TES	Ac	(53)										
TBDMS	THP	(64)										
	<i>m</i> -CPBA	(—)	811									
	1. DMDO, THF, -78° to rt 2. Bu ₄ NF, THF, rt	 (79) +  (5)	240									
	1. <i>m</i> -CPBA, CH ₂ Cl ₂ , NaHCO ₃ , -78°, 3 h 2. Bu ₄ BF, 0° to rt, 14 h	 (57)	812									
	1. <i>m</i> -CPBA, hexane, -13° to rt, 2 h 2. 2N HCl, rt, 2 h	 (53) +  (16)	96									
	DMDO, CH ₂ Cl ₂ , NaHCO ₃	 (51)	802									
	1. <i>m</i> -CPBA, CH ₂ Cl ₂ , -78°, 10 min; rt, 30 min 2. Bu ₄ NF, hexane, overnight	 (28) ^b +  (29) ^b	813									
	1. DMDO, CH ₂ Cl ₂ , Me ₂ CO, -78°, 30 min 2. NH ₄ NF, MeOH, to rt, 3 h	 (96) 30% dc	111									
	<i>m</i> -CPBA, NaHCO ₃ , CH ₂ Cl ₂ , 0°	 (57)	814									
	<i>m</i> -CPBA, Et ₂ O	(—)	122									
	1. <i>m</i> -CPBA, Et ₂ O 2. TsOH (cat.), Et ₂ O, reflux, 1 h	 (74)	122									

TABLE 16B. α -HYDROXYLATION OF CYCLIC KETONE SILYL ENOL ETHERS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	O ₃ , PPh ₃ , MeOH	(38)	346
	1. O ₂ , hv, rose bengal, THF, -78°, 3.5 h 2. PPh ₃ , MeOH	I (22) + II (54)	78
	1. O ₂ , hv, rose bengal, THF, -78°, 3.5 h 2. PPh ₃ , MeOH	I (20) + II (28)	78
	(PhIO) _n , PF ₆ ⁻ (cat.), MeCN, 25°, 45 min	I (26) + II (64)	145
	(PhIO) _n , PF ₆ ⁻ (cat.), MeCN, 25°, 1 h	I (25) + II (48) 14% ee	145
	1. I ₂ , AgO ₂ CR, CH ₂ Cl ₂ , 2 h 2. Et ₃ NHF, rt, 2 h	 R Me (15) Ph (33)	189
C ₁₃ 	1. <i>m</i> -CPBA, THF 2. HCl, H ₂ O, THF	(86)	216
	DMDO, CH ₂ Cl ₂ , Me ₂ CO, -78 to 0°	(>67)	192
	<i>m</i> -CPBA or HO ₂ Ac, buffer	(—)	192
	1. <i>m</i> -CPBA, hexane 2. 1N HCl, 1 h	(75)	815
	1. <i>m</i> -CPBA, hexane, 0°, 30 min 2. HCl, THF, 25°, 1 h	(74)	816

TABLE 16B. α -HYDROXYLATION OF CYCLIC KETONE SILYL ENOL ETHERS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.						
	<i>m</i> -CPBA, CH ₂ Cl ₂ , NaHCO ₃	 (10) 95% de	802						
	1. <i>m</i> -CPBA, NaHCO ₃ , CH ₂ Cl ₂ , -78 to 20° 2. MeOH, reflux	 (>50)	817						
	1. <i>m</i> -CPBA, CH ₂ Cl ₂ , rt, 1 h 2. 1N HCl, MeCN	 (70)	818						
	1. <i>m</i> -CPBA, CH ₂ Cl ₂ , rt, 1 h 2. HF•Py, Py, THF	I (65)	818						
	1. <i>m</i> -CPBA, CH ₂ Cl ₂ , 0°, 1 h 2. 2N HCl	 (50)	819						
	OsO ₄ (cat.), ligand, K ₂ CO ₃ , K ₃ Fe(CN) ₆ , MeSO ₂ NH ₂ , <i>t</i> -BuOH, 0°	 (23-32)	<table border="1"> <thead> <tr> <th>Ligand</th> <th>% ee</th> </tr> </thead> <tbody> <tr> <td>(DHQD)₂-PHALR</td> <td>89</td> </tr> <tr> <td>(DHQD)₂-PYR R</td> <td>84</td> </tr> </tbody> </table>	Ligand	% ee	(DHQD) ₂ -PHALR	89	(DHQD) ₂ -PYR R	84
Ligand	% ee								
(DHQD) ₂ -PHALR	89								
(DHQD) ₂ -PYR R	84								
	DMDO	 (85) >96% de	111						
	1. <i>m</i> -CPBA, hexane, -30 to 0°, 10 min 2. 1N HCl, rt, 17 h	 (90)	820						
	OsO ₄ , NMO, Me ₂ CO, H ₂ O, rt, 2 h	 (71)	563						
	1. <i>m</i> -CPBA, NaHCO ₃ , hexane, rt, 6 h 2. HCl (10%), 7 h	 (16) + (-)	821						
	<i>m</i> -CPBA, NaHCO ₃ , CH ₂ Cl ₂ , 0°, 1 h	 (8)	568						
	DMDO, NaHCO ₃ , CH ₂ Cl ₂	 (50)	802						

TABLE 16B. α -HYDROXYLATION OF CYCLIC KETONE SILYL ENOL ETHERS (Continued)

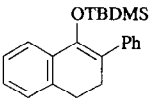
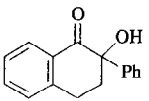
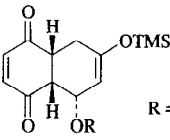
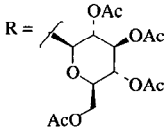
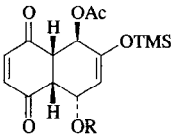
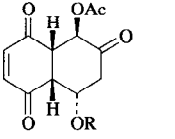
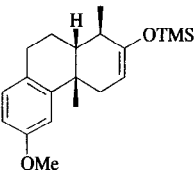
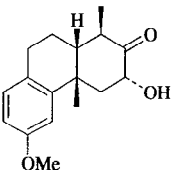
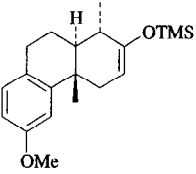
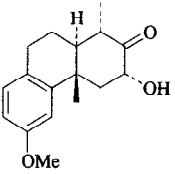
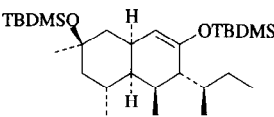
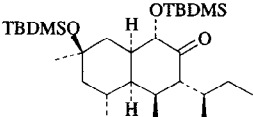
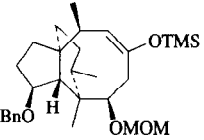
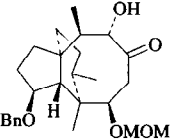
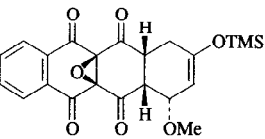
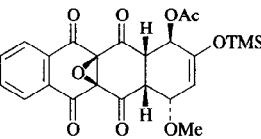
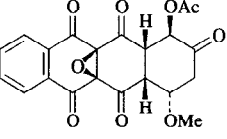
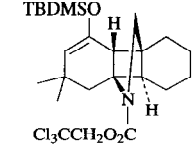
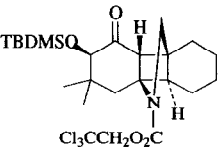
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.										
C ₁₆ 	OsO ₄ (cat.), ligand, K ₂ CO ₃ , K ₃ Fe(CN) ₆ , MeSO ₂ NH ₂ , <i>t</i> -BuOH, 0°	 (94-98)	<table border="1"> <thead> <tr> <th>Ligand</th> <th>% ee</th> </tr> </thead> <tbody> <tr> <td>(DHQD)₂-PHAL</td> <td>R 93</td> </tr> <tr> <td>(DHQ)₂-PHAL</td> <td>S 95</td> </tr> <tr> <td>(DHQD)₂-PYR</td> <td>R 95</td> </tr> <tr> <td>(DHQ)₂-PYR</td> <td>S 97</td> </tr> </tbody> </table>	Ligand	% ee	(DHQD) ₂ -PHAL	R 93	(DHQ) ₂ -PHAL	S 95	(DHQD) ₂ -PYR	R 95	(DHQ) ₂ -PYR	S 97
		Ligand	% ee										
		(DHQD) ₂ -PHAL	R 93										
		(DHQ) ₂ -PHAL	S 95										
(DHQD) ₂ -PYR	R 95												
(DHQ) ₂ -PYR	S 97												
 R = 	Pb(OAc) ₄ , CH ₂ Cl ₂	 (42)	369										
	1. Pb(OAc) ₄ , CH ₂ Cl ₂ 2. 0.1N HCl, THF	 (20)	369										
C ₁₇ 	1. <i>m</i> -CPBA, hexane, 0° to rt, 1 h 2. Bu ₄ NF, CH ₂ Cl ₂ , 1 h	 (55)	822										
			 (74)	822									
			 (83)	823									
	1. <i>m</i> -CPBA, KHCO ₃ , CH ₂ Cl ₂ , 0 to 25°, 2 h 2. Bu ₄ NF, THF, 25°, 45 min	 (62)	824										
C ₁₈ 	Pb(OAc) ₄ , CH ₂ Cl ₂	 (56)	369										
		1. Pb(OAc) ₄ , CH ₂ Cl ₂ 2. 0.1N HCl, THF	 (43)	369									
		<i>m</i> -CPBA	 (79)	825									

TABLE 16B. α -HYDROXYLATION OF CYCLIC KETONE SILYL ENOL ETHERS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. <i>m</i> -CPBA 2. NaOH (5%)	(51)	580
C ₁₈₋₁₉ 	<i>m</i> -CPBA	 I II R I II H (80-92) Me (92) (6)	210
C ₁₉ 	1. <i>m</i> -CPBA, NaHCO ₃ , CH ₂ Cl ₂ , 0°, 30 min 2. Py•TsOH, THF, H ₂ O, 20 min	(82)	213
	<i>m</i> -CPBA, CH ₂ Cl ₂ , -20°, 25 min	(62)	826, 827
	<i>m</i> -CPBA	(—)	581
	<i>m</i> -CPBA, CH ₂ Cl ₂ , 25°, 0.5 h	(92)	157
	OsO ₄ (cat.), NMO, <i>t</i> -BuOH, H ₂ O, 25°, 10 h	(60)	157
	<i>m</i> -CPBA, hexane, 25°, 5 h	(86)	828
	1. <i>m</i> -CPBA, CHCl ₂ , -15 to 25°, 3.5 h 2. Bu ₄ NF, 25°, 12 h	(57)	829

TABLE 16B. α -HYDROXYLATION OF CYCLIC KETONE SILYL ENOL ETHERS (Continued)

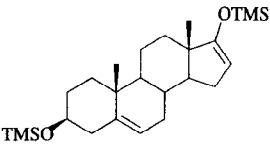
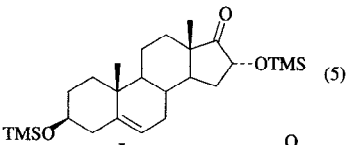
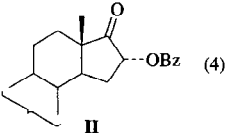
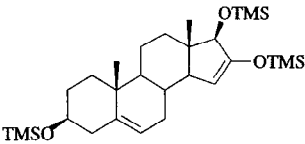
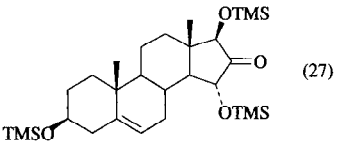
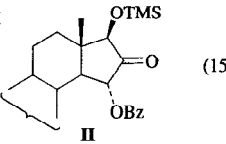
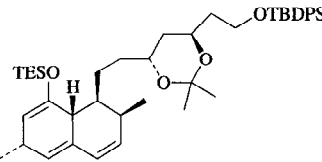
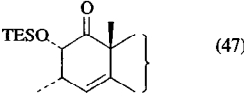
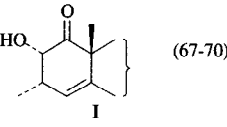
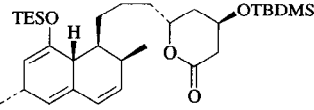
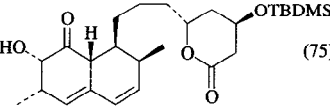
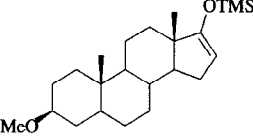
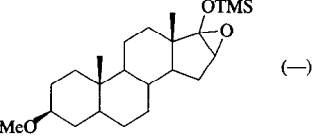
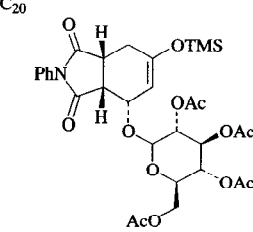
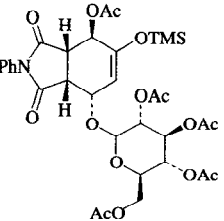
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	(PhCO ₂) ₂ , 60°, 24 h	 (5) +  (4)	104
	(PhCO ₂) ₂ , hv, 24 h	I (18) + II (3)	104
	(PhCO ₂) ₂ , 60°, 24 h	 (27) +  (15)	104
	(PhCO ₂) ₂ , hv, 24 h	I (60) + II (5)	104
	hv, 24 h	I (60)	104
	<i>m</i> -CPBA	 (47)	210
	<i>m</i> -CPBA, NaHCO ₃ , EtOAc	 (67-70) I	210
	1. KHMDS 2. NPSO	I (—)	210
	1. <i>m</i> -CPBA, EtOAc, 0°, 30 min 2. Na ₂ SO ₃ (10%), 0°, 5 min	 (75)	205
	<i>m</i> -CPBA, hexane, 0°, 1 h	 (—)	807
	Ph(OAc) ₄ , CH ₂ Cl ₂	 (84)	369

TABLE 16B. α -HYDROXYLATION OF CYCLIC KETONE SILYL ENOL ETHERS (Continued)

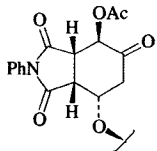
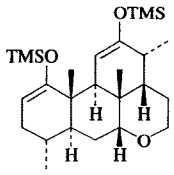
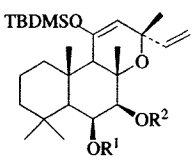
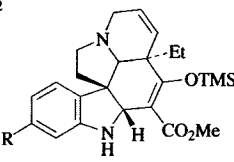
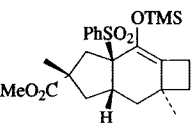


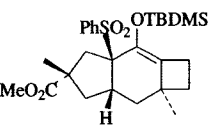
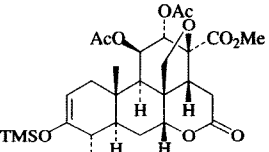
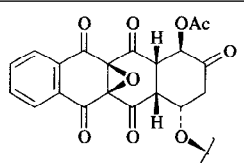
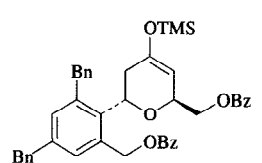
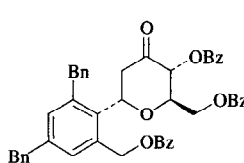
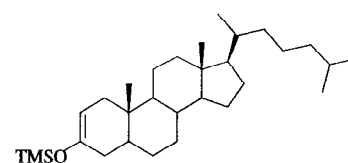
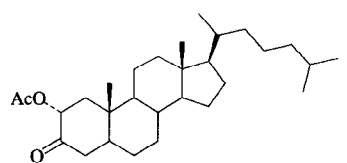
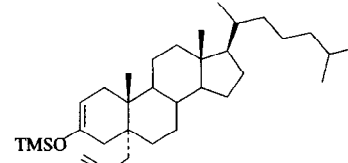
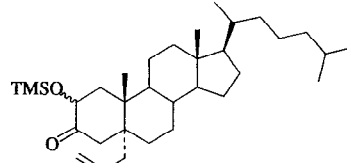
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.									
	1. Pb(OAc) ₄ , CH ₂ Cl ₂ 2. 0.1N HCl, THF	(51)	369									
	1. <i>m</i> -CPBA, K ₂ CO ₃ , CH ₂ Cl ₂ , 0°, 26 h 2. 2N HCl, THF, rt, 1 h	(65)	830, 588									
	<i>m</i> -CPBA, K ₂ CO ₃ , CH ₂ Cl ₂ , -78 to 0°, 24 h	<table border="1" data-bbox="1189 849 1345 941"> <tr> <td>R¹</td> <td>R²</td> <td></td> </tr> <tr> <td>Ac</td> <td>TMS</td> <td>(43)</td> </tr> <tr> <td>TMS</td> <td>Ac</td> <td>(31)</td> </tr> </table>	R ¹	R ²		Ac	TMS	(43)	TMS	Ac	(31)	831
R ¹	R ²											
Ac	TMS	(43)										
TMS	Ac	(31)										
	1. <i>m</i> -CPBA, DCE, 0° to rt, 1 h 2. Na ₂ CO ₃ (10%)	<table border="1" data-bbox="1241 1033 1328 1125"> <tr> <td>R</td> <td></td> </tr> <tr> <td>H</td> <td>(88)</td> </tr> <tr> <td>OMe</td> <td>(89)</td> </tr> </table>	R		H	(88)	OMe	(89)	217			
R												
H	(88)											
OMe	(89)											
	<i>m</i> -CPBA, NaHCO ₃ , CH ₂ Cl ₂ , 20°	(86)	127									
	1. <i>m</i> -CPBA, NaHCO ₃ , CH ₂ Cl ₂ , 20° 2. BzOH (cat.), CH ₂ Cl ₂ , rt, 24 h	(77)	127									
	<i>m</i> -CPBA, NaHCO ₃ , CH ₂ Cl ₂ , 26°	I (76) + II (10)	127									
	<i>m</i> -CPBA, CH ₂ Cl ₂ , rt	(66)	832									
	1. <i>m</i> -CPBA, NaHCO ₃ , CH ₂ Cl ₂ , 0°, 40 min 2. 2M HCl, THF, rt, 1 h	(39)	833									

TABLE 16B. α -HYDROXYLATION OF CYCLIC KETONE SILYL ENOL ETHERS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.									
<p>C₂₂</p>	OsO ₄ , NMO, Me ₂ CO, H ₂ O, -5°, 19 h	(52)	126									
	<i>m</i> -CPBA, DCE, -15° to rt	(68)	834									
		(9)										
	1. <i>m</i> -CPBA, DCE, -15° to rt 2. Dowex-H ⁺ , MeOH, rt, 24 h	(64)	834									
<p>C₂₂₋₂₃</p>	<i>m</i> -CPBA, DCE, 0°, 30 min	I II	835 <table border="1"> <thead> <tr> <th>R</th> <th>I</th> <th>II</th> </tr> </thead> <tbody> <tr> <td>H</td> <td>(88)</td> <td>(—)</td> </tr> <tr> <td>OMe</td> <td>(52)</td> <td>(37)</td> </tr> </tbody> </table>	R	I	II	H	(88)	(—)	OMe	(52)	(37)
R	I	II										
H	(88)	(—)										
OMe	(52)	(37)										
<p>C₂₄</p>	OsO ₄ , NMO, <i>t</i> -BuOH, H ₂ O, 0°, 5 min	I II III IV	600 I+II+III+IV = (39) ^b ; I:II:III:IV = 2:1:8:4									
	Pb(OAc) ₄ , CH ₂ Cl ₂ , rt	(48) (51)	<table border="1"> <thead> <tr> <th>R</th> <th>Yield (%)</th> </tr> </thead> <tbody> <tr> <td>TMS</td> <td>(48)</td> </tr> <tr> <td>TBDS</td> <td>(51)</td> </tr> </tbody> </table> 369	R	Yield (%)	TMS	(48)	TBDS	(51)			
R	Yield (%)											
TMS	(48)											
TBDS	(51)											

TABLE 16B. α -HYDROXYLATION OF CYCLIC KETONE SILYL ENOL ETHERS (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. $\text{Pb}(\text{OAc})_4$, CH_2Cl_2 , rt 2. 0.1N HCl, THF	 (39)	369
C ₂₇ 	1. <i>m</i> -CPBA, PhH, 30 min 2. MeOH, oxolane, 6 h 3. PhCOCl , Py, 2 h	 (17)	836
	1. $\text{Pb}(\text{OAc})_4$, CH_2Cl_2 , 20°, 1 h 2. $\text{BF}_3 \cdot \text{Et}_2\text{O}$, 20°, 2 h	 (72)	366
C ₃₀ 	<i>m</i> -CPBA, hexane, 0° to rt, 5 h	 (62)	837, 212

^a The yield was determined by gas chromatography prior to treatment with KF.

^b The yield includes preparation of the substrate.

TABLE 17A. α -HYDROXYLATION OF 1-SILYLOXY-1,3-DIENES







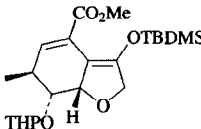
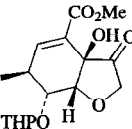
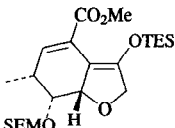
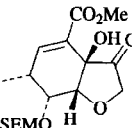
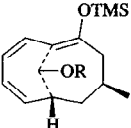
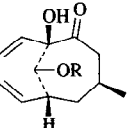
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₇ 	1. Pb(OBz) ₄ , CH ₂ Cl ₂ , 0° to rt, 0.5 h 2. TEAF, rt, 8 h	 (92)	161, 370
	1. Pb(OBz) ₄ , CH ₂ Cl ₂ , 0° to rt, 0.5 h 2. TEAF, rt, 8 h	 (42)	370
C ₉ 	1. <i>m</i> -CPBA, hexane, -15°, 10 min; rt, 1 h 2. Et ₃ NHF, rt, 10 h 3. Ac ₂ O, DMAP, Et ₃ N, rt, 24 h	 (55)	803
C ₁₁ 	<i>m</i> -CPBA, CH ₂ Cl ₂ , 0°, 0.5 h	 (61)	810
	<i>m</i> -CPBA, CH ₂ Cl ₂ , 0°, 0.5 h	 (57)	810
C ₁₂  R = MEM	<i>m</i> -CPBA, hexane, -15°, 15 min	 (50)	203

TABLE 17A. α -HYDROXYLATION OF 1-SILYLOXY-1,3-DIENES (Continued)

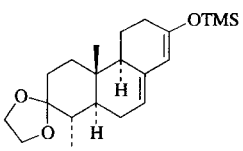
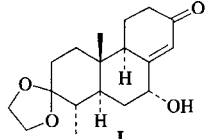
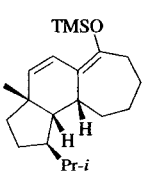
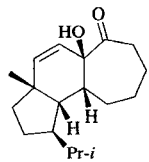
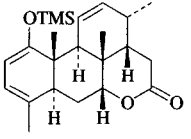
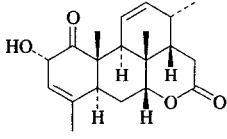
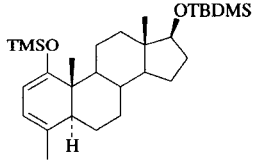
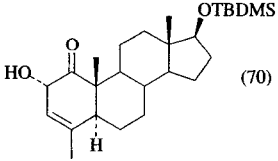
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
<p>C₁₆</p> 	<p>[2 KHSO₅•KHSO₄•K₂SO₄], NaHCO₃, THF, H₂O, 1 h</p>	 (25)	95
	<p><i>m</i>-CPBA, THF, H₂O, 2 h</p>	I (48)	95
	<p>(PhIO)_n, MeOH, H₂O, 3 h</p>	I (25)	95
<p>C₁₈</p> 	<p><i>m</i>-CPBA</p>	 (—)	577
<p>C₂₀</p> 	<p>1. <i>m</i>-CPBA, NaHCO₃, CH₂Cl₂, -23°, 45 min 2. Bu₄NF, -23°, 1 h</p>	 (50)	838, 839
	<p>1. <i>m</i>-CPBA, CH₂Cl₂, -78°, 12 h 2. Bu₄NF, CH₂Cl₂, 1.5 h</p>	 (70)	334

TABLE 17B. α -HYDROXYLATION OF 2-SILYLOXY-1,3-DIENES

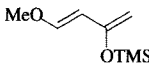
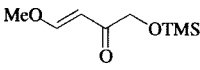
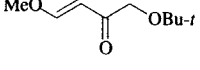
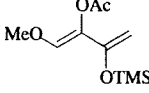
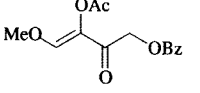
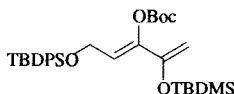
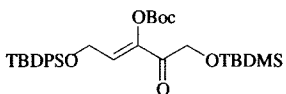

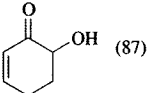
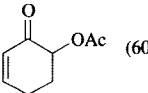
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₄ 	<i>m</i> -CPBA, hexane, -78° to rt	 (90)	840
	<i>t</i> -BuOCl, Pd(PPh ₃) ₄ , HgO, PhMe, -78°, 1 h	 (45)	185
	1. <i>m</i> -CPBA, pentane, -78°, 1 h, then to rt 2. MeOH 3. BzCl, DMAP	 (50)	841
C ₅ 	<i>m</i> -CPBA, hexane, 0°, 3 h	 (79)	209
C ₆ 	1. O ₂ , Co(mac) ₂ , EtCH(OEt) ₂ , 4Å MS, 45°, 10 h 2. Bu ₄ NF, THF, rt, 3 h	 (87)	66, 65
	1. Triphenylphosphite ozonide, CH ₂ Cl ₂ , -78°, 3 h 2. PPh ₃ , -78° to rt, 1 h	I (58)	82
	1. <i>m</i> -CPBA, hexane, -15° to rt, 1 h 2. TEAF, CH ₂ Cl ₂ , 5-10 h	I (70)	253, 82
	1. <i>m</i> -CPBA, hexane, -15° to rt, 1 h 2. Ac ₂ O, TEAF, NEt ₃ , 12 h	 (60)	253

TABLE 17B. α -HYDROXYLATION OF 2-SILYLOXY-1,3-DIENES (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. Pb(OBz) ₄ , CH ₂ Cl ₂ , -18°, 5 min; rt, 1 h 2. Et ₃ NHF, rt, 2-8 h	 (33) + (33)	370
	1. Pb(OBz) ₄ , 10 min; 2. Et ₃ NHF	 (-)	370
	<i>m</i> -CPBA, hexane, -16°, 30 min	 (66)	842
C ₆₋₉ 	$\begin{matrix} R^1 & R^2 \\ H & H \\ Me & H \\ H & Me \\ Me & Me \end{matrix}$ 1. <i>t</i> -BuO ₂ H, CuCl, C ₆ H ₆ , 50°, 19 h 2. H ₃ O ⁺	 (30-60)	93
C ₇ 	1. Triphenylphosphite ozonide, CH ₂ Cl ₂ , -78°, 3 h 2. PPh ₃ , -78° to rt, 1 h	 I (41) + II (20)	82
	<i>m</i> -CPBA	I (26) + II (39)	82
	<i>m</i> -CPBA, CH ₂ Cl ₂ , -50°, 30 min	 (32) + (47)	843
	1. Triphenylphosphite ozonide, CH ₂ Cl ₂ , -78°, 3 h 2. PPh ₃ , -78° to rt, 1 h	 I (69)	82
	1. <i>m</i> -CPBA, hexane, 25°, 1 h 2. Bu ₄ NF, 0 to 25°, 2 h	I (73)	844
	1. Pb(OBz) ₄ , CH ₂ Cl ₂ , -18°, 5 min; rt, 20 h 2. Et ₃ NHF, rt, 2-8 h	 (47)	370
	1. Pb(OBz) ₄ , 1 h 2. Et ₃ NHF	 + (-)	370
	1. <i>m</i> -CPBA, hexane, -15°, 15 min; 22°, 1 h 2. TBDMSCl, imidazole, DMF, rt, 12-24 h	 (29) + (61)	121
	<i>m</i> -CPBA, pentane	 (-)	845

TABLE 17B. α -HYDROXYLATION OF 2-SILYLOXY-1,3-DIENES (Continued)

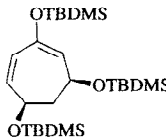
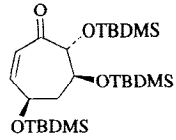
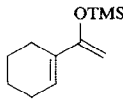
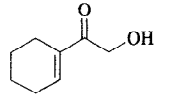
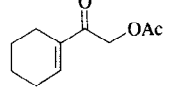
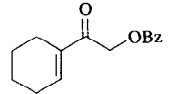
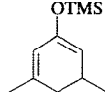
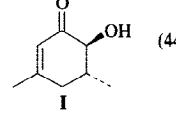
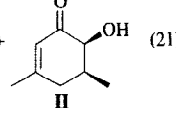
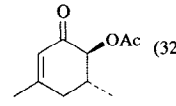
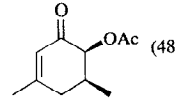
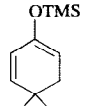
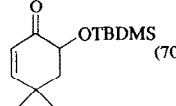
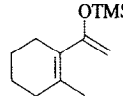
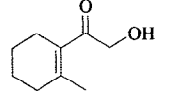
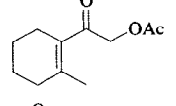
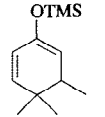
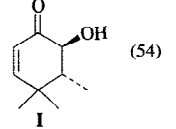
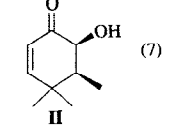
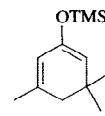
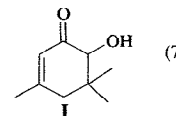
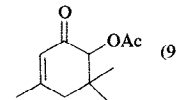
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	<i>m</i> -CPBA, pentane, -20° to rt	 (83)	846
C ₈ 	1. <i>m</i> -CPBA, hexane, -15° to rt, 1 h 2. TEAF, CH ₂ Cl ₂ , 5-10 h	 (83)	253
	1. <i>m</i> -CPBA, hexane, -15° to rt, 1 h 2. Ac ₂ O, TEAF, Et ₃ N, 12 h	 (74)	253
	1. Pb(OBz) ₄ , CH ₂ Cl ₂ , 0° to rt, 0.5 h 2. TEAF, rt, 8 h	 (54)	370
	1. Triphenylphosphite ozonide, CH ₂ Cl ₂ , -78°, 3 h 2. PPh ₃ , -78° to rt, 1 h	 (44) +  (21)	82
	1. <i>m</i> -CPBA, hexane, -15° to rt, 1 h 2. TEAF, CH ₂ Cl ₂ , 5-10 h	I (35) + II (52)	253, 82
	1. <i>m</i> -CPBA, hexane, -15° to rt, 1 h 2. Ac ₂ O, TEAF, Et ₃ N, 12 h	 (32) +  (48)	253
C ₉ 	1. <i>m</i> -CPBA, hexane, -15°, 15 min; 22°, 1 h 2. Bu ₄ NF, rt, 3-5 h 3. TBDMSCl, imidazole, DMF, rt, 12-24 h	 (70)	121
		1. <i>m</i> -CPBA, hexane, -15° to rt, 1 h 2. TEAF, CH ₂ Cl ₂ , 5-10 h	 (68)
1. <i>m</i> -CPBA, hexane, -15° to rt, 1 h 2. Ac ₂ O, TEAF, Et ₃ N, 12 h		 (89)	253
	1. Triphenylphosphite ozonide, CH ₂ Cl ₂ , -50°, 3 h 2. PPh ₃ , -50° to rt, 1 h	 (54) +  (7)	82
	<i>m</i> -CPBA	I (30) + II (40)	82
	1. Triphenylphosphite ozonide, CH ₂ Cl ₂ , -50°, 3 h 2. PPh ₃ , -50° to rt, 1 h	 (79)	82
	1. <i>m</i> -CPBA, hexane, -15°, 20 min; 30°, 2 h 2. TEAF, CH ₂ Cl ₂ , rt, 2 h	I (70-73) ^a	254, 82, 253
	1. <i>m</i> -CPBA, hexane, -15° to rt, 1 h 2. Ac ₂ O, TEAF, Et ₃ N, 48 h	 (98)	253

TABLE 17B. α -HYDROXYLATION OF 2-SILYLOXY-1,3-DIENES (Continued)

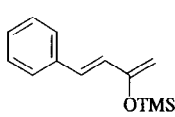
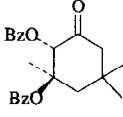
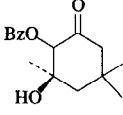
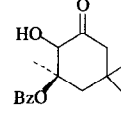
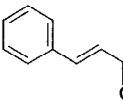
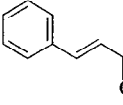
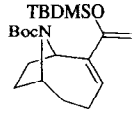
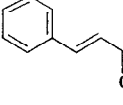
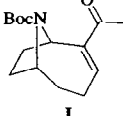
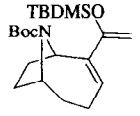
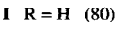
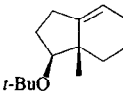
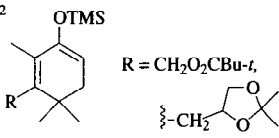
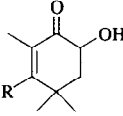
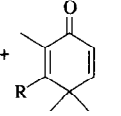
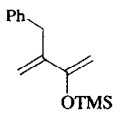
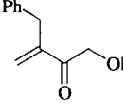
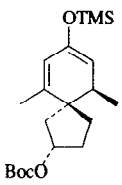
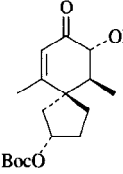
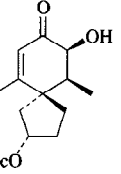
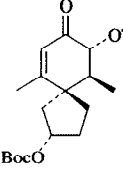
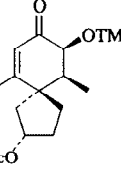
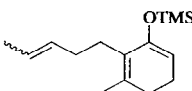
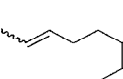
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
 C_{10}	1. $Pb(OBz)_4$, CH_2Cl_2 , -18° , 5 min; rt, 20 h 2. TEAF, rt, 2-8 h	 (55)	370
	1. $Pb(OBz)_4$, 1 h 2. TEAF	 +  (—)	370
	1. <i>m</i> -CPBA, hexane 2. MeOH, rt, 2 h	 (74)	847
	1. $Ph(OAc)_2$, CH_2Cl_2 , rt, 2-8 h 2. H_2O	 (78)	365
 C_{11}	1. $Pb(OBz)_4$, CH_2Cl_2 , 0° to rt, 0.5 h 2. TEAF, rt, 8 h	 (78)	370
	<i>m</i> -CPBA, hexane, -10° to rt, 0.5 h	 R = TBDMS (100)	303
 C_{12}	1. <i>m</i> -CPBA, hexane, -10° to rt, 0.5 h 2. HF, MeCN, rt, 20 min	 I R = H (80)	303
	<i>m</i> -CPBA, hexane, <i>t</i> -BuOH, 0°	 (—)	848
 C_{10-12}	CrO_3 ·dimethylpyrazole, CH_2Cl_2 , -25°	 (10-12) +  (40-45)	849
 C_{11}	1. <i>m</i> -CPBA, hexane 2. MeOH, rt, 2 h	 (94)	847
 C_{12}	1. Triphenylphosphite ozonide, CH_2Cl_2 , -50° , 3 h 2. PPh_3	 (63) +  (8)	850, 737
	<i>m</i> -CPBA, hexane, -15° to rt, 30 min	 (33) +  (30)	737
 C_{12}	<i>m</i> -CPBA	 (80)	851

TABLE 17B. α -HYDROXYLATION OF 2-SILYLOXY-1,3-DIENES (Continued)

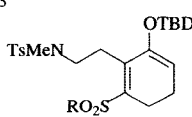
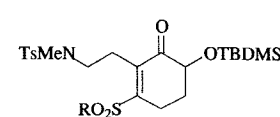
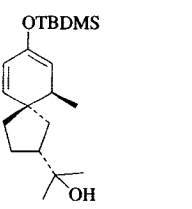
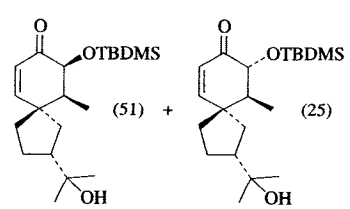
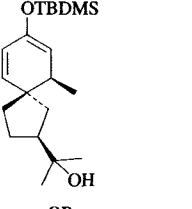
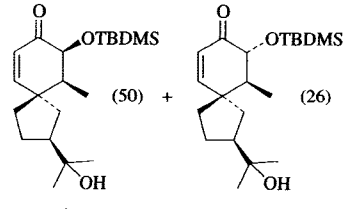
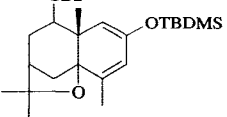
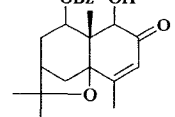
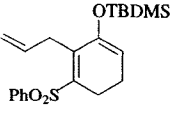
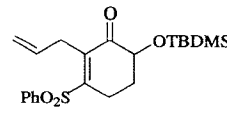
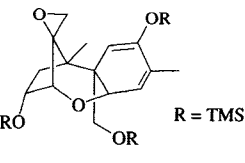
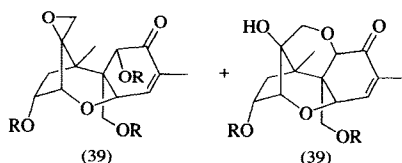
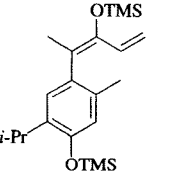
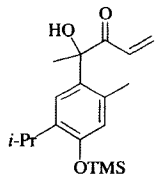
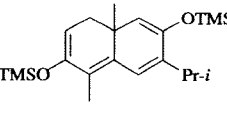
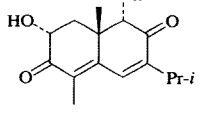
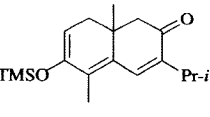
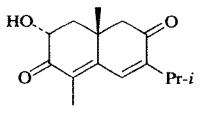
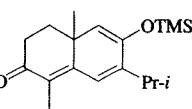
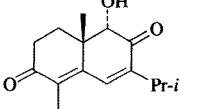
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.	
C ₁₃₋₁₅ 	<i>m</i> -CPBA, CH ₂ Cl ₂ , -78 to 25°, 0.5-4 h		R <i>t</i> -Bu (65) Ph (68)	852
C ₁₄ 	PhCO ₃ H, hexane, -15° to rt, 1.5 h	 (51) + (25)		134, 135
	PhCO ₃ H, hexane, -15° to rt, 1.5 h	 (50) + (26)		134
C ₁₅ 	1. <i>m</i> -CPBA, hexane, 25°, 4 h 2. HCl, THF, 25°, 20 h	 (50)		749
	<i>m</i> -CPBA, CH ₂ Cl ₂ , -78 to 4°, 2.5 h	 (62)		852, 853
 R = TMS	<i>m</i> -CPBA, hexane, -15°, 30 min; 30°, 2 h	 (39) + (39)		211
	<i>m</i> -CPBA, petroleum ether	 (—)		742
	<i>m</i> -CPBA, petroleum ether	 (—)		742
	<i>m</i> -CPBA, petroleum ether	 (—)		742
	<i>m</i> -CPBA, petroleum ether	 (—)		742

TABLE 17B. α -HYDROXYLATION OF 2-SILYLOXY-1,3-DIENES (Continued)

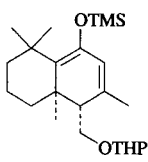
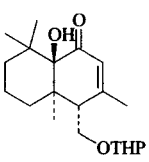
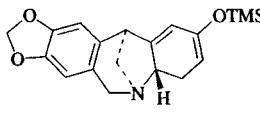
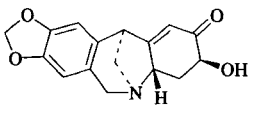
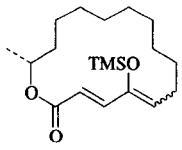
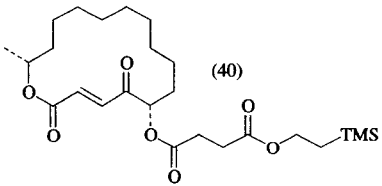
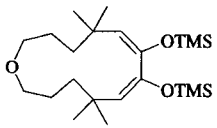
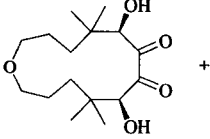
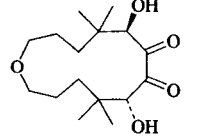
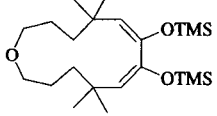
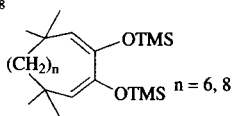
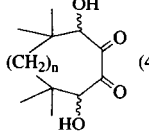
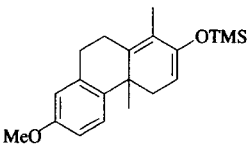
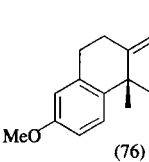
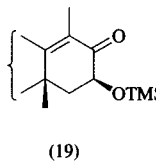
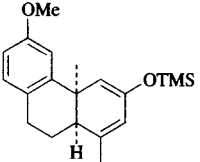
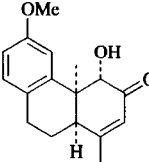
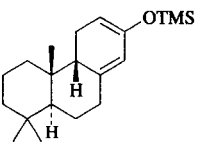
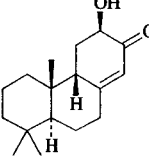
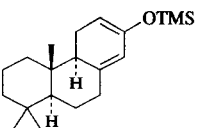
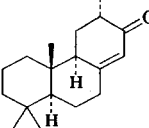
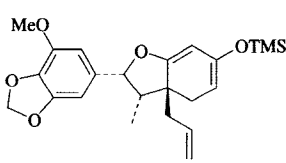
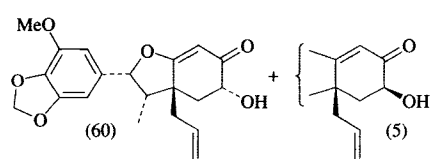
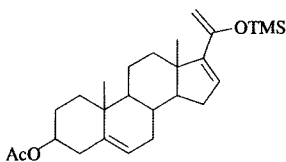
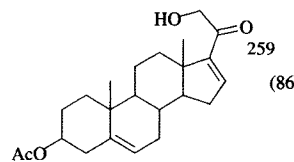
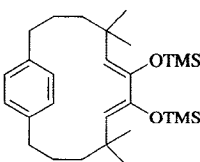
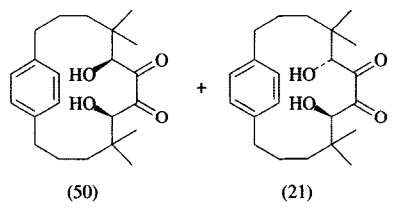
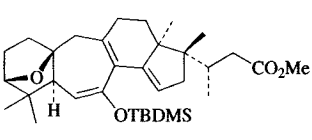
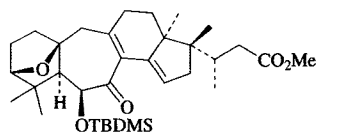
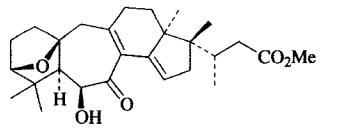
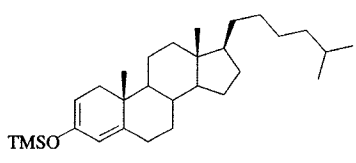
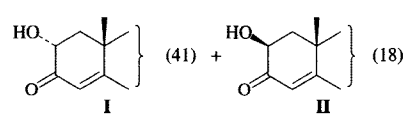
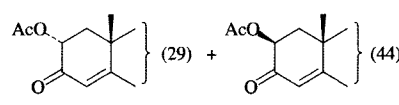
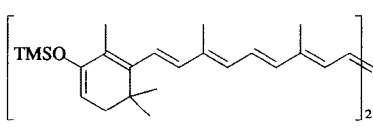
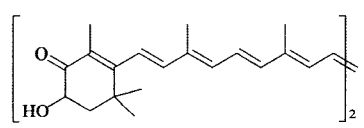
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. <i>m</i> -CPBA 2. H ₃ O ⁺	 (—)	231
C ₁₆ 	OsO ₄ (cat.), NMO, <i>t</i> -BuOH, H ₂ O, 0 to 23°, 5 h	 (89)	348
320 	Pb(O-C(=O)-CH ₂ -CH ₂ -C(=O)-O-CH ₂ -CH ₂ -TMS) ₄	 (40)	163
	1. <i>m</i> -CPBA, CH ₂ Cl ₂ , rt; reflux several h 2. NaHSO ₃ , H ₂ O 3. MeOH, reflux	 I (66) +  II (9)	854
	1. <i>m</i> -CPBA, Et ₂ O, rt, 1 h 2. NaHSO ₃ , H ₂ O 3. MeOH, reflux	I (12) + II (73)	854
C ₁₆₋₁₈ 	<i>m</i> -CPBA, CH ₂ Cl ₂	 (47)	855
C ₁₇ 	<i>m</i> -CPBA, hexane, rt, 18 h	 (76) +  (19)	856
	1. <i>m</i> -CPBA, hexane, 0° to rt, 2 h 2. Bu ₄ NF, CH ₂ Cl ₂ , 3 h	 (33)	822
	1. <i>m</i> -CPBA, hexane, -15° to rt, 40 min 2. Bu ₄ NF, CH ₂ Cl ₂ , overnight	 (71)	857
	1. <i>m</i> -CPBA, hexane, -15° to rt, 2 h 2. Bu ₄ NF, CH ₂ Cl ₂ , rt, overnight	 (89)	858

TABLE 17B. α -HYDROXYLATION OF 2-SILYLOXY-1,3-DIENES (Continued)

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
C ₂₀ 	1. <i>m</i> -CPBA, CH ₂ Cl ₂ , NaHCO ₃ , -15° to rt, 1 h 2. Bu ₄ NF, rt, 13 h		859
C ₂₁ 	1. <i>m</i> -CPBA, hexane, -15° to rt, 4 h 2. Bu ₄ NF, CH ₂ Cl ₂ , rt, 24 h		787
C ₂₂ 	1. <i>m</i> -CPBA, CH ₂ Cl ₂ , 0° to reflux, 16 h 2. MeOH, H ₂ O, reflux, 2 h		860
C ₂₇ 	<i>m</i> -CPBA, CH ₂ Cl ₂ , 23°		861
	1. <i>m</i> -CPBA, CH ₂ Cl ₂ , 23° 2. HF, MeCN		861
	1. Triphenylphosphite ozonide, CH ₂ Cl ₂ , -50°, 3 h 2. Ph ₃ P, -50° to rt, 1 h		82
	<i>m</i> -CPBA	I (32) + II (48)	82
	1. <i>m</i> -CPBA, CH ₂ Cl ₂ , -15° to rt, 1 h 2. TEAF, CH ₂ Cl ₂ , rt, 5-10 h	I+II (80)	253
	1. <i>m</i> -CPBA, CH ₂ Cl ₂ , -15° to rt, 1 h 2. Ac ₂ O, TEAF, Et ₃ N, 48 h		253
C ₄₀ 	PSPO		238

^a The yield includes preparation of the substrate.

TABLE 18. α -HYDROXYLATION OF ALKYL TRIALKYLSILYL KETENE ACETALS AND RELATED SYSTEMS


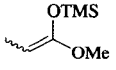
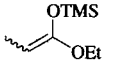
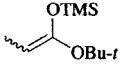
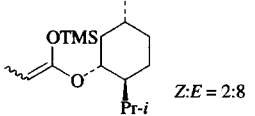
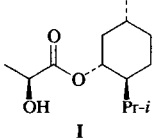
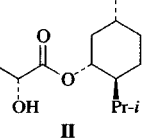
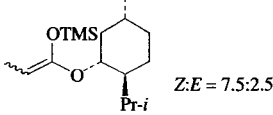
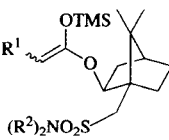
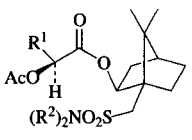
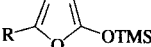
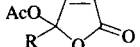
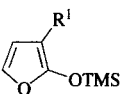
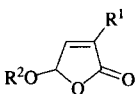
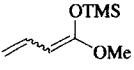
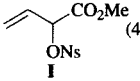
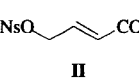
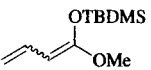
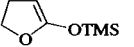

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																		
C ₂ 	(NsO) ₂ , EtOAc, MeOH, 0°, 2 h; rt, 16 h	NsO-CH(OH)-CO ₂ Pr- <i>i</i> (68)	107																		
C ₃ 	(NsO) ₂ , EtOAc, MeOH, 0°, 2 h; rt, 16 h	NsO-CH(OH)-CO ₂ Me (75)	107																		
	(NsO) ₂ , EtOAc, NaOMe, 0°, 2 h; rt, 16 h	I (88)	107																		
	(NsO) ₂ , EtOAc, MeOH, 0°, 2 h; rt, 16 h	NsO-CH(OH)-CO ₂ Et (77)	107																		
	(NsO) ₂ , EtOAc, NaOMe, 0°, 2 h; rt, 16 h	I (79)	107																		
	(NsO) ₂ , EtOAc, MeOH, 0°, 2 h; rt, 16 h	NsO-CH(OH)-CO ₂ Bu- <i>t</i> (low)	107																		
	(NsO) ₂ , EtOAc, NaOMe, 0°, 2 h; rt, 16 h	I (82)	107																		
 Z:E = 2:8	MoOPH	 +  I+II = (-); I:II = 8:2	344																		
 Z:E = 7.5:2.5	MoOPH	I+II (-); I:II = 2.5:7.5	344																		
C ₃₋₆ 	1. Pb(OAc) ₄ , CH ₂ Cl ₂ , -15°, 15 min; 20°, 30 min 2. Et ₃ NHF, 20°, 4 h	 <table border="1" data-bbox="1189 1246 1397 1338"> <thead> <tr> <th>R¹</th> <th>R²</th> <th>% de</th> </tr> </thead> <tbody> <tr> <td>Me</td> <td><i>i</i>-Pr</td> <td>(60) 88</td> </tr> <tr> <td><i>n</i>-Bu</td> <td><i>c</i>-C₆H₁₁</td> <td>(55) 90.5</td> </tr> </tbody> </table>	R ¹	R ²	% de	Me	<i>i</i> -Pr	(60) 88	<i>n</i> -Bu	<i>c</i> -C ₆ H ₁₁	(55) 90.5	372									
R ¹	R ²	% de																			
Me	<i>i</i> -Pr	(60) 88																			
<i>n</i> -Bu	<i>c</i> -C ₆ H ₁₁	(55) 90.5																			
C ₄₋₅ 	PhI(OAc) ₂ , CH ₂ Cl ₂ , -21° to rt, 1 h	 R H (87) Me (76)	162																		
C ₄₋₁₁ 	(PhIO) _n , R ² OH, BF ₃ ·Et ₂ O, CH ₂ Cl ₂ , rt	 <table border="1" data-bbox="1154 1499 1293 1682"> <thead> <tr> <th>R¹</th> <th>R²</th> <th>% de</th> </tr> </thead> <tbody> <tr> <td>H</td> <td>Ms</td> <td>(67)</td> </tr> <tr> <td>H</td> <td>Ac</td> <td>(72)</td> </tr> <tr> <td>H</td> <td>Et</td> <td>(55)</td> </tr> <tr> <td>Ms</td> <td>Ms</td> <td>(74)</td> </tr> <tr> <td>H</td> <td>Ts</td> <td>(66)</td> </tr> </tbody> </table>	R ¹	R ²	% de	H	Ms	(67)	H	Ac	(72)	H	Et	(55)	Ms	Ms	(74)	H	Ts	(66)	351
R ¹	R ²	% de																			
H	Ms	(67)																			
H	Ac	(72)																			
H	Et	(55)																			
Ms	Ms	(74)																			
H	Ts	(66)																			
C ₄ 	(NsO) ₂ , EtOAc, NaOMe, 0°	 (40) +  (33)	108																		
	(NsO) ₂ , EtOAc, NaOMe, -78°	I (75) + II (25)	108																		
	(NsO) ₂ , EtOAc, ZnCl ₂ , -90°	I (80) + II (20)	108																		
	(NsO) ₂ , EtOAc, ZnCl ₂ , -78°	I (60) + II (23)	108																		
	(NsO) ₂ , EtOAc, MeOH, 0°, 2 h; rt, 16 h	 (low)	107																		
	(NsO) ₂ , EtOAc, NaOMe, 0°, 2 h; rt, 16 h	I (61)	107																		

TABLE 18. α -HYDROXYLATION OF ALKYL TRIALKYLSILYL KETENE ACETALS AND RELATED SYSTEMS (Continued)


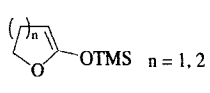

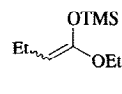



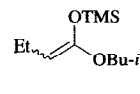

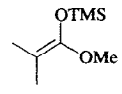




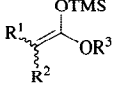

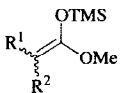

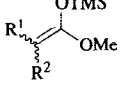

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	1. $\text{Pb}(\text{O}_2\text{CR})_4$, C_6H_6 , rt, 30 min 2. TEAF, rt	 $\begin{matrix} \text{R} \\ \text{Me (47)} \\ \text{Ph (31)} \end{matrix}$	371
C ₄₋₅  n = 1, 2	$(\text{PhIO})_n$, MeOH, rt	 (—)	352
C ₄ 	$(\text{NsO})_2$, EtOAc, MeOH, 0°, 2 h; rt, 16 h	 (54) I	107
	$(\text{NsO})_2$, EtOAc, NaOMe, 0°, 2 h; rt, 16 h	I (84)	107
	$\text{PhI}(\text{OH})\text{OMs}$, CH_2Cl_2 , rt, 2 h	 (65)	378
	$\text{PhI}(\text{OH})\text{OTs}$, CH_2Cl_2 , rt, 2 h	 (65)	378
	$(\text{NsO})_2$, EtOAc, MeOH, 0°, 2 h; rt, 16 h	 (67)	107
	$(\text{NsO})_2$, EtOAc, NaOMe, 0°, 2 h; rt, 16 h	 (67)	107
	1. <i>m</i> -CPBA, hexane, rt, 30 min 2. TEAF, 30 min	 (67)	124
	1. $\text{Pb}(\text{OAc})_4$, CH_2Cl_2 , rt, 30 min 2. TEAF, rt	 (81)	371
	1. $\text{Pb}(\text{OBz})_4$, CH_2Cl_2 , rt, 30 min 2. TEAF, rt	 (69)	371
C ₄₋₉ 	$(\text{PhIO})_n$, MeOH, rt	 $\begin{matrix} \text{R}^1 & \text{R}^2 & \text{R}^3 \\ \text{MeO} & & \end{matrix}$	352
		$\begin{matrix} \text{R}^1 & \text{R}^2 & \text{R}^3 \\ \text{Me} & \text{Me} & \text{Me (64)} \\ \text{H} & \text{C}_6\text{H}_4\text{Cl-4} & \text{Me (57)} \\ \text{H} & \text{Ph} & \text{Me (74)} \\ \text{H} & \text{Ph} & \text{Et (65)} \\ \text{H} & \text{C}_6\text{H}_4\text{OMe-4} & \text{Me (73)} \\ \text{H} & \text{C}_6\text{H}_4\text{Me-4} & \text{Et (71)} \end{matrix}$	
C ₄₋₁₄ 	1. H_2O_2 •urea, MeReO_3 (cat.), Py, MeCN:HOAc (99:1), 0°, 10 min 2. KF, MeOH, 1 h	 $\begin{matrix} \text{R}^1 & \text{R}^2 \\ \text{HO} & \end{matrix}$	92
		$\begin{matrix} \text{R}^1 & \text{R}^2 \\ \text{Me} & \text{Me (71)} \\ \text{CH=CHMe} & \text{H (70)} \\ \text{-(CH}_2\text{)}_5\text{-} & \text{(77)} \\ \text{C}_5\text{H}_{11} & \text{H (45)}^d \\ \text{Ph} & \text{H (81)} \\ \text{C}_6\text{H}_{13} & \text{H (50)}^d \\ \text{Ph} & \text{Me (85)} \\ \text{Ph} & \text{Ph (75)} \end{matrix}$	
	1. O_2 , hv, tetraphenylporphine, CCl_4 , 0°, 60-90 min 2. MeOH, 0°	 $\begin{matrix} \text{R}^1 & \text{R}^2 \\ \text{HO}_2 & \end{matrix}$	75
		$\begin{matrix} \text{R}^1 & \text{R}^2 \\ \text{Me} & \text{Me (64)} \\ \text{H} & \text{t-Bu (71)} \\ \text{H} & \text{1-adamantyl (55)} \\ \text{Ph} & \text{Ph (50)} \end{matrix}$	

TABLE 18. α -HYDROXYLATION OF ALKYL TRIALKYLSILYL KETENE ACETALS AND RELATED SYSTEMS (Continued)

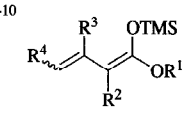
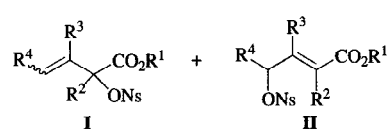
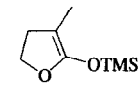

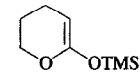



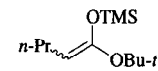
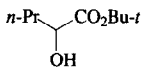
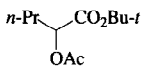
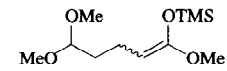
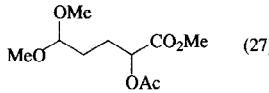
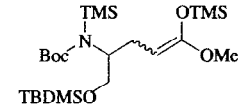
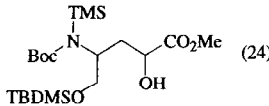
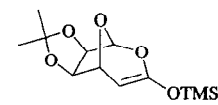
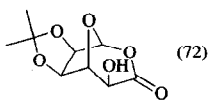
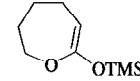


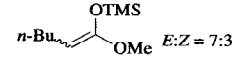
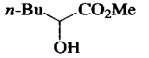
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																																																						
C ₄₋₁₀ 	(NsO) ₂ , EtOAc, ZnCl ₂ , -78°	 I + II	108																																																						
		<table border="1"> <thead> <tr> <th>R¹</th> <th>R²</th> <th>R³</th> <th>R⁴</th> <th>I</th> <th>II</th> </tr> </thead> <tbody> <tr> <td>Me</td> <td>H</td> <td>H</td> <td>H</td> <td>(62)</td> <td>(14)</td> </tr> <tr> <td>Et</td> <td>H</td> <td>H</td> <td>H</td> <td>(56)</td> <td>(18)</td> </tr> <tr> <td>Et</td> <td>H</td> <td>Me</td> <td>H</td> <td>(50)</td> <td>(28)</td> </tr> <tr> <td><i>t</i>-Bu</td> <td>H</td> <td>Me</td> <td>H</td> <td>(0)</td> <td>(100)</td> </tr> <tr> <td>Me</td> <td>H</td> <td>H</td> <td>Me</td> <td>(0)</td> <td>(68)</td> </tr> <tr> <td>Me</td> <td>Me</td> <td>H</td> <td>H</td> <td>(0)</td> <td>(71)</td> </tr> <tr> <td>Me</td> <td>H</td> <td>H</td> <td>Et</td> <td>(0)</td> <td>(43)</td> </tr> <tr> <td>Et</td> <td>H</td> <td>Ph</td> <td>H</td> <td>(80)</td> <td>(0)</td> </tr> </tbody> </table>	R ¹	R ²	R ³	R ⁴	I	II	Me	H	H	H	(62)	(14)	Et	H	H	H	(56)	(18)	Et	H	Me	H	(50)	(28)	<i>t</i> -Bu	H	Me	H	(0)	(100)	Me	H	H	Me	(0)	(68)	Me	Me	H	H	(0)	(71)	Me	H	H	Et	(0)	(43)	Et	H	Ph	H	(80)	(0)	
R ¹	R ²	R ³	R ⁴	I	II																																																				
Me	H	H	H	(62)	(14)																																																				
Et	H	H	H	(56)	(18)																																																				
Et	H	Me	H	(50)	(28)																																																				
<i>t</i> -Bu	H	Me	H	(0)	(100)																																																				
Me	H	H	Me	(0)	(68)																																																				
Me	Me	H	H	(0)	(71)																																																				
Me	H	H	Et	(0)	(43)																																																				
Et	H	Ph	H	(80)	(0)																																																				
C ₅ 	1. Pb(O ₂ CR) ₄ , CH ₂ Cl ₂ or C ₆ H ₆ , rt, 30 min 2. TEAF, rt	 R = Me, Ph (0)	371																																																						
	(NsO) ₂ , EtOAc, MeOH, 0°, 2 h; rt, 16 h	 I (low)	107																																																						
	(NsO) ₂ , EtOAc, NaOMe, 0°, 2 h; rt, 16 h	I (73)	107																																																						
	1. Pb(OAc) ₄ , CH ₂ Cl ₂ , rt, 30 min 2. TEAF, rt	 (66)	371																																																						
	1. Pb(OBz) ₄ , C ₆ H ₆ , rt, 30 min 2. TEAF, rt	 (50)	371																																																						
	1. <i>m</i> -CPBA, hexane, rt, 30 min 2. TEAF, 30 min	 (84)	124																																																						
	1. Pb(OAc) ₄ , CH ₂ Cl ₂ , rt, 30 min 2. TEAF, rt	 (85)	371																																																						
	1. Pb(OAc) ₄ , CH ₂ Cl ₂ , rt, 30 min 2. TEAF, 20 min	 (27)	373																																																						
	<i>m</i> -CPBA, hexane	 (24)	862																																																						
C ₆ 	<i>m</i> -CPBA, CH ₂ Cl ₂ , -20° to rt, 30 min	 (72)	214, 215																																																						
	1. Pb(O ₂ CR) ₄ , CH ₂ Cl ₂ , rt, 30 min 2. TEAF, rt	 R Me (82) Ph (74)	372																																																						
	PhI(OH)OTs, hexane, rt, 8 h	 (69)	378																																																						
 <i>E:Z</i> = 7:3	1. O ₂ , Ni(mac) ₂ , Me ₂ CHCHO, EtOAc, CF ₃ CONMeTMS, rt, 13 h 2. KF, MeOH	 (78)	67																																																						

TABLE 18. α -HYDROXYLATION OF ALKYL TRIALKYLSILYL KETENE ACETALS AND RELATED SYSTEMS (Continued)

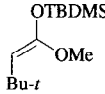
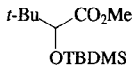
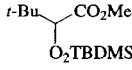
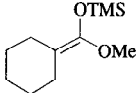
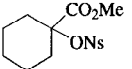
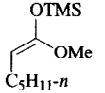
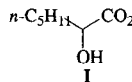
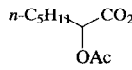
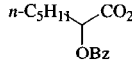
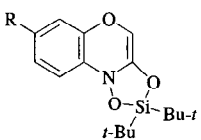
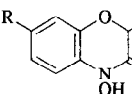
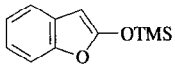
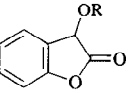
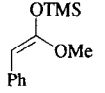
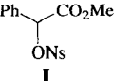
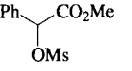
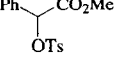
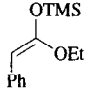
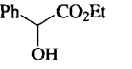
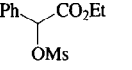
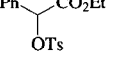
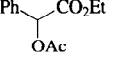
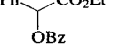
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.
	DMDO, Me ₂ CO, -40°, 1 h	 (100)	350
	O ₂ , hv, tetraphenylporphine, CH ₂ Cl ₂ , -90°, 2 h, then 30°, 8 h	 I (—) + <i>t</i> -BuCHO II (—); I:II = 97:3	71
C ₇ 	(NsO) ₂ , NaOMe, EtOAc, 0°, 2 h; rt, 16 h	 (69)	107
	O ₂ , TAS-F, Ph ₃ P	 I (81)	68
	1. <i>m</i> -CPBA, hexane, rt, 30 min 2. TEAF, 30 min	I (81)	124
	1. Pb(OAc) ₄ , CH ₂ Cl ₂ , rt, 30 min 2. TEAF, rt	 (92)	371
	1. Pb(OBz) ₄ , CH ₂ Cl ₂ , rt, 30 min 2. TEAF, rt	 (85)	371
C ₈₋₉ 	1. <i>m</i> -CPBA, CH ₂ Cl ₂ , 2 h 2. Bu ₄ NF, THF, 2 h	 $\frac{R}{H}$ (41) $\frac{R}{MeO}$ (32)	354
C ₈ 	(PhIO) _n , ROH, BF ₃ ·Et ₂ O, CH ₂ Cl ₂ , rt	 $\frac{R}{Ms}$ (65) $\frac{R}{Ts}$ (62)	351
	(NsO) ₂ , EtOAc, MeOH, 0°, 2 h; rt, 16 h	 I (78)	107
	(NsO) ₂ , EtOAc, NaOMe, 0°, 2 h; rt, 16 h	I (79)	107
	PhI(OH)Ms, CH ₂ Cl ₂ , rt, 2 h	 (65)	378
	PhI(OH)Ts, CH ₂ Cl ₂ , rt, 2 h	 (81)	378
	1. <i>m</i> -CPBA, hexane, rt, 30 min 2. TEAF, 30 min	 (70)	124
	PhI(OH)Ms, CH ₂ Cl ₂ , rt, 2 h	 (85)	378
	PhI(OH)Ts, CH ₂ Cl ₂ , rt, 2 h	 (60)	378
	1. Pb(OAc) ₄ , CH ₂ Cl ₂ , rt, 30 min 2. TEAF, rt	 (75)	371
	1. Pb(OBz) ₄ , CH ₂ Cl ₂ , rt, 30 min 2. TEAF, rt	 (92)	371

TABLE 18. α -HYDROXYLATION OF ALKYL TRIALKYLSILYL KETENE ACETALS AND RELATED SYSTEMS (Continued)

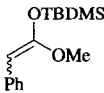
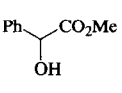
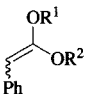
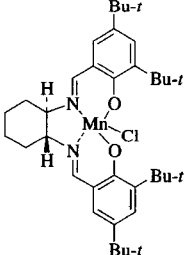
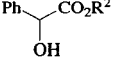
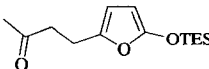
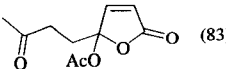
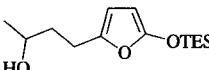
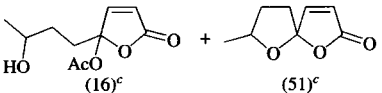
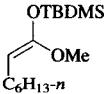
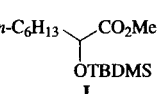
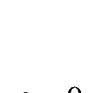
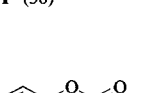
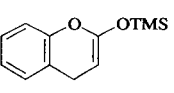
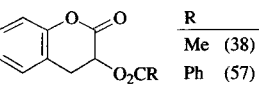
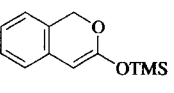
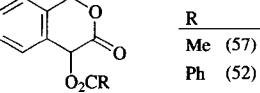
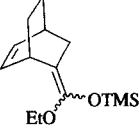
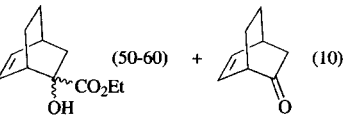
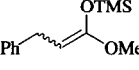
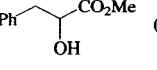
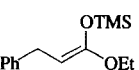
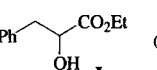

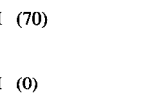
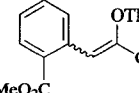
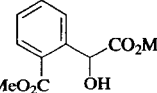

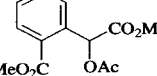


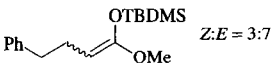
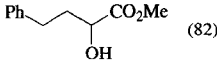
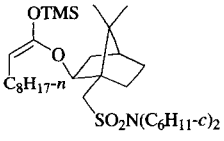
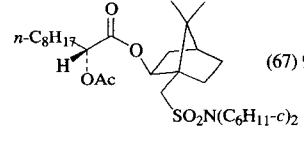
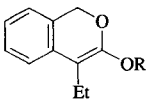
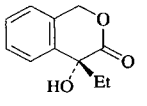
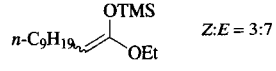
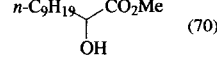

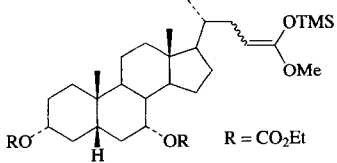
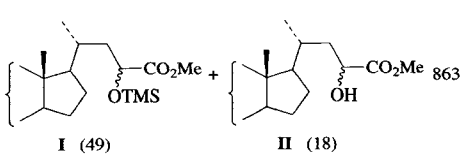
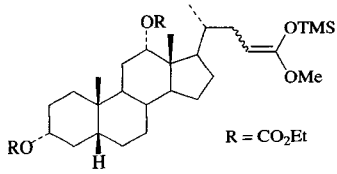
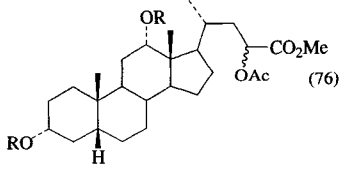
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.																				
	1. NPSO, CHCl ₃ , 25°, 6 min 2. HCl (5%), THF	 (54)	180																				
	1. [O], 4-phenylpyridine <i>N</i> -oxide,  CH ₂ Cl ₂ , cosolvent, 0°, 24 h 2. HCl, MeOH, 2 h	 <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th>R¹</th> <th>R²</th> <th>[O]</th> <th>Cosolvent</th> <th>% ee</th> </tr> </thead> <tbody> <tr> <td>TMS</td> <td>OMe</td> <td>NaOCl</td> <td>H₂O</td> <td>(64)^b S 22</td> </tr> <tr> <td>TBDMS</td> <td>OMe</td> <td>NaOCl</td> <td>H₂O</td> <td>(70)^b S 57</td> </tr> <tr> <td>TMS</td> <td>SEt</td> <td>(PhIO)_n</td> <td>—</td> <td>(35)^b S 18</td> </tr> </tbody> </table>	R ¹	R ²	[O]	Cosolvent	% ee	TMS	OMe	NaOCl	H ₂ O	(64) ^b S 22	TBDMS	OMe	NaOCl	H ₂ O	(70) ^b S 57	TMS	SEt	(PhIO) _n	—	(35) ^b S 18	273, 783
R ¹	R ²	[O]	Cosolvent	% ee																			
TMS	OMe	NaOCl	H ₂ O	(64) ^b S 22																			
TBDMS	OMe	NaOCl	H ₂ O	(70) ^b S 57																			
TMS	SEt	(PhIO) _n	—	(35) ^b S 18																			
	Pb(OAc) ₄ , C ₆ H ₆ , 4°	 (83)	162																				
	Pb(OAc) ₄ , THF, -10° to rt, 2 h		162																				
	O ₂ , Co(mac) ₂ , EtCH(OEt) ₂ , 4Å MS, 45°, 14 h O ₃ , MeOH, CH ₂ Cl ₂ , -78°	 (95)	66, 65																				
	O ₃ , MeOH, CH ₂ Cl ₂ , -78°	 (50)	85																				
C ₉ 	1. Pb(O ₂ CR) ₄ , CH ₂ Cl ₂ , rt, 30 min 2. TEAF, rt	 <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th>R</th> <th>Yield (%)</th> </tr> </thead> <tbody> <tr> <td>Me</td> <td>(38)</td> </tr> <tr> <td>Ph</td> <td>(57)</td> </tr> </tbody> </table>	R	Yield (%)	Me	(38)	Ph	(57)	371														
R	Yield (%)																						
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Ph	(57)																						
	1. Pb(O ₂ CR) ₄ , CH ₂ Cl ₂ , rt, 30 min 2. TEAF, rt	 <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th>R</th> <th>Yield (%)</th> </tr> </thead> <tbody> <tr> <td>Me</td> <td>(57)</td> </tr> <tr> <td>Ph</td> <td>(52)</td> </tr> </tbody> </table>	R	Yield (%)	Me	(57)	Ph	(52)	371														
R	Yield (%)																						
Me	(57)																						
Ph	(52)																						
	1. <i>m</i> -CPBA, 2. H ₃ O ⁺		124																				
 <i>E:Z</i> = 2:1	1. O ₂ , Ni(mac) ₂ , Et ₂ CHCHO, EtOAc, CF ₃ CONMeTMS, rt, 13 h 2. KF, MeOH	 (77)	67																				
 <i>E</i>	1. O ₂ , Co(mac) ₂ , EtCH(OEt) ₂ , 4Å MS, 45°, 10 h 2. Bu ₄ NF, THF, rt, 1 h	 (96)	66, 65																				
	1. <i>m</i> -CPBA, hexane 2. H ₂ O	 (70)	66																				
	<i>m</i> -CPBA, CH ₂ Cl ₂	 (0)	66																				
C ₁₀ 	<i>m</i> -CPBA, hexane, 0° to rt, 30 min	 (44)	164, 165																				
	Pb(OAc) ₄ , C ₆ H ₆ , rt, 2 h	 (83)	164, 165																				

TABLE 18. α -HYDROXYLATION OF ALKYL TRIALKYLSILYL KETENE ACETALS AND RELATED SYSTEMS (Continued)

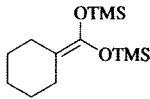
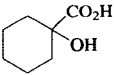
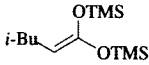
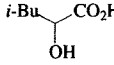
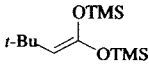
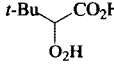
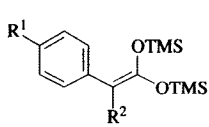
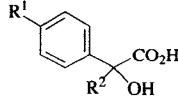
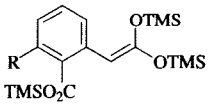
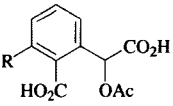
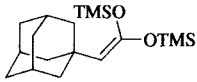
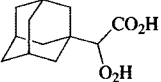
Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.						
	1. O ₂ , Ni(mac) ₂ , Me ₂ CHCHO, EtOAc, CF ₃ CONMeTMS, rt, 13 h 2. KF, MeOH	 (82)	67						
	1. Pb(OAc) ₄ , CH ₂ Cl ₂ , -15°, 15 min; 20°, 30 min 2. Et ₃ NHF, 20°, 4 h	 (67) 94% de	372						
C ₁₁ 	(DHQD) ₂ -PHAL, AD-mix- β	 <table border="1" style="display: inline-table; vertical-align: middle;"> <thead> <tr> <th>R</th> <th>% ee</th> </tr> </thead> <tbody> <tr> <td><i>i</i>-Pr₃Si (67)</td> <td>30</td> </tr> <tr> <td>TBDMS (70)</td> <td>40</td> </tr> </tbody> </table>	R	% ee	<i>i</i> -Pr ₃ Si (67)	30	TBDMS (70)	40	353
R	% ee								
<i>i</i> -Pr ₃ Si (67)	30								
TBDMS (70)	40								
	1. O ₂ , Ni(mac) ₂ , Me ₂ CHCHO, EtOAc, rt, 15 h 2. KF, MeOH	 (70)	67						
	1. O ₂ , Ni(mac) ₂ , Me ₂ CHCHO, EtOAc, CF ₃ CONMeTMS, rt, 13 h 2. KF, MeOH	 (88)	67						
C ₂₄ 	1. O ₃ , BF ₃ ·Et ₂ O, CH ₂ Cl ₂ , -78°, 1 h 2. Zn, HOAc, rt, 1 h		863						
	O ₃ , BF ₃ ·Et ₂ O, CH ₂ Cl ₂ , -18°, 1.5 h <i>m</i> -CPBA, hexane, -15° to rt, 1 h OsO ₄ , dioxane, rt, 16 h	II (49) II (55) II (59)	863 863 863						
	Pb(OAc) ₄ , CH ₂ Cl ₂ , -15° to rt, 30 min	 (76)	863						

^a The yield was determined by NMR spectroscopy before treatment with KF.

^b The number is the conversion.

^c The yield is for the two steps including the preparation of the substrate by LiAlH₄-reduction of the corresponding ketone.

TABLE 19. α -HYDROXYLATION OF BIS(TRIALKYLSILYL) KETENE ACETALS

Substrate	Conditions	Product(s) and Yield(s) (%)	Refs.												
C ₆ 	1. <i>m</i> -CPBA, hexane, 0° to rt, 30 min 2. 1.5N HCl	 (80)	125												
	1. <i>m</i> -CPBA, hexane, 0° to rt, 30 min 2. 1.5N HCl	 (50)	125												
	1. O ₂ , hv, sensitizer 2. MeOH	 (100)	77												
C ₈₋₁₄ 	1. <i>m</i> -CPBA, hexane, 0° to rt, 30 min 2. 1.5N HCl	 <table border="1" style="display: inline-table; vertical-align: middle;"> <thead> <tr> <th>R¹</th> <th>R²</th> <th></th> </tr> </thead> <tbody> <tr> <td>H</td> <td>H</td> <td>(82)</td> </tr> <tr> <td>MeO</td> <td>H</td> <td>(83)</td> </tr> <tr> <td>H</td> <td>Ph</td> <td>(81)</td> </tr> </tbody> </table>	R ¹	R ²		H	H	(82)	MeO	H	(83)	H	Ph	(81)	125
R ¹	R ²														
H	H	(82)													
MeO	H	(83)													
H	Ph	(81)													
C ₁₂₋₁₃ 	1. Pb(OAc) ₄ , C ₆ H ₆ , rt 2. HCl (5%)	 <table border="1" style="display: inline-table; vertical-align: middle;"> <thead> <tr> <th>R</th> <th></th> </tr> </thead> <tbody> <tr> <td>H</td> <td>(100)</td> </tr> <tr> <td>MeO</td> <td>(97-100)</td> </tr> </tbody> </table>	R		H	(100)	MeO	(97-100)	164, 165						
R															
H	(100)														
MeO	(97-100)														
C ₁₂ 	1. O ₂ , hv, sensitizer 2. MeOH, -20°	 (90)	73												

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